Evaluation of the Regulatory Requirements for Development and Approval of Biosimilar Medicines in the BRICS-TM Countries: Improving Patients' Access

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ABSTRACT

Biosimilars are affordable medicines of the original innovator biologic products that has the potential to improve access and create valuable savings for patients and the overall healthcare systems. Biosimilars are expected to emerge as a rapidly growing segment in emerging economies, as the treatment rates with biologics are low in these economies combined with constraints on affordability. However, unlike small molecule generics, biosimilars are complex molecules and have high associated cost of development. The biosimilar industry faces multiple challenges and obstacles in developing and marketing these complex products. While a common regulatory framework has been proposed by World Health Organisation (WHO), countries have only partially adopted them. Regulatory principles governing biosimilars in emerging economies like BRICS-TM (Brazil, Russia, India, China, South Africa, Turkey, Mexico) are still in an evolving stage. There is differing regulatory guidelines for biosimilar development and registration in these countries; hence there remains scope for improving transparency in the national regulatory frameworks and aligning regulatory standards among these countries. Standardisation of regulatory requirements would assist in the common biosimilar development process across these economies. Comparisons of the regulatory requirements with mature regulatory agencies of countries such as Australia, Canada, Singapore and Switzerland (ACSS consortium) will facilitate benchmarking best practices leading to convergence of regulatory processes in BRICS-TM countries. This would impact the overall review and approval process as well as enabling a common development programme across these countries. Also, biosimilars are similar but not identical to the innovator product and therefore prescribers are sometimes unsure about the safety and efficacy profile of these medicines. Due to such roadblocks, the healthcare system and patients are yet to realize the full benefits of biosimilars.

The aim of the research study was to explore, identify and evaluate the biosimilar regulatory framework in terms of resources in biosimilar domain, biosimilar development criteria i.e., biosimilarity principle, comparative studies including physicochemical characterisation, non-clinical studies, clinical studies and biosimilar marketing authorisation approval pathway, of regulatory agencies in BRICS-TM

(Brazil, Russia, India, China, South Africa, Turkey, Mexico) countries. This was achieved by identifying and comparing the regulatory requirements of the selected emerging economies with those of mature agencies to understand the differing regulatory expectations for biosimilar development and approval process. The study also focused on understanding the perspectives of different stakeholders like industry, regulators, physicians and patients on the challenges for the development and uptake of biosimilars in these emerging economies. The outcome from the assessment of the challenges faced by the stakeholders, biosimilar development criteria, content of the marketing authorization application and approval pathway were likely to form the basis of a proposed standardized model for the BRICS-TM countries.

The research programme considered various methodologies for determining the appropriate study design including a combination of self-administered questionnaires and interviews to achieve the study objectives. A semi-quantitative questionnaire was developed covering the different criteria used in biosimilar development and registration process. Eleven regulatory agencies from BRICS-TM and ACSS countries were invited to take part in the study. Similarly, another semi-quantitative questionnaire was designed based on secondary research for the representatives from biopharmaceutical industry specifically to understand the perceptions of industry on the barriers faced by them in terms of complexity, costs for biosimilar development and time-to-market of biosimilar product. Following completion of the questionnaires, interviews were carried out and recorded verbatim to exclude any misinterpretations. Another set of questionnaires were prepared for the physicians and patients to identify challenges to the uptake of biosimilar medicines by physicians and patients in the developing countries.

The results indicated that the perspectives of the BRICS-TM regulatory agencies varied on a number of aspects relating to the review criteria for biosimilar development and licensing process. The most prevalent model for data assessment was the ‘full review’ of a marketing authorisation application and absence or partial reliance approach across most of these economies. The biggest hurdles in the development of biosimilar product were the sourcing of the reference biological product (RBP); there was lack of a standard approach or flexibility in the regulatory standards across the BRICS-TM agencies on sourcing of the reference biological product and hence posed as key concern for facilitating cost-effective development of biosimilar products.

Despite alignment over biosimilarity, the mandate for *in vivo* non-clinical studies and additional local clinical studies in some of the BRICS-TM countries illustrated a lack of effective implementation of a step-wise approach. Most agencies limited interaction with biosimilar developers and any scientific advice was non-binding. The marketing authorisation approval was dependent on scientific assessment of the dossier, sample analysis and GMP certification. The BRICS-TM agencies except ANVISA (Brazil), did not issue any public assessment report specifying the summary basis of biosimilar approval. The results also revealed that physicians have significant knowledge gaps in the area of biosimilar medicines. While they understand the importance of improving patients' access to biological therapies, they expect to gain complete confidence in the quality, efficacy, safety, and immunogenicity of these medicines to underpin their decision to prescribe them. For the patients, access to affordable biosimilar medicines was the single biggest factor that greatly influenced their wider adoption.

The findings from this study indicated the scale of the challenges that could exist across the emerging economies (i.e. BRICS-TM), the need for fresh perspectives in guidelines and policies facilitating wider adoption of biosimilars as well as improved patients' access. The outcomes from these studies formed the basis of a proposed standardized model for the BRICS-TM countries. This proposed regulatory model is likely to simplify new biosimilar development programmes and pave the way for patients' access to quality and affordable biosimilar medicines. It is hoped that the outcomes of this study will help in streamlining of the regulatory standards in these countries, leading to improved patient access to affordable medicines without compromising their quality, safety, or efficacy.

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LIST OF ABBREVIATIONS

3R	Replace, Reduce, Refine
AARDA	American Autoimmune Related Diseases Association
Ab	Antibody
aBLA	abbreviated Biologics License Application
ABLE	Association of Biotechnology Led Enterprises
ABN	Approved Biological Name
ACB	Advisory Committee on Biologicals
Access	Australia, Canada, Singapore, Switzerland, United Kingdom Consortium
ACCS	Advisory Committee on Chemicals Scheduling
ACCM	Advisory Committee on Complementary Medicines
ACM	Advisory Committee on Medicines
ACSS	Australia, Canada, Singapore, Switzerland
ACV	Advisory Committee on Vaccines
ADCC	Antibody Dependent Cell-Mediated Cytotoxicity
AE	Adverse events
AMANC	Asociación Mexicana de Ayuda a Niños con Cáncer
AMCP	Academy of Managed Care Pharmacy
ANVISA	Agência Nacional de Vigilância Sanitária
ARDS	Acute Respiratory Distress Syndrome
API	Active Pharmaceutical Ingredient
ARP	Australian Reference Product
ASA	Australia Specific Annex
ASCO	American Society of Clinical Oncology
AUC	Area under the Curve
$AUC_{0\text{-}inf}$	AUC to infinite time
$AUC_{0\text{-}tau}$	AUC to the end of the dosing period
AusPAR	Australian Public Assessment Reports
BD	Business Development
BDEA	Biosimilar Development, Evaluation and Authorisation
BDSR	Biosimilar Development, Submission and Review
BfArM	Federal Institute for Drugs and Medical Devices

BGTD	Biologics and Genetic Therapies Directorate
BLA	Biologics License Application
Bn	Billion
BPAQ	Biosimilar Patients' Access Questionnaire
BPCI	Biologics Price Competition and Innovation
BPCIA	Biologics Price Competition and Innovation Act
BPQ	Biosimilar Physician Questionnaire
BRDD	Biologic and Radiopharmaceutical Drugs Directorate
BRICS	Brazil, Russia, India, China, South Africa
BRICS-TM	Brazil, Russia, India, China, South Africa, Turkey, Mexico
B.Sc.	Bachelor of Science
BsUFA	Biosimilar User Fee Amendment
CACA	China Anti-Cancer Association
CADTH	Canadian Agency for Drugs and Technologies in Health
CAGR	Compound Annual Growth Rate
CAT	Committee for Advanced Therapies
CBER	Center for Biologics Evaluation and Research
CDC	Center for Disease Control and Prevention
CDE	Centre for Drug Evaluation
CDER	Center for Drug Evaluation and Research
CDR	Complementarity-Determining Regions
CDSCO	Central Drugs Standard Control Organisation
CECMED	Regulatory Authority of Medicines, Equipment and Medical Device
CEO	Chief Executive Officer
CERB	Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics
CFDA	China Food and Drug Administration
CHMP	Committee for Medicinal Products for Human Use
CHOC	Childhood Cancer
CIRS	Centre for Innovation in Regulatory Science
CLA	Central Licensing Authority
CMC	Chemistry, Manufacturing and Control
CME	Continuous Medical Education

COFEPRIS	Comisión Federal para la Protección contra Riesgos Sanitarios
COMP	Committee for Orphan Medicinal Products
CORD	Chinese Organisation for Rare Disorders
COVID-19	Coronavirus disease
CPP/ CoPP	Certificate of Pharmaceutical Product
CR	Clarification Request
CRO	Clinical Research Organisation
CTA	Clinical Trial Application
CTD	Common Technical Document
C_{max}	Maximum plasma concentration of a drug
C_{trough}	Lowest concentration of a drug just before the next dose
C1q	Complement component 1q
CVMP	Committee for Medicinal Products for Veterinary Use
DBT	Department of Biotechnology
DNA	Deoxyribonucleic acid
DR	Discipline Reviews
E2E	*End-to-end*
EAEU	Eurasian Economic Union
EAFO	Eurasian Federation of Oncology
EC	European Commission
EC*	Ethics Committee
ECDA	European Chronic Disease Alliance
ECRP	Federal Expert Commission for Radiopharmaceuticals
eCTD	Electronic Common Technical Dossier
eDok	Swissmedic submission format for authorisation applications
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFTA	European Free Trade Association
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPO	Erythropoietin
EU	European Union

Fab	Antigen binding fragment
FAC	Foreign Acceptable Comparator
Fc	Fragment crystallizable
FcRn	Neonatal Fc- receptor
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
FD&C	Federal Food, Drug and Cosmetic
FGs	Finished Goods
FOBs	Follow-on-Biologics
FSBI-SCEMP	Federal State Budgetary Institution - Scientific Centre for Expert Evaluation of Medicinal Products
FY	Financial Year
GaBI	Generics and Biosimilars Initiative Journal
GBT	Global Benchmarking Tool
GCC	Gulf Cooperation Council
GDP	Gross Domestic Product
GDP**	Good Distribution Practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
GRP	Good Regulatory Practice
GVP	Good Pharmacovigilance Practices
HC	Health Canada
HCOs	Healthcare Organisations
HED	Human Equivalent Dose
HER2	Human Epidermal Growth Factor Receptor 2
HPLC	High-Performance Liquid Chromatography
HMEC	Human Medicines Expert Committee
HSA	Health Sciences Authority
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEF	Isoelectric Focusing
IEIS	İlaç Endüstrisi İşverenler Sendikası
IGBA	International Generic and Biosimilar Medicines Association

IgG	Immunoglobulin G
IMCTs	International Multicenter Clinical Trials
IND	Investigational New Drug
INN	International Non-proprietary Name
IP	Intellectual Property
IPA	Indian Pharmaceutical Association
IPASA	The Innovative Pharmaceutical Association South Africa
iPSP	Initial Pediatric Study Plan
IQVIA	Quintiles and IMS Health
IR	Informative requests
IRDAI	Insurance Regulatory and Development Authority
LMWH	Low Molecular Weight Heparins
MAA	Marketing Authorisation Application
mAbs	Monoclonal Antibodies
MCC	Medicines Control Council
MD	Doctor of Medicine
MHRA	Medicines and Healthcare products Regulatory Agency
MIST	Mexico, Indonesia, South Korea, Turkey
MOA	Mechanism Of Action
MoH	Ministry of Health
MOU	Memorandum Of Understanding
MRAs	Mutual Recognition Agreements
MS	Mass Spectrometry
MS***	Milestone
n/a	Not available
n/d	Not defined
NA	Not Applicable
NBEs	New Biological Entities
NCEs	New Chemical Entities
NDA	New Drug Application
NDS	New Drug Submission
NDCTR	New Drug Clinical Trial Rules
NHPs	Non-Human Primates

NHS	National Health System
NMC	New Molecules Committee
NMPA	National Medical Products Administration
NOBs	Non-Original Biologics
NRAs	National Regulatory Authorities/ Authority
OSIP	Office of Submissions and Intellectual Property
OOP	out-of-pocket
PAHO	Pan American Health Organisation
PAR	Public Assessment Report
PD	Pharmacodynamic
PDCO	Paediatric Committee
PharmD	Doctor of Pharmacy
PhD	Doctor of Philosophy
Ph.Eur.	European Pharmacopoeia
PHS	Public Health Service
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PPF	Pre-submission Planning Form
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
Q,S,E	Quality, Safety, Efficacy
QA	Quality Assurance
QTPP	Quality Targeted Product Profile
R&D	Research and Development
RA	Regulatory Affairs
RBP	Reference Biologic Product
RCGM	Review Committee on Genetic Manipulation
RDC	Resolution of the Board of Directors
REMS	Risk Evaluation and Mitigation Strategy

Rmb	Renminbi
RMP	Risk Management Plan
ROA	Route of Administration
RoW	Rest of the World
RPM	Regulatory Project Manager
RTF	Refuse-To-File
SA	Scientific advice
SAGES	South Africa Gastroenterology Society
SAHPRA	South African Health Products Regulatory Authority
SAL	Screening Acceptance Letter
SRA	Stringent Regulatory Authority
SRL	Screening Rejection Letter
S and E	Safety And Efficacy
SBCO	Brazilian Society of Surgical Oncology
SBMP	Similar Biological Medicinal Product
SBP	Similar Biotherapeutic Product/ Similar Biologic Product
SCoRE	Summary of Critical Regulatory Elements
SDS-PAGE	Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis
SEC	Subject Expert Committee
SEP	Single Exit Price
SEPB	Subcommittee On Evaluation of Biotech Products
SMEC	Swissmedic Medicines Expert Committees
SNDS	Supplement to New Drug Submission
SPSS	Statistical Product and Service Solutions
SUS	Unified Health System
SwissPAR	Swiss Public Assessment Report
$t_{1/2}$	Half-life
T_{max}	Transport maximum
TACRC	Turkish Association for Cancer Research and Control
TGA	Therapeutic Goods Administration
ToE	Totality-of-the-Evidence
TUSPA	Turkish Scientists and Physicians Association
TITCK	Türkiye İlaç ve Tıbbi Cihaz Kurumu

TK	Toxicokinetic
TMMDA	The Turkish Medicines and Medical Devices Agency
TPA	Therapeutic Products Act
TPO	Therapeutic Products Ordinance
TPLO	Licensing of Therapeutic Products
TRS	Technical Report Series
UNESCO	The United Nations Educational, Scientific and Cultural Organisation
US	United States
USA	United States of America
USAN	United States Adopted Names
USFDA	United States Food and Drug Administration
V_{ss}	Steady state volume of distribution
VMEC	Veterinary Medicines Expert Committee
WHA	World Health Assembly
WHO	World Health Organisation
WHOPAR	WHO Public Assessment Report
ZaZiBoNa	Zambia, Zimbabwe, Botswana, Namibia

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CHAPTER 1

General Introduction

BACKGROUND

Biologics and Their Importance

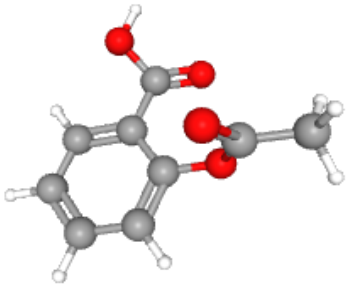
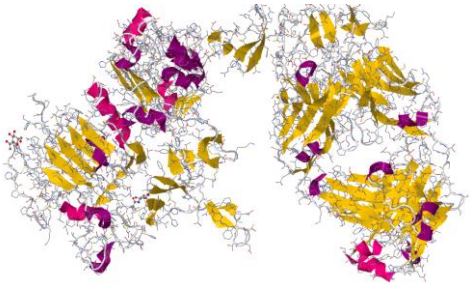
Biological products are a relatively new class of medicines that have evolved rapidly over the last 30 years. It includes a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. In contrast to conventional medicines (small-molecule drugs) which are made from chemical substances, biologics are isolated from a variety of natural sources including humans, animals, and microorganisms (USFDA, 2018a). Biologics have complex large molecule structures compared to small molecule medicines, and can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances. They are up to 1000 times the size of small molecules. Hence, they are not easily identified or characterised (Biosimilars Resource Center, 2020).

Both conventional and biologic drugs work by interacting and interfering with the disease process. Conventional medicines or small molecule drug discovery has been focusing on finding new compounds that disrupt only disease-associated processes. The large size of biologic drugs gives them an advantage in terms of specificity as they can bind with target molecules with extremely high precision. This specificity allows the biologics to avoid many other off-target interactions which could have led to several side effects seen with conventional medicines. Biologics are therefore able to target highly specific molecular processes which small molecules are unable to, and so they can target many new diseases with high therapeutic efficacy. A comparison of small molecules and biologics is presented in Figure 1.1 (PubChem, 2021; Harrison, 2019; Makurvet, 2021).

Early biologics such as insulin, erythropoietin and growth hormones helped address the therapeutic vacuum in the treatment of serious illnesses like diabetes, anaemia, and renal diseases. Later, more complex biologics such as monoclonal antibodies (mAbs) were launched which have helped to revolutionise the treatment of many difficult-to-treat diseases such as cancer, autoimmune disorders etc. Further, newer classes of biologics such as gene-based and cellular therapies are evolving as next generation of biomedical research and are being used to treat several critical medical

conditions such as rheumatoid arthritis, inflammatory bowel disease, psoriasis, and different types of cancer (Deloitte, 2020).

Figure 1.1 Comparison between small molecules and biologics

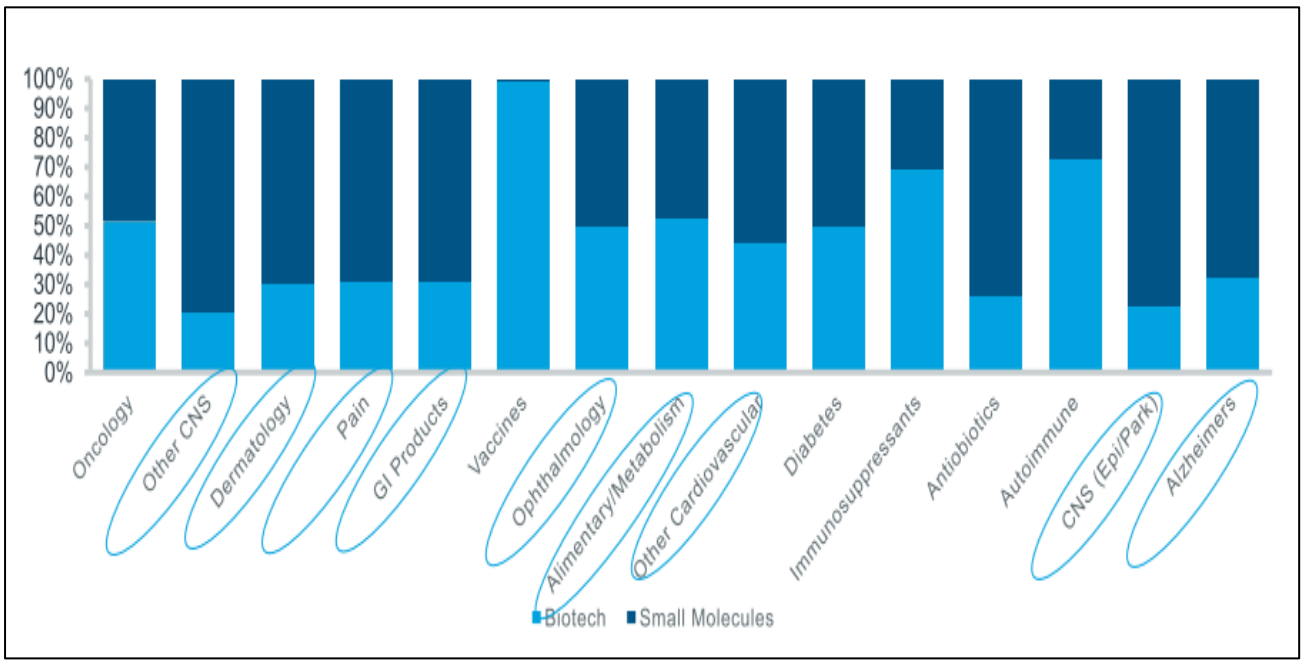
	Small molecules [e.g., Aspirin, 21 atoms]	**Biologics** [e.g., Trastuzumab ≈ 25,000 atoms]
Structure		
Molecular weight	Low	High
Production	Chemical synthesis	Natural sources/ Living systems
Immunogenicity	Usually not immunogenic	Potentially immunogenic
Characterisation	Well-characterised	Less easily characterised
Process	Fewer critical process steps	Many critical process steps
Target affinity and specificity	Low	Significantly high

The development and manufacturing process of biologics is complex and expensive and involves use of cutting-edge technologies. Biologics therefore usually cost considerably more than conventional medications. According to one estimate, the average cost for a biologic is 22 times greater than the cost for a conventional medication (Makurvet, 2021). As per available data, the average cost of therapy with biologics in the US ranges from $10,000-$30,000 per year; they can even exceed US$500,000 for the most advanced products which causes considerable stress on the healthcare system and insurers (Higuera, 2020). The high cost of these medicines keeps them out of reach for most of the population in developing countries thereby resulting in considerably lower treatment number with biologics compared to the populations in developed countries.

Market insight on biologics

The first biologic (human insulin) was marketed in 1982. Despite the high cost of therapy, the clinical efficacy and safety profile of biologics has helped them to drive huge growth of the segment across the world. Today, biologics are one of the largest and fastest growing components of the prescription medicine market. The market share of biologics has been steadily growing relative to small molecules. Further, the new product pipelines of leading companies suggest that this growth dynamic will continue and be broad-based across various therapeutic areas. Figure 1.2 depicts the therapeutic areas where biologics are used (IQVIA, 2020b).

Figure 1.2 Broad basing of biologics across therapeutic areas



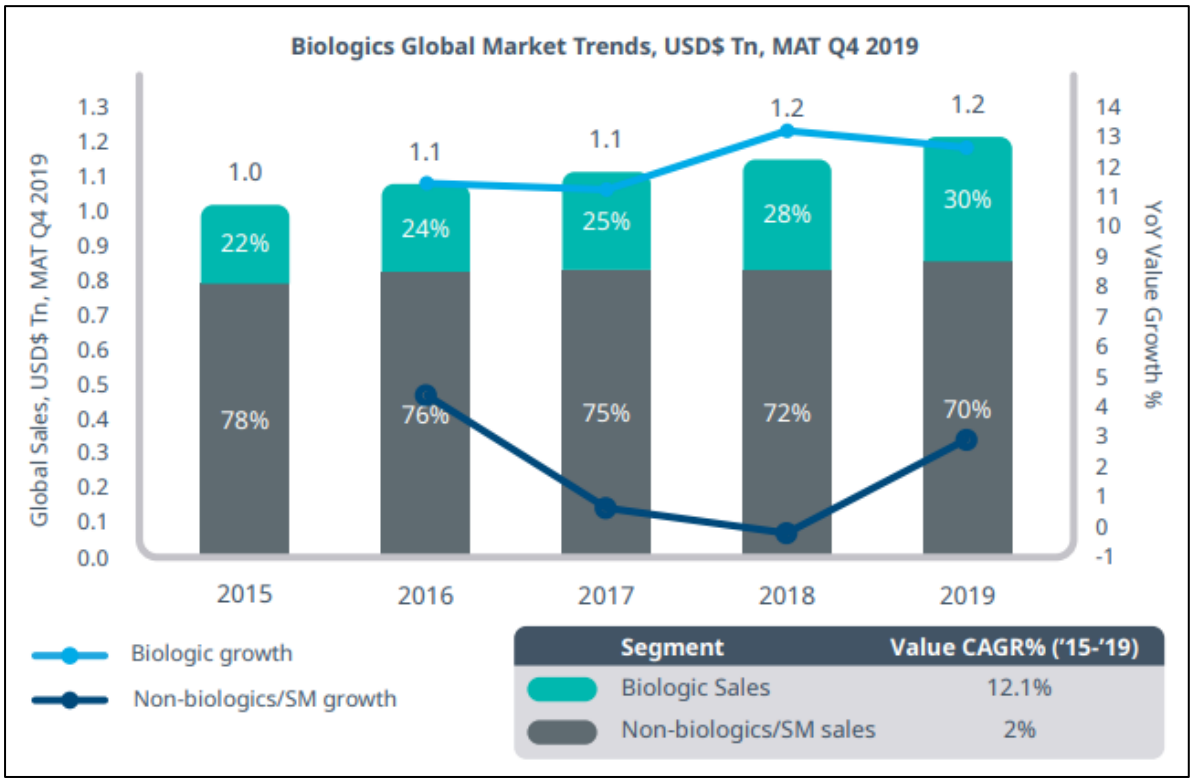
Adopted from IQVIA Pipeline Intelligence, 2019

Note: X-axis: Therapeutic areas - encircled areas are the new therapeutic areas with entry of biosimilars; Y-axis: CAGR (%)

The overall global pharmaceutical market is expected to exceed $1.5 trillion by 2023 growing at a compounded annual growth rate of 3–6% over the next five years (Miglierini, 2019). In the period of 2014-2023, the global pharmaceutical market for biologics is expected to double in size from 194.4 billion in 2014 to over 400 billion US dollars in 2023 (Mikulic, 2020). The worldwide market for biologics has reached $269,152.8 million in 2019 with a compound annual growth rate (CAGR) of 12.6. The market declined in 2020 at a rate of -11.1% to $239,168.6 million due to lockdown

because of COVID-19 pandemic outbreak. It is expected that the market would regrow from 2021 to 2023 at CAGR of 14.7%. The market is expected to reach $610,253.2 million in 2025, and $1,234,925.6 million in 2030 (PR Newswire, 2021). According to Coherent Market Insights, the global biologics market is estimated to be valued at $ 255.19 billion in 2019 and is expected to exhibit a CAGR of over 7% over the next 7 years, thereby growing to nearly $456 billion by 2027 (Coherent Market Insights, 2020a). The sharp increase in size and share of biologics is due to the high revenues arising from the increasing burden of chronic diseases and higher acceptability for innovative therapies (McKinsey & Company, 2020). The market share of biologics is increasing from 2015 to 2019 and reached 30% in 2019 as compared to 70% share of non-biologics. During this period, there had been an impressive growth rate of 12.1% CAGR (Bassil et al., 2020). Figure 1.3 highlights the global biologics and non-biologics sales.

Figure 1.3 Biologics Global Market Trends (Biologics vs Non-biologics)



Adopted from Bassil et al., 2020

The global biologics market is estimated to be valued at US$ 255.19 Billion in 2019 and is expected to exhibit a CAGR of 7.6% over the forecast period (2019-2027). (Coherent Market Insights, 2020b).

Most leading pharmaceutical companies have increased investments in the biologics space. Major players operating in the global biologics market include Roche, Merck KGaA, Bristol-Myers Squibb (BMS), Merck & Co., AstraZeneca, Regeneron Pharmaceuticals, Novartis International, Pfizer, Amgen, AbbVie, Sanofi, Eli Lilly & Company, Novo Nordisk, Johnson & Johnson, GlaxoSmithKline, Teva, Ipsen and Allergan (Coherent Market Insights, 2020b). Several smaller specialty companies have also entered the space with limited but exciting biologic candidates in their pipeline (Med Ad News, 2019).

BIOSIMILARS – STATE OF THE ART

Biosimilars are biologic products that are similar but not identical to reference/originator biologic products. Although the terminology (Table 1.1) and definition of biosimilars (Table 1.2) varies with the different global health agencies, biosimilars generally are large molecular-weight, complex molecules that are produced in living cells through genetic engineering**.**

Table 1.1 Biosimilar terminology across agencies

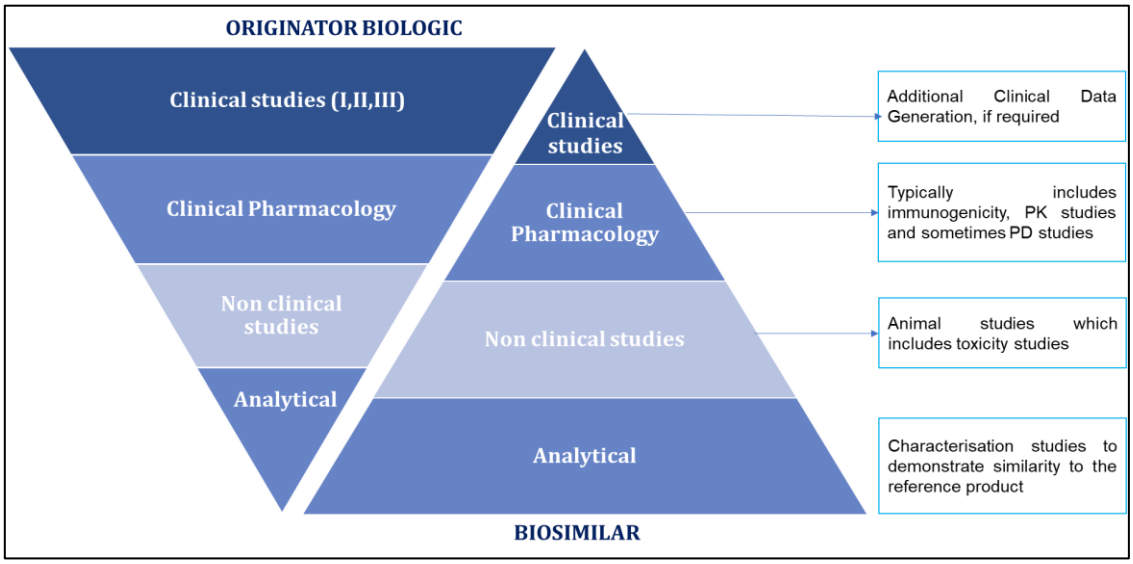
Agency (Country name)	Terminology
EMA, Europe	Biosimilars
FDA, USA	Biosimilars
WHO	Similar biotherapeutic product (SBP)
TGA, Australia	Biosimilars/ similar biological medicinal product (SBMP)
BRDD, Canada	Biosimilar/ Biosimilar biologic drug
HSA, Singapore	Biosimilars
Swissmedic, Switzerland	Biosimilars
ANVISA, Brazil	Biological product/ Follow-on-biologics
Russian MoH	Biosimilars
CDSCO, India	Similar Biologic
NMPA, China	Therapeutic biologic products
SAHPRA, South Africa	Biosimilars
TITCK, Turkey	Similar biologic product
COFEPRIS, Mexico	Bio-comparable

Table 1.2 Biosimilar definition across global health agencies

Agency, Country	Definition
EMA, Europe	Biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA.
FDA, USA	A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product.
WHO	SBP is a biotherapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product (RBP).
TGA, Australia	A biosimilar medicine is a version of an already registered biological medicine (the reference medicine).
BRDD, Canada	A biosimilar is a drug demonstrated to be highly similar to a biologic drug that was already authorized for sale (known as the reference biologic drug).
HSA, Singapore	A biosimilar is a biological therapeutic product demonstrated to be similar, in physicochemical characteristics, biological activity, safety and efficacy to an existing registered biological product.
Swissmedic, Switzerland	A biosimilar is a biological medicinal product having sufficient similarity with a reference product authorised by Swissmedic and which refers to its documentation (Art. 4 para. 1 let. a^{novies} TPA).
ANVISA, Brazil	Biological drug that is not new or is known, containing molecule with known biological activity, already registered in Brazil and that has undergone all stages of manufacturing (formulation, bottling, lyophilization, labeling, packaging, storage, quality control and release of the biological product batch for use).
Russian MoH	Biosimilar medicinal product (biosimilar) is a biological medicinal product similar in quality, efficacy and safety parameters to a reference biological medicinal product in the same dosage form and having an identical route of administration.
CDSCO, India	A Similar Biologic product is that which is similar in terms of quality, safety and efficacy to an approved Reference Biological product based on comparability.
NMPA, China	Biosimilar refer to a therapeutic biological product that has similarity with a reference drug that has been approved for registration in terms of quality, safety, and efficacy.
SAHPRA, South Africa	Biological medicines that are manufactured to be similar to registered originator medicines (unlike generic pharmaceutical medicines which are identical) are known as biosimilar.
TITCK, Turkey	Biosimilar is the name of medicines which show similarity to an authorized biological reference medicine.
COFEPRIS, Mexico	A biosimilar is a biotherapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference product. Biocomparables are clearly not defined in the guideline.

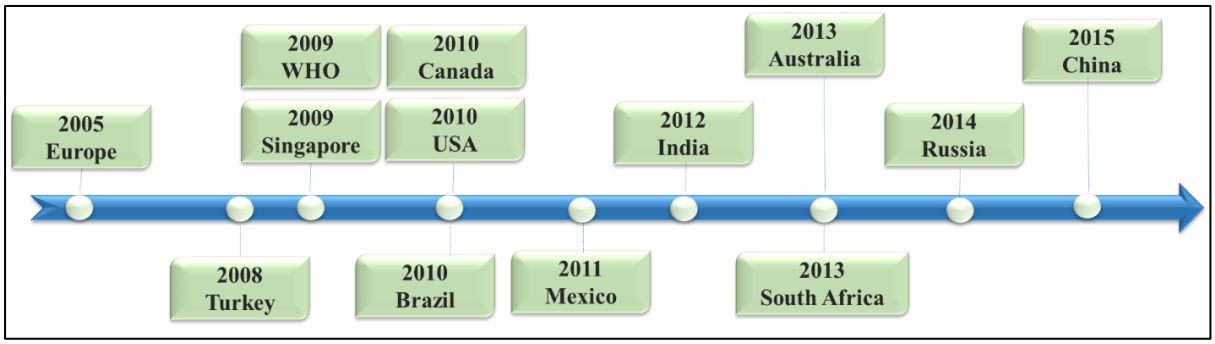
The development of a biosimilar must include data demonstrating biosimilarity to the reference product (the original biologic). The FDA follows a “Totality-of-evidence” approach for evaluating biosimilarity. This includes detailed analytics (structural and functional characterisation), non-clinical evaluation (animal studies), clinical pharmacology (PK/PD data), clinical immunogenicity data, and other comparative clinical studies. By definition, a biosimilar need to demonstrate that it is highly similar to the reference product and that there are no clinically meaningful differences between the biosimilar product and the reference product in terms of safety, purity, and potency of the product (Figure 1.4).

Figure 1.4 Comparison of development pathways – Original biologic versus Biosimilar



The European Union (EU) was the pioneer for developing and establishing regulatory requirements for biosimilars in 2005. The EMA is also the first regulatory agency to issue the marketing authorisation of biosimilars for use by patients in Europe. Various other guidelines were subsequently developed for biosimilars in other countries like Australia, Canada, Singapore, Switzerland (ACSS) (currently renamed to ACCESS Consortium with the joining of UK MHRA in October 2020, (TGA, 2020), Brazil, Russia, India, China, South Africa, Turkey and Mexico (BRICS-TM) countries. The establishment of biosimilar guidelines by different countries is shown in Figure 1.5.

Figure 1.5 Initiation of regulatory requirements across the globe



Despite the release of biosimilar regulatory guidelines by different agencies at different points in time, the actual implications and outcome have varied significantly across countries. While Europe and developing countries such as India have demonstrated a higher degree of adoption and implementation by approving significant number of biosimilars, most other countries still have limited approvals, despite several original biologics going off patent (Kang et al., 2020).

Although there is a significant number of biosimilar approvals, often the approved products are categorised as Non-Original Biologics (NOBs) in emerging markets by the international community. The NOBs are copy-biologics which have not gone through a biosimilar pathway with strict regulatory scrutiny such as the biosimilar guidelines for the EMA, FDA or WHO. They have been preferred in the emerging markets due to their early access and lower price relative to true biosimilars (Kabir et al., 2019).

Pharmacoeconomics of Biosimilars

With the strong growth of biologic prescriptions and usage, original branded biologics are the most significant driver of prescription drug spending across most countries. In the United States, since 2014, branded biologic drugs have accounted for more than 90% of prescription drug spending growth. Biologics overall account for 36% of total prescription drug spending in the US (IQVIA, 2019b).

Biosimilar products are usually made available at a significant discount to original biologics, and therefore have the potential of creating valuable savings for patients and the overall healthcare systems (Rifkin & Pourmahram, 2020). Government healthcare and insurers can gain significant savings by the widespread prescription of

biosimilars. In developing countries where most healthcare costs are out-of-pocket (OOP) for patients, biosimilars provide patients with a significantly lower cost burden leading to wider coverage, increased adherence and better patient outcomes. Overall, the introduction of biosimilars has broadened treatment choices for clinicians and patients, increased the competition and thereby positively reduced healthcare expenditures. The biosimilar market in Europe is the largest in the world, representing approximately 60% of the global biosimilar market and growing consistently year on year. As of October 2019, 54 biosimilars of 15 originator biological medicines have marketing authorisation in Europe (Schneider & Reilly, 2020).

The uptake of biosimilars in the US has followed a different trajectory. It is observed that almost around 51% of current biologics spending are facing biosimilar competition or will face competition in the next 10 years. The other 49% drugs include those drugs which are still protected and/or have less revenue generation. With the launch of the first biosimilar in the US in 2015, through the end of 2020, an acceleration has been seen in the development and approval of biosimilars with 33 approvals across 13 molecules. It is expected that biosimilar aggregate sale could reach $ 80 billion in the next five years (IQVIA, 2020a). From a white paper published by the Biosimilars Council of US (Biosimilars Council, 2019), it was estimated that barriers to the launch of biosimilars have cost the US health care system a total of $9.8 billion in savings from 2015 to 2018 alone.

To encourage the introduction of biosimilars and reduce the cost of biologics, the Biologics Price Competition and Innovation Act (BPCIA) was introduced in 2009 by the FDA. As part of the BPCIA initiative, an abbreviated pathway known as the abbreviated Biologics License Application (aBLA) was implemented by the FDA in 2010. Under the aBLA, there is no standardised approval process for biosimilars. Each biosimilar has its own unique set of guidelines under the aBLA based on the specific drug class, due to their structural complexities and risk for immunogenicity. Establishing specific guidelines by drug class is a long and complicated process and therefore many of these abbreviated biosimilar guidelines, including those for monoclonal antibodies, are yet to be defined in the aBLA. This in turn prompted companies to utilise the Biologics License Application (BLA) for the registration of their biosimilars (Wiatr, 2011), which was traditionally used for approval of biologics by the

FDA. The BLA is a lengthy approval process that grants biologics 12-year marketing exclusivity, patent protection, and nondisclosure of proprietary data.

Considering the data and time requirement to follow the BLA process, biosimilars authorised through this route often only marginally discounted compared to the branded drugs and therefore provide limited cost benefit to payers and patients. This is unlike generic medicines competition which leads to much greater cost savings. As a point of comparison, when the first generic copy of a small-molecule drug is launched in the market, there is typically about a 30% drop in price. This reduction often reaches as much as 80% as additional generic versions appear. However, the comparable reduction in cost from a biosimilar is usually only about 15% to 30% (DeRosier, 2020).

A 2019 report from the IQVIA Institute of Data Science indicates that by 2023, biosimilar competition in the biologics market will be nearly three-times larger than it is today. This will result in approximately $160 billion in lower spending over the next few years than it would have if biosimilars did not enter the market (IQVIA, 2019a). However, unless the framework for approvals of biosimilars is simplified significantly, patients will not be able to enjoy the full benefits of cost reduction that biosimilars can bring.

Evolving Landscape of Biosimilars and the Existing Challenges

When the concept of biosimilars was first introduced, it generated high expectations from the access and cost savings potential that the medicines could bring to patients globally. However, due to several roadblocks, the health care system is yet to realise the true benefits of biosimilars. Significant challenges persist from the perspective of all key stakeholders involved – industry, regulators, patients and physicians. Some of these challenges are discussed below.

Challenges faced by the bio-pharmaceutical industry in the biosimilar space

Regulatory uncertainty

Compared to the well-established approval process for New Chemical Entities (NCEs) and small-molecule generics, the framework for approval of New Biological Entities (NBEs) and biosimilar products is in nascent stages across most countries. Industry faces major challenges in terms of getting appropriate advice for development which

delays launch of the product and consequently a late return on the investment. In addition, most of the emerging country agencies have unclear regulatory processes which creates confusion amongst industry players. Also, there is close to little convergence across the regulatory agencies on the key guidelines which can make global or multi-country developments risky (Druedahl et al., 2020).

High cost of development

The cost to develop and gain approval for a biosimilar medicine in the US ranges between US$100 million to US$200 million. Average cost estimates for development without regulatory fees is more than US$100 million (Pfizer, 2018). Development costs are high due to greater clinical trial requirements, need for sophisticated manufacturing facilities and cutting-edge technologies, investment in more technically skilled and competent manpower resources and other promotional activities for physicians and patients (Makurvet, 2021). In addition, the requirement of reference biological product (RBP) plays a critical role in the development process. Its availability and cost have significant impact on the total costing of biosimilars (Kang et al., 2021).

Limited market opportunity

Compared to the initial expectations, the actual commercial returns on biosimilars are much lower. This is mainly because of the high investment in developing the product, while uptake remains much slower and market penetration is less than small molecule generics. Also, in several countries, price discounts have been unexpectedly high with many categories also coming under price control (McKinsey & Company, 2018).

Production complexity

Biologics vary greatly in structure and are not very well-defined. There is a possibility of batch-to-batch variations in biologic molecules and therefore their reproducibility is a huge challenge. Biosimilars are thus more complex to develop and manufacture due to this inherent variability. In such a scenario, the onus falls on the manufacturer to prove that any such differences from the originator are not having clinically meaningful differences (Agbogbo et al., 2019).

Dearth of experienced and skilled manpower

Since the biosimilar industry is in nascent stage, the availability of skilled manpower who are experienced in the development and manufacturing of biosimilars is still a big challenge. This issue is more pronounced in developing countries (Wroblewski et al., 2009). Although the biopharmaceutical industry is growing at a faster rate with new development and guidelines, the challenge remains in this fast-growing pharma industry. There are gaps in the growing talent as the growth rate of pharma workforce is comparatively slow (Marison & Levison, 2019).

Expensive Litigations

Original branded biologics are protected by wide-ranging patents across the molecule, formulations, uses, devices, manufacturing processes and trade dress. To bring a product to market, the company's manufacturing biosimilars must assess and navigate the complex IP landscape. This is particularly difficult in the areas of process patents, where tweaking the process can often negatively influence the sensitivity and biosimilarity of the product (UW–Madison School of Pharmacy, 2020).

Challenges faced by regulators towards establishing biosimilar guidelines

In the last two decades, the global regulatory agencies have made significant progress towards establishing, revising, and updating biosimilar guidelines to match the constant innovation in biologic product pipelines. However, there still remains a substantial scope for improvement in establishing a simplified and effective regulatory framework that allows better access to biosimilars across the globe. Some of the challenges faced by regulators across the world, in the area of biologic products and biosimilars in particular are as follows:

Complexity of the molecules

By their very nature, biopharmaceuticals are intrinsically variable. The data required during the review and approval of biosimilar products will vary considerably based on the type of biosimilar product. This makes it difficult for regulators to establish a common development pathway across all categories of biosimilars (TOPRA, 2019).

Lack of expertise and resources

The biologic space is rapidly evolving, and new targets are being identified at a rapid pace. The regulators in all countries, especially developing countries must keep up with the pace of change in this field, which is not an easy task considering the limitations of expertise that they face in this space. In developing countries, the gap between optimal resources and reality on the ground is wide and well acknowledged (Ferreri, 2020).

Lack of common global regulatory framework on biosimilars

Absence of a common regulatory framework leads to multiple country level iterations and specifics. The regulatory authority in each country in turn has its own learning curve for biologic products (Kang et al., 2020). Establishing a global biosimilar development framework could help reduce the regulators workloads through regulatory convergence and international collaboration.

Multi-layer organisations within the health agency

The complex regulatory approval process involves multiple departments. This results in delayed approval decision making for approval and inappropriate or non-aligned development advice (Ferreri, 2020).

Political will and objectives

While the intellectual property laws converged on a global basis over two decades ago, the standardisation of regulatory standards especially across developing agencies is still a distant objective. Regulatory standards, including those for biosimilars continue to be very diverse. Very often, this is also a fallout of the political support and objectives set out by the country level leadership. The regulatory requirements of a country are often aligned with the politically perceived needs of the local population and thereby have implications such as protectionism, price control and simpler regulation to enable more local launches etc (CED, 2017; Davio, 2019).

Challenges from the physicians' perspective

The adoption of biosimilars has differed amongst physicians in different countries. While most prescribers understand that biosimilars can be as effective as reference products and provide considerable cost savings for their patients, they also harbour

several concerns on using a biosimilar to treat critical indications. A systemic review on physicians' perceptions of the uptake of biosimilars stated that 54-94% physicians were confident in prescribing biosimilars. Physicians seemed to prefer originator products to biosimilars and prescribed biosimilars mainly for biologic-naive patients. They considered cost savings and the lower price compared with the originator biologic medicine as the main advantages of biosimilars, while their doubts were often related to safety, efficacy and immunogenicity. 64%–95% of physicians had negative perceptions of pharmacist-led substitution of biologic medicines. The study concluded that physicians' knowledge and attitudes towards biosimilars vary. Although physicians had positive attitudes towards biosimilars, prescribing was limited, especially for patients already being treated with biologic medicines. Perceptions of pharmacist-led substitution of biologic medicines were often negative. It was also concluded that the physician knowledge on biosimilar varies and even though have good knowledge still could be reluctant in prescribing biosimilars especially for patients which were on biologic treatment (Sarnola et al., 2020).

Our retrospective evaluation of clinical studies supporting biosimilar development programs in the EU and US revealed that the efficacy endpoints in comparative efficacy studies added no value to the successful biosimilar development programs (Schiestl et al., 2020). Further, secondary research on biosimilar approvals has revealed that usually no submission gets rejected following a full review due to a finding of clinical inequivalence between the biosimilar and its RBP if the two products have been found to be highly similar in analytical and PK studies (Webster et al., 2019). Also, the interim findings from the review of European Public Assessment Reports (EPARs) and FDA assessments published between 2006 and May 2019 indicated, in 33 (i.e., 94 %) of 35 biosimilar programs, the comparative efficacy/safety trials just confirmed biosimilarity and would not have been necessary from a retrospective view. In only 2 (i.e., 6 %) of 35 biosimilar programs, the efficacy and safety study results triggered manufacturing process improvements to enable approval in EU and/or US; issues in both cases were caused by process impurities, while efficacy remained equivalent (IGBA, 2019).

In order for the physicians to gain confidence and ensure their support for prescribing biosimilars, robust evidence for clinical efficacy and safety of biosimilars is needed. A

2018 statement by the American Society of Clinical Oncology (ASCO) on the appropriate use of biosimilars in clinical practice highlighted the need for post-marketing evidence to enhance physician and patient confidence (Lyman et al., 2018). The authors of the statement pointed that this was specifically pertinent because regulatory review of biosimilars relies less on clinical data and more on structural, functional, and pharmacologic data. Some of the key concerns faced by the prescribers are described below:

Lack of robust clinical data

Most physicians would want to see more rigorous clinical data for biosimilars before considering them as of equivalent therapeutic potential to the original biologics (Halimi et al., 2020).

Uncertainty related to extrapolation of indications

Many biologics are well established for use in treating multiple indications. Identification of the right indications for appropriate use of a biosimilar poses another challenge. For a biosimilar, approval for one indication can be followed by a simultaneous approval in any or all of the other indications for which the reference product has been approved, without the requirement for clinical trial data in each disease. This process eliminates the need for costly repetitive comparative trials for biosimilar in each indication. However, extrapolation guidelines are unclear and not consistent across geographies. Also, prescribers are often uncomfortable using a biosimilar in an indication where it has not specifically been tested. On the flipside, even if physicians can infer how to use a biosimilar in secondary indications, they may be restricted by reimbursement guidelines for its use in only the indication for which the biosimilar was tested (Halimi et al., 2020).

Interchangeability

An interchangeability designation allows the biosimilar to be substituted for the original biologic by way of substituting the product at the prescriber level. Interchangeability guidelines are also evolving, and many countries do not have any clear guidelines around this. As with any biologic product, physicians have concerns about immunogenicity with biosimilars. They are also not very confident about switching patients from an original biologic to a biosimilar or vice versa due to fear of a

hypersensitivity reaction. The lack of clear guidelines on substitutability, switching and interchangeability with original biologics further cause physicians to exercise more caution in prescribing biosimilars for their patients (McKinsey & Company, 2018; Halimi et al., 2020).

Lack of awareness and adequate information

Physicians continue to face significant knowledge gaps about approved biosimilars, and sometimes harbour negative perceptions about their efficacy and safety (Cohen & McCabe, 2020; Halimi et al., 2020).

Availability and affordability

As discussed earlier in this chapter, the actual availability and affordability of biosimilars for patients is far from optimal (Kang et al., 2020).

Uncertainty pertaining to quality standards

This is a critical concern for physicians particularly in developing countries where the local regulations may not be evolved enough to ensure stringent and equivalent quality standards of all approved biosimilars or NOBs (Kang et al., 2020). Overall, surveys point out that the majority of the prescribers are comfortable treating patients with a biosimilars if equivalent safety and efficacy had been demonstrated (Karateev & Belokoneva, 2019). Further improving access to biosimilars could help provide better coverage and compliance to treatment.

Challenges from patient's perspective

Given the high costs of biological therapies and the absence of effective healthcare coverage across most of the developing world, globally many patients do not have access to these effective treatments. Equitable access to biosimilars can unlock better treatment possibilities for patients globally.

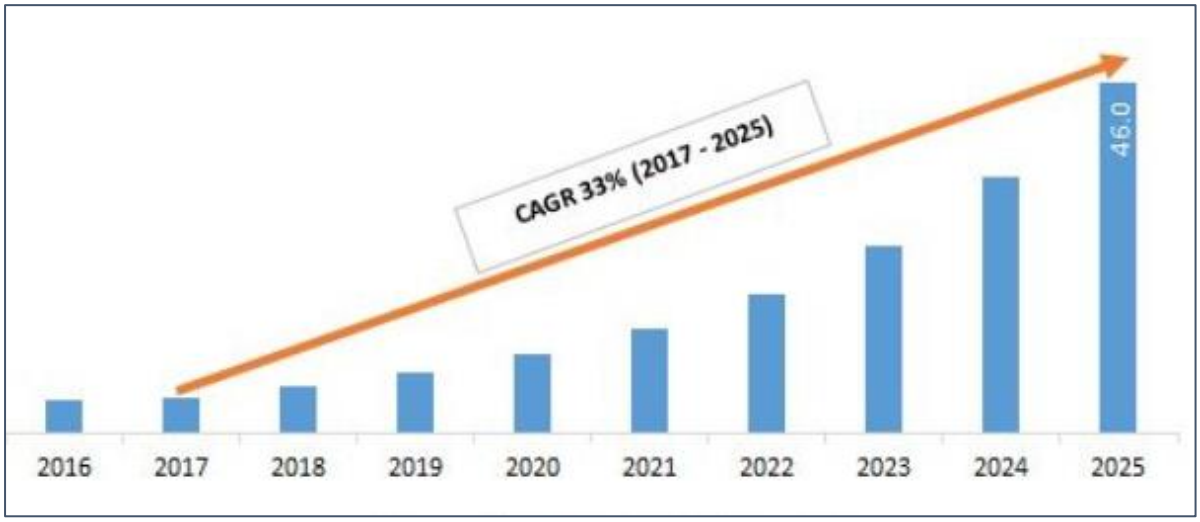
A survey was conducted in November 2019 post the implementation of Biosimilar Initiative in British Columbia and subsequently in July 2020 to observe the patients' perception on biosimilar switching. This survey revealed good understanding among the participants on the differences between biologics and biosimilar and were well-informed about switching (Chew et al., 2021).

However, there exist several gaps in patients' understanding of the concept of biosimilars and their place in the treatment continuum in few places. For instance, a survey conducted in 2019 on French patients treated for rheumatic inflammatory diseases revealed that 57% of respondents did not have knowledge on biosimilars. Their main concern were non-similar molecular structure, efficacy and safety as compared to reference product (Frantzen et al., 2019). The situation is no different in other countries, and the level of understanding in developing countries is at an even lower level. There is therefore the need for effective and essential communication from the industry, government, payers and regulators to patients which can help them to make informed decisions towards their treatment. The ASCO recommendations call for healthcare professionals to educate patients around biosimilars and for medical societies, government sources, and patient advocacy organisations to provide public awareness and education programs.

Biosimilars in the emerging markets – challenges and opportunities

The BRICS is a term used to describe a group of countries once considered to have similar characteristics of emerging economies. The term has been created from the first letters of their names, namely: B—Brazil, R—Russia, I—India, C—China, S—South Africa. Together, these countries account for 25.34% of the world's gross domestic product (GDP) (IMF, 2020). The BRICS countries along with Turkey and Mexico are a group of growing emerging countries. For instance, in 2021, the GDP share of BRICS-TM countries account for 25.67% of the world GDP. This 25.67% consist of 1.59% from Brazil, 1.82% from Russia, 3.25% from India, 17.73% from China, 0.004% from South Africa, 0.01% from Turkey and 1.27% from Mexico (IMF, 2021) against the 43.75% population of BRICS-TM countries - 2.69% from Brazil, 1.85% from Russia, 17.50% from India, 18.25% from China, 0.75% from South Africa, 1.07% from Turkey and 1.63% from Mexico as recorded in 2020 (Worldometer, 2020a). Biosimilar market size is estimated to reach $46 US Billion by 2025 with CAGR growth of 33% from 2017 to 2025 as depicted in Figure 1.6 (Sharma, 2021).

Figure 1.6 Global biosimilar market size and forecast (2016-2025)



Adopted from Sharma, 2021

In China, 20 – 25% of newly diagnosed breast-cancer patients are treated with biologics, compared with more than 70% in the United States. Other therapeutic areas show similarly wide gaps. Less than 10% of colorectal-cancer patients are treated with biologics in China, compared with 55% in the United States. Corresponding shares for rheumatoid arthritis are 5% in China and 25% in the United States. In Brazil and Mexico, up to 40% of patients with tumour types eligible for treatment with biologics do not receive therapy (McKinsey & Company, 2019). The US is the most expensive country for biologics. Among Latin America countries, Brazil has highest biologic cost which is followed by Mexico and Colombia (Mosegui et al., 2021). The development cost of a biosimilar in the India is estimated between $10 to $20 million, while in EU or US, it costs $100 and $200 million (Pategou, 2021). A McKinsey & Company survey found out that, in China, only 20-25% of breast cancer patients, <10% of colorectal cancer patients receive biologic as compared to 70%, 55% in US, respectively. Likewise, 40% of tumor patients from Brazil and Mexico don't receive biologic treatment (McKinsey & Company, 2019).

This may actually indicate the presence of large pockets of non-consumption. Despite an inherent demand linked to high disease burden, consumption of biologics is blocked by high out-of-pocket costs and consumers' low ability to pay. Concerns with low pricing and therefore low margins often make it commercially unviable for several big pharmaceutical companies to launch biologics in developing markets. The investment to enter the market with country-specific data and trials is not easily recoverable due

to low margins. Most players prefer a presence in developed markets, but a considerable opportunity for high volumes exists in emerging markets for biosimilars. To have a commercially viable business case in these markets, biosimilar players will need to adopt a long-term strategy to provide affordable products and improved access to the large pockets of non-consumption. The companies need to carefully select therapeutic areas that have the largest potential impact. As the economies grow and with them the healthcare coverage and spend increases, the companies will be able to ensure good returns on their products along with high volumes. At the same time, by easing the regulatory barriers for entry and enabling acceptance of global data, the regulators can facilitate access to high-quality medicines for their local populations. The developing markets therefore represent a key opportunity to increase healthcare coverage with affordable medicines.

The BRICS-TM countries are a good example of the diverse regulations in general. Before any biosimilar companies establishes the strategies to enter these markets, they should consider various factors such as regulatory pathways, payer perceptions, pricing, affordability and competitive landscapes (McKinsey & Company, 2019). Some of these key factors are detailed in Table 1.3.

Table 1.3 Summary of key factors to be considered by biosimilar companies

	Regulatory	Payers	Procurement
Brazil	Pathway based on WHO and EMA guidelines in place since 2010	Mainly public, biologics account for <5% of volume but approx.40% of health ministry spending on drugs	Central procurement, focus on public hospitals through national public health insurance
Russia	Pathway established since 2014, following EMA guideline	Public reimbursement of cancer and diabetes broader than of immunology treatments	Central- and regional-government procurement, focus on public hospitals
India	Pathway defined but not yet fully implemented	Limited reimbursement for mAbs with none featuring in national RDL to date	Procurement through private segment, focus on hospitals
China	Technical guideline in place since 2015	New national RDL effective since 2017 includes multiple mAbs, especially for cancer treatment	Focus on hospitals through engagement with formulary committees in large centers
South Africa*	Pathway based on WHO and EMA guidelines in place since 2012	Engagement and advocacy from payer in favor of biosimilars is high	Central government procurement via tenders, sold in all pharmacies in the public health care system.
Turkey	Comparability pathway defined, followed EMA guidelines	Well covered in national healthcare system	Procurement via national or regional tender, focus on hospital channel
Mexico	Comparability pathway defined	Mainly public through the health insurance system	Procurement through insurance company tenders offered through hospital channel

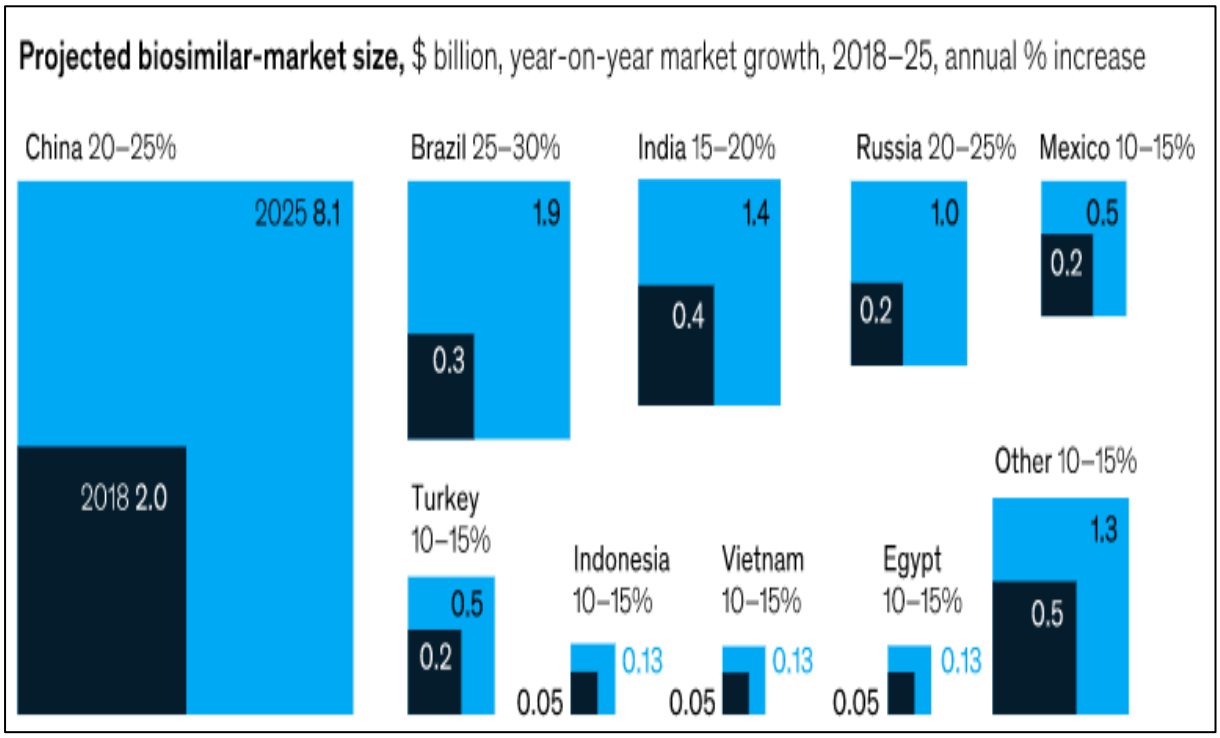
RDL: Reimbursement Drug List

Source: Exhibit from "What's next for biosimilars in emerging markets?", April 2019, McKinsey & Company, www.mckinsey.com. Copyright (c) 2021 McKinsey & Company. All rights reserved. Reprinted by permission.

**Jacoby et al., 2015; Wouters et al., 2019*

It is evident from Table 1.3 that the biosimilar therapy in BRICS-TM and other emerging markets is still in the nascent stage with little or no presence, thus, providing a significant opportunity for biosimilars in these countries. The biosimilar market is expected to show strong growth in BRICS-TM countries (Figure 1.7) (McKinsey & Company, 2019), but this will only be realised if the identified challenges are addressed in a timely and effective manner.

Figure 1.7 Projected biosimilar market size in emerging markets



Source: Exhibit from "What's next for biosimilars in emerging markets?", April 2019, McKinsey & Company, www.mckinsey.com. Copyright (c) 2021 McKinsey & Company. All rights reserved. Reprinted by permission.

Biological landscape in BRICS-TM countries

Brazil

Brazil is a developing economy with 2.73% (Worldometer, 2020b) of world population, ninth largest in the world by nominal GDP and eighth largest by purchasing power parity in 2019. Brazil's economy is the largest in Latin America. The size of the pharmaceutical market is over $18B (World Bank Group, 2020). Brazil is the only Latin American country that ranks amongst the top pharmaceutical markets worldwide. In the Brazil market, domestic companies are ranked higher on the manufacturing side. International companies have entered the market through partnerships and acquisitions (e.g., Pfizer's 40% stake in Teuto, Sanofi's acquisition of Medley and Merck's joint venture with Supera, co-owned by Cristalia and Eurofarma) (Staton, 2012). Also, under law 8080/1990 health is defined as a right of everybody and the duty of the state. The people therefore have a right to universal access to health and health financing through tax collection. The Brazilian National Health System, in theory, is a model for several countries. However, in practice, there exist significant challenges due to scarcity of funding, even though the demand for efficient

National Health System (NHS) is high. Health expenditures in Brazil need to be prioritised by the Government to promote an effective health coverage in an equitable way for the population. In 1980, the government came up with a Unified Health System (SUS) (Santos & de Sousa Campos, 2015) which faced many hurdles but had achieved improvement in health status and some reduction in health inequalities.

Brazil led the way with the development of biosimilars regulations in Latin America and released biosimilars guidance in 2010. ANVISA, Brazil have developed their own abbreviated regulatory pathways for similar biotherapeutic products in 2010 titled "Resolution no. 55/2010". This was achieved by merging WHO and EMA guidelines for biosimilars. The Brazilian guidelines include two approval regulations to oversee registration of new biologicals through the path of individual development or development by comparability. These regulatory measures were developed in line with its political and economic needs to promote the local production of biological drugs and to reduce the cost of these medicines for the local population (ANVISA, 2010). There are 22 biosimilars currently approved in Brazil through August 2019 (PR Newswire, 2019; Kang et al., 2020).

Russia

Russia is an upper-middle income mixed economy with 1.87% (Worldometer, 2020c) of the world population, fifth largest in Europe and eleventh largest nominal GDP in the world. The size of the pharmaceutical market is close to $17 B (World Bank Group 2020). Russia ranks 30th globally in terms of medicines per capital sales. Russia has rebuilt its pharmaceutical industry following demise of Soviet led government by making significant investments in its generic and biosimilar drug development industry. After gaining success in the initiative, the government has extended their support till 2030 and will not only concentrate on generics and biosimilars but also original drugs (Jeremias, 2020). The leading multinational companies in Russia are Sanofi, Novartis and Bayer whereas the leading local suppliers are OTCharm, Pharmstandard and Biocad. In Russia, currently it is difficult to manufacture many important drugs locally since government bargain with manufacturer for price, hence the manufacturer has backed from pharmaceutical market. The main issue the patients faced was the drug shortage and logistic issues with sudden vanishing of the medicine from the market. Other can be misleading advertisement, rampant price change. To address this issue,

the Ministry of Industry and Trade has developed ‘Pharma 2030 Strategy’ wherein a strong growth in generic/biosimilars can be seen due to incentives from the government (Shekhar et al., 2020). The Russian market is dominated by generic drugs. Only 14.4% of medicines sold in the country in 2018 were ‘original drugs’, equivalent to 38.7% of the total market value. The strong preference and benefits for local manufacturers requires foreign companies to engage in partnerships with Russian companies (Macdonald, 2020).

The constitution of the Russian Federation, which was adopted in 1993, gave citizens the right to state-funded healthcare. The Russian pharmaceutical reimbursement system consists of several programmes, including the ‘vital and essential drugs list’, which includes products whose price is fixed at the federal level, and the Seven Nosologies Program for expensive medicines. Russia released a federal “Law on Circulation of Medicines” in 2010 for market approval of drugs. The biosimilar drugs such as filgrastim, epoetin, interferon which were approved before this law were without comparative clinical trials and complete dossiers. It was only in 2014 that the country’s own common for small and large molecule pathway guideline was released which is nearly identical to the EMA guideline. In addition, Russian MoH follows decision no 89 of Eurasian Economic Commission Council approved on December 23, 2014 for "Approval of Rules for conducting research of biological medicines of the Eurasian Economic Union (EAEU)” (Eurasian Economic Union, 2014). Before 2014, biosimilars were handled as new biologics. A rituximab biosimilar, developed by Russian company Biocad, was the first mAb biosimilar approved in Russia in April 2014. From the WHO survey conducted between 2019-2020 (Kang et al., 2020), Russia has 31 approved biosimilars the first being approved in 2010, and includes filgrastim, erythropoietin, interferon alfa-2b, interferon beta, many insulins, and some mAbs. However, as per the details available from other sources (Melao, 2018; The Center for Biosimilars Staff, 2019), there are only 4 approved biosimilars in Russia. Further, as per Generics And Biosimilar Initiative (GaBI), the number of approved biosimilars in the country is considered as only 8 and since Russian law is yet to define biosimilar, these approved products are considered as NOBs (GaBI, 2020c).

India

India is a developing economy with 17.7% (Worldometer, 2020d) of the world population, fifth largest in the world by nominal GDP and third largest by purchasing power parity in 2019. The Government's expenditure on healthcare sector has grown to 1.6% of the GDP in FY20 but is still amongst the lowest in the world. The life insurance penetration rate in India continues to be one of the lowest across the globe at 2.74% as per the latest annual report by the IRDAI (Agarwal, 2020). While in a country like India with challenges on affordability, it is important to allow maximum launches to spur competition and lower prices. Also, it remains equally critical to ensure a high and comparable standard of quality for biologic medicines. The size of the pharmaceutical market was $25 Bn in 2019 (World Bank Group, 2020) and it continues to be amongst the fastest growing large markets in the world. India has a strong local manufacturing industry with less than 30% share from foreign manufacturers. Within the biopharmaceutical space, the local Indian companies have made strides and launched biosimilars of nearly all leading biologic products. Some of the major domestic players are Biocon, Intas, Glenmark, Torrent, Zydus, Reliance, USV and Dr. Reddy's Laboratories.

The Indian biosimilar guideline was drafted in 2012 by two Indian government agencies - Central Drugs Standard Control Organisation (CDSCO) and the Department of Biotechnology (DBT), and further revised in 2016. Several biosimilars were approved before the adoption of the Indian guidelines for biosimilar evaluation in 2012; the first "similar biosimilar" approval was in 2000 for Hepatitis B. The regulatory framework for these products is unclear, leading to concerns about their safety (WHO, 2009). More than 98 biosimilars have been approved in the country over the past two decades. Of these, the majority are classified by international regulators as NOBs and therefore do not have robust enough data for approval through the mature agencies (Meher et al., 2019). These therapeutic products approved after 2012 have been identified with regulatory lapses, and it is important that these products be also reviewed and brought up to the standard.

Partnerships between global pharmaceutical companies and domestic companies are helping to improve the quality of biosimilars marketed in India. Considering their extensive experience with generics, many companies have made in-roads into other

countries as well through exports. India’s Biocon has launched Trastuzumab, Pegfilgrastim, Bevacizumab, rh-Insulin, Insulin Glargine, Adalimumab, Etanercept, Insulin Aspart, in more than 20 emerging markets, including Malaysia (through CCM Pharmaceuticals), Mexico (PiSA Farmacéutica), and Algeria (Abdi Ibrahim). Similarly, Dr. Reddy’s has launched its rituximab biosimilar Reditux in Chile, Ecuador, Peru, Russia, Venezuela, and Vietnam and recently obtained approval for it in Turkey. There are now 98 biosimilars approved in the country (including NOBs) (GaBI, 2019; Kang et al., 2020; EP News Bureau, 2020a, GaBI, 2020a; EP News Bureau, 2020b).

China

China is the world’s fastest developing economy with 18.47% (Worldometer, 2020e) of the world population, second largest in the world by nominal GDP and largest by purchasing power parity in 2019. China has been characterised as an emerging superpower. The size of the pharmaceutical market is $80 B (World Bank Group, 2020). Over the last two decades China has carried out large scale reforms in the fields of health infrastructure and insurance. It has also opened up its healthcare market. The country has focused on developing urban areas and also making healthcare more accessible in rural China, with a significant increase in the number of hospitals, doctors and medical equipment. The World Bank described China's achievement in extending health insurance to 1.3 billion people as an "unparalleled" accomplishment. The local Chinese companies have built a strong niche for themselves as Active Pharmaceutical Ingredient suppliers (API suppliers) for most of the global industry. The government is now investing and incentivising development in the Finished Goods (FGs) sector. As the second largest pharmaceutical market in the world, after the USA, and a booming local healthcare delivery infrastructure, the country has become a key market for multinational pharmaceutical companies in which to develop, manufacture and commercialise their products. However, there continues to be several regulatory and cultural obstacles encountered by foreign companies and therefore most global companies plan their entry strategy into the Chinese market through partnering with a local established pharmaceutical player. In the biologics space as well, China has seen local partnerships for global launches. The biosimilars market in China has developed rapidly in the last few years.

The Centre for Drug Evaluation (CDE), China released draft regulatory development guideline for biologics in 2014 mirroring European and USA guidelines. This draft guideline was reviewed by the industry and the final guideline was released in 2015. At the end of 2014, CFDA released a new guideline on multi-region clinical trials. In 2020, China published draft clinical trial guidelines for various mAb biosimilars. The Chinese biosimilar market is expected to see tremendous growth over the next 5-10 years and reach Rmb 33 bn by 2025 (with a 55% CAGR between 2019 and 2025), partly driven by Bevacizumab, Etanercept, Trastuzumab and Adalimumab, each with biosimilar sales above Rmb 4 bn (Yang et al., 2019). Currently there are 10 biosimilar approved in the country from 2015 (Businesswire, 2019; Kang et al., 2020; GaBI, 2020b; PR Newswire, 2020a; PR Newswire, 2020b; PR Newswire, 2020c; Shanghai Henlius Biotech, 2020a; Shanghai Henlius Biotech, 2020b; Shanghai Henlius Biotech, 2020c).

South Africa

South Africa is an upper middle-income economy with 0.76% (Worldometer, 2020f) of the world population in 2020. The South African economy is the second largest in Africa. The major challenges in the healthcare system of the country pertain to service delivery, financial constraints, general capacity constraints, inadequate supply of well-trained nurses and specialist practitioners (Malakoane et al., 2020). The size of the pharmaceutical market is $ 3.9 Bn (World Bank Group, 2020) and growing well. In 2019, South Africa was the world's 5th highest per capita expenditure on pharma as reported by Chemistry World. South Africa also shows potential growth in emerging therapeutic areas like heart disease and diabetes (Parrish, 2020).

Medicines Control Council (MCC), now known as South African Health Products Regulatory Authority (SAHPRA), South Africa first published biosimilar guidelines in March 2012, which are fully aligned with European and WHO biosimilar guidelines. (SAHPRA, 2021). This guideline was then amended in 2014 to include requirements for monoclonal antibodies. Like USFDA, the mission of SAHPRA is based on safety, efficacy and quality. To meet the huge backlog of drug application, SAHPRA had set two goals which was by reducing the regulatory decision average timeframe from 1422 calendar days in 2017 to 275 working days and by removing 3000 non relevant or no commercial interest applications (Parrish, 2020). Until recently, no biosimilars had

been registered in South Africa, despite the fact that several biosimilar applications for products including erythropoietin, filgrastim, and insulin have been received by the MCC. Upon review, none of those candidates had complied with the local registration requirements for a biosimilar medicine. In October 2019, a global report by the International Generic and Biosimilar Medicines Association identified two biosimilars approved in South Africa (filgrastim-Teva in 2018 and Biocon and Mylan's trastuzumab Ogivri in 2019). In South Africa, Teva has established a strategic agreement with Cipla, South Africa's third-largest pharmaceutical manufacturer, to launch the country's first biosimilar for the oncology and hematology markets. There are 3 biosimilars approved in the country since 2015 (Blignaut, 2020; Pategou, 2020).

Turkey

Turkey is an emerging economy with 1.08% (Worldometer, 2020g) of the world population, nineteenth largest in the world by nominal GDP and thirteenth largest by purchasing power parity in 2019. The size of the pharmaceutical market is $7.5 billion (World Bank Group, 2020). The biopharma sector was only 17% of total prescriptions share out of which biosimilars market rose by 42.2% in 2018. Biologic markets mostly rely on imported products, however international biotech companies were reluctant in transferring sophisticated technology to Turkey. This led to building of local pharma sector with biosimilar space becoming over-crowded even before the launch of product. The current pricing system tends to close the biosimilar market, hence there is a need for defined legal framework for biosimilars (GBR & IEIS, 2020). The major local players are Abdi İbrahim, Atabey, Centurion, CinaGen, Dem Ilac, Ilko Ilac, Kocak Farma and Nobel Illac, along with ths US major, Amgen (Fidan, 2019).

Abdi Ibrahim, the leading local company, has built the largest biotech manufacturing facility in Turkey and forged a partnership with Alvotech in June 2019 to introduce next generation biosimilars into the country (ABDI IBRAHIM, 2019). Indian companies such as Dr. Reddy's (GaBI, 2016) and Zydus Cadila (The Hindu Business Line, 2018) have also tied up with local companies to introduce biosimilars in the country. The pharma market is gradually changing as five years ago, there was only 19 companies and now it is more than 39 projects in biotech. These 39 projects include one biobetter which is expected to launch by 2024 (GBR & IEIS, 2020). The Turkish Medicines and Medical Devices Agency (TMMDA) under the Health Ministry published the "Guideline on

Biosimilar Medicinal Products" in 2009 in line with EMA regulations on biosimilars and further revised on September 14, 2021 (TITCK, 2021). However, to date only 2 biosimilars have been approved in Turkey (GaBI, 2014; DiGrande, 2018).

Mexico

Mexico is a developing economy with 1.65% (Worldometer, 2020h) of the world population, fifteenth largest in the world by nominal GDP and eleventh largest by purchasing power parity. Mexico ranks among the Latin American nations with the highest private healthcare spending, with out-of-pocket expenses accounting for more than 41 percent of total spending in 2017. The size of the pharmaceutical market is $10.5 B and is the second largest pharmaceutical market in Latin America, after Brazil (Rios, 2020). Despite its significant role in the national economy, the pharmaceutical industry relies mostly on imports.

In 2009, the General Health Law was reformed to address the issue of biologicals by the inclusion of Article 222 bis in the Mexican Health Law (GaBI, 2015). Mexico established a government-incentivised market for biosimilars. The demand for low cost Biosimilars was spurred by high out-of-pocket health care spending (estimated at +90%). The country developed a dynamic market of non-original biologics known as "biolimbos" which had not undergone marketing authorisation review consistent with globally accepted standards (Scheinberg et al., 2018). The first guidelines for 'Biocomparables' was published in Oct 2011 and came into force by April 2012. However, by then Mexico had already approved several biological medicines, representing more than US$2.3 billion dollars of biosimilars sales (Silva, 2012). In order to address this, the Federal Commission for the Protection against Sanitary Risk (COFEPRIS) issued a regulation in 2013, setting out tests and methods for drug interchangeability, including biosimilarity. The agency subsequently also issued a new Standard 257, allowing time for manufacturers of biolimbos already on the market to carry out the necessary biocomparability tests and meet new safety, efficacy and quality requirements. In 2021, Decree was published which significantly modifies several aspects of the regulatory approval system of medicines like process change to obtain or transfer or renew Marketing Authorisation (MA) for biosimilars (GaBI, 2021a). There are currently 16 biosimilars approved in the country (COFEPRIS, 2019).

SUMMARY

The biologic therapies have evolved as the fastest growing and highest value category of medicines for several critical disease states. These complex molecules have a more targeted approach to disease treatment and therefore are being prescribed widely despite their high costs to the patient. This, in turn, has put a significant burden on healthcare systems, payers and patients across the globe. The prohibitive price of biologics has also prevented patients' access in several countries where either the patient has to bear the burden of medical costs or governments are unable to fund their healthcare budgets.

The introduction of biosimilars into this space is a welcome one and was expected to bring about a significant shift in the access and affordability parameters of the biologic medicines. However, there exist significant challenges in this space, which range across the development, approval process and then the acceptability at both prescriber and patient level. These challenges have so far prevented biosimilars from reaching their full potential of providing equitable access to patients globally, at an affordable price. The challenges for the uptake of biosimilars are more pronounced in the developing/emerging economies like BRICS-TM; and hence, it is important to explore the challenges and opportunities in BRICS-TM countries for the development and approval of biosimilars.

AIM AND OBJECTIVES OF THE STUDY

AIM

The aim of the study is to explore the biosimilar development and regulatory approval process in BRICS-TM countries with a view to conceptualise, design and propose a standardised regulatory model for adoption across BRICS -TM agencies.

OBJECTIVES

The main objectives of research are as below;

- Identify the challenges pertaining to the development and approval of biosimilars from the perspective of different stakeholders and highlight key issues specifically in BRICS-TM countries.
- Identify, critically review and summarise regulatory guidelines pertaining to biosimilar development with regard to quality, non-clinical and clinical studies from mature regulatory agencies such as EMA, USFDA, WHO, TGA (Australia), BRDD (Canada) and Swissmedic.
- Compare biosimilar requirements of mature agencies with BRICS-TM agencies to identify the regulatory challenges faced by the BRICS-TM countries and areas for improvement.
- Explore concerns pertaining to biosimilar development and approval faced by the biopharmaceutical industry in BRICS-TM countries.
- Determine issues related to biosimilar medicines' access for patients and knowledge gaps for physicians.
- Validate the identified challenges through data to be collected from the 4 agencies (i.e. Australia, Canada, Switzerland (ACSS) and comparison of the outcomes with Brazil, Russia, India, China, South Africa, Turkey, Mexico (BRICS-TM) agencies to support development of a proposed standardised model.

CHAPTER 2

Study Rationale and Methodological Framework

STUDY RATIONALE

With steady evolution and better understanding of genetics and disease processes, new and more specific biologic targets for arresting and treating diseases are being constantly identified. In 2018, the global spending on medicines reached $1.2 trillion and it is predicted to pass $1.5 trillion by 2023 (IQVIA, 2019a). In the US, biologic medicines accounted for 32.3% of total pharmaceutical sales in 2018 (Statista, 2021). It was assumed that by 2023, biosimilar competition in biologic markets would increase this threefold subject to patent expiries (IQVIA, 2019a). However, biologics also continue to be amongst the most expensive therapies because of the complex nature of the molecule, the high cost of development and the advanced manufacturing requirements. As per IQVIA reports, biologic medicines represented 2% of all US. prescriptions but 37% of drug spending in 2017 (IQVIA, 2019b). The situation is not very different across the rest of the world and is only becoming further unbalanced. In such a situation, the launch of a steady pipeline of high quality and clinically safe and efficient biosimilars should be of high priority for governments, regulators and pharmaceutical companies around the world. However, as detailed in Chapter 1, a combination of factors has led to a less than desirable outcome in terms of access to biosimilars. These challenges are even more overwhelming for the developing countries, from which BRICS-TM group of countries have been chosen as a representative.

In the light of the above, and in order to arrive at the study rationale for the research study, detailed secondary research via survey of published literature was carried out to identify challenges and potential opportunities for biosimilars globally and more specifically in BRICS-TM countries. The extensive literature search as described in the first chapter, revealed existence of significant roadblocks in the equitable access to biosimilars that are more pronounced in the developing countries. The global regulatory framework remains significantly divergent, although global bodies such as the International Generic and Biosimilar Medicines Association (IGBA) have put in immense efforts towards advocating and enabling standardization of regulatory pathways and processes for biosimilars along with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the World Health Organisation (WHO). Regulatory convergence of the

development and approval pathways could certainly be one of the key milestones which would encourage more companies to invest in the global development of biosimilars, thus paving the way for more product launches delivering major therapies at a lower cost to patients. On detailed perusal of the regulatory landscape of BRICS-TM, no specific standardisation work could be identified with a focus on these countries. This establishes the scope for detailed research into the biosimilar landscape for BRICS-TM regulatory agencies by comparing it to mature agencies (i.e, ACSS – Australia, Canada, Singapore, and Switzerland) and forms the rationale for this research.

Therefore, the study rationale was designed on the understanding that the biosimilars continue to have non-equitable and reduced access and penetration across BRICS-TM countries. Standardisation of the development and approval pathways across these countries could help in mitigating the challenges of access and affordability. Hence, a standard model to simplify the biosimilar development and approval process for adoption across BRICS-TM agencies could be of significance. On the basis of the study rationale, the following research questions/ hypotheses have been identified.

- There is a lack of standardisation in BRICS-TM markets for biosimilar development and approval processes.
- The biosimilar approval process suffers due to process in-efficiency, lack of clarity in development and marketing authorisation approval guidelines.
- Absence of abridged regulatory or work sharing/joint review approval pathways leads to exhaustive development requirements with longer duration of evaluation in individual countries, which result in delayed and commercially unviable projects for bio-pharma industry.
- Physicians across countries continue to face impediments to facilitate the availability of high quality biosimilars alongside improving the understanding and implementation of interchangeability and the availability of robust safety and efficacy data for biosimilars.
- Finally, patients continue to face challenges in availability and affordability of biosimilar medicines.

Based on the listed research enquiries / hypotheses, the research study was designed to carry out surveys among four key stakeholders in the biosimilar area, across the

BRICS–TM countries. To develop a standardised model of approval process, the views of ACSS agencies will also be taken into consideration. The rationale for the selection of regulatory agencies of ACSS Consortium was due to their work-sharing approach and employing regulatory reliance mechanism to manage resources effectively, allowing rapid assessment and product approval.

The following five studies will be carried out:

- Review of biosimilar development guidelines issued by EMA, WHO, USFDA, BRDD, TGA and Swissmedic Health Agencies and compare with emerging economies agencies (ANVISA, Russian MoH, CDSCO, NMPA, SAHPRA, TITCK, COFEPRIS) (Study 1)
- A detailed understanding /verification of biosimilar regulations across regulatory agencies in BRICS-TM markets by face to face/ virtual /telecom meeting /questionnaire-based semi-structured interview with each agency to identify and verify gaps and opportunities (Study 2).
- In addition to BRICS-TM, ACSS (a consortium of medium sized regulatory agencies) agencies' questionnaire based semi-structured interview would be conducted to define benchmark for proposing a standardised model (Study 3).
- Research across the bio-pharmaceutical industry in each BRICS-TM country, to understand the challenges faced by companies pertaining to the regulatory framework for development of biosimilars, regulatory pathways, marketing authorisation approval process and commercial viability (Study 4).
- A physician survey across BRICS-TM markets to understand their perspectives on the availability and affordability of biosimilars; challenges in regulations and suggestions on improvement (Study 5).
- A patient survey across BRICS-TM markets to understand their perception on the availability and affordability of biosimilars (Study 5).

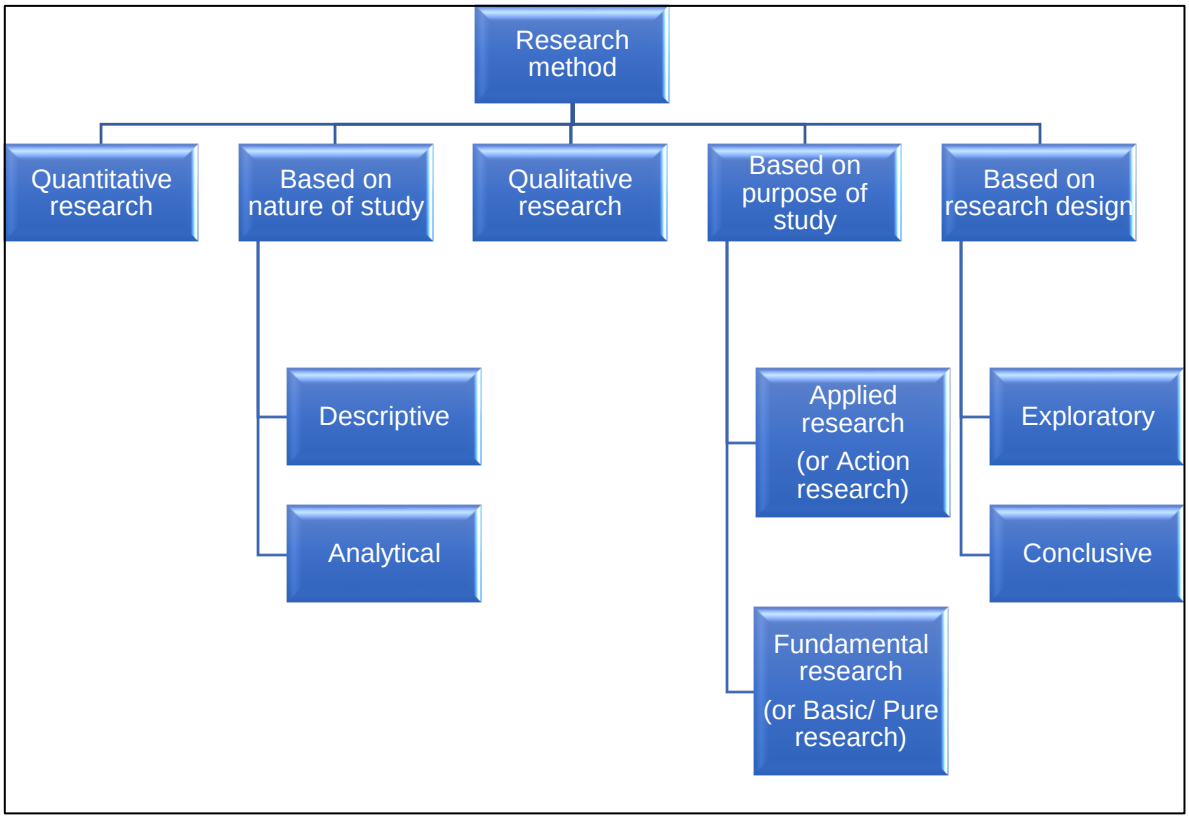
The results from these studies will be analysed and used for developing a set of recommendations that could be adopted by BRICS-TM countries to improve the biosimilar development and approval process and overall regulatory performance to ensure patients' timely access to these medicines. The study rationale and methodological framework applied in conceptualising these studies have been documented in this chapter.

STUDY DESIGN AND METHODOLOGICAL FRAMEWORK

Research methods

Research methods are specific procedures for collecting and analysing data. Developing research methods is an integral part of research design. The type of research methods to be used in the study depend on what type of data is needed to answer the research questions. Figure 2.1 illustrates the classification of research methods (Pedamkar, 2020).

Figure 2.1 Classification of research methods



Applied research supports in solving certain problems employing well known and accepted theories and principles, and the outcome of the research has immediate application. Such research is of practical use to current activity/ situation (Pedamkar, 2020). Quantitative research involves the generation of data in quantitative form which can be subjected to rigorous quantitative analysis in a formal manner. It is numerical, non-descriptive, applies statistics and uses numbers. The results are often presented in tables and graphs. Such research is often conclusive, and it investigates what, where and when of decision making (International Network for Natural Sciences,

2020). Hence it is used in research relating to the collection of numerical data and the analysis thereof using statistical tests in the case of “hypothesis testing” design and descriptive statistics and graphs in the case of the “exploratory or hypothesis generating” design (Mishra et al., 2019). However, qualitative research is non-numerical, descriptive, applies reasoning and uses words. This research is concerned with subjective assessment of attitudes, opinions and behaviour and describes the current existing situation. Qualitative data mostly cannot be depicted numerically or in the form of graphs, charts etc. It is often also known as exploratory research and investigates the why and how of decision making (International Network for Natural Sciences, 2020). Research in such a situation is a function of researcher’s insights and impressions. Generally, the techniques of focus group interviews, projective techniques and in-depth interviews are used (Pedamkar, 2020). Further, the research method choice relates to the decision to use a mono-method (the single use of either quantitative or qualitative methods) or multiple-method (the mixed use of quantitative or qualitative methods), where the research findings are presented through numeric, words and images (International Network for Natural Sciences, 2020).

Selected research method

In order to examine the research questions, primary research shall be carried out across four key stakeholders using mixed methods approach, that is both quantitative and qualitative, to exploit the strengths of both methods for addressing the research questions in a broader perspective. Qualitative methods including questionnaires and focus groups will be used as part of the different studies as follows:

- Critical literature review to identify biosimilar development guidelines issued by EMA, WHO, USFDA, BRDD, TGA and compare with ANVISA, Russian MoH, CDSCO, NMPA, SAHPRA, TITCK, COFEPRIS agencies (Study 1);
- Development of a questionnaire based on a CIRS questionnaire (CIRS, 2017; McAuslance, 2009), which will be used to evaluate the BRICS-TM agencies in terms of organisation of agency, biosimilar development criteria and marketing authorisation approval pathway (Study 2);
- Development of a questionnaire based on a CIRS questionnaire (CIRS, 2017; McAuslane, 2009), which will be used for comparing the regulatory practices of BRICS-TM agencies with the mature (ACSS) agencies for agency organisation,

biosimilar development criteria and marketing authorisation approval pathway (Study 3);

- Development of a questionnaire and focus group to identify the challenges faced by the biopharmaceutical industry in BRICS-TM countries (Study 4); and
- Development of two questionnaires and focus group to assess physicians' and patients' views on biosimilar access in BRICS-TM countries (Study 5).

Quantitative research methods will be used in all the studies, as required, to perform statistical analyses of the data collected. The results from the qualitative research along with the quantitative data will provide a basis for identifying the areas for improvement within the BRICS-TM regulatory agencies. This will assist in the development of a proposed improved model for standardization of regulatory requirements and review process in BRICS-TM markets.

Study participants

While there are five studies within this programme of research, only four of the studies required the recruitment of study participants. An overview of the study participants recruited for this research is summarised in Table 2.1.

Table 2.1 An overview of the study participants

Study details	Study Participants
STUDY 1 **Review of Biosimilar guidelines from Regulatory Agencies and Literature from public domain**	Not applicable (Secondary Research)
STUDY 2 **Evaluation of the biosimilar development and regulatory review process in BRICS-TM countries**	QUESTIONNAIRE shared to representative from each of these agencies ▪ ANVISA (Brazil) ▪ Russian MoH (Russian Federation) ▪ CDSCO (India) ▪ NMPA (China) ▪ SAHPRA (South Africa) ▪ TITCK (Turkey) ▪ COFEPRIS (Mexico)

Study details	Study Participants
STUDY 3 **Comparison of biosimilar development and regulatory review processes of the BRICS-TM countries with the regulatory agencies in Australia, Canada, Switzerland and Singapore (ACSS)**	QUESTIONNAIRE shared to representative from each of these agencies *BRICS-TM regulatory agencies* ▪ ANVISA (Brazil) ▪ Russian MoH (Russian Federation) ▪ CDSCO (India) ▪ NMPA (China) ▪ SAHPRA (South Africa) ▪ TITCK (Turkey) ▪ COFEPRIS (Mexico) *ACSS regulatory agencies* ▪ TGA (Australia) ▪ BRDD, Health Canada (Canada) ▪ HSA (Singapore) ▪ Swissmedic (Switzerland)
STUDY 4 **Identify and evaluate challenges faced by biopharmaceutical industries in BRICS-TM countries**	QUESTIONNAIRE & FOCUS GROUP ▪ Approximately 20 participants representing companies active in biosimilar space across each country.
STUDY 5 **Identify and evaluate physicians' and patients' views on biosimilar access in BRICS-TM countries**	QUESTIONNAIRE & FOCUS GROUP ▪ Approximately 100±20 participants representing physicians/clinicians with only having speciality in oncologists, rheumatologists, gastroenterologists, dermatologists and active in biosimilar space. ▪ Approximately 250 participants representing patients/patient groups who have been prescribed biosimilars at any point of time.

Abbreviations= ANVISA- Agência Nacional de Vigilância Sanitária; BRDD- Biologic and Radiopharmaceutical Drugs Directorate; CDSCO- Central Drugs Standard Control Organisation; HSA- Health Science Authority; NMPA- National Medical Products Administration; SAHPRA- South African Health Products Regulatory Authority; TGA- Therapeutic Goods Administration; TITCK- Türkiye İlaç ve Tıbbi Cihaz Kurumu; COFEPRIS- Comisión Federal para la Protección contra Riesgos Sanitarios

DATA SOURCE

To achieve the objectives of this research, data will be collected from the public domain as well as directly from representatives representing the four key stakeholders, namely, National Regulatory Authorities (NRAs), biopharmaceutical industries, physicians/clinicians and patient groups from different jurisdictions. The inclusion and exclusion criteria for data sources have been determined as follows:

Inclusion criteria

Data collected will include information related to biosimilar products. A questionnaire technique (see Appendix 1) will be used to collect the data required to evaluate the biosimilar development and marketing authorisation process in the BRICS-TM countries (Chapter 5) and compare the BRICS-TM biosimilar approval process with that of mature regulatory agencies such as ACSS (Chapter 6). Another questionnaire will be used to obtain data directly from a number of representatives from biopharmaceutical industries to assess the challenges faced by the industries for the development of biosimilar products (Chapter 7). Further, a questionnaire (Chapter 8) will also be used to understand the views of physicians and patients on the challenges for the uptake of biosimilars in the BRICS-TM countries.

Exclusion criteria

Data related to generic medicines, complementary medicines and veterinary medicines will be excluded from this study.

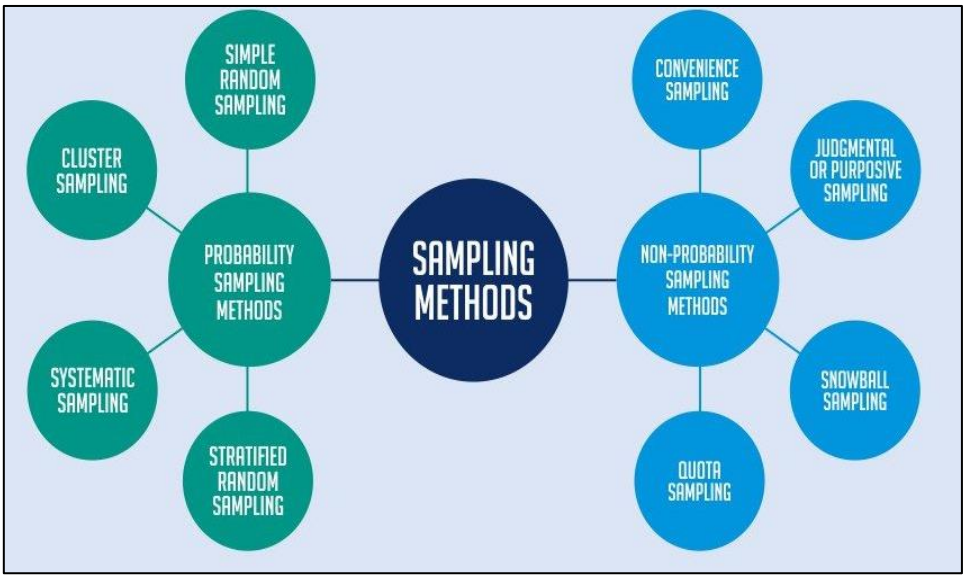
Public domain sources

Published literature, review articles, correspondence, meeting reports, opinions and abstracts, available in the public domain, will be obtained through various search engines such as bibliographic databases (e.g., PubMed), Open Access and Google Scholar. Scientific journal articles and textbooks will be examined, and the information obtained from the websites of NRAs, guidelines of organisations such as the WHO, and ICH as well as presentations made during regulatory conference proceedings will be surveyed for the purposes of this research.

SAMPLING TECHNIQUES

Sampling is a method that allows researchers to infer information about a population based on results from a subset of the population, without having to investigate every individual (QuestionPro, 2020). The various types of sampling methods are shown in in Figure 2.2.

Figure 2.2 Types of sampling techniques



Adopted from QuestionPro 2020

The sampling techniques used for this research will be a combination of probability sampling methods (including cluster sampling and stratified sampling) and non-probability sampling method (such as convenience sampling and purposive sampling).

Probability sampling - In this method, the researcher sets a few criteria for the selection and then chooses members of a population randomly. All members have an equal opportunity to be a part of the sample with this selection parameter. Within probability sampling, the following methods have been used in the study:

Simple Random Sampling - This is a sampling technique where every item in the population has an even chance and likelihood of being selected. Here the selection of respondents depends on luck or probability, and therefore this sampling technique is also sometimes known as a method of chances. The main attribute of this sampling method is that every sample has the same probability of being chosen.

Cluster sampling – This is a method where the researchers divide the entire population into sections or clusters that represent a population.

Stratified random sampling - This is a method in which the researcher divides the population into smaller groups that do not overlap but represent the entire population (QuestionPro, 2020; Bhardwaj, 2019).

Non-probability sampling - In non-probability sampling, the researcher chooses members for research in an arbitrary manner. This sampling method is not a fixed or predefined selection process. This makes it difficult for all elements of a population to have equal opportunities to be included in a sample. The following types of non-probability sampling methods have been utilised in this research:

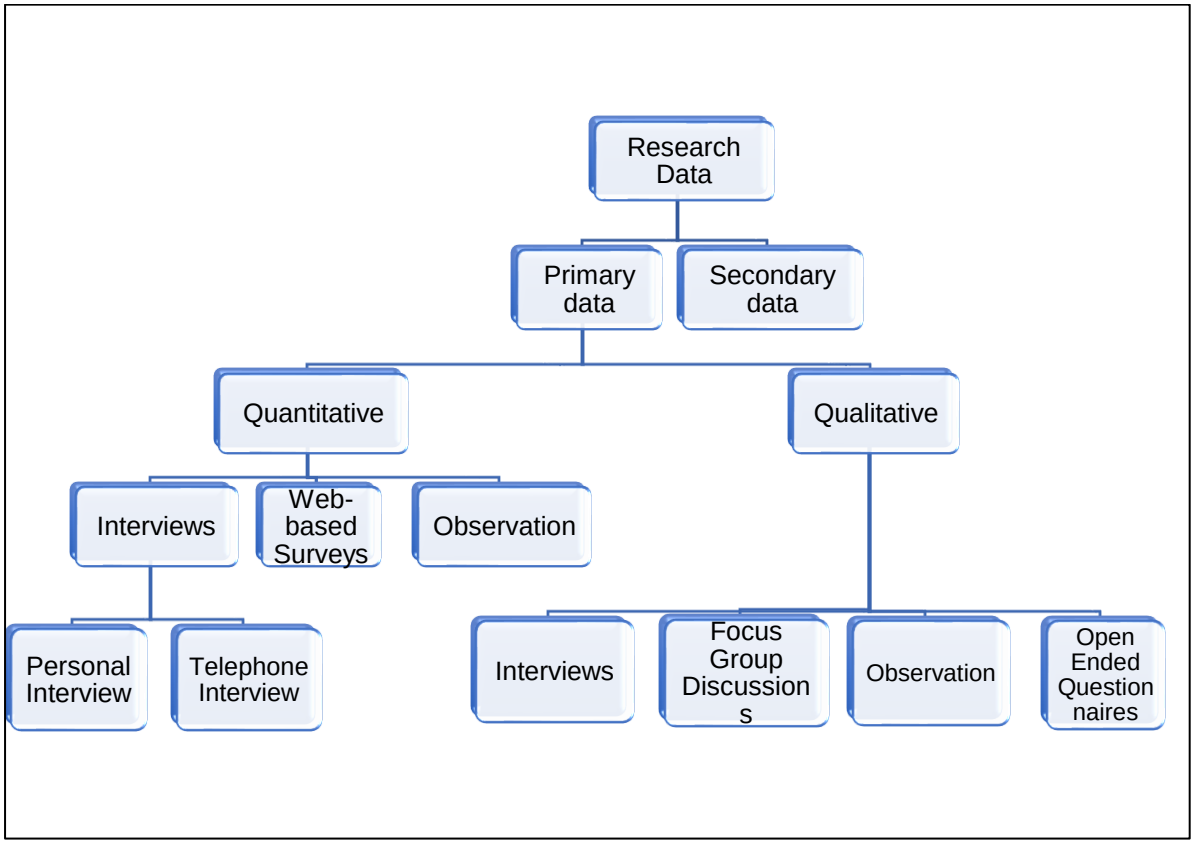
Convenience sampling - This method is dependent on the ease of access to subjects. Researchers have nearly no authority to select the sample elements, and it is purely done based on proximity and not representativeness. This non-probability sampling method is used when there are time and cost limitations in collecting feedback. In situations where there are resource limitations such as the initial stages of research, convenience sampling is used.

Judgemental or purposive sampling - Here the sample subset is formed by the discretion of the researcher. Researchers purely consider the purpose of the study, along with the understanding of the target audience. Judgmental or expert sampling is usually used in situations where the target population comprises of highly intellectual individuals who cannot be chosen by using any other probability or non-probability sampling technique (Bhardwaj, 2019).

DATA COLLECTION TECHNIQUES

Data collection is a crucial aspect of any research. Inaccurate data collection can impact the results of a study and lead to invalid results. There are several ways of collecting the appropriate data which differ considerably in the context of costs, time and other resources. The researcher should select one of these methods taking into consideration the nature of research, objective and scope, financial resources, available time and the desired degree of accuracy. Figure 2.3 shows the different tools for collecting data for primary or secondary research (QuestionPro, 2021a).

Figure 2.3 Data collection techniques



The main methods of data collection and tools used for this study have been summarised. Techniques for both primary (qualitative and quantitative) and secondary data collections have been utilised in the research study. The most appropriate data collection techniques considered for this research were selected based on a review of their strengths, weaknesses and the applicability of such techniques to achieve the research objectives for each of the studies that will be conducted throughout this programme of research.

Primary data collection - This is the process of gathering data through one's own means and efforts for the purpose of specific research (Blog, 2020). The following techniques for primary data collection will be used in this study:

Interview - In this technique, the researcher follows a specific procedure through a one-on-one conversation and seeks answers to a set of pre-determined questions through personal interviews. This conversation can be done in person or through phone calls/ web-based calls. Personal Interviews can be structured, semi-structured and unstructured (Blog, 2020). Structured interviews are a verbally administered

questionnaire. Semi-structured interviews follow a specific laid down questionnaire but have the scope of several exploratory discussions with the respondents which allow more depth of information to be gathered. Unstructured interviews are much more in-depth and allow the researcher much more flexibility to delve into areas of interest. This interview technique demands deep knowledge and greater skill on the part of the interviewer. They happen to be the central technique of collecting information in case of exploratory research studies.

Mailing of questionnaire - In this method, the questionnaires are mailed to the respondents with a request to complete them and return them after completion. It is the one of the most extensively used method in various industry surveys. The researcher and the respondents establish contact, and once the respondent agrees to participate, the researcher sends the questionnaire. This method is adopted to enable convenience and flexibility of the respondent.

Online surveys - In order to reach a larger group of respondents, links to questionnaires were put up on social media, websites or other webpages where the target respondent population is expected to be present. This is helpful to gather larger number of responses in a shorter period and is also relatively less expensive. However, only simple short questionnaires can be administered via this method, and in-depth data or insights cannot be captured (Kabir, 2016; Ball, 2019).

Secondary data collection - Secondary data is data that has already been collected and published through the primary research carried out at an earlier point in time and is now available for the perusal of other researchers. Sources of secondary data includes academic books, medical and scientific journals, websites, government records and others (Blog, 2020).

Literature review

An initial literature review will be performed to gain an understanding of the global and regional biosimilar regulatory environment on development, marketing authorisation process and challenges and opportunities for the access of biosimilars by patients. Conducting such literature reviews will allow for exploratory search of other studies related to the improvement of the biosimilar regulatory pathways and obtaining other information that can support the designing and validation of data collection tools like questionnaires, interviews etc planned for the research.

Questionnaires

The main data collection tool that will be used in this research programme is a pre-defined questionnaire (Study 2, 3, 4, 5). These four questionnaires will be developed based on the objective and target group of subjects for the study.

The questionnaire is central to data collection in research. It can either be structured or unstructured questionnaire. Structured questionnaires are those questionnaires in which there are definite, concrete and pre-determined questions. Structured questionnaires are simple to administer, reliable and easier to analyse. In an unstructured questionnaire, there exists a general guide on the type of information to be obtained, but the exact question formulation is largely the responsibility of the interviewer. The replies to questions are also taken down in the respondent's words. This leads to a more qualitative data collection and can help with better depth of information and insight on exploratory topics (QuestionPro, 2021b).

Another important aspect of a questionnaire is the question-sequence. The question-sequence must be clear and smooth. The flow of questions must be logical with a smooth connect between subsequent questions. Ideally simple questions that are easiest to answer should be put in the beginning. One should limit questions to those that are critical to the research problem and a connecting thread should run through successive questions. Overall, the questions must be very clear, easily understood and relevant. The form of the question may be either closed/ dichotomous (with 'yes' or 'no' responses) or open ended. Multiple choice or closed questions have the advantages of being simple to answer, quick and easier to analyse. They are mostly amenable to statistical analysis. However, when complex or exploratory issues are central to the research, multiple-choice questions will not help. In such cases, open-ended questions are often employed which can help with a more detailed and un-guided response from the respondent (QuestionPro, 2021b).

Validation of questionnaire

The development of a questionnaire is a complex process and requires verification of its reliability and usefulness before it can be used with the respondents. An ideal questionnaire must be simple, reliable and valid in terms of content and construct. The questionnaires developed for this study will be assessed for their validity via pilot surveys and expert opinion. Pilot surveys will help to define the feasibility and

applicability of the survey in terms of time, cost and complexity. Therefore, it is important to assess how simple or practical the format is, time used for their application, interest of respondents, the ease of scoring the questions and compiling the data, and whether they can be coded and interpreted. These are all parameters by which the feasibility of questionnaires can be judged. Validity of content is the degree with which the questionnaire covers most of the aspects of the concept under study. Evaluation of content validity is based on expert judgements, medical literature review, comparative evaluation of existing regulatory norms identified in review articles, expert opinion and pilot studies. Face validity involves the expert looking at the items in the questionnaire and agreeing that the test is a valid measure of the concept which is being measured. This is a subjective assessment of experts who hold a high degree of expertise in the area, e.g., the content validity of the regulatory agency questionnaire should be carried out based on discussions with high-ranking officials of another agency who would be best suited to provide an unbiased opinion on the construct of the questionnaire. Expert opinion will be sought while designing the agency (Study 2, 3) and industry (Study 4) questionnaire, which will be used as a measure of the 'content validity of the questionnaire'. Based on the feedback received from the pilot surveys and the expert opinion, changes will be made to the questionnaire. A detailed version control record will be maintained for all edits carried out (Zolkipli et al., 2018).

Focus groups

Focus groups are group discussions conducted with the participation of 7 to 12 people to capture their experiences and views regarding specific issues closely related to the research question(s). Focus group data collection methods are most suitable for types of studies where multiple perspectives needed to be obtained regarding the same problem. Advantages of focus groups include the possibility of obtaining primary data through non-verbal channels, as well as verbal channels and approaching the research area from various perspectives. However, data collection and data analysis using focus groups is much more difficult compared to questionnaires and interviews. Focus groups are led by a moderator who is responsible to ensure that group discussions remain focused on the research area (Gundumogula, 2020).

Self-administered questionnaires will be used in the research programme to obtain information from regulatory agencies (BRICS-TM and ACSS) on organisation of regulatory agency, biosimilar development and marketing authorisation processes. (Study 2 and Study 3) (CIRS, 2017). The questionnaires will be sent electronically to representatives identified from each of the regulatory agencies. Given the geographical spread of the participants and the researcher, this method of data collection will conserve resources. The focus group technique will be applied to understand the challenges faced by the biopharmaceutical industry in the development of biosimilars (Study 4). It will also be used to explore the challenges and understand the perspectives of physicians and patients for prescribing or accessing biosimilars respectively (Study 5).

Summary of the selected data collection techniques

Table 2.2 provides a summary of the data collection techniques that have been selected for the purpose of this research and the relevant research objectives and studies to which these will be applied.

Table 2.2 Summary of the planned data collection techniques

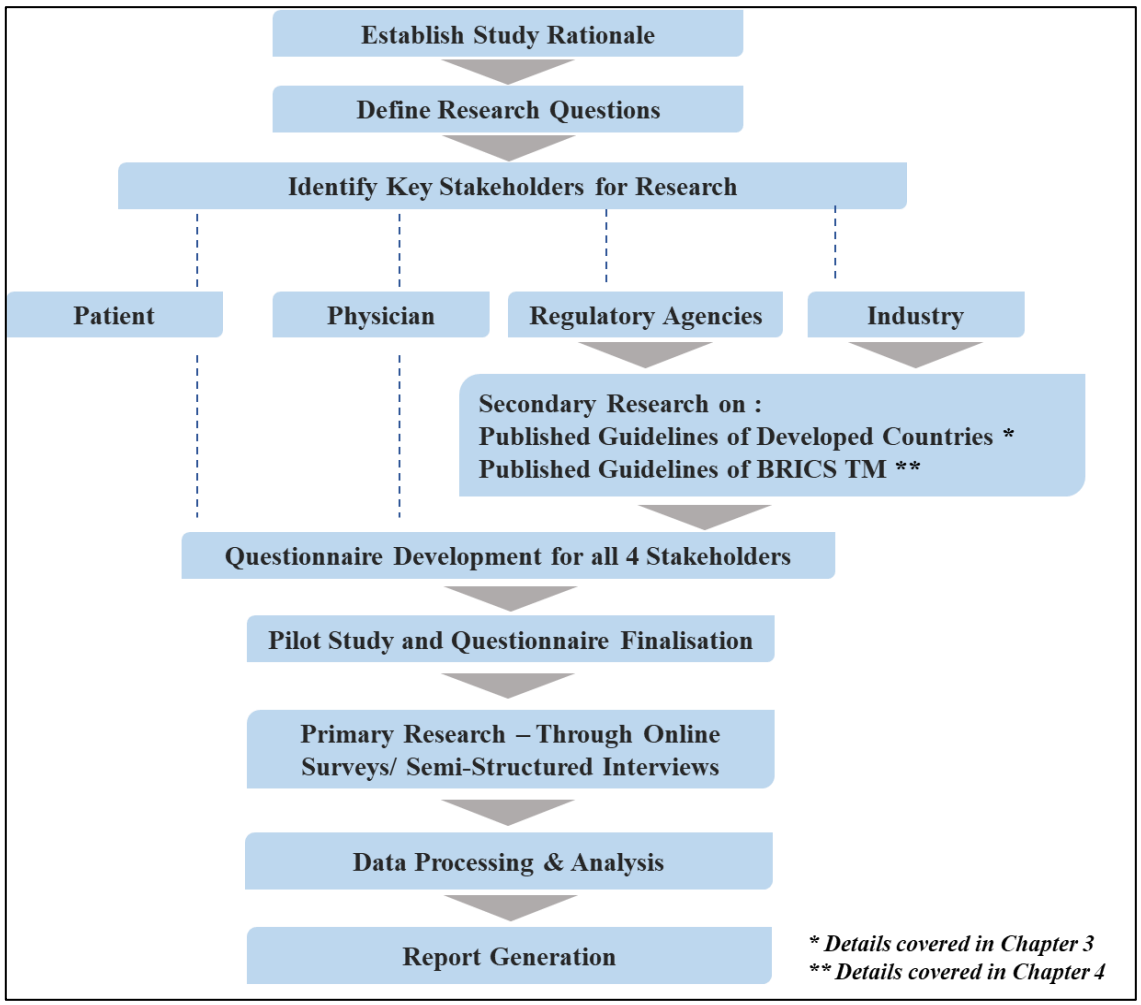
Data collection technique	Research Objectives	Thesis Chapter
Literature review	General Introduction	Chapter 1
Literature review	Study Rationale and Methodological framework	Chapter 2
Literature review	Evaluation of biosimilar development guidelines issued by EMA, WHO, USFDA, BRDD, TGA Swissmedic Health Agencies (Secondary Research)	Chapter 3 **(Study 1- Part A)**
Literature review	Comparison of biosimilar regulatory guidelines in Emerging Economies-against Mature Agency Regulations (Primary Research)	Chapter 4 **(Study 1- Part B)**
Self-administered questionnaires	Evaluation of the regulatory review process and assessment criteria for biosimilar development in BRICS-TM countries	Chapter 5 **(Study 2)**
	Comparative evaluation of practices followed by mature (ACSS) and emerging (BRICS-TM) agencies for type of data assessment, criteria for biosimilar development and pathway for marketing authorisation approval	Chapter 6 **(Study 3)**
	Challenges faced by biopharmaceutical industry in BRICS-TM countries	Chapter 7 **(Study 4)**
	Evaluation of physicians' and patients' views about biosimilar access in BRICS-TM countries	Chapter 8 **(Study 5)**

Note: Health Canada updated to BRDD

STUDY PLAN

To achieve the research objectives, a study flow was laid down to be followed for the overall research as depicted in Figure 2.4. The research programme starts with establishing the study rationale which will be achieved by literature review (Study 1). This is followed by conceptualising the studies, identifying and defining the research questions and study design. The studies will be targeted towards the four identified key stakeholders (regulatory agencies, biopharmaceutical industries, physicians/ clinicians, patients) involved from the development of the biosimilar product through to the access of the biosimilar by the patient community. The challenges pertaining to the development and approval of biosimilars will be studied from the perspective of regulatory agencies in BRICS-TM countries by using self-administered semi-quantitative questionnaire (see Appendix 1) (Study 2). The same questionnaire (modified administratively only) will be used to compare the biosimilar development and approval pathways of BRICS-TM agencies with other similar but matured regulatory agencies such as ACSS (Study 3). The data on challenges and issues in the biosimilar regulatory pathway in BRICS-TM collated from these studies will be assessed against the perspectives of the biopharmaceutical industries (Study 4) (see Chapter 7 for the self-administered semi-quantitative questionnaire) and physicians/patients (Study 5) (see Chapter 8 for self-administered questionnaire) through focus group techniques in BRICS-TM countries. A pilot study will be conducted followed by primary research through interviews. Both the quantitative and qualitative data obtained from these studies will be processed and analysed. It is hoped that the results of these analyses will yield a set of key recommendations or areas for improvement for designing/proposing a standardised improved model for biosimilar development and approval pathway for BRICS-TM agencies.

Figure 2.4 Study Plan



DATA PROCESSING AND ANALYSIS

After collection of the required data, the data has to be collated, processed, analysed and interpreted in order to the research objectives. The five studies designed for this research programme contain both qualitative and quantitative data and hence shall be analysed via a combination of statistical, qualitative/content analysis methods. Qualitative data will be generated through the review of literature of published articles, reviews available in the public domain and guidelines from the official websites of the regulatory agencies (Study 1). Hence, no statistical tests will be used to analyse the qualitative data collected in these studies. The conclusions from these hypotheses generating qualitative data may be considered for further research. The quantitative and qualitative data collected in exploratory studies; Study 2, 3, 4 and 5 by the application of questionnaires and focus groups discussions will be entered into Microsoft Excel for data analysis. The results of these analyses will be presented using

descriptive statistics (i.e., mean, standard deviation, median, range and mode) for quantitative data and content analysis will be employed to generate themes and sub-themes for qualitative data. The study results may also be presented in the form of graphs/charts to depict certain comparative data. The data analysis for each study and the results thereof will be documented in separate chapters. The key recommendations derived out of these chapters will be consolidated into a set of key recommendations for the proposed standardised improved regulatory model for biosimilar development and approval in BRICS-TM regulatory agencies.

SUMMARY OF RESEARCH METHODOLOGY OF FOUR KEY STAKEHOLDER STUDIES

Regulatory agencies

Target agencies - *BRICS-TM agencies* - ANVISA (Brazil), Russian MoH (Russia), CDSCO (India), NMPA (China), SAHPRA (South Africa), TITCK (Turkey), COFEPRIS (Mexico); ACSS agencies – TGA (Australia), BRDD (Canada), HSA (Singapore), Swissmedic (Switzerland) (Table 2.3).

Table 2.3 List of Target agencies

Category	Agency	Type of Research
Mature Agencies	EMA USFDA WHO	Secondary research through literature search and guideline review
ACSS Consortium	TGA BRDD HSA Swissmedic	Primary and Secondary research
BRICS-TM	ANVISA Russian MoH CDSCO NMPA SAHPRA TITCK COFEPRIS	Primary and Secondary research

Key objectives

- To document procedures and practices relating to biosimilar applications across BRICS-TM including approval pathway, key milestones and target timeline for approval and cross verify gaps identified based on review of published literatures and guidelines.
- To understand agencies' views on biosimilar development criteria.
- To identify challenges and improvement areas in the biosimilar development and approval process and resource allocation in each agency.
- To understand ACSS consortium biosimilar development, approval process, resource allocation and work sharing procedure/standardisation process.
- To compare BRICS-TM with ACSS and arrive at common challenges and opportunities for standardising the pathway for biosimilar development and approval across BRICS-TM markets.

Questionnaire design

A questionnaire will be prepared to understand the challenges and gaps pertaining to the biologics/biosimilar guidelines for submission to the regulatory agencies. The questionnaire will have a combination of qualitative, quantitative, dichotomous and open-ended questions. In order to identify the key areas which, need specific insights, a thorough analysis of EMA, USFDA, WHO, BRDD, TGA guidelines will be performed, and a master data extraction template will be created. This will be covered in detail in Chapter 3. As next steps there will be a detailed study of the BRICS-TM agencies' guidelines to identify gaps by comparing against mature agency (ACSS) guidelines. Details on the comparison of regulatory guidelines between the agencies will be presented in Chapter 4. Based on the above secondary research, a detailed questionnaire will be designed, and the flow of topics will be decided. Two different parts of the questionnaire will target different aspect of the registration and approval process. Part I of the questionnaire will focus on organisation structure and views on biosimilarity development criteria whereas Part II will focus on the marketing authorisation process. Edits to the questionnaire will be made based on feedback from the research team and senior regulators from at least two regulatory agencies (one outside BRICS-TM). Version control of all questionnaires will be maintained, and key changes made in the pilot questionnaire will be captured with details on the topic and

suggested changes. The final version of the regulatory agency questionnaire will be administered across the seven BRICS-TM countries.

Research Methodology

The planned methodological framework that will be followed is explained in Figure 2.5.

Figure 2.5 Research Methodology for regulatory agencies' study

Research setting

- BRICS-TM regulatory agencies and agencies of ACSS Consortium

Sampling description

- ***Sample size***- Representatives from seven regulatory agencies across BRICS-TM countries (ANVISA (Brazil), Russian MOH, CDSCO (India), NMPA (China), SAHPRA (South Africa), TITCK (Turkey), COFEPRIS (Mexico) and four regulatory agencies of ACSS Consortium (TGA (Australia), BRDD (Canada), HSA (Singapore) and Swissmedic (Singapore).
- ***Respondent***- Senior Executives in Biosimilar/Biologic Department.

Sampling technique

- Judgemental/Purposive sampling across total population, semi-structured/ unstructured interviews through face-to-face meeting/tele/video-conferencing, self-administred questionnaire followed by closing gaps if any, employing local consultants, where needed to enable meaningful discussion with agency experts/assessors/committee.

Data collection techniques

- Self-administered questionnaires shared through electronic mails to representatives or leading consultants associated with BRICS-TM and ACSS agencies.

Data collection process

- Confidential procedures will be used for all parts of the study.

Survey Language

- English

Data processing and analysis

- Data will be entered into Microsoft Excel and developed specifically for each study. If the data is quantitative, descriptive statistics such as mean, median, range will be used and if the data is qualitative, content analysis will be employed to generate themes and sub-themes.

Biopharmaceutical industries across BRICS-TM

Key Objectives

- To identify the challenges faced by the industry in the biosimilar development, manufacturing and approval process in their respective countries.
- To understand concerns on pricing and market access.
- To evaluate the perception of the companies regarding the effectiveness and efficiency of the current regulatory process
- To gather suggestions on potential improvements in the biosimilar development and approval process in their respective countries.

Questionnaire design

The industry questionnaire will be prepared targeting various areas. The key aspects around biosimilar development and approval will be identified based on literature survey, evaluation on published guidelines and feedback and comments received from expert opinions. The questionnaire will also utilise information from the research detailed in Chapter 3 and Chapter 4. Further, a pilot survey will be carried out for content validity and finalisation of the questionnaire. Version control of all questionnaires will be maintained, and key changes made in the pilot questionnaire will be captured with details on the topic and suggested changes.

Research methodology

The planned methodological framework that will be followed is explained in Figure 2.6.

Figure 2.6 Research Methodology for biopharmaceutical industry's study

Research setting

- Biopharmaceutical industries from BRICS-TM countries

Sampling description

- ***Sample size***- 15-25 participants across BRICS TM markets.
- ***Limitation*** - Limited population of target group: Number of companies active in the biosimilar space - ~15 in India; ~5 in Brazil; ~5 in Russia; ~4 in China; ~4 in South Africa; ~3 in Turkey; ~1 in Mexico.
- ***Inclusion criteria*** - Companies active in the biosimilar space in the respective country.
- ***Respondent***- Senior Executives in Biosimilar/Biologic Department.

Sampling technique

- Purposive sampling through expert elicitation (Purposive sampling, also known as judgmental, selective or subjective sampling, is a type of non-probability sampling technique. Expert sampling is a type of purposive sampling technique that is used when the research needs to collate knowledge from individuals that have a particular expertise).

Data collection techniques

- Semi-structured interviews, questionnaires administered over telephone/ videoconferencing, employing local consultants in BRICS-TM markets to enable meaningful discussion with industry experts, connect with local industry association to get in touch with industry experts.

Data collection process

- Confidential procedures will be used for all parts of the study. All the company specific information may be redacted to avoid identification.

Survey Language

- English

Data processing and analysis

- Data will be entered into Microsoft Excel and developed specifically for each study. Data processing and analysis will be carried out using Microsoft Excel and the Statistical Product and Service Solutions (SPSS); if the data is quantitative, descriptive statistics such as mean, median, range will be used and if the data is qualitative, content analysis will be employed to generate themes and sub-themes.

Physicians/Clinicians prescribing biosimilars across BRICS-TM countries

Key Objectives

- To understand the biosimilar prescribing habits of physicians and the factors driving their choice of prescribed product
- To understand their views on biosimilar naming, interchangeability, switching, and substitution
- To gauge perception of biosimilar's safety and efficacy as compared to the original biologic
- To understand the challenges pertaining to biosimilars, including access and affordability for patients; further to gain information on potential areas of improvement to overcome these challenges.

Questionnaire design

To understand their perception, a common questionnaire will be prepared for physicians across BRICS-TM countries. The questionnaire will be based on perceived challenges and opportunities with biosimilars across the countries. Most of the questions will be quantitative in nature such as rating questions, in order to enable comparisons and statistical analysis of the responses. The questionnaire will have three parts - Part I will target the understanding of the physicians' knowledge pertaining to biosimilars; Part II will focus on understanding their views from the patient perspective; Part III will focus on the main challenges related to biosimilar medicines. A pilot study with at least 2 physicians will be carried out to assess the feasibility and content validity. The feedback received will be incorporated in the final version. Version control of all questionnaires will be maintained, and key changes made in the pilot questionnaire will be captured with details on the topic and suggested changes.

Research methodology

The planned methodological framework that will be followed is explained in Figure 2.7.

Figure 2.7 Research Methodology used for Physician's study

Research setting

- Physicians located in BRICS-TM countries

Sampling description

- ***Sample size*** - 100 ± 20 physicians across the BRICS-TM markets. Pilot study for questionnaire validation to be carried out with two physicians from each of the seven country.
- ***Limitation*** - Inability to include large numbers due to language barrier and high cost.
- ***Inclusion criteria*** - Doctors who have prescribed biosimilars to their patients; doctors belonging to following specialties; oncologists, rheumatologists, gastroenterologists, dermatologists.

Sampling technique

- Stratified sampling will be used for the study, which involves the use of "stratum", or a subset of the target population wherein the members possess one or more common attribute (oncologists, rheumatologists, gastroenterologists, dermatologists).

Data collection techniques

- Self-completion questionnaires administered through online physician groups, third parties and through telephone interviews.

Data collection process

- Confidential procedures will be used for all parts of the study. All the personal specific information will be redacted to avoid identification. The electronic or interviewer delivered questionnaires will be used to collect data which may allow the confidentiality and/or anonymity of the procedure. Due to confidentiality and sensitive nature of information on biosimilars as well as personal data, no recordings are to be carried out. Confidentiality clause will be part of the questionnaire administration.

Survey Language

- English, Portuguese, Mandarin, Russian, Spanish

Data processing and analysis

- Data will be entered into Microsoft Excel and analysed using standard techniques.

Patients study - Patients receiving biosimilar treatments across the BRICS-TM countries

Key Objectives

- To understand the perception of patient/patient support groups towards affordability and access to biosimilars
- To establish other challenges in biosimilar treatment, from the patients' perspective.

Questionnaire design

A simple questionnaire with quantitative, dichotomous and rating based questions will be designed for the patient study. The questions will focus on establishing the key challenges faced by patients in areas related to biosimilar therapy. A pilot study will be carried out with at-least 15 patients. The feedback from this will be built into the final version of the questionnaire. Version control will be maintained for all edits in the questionnaire.

Research methodology

The planned methodological framework that will be followed is explained in Figure 2.8.

Figure 2.8 Research Methodology used for patients' study

Research setting

- Patients located in BRICS-TM countries

Sampling description

- ***Sample size***- 250 patients across the BRICS-TM markets.
- ***Inclusion criteria*** - Patients/guardians of patients who have been prescribed biosimilars at any point in time (even if not having finally consumed biosimilars); Age >18 years.
- ***Limitation*** - Issues on confidentiality around patients and their disease states prevent/limit this study in some situations.

Sampling technique

- Simple random sampling technique

Data collection techniques

- Self-completion questionnaires administered through patient groups via social media i.e, Facebook, Twitter etc.; self-completion questionnaires administered through patient origanization group or through physician/medical associations.

Data collection process

- Confidential procedures will be used for all parts of the study. All the patients' personal information may be redacted to avoid identification. The electronic or interviewer delivered questionnaires will be used to collect data which will allow the confidentiality and/or anonymity of the procedure.

Survey Language

- The primary language for the survey will be English. However, wherever necessary, the questionnaire will be translated into other languages i.e, Portuguese, Mandarin, Russian, Spanish for ease of understanding of the questions by the respective native participants.

Data processing and analysis

- Data will be entered into Microsoft Excel and developed specifically for each study. Data processing and analysis will be carried out using Microsoft excel and the Statistical Product and Service Solutions (SPSS); if the data is quantitative, descriptive statistics such as mean, median, range will be used and if the data is qualitative, content analysis will be employed to generate themes and sub-themes.

ETHICAL APPROVAL

The study has been approved by the Health, Science, Engineering and Technology ECDA, University of Hertfordshire [Reference Protocol number: aLMS/PGR/UH/03332(1)].

SUMMARY

- This chapter describes the theory as well as the practical design of the primary research methodology to be followed for this PhD research project.
- It provides an outline of the five proposed studies that are planned to be conducted to achieve the objectives of this research.
- The broad hypotheses testing of non-equitable and insignificant reach and penetration of biosimilars across BRICS-TM countries, with a proposal for standardisation of the biosimilar development and approval pathways across BRICS-TM countries that could help in mitigating the challenges of access and affordability has been explained.
- A detailed study design for research across regulatory agencies, industry experts, physicians and patients has been detailed and the relationship between the four empirical studies to be conducted and the aims and objectives of the research programme were outlined.
- The data collection and sampling techniques along with the designing and validation of questionnaires to be used for the four studies covering this research were described.
- The data sources like detailed secondary research on the published guidelines from mature and emerging agencies (Study 1) for designing the agency and industry questionnaires has been explained. The detailed assessment of guidelines and the findings from the studies will be detailed in Chapter 3 and Chapter 4. The findings from the secondary research are deemed to help identify the similarities and differences that need to be verified for the primary research (Study 2, 3, 4, 5).

CHAPTER 3

Evaluation of biosimilar development guidelines issued by EMA, WHO, USFDA, Health Canada, TGA and Swissmedic Health Agencies

INTRODUCTION

Biosimilars are biotherapeutic products having identical quality and similar safety and efficacy profile as the Reference Biological Product (RBP). Developing a clinically equivalent biosimilar and proving comparability with a RBP raises multiple challenges starting from reference product selection, characterisation (physico-chemical, manufacturing process, non-clinical (*in vitro/ vivo* assays), clinical safety and efficacy (Kos et al., 2018). Regulatory agencies such as the European Medicines Agency (EMA), the World Health Organisation (WHO), United States of Food and Drug Administration (USFDA), Biologic and Radiopharmaceutical Drugs Directorate (BRDD, Canada) formerly called as Biologics and Genetics Therapies Directorate (BGTD, Canada), Therapeutic Goods Administration (TGA, Australia) and Swissmedic (Switzerland) have set out specific guidelines and questions and answers documenting and clarifying doubts related to the development and marketing authorisation of biosimilars. All relevant guidelines were reviewed to define the biosimilar development criteria and generate master data templates for the comparability study. Furthermore, the worldwide outbreak of COVID-19 has compelled the agencies to relax their regulatory standards for expediting approval of specific medicines and such guidelines were also retrieved and evaluated.

OBJECTIVES

The objectives of this chapter were to identify and critically review the current regulatory guidelines pertaining to biosimilar development from mature agencies. The objectives were as follows;

- Identification and retrieval of biosimilar guidelines from official website of relevant agencies (EMA, WHO, USFDA, BRDD, TGA, Swissmedic and ICH)
- Critically evaluate guidelines to understand biosimilar development criteria for each agency
- Compare biosimilarity criteria within mature regulatory agencies to identify similarities and differences
- Perform literature survey on the organization of the agencies, data assessment review and approval processes
- Prepare a master checklist of requirements for biosimilarity development criteria, data assessment and approval process considering each agency

- Using a master checklist to compare requirements against the BRICS-TM markets.

HYPOTHESES

This study examined the following hypotheses:

- Biosimilarity principles for biosimilar development is uniform across EMA, USFDA, WHO, TGA, BRDD and Swissmedic.
- The comparability criteria i.e, characterisation, non-clinical and clinical development for biosimilar monoclonal antibodies varies to a certain extent between EMA, USFDA, WHO, TGA, BRDD and Swissmedic.
- The post-marketing requirements for interchangeability, substitution and extrapolation of indications varies within each agency.
- The organization of the agencies, data assessment, review and approval process vary among the agencies.

METHODS

Data source

Current and valid English-language guidelines including published questions and answers documents like the EMA guidelines pertaining to biosimilar medicinal products and monoclonal antibodies (mAbs), technical report series (TRS) and pertinent annexes from the WHO, guidance for industry from the USFDA, guidance documents issued by BRDD/Canada, biosimilar medicines regulation TGA/Australia and the guidance document with questions and answers from Swissmedic were obtained from official websites of the respective regulatory agency for the period January 2014 to December 2020.

Apart from the national guidelines, the quality considerations based on ICH guidelines [ICH Q5A to Q5E (Quality of biotechnological products), ICH Q6B (Specifications: Test procedures and acceptance criteria for biotechnological/ biological products) and ICH Q11 (Development and manufacture of drug substances, chemical entities and biotechnological/biological entities) published initially between November 1995 - November 2004 and relevant updates were also reviewed.

Further, a literature search was conducted to explore the expertise of the agencies in biosimilar space in terms of type of data assessment, capability and capacity of the agencies and to understand the biosimilar approval process followed by these agencies.

Data Processing and Analysis

The data concerning biosimilarity principles, selection of a RBP, comparability studies covering quality considerations, *in vitro* and *in vivo* non-clinical studies, clinical pharmacokinetic (PK) and pharmacodynamics (PD) studies, immunogenicity assessment, comparative clinical safety and efficacy studies, post marketing requirements including extrapolation to other indications, interchangeability, switching, substitutions, pharmacovigilance and Risk Management Plan (RMP) were extracted from the aforementioned guidelines. The data was qualitatively analysed to prepare a set of standard development criteria for biosimilars and create a master checklist for defining biosimilarity requirements in the BRICS-TM countries.

RESULTS

The regulatory guidelines published by EMA, USFDA, WHO, BRDD, TGA and Swissmedic agencies (Table 3.1) were studied to understand different aspects of biosimilar development criteria (Figure 3.1). Based on the information retrieved from the agencies' official guidelines on biosimilar development criteria for the stringent regulatory agencies (SRA) (USFDA, EMA, WHO) and the ACSS agencies (TGA, BRDD and Swissmedic), master data templates were created for the following parameters: Part I - Biosimilarity principles; Part II - Reference product selection; Part III - Comparability studies (quality, non-clinical and clinical studies) and Part IV- Post-marketing requirements (extrapolation to other indications, interchangeability/ switching and substitution, pharmacovigilance and RMP).

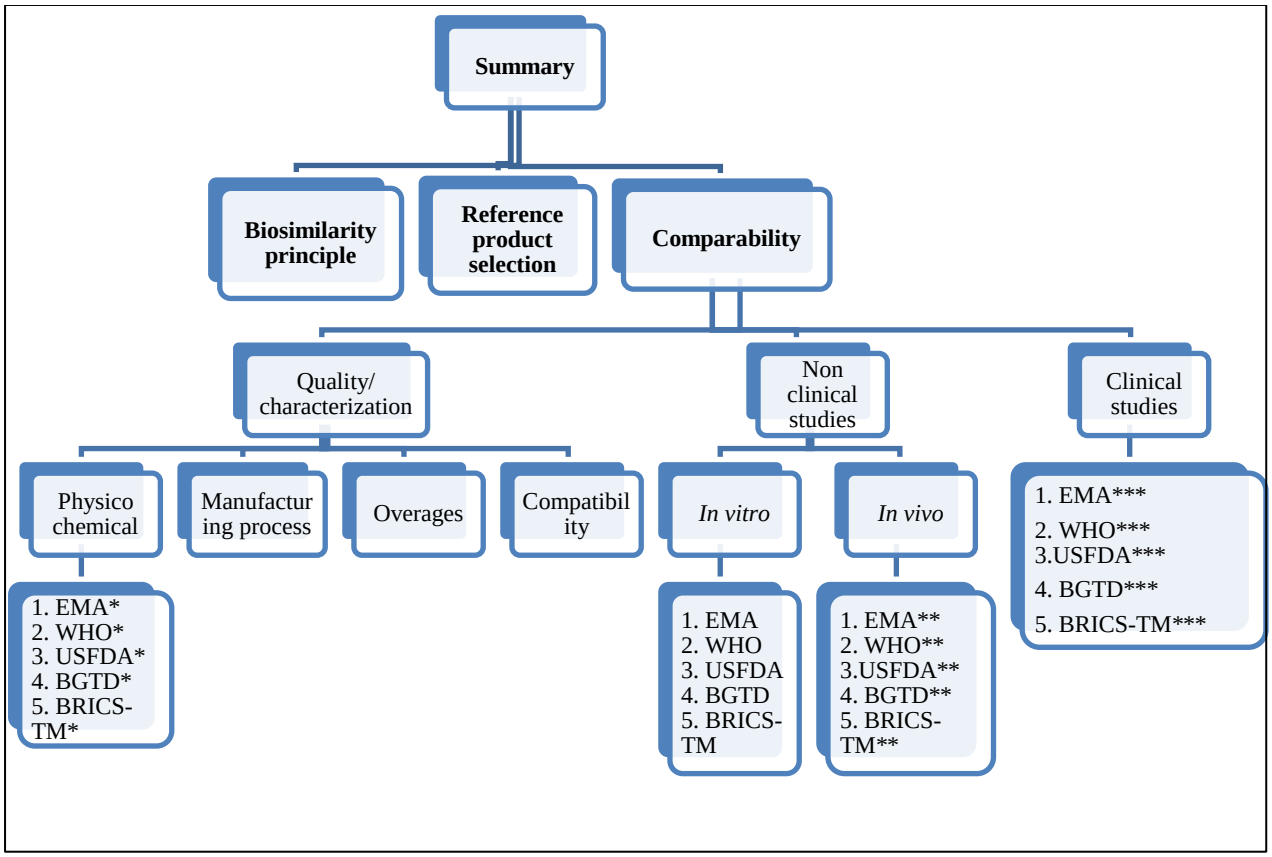
Table 3.1 List of biosimilar guidelines from regulatory agencies

Agency name	Reference guidelines
EMA (CHMP)	Clinical pharmacology and pharmacokinetics: questions and answers (2020)
	Guideline on Comparability of Biotechnology-Derived Medicinal Products after a change in the manufacturing process-non-clinical and clinical issues CHMP/BMWP/101695/2016 (2016)
	Guideline on development, production, characterisation and specification for monoclonal antibodies and related products EMA/CHMP/BWP/532517/2008 (2016)
	Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission EMA/CHMP/BWP/187338/2014 (2016)
	Guideline on similar biological medicinal products CHMP/437/04 Rev 1 (2014)
	Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1 (2014)
	Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1) EMA/CHMP/BWP/247713/2012 (2014)
	Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues EMA/CHMP/BMWP/403543/2010 (2012)
	Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins CHMP/EWP/89249/2004 (2007)
	Guideline on Immunogenicity assessment of Biotechnology-Derived Therapeutic Proteins EMEA/CHMP/BMWP/14327/2007 (2007)
	Development pharmaceutics for biotechnological and biological products EMA/CHMP/BMWP/403543/2010 (1999)
USFDA (CBER)	Paediatric Study Plans: Content of and Process for Submitting Initial Paediatric Study Plans and Amended Initial Paediatric Study Plans, Guidance for Industry (2020)
	Paediatric Study Plans for Oncology Drugs: Transitional Information Until Full Implementation of FDARA Section 504 Questions and Answers, Guidance for Industry, DRAFT GUIDANCE (2020)
	Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act, Guidance for Industry, DRAFT GUIDANCE (2020)

Agency name	Reference guidelines
	Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products, Guidance for Industry, DRAFT GUIDANCE (2019)
	Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations", Guidance for Industry, DRAFT GUIDANCE (2019)
	Considerations in Demonstrating Interchangeability with a Reference Product, Guidance for Industry (2019)
	Questions and Answers on Biosimilar Development and the BPCI Act (Revision 1), Guidance for Industry (2018)
	New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Revision 2), Guidance for Industry, DRAFT GUIDANCE (2018)
	Biosimilars: additional questions and answers regarding implementation of the biologics price competition and innovation act of 2009 (2018)
	Formal meetings between the FDA and sponsors or applicants of BsUFA products, Guidance for Industry, Draft Guidance (2018)
	Scientific considerations in demonstrating interchangeability with a reference product guidance for industry (2017)
	Clinical pharmacology data to support a demonstration of biosimilarity to reference product guidance for industry (2016)
	Quality considerations in demonstrating biosimilarity of a therapeutic protein product to reference product guidance for industry, 2015 biosimilarity. (2015)
	Scientific considerations in demonstrating biosimilarity to a reference product guidance for industry (2015)
	Formal meetings between the FDA and biosimilar biological product sponsors or applicants (2015)
	Points to consider in the manufacture and testing of monoclonal antibody products for human use docket no. 94D-0259 (1997)
WHO	Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs) WHO TRS No. 1004, 2017 Annex 2, Sixty-seventh report (2017).
	WHO questions and answers similar biotherapeutic products WHO/SBP_Q&A/DRAFT/DEC (2017)

Agency name	Reference guidelines
	Guidelines on evaluation of similar biotherapeutic products (SBPs) WHO TRS No. 977, 2013 Annex 2, Sixtieth report (2013).
	Guideline for assuring the quality of monoclonal antibodies for use in humans WHO TRS No, 822 (1992)
TGA	Biosimilar medicines regulation, Version 2.2 (2018)
Health Canada/ BRDD	Biosimilar biologic drugs in Canada: Fact Sheet (2019)
	Fact sheet: biosimilars (2017)
	Guidance document: information and submission requirements for biosimilar biologic drugs. (2016)
	Guidance document: conduct and analysis of comparative bioavailability studies, file number: 12-105972-31 (2012)
Swissmedic	Questions and answers on the authorisation of biosimilars (2020).
	Guidance document Authorisation biosimilar HMV4 (2020).
ICH	Development and manufacture of drug substances (chemical entities and biotechnological/biological entities) Q11 (2012)
	Pharmacovigilance planning E2E (2004)
	Comparability of biotechnological/biological products subject to changes in their manufacturing process Q5E (2004)
	Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: chemical substances Q6A (1999)
	Specifications: test procedures and acceptance criteria for biotechnological/biological products Q6B (1999)
	Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin Q5A (R1), Version 4 (1999).
	Derivation and characterisation of cell substrates used for production of biotechnological/biological products Q5D (1997)
	Quality of biotechnological products: analysis of the expression construct in cells used for production of r-DNA derived protein products Q5B (1995)
	Quality of biotechnological products: stability testing of biotechnological/biological products Q5C (1995)

Figure 3.1 Comparability criteria for biosimilar development



**Under each agency, the physicochemical requirements covered are structure, immunological properties, biological activity, purity impurity & contaminants, expression system/cell lines, quantity, specifications*

*** Under each agency, the in vivo (nonclinical) studies requirements covered are pharmacokinetics, pharmacodynamics, immunogenicity, safety pharmacology, toxicology, carcinogenicity, local tolerance*

****Under each agency the clinical requirements covered are pharmacokinetics, pharmacodynamics, clinical efficacy, clinical safety, extrapolation to other indications, pharmacovigilance, risk management plan*

A. Literature Search – Biosimilar Expertise

USFDA - US

The Center for Biologics Evaluation and Research (CBER) is the center within FDA that regulates biological products for human use under applicable federal laws, including the Public Health Service (PHS) Act and the Federal Food, Drug and Cosmetic (FD&C) Act. The CBER protects and advances the public health by ensuring that biological products are safe, effective and available to those who need them as well as providing the public with information to promote the safe and appropriate use of biological products. Federal law defines the procedures for the CBER to establish advisory committees (USFDA, 2018c) which may further be divided into panels and

must be renewed every two years (USFDA, 2018d). As of 2021 the FDA has 47 advisory committees.

EMA - Europe

The EMA has seven scientific committees and a number of working parties and related groups which conduct the scientific work of the Agency - Committee for Medicinal Products for Human Use (CHMP), Pharmacovigilance Risk Assessment Committee (PRAC), Committee for Medicinal Products for Veterinary Use (CVMP), Committee for Orphan Medicinal Products (COMP), Committee on Herbal Medicinal Products (HMPC), Committee for Advanced Therapies (CAT) and Paediatric Committee (PDCO) (EMA, 2013). The committee's evaluation of marketing-authorisation applications submitted through the centralised procedure provide the basis for the authorisation of medicines in Europe. To carry out a scientific assessment, usually a committee appoints a rapporteur to prepare an assessment report, which the committee will consider and eventually adopt as part of a scientific opinion or recommendation. For certain procedures, a 'co-rapporteur' also prepares an assessment independently from the rapporteur. An assessment team supports the rapporteur and co-rapporteur with necessary expertise and resources. The EMA secretariat provides technical, scientific and administrative support for each assessment. Rapporteurs and co-rapporteurs can establish multinational assessment teams by including experts from other Member States as well as their own. This is intended to mobilise the best expertise for medicines evaluation regardless of where experts are geographically based. A peer-review process provides additional quality assurance of certain scientific assessments. EMA publishes the dates, agendas, minutes and outcomes of committee meetings on its website. In addition, EMA publishes information on the medicines evaluated by its scientific committees at various stages of the regulatory process, including public versions of scientific assessment reports and public-friendly information for non-experts (EMA, 2021b).

BRDD - Canada

The directorate contains the following centres and supporting offices: Centre for Biologics Evaluation, Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics, Centre for Regulatory Excellence, Statistics and Trials, Office of

Policy and International Collaboration, Office of Quality and Information Management and Office of Business Integration. The Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics (CERB) is responsible for the regulatory and scientific evaluation of radiopharmaceutical drugs and a wide range of biologic products including biotechnology-derived products such as monoclonal antibodies, cytokines, hormones and enzymes, that are made by manipulating living organisms. The CERB evaluates the quality data (chemistry and manufacturing) and clinical data for these products at the pre-market application stages, and quality data for clinical trials involving them (BRDD, 2021).

TGA - Australia

The TGA has seven statutory expert committees to obtain independent advice on scientific and technical matters - Advisory Committee on Biologicals (ACB), Advisory Committee on Chemicals Scheduling (ACCS), Advisory Committee on Complementary Medicines (ACCM)), Advisory Committee on Medical Devices (ACMD), Advisory Committee on Medicines (ACM), Advisory Committee on Medicines Scheduling (ACMS), Advisory Committee on Vaccines (ACV). The majority of committee members are appointed by the Minister (some specific members are determined by the relevant State and Territory jurisdictions) and must have expertise in relevant clinical or scientific fields or appropriate consumer health issues. The advice provided by these committees is an important element in the regulatory functions of the TGA and while a TGA delegate considers this information when making a regulatory decision under the *Therapeutic Goods Act 1989* , they are not obliged to follow it. Information about advice provided by a committee becomes available in Australian Public Assessment Report (AusPAR) (TGA, 2021a).

Swissmedic - Switzerland

The Swiss Agency for Therapeutic Products is involved in the entire life cycle of a medicinal product because of its mandated areas of responsibility in the sectors of licensing and the authorisation and monitoring of medicinal products. In scientific matters, Swissmedic obtains specialist advice from the Swissmedic Medicines Expert Committees (SMEC). These consist of the Human Medicines Expert Committee (HMEC) in the case of medicinal products for human use and the Veterinary Medicines

Expert Committee (VMEC) where veterinary medicinal products are involved. The members of both bodies are appointed by the Agency Council of Swissmedic. The SMEC support Swissmedic by providing expert reports and advice on the scientific assessment of documentation relating to the authorisation, market surveillance and approval of medicinal products. They perform these activities by answering specialised questions posed both in relation to and independently of pending cases. On the basis of Art. 67 para. 1 Therapeutic Products Act (TPA) and the implementing provisions of Art. 68 para. 1 let. e Therapeutic Products Ordinance (TPO), the Agency publishes a SwissPAR summary evaluation report for all human medicinal products with a new active substance, for which a decision to approve or reject authorisation has been issued. The Federal Expert Commission for Radiopharmaceuticals (ECRP) assesses applications for the authorisation and approval of radiopharmaceuticals. Companies that manufacture or distribute medicinal or transplant products in Switzerland (manufacturing, wholesale, import, export and trade in foreign countries) require an establishment licence. Swissmedic issues this licence on the basis of a successful inspection or other evaluation (Swissmedic, 2020a).

B. Literature survey- Biosimilar Approval Process

USFDA

The Congress, through the Biologics Price Competition and Innovation Act (BPCI Act) of 2009, created an abbreviated licensure pathway for the biosimilars as a way to provide more treatment options, increase access to lifesaving medications, and potentially lower health care costs through competition. All new marketing applications for products subject to licensure under the PHS Act are handled as BLAs. A signed Form FDA 356h should be submitted with all BLA/NDA-related applications and correspondences to CBER. Review assessment and its documentation starts when the application is received and progresses throughout the review timeline. Before submitting a BLA, applicants should identify a review committee and arrange a meeting with the FDA and also should schedule a bioresearch monitoring inspection, so as to take into consideration the schedule and the needs of an advisory committee. The Mid-Cycle Meeting provides the status of the review and covers up informative requests (IRs) regarding additional information and Discipline Reviews (DR) to convey information about deficiencies. The Late-Cycle Meetings provide the FDA with an

opportunity to proactively communicate its interim assessment and major deficiencies in the BLA. The Wrap-up Meeting is conducted after 8 months of the submissions and it aims at finding resolutions for outstanding issues if any. Also, it triggers the necessary Regulatory action to be taken. Once the complete review of the BLA is finished, the committee will meet and identify any issues, agreements, and other commitments. However, if the FDA approves the BLA, it will issue an approval letter which certifies that the biological product is safe, pure and potent, and the manufacturing facilities are compliant. Under normal circumstances product lot(s) should be available for distribution at the time of approval of most BLAs. Exceptions will be made on a case-by-case basis (CBER, 2020b). For products subject to the Biosimilars User Fee Amendment (BsUFA) Programs, the CBER Review Committee Members and the applicant may agree at the pre-submission meeting on minor application components that are allowed to be submitted not later than 30 calendar days after receipt of the original submission of the application that include stability and clinical safety updates. Incomplete submission of an application, including failure to provide agreed upon information within 30 days of receipt of the application, will be subject to a refuse-to-file (RTF) decision (SOPP 8404: Refusal to File Procedures for additional information) (CBER, 2020a). There are also provisions for fast track, breakthrough therapy, priority review, accelerated approval, and/or rolling review. For products subject to BsUFA Programs, the review timeline begins upon the acceptance of the original application submission for filing, no later than 60 calendar days from the date that CBER receives the application. A Reviewer Report that summarizes substantive issues copied from the primary review memorandum and a proposed plan to address these issues must be provided by email to the Regulatory Project Manager (RPM) in advance of the meeting.

EMA

The EMA evaluates biosimilars according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines approved in the EU. The EMA's scientific committees evaluate the marketing authorisation applications for the majority of biosimilar medicines, with support from the Biologics Working Party and the Biosimilars Working Party. Applicants preparing to request marketing authorisation for a biosimilar medicine via EMA should follow the Agency's procedural

advice for the centralised authorisation of biosimilar medicines. The EMA launched a tailored scientific advice pilot project in February 2017 to support the development of new biosimilars. The tailored procedure advises developers on the studies they should conduct, based on a review of the quality, analytical and functional data they already have available. The pilot is open to all types of biosimilars and includes a pre-submission meeting to review the suitability of the data package. Marketing authorisation applications for a similar biological medicinal product should follow the structure of the CTD format. The role of EMA is to make a recommendation to the European Commission which then takes a final legally binding decision on whether the medicine can be marketed in the EU. This decision is issued within 67 days of receipt of EMA's recommendation. The Commission is thus the authorising body for all centrally authorised products (EMA, 2021c).

BRDD

Health Canada, the federal regulatory authority evaluates the safety, efficacy, and quality of drugs available in Canada. Pre-submission or pre-application meetings (face to face or teleconference) are usually required to be requested by sponsors prior to filing a submission/application to discuss the data in support of the proposed submission/application by the sponsor with the agency. Electronic documents should be provided in electronic common technical document (eCTD) format. Sponsors should provide a note to reviewers indicating the location and organization of the similarity assessment. The biosimilar sponsor is encouraged to consult the agency for further guidance. Biosimilar biologic drugs, like all new drugs, are subject to Part C, Division 8 of the Food and Drug Regulations for authorization and oversight. Submissions for Biosimilar Biologic drug products should be filed as a New Drug Submission (NDS)/ Supplement to New Drug Submission (SNDS) and have the same performance standards as the corresponding NDS/ SNDS. The target time for review of a biosimilar is the same as that for an NDS. During the processing period, Office of Submissions and Intellectual Property (OSIP) assigns a control number and Dossier ID (only when applicable) to the submission/application, verifies the eCTD structure and other administrative and patent related information and the package can be placed in any of these administrative holds- Process Hold – Initial; Cost Recovery Hold, Patent Form V Hold, or Data Protection Refused Hold. When the hold is resolved or

the initial information package is considered administratively complete, the information package becomes a submission/application, and the appropriate review Centre/Bureau/Office is notified that the submission/application has been processed. A Screening Acceptance Letter (SAL) or Screening Rejection Letter (SRL) might be sent to the sponsor if the application is deficient. Once SAL is received (Health Canada, 2021), the scientific review is carried out and the agency can issue Clarification Request (CR) to the sponsor with defined response time. Upon satisfactory clearance of the CRs, and completion of a review, a decision (either negative or positive) is informed to the sponsor.

TGA

The registration process consists of eight phases with eight milestones, allowing effective planning and tracking by the TGA and applicants. Each phase has a milestone that must be completed before commencement of the following phase. This approach allows effective and transparent management of resources and timelines for all applications (TGA, 2021b).

1 - Pre-submission (MS1)- Outcome of pre-submission planning sent
2 - Submission (MS2)- Outcome of application consideration sent
3 - First round assessment (MS3)- Outcome of first round assessment and section 31 request for information or documents sent
4 - Consolidated section 31 request response (MS4)- End of section 31 request response period
5 - Second round assessment (MS5)- Outcome of second round assessments sent
6 - Expert advisory review (MS6)- Outcome of expert advisory committee review sent
7 - Decision (MS7)- Decision made by delegate
8 - Post-decision (MS8)- Administrative and regulatory activities complete

Each phase has established timeframes. To facilitate management by milestones, all applications received in a given intake will proceed as a group through the phases and milestones, a process known as 'batch processing'. Should a dossier not meet the regulatory requirements, it will be considered 'not effective' and will not be accepted for evaluation. Pre-submission meetings may be requested where appropriate - the pre-submission phase does not replace the opportunity for applicants to conduct face-

to-face discussions with the TGA regarding aspects of their proposed application. Pre-submission meetings may occur at any stage prior to PPF lodgement.

Swissmedic

Medicinal products may only be distributed in Switzerland if they are authorised by Swissmedic. Submissions for authorisation applications can be submitted to Swissmedic in the eCTD and eDok formats and on paper, either via the Swissmedic portal or by post. Within the framework of the authorisation procedure, Swissmedic assesses the quality, safety and effectiveness of the medicinal product in question on the basis of the comprehensive scientific documentation that is submitted. If the criteria for authorisation are fulfilled, Swissmedic grants the marketing authorisation, specifies the method of sale (on prescription only/dispensing point) and approves the information for healthcare professionals and the patient information. From 2019, it has been possible to use Art. 13 TPA, if the biosimilar is authorised by USFDA or EU and also fulfills the as in the guidance document “Authorisation in accordance with Art. 13 TPA” (e.g. documents not more than five years old, etc.; see also Art. 17 of the Therapeutic Products Ordinance, TPO; SR 812.212.21 and sections 1.1.3 and 4 of WL Biosimilar) (Swissmedic, 2020c). LMWH biosimilars can only be notified for authorisation in Switzerland under Art. 13 TPA if the European Commission has authorised them in a centralised procedure.

C. Biosimilar Development Criteria

Part I - Biosimilarity principles

The biosimilarity principles mainly relate to the biosimilar approach, demonstration of biosimilarity and the newer concept of a simplified approach. The critical part of the biosimilarity principle is the stepwise development of biosimilars and demonstrating similarity against a reference product by performing comprehensive comparability studies. This allows the industry to develop biosimilars in sequential manner starting from quality (characterisation), non-clinical (*in vitro* and *in vivo*) studies and clinical studies by justifying differences between the biosimilar and the RBP at each level through subsequent studies (Table 3.2).

Stringent Regulatory Authority (SRA) – A stepwise approach is followed by USFDA for demonstrating the biosimilarity of a proposed biological product, that needs to be based on *totality-of-the-evidence.* Any quality differences can be justified by preclinical or clinical studies. A standalone application based on a full development is required if the biosimilarity is not proved against the reference product in quality, non-clinical and clinical comparative studies (CDER & CBER, 2015a). The EMA applies the fundamental guideline "similar biological medicinal products, CHMP/437/04/ Rev 1 2014", for evaluation of biosimilar applications. The agency uses the concept of "simplified approach", in which safety and efficacy is deduced based on physicochemical characteristics, biological activity/potency and PK/PD profile of the reference and biosimilar product *in lieu* of confirmatory clinical trials. Such an approach needs prior discussion with the regulatory agency (EMA, 2015). For claiming the product to be a biosimilar to the RBP, the agency requires posology, route of administration to be same as the RBP and also accepts variation in strength, pharmaceutical form and formulation with appropriate justification. Also, low impurity profile, lower immunogenic response in comparison with RBP are accepted for claiming similarity with the RBP. Companies might use technical advice or consultation on scientific matters by discussing with the agencies through formal meetings (CDER & CBER, 2018a; CDER & CBER, 2018b). In addition to the step-wise approach as defined by EMA and USFDA, WHO indicates the need for safety data for differences that are not explained in detail in the guidelines (WHO, 2013).

ACSS Consortium – BRDD, Canada also follows a stepwise approach, similar to USFDA, for demonstrating biosimilarity and the fact sheet for 'Biosimilar biologics drugs' (Health Canada, 2017) clearly indicates the differences in the type of data required to support biosimilar authorisation and a stand-alone biologic drug. The fundamental guidelines published by the TGA, biosimilar medicines regulation version 2.2, April 2018 and Swissmedic, HD Guidance document – Authorisation biosimilar HMV4, January 2020 (TGA, 2018; Swissmedic, 2020a; Swissmedic, 2020b) are based on the framework of the EMA guidelines and other relevant guidelines issued by issued by the Committee for Medicinal Products for Human Use (CHMP) or ICH. Legally, biosimilar applications are not eligible for simplified authorisation as per Art. 12 para. 5 let. d Licensing of Therapeutic Products (TPLO), however in certain justified cases, the requirements can be reduced by Swissmedic.

Critical evaluation of these guidelines reveals that a stepwise development approach and comprehensive comparability study requirements are uniform across EMA, USFDA, WHO, BRDD, TGA and Swissmedic. Extrapolation of indications, interchangeability, switching, substitution, paediatric research, labelling and biosimilar naming can be evaluated based on consultation with the agency. Table 3.2 indicates biosimilarity criteria and expectations defined by EMA, WHO, USFDA, BRDD, TGA and Swissmedic (EMA, 2015; CDER & CBER, 2015a; CDER & CBER, 2015b; Health Canada, 2017; WHO, 2017a; TGA, 2018; Swissmedic, 2020b).

This list of biosimilarity criteria will eventually become part of a master checklist (as in Chapter 4) for comparing requirements of BRICS-TM agencies against these mature/ advanced agencies and will form the basis for creation of the questionnaire.

Table 3.2 Biosimilarity principles

	EMA (EU)	WHO	USFDA (USA)	TGA (Australia)	BRDD (Canada)	Swissmedic (Switzerland)
Terminology	Similar biological medicinal product	Similar biological product	Biosimilars	Biosimilar	Biosimilar biologic drug or Biosimilar	Biosimilar
Development approach	Stepwise approach for development	Stepwise comparability exercise(s) for quality, non-clinical and clinical studies.	Stepwise approach with intention to consider the totality of the evidence	Stepwise approach for development	Similarity is demonstrated using a step-wise approach beginning with structural and functional studies, continuing further with human clinical studies.	Stepwise approach for development
Biosimilarity approach	The biosimilarity to be proved based on comprehensive comparability studies.	High similarity is based on totality of evidence and not on individual variable or physico-chemical tests.	FDA intends to consider the totality of the evidence	As per EMA guidelines	n/d	Totality of evidence
Demonstration of biosimilarity with reference product	Clinical data required to compare clinical performance and difference in previous steps, not to justify difference between Quality attributes	The difference between SBP and RBP at any steps to be investigated, explained and justified with additional safety data.	Assessment of effects due to differences but not to independently establish the safety and effectiveness	As per EMA guidelines	n/d	Agency decides the extent to which the data from earlier versions of the biosimilar are relevant for the proof of biosimilarity.

	EMA (EU)	WHO	USFDA (USA)	TGA (Australia)	BRDD (Canada)	Swissmedic (Switzerland)
Full or partial application	If biosimilarity cannot be proved then standalone full development of product	Biotherapeutics that are not shown to be similar could be licensed through the usual processes, using more extensive nonclinical and clinical data sets or full licensing applications.	If the reference product or the proposed product cannot be adequately characterised with state-of-the-art technology, the application for the proposed product may not be appropriate for submission under section 351(k) of the PHS Act; and the sponsor should consult FDA for guidance on the appropriate submission pathway.	n/d	n/d	n/d
Simplified Approach	Reduced confirmatory clinical trial (Smaller clinical trial if bioassay is known to be clinically relevant or number of patients may vary depending	The reduction of clinical data is dependent on two issues: complexity of the product and the performance of the analytical methods. In general, confirmatory safety and efficacy studies	Comparative human PK and PD studies and clinical immunogenicity assessment expected. An additional comparative clinical study or studies would be needed in	n/d	n/d	n/d

	EMA (EU)	WHO	USFDA (USA)	TGA (Australia)	BRDD (Canada)	Swissmedic (Switzerland)
	upon the endpoints) can be performed based on regulatory authority opinion, Safety and efficacy can be deduced based on physicochemical characteristics, biological activity/ potency and PK/PD profile of reference and biosimilar product.	are not always necessary.	case of residual uncertainty.			
Applicable guideline	Guideline on similar biological medicinal products. CHMP/437/04 Rev 1	Guidelines on evaluation of similar biotherapeutic products (SBPs), Annex 2. WHO TRS No. 977, 2013	Scientific considerations in Demonstrating Bio similarity to a Reference Product Guidance for Industry: April 2015	Biosimilar medicines regulation, version 2.1, February 2018	Fact Sheet: Biosimilars (2017-08-03)	HD-Guidance document Authorisation biosimilar HMV4
Regulatory framework	Regulation (EC No. 726/2004) via centralised procedure to EMA	WHO Prequalification Programme	Abbreviated licensure pathway in section 351(k) of the PHS (Public	Therapeutic Goods Act, 1989	Biosimilars are regulated as new drugs under the Food and Drugs Act and the Food and Drug	HMV4

	EMA (EU)	WHO	USFDA (USA)	TGA (Australia)	BRDD (Canada)	Swissmedic (Switzerland)
			Health Services) Act		Regulations. Health Canada's Biologics and Genetic Therapies Directorate (BGTD) regulates biosimilars in collaboration with the Regulatory Operations and Regions Branch (RORB) and the Marketed Health Products Directorate (MHPD).	
Posology	Same as RBP	n/d	Same as RBP	Same as RBP	n/d	Same as RBP
Route of administration	Same as RBP	Same as RBP	Same as RBP	Same as RBP	Same as RBP	Same as RBP
Strength, Pharmaceutical form, Formulation	Variation acceptable with justification, no compromise with safety. Molecularly and biologically same active ingredient	Change acceptable without impact on Q,S,E	Strength can be different, Pharmaceutical form must be same as reference product, Formulation can be different, Inactive part can be different, acceptable with clinically no meaningful difference	Variation acceptable with justification, no compromise with safety. Molecularly and biologically same active ingredient	Strength and form should be same as RBP, not specified for formulation	Strength and form should be same as RBP, not specified for formulation

	EMA (EU)	WHO	USFDA (USA)	TGA (Australia)	BRDD (Canada)	Swissmedic (Switzerland)
Improved efficacy	Not suitable	Not suitable	n/d	Not suitable	n/d	Not suitable
Improved safety	Low impurity profile or less immunogenicity, acceptable	Low impurity acceptable	n/d	Low impurity profile or less immunogenicity, acceptable	Highly similar or same level (% of impurities)	Low impurity profile or less immunogenicity, acceptable
Extrapolation of indications	Acceptable with justification	Acceptable under certain circumstances	Acceptable with scientific justification, recommended to perform comparability studies in sensitive condition and studied under post-marketing surveillance	Acceptable with justification	Acceptable with justification	Acceptable with justification
Biosimilarity post approval	No need to prove biosimilarity	n/d	n/d	n/d	n/d	No need to prove biosimilarity
Interchangeability, Switching and Substitution	To be regulated by member states and not EMA	To be defined by NRA	Interchangeability approved subject to clinical result is same as reference product in any given patient and proved for all licensed conditions of use	n/d	Interchangeability authorised by provinces and territory.	Interchangeability decision made exclusively by the prescriber or attending physician

	EMA (EU)	WHO	USFDA (USA)	TGA (Australia)	BRDD (Canada)	Swissmedic (Switzerland)
Pediatric research	Paediatric Investigational plan and/or pediatric waiver/deferral submission not applicable for biosimilar	n/d	Extrapolation of efficacy in paediatric population is permitted under PREA subject to conditions are met	n/d	n/d	Paediatric Investigational plan and/or pediatric waiver/deferral submission not applicable for biosimilar

n/d- Not defined

Part II - Reference product selection

A reference product is the single biological product, already approved in their own country/ICH aligned countries, against which a proposed biosimilar product is compared. A reference product is approved based on a complete evaluation i.e., quality, safety and efficacy. A proposed biosimilar product is compared to and evaluated against a reference product to ensure that the product is highly similar and has no clinically meaningful differences. An applicant needs to perform side-by-side quality/characterisation analysis to prove similarity of the proposed biosimilar product with the reference product. Most of the criteria for reference product selection remains common across agencies (Table 3.3), and are summarised as follows:

- Sourcing of reference products from the local country is mandatory. In certain cases, sourcing outside the territory is allowed subject to fulfilment of certain stipulated conditions.
- Reference products must be approved in the country of origin and marketed in the country of intended approval, with a full registration dossier i.e., quality, safety and efficacy data.
- Identity of the reference product i.e., brand name, pharmaceutical form, manufacturing site details, expiration details and other labelling requirements are mandatory to submit as part of the application.
- Any change of reference product during development is to be done during the early stage of development and based on scientific consultation with the agency.
- It is expected that multiple lots of reference product may be used during development, however no specific number of lots are pre-defined in the guidelines.

SRAs- As per USFDA guidelines, to successfully achieve biosimilar medicine approval under section 351(k) of the PHS act, sponsors are advised to use US licensed reference products for development, mandatorily for quality, PK and PD studies (CDER & CBER, 2018a). However, prior scientific advice from the agency is required to use non-US licensed reference products for animal or clinical studies (CDER & CBER, 2015b) along with bridging studies (CDER & CBER, 2018a). Similar to USFDA, the EMA also requires the reference product to be approved in the European Economic Area (EEA), as per article 8 of 2001/83/EC and permits the use of non-EEA reference product from ICH countries for non-clinical and clinical studies supported by

bridging studies. The agency will consider reference products manufactured at a different location as the same if it is authorised under a single licence for global distribution (EMA, 2015). The WHO leaves the decision to the NRA to define criteria for the reference product selection (WHO, 2013).

ACSS - TGA has explicitly indicated prerequisites of reference product criteria for development of a biosimilar. In this, the biological medicines, designated as "Australian Reference Product (ARP)" must be registered based on full quality, safety and efficacy data along with substantial period of commercialisation of the reference product with sufficient volume use of the marketed product resulting in enough safety and efficacy data for the approved indication. The agency also allows the applicant to use a non-authorised global reference product (preferably EMA or USFDA approved) in certain clinical and *in vivo* non-clinical studies supported by bridging study needs with an ARP. In case the applicant has utilised a global reference product which has a single manufacturing site for global distribution, a bridging study can be waived, subject to submission of evidence for the single manufacturing site (TGA, 2018). In accordance with Article 11 Therapeutic Products Act (TPA) of Swissmedic, the reference product must be authorised in Switzerland on the basis of complete documentation. The reference product which is used as part of a comprehensive comparability study for the development of a biosimilar is designated as the "Comparator Product" and should be authorised by Swissmedic, EU or USFDA and available in the market. In addition, as per Article 16, Therapeutic Products Ordinance (TPO), Swissmedic recognises Australia, European Free Trade Association (EFTA) member states, Japan, Canada, New Zealand and Singapore for sourcing of comparator products, complemented by additional bridging studies. It is explicitly indicated that biosimilar medicines cannot act as reference medicine products (Swissmedic, 2020b). The expectations from BRDD on the reference product are aligned with TGA. The agency further allows non-Canadian reference biologic drug from ICH countries, however, requires bridging studies on analytical and PK/PD comparison for biosimilars (Health Canada, 2016).

Thus, the requirements for reference product selection criteria are aligned between the SRAs and mature agencies of ACSS. Table 3.3 indicates reference product selection criteria and expectations defined by EMA, WHO, USFDA, BRDD, TGA and Swissmedic.

Table 3.3 Reference product selection criteria in established regulatory agencies

Reference product selection	EMA (EU)	WHO	USFDA (USA)	TGA (Australia)	BRDD (Canada)	Swissmedic (Switzerland)
Selection of Reference product	Must be approved in EEA as per Article 8 of 2001/83/EC, as amended	Approved with full registration dossier regarding quality, efficacy, safety	FDA licensed single reference product	Must be registered in Australia based on full quality, safety and efficacy data ('the Australian reference medicine'), marketed in Australia for a substantial period, volume of marketed use	Approved in Canada	Must be registered in Switzerland and authorised based on complete documentation. Designated as "Comparator product" if used in comprehensive comparability study to prove quality, safety and biological activity of biosimilar product.
Non-authorized Reference product usage	Approved by ICH countries, can be used in certain non-/clinical, need to prove sameness between non-/ EEA RBP	Commercially available in well-established regulatory agency's market	Can be used for *in vivo* and clinical studies, bridging data with US reference product, prior consultation with FDA	Allows to facilitate global development, can be used in certain clinical and *in vivo* non-clinical studies.	Non-Canadian reference biologic drug from ICH guidelines adopting countries and Canada equivalent standards for comparability, evaluation and post-marketing surveillance	Allows non-authorised reference product from Swissmedic recognised countries.

Reference product selection	EMA (EU)	WHO	USFDA (USA)	TGA (Australia)	BRDD (Canada)	Swissmedic (Switzerland)
Acceptable sourcing countries for non-authorised reference product	ICH countries	Well-established regulatory market	Well-established regulatory market	USFDA and EMA	ICH countries	As per Art. 16 para 4, comparator product can be used from Australia, EU and EFTA member states, Japan, Canada, New Zealand, Singapore and USA
Bridging	To be provided in case of using non-EEA product	n/d	Non-US licensed product can be used for animal and clinical studies, must use US licensed product for analytical studies, PK and PD study one each, adequate bridging data justifying clinical trial design supporting conditions of use and patient population, relationship between non-licensed, component manufacturers if	Bridging study with Australian Reference Product, study can be waived, if evidence submitted for single manufacturing site of non-authorised reference product for global distribution	Analytical and PK/PD comparison for all product	Complementary studies with comparator medicinal product and suitability of the reference product need to be demonstrated.

Reference product selection	EMA (EU)	WHO	USFDA (USA)	TGA (Australia)	BRDD (Canada)	Swissmedic (Switzerland)
			any and BLA licence holder, relevance of GMP issuing authority for non-licensed product			
Identity of Reference product	n/d	Should be identifiable	n/d	Not defined but referred to number of EMA's and ICH comparability guideline	The same reference biologic drug should be used throughout the studies supporting the Q,S,E of the product	n/d
Sameness of Reference product	Non-EEA product can be used together with EEA product for defining QTPP during development, analytical and clinical PK/PD studies between non-EEA, EEA and proposed biosimilar, Prior consultation with agency	The same RBP should be used throughout the comparative quality, nonclinical, and clinical studies	n/d	Not defined but referred to number of EMA's and ICH comparability guideline.	Possible to use more than one reference biologic drug in clinical studies, sourced from non-Canadian markets	If additional comparator product from the EU or US market is used for a clinical efficacy trial, a three-way bridging study between the biosimilar

Q, S, E: Quality, Safety, Efficacy; n/d: Not defined

Part III - Comparability studies

Comparability is crucial for the development of a proposed biosimilar in proving similarity to the reference product. It involves side by side comparison of the proposed biosimilar product against a reference biologic product starting from comparative quality studies at drug substance and drug product stages, followed by comparative non-clinical and clinical studies (WHO 2013; EMA, 2015; Health Canada, 2019; CDER & CBER, 2019a).

Quality

The first step of comparability starts with the initiation of a comparative quality study of the proposed biosimilar with the reference product. The quality characterisation part comprises physicochemical characterisation i.e, structure, immunological properties, biological activity, purity impurity and contaminants, cell lines, quantity, specification, manufacturing process, overages and compatibility studies (WHO, 2013; EMA, 2015). Table 3.4 shows a list of studies required by the WHO for comparability studies for SBP development (WHO, 2013).

Table 3.4 Comparability criteria for SBP development by WHO

Comparability studies	Criteria
1. Physicochemical characterisation	a) Structure
	b) Immunological properties
	c) Biological activity
	- Purity, impurity and contaminants
	- Expression system/cell lines
	- Quantity
	- Specifications
	d) Manufacturing process
	e) Overages
	f) Compatibilities
2. Non-clinical studies	*a) In vitro*
	b) In vivo
	- PK/PD studies
	- Repeat dose toxicity study
	- Immunogenicity studies
	- Local tolerance studies
3. Clinical Studies	a) Clinical PK/PD
	b) Clinical safety
	c) Clinical efficacy

PK: Pharmacokinetic; PD: Pharmacodynamic

SRAs - The EMA explicitly defines comparability requirements in quality, nonclinical and clinical segments and expects applicants to follow a stepwise development approach (EMA, 2015). The CBER division of USFDA has released a draft document related to comparative analytical assessments and quality considerations for therapeutic protein biosimilar development. This draft guidance details on the important scientific considerations to support demonstration of biosimilarity, with detailed guidance on nine factors to be considered during comparability studies (CDER & CBER, 2019a).

ACSS - The TGA has adopted EMA guidelines for quality, non-clinical and clinical data requirements in establishing comprehensive comparability studies with the reference biological product (TGA 2018) and refers to the ICH Q5E pertaining to “Comparability of Biotechnological/Biological products” for quality comparison. Swissmedic primarily looks for scientific evidence pertaining to physicochemical and biological characterisation between the proposed biosimilar and the comparator product (Swissmedic, 2020b). In addition, comparative preclinical and clinical data along with critical evaluation of totality of evidence is expected.

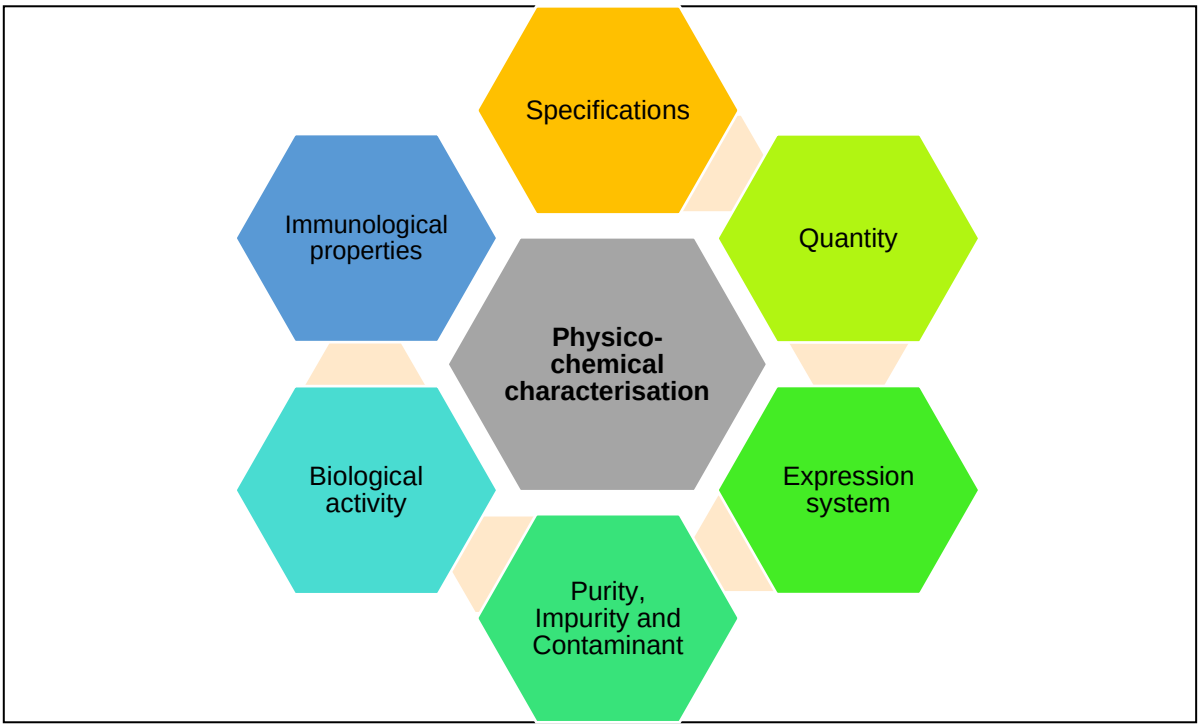
Once quality comparison indicates molecular similarities between the proposed biosimilar and reference product, it gives the essential rationale to predict a similar profile in terms of clinical safety and efficacy. Thus, both the SRAs and the mature agencies are aligned in terms of requirements of comprehensive comparability studies as part of the biosimilar development program. In general, agencies expect quality studies performed in line with ICH Q5E (ICH, 2004).

Physico-chemical characterisation

SRAs - In the US, it is expected that applicants use modern and highly qualified methods and techniques to prove structural similarities using side-by-side comparison of active substances, excipients and formulated products. Sponsors should conduct extensive structural characterisation of both the proposed product and the reference product in multiple representative lots to understand the lot-to-lot variability of both products in the manufacturing processes. Lots used for the analyses should support the biosimilarity of both the clinical material used in the clinical study(ies) intended to support a demonstration of biosimilarity, and the to-be-marketed proposed product, to

the reference product (CDER & CBER, 2015a). The physicochemical requirements for a biosimilar as defined by EMA (EMA, 2014a) is indicated in Figure 3.2.

Figure 3.2 Parameters for Physicochemical characterisation of biosimilar product



While performing characterisation of a reference product containing interfering excipients (like albumin), appropriate extraction methods are expected to be used, not modifying the structure of the biosimilar product. The WHO expects physico-chemical interactions between the active substance and excipients to be investigated and the primary structure of the Similar Biologic Product (SBP) to the RBP. Extensive characterisation studies need to be performed on the proposed biosimilar to demonstrate a high level of equivalence (WHO, 2013).

Structure

SRA - The USFDA follows ICH Q6B (ICH, 1999) and has elaborated the requirement of characterisation of the biosimilar product and its variants, including different isoforms and those resulting from post translational modifications. The PEGylation characterisation is unique to USFDA requirements. Appropriate physicochemical methods i.e. sodium dodecyl sulfate polyacrylamide (SDS-PAGE), isoelectric focusing

(IEF), high-performance liquid chromatography (HPLC), mass spectrometry (MS) are required to be used. Binding assays to be performed and epitope should be defined biochemically. The quantification of antibody binding activity needs to be performed by a combination of tests like affinity, avidity and immunoreactivity. Though orthogonal methods are necessitated, validated methods are not mandated during characterisation if highly sensitive tests with reproducible results are used. Evaluation of differences in the 3D confirmation is required in terms of potential effect on function and stability (CDER & CBER, 2015b). The comparative physicochemical characterisation requirements i.e., primary and higher order structure identification including class and subclass determinations (for mAbs), detailed characterisation of primary structure and description for structural elements such as active sites, receptors, ligand binding sites and features for signal transduction is required by EMA (EMA, 2016b). EMA guidelines further specify requirements pertaining to amino acid sequencing, as well as conformation of amino and carboxy terminal. The intra and inter disulfide bridges to be determined along with their integrity and mismatches with respect to the reference medicinal products. The free sulfhydryl groups are to be identified as well. The carbohydrate content, its structure and oligosaccharide pattern are to be identified and confirmed. The glycosylation site is required to be analysed for its presence or absence and characterisation to be done. Extensive glycan structure characterisation for mannosylation, galactosylation, fucosylation and sialylation with distribution of main glycan structure to be carried out (EMA, 2015; EMA, 2016b). Additional characterisation with respect to *in vivo* disposition of active substance while administering the product and interactions between active substance and excipients would be necessary. Although the WHO has defined primary and higher order structure characterisation, specific mandates pertaining to class and sub-class determination and kappa and/or lambda chain confirmation remain unspecified, as is the case with the EMA. The carbohydrate structure, glycosylation pattern and glycan evaluation requirement are the same as those of the EMA. WHO does not refer to structural elements, *in vivo* disposition, interactions, amino acid sequencing with variability at N- and C- terminal, disulfide bridges and free sulfhydryl group requirements (WHO, 2013). Table 3.5 presents differences between EMA and WHO for physicochemical characterisation requirements. The same will become the basis for creating a master checklist for defining further the questionnaire for agencies.

ACSS- The requirements of primary and higher order structure characterisation from TGA and Swissmedic are in line with the EMA (TGA, 2018; Swissmedic, 2020b). The HC/BRDD agency advises reference to ICH Q5E pertaining to comparability of biotechnological/biological products subject to changes in their manufacturing process. In line with ICH Q5E, higher order (secondary, tertiary and quaternary) structures are to be determined for proving a suitable comparability exercise for the proposed biosimilar. The requirements on amino acid sequencing, disulfide bridges, characterisation and carbohydrate content are not specified by the agency (Health Canada, 2016).

Immunological properties

SRA - Among biosimilars, the immunological properties are very significant for mAbs. Comparative immunological studies including antigen binding assay, cytotoxicity and cross-reactivity evaluation, epitope characterisation, identification of complementarity region is recommended by the EMA. It is further stated that evaluation of binding and activation and/or effector functions should be evaluated even though the proposed biological activity does not demand such function (EMA, 2016b). The WHO spells out the expectations pertaining to binding assays in guidelines without further detail (WHO, 2013). USFDA requirement is in line with WHO immunological properties (CDER & CBER 2015b).

ACSS - HC/BRDD, TGA and Swissmedic are aligned with the EMA on conduct of comparative characterisation (Health Canada, 2017; TGA, 2018; Swissmedic, 2020b). In Health Canada, the requirements (i.e., the antigen binding assay and epitope requirements for mAb biosimilars) are aligned with EMA guidelines (Health Canada, 2017).

Biological activity

The biological activity is generally defined as the ability of a product to give biological results/effects.

SRA - For USFDA, *in vitro* and *in vivo* assays are required without further recommendation on product effector functions (CBER, 1997). However, EMA expect appropriate *in vitro* assay(s) for assessment of biological activity and needs detailed justification for conduct of *in vivo* assays. The mechanism of action including its

importance and consequences of product effector functions (antibody-dependent cell-mediated cytotoxicity (ADCC), cytotoxic properties (e.g, apoptosis), complement binding and activation ability, other effector functions i.e., Fc- gamma receptor binding activity and neonatal Fc- receptor (FcRn) binding activity) with respect to safety and efficacy of the product calls for discussions. The biological studies are expected to be performed against the reference biological product and must be comparative in nature (EMA, 2016b). WHO expects appropriate assays to be performed; however, there is no clarity with respect to *in vitro* or *in vivo*. Similar to the EMA, the effector functions need to be confirmed by appropriate assays. But it is unclear whether such tests are required, in the case where the related mechanism of action does not impact safety and efficacy (WHO, 2013).

ACSS - In HC/BRDD, relevant functional assays are indicated to be performed but details on the assays remain undeclared (Health Canada, 2016). TGA and Swissmedic remain consistent with EMAs approach (TGA, 2018; Swissmedic, 2020b).

Purity, Impurity and Contaminants

Biosimilar products that can express heterogeneity, like mAbs (C-terminal lysine processing, N-terminal pyroglutamate, deamidation, oxidation, isomerisation, fragmentation, disulfide bond mismatch, N-linked oligosaccharide, glycation) results in different molecular entities. To identify purity or impurity profiles of such biosimilar products, the orthogonal methods which include physicochemical property determinations need to be performed.

SRA - EMA expects the formation of aggregates, sub-visible and visible particulates need investigation to be closely monitored during batch release and stability studies. Multimers and aggregates need to be characterised appropriately. Process related impurities such as host cell DNA, cell culture residues, downstream processing residues demand identification as well as qualitative and/or quantitative evaluation. Contaminants (outside the scope of the manufacturing process) are expected to be controlled or restricted. Appropriate additional testing is required to be done if pro-inflammatory contaminants are suspected (EMA, 2016a). For USFDA, additional concerns for biological products are the risk of impurities and contaminants due to usage of living systems for manufacturing (Christl et al., 2017). It is expected that

structural heterogeneity and aggregates will be characterised. The purity and impurity tests are to be performed using orthogonal methods whereas there is need to characterise for known and potential impurities. The contaminants expectation remains in line with those of the EMA (CDER & CBER, 2015a). The WHO expectations are similar to the EMA, however use of orthogonal methods is not defined, either for purity or impurity tests. The status of non-clarity prevails for multimers, aggregates, particulates and contaminants (WHO, 2013).

ACSS - The fact sheets of BRDD/Canada demand purity testing for both the drug substance and the drug product. It also specifies identification, characterisation and biological activity evaluation of impurities, if non-relevant with reference product. BRDD expects to have a highly similar or same level (% of impurities) to comply with biosimilarity principles. The general requirement for molecular heterogeneity is stated; however qualitative or quantitative nature of methods is not specified. The requirements pertaining to multimers, aggregates and particulates are in line with those of the WHO, whereas contaminants are as per EMA requirements (Health Canada, 2017). TGA and Swissmedic are aligned with EMAs expectations (TGA, 2018; Swissmedic, 2020b).

Expression system/ Cell lines

SRA - The USFDA recommends minimising the differences between the reference product's expression construct and the one proposed for the biosimilar product; justification for differences is to be provided (CBER, 1997). Sufficient information on the expression system or monoclonal cell line information is expected, but detailed specific procedures prior to the isolation of the monoclonal cell line i.e., cell fusion, viral transformation, gene library of phage display screening, application of in silico, *in vitro* or *in vivo* technologies are not required to be described in great detail by EMA. Origin and characteristics of cell banks and parental cells need to be documented and an immortalisation approach to be defined (EMA, 2016b). For WHO, the SBP manufacturer/applicant can use a different expression system/ monoclonal cell lines than the RBP to produce a biosimilar, when the structure of the molecule and its clinical profile remain unchanged; but in-depth requirement is not specified. However, it is recommended to use the same monoclonal cell line as the RBP (WHO, 2013).

ACSS - Almost all the agencies expect the expression system or cell line similar to the RBP.

Quantity

SRA - The quantity of finished product should be determined based on appropriate physicochemical and/or immunochemical assays. The same can be determined based on biological assays subject to demonstration of correlation between quantity and biological activity (EMA, 2016b). The quantity of biosimilar product in the final presentation is determined based on biological activity and expression system (WHO, 2013). Potency must be defined based on assay(s) (CDER & CBER, 2015b).

ACSS - In HC/BRDD, the expectation of cell lines as well as depth of information required in the marketing application for a biosimilar, is yet to be spelled out. The views of BGTD/Canada for quantity determination of finished product need to be specified in the guideline (Health Canada, 2016). The TGA and Swissmedic expectations are in line with EMA.

Specifications

SRA - Specification is determined based on batch data, manufacturing experience, characteristics of the product, other controls used in the process etc. The ICH Q6B should be followed for drug substance and drug product for test selection. In general, more than one specific identity test, purity, impurities, potency and biological activity test are to be included. The glycosylation test should be performed for the products where post-translational modification could occur. Other general tests as applicable to formulations need to be covered e.g., solubility, extractable volume, bacterial endotoxin. The acceptance criteria need to be defined based on lots used in studies i.e., manufacturing consistency, non-clinical and clinical studies, stability studies and other relevant development data. The analytical method validation is to be submitted as part of the marketing authorisation application dossier. Compendial reference methods are expected to be used from the European pharmacopoeia (Ph Eur) and from the WHO. During pre-formulation studies, the stability of active substances needs to be proved by establishing degradation pathways whereas for formulation, experimental data with different quantities of suitable excipients is expected. If the product is lyophilised, then the usage of lyoprotectant must be determined for process

optimisation through an in-process stability study. Real time, real condition stability studies are required as part of routine stability studies in line with ICH Q5C (EMA, 2000; EMA, 2014a; EMA, 2016a). In USFDA, accelerated and stress stability studies under multiple stress conditions such as high temperature, freeze thaw, light exposure and agitation are required for appropriate physicochemical and functional comparison of the stability profile of the proposed product against that of the reference product. Sufficient real time and real condition data of the proposed product is to be provided in support of the shelf life (CDER & CBER, 2015a; CDER & CBER, 2015b).

The WHO expects specifications to be determined based on the manufacturer's experience with the similar biotherapeutic product (SBP) and experimental results with SBP and RBP. The tests are to be performed as per the pharmacopeia monograph plus additional tests as appropriate. The acceptance criteria are to be decided based on a sufficient number of lots and should not be wider than the variability range of the RBP during its entire shelf life. The analytical methods for characterisation should be scientifically sound and qualified but it is not necessary that they be validated, whereas for lot release validation is expected. The reference materials and standards are expected to be sourced from the WHO. Real time and stability under real conditions for the SBP is expected, whereas experimental stability data and in process stability data are not defined. It is expected to have comparative head-to-head accelerated stability studies between SBP and RBP and non-comparable stress studies. Apart from this drug product and drug substance stability studies are expected in intended and in the representative container closure system (WHO, 2013; WHO, 2017b).

ACSS - HC/BRDD indicates appropriate specifications to be chosen for the biosimilar, but further information such as determination of specifications, acceptance criteria, method of analysis and its validation and criteria for stability studies are not provided in detail (Health Canada, 2016). The TGA and Swissmedic requirements are as per ICH Q6B (TGA, 2018; Swissmedic, 2020b).

Manufacturing process

SRA - Comparative characterisation of the manufacturing process would be challenging since reference product manufacturing process detail would be confidential. However, the agency's expectation for the manufacturing process is to

produce the targeted product with a comparable molecular and quality profile. Apart from that, the process must be capable of manufacturing product of consistent quality. Appropriate in-process control parameters need to be defined at the time of process development. The platform manufacturing approach can be utilised with proper justification and evidence (EMA, 2016a). The process needs to be fully validated including validation of a viral reduction study as per ICH Q5A; also, if material of animal origin is used then TSE guidelines are to be considered. The WHO recommends to optimise the process so as to minimise differences between the SBP and RBP for reduced clinical testing and lesser impact on safety and efficacy (WHO, 2017b).

ACSS - The BRDD expects that the applicant submits the proposed comparison in the manufacturing process to the reference biologic drug, where such information is available (Health Canada, 2016). The TGA states that the process of manufacturing of the proposed biosimilar product used in clinical trials and of that in commercial distribution should be the same. In a situation where the manufacturing process changes between clinical trial and commercial distribution, an additional comparability study, involving reference biologic medicines and biosimilar product from both processes is preferred. Alternatively, the applicant can provide a link between clinical and commercial biosimilar medicines. In any case, no more than two linked studies are acceptable to the TGA, owing to difficulties in drawing a robust comparison between the reference biologic medicine and the biosimilar with evolving manufacturing processes (TGA, 2018).

Overages

Appropriate overages to be included based on variability of bioassay in *in vivo* condition.

Compatibility

It is required to perform compatibility between the biological substance and excipients. The investigation of an interaction study is mandatory if primary packing materials are different from the reference product.

Table 3.5 Comparative evaluation of physicochemical characterisation – EMA Versus WHO

	EMA	WHO
Structure		
Primary and higher order structure	Primary and higher order structure to be characterised (Class and subclass determination, chain determination)	To be characterised but not specified requirement
Amino acid	Amino acid sequencing and variability of N- and C- terminal to be confirmed	n/d
Groups and bridges	Free sulphydryl groups and disulfide bridges to be determined, integrity and mismatch of bridge to be analysed	n/d
Carbohydrate	Carbohydrate content and structure, oligosaccharide pattern to be confirmed	Carbohydrate structures to be defined
Glycosylation	Presence or absence of additional glycosylation site(s) to be confirmed, glycosylation site(s) with occupancy to be analysed	Evaluation of glycosylation pattern including site occupancy
Glycan/ Isoforms	Glycan structure to be characterised for degree of mannosylation, galactosylation, fucosylation and sialylation with distribution of main glycan structures to be determined	Comprehensive evaluation including number or type of glycans and qualitative identification in case glycan non-existent in human, analysis of glycan attached
Immunological properties (for mAbs)		
Antigen binding assay	Antigens binding assay at defined regions including affinity, avidity and immunoreactivity as feasible	Binding assays to be performed but not defined in detailed
Cytotoxicity evaluation	For unintended target tissue to be evaluated	n/d
Cross-reactivity	To be determined	n/d
CDR	To be identified	n/d
Epitope	Characterisation, biochemical identification and determination of epitope including bearing molecules	n/d
Complementary ability evaluation	Evaluation of binding and activation and/or effector functions	n/d

	EMA	WHO
Biological activity		
***In vitro/vivo* assay**	Assessment of biological activity by *in vitro*/*vivo* assay to be justified if required	Indicated as appropriate assay to be done but not defined
Product effector functions	ADCC analysis, cytotoxic properties (e.g., apoptosis), complement binding ability, Fc- gamma receptor binding activity and neonatal receptor binding ability performed in case MoA impact S and E	ADCC, binding ability to receptors (Fcɣ and neonatal Fc) to be performed, not specified if no impact of MoA on S and E, complement C1q test required, Fc- and Fab- related function to be evaluated
Purity, impurity and contaminants		
Purity	Orthogonal methods	Methods not defined
Structural heterogeneity	Qualitative and quantitative analysis to be investigated	To be investigated, identified and quantified
Multimers,aggregates and particulates	To be characterised and monitored	n/d
Impurity profile and Process-related impurities	Qualitative and/or quantitative evaluation	System- specific process impurities to be considered.
Contaminants	Controlled/additional testing to be done	n/d
Cell lines/ Expression system		
Cell lines/ Expression system	Sufficient information to be provided but detailed procedures not required	Different cell lines allowed, advised to use RBP similar system
Immortalisation approach	To be justified	n/d
Cell banks/ Hybridoma cell lines	Origin and characteristics of parental cell to be documented	n/d
Quantity		

	EMA	WHO
Basis for quantity determination	Biological assay if correlated	Biological activity and expression system
Specifications		
Specification determination	Based on number and age of lots, time of testing and types of quality attributes	Based upon the manufacturer's experience with SBP and experimental results of SBP and RBP
Test selection	As per ICH Q6B, product specific for drug substance and drug product	Pharmacopoeial monograph plus additional test
Acceptance criteria	Based on lots used in different studies (manufacturing consistency, clinical and non-clinical studies, stability studies and relevant development data)	Based on sufficient lots, should not be wider than variability range of RBP during shelf life
Validated methods for characterisation	To be submitted in dossier	Scientifically sound and qualified but not necessarily validated
Analytical methods for lot release	To be validated	To be validated
Reference materials and Standard	Ph Eur. and WHO	WHO
Accelerated stability data	Should be part of characterisation study	Accelerated degradation and stress studies (non-comparable), Comparative head-to-head accelerated stabilities studies between SBP and RBP, drug product and drug substance stability in intended and representing container closure system simultaneously
Experimental stability data	Formulation data with different quantities of excipient	n/d
In-process stability data	To be performed in-case of lyophilisation	n/d
Routine stability study	Based on ICH Q5C	Based on NRA

n/d- Not applicable; S and E- Safety and efficacy; MoA- Mechanism of action; Ph.Eur.- European Pharmacopoeia, NRA- National Regulatory Authorities

Non-clinical studies

As per the step-wise approach of demonstrating biosimilarity, non-clinical studies are to be performed before initiating clinical studies and to justify differences observed during the comparative exercise of quality and non-clinical studies. The non-clinical studies are further categorised into *in vitro* and *in vivo* studies. *In vitro* studies are performed on cell lines which can be extracted from humans and rats. Generally, hybridoma myeloma cell lines are used for *in vitro* analysis. Before analysis on any animal, it is necessary to check or qualify its safety and efficacy on cell lines. Ethical committees restrict the usage of animals for tests and hence more emphasis is on cell line analysis. Based on results obtained from *in vitro* studies, the extent to which *in vivo* studies should be performed is usually decided. The specific requirements defined by EMA, USFDA, WHO, BRDD, TGA and Swissmedic are depicted in Table 3.6.

In vitro studies

SRA - EMA recommends performing *in vitro* non-clinical studies in a step-wise manner, starting with comparative in vitro studies for binding and functional assays following which a second step of additional *in vivo* studies should be performed, if necessary. The non-clinical studies should be performed in sufficient batches showing representation with the proposed clinical trial batch. These studies should be sensitive enough to detect differences in concentration activity relationship. Binding and functional assays should include binding target antigen(s) assay, receptor binding assays (for mAbs, FcRn and complement (C1q), Fab- associated functions e.g. soluble ligand neutralisation, activation or blockade of receptor, Fc-associated functions-ADCC, CDC, complement activation, depending on the type of mAb). Although all attributes are not to be considered essential for therapeutic mode of action, still it should be studied in *in vitro* studies (EMA, 2014a). WHO is aligned with EMA on the *in vitro* study requirements (WHO, 2013). The USFDA also recommends the pharmacologic activity of protein products should be evaluated by *in vitro* functional assays such as biological assays, binding assays, and enzyme kinetics. These assays should be comparative thus they can provide evidence of similarity or reveal differences in the performance of the biosimilar. The requirements are similar to EMA and WHO (CBER, 1997).

ACSS - As for BRDD, no details are provided on how to perform a particular assay, or type of assays to be performed. The TGA, Australia and Swissmedic follow EMA guidelines for non-clinical study requirements (TGA, 2018; Swissmedic, 2020b).

In vivo studies

SRA - *In vivo* studies refer to experimentation using a whole, living organism as opposed to a partial or dead organism. For USFDA, *in vivo* studies are advised to be performed in line with preclinical safety evaluation of biotechnology-derived pharmaceuticals S6 (R1) (CBER, 1997; EMA, 2007). Animal toxicity studies are considered useful if there are uncertainties about the safety of the biosimilar product after extensive structural and functional characterisation. The scope and extent of animal toxicity data is dependent upon information on the reference product, biosimilar product and known similarities and differences between the two. Discussion with the agency is strongly recommended if not conducting animal studies or scope and extent of the studies. Even if animal PK and PD studies are conducted the need for human PK and PD studies remains. Animal immunogenicity assessment helps to interpret animal study results but generally does not predict the potential immune response in humans (CDER & CBER, 2015a).

EMA suggest *in vivo* studies be performed if significant differences such as new/modified structure, quantitative difference in quality attributes, formulation difference etc. of proposed biological product with the reference product. It is expected to consider a flexible approach where a non-human primate is the relevant species. Comparative studies with inclusion of one single dose of reference product and biosimilar and/or one gender and/or no recovery animals/evaluation of in-life safety parameters need to be performed. The highest dose of the range can be selected for one-dose evaluation and justification to be given accordingly. For additional information transgenic animal/transplant models can be considered. Direct human studies can be done if a relevant animal model is unavailable. The duration of the study should be justified based on the PK behaviour of the biosimilar product and its clinical use. Local tolerance test results are important for novel excipients and if such a study is included in other *in vivo* studies. In case of repeat dose toxicity, in the *in vivo* study the highest dose is selected for evaluation if quantitative differences are identified (EMA, 2014b). The WHO also do not mandate the need for *in vivo* studies, however,

if deemed necessary, the agency recommends performing dose concentration-response assessment studies (PK/PD) considering the targeted human dose, in comparison with the reference product. Also, a repeat dose toxicity study combined with a local tolerance study, using a relevant species (human primates) is preferred. Safety pharmacology, reproductive toxicology, genotoxicity and carcinogenicity studies are generally not required (WHO, 2013)

ACSS - Similar to the EMA and the WHO, HC/BRDD, do not mandate the need for *in vivo* studies and have similar requirements as EMA and WHO (Health Canada, 2017). The TGA and Swissmedic (TGA, 2018; Swissmedic, 2020b) is in line with the EMA guidelines.

Table 3.6 Non-clinical studies attributes for developed regulatory agencies

Non-Clinical	EMA (EU)	WHO	USFDA (USA)	TGA (Australia)	BRDD (Canada)	Swissmedic (Switzerland)
In vitro	Comparative binding and functional assays	Comparative binding and functional assays	Comparative Functional assay	Comparative binding and functional assays	Recommended	Comparative binding and functional assays
In vivo	PKPD studies, repeat dose toxicity, toxicity for novel excipients	PKPD studies, repeat dose toxicity, blood samples withdrawn for PK/TK, local tolerance depends on ROA	PKPD studies, toxicity studies, immunogenicity assessment	PKPD studies, repeat dose toxicity, toxicity for novel excipients	Not require, if *in vitro* similarity is proved	PKPD studies, repeat dose toxicity, toxicity for novel excipients

PKPD- Pharmacokinetic Pharmacodynamic; TK- Toxicokinetic

Clinical studies

Clinical studies encompass the following studies for proving biosimilarity: 1) Pharmacokinetics 2) Pharmacodynamics 3) Clinical Efficacy and 4) Clinical Safety. Table 3.7 illustrates the clinical study requirements as defined by different regulatory agencies.

Pharmacokinetics (PK) and Pharmacodynamics (PD)

USFDA - The PK and PD response assessment, evaluation of residual uncertainty and analytical quality and similarities are defined as three basic concept requirements for a proposed biosimilar development. To evaluate clinical pharmacology similarity, inclusion of PK similarity and PD similarity (if applicable) are essential. The PD response can be measured by using a single or a composite biomarker. It is expected to use material from the final manufacturing process when performing a clinical pharmacology study. Analytical and PK bridging study with the to-be-marketed product will be necessary in case material is used from different manufacturing processes. The PK study design is recommended as a crossover for a short half-life product, having rapid PD onset and lower expected immunogenicity. The PD assessment has to be multi-dose as against the single dose of the PK study. The products with long half-life, requiring repeated doses and chances of increased immune responses will require parallel design studies. Healthy subjects are acceptable if the product can be administered safely. However, the patient population can be chosen if there are ethical challenges or there are available PD markers in patients (CDER & CBER, 2016). If drug-drug interaction and QT/QTc prolongation and proarrhythmic potential studies are on-going for the BLA holder, then such studies would be essential for the biosimilar manufacturer as part of the post-marketing approval (CDER & CBER, 2015a). The most sensitive dose should be selected for evaluation of PK/PD similarity; based on the condition of the patient, the dosing regimen can be decided. The route of administration of the proposed product should be the same as that of the reference product.

PK measurement - peak of concentration (C_{max}), the total area under the curve (AUC) for the reference product and proposed biosimilar. For a single dose study AUC to be calculated as $AUC_{(0-\infty)}$. For a multiple dose study, the total exposure to be calculated as time concentration profile starting from zero to end of dosing interval, at steady state, as $AUC_{(0-tau)}$. The average equivalence statistical approach is expected to compare clinical PK and PD similarity. To prove similarity the expected calculated confidence interval limit is 80-125% if the limit varies then justification is expected. With reference to safety and immunogenicity, the data is expected to be collected from clinical PK and PD study. To evaluate clinical pharmacology similarity, FDA

recommends three types of bio-analytical assays as ligand binding assays, concentration and binding assay, and PD assay (CDER & CBER, 2016).

EMA - The clinical data need to be obtained using the proposed biosimilar product, from a commercial batch, to ensure similarity of quality profile between comparability and commercialised batch. Comparative PK is expected, and comparability needs to be proved considering clearance and/or half-life of therapeutic protein. Methods used for analysing immunoassays and bioassays should be validated. The bio-analytical method should be capable of identifying and analysing the parent molecule and/or degradants, if any. PK studies should be performed in healthy volunteers, screened for homogeneity to perform single-dose study. The preference is single-dose, cross-over with PK profile characterisation including late elimination phase. Parallel group design can be explored for longer half-life and/or higher immunogenicity risk. When PK studies are performed in healthy volunteers, data needs to be extrapolated to the target population. In case it is not possible to enrol healthy volunteers in single-dose PK studies, then patients can be used in a multi-dose PK study. The relative bioavailability needs to be investigated for individual administration sites. The dose proportionality needs to be evaluated in single or multiple doses with discussion of the clinical impact. Studies are to be performed at several dose levels and occasions. PK/PD relationship needs to be established and evaluated. The EMA also clarified its view on PK study data, wherein expectation of disposition (distribution and elimination) has been specified in addition to absorption (EMA, 2020b).

PK characteristics of reference product - Designing of the PK study should be done considering PK of the reference product (especially for mAbs). The PK studies should be designed based on elimination mechanisms (target mediated/non-target mediated). If it is eliminated by both means, comparable PK in healthy volunteers should be performed for non-target mediated whereas the other one should be performed in the patient population as support data. If receptor shedding is involved, then baseline comparability studies should be performed. The PK profile is not required for all conditions specified for licensed mAb unless the therapeutic category is different. The lowest therapeutic dose in patients should be sufficient enough to identify difference in target mediated clearance. Subcutaneous routes should be sufficient since this will characterise absorption and elimination. The sampling to be selected at first and last

administration for a single dose study whereas for multiple dose study steady state sampling is most preferred. A single-dose, cross-over with PK profile characterisation including late elimination phase is most preferred. Parallel group design can be explored for longer half-life and/or higher immunogenicity risk. Regarding the route of administration, if two different routes such as intravenous and subcutaneous are assigned to the reference product, comparability PK study with subcutaneous route alone would be sufficient with justification. Acceptable range should be based on clinical judgment.

PK measurement - Primary parameter should be $AUC_{(0\text{-}inf)}$ in single dose study. C_{max}, T_{max}, volume of distribution and half-life and other secondary parameters should be estimated and for subcutaneous administration C_{max} should be co-primary parameter. As to multiple-dose study, primary truncated AUC after first until second administration $AUC_{(0\text{-}t)}$ and steady state AUC over dosage interval, secondary- At steady state C_{max} and C_{trough} should be primary parameters (EMA, 2014b).

WHO - Single-dose pharmacokinetic data studies are sufficient in general, however for mAbs, parallel group design with a larger number of subjects is required (due to long half-life of mAbs, single-dose, cross-over design may be inappropriate). WHO also recommends using commercial scale proposed product for clinical studies. In cases where non-commercial product is used for clinical studies, WHO insists on PK bridging studies to prove PK profile comparison between two different formulations.

Factors to be considered (for mAb biosimilars)

- Healthy subjects to be used due to higher sensitivity and homogeneity in comparison to a patient population.
- Sub-therapeutic dose to be considered due to ethical issues.
- Study in the patient population could be mandatory due to safety risks in healthy volunteers (antigen/receptor level, presence of target-mediated clearance and/or receptor shedding of reference mAb has to be considered for selection of the population to be studied) (WHO, 2013).
- It may be necessary to perform a PK study in a different population considering different therapeutic indications under development.

Drug interactions and special population studies are not required. For mAb biosimilars, it is not required to perform a PK study for each authorised indication of the reference biological product. It is expected that comparative PK for mAbs will be performed, considering monotherapy to reduce variability source. However comparative PK for both mono and combination therapies have to be considered if concomitant therapy alters the PK of the mAb considered as a biosimilar. The lowest recommended therapeutic dose needs to be used for PK profiling. A higher dose may be required based on mAb clearance characteristics. To measure $C_{max,}$ sufficient sampling is expected at early time points. For a single-dose study, sampling has to be done until last quantifiable concentration reached. In multi-dose studies sampling has to be done at first dose and at steady state (expected to reach after five half-lives of mAb). However, there is no clarity on the type of five half-lives as PK half-life or biological half-life.

Equivalence margin - For primary parameters 80-125% of comparability margin is acceptable with justification (WHO, 2017a).

ACSS

The TGA and Swissmedic follow EMA guidelines for clinical studies (TGA, 2018; Swissmedic, 2020b).

HC/BRDD - The guidance document pertaining to information and submission requirements for biosimilar biologic drugs indicates PK requirements. It covers a comparative PK study at low or sub-therapeutic dosage in healthy subjects or patients with appropriate justifications. The design of the study needs to be decided, based on set parameters. The equivalence margin for primary parameters is expected as 90-125%.The guidance document also states that comparative PK criteria are to be defined based on the bioequivalence guidance document “Conduct and analysis of comparative bioavailability studies and comparative bioavailability standards: Formulations used for systemic effects”. However, the said guidance document excludes applicability to subsequent entry biologics under scope (Health Canada, 2016).

Pharmacodynamics (PD)

EMA - For PD studies, considering mAb biosimilars, two types of possibilities exist depending upon the availability of PD markers. One in which PK and PD can be combined together if a PD marker is available. In case PD markers are not available *in vitro* testing should be performed. To prove comparability dose concentration response relationship or time response relationship should be established. If the fingerprinting approach is used by selecting non-surrogate PD markers, then advice from the regulatory agency is essential (EMA, 2014b).

WHO – The WHO recommends including PD markers as part of the clinical comparability exercise or confirmatory PD studies may be performed in place of clinical safety or efficacy studies.

ACSS

HC/BRDD - The guidance recommends characterising the PK/PD relationship if both studies are combined. Apart from an equivalence trial expectation, PD markers can be used, subject to justification. For Canada, the calculations for PK studies should follow those outlined for Bioequivalence studies as in the Guidelines for Generic products. Acceptability of a fingerprinting approach is unclear with BRDD/Canada (Health Canada, 2016).

Clinical Safety

EMA - Comparative safety data is expected to be obtained before product authorisation and the follow-up period chosen needs to be justified. The adverse reactions are required to be compared in terms of type, frequency and severity. Immunogenicity and other risks need to be evaluated and incorporated in the application dossier. Increased immunogenicity as compared to the reference product may lead to products not considered to be truly biosimilar. Double-blind, parallel analysis needs to be done for measuring immunogenicity. The analytical assays should have the capability to detect reference and proposed product antibodies and in addition all possible antibodies of the proposed product. The antibody titers, cross-reactivity, targeted epitopes and antigen neutralising capacity are required to be determined. The immunogenicity study duration should be a minimum of four weeks in

case immunosuppressive agents are used or otherwise justified based on treatment duration and removal of product from the circulation as well as the start of a humoral immune response. Follow-up duration of six months during pre-authorisation studies can be justified based on the immunogenicity profile and for chronic diseases one-year follow-up data before a marketing authorisation application is essential. Further follow-up data can be submitted post-authorisation (EMA, 2014b).

WHO - The comparative clinical safety requirement is in line with EMA's guideline; however, WHO presents a multi-disciplinary approach for evaluation of immunogenicity in mAbs. It covers risk assessment, risk-based immunogenicity programme, comparative immunogenicity, assays and mAb characterisation and clinical immunogenicity assessment (WHO, 2013; WHO, 2017a).

ACSS - Comparative clinical safety data (in terms of adverse events including nature, severity and frequency) in sufficient numbers of patients treated for a suitable duration is required as part of the biosimilar application. The BRDD has not defined immunogenicity requirements in a precise manner but accepts what is submitted provided it is clearly laid out, well explained and justified. In general, the expectations for comparative immunogenicity studies are aligned with those of the WHO (Health Canada, 2012). The follow-up duration for pre- and post-authorisation study is not defined precisely however the agency accepts what is submitted if the plan is clearly laid out, well explained and justified.

Clinical efficacy

EMA - The clinical efficacy studies are carried out to establish that a biosimilar will not perform in a manner that differs from the originator in a clinically significant manner. The principle is to demonstrate similar efficacy compared to the reference medicinal product, not only the patient benefit which is already proven by the reference medicinal product.

Study type - Parallel design, random, double-blind adequately powered comparative clinical studies using efficacy end-points in the absence of surrogate markers for efficacy.

Population- Patients for the approved therapeutic indication of the reference product, in case of unapproved indication, justification should be provided.

Design - Equivalence design expected, non-inferiority design needs consent from the agency.

Endpoints - secondary endpoints of reference product are sufficient for comparison with the reference product.

Comparability margin - To be justified with some statistical and clinical grounds by considering assay sensitivity.

The clinical studies in paediatric and elderly populations are not required. The inclusion of patients from non-European countries may increase heterogeneity but if there are no known intrinsic differences then it is possible to include mixed populations (EMA, 2014b).

WHO - *Design* **-** An equivalence trial design is expected, with emphasis on the additional benefits for extrapolation of indications.

The rest of the requirements for efficacy trials are equivalent to those of the EMA.

ACSS - Comparative clinical trials with equivalence design are expected.

Table 3.7 Clinical studies criteria in developed regulatory agencies

Clinical	EMA (EU)	WHO	USFDA (USA)	TGA (Australia)	BRDD (Canada)	Swissmedic (Switzerland)
Pharmacokinetics						
Dose	Lowest therapeutic dose	Lowest therapeutic dose	Most sensitive dose	Lowest therapeutic dose	Low/ sub-therapeutic dosage	Lowest therapeutic dose
ROA	Subcutaneous route	n/d	Same as RBP	Subcutaneous route	Same as RBP	Subcutaneous route
Sampling	n/d	Single dose: till last quantifiable concentration; Multiple dose: first dose and at steady state	n/d	n/d	n/d	n/d
Design	Single-dose crossover for late elimination phase; Parallel group for long half-life	Single-dose crossover, Parallel group design for mAb clearance study	crossover for short half-life product, parallel design for long half-life	Single-dose crossover for late elimination phase; Parallel group for long half-life	Base on set parameters	Single-dose crossover for late elimination phase; Parallel group for long half-life
Primary parameters	Single dose: AUC $_{(0\text{-inf})}$, Multiple dose: truncated AUC, C_{max} and C_{trough}	n/d	n/d	n/d	n/d	Single dose: AUC $_{(0\text{-inf})}$, Multiple dose: truncated AUC, C_{max} and C_{trough}
Secondary parameters	Single dose: C_{max}, Tmax, V_{ss}, $t_{1/2;}$ Multiple dose: steady state AUC	n/d	n/d	n/d	n/d	Single dose: C_{max}, Tmax, V_{ss}, $t_{1/2;}$ Multiple dose: steady state AUC
Acceptable range	n/d	80-125%	80-125%	n/d	90-125%	n/d
Pharmacodynamics						
Combined PKPD	If PD marker	If PD marker	If single/composite PD marker	If PD marker	If PD marker	If PD marker

Clinical	EMA (EU)	WHO	USFDA (USA)	TGA (Australia)	BRDD (Canada)	Swissmedic (Switzerland)
Fingerprinting approach	If non-surrogate PD marker	n/d	n/d	If non-surrogate PD marker	n/d	If non-surrogate PD marker
Clinical efficacy						
Study type	Parallel design, random, double-blind	Parallel design, random, double-blind	Parallel design	Parallel design, random, double-blind	n/d	Parallel design, random, double-blind
Population	Patient for approved therapeutic indication	Patient for approved therapeutic indication	n/d	n/d	n/d	Patient for approved therapeutic indication
Design	Equivalence design	Equivalence design	n/d	n/d	Equivalence design	Equivalence design
Endpoints	Secondary endpoints	Secondary endpoints	n/d	n/d	n/d	Secondary endpoints
Comparability margin	To be justified	To be justified	n/d	n/d	n/d	To be justified
Paediatric population	Not required	Not required	Not required	Not required	n/d	Not required
Clinical	EMA (EU)	WHO	USFDA (USA)	TGA (Australia)	BRDD (Canada)	Swissmedic (Switzerland)
Clinical safety						
Immunogenicity	Double-blind, parallel analysis	Double-blind, parallel analysis, multi-disciplinary approach	During PKPD study	To be performed	Double-blind, parallel analysis, multi-disciplinary approach	Double-blind, parallel analysis
Comparative safety data	Before product authorisation	Before product authorisation	During PKPD study	To be performed	Adverse events including nature, severity and frequency	Before product authorisation
Follow-up duration	6-12 months	6-12 months	n/d	n/d	n/d	6-12 months

n/d- Not define; PKPD- Pharmacokinetic Pharmacodynamic

Part IV - Post-marketing requirements and commitments (interchangeability, switching and substitution, extrapolation to other indications, risk management plan and pharmacovigilance)

The phase “post-marketing requirements and commitments” refers to studies and clinical trials that sponsors conduct after approval to gather additional information about a product's safety, efficacy, or optimal use. Some of the studies and clinical trials may be required; others may be studies or clinical trials a sponsor has committed to conduct. Further, it is important to establish a formal Risk Management Plan to monitor and detect both known inherent safety concerns and potential unknown safety signals that may arise from the biosimilar after authorisation. The risk management plan includes the pharmacovigilance plan, adverse drug reaction reporting and post-marketing studies (Phase IV Study).

Extrapolation to other indications

SRA

USFDA - A proposed biosimilar product can be licensed for additional indications, provided one indication which is approved for the reference product was the subject of biosimilarity studies and biosimilarity has been proven. In addition, there needs to be consideration on whether the clinical study scientifically justifies the extrapolation. Apart from that, extrapolation of indications in a paediatric population is also possible, subject to scientific justification. The issues pertaining to mechanism of action, PK and bio-distribution in varied patient populations, immunogenicity, anticipated toxicity differences and other relevant factors impacting efficacy should be scientifically justified for the tested and all other extrapolated indications (CDER & CBER, 2015b).

EMA - The EMA considers extrapolation (or extension of the indication) based on scientific justification of quality (physico-chemical, structural and in vitro function test), non-clinical (PK/PD) and clinical (safety/efficacy) comparability in one indication. It might be challenging to extrapolate if the active substance acts on several or multiple receptors with different clinical outcomes in varied indications or has more than one active site or the studied indication is irrelevant in terms of safety and efficacy to the other indications. Extrapolation of immunogenicity to other indications would require

justification (based on whether the therapy is one agent, or the biological is added to another immunosuppressant) (EMA, 2015; EMA, 2019).

WHO - The WHO considers extrapolation to other indications subject to usage of a sensitive clinical model for identification of differences, the same mechanism of action and/or applicable receptors, no new safety issues are expected when extrapolating indications and equivalence design efficacy trials have been performed (WHO, 2017b).

ACSS

HC/BRDD - All indications can be authorised based on one indication, subject to provision of a scientific rationale. However, if the reference product's specific indication is not approved in Canada, then extrapolation may not be possible (Health Canada, 2017).

TGA - The expectations from the TGA agency are in line with EMEA/CHMP/BMWP/42832/2005 Rev 1 guideline (TGA, 2018).

Swissmedic - An extrapolation of indications and dosage recommendations for the reference product to the biosimilar is possible only if it is scientifically justified and the associated safety risk to patients is acceptable. The extrapolation to further indications and dosage recommendations, must be demonstrated in at least one sensitive indication and dosage or, if required, separately for each of the indications and dosage recommendations applied for. Sensitive clinical or pharmacodynamic endpoints should be selected depending on the indication and the nature of the biosimilar. The proof of safety and efficacy is based, for example, on clinical experience with the reference product and already authorised biosimilars, on available data from literature, on the mechanism of action of the active substance of the reference product in each indication, or on the receptors involved (Swissmedic, 2020b).

Interchangeability

SRA

USFDA - The first agency to come up with an interchangeability guidance document in May 2019 and it requires meeting the standards described in section 351(k)(4) of the PHS Act to justify the relevance of the data obtained using the non-US-licensed

comparator. As it explains, interchangeability designation allows a biological product to be substituted for the reference product without intervention of a healthcare provider or prescriber, subject to approval by the agency (CDER & CBER, 2019b). Subsequently, in November 2020, the agency clarified its current thinking about interchangeability by publishing a questions and answers document. The guidance document amply expresses the type and amount of data required to be submitted as part of the application to claim an interchangeable product (CDER & CBER, 2020a). The agency suggests "2-arm switching studies", where all patients start on the reference product; one arm remaining on the reference product throughout, and the other arm switching back and forth twice, ending on the biosimilar product. Critically, the main comparison is on PK/PD markers, not efficacy markers (which FDA considers less sensitive). The interchangeability decision falls within the scope of each member state of the EU (EMA, 2015).

ACSS – The interchangeability decision is outside the scope of regulators in Canada and TGA (Health Canada, 2017; TGA, 2018). The Swissmedic agency has made it clear that biosimilar authorisation does not reflect interchangeability between the biosimilar and the reference product and such a decision is left to the attending physician or prescriber (Swissmedic, 2020a).

Pharmacovigilance (PV) and Risk management plan (RMP)

SRA - Pharmacovigilance system details will be required by the EMA and needs to be fully described in marketing authorisation applications. Suspected adverse reactions will need appropriate tracing with brand name and batch details of each product. An RMP, defining all known and potential unknown risks needs to be monitored post market authorisation of the product. In addition, the safety studies of biosimilars should cover all ongoing safety expectations of the reference product (EMA, 2014b). In USFDA, Risk evaluation and mitigation strategy (REMS) in line with the reference product are required to be submitted for the proposed biosimilar product (USFDA, 2015). WHO has advised applicants to refer to ICH E2E for PV planning. In general, PV requirements are according to EMA’s expectations (WHO 2017b).

ACSS - For HC/ BRDD, an RMP needs to be prepared in consultation with the agency. In general, it covers requirements mentioned in the EMA guideline and/or specific

guidance document - Submission of risk management plans and follow-up commitments published by Health Canada/BRDD (Health Canada, 2016). The TGA and Swissmedic requirement on PV and RMPs are mainly based on EMA guidelines with additional requirements on Australia Specific Annex (ASA) for RMP to be submitted in the ARTG. In Swissmedic, biosimilar authorisation is granted subject to submission of periodic safety update reports (PSUR) (in accordance with Art. 58, para. 2 TPA in conjunction with Arts. 58 and 60 TPO). For reporting suspected adverse reactions to biological medicinal products when the biosimilar is substituted, product identification regarding manufacturing process is of utmost importance (i.e., clear differentiation between reference product and biosimilar) (Swissmedic, 2020b).

Paediatric studies

In a final guidance document, the USFDA provides a detailed framework on paediatric study plans, including, preparation, submission and review timelines supplemented with a sample template. The agency revised its stand on initial Pediatric Study Plan (iPSP) for orphan designated products earlier proposed in PREA, requiring submission of iPSPs for all such products, starting 18 August 2020 (CDER & CBER, 2020b). Details on extrapolation strategy and conditions for paediatric assessment waivers or deferrals for “impossible” or “highly impracticable” cases are also laid out in the guidance (CDER & CBER, 2020b). While TGA is aligned with EMA on non-requirement for a Paediatric Investigation Plan (PIP), Swissmedic mandates justification for the non-submission of paediatric data.

COVID-19 pandemic and regulatory flexibilities

During 2020, the global health and economy suffered significantly due to the Coronavirus disease (COVID-19) pandemic, caused by an infectious virus – ‘Severe Acute Respiratory Syndrome Coronovirus-2’. This resulted in the disruption of medicines supply, lack of relevant treatment therapies, increased demand of products pertaining to critical care and delivery of adequate healthcare services in many countries. Due to the COVID-19 pandemic, major regulatory agencies have relaxed certain standards to facilitate speedy product approval and support patients with continuous availability of the essential medicines. Some of these measures include fast track approval, relaxation in compliance with regulations, electronic (digitalised)

platform for large dossier submission, special task force for development and approval of medicines, extension of GMP or Good Distribution Practices (GDP) certificate validity, desk GMP inspection and streamlined dissemination of disease related information to patients and healthcare professionals. Such guidelines were also identified and retrieved from the established regulatory agencies to evaluate the relaxations in the regulations for biosimilar development and approval process. Most of the regulatory flexibilities were pertaining to medicines that could be potentially used for the treatment of COVID-19. Table 3.8 represents regulatory guidelines issued by different agencies during the COVID-19 pandemic.

Table 3.8 Regulatory flexibilities during COVID-19 pandemic

Country	Agency	Reference Guidelines
Europe	EMA (CHMP)	Questions and Answers on Regulatory Expectations for Medicinal Products for Human Use during the Covid-19 Pandemic (2020)
		EMA initiatives for acceleration of development support and evaluation procedures for COVID 19 treatments and vaccines (2020)
USA	USFDA (CBER)	Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency", Guidance for Industry (2020)
		Good manufacturing Practice considerations for responding to COVID-19 infection in employees in drug and biological products manufacturing", Guidance for Industry (2020)
		COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products", Guidance for Industry and Investigators (2020)
		Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers", Guidance for Industry (2020)
Australia	TGA	Clinical trial processes: Information relating to COVID (2020)
Switzerland	Swissmedic	Authorisation procedure for COVID 19 medicinal product during pandemic (2021)

In addition, to the above-mentioned guidelines, Australia, Canada, Singapore and Switzerland- jointly known as the ACSS consortium, are running a pilot project of work-sharing among the health agencies that comprise the consortium. During the pandemic, it has been made possible to process reviews under the ACSS work-sharing programme by submitting applications in at least two of these four agencies.

DISCUSSION

The literature review on the biosimilar approval process across EMA, WHO, USFDA, HC/BRDD, TGA and Swissmedic revealed defined processes for the assessment of biologics/biosimilar applications. The agencies are organized into specific committees for dossier evaluation and review process. There is a defined regulatory approval process followed by all the agencies with timelines fixed for each stage in the marketing authorisation process. The general approach of the biosimilarity principles including development approach, basis of biosimilarity and demonstration of biosimilarity with reference product is quite uniform across EMA, WHO, USFDA, HC/BRDD, TGA and Swissmedic. The EMA and the USFDA follow a stepwise development approach for biosimilar products in which *Totality-of-the-Evidence* is considered to assess biosimilar applications. A simplified approach is adopted by EMA in which safety and efficacy of biosimilars is deduced based on the PK/PD profile of the biosimilar product compared to the reference product, in lieu of clinical efficacy data. However, this needs to be discussed and agreed upon in advance with the respective regulatory agency. In 2020, the EMA has also clarified its view on PK study data in which expectation of disposition (distribution and elimination) has been specified in addition to absorption.

Most agencies designate the reference product as their own locally licensed product, sourced from their own country and require additional bridging studies in case a non-authorised reference product is used. TGA and Swissmedic agency prefer to have the reference product sourced from their own market, which is authorised based on submission of a full dossier. There is still a possibility to use a non-authorised reference product from another market having a similar regulatory system, subject to establishing a bridging study between the authorised, non-authorised reference product and the proposed biosimilar product. The waiver of a bridging study can be obtained by providing the evidence of a global reference product being manufactured at and

supplied from a single global site. The expectation of comparability studies is based on ICH Q5E, EU or USA guidance.

Comparative analytical testing forms the core of biosimilar development. The USFDA has drafted a new guidance on comparative analytical assessment revising (CDER & CBER 2019a). Besides the change in the terminology from “analytical similarity” to “analytical assessment,” the agency encourages the manufacturers to take a more scientific approach to demonstrate the observed differences in the biosimilar product. The comparative characterisation exercise for biosimilar product is broadly aligned with EMA and WHO. The TGA and Swissmedic have adopted ICH/EMA guidelines for comparability studies.

On the non-clinical front, the USFDA has considered ICH S6 (R1). The requirement for *in vitro* studies and the *in vivo* toxicity studies (repeat-dose toxicity, local tolerance, safety pharmacology, reproductive toxicity, carcinogenicity) are aligned with EMA and WHO. The TGA and Swissmedic have imbibed EMA regulations with almost all the regulatory agencies integrating the 3R principle – replace, reduce, refine; for the ethical use of animals for non-clinical studies.

There had not been many changes in the approaches for PK/PD studies during the study period, however, EMA has spelt out the provision of active substance disposition data in addition to the other criteria for PK/PD studies as part of their “Questions and Answers” document (EMA 2020b). The usage of commercial batch supply for clinical study is the same for EMA and WHO, whereas WHO requires a bridging PK study if two different formulations are used. The PK study should be a single dose, parallel design with late elimination stage by both agencies for mAb biosimilars. WHO expects 80-125% comparison margin for primary parameters. Efficacy trials are required to be parallel design, random, double-blind, adequately powered with efficacy endpoints. Equivalence trials are expected, and non-inferiority needs agency’s consent. The efficacy trial design and type remain the same for EMA and WHO. Pharmacovigilance and RMP data are required across all the agencies.

There have been a considerable number of guidance (some in draft stage) published by different regulatory agencies during the study period. Amongst all the reviewed regulatory agencies, the USFDA was highly active with updates in the biosimilar space

during the last couple of years. The agency issued guidance covering different aspects of biosimilarity including, comparative analytical assessment, interchangeability, paediatric study plans and clinical immunogenicity. Though WHO has prequalified trastuzumab and rituximab biosimilar versions in 2019 and 2020 respectively, the regulatory standards for monoclonal antibodies (mAb) are yet to be upgraded in line with EU or FDA. The BRDD Canada has also awarded multiple approvals, however only the fact sheet document has been partly revised. Swissmedic has revised its TPA to authorise EC approved low molecular weight heparins (LMWH) as biosimilars since the beginning of 2019, and thereby allowing for switching from an ongoing authorisation procedure for a biosimilar to an Art. 13 procedure.

The USFDA has revised its stand on the necessity for paediatric study plans for orphan drugs, making iPSP submission mandatory for the sponsors who intend to submit a marketing application for the following cases including an API, any new indication, a new dosage form or a new administration mode. The TGA is aligned with EMA, and Swissmedic relies on justification for absence of paediatric studies.

SUMMARY AND CONCLUSION

Biologics are complex products requiring a stepwise and comprehensive development strategy considering quality, non-clinical and clinical aspects to obtain biosimilar approval from mature regulatory agencies. Based on the biosimilar guidelines identified and evaluated from the mature regulatory agencies – EMA, USFDA, WHO, BRDD, TGA and Swissmedic, through this study, the key aspects to be considered for demonstration of biosimilarity are summarised below;

- The biosimilarity principles including development approach, basis of biosimilarity, demonstration of biosimilarity with reference product and type of applications are quite uniform across EMA, WHO, USFDA, HC/BRDD, TGA and Swissmedic.
- In general, mature agencies expect the reference product to be sourced from their own territory having licensed the product based on full development data. Bridging data for a reference product sourced from territories outside their own, for certain comparability studies, are required by all the agencies.
- The comparative characterisation exercise of the proposed biosimilar in relation to the reference product specifies physicochemical studies, manufacturing process,

overages and compatibility in the EMA and WHO guidelines. The mAb characterisation requirement of USFDA is aligned with ICH member states.

- The comparative *in vitro* and *in vivo* non-clinical study requirements are defined by all the mature regulatory agencies and are broadly aligned. The USFDA has considered ICH S6 (R1) whereas BRDD lacks detailed information except non-requirement of *in vivo* studies if similarity is proven in previous steps.
- Comparative PK/PD are expected by all the agencies; whereas comparative clinical safety or efficacy could be enough with EMA, WHO and BRDD, subject to inclusion of PD markers in PK/PD studies.
- Clinical efficacy trial design and type remain the same for EMA, WHO and BRDD. The extrapolation of one indication to others is acceptable based on scientific justification.

Based on this critical evaluation of regulatory guidelines, a master check list of parameters has been created to further compare biosimilar guidelines of BRICS-TM agencies with mature agencies (ACSS), which will be detailed in the subsequent chapter (Chapter 4). It is, therefore, intended to carry out future research focusing on ACSS and BRICS-TM countries to identify challenges for biosimilar development and regulatory approval processes with a single outcome of proposing a standardised regulatory model for future implementation.

CHAPTER 4

Comparison of Regulatory Guidelines in the Emerging Economies with Mature Agency Regulations

INTRODUCTION

The introduction of biosimilar medicines plays a key role in improving patients' access to wider treatment choices worldwide and addresses concerns regarding the escalating cost of healthcare. In Chapter 3, a critical evaluation of the regulatory guidelines for biosimilar development published by mature agencies such as the EMA, USFDA, WHO, BRDD, TGA and Swissmedic has been explained. From these assessments, it is worthwhile to note that the regulatory development pathways for biosimilars applied by the major regulatory agencies worldwide are, to a broad degree, scientifically aligned (Cazap et al., 2018). However, owing to regional differences in healthcare priorities, policies, and resources, some important regulatory inconsistencies are evident in emerging economies. Some of these challenges such as lack of a step-wise approach, difference in selection and sourcing of RBP, regulatory expectations of clinical efficacy trial design and opacity regarding interchangeability, switching and substitution norms, have been identified. In addition to the biosimilar development criteria, literature search on the biosimilar review and approval pathway among the mature regulatory agencies has also been described in Chapter 3. The literature search clearly demonstrates a well-established, rigorous review and approval process among the mature regulatory agencies to assure the efficacy, safety, and quality of these products for faster access of these products by the patients. Therefore, considering the biosimilar regulatory pathways in emerging economies are in the evolving stage, it becomes necessary to understand the biosimilar approval process along with the development pathways in these economies.

Emerging economies have accounted for almost two-thirds of the world's GDP growth and more than half of new consumption over the past 15 years (Woetzel et al., 2018). Hence it is crucial to evaluate the biosimilar development criteria and marketing authorisation pathway of the biosimilars in these markets. Based on the potential market for biosimilars in emerging economies, a master checklist (Table 4.1) was created by collating the requirements for demonstrating biosimilarity across the developed agencies, for comparison with the biosimilar development criteria expected by emerging agencies of BRICS-TM countries. This chapter describes in detail the review of all the guidelines pertaining to biosimilar development and approval for the Agência Nacional de Vigilância Sanitária (ANVISA/ Brazil), Russian federation

(Russia), Central Drugs Standard Control Organisation (CDSCO/ India), National Medical Product Administration (NMPA/ China; previously known as CFDA), South African Health Products Regulatory Authority (SAHPRA/ South Africa previously known as MCC), Türkiye İlaç ve Tıbbi Cihaz Kurumu (TITCK/ Turkey) and Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS/ Mexico).

Table 4.1 Master Checklist

Master Checklist	
A	**Biosimilarity criteria**
1	Demonstration of biosimilarity with reference product
2	Posology and route of administration
3	Pharmaceutical form
4	Strength/ Biological activity
5	Formulation
6	Pack Presentation
7	Extrapolation of indications
8	Pediatric research requirements
9	Biosimilars naming convention
10	Labelling requirements
B	**Choice of Reference product selection**
1	Selection criteria for RBP
2	Acceptance of non-authorised RBP
3	Expectations on identity of RBP
4	Acceptance on changeover of RBP
5	Presence of data sharing arrangement
6	Expectations of locally sourced RBP
7	Bridging study requirements
8	Number of batches of RBP
C	**Comparability exercise (Quality, Non-clinical and Clinical aspects)**
1	**Quality**
i	Physico-chemical characterisation requirements
	Primary and higher order structure elucidation
	Amino acid sequencing
	Determination of groups and bridges
	Determination of carbohydrate content and structure
	Determination of glycosylation profile
	Glycan/ Isoforms structure characterization
ii	*Assay requirements for demonstrating Immunological properties*
	Antigen binding assay
	Cytotoxicity evaluation
	Cross-reactivity determination
	Complementarity-determining region (CDR) identification
	Epitope characterization
iii	*Biological activity*
	In vitro/vivo assay requirements

Master Checklist	
	Characterization of effector functions (Antibody-dependent cellular cytotoxicity (ADCC) analysis, Complement binding ability, Cytotoxic properties, Fc- gamma receptor binding activity and neonatal receptor binding ability)
iv	*Purity, impurity and contaminants requirements*
	Purity
	Structural heterogeneity
	Multimers, aggregates and particulates
	Impurity profile and Process-related impurities
	Contaminants
v	*Data Expectations on cell lines/expression system used*
	Origin and characteristics
	Immortalisation related data
vi	*Quantity determination*
	Basis for quantity determination (Number of batches, expected minimum batch size)
vii	*Specifications*
	Specification determination
	Tests selection basis
	Expectations on validated methods for characterisation
	Expectations on analytical methods for lot release exp
	Reference materials and Standard
viii	*Stability study requirements*
	Comparative accelerated and stress stability data expectations
	In-process stability data expectations
	Routine stability study requirements
	Stability storage conditions requirements
	Container Closure System requirements
2	**Non-clinical studies**
	Comparative *in vitro study requirements*
	Comparative *in vivo study requirements*
	Expectations on mandatory local studies at GLP centres
3	**Clinical studies**
i	*Pharmacokinetics (PK) study expectations*
	Dose
	Route of Administration (ROA)
	Sampling points (single or multidose study)
	Study Design (for short and long half-life products)
	Endpoints (Primary and Secondary)
ii	*Pharmacodynamics (PD) study expectations*
	Acceptance of combined PKPD
	Acceptance of fingerprinting approach
iii	*Clinical efficacy study expectations*
	Study type
	Population
	Study Design
	Sample size
	Endpoints
	Local clinical studies
	Pediatric/Elderly population
iv	*Clinical safety study expectations*

Master Checklist	
	Immunogenicity studies
	Comparative safety data
	Post-marketing requirements
	Basis for extrapolation to other indications
	Requirement of local conduct of clinical studies in specific accredited study centre (PK/PD, combined PK/PD, clinical efficacy, clinical safety, combined clinical safety and efficacy)
D	**Post-marketing requirements**
	Basis for interchangeability, switching and substitution
	Expectations on Pharmacovigilance (PV)
	Expectations on Risk management plan (RMP)

OBJECTIVES

The main objectives of this work were:

- To identify and collate the biosimilar guidelines of emerging agencies (ANVISA, Russian Federation, CDSCO, NMPA, SAHPRA, TITCK, COFEPRIS)
- Critically evaluate and review the guidelines of BRICS-TM agencies against a master checklist created by studying regulations of mature agencies
- To perform literature search on the biosimilar data assessment and approval process in BRICS-TM countries
- Comparison of biosimilar regulations of mature agencies with BRICS-TM agencies to identify similarities and differences in biosimilar development criteria
- Develop a list of challenges for BRICS-TM agencies pertaining to biosimilar development, data assessment and approval process.

HYPOTHESES

This study was conducted to test the following hypotheses:

- Biosimilarity principles and comparability criteria i.e, characterisation, non-clinical and clinical development for a biosimilar between mature agencies and emerging agencies are not fully aligned
- Within BRICS-TM agencies, the biosimilar development requirements might not be uniform (different in certain aspects like clinical efficacy studies)
- The post-marketing requirements including interchangeability, substitution and extrapolation of indications and pharmacovigilance are unresolved challenges in some or all of BRICS-TM agencies
- The data assessment, review and approval process among the BRICS-TM agencies might not be fully aligned.

METHODS

Data source

The current and valid English-language guidelines including published questions and answers for SAHPRA, South Africa (previously known as MCC) and 'Guidelines on Similar Biologics' from India were obtained from official websites of the respective regulatory agencies. Non-English language guidelines like resolution RDC nº 55/2010 published by ANVISA, technical guidelines for R&D and evaluation of biosimilar issued by Centre of Drug Evaluation (CDE) China, Guidelines on biosimilar medicinal product, Turkey and Official Mexican standard NOM-257-SSA1-2014 for biotechnological medications from Mexico were translated into English by a professional agency and/or a translated version was obtained from local resources for further review. All the relevant national guidelines for biosimilars and the related guidelines that were currently valid for biosimilar evaluation by each agency were gathered for the period 2014 to 2020. A literature review was conducted on the public domain including published literature, review articles from various search engines (like PubMed, Google Scholar) to understand the biosimilar review and approval processes in the BRICS-TM countries.

Data Processing and Analysis

The data pertaining to biosimilarity principles, comparability studies, selection of reference product, physico-chemical characterisation, manufacturing process and specifications determination, non-clinical studies (*in vitro* and *in vivo* studies, pharmacokinetic (PK) and pharmacodynamics (PD) studies), immunogenicity assessment), PK and PD studies in human, comparative clinical trials, clinical safety studies, extrapolation to other indications, interchangeability, switching and substitutions and pharmacovigilance and risk management plan were extracted from aforementioned guidelines. The data was qualitatively analysed to identify gaps within the emerging agencies and then compared to the guidelines from mature agencies. Further, the information related to biosimilar review and approval processes within the BRICS-TM countries retrieved from the public domain were analysed.

RESULTS

The results obtained from the evaluation of information obtained for BRICS-TM countries are presented as follows;

A. Literature review – Biosimilar expertise, review and approval process

An extensive literature search was conducted in the public domain using different search engines on data assessment, review and approval process for biosimilars in the BRICS-TM countries.

ANVISA, Brazil

Based on the information obtained from the literature search, the total number of staff at ANVISA, Brazil was found to be approximately 1,600, including 200 reviewers of marketing authorization/product licenses, who were primarily pharmacists. The agency performed full reviews of the dossier for New Chemical Entity (NCE) applications. However, prolonged regulatory timelines have been stated as limitation to patient access to medicines and performing full reviews, protracted company response times, and the requirement for a Certificate of Pharmaceutical Product (CPP) for product approval were the factors that contributed to lengthy review times. The new law, Law Number 13,411 (enacted in December 2016) that came into effect in March 2017 with risk-based approach to address the technical complexity of products. Based on clinical, economic, and social benefits of the medication, categorised them into regulatory review category I—a priority medicines, for which reviews are to be conducted in 120 days of receipt of the marketing authorization application (MAA) or category II—an ordinary medicine, for which reviews are to be conducted within 365 days of MAA receipt with provision for extension up to one-third of the original deadline. In 2017 and 2018, ANVISA published three new resolutions with the purpose of accelerating the approval of medicines: Resolution nº 204/2017, Resolution nº 205/2017, and Service Orientation nº 45/2018. Resolution nº 204/2017 established “Priority Review” criteria for medicines for neglected diseases, and vaccines to be incorporated in the national immunization program and post-approval applications when there is a public health risk of drug shortages. Resolution 205/2017 establishes a special procedure for the consent of clinical trials, certification of GMP, and registration of new medicines for treatment, diagnosis, or prevention of rare diseases.

Service Orientation 45, which establishes optimized review for registration and post-registration changes for biological products, is being considered a “Reliance Pilot Project.” Products already approved by the USFDA and EMA with same indications, dosage, adverse reactions, and precautions were eligible (Patel et al, 2020). Applicants must submit reports containing the criteria used by both agencies to review and approve these applications, thus allowing for efficient use of agency resources, while allowing the reviewers to maintain their ability to apply their expertise to the country-specific issues of the product (WHO, 2016b).

Russian Federation

The Russian law allowed the registration of biological drugs defined as medicinal products containing a biological active substance. An applicant is required to submit a registration dossier to the MoH, the regulatory body for drugs evaluation, with its affiliation Federal State Budgetary Institution - Scientific Centre for Expert Evaluation of Medicinal Products (FSBI-SCEMP). The complete dossier in Russian must be submitted to the MoH, and should include administrative documents, description of pharmaceutical properties and data about the manufacturing process, quality control, preclinical studies (pharmacological and toxicological) and clinical studies regarding the biological drug. Russia follows the European Guidelines for biosimilars for data requirements for the registration of a biological drug (Shekhar et al., 2020). The Russian regulator, The Ministry of Healthcare of the Russian Federation (the Ministry), is responsible for evaluating all regulatory submissions for novel biologics and biosimilar analytical and clinical data. However, manufacturing compliance and other GxP matters are handled separately by The Ministry of Trade. In Russia, there is no system in place for scientific advice meetings and all regulatory communications are carried out in writing. Yet, the approval process in Russia is quite timely. Regulatory decisions are made within a period of 200 days. During that time, a manufacturer is capable of sending and receiving responses to multiple written requests (Welch, 2017). The submission of documents and timelines for biosimilars is the same as for the registration of a biological product (which is considered to be a “pharmaceutical product”) (Roszdravnadzor). Registration is a procedure of expertise of the pharmaceutical product quality, efficacy and safety by State Regulatory Authority, post which the Registration Certificate (Marketing Authorization) is granted, and the product is introduced in the database of registered products in Russian Federation (Shekhar

et al., 2020). Pharmaceutical products pass more detailed and strict examination; need more documentation and additional expertise compared to the cosmetics. Local clinical trials must be conducted at medical institutions accredited by the MoH and on an average, clinical trial approval takes 90 Calendar days. The procedures for authorizing local clinical trials and international multicenter clinical trials (IMCTs) will include scientific and ethical review, and the duration for both types of studies will be 40 business days. Sponsors should include the results of local clinical trials in their drug registration dossier (Shekhar et al., 2020).

CDSCO, India

The authorities responsible for overseeing the approval process included Institutional Biosafety Committee (IBSC), for implementation of the biosafety regulatory framework; Review Committee on Genetic Manipulation (RCGM), to monitor the safety related aspect in respect of on-going research projects or activities involving hazardous microorganisms; Genetic Engineering Appraisal Committee (GEAC), a body established by the Ministry of Environment, Forest and Climate Change ("Environment Ministry") to appraise activities involving large scale use of hazardous microorganisms, GMOs or cells in research, industrial production and experimental field trials; and CDSCO, the apex regulatory body with respect to clinical trials, import and manufacture of all drugs in India including biologics and biosimilars. The Central Drug Authority, CDSCO defines information to be submitted for marketing authorization of new biological drug in a predefined format to simplify submission requirements. The approval process for biosimilar drugs is divided into pre-clinical trial, clinical trial and post clinical trial stages with each stage having different data package requirements. Thus, there are several challenges for filling up for approvals of biologics as they are extensive, exhaustive and at times excessive level of details required for description of a biological product. The biosimilar can be developed in India only if the reference innovator is registered here. Otherwise, it needs to be marketed for a minimum of 4 years in a well-regulated market to gain marketing authorization (Pharmaboardroom, 2020c).

NMPA, China

In 2015, China created a standardized regulation for the development and evaluation of biosimilars. The country since 2018 has allowed priority review and approval for drugs that address urgent clinical needs and potential clinical trial exemptions for drug applications supported by robust clinical data from trials conducted overseas. Each of the timeframes from IND application to drug marketing authorization is measured in days, with the single longest step taking only 90 days. If an IND applicant does not receive any negative or questioning opinions from the NMPA within 60 days of the date of application acceptance and payment of the fee, clinical trials may be conducted in accordance with the plan that has been submitted. In 2018 and 2019 the Chinese government identified 78 priority drugs for which approval processes could be expedited and overseas clinical trial data used to support the applications (Hagen, 2021).

SAHPRA, *South Africa*

In SAHPRA, the Biologicals Sub-Unit is responsible for a) biological new registration applications and responses to resolutions, and matters pertaining to biological medicines during review for registration; b) evaluation of technical changes to registered biological medicines and “old” biological medicines; c) evaluation of clinical aspects of the Professional Information and relevant changes to Professional Information for biological medicines; d) technical support to other units with respect to biological matters. The new registration applications need to comply with current guidelines and submitted in eCTD or eSubmission format. SAHPRA will be implementing reliance models for qualifying applications. SAHPRA follows one of four evaluation / review pathways: a) Full review b) Abridged review c) Verified review d) Recognition Review pathways (b), (c) and (d) represent reliance-based evaluations.Wherever possible, SAHPRA will leverage these pathways. A GMP certificate or equivalent manufacturing licence is required as evidence of GMP compliance. The Summary of Critical Regulatory Elements (SCoRE) document is designed to enable a top- down summary-driven approach to reviews, reducing evaluation time of all applications. All new registration applications will require a completed SCoRE document. SAHPRA has adopted the EMA format for Professional Information and Patient Information Leaflets. Before an application is evaluated, it will

go through a screening process. The screening process will confirm that all SAHPRA's requirements have been met, ensuring that only high-quality dossiers are allocated for evaluation. Applicants are required to complete and submit a validation template. If an application fails a screening step, two outcomes are possible: 1. If the failure does not affect the next validation step, the application can proceed to the next screening step. When the next updated sequence is submitted, all previous queries will be consolidated and will need to be updated in a single sequence; 2. If the failure prevents the application from proceeding to the next validation step, a query round will be started and the applicant will need to submit an updated sequence. Applicants will be kept informed of their application's status via an online tracker, which will be updated when an application passes screening. After passing screening, the application will be allocated to an evaluator from each relevant SAHPRA unit (e.g. Clinical, Quality (Pharmaceutical and Analytical), Inspectorate, Names and Scheduling, for a new registration application). The primary evaluation from each unit will then be peer reviewed by a senior evaluator. Should there not be consensus on the final outcome or outstanding queries, then the application will be allocated to an Advisory Committee for input. This re-engineered process is intended to streamline evaluations, reserving the Advisory Committee for the evaluation of relatively complex evaluations and responses. If an application passes evaluation, recommendations will be consolidated for final review and registration or rejection by SAHPRA. If either the number of query rounds or the time to respond to queries is exceeded, the application will be at risk of rejection. Should a longer query response time be needed by an applicant, motivation should be provided. Extensions can be requested and they will be reviewed on a case by case basis (SAHPRA, 2019a).

TITCK, Turkey

The TITCK performs a full review for all new active substance (NAS) applications. Submission of a CPP with an application is not required; however, evidence of approval in another country is required for final authorization by the TITCK. Pricing data are not required by the TITCK at the time of submission; however, pricing must be completed to enable products to be commercially available. Measures of Good Review Practices (GRevP) are in place, but the implementation by the TITCK is not currently formalized (Mashaki Ceyhan et al., 2018).

COFEPRIS, Mexico

Biologics are treated differently to non-biologic drugs for the purposes of gaining regulatory approval. The biologics-specific path is mainly provided in the Mexican official standard Rule, NOM-257-SSA1-2014 “Regarding biologic medicines” and must comply with additional dossier requirements including proof of GMP for medicinal products. The agency considers prior registration of the product in reference country followed by a request meeting by the foreign manufacturer with New Molecules Committee (NMC). A third party evaluates the technical file and issues report post which the manufacturer can submit registration request to COFEPRIS. If the foreign manufacturer has no prior registration in reference country, a request for GMP certificate in country of origin and a local clinical studies in the Mexican population is required before the NMC meeting. Once the application is submitted, COFEPRIS takes about 180 calendar days for review of the dossier. Different approaches can be followed based on the type of product and its application. Drug manufacturers must renew their marketing authorization every five years, subject to the relevant tests, including submission of a certificate of good manufacturing practices in force (Pharmaboardroom, 2021).

B. Identification and retrieval of guidelines - Biosimilar Development Criteria

An extensive search was carried out to gather the regulatory guidelines pertaining to biosimilar products from the official website of emerging regulatory agencies of the BRICS-TM countries. The list of reference guidelines that were identified and retrieved from each agency for critical evaluation are presented in Table 4.2.

The retrieved guidelines were subsequently extensively studied and scrutinised qualitatively for biosimilar medicines development and approval. For comparative evaluation, parameters including biosimilarity principle, comparability criteria, quality comparison, non-clinical development, clinical development were considered to identify gaps in these aspects in the BRICS-TM countries. Accordingly, the results are presented under four sections as below:

Part I - Biosimilarity principles

Part II - Reference product selection

Part III - Comparability studies (quality, non-clinical and clinical studies)

Part IV - Post-marketing requirements, extrapolation to other indications, including interchangeability, switching and substitution, pharmacovigilance, and risk management plan.

Table 4.2 List of reference regulatory guidelines from BRICS-TM agencies

Country	Agency name	Reference guidelines
Brazil	ANVISA	Registration of new biological products and biological products, and other provisions, Resolution - RDC No. 55, December 16 (2010)
Russia	MoH	Registration dossier for finished medical product, Russian federal law no. 61-FZ (2014)
India	CDSCO	The New Drugs and Clinical Trials Rules, 2019, The Gazette of India (2019)
		Guideline on similar biologics: regulatory requirements for marketing authorisation in India (2016)
		Guideline on similar biologics: regulatory requirements for marketing authorisation in India (2012)
China	NMPA	Appendix Technical Guidelines for R&D and Evaluation of biosimilar (Trial) (2015)
South Africa	SAHPRA	Biosimilar medicines quality, non-clinical and clinical requirements 2.30_Biosimilars_Aug14_v3 (2014)
Turkey	TITCK	Draft guideline on biosimilar medicinal products (2015)
Mexico	COFEPRIS	Official Mexican standard NOM-257-SSA1-2014, biotechnological medications (2014)

Part I - Biosimilarity Principles

A biosimilar is a biological product that is very similar to a reference biologic and for which there are no clinically meaningful differences in terms of safety, purity, and potency (Anderson, 2021). The objective of the development plan of such products is to prove similarity in terms of quality and efficacy to the reference biological product. With regards to safety, a better safety profile is allowed; they can also be expected to have a lower impurity profile than the originator. The biosimilarity principles encompass terminology, development approach, basis of biosimilarity, demonstration of biosimilarity with the chosen reference product, simplified approach and regulatory framework across advanced regulatory agencies and national regulatory authorities of the BRICS-TM.

SRAs - Different terminologies such as similar biological medicinal product, biosimilar, similar biological product, biosimilar biological drug is being used to define similar versions of reference biological/ biotechnological products, as explained in Chapter 1. The stepwise development approach for characterisation, *in vitro* and *in vivo* non-clinical studies and clinical studies is uniform across mature regulatory agencies and a *totality-of-evidence* approach for assessment of biosimilarity is followed (EMA, 2015; CDER & CBER, 2015b; Health Canada, 2017; WHO, 2017b), which is described in Chapter 3. Also, the biosimilarity principles considered under biosimilar medicine regulation of TGA and Swissmedic guidance document for authorisation of biosimilars are based on a stepwise demonstration of the proposed biosimilar product with the reference biological product (RBP), broadly aligned with EMA (TGA, 2018; Swissmedic, 2020b). However, the approach to biosimilarity is not clear in some of the agencies of the BRICS-TM countries.

BRICS-TM - The regulatory standards and framework developed in the BRICS-TM countries are based on the WHO guidelines. Depending on the demonstration of biosimilarity, the application can either be filed as a stand-alone or an abbreviated dossier with ANVISA, Brazil. A simplified approach (in terms of smaller clinical trial if bioassay is known to be clinically relevant or number of patients may vary depending upon the endpoints) is defined with EMA, WHO and USFDA with prior regulatory opinion; however, such transparency is yet to be defined in detail by other BRICS-TM agencies except TMMDA and SAPHRA (ANVISA, 2010; CFDA, 2014; COFEPRIS, 2014; MCC, 2014, Russian federation, 2014a; CDSCO, 2016; TITCK, 2017; WHO, 2017b; WHO, 2017c). Brazil, Russia and Mexico stresses either on comparative clinical studies or no defined recommendations in their published guidelines.

Table 4.3 indicates differences and similarities within the BRICS-TM agencies pertaining to biosimilarity principles. The other parameters i.e., posology, route of administration, strength, pharmaceutical form, formulation, improved efficacy and safety, extrapolation of indications, biosimilarity post approval, interchangeability, switching and substitution seems unclear in most of the emerging markets. Hence, comparison of the BRICS-TM regulatory guidelines with established agencies shows that the expectations on biosimilarity principles by the BRICS-TM agencies are yet to be updated as per the EMA or the USFDA.

Table 4.3 Biosimilarity principles in BRICS-TM regulatory agencies

	ANVISA	Russia MoH	CDSCO	NMPA	SAHPRA	TITCK	COFEPRIS
Terminology	Biological product	Biosimilar	Similar biologic	Therapeutic biological products	Biosimilar	Similar biological medicinal product	Biocomparable biotechnological medications
Development approach	n/d	n/d	Sequential process	Gradual progressive sequence	Stepwise clinical development	Stepwise approach	n/d
Basis of biosimilarity	n/d	n/d	Sufficient testing to ensure acceptable levels of Q, S, E	Based on comparable, Q, S, E	Appropriate comparability exercise	Comprehensive comparability studies	n/d
Demonstration of biosimilarity with reference product	n/d	n/d	Confirmatory clinical safety and efficacy can be waived subject to conditions met	Comparative clinical trial study	Necessary comparative clinical trials (not the clinical efficacy de novo)	By comparing clinical performance and differences	n/d
Stand-alone/ abbreviated application	Stand alone or biosimilar pathway for approval but not defined in detail	n/d	1. Extensive non-clinical/clinical study if significant differences in Q, S, E or 2.Non-qualification of similar biologic	n/d	Full clinical submission if similarity not proved	New substance application if biosimilarity not proved	n/d

	ANVISA	Russia MoH	CDSCO	NMPA	SAHPRA	TITCK	COFEPRIS
Simplified Approach	Waiver/reduction of preclinical and/or clinical study not identified	n/d	Reduced preclinical and/or clinical data based on comparability demonstration and consistent production processes	n/d	Reduced non-clinical and clinical data if none differences	No confirmatory clinical trial, acceptable with regulatory authority opinion, safety and efficacy to be deduced based on physicochemical characteristics, biological activity/ potency and PKPD profile of reference and biosimilar product	n/d
Regulatory framework	General Office of Biologicals of ANVISA responsible for biosimilar evaluation and regulated by RDC nº 55/2010	Russian Federation Law No. 61-FZ On the Circulation of Medicines	Regulated as per the Drugs & Cosmetics Act, 1940, the Drugs and Cosmetics Rules, 1945 (as amended)	Guidelines on Biosimilars: Research, Development and Evaluation, dated 28 February 2015	Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended & the relevant Regulations	Legislation of Marketing Authorisation for Human Medicinal Products (10.01.2005/25705)	Official Mexican STANDARD NOM-257-SSA1-2014, Biotechnological Medications

BRICS-TM- Brazil, Russia, India, China, South Africa, Turkey, Mexico; *Q, S, E- Quality, Safety, Efficacy*; *n/d- Not defined*

Part II - Reference product selection

The RBP selected for comparability studies must be licensed with a full dossier including quality, safety and efficacy. For most regulatory agencies, it must be sourced from the same territory where the biosimilar authorisation is requested. This is also true for established agencies.

SRAs - According to the EMA norms, the RBP must be approved in the European Economic Area (EEA), as per article 8 of 2001/83/EC, as amended. However, in addition to EEA, the agency allows the applicant to utilise non-authorised reference product from ICH countries, to be used in certain non-clinical and clinical studies subject to sameness being proved with EEA authorised reference product. In the US, to successfully achieve biosimilar medicine approval under section 351(k) of the PHS act, sponsors are advised to use US licensed reference product for development. In case non-US licensed reference products are utilised for animal or clinical studies, sponsors are encouraged to take prior scientific advice from the agency. WHO advises NRAs to define criteria for selection of a reference product while demonstrating biosimilarity between SBP and proposed biosimilar. Both TGA and Swissmedic agencies prefer to have the reference product sourced from their own market, which is authorised based on submission of a full dossier. However, similar to EMA, the agencies have provisions for using non-authorised reference product from another market having a similar regulatory system, supported by bridging studies.

BRICS-TM - a similar approach for using an authorised reference product by another regulatory agency for comparability studies or using bridging studies or seeking prior advice from agencies on such an approach is yet to be defined (ANVISA, 2010; CFDA, 2014; COFEPRIS, 2014; MCC, 2014; Russian federation, 2014a; CDSCO, 2016; TITCK, 2017). The following gaps have been identified in emerging agencies requirements pertaining to reference product selection:

- Sourcing of reference product from their own country is mandatory. ANVISA, CDSCO, SAHPRA allows sourcing from other jurisdictions subject to certain conditions. No defined criteria from the rest of the agencies for non-availability of reference products in their country
- The criteria of approval and marketing in their own country with a full registration dossier i.e., quality, safety and efficacy data varies in BRICS-TM agencies

- The expectation on identity i.e., brand name, pharmaceutical form, manufacturing site details, expiration details and other labelling requirement of the reference product remains undefined by BRICS-TM agencies
- No information from the agencies on usage of alternate reference product and requirement of the bridging data
- It is expected to use multiple lots of reference products during development and no specific number of lots are pre-defined in the guidelines
- Biosimilar products are not allowed to be used as reference products across the BRICS-TM agencies
- RBP sourcing approved by other emerging regulatory agencies are not acceptable.

Table 4.4 lists the criteria of the BRICS-TM agencies for reference product selection.

Table 4.4 Reference product selection criteria in BRICS-TM agencies

Reference product selection	ANVISA	Russia MoH	CDSCO	NMPA	SAHPRA	TITCK	COFEPRIS
Selection of Reference product	Approved based on full registration dossier with ANVISA Brazil	Biosimilar products	Should be licensed in India or ICH countries, Innovator product, approved by full dossier including quality, safety and efficacy	China approved product is mandatory for clinical comparison study	Registered with MCC based on complete quality, safety and efficacy data and innovator product	Reference medicinal product must be authorised with complete dossier by competence authorities	Should have valid registration issued by COFEPRIS, commercially available in Mexico
Non-Reference product	Non-Brazil reference product from countries having similarity with ANVISA and access to full dossier.	n/d	Non-ICH reference product sourcing not defined	n/d	Sourced from MCC aligning countries	n/d	Biosimilar can be used as reference product subject to biosimilarity being demonstrated
Bridging	n/d	n/d	n/d	n/d	n/d	No need	n/d
Identity of Reference product	n/d	n/d	n/d	n/d	n/d	Should be identifiable (brand name, pharmaceutical form, formulation, manufacturing and expiration date)	n/d
Sameness of Reference product	Same biological product is used throughout the comparability exercise	n/d	Same reference product throughout comparability study	Expected to use same source of origin throughout comparability study	n/d	Single reference product throughout comparability study of Q,S,E	n/d

n/d- Not defined; Q,S,E- Quality Safety Efficacy

Part III - Comparability studies

Quality

The primary step of the comparability exercise starts with characterisation of a RBP to establish a Quality Targeted Product Profile (QTPP) of the proposed biosimilar. Table 4.5 demonstrates comparative quality attributes across the BRICS-TM agencies.

SRAs - As evident in Chapter 3, the established agencies have defined the comparability studies requirements to a great extent. In addition to biosimilarity principles and selection of a reference product, the EMA explicitly defines comparability requirements in quality, nonclinical and clinical segments and expects applicants to a follow step-wise development approach. The quality characterisation part comprises of physicochemical characterisation i.e, structure, immunological properties, biological activity, purity impurity and contaminants, cell lines, quantity, specification, manufacturing process, overages and compatibility studies. The non-clinical studies are further categorised into *in-vitro* and *in-vivo* toxicological studies whereas clinical studies encompass clinical safety, efficacy and pharmacodynamics (PD) studies. The *Totality-of-the-Evidence* approach followed by the USFDA encompasses data for structural and functional characterisation, non-clinical evaluation, human PKPD data, clinical immunogenicity data and comparative clinical studies data. WHO and BRDD has also broadly covered all four components of characterisation. The expectation of comparability studies from TGA and Swissmedic is based on ICH Q5E, EU or USA guidance.

BRICS-TM - The critical evaluation of regulatory guidelines from the BRICS-TM agencies on comparative characterisations revealed differences among the agencies. Table 4.5 depicts the comparative quality attributes for biosimilar development across the BRICS-TM markets.

ANVISA

Resolution RDC nº 55/2010 specifies requirements pertaining to primary, secondary, tertiary and quaternary structure characterisation; however immunological properties of biological products are not defined. The agency expects biological activity to be determined, however type of assays required are not defined in the guidelines.

Impurity profile, process related impurities and contaminants are expected to be characterised, without clarity on requirements for purity and heterogeneity. The criteria regarding cell lines (expression systems), quantity and specifications are not defined (ANVISA, 2010).

Russia MoH

The Russian Federation Law number 61-FZ on the circulation of medicines in Russia contains little on biosimilars. Hence characterisation specifics for biotechnological/ biological products are difficult to understand for manufacturers (Russian federation, 2014b).

CDSCO

The CDSCO India has established guidelines on similar biologics based on WHO guidelines. The requirements for similar biologic characterisation remain in line with WHO, with expectations on qualified assays. However, detailed requirements on characterisation are not available. The biological assays are expected to be determined; however, the types of assays are not defined. Evaluation of multimers, aggregates and process related impurities are expected to be carried out, but the expectations on orthogonal methods for purity, contaminants, heterogeneity remain unclear. The cell lines and quantity essentials are not spelled out (CDSCO, 2016).

NMPA (previously known as CFDA)

The agency recommends identifying and characterising primary and advanced structure (secondary/ tertiary/ quaternary), structural heterogeneity and glycosylation for the biosimilar product. The expectations for immunological properties, specifically for mAb biosimilars are to have comparative qualitative and quantitative analysis for Fab- and Fc- fragment including affinity for antigens, CDC and ADCC activity, affinity for FcRn, Fc gamma and C1q receptors. Purity is to be determined in terms of hydrophobicity, charge and molecular size variant and various type of post translational modifications including glycosylation. Process impurities and other new impurities to be characterised. The agency expects biological activity to be performed, consistent with the reference drug, however, details are not provided. The cell lines

and quantity criteria remain undefined. The specifications should be consistent with the reference drug and sensitive and advanced analytical methods to be used to detect potential differences between the candidate drug and reference drug. It is recommended to use sensitive conditions for accelerated and forced degradation stability studies (CFDA, 2014).

SAHPRA (previously known as MCC)

The biosimilar and reference product should be structurally, physico-chemically and biologically similar as per SAHPRA guidelines. The agency's requirement on biosimilar characterisation remains consistent with WHO/EMA. The immunological properties, cell lines and quantity criteria are undefined, whereas biological activities are expected to be characterised by both *in vitro* and *in vivo* assay(s). Heterogeneity and contaminants are not specified but are expected to have test performed for aggregate formation and for quantifications of impurities. The process related impurities should be characterised and validated analytical techniques are expected to be used for characterisation (MCC, 2014).

TITCK

Turkish draft biosimilar guideline is in parallel with EMA's overarching biosimilar guidelines. It is stated that this guideline could apply for any biological medicines, including mAbs. According to the guideline, a physico-chemical characterisation programme should include primary and higher order structures of the biosimilar. Any detected differences between the biosimilar and the reference medicinal product should be justified with respect to the micro-heterogeneous pattern of the reference product. The immunological functions of mAbs (for example) and related substances (e.g., fusion proteins based on IgG Fc) should be fully compared. This would normally include a comparison of affinity of the products to the intended target. In addition, binding affinity to relevant receptors (e.g., FcγR, C1q, and FcRn) should be compared unless otherwise justified. Appropriate methodology should also be employed to compare the ability to induce Fab- and Fc-associated effector functions. Biological assays using different and complementary approaches to measure the biological activity should be considered, as appropriate. Depending on the biological properties of the product, different assay formats can be used (e.g., ligand or receptor binding

assays, enzymatic assays, cell-based assays, functional assays), recognising their limitations. Complementary or orthogonal approaches should be followed to accommodate limitations regarding validation characteristics of single bioassays. State-of-the-art analytical technologies following existing guidelines and pharmacopoeial requirements are to be applied to identify both product-related and process-related substance and impurities and the potential risks related to these identified impurities (e.g., immunogenicity) will have to be appropriately documented and justified. The cell lines criteria remain unspecified. The rationale used to establish the proposed range of acceptance criteria for routine testing is expected by the agency. The claimed shelf life of the product should be justified with full stability data obtained with the biosimilar medicinal product. Comparative real-time, real-condition stability studies between the biosimilar and reference medicinal product are not required (TITCK, 2017).

COFEPRIS

In Mexico, WHO Similar Biologic Products (SBP) guidelines have been used as reference to establish the Official Mexican Standard NOM-257-SSA1-2014. The standards provide an overall expectation for the biocomparable product. There is no specific guideline pertaining to mAbs biosimilar yet. Characterisation criteria are undefined. Further, the immunological properties, biological activity, purity, impurity, contaminants, cell lines, quantity and specifications are unclear (COFEPRIS, 2014).

The requirements pertaining to the manufacturing process, overages and compatibility remains unclear across the BRICS-TM countries.

Table 4.5 Comparative quality attributes across BRICS-TM agencies

Characterisation	ANVISA	Russia MoH	CDSCO	NMPA	SAHPRA	TITCK	COFEPRIS
Structure							
Primary and higher order structure	To be characterised	n/d	To be characterised but not specified requirement	To be characterised	Primary and higher order structure to be characterised (including class and subclass determination, kappa and/or lambda chain)	To be characterised	To be characterised but not specified requirement
Amino acid	n/d	n/d	n/d	n/d	Amino acid sequencing and variability of N- and C- terminal to be confirmed	n/d	n/d
Groups and bridges	n/d	n/d	n/d	To be characterised	Free sulphydryl groups and disulfide bridges to be determined, integrity and mismatch of bridge to be analysed	To be justified if difference detected with reference product	n/d
Carbohydrate	n/d	n/d	Carbohydrate structures to be defined	n/d	Carbohydrate content and structure, oligosaccharide pattern to be confirmed	n/d	Carbohydrate structures to be defined
Glycosylation	n/d	n/d	Evaluation of glycosylation	To be characterised	Presence/absence of additional glycosylation site(s)	n/d	Evaluation of glycosylation

Characterisation	ANVISA	Russia MoH	CDSCO	NMPA	SAHPRA	TITCK	COFEPRIS
			pattern including site occupancy		to be confirmed, glycosylation site(s) with occupancy and to be analysed		pattern including site occupancy
Glycan/ Isoforms	n/d	n/d	Comprehensive evaluation including number or type of glycans and qualitative identification in case glycan non-existent in human, analysis of glycans	n/d	Glycan structure to be characterised for degree of mannosylation, galactosylation, fucosylation and sialylation with distribution of main glycan structures to be determined	n/d	Comprehensive evaluation including number or type of glycans and qualitative identification in case glycan non-existent in human, analysis of glycan
Immunological properties (specifically for mAbs)							
Antigen binding assay	n/d	n/d	n/d	Fab and Fc region	n/d	Fab and Fc region	n/d
Cytotoxicity evaluation	n/d	n/d	n/d	CDC and ADCC activity	n/d	n/d	n/d
Cross-reactivity	n/d	n/d	n/d	n/d	n/d	n/d	n/d
CDR	n/d	n/d	n/d	n/d	n/d	n/d	n/d
Epitope	n/d	n/d	n/d	n/d	n/d	n/d	n/d
Complementary ability evaluation	n/d	n/d	n/d	FcRn and Fc and C1q receptor affinity	n/d	FcRn and Fc and C1q receptor affinity	n/d
Biological assays							
In vitro/vivo assay	Required but no detailed guideline	n/d	Required but no detailed guideline	Bioactivity test	Required but no detailed guideline	Binding, enzymatic, cell-based, functional assays	n/d

Characterisation	ANVISA	Russia MoH	CDSCO	NMPA	SAHPRA	TITCK	COFEPRIS
Approach	n/d	n/d	n/d	n/d	n/d	Complementary or orthogonal approaches	n/d
Product effector functions	n/d	n/d	n/d	n/d	n/d	n/d	n/d
Purity, impurity and contaminants							
Purity	n/d	n/d	Orthogonal method remains unspecified	Hydrophobicity, charge and molecular size variant, post translation modification	n/d	In line to EMA	n/d
Structural heterogeneity	n/d	n/d	Orthogonal method remains unspecified	n/d	n/d	n/d	n/d
Multimers, aggregates and particulates	n/d	n/d	Should be evaluate	n/d	aggregates formation test	n/d	n/d
Impurity profile and Process-related impurities	To be performed	n/d	Process-related impurities should be evaluated	Required but no detailed guideline	Required but no detailed guideline	Process and product-related impurities should be evaluated	n/d
Contaminants	To be performed	n/d	Unspecified	n/d	n/d	In line to EMA	n/d
Cell lines							
Cell lines/ Expression system	n/d	n/d	n/d	n/d	n/d	n/d	n/d
Immortalisation approach	n/d	n/d	n/d	n/d	n/d	n/d	n/d
Hybridoma cell lines	n/d	n/d	n/d	n/d	n/d	n/d	n/d

Characterisation	ANVISA	Russia MoH	CDSCO	NMPA	SAHPRA	TITCK	COFEPRIS
Quantity							
Basis for quantity determination	n/d	n/d	n/d	n/d	n/d	Should be described	n/d
Specifications							
Specification determination	n/d	n/d	n/d	consistent with reference product	n/d	n/d	n/d
Tests selection	n/d	n/d	n/d	Sensitive and advanced	n/d	n/d	n/d
Acceptance criteria	n/d	n/d	n/d	n/d	n/d	n/d	n/d
Validated methods for characterisation	n/d	n/d	Qualified assay	n/d	Qualified assay	n/d	n/d
Analytical methods for lot release	n/d	n/d	n/d	Advanced method to be used	n/d	n/d	n/d
Reference materials and Standard	n/d	n/d	n/d	n/d	n/d	n/d	n/d
Accelerated stability data	n/d	n/d	n/d	Required but no detailed guideline	n/d	n/d	n/d
Experimental stability data	n/d	n/d	n/d	n/d	n/d	n/d	n/d
In-process stability data	n/d	n/d	n/d	n/d	n/d	n/d	n/d
Routine stability study	n/d	n/d	n/d	Required but no detailed guideline	n/d	Claimed shelf life obtained from full stability data	n/d

n/d: Not defined

Non-clinical studies

In vitro studies

The *in vitro* assay related information is not defined in the guideline published by ANVISA, Russian MoH, NMPA and COFEPRIS (ANVISA, 2010; CFDA, 2014; COFEPRIS, 2014; Russian federation, 2014). The CDSCO defines *in vitro* cell based bioassays i.e., cell proliferation/cytotoxicity/neutralising/receptor binding assays to be performed as part of *in vitro* studies (CDSCO, 2016). The requirements for SAHPRA and TITCK are defined in line with EMA's overarching biosimilar guidelines (MCC, 2014; TITCK 2017).

In vivo studies

ANVISA - The agency insists on comparative *in vivo* non-clinical studies covering pharmacodynamics studies for intended indications and repeat dose-toxicity studies with toxico-kinetics in relevant species (ANVISA, 2010).

Russia MoH, COFEPRIS - Information on PD studies and toxicity studies is not available (COFEPRIS, 2014; Russian federation, 2014).

SAHPRA - The SAHPRA guideline requires *in vivo* animal studies, with at least one repeat-dose toxicity study with toxico-kinetic measurements to show comparative toxicity and bioactivity. Such a study should analyse immunogenicity as well as relevant specific safety concerns. Other toxicological studies are not required unless needed, based on the reference product (MCC, 2014).

CDSCO - As per CDSCO guidelines, *in vivo* studies might not be required if similarity is proven in the previous steps. A repeat-dose toxicity study is recommended to be performed, at a minimum one repeat-dose study, with at least 1X of human equivalent dose (HED), in a relevant animal model, with intended route of administration, for not less than 28 days with a 14 days recovery period. For a pharmacologically relevant animal model, the intended route of administration should be included. In case a relevant model is not available, studies should be performed in two species i.e. one rodent and other non-rodent species. For immunogenicity studies, the CDSCO requires comparative antibody responses in a suitable animal model study, which should be part of a sub-chronic repeated-dose study. The local tolerance studies and other toxicological studies requirements are aligned with WHO, whereas safety

pharmacology, reproductive toxicology, mutagenicity and carcinogenicity studies are generally not required unless justified based on the RBP's properties (CDSCO, 2016). NMPA - The NMPA needs comparative non-clinical *in vivo* studies - single dose and repeat-dose toxicity studies are essential to be performed (CFDA, 2014).

TITCK – The requirements are defined in line with EMA's overarching biosimilar guidelines (TITCK, 2017).

Table 4.6 illustrates the comparative non-clinical (*in vitro* and *in vivo*) requirements across the BRICS-TM agencies. Unlike WHO, EMA and FDA, that has described comparative non-clinical evaluation in a stepwise manner as seen in Chapter 3, there is no defined step-wise approach followed across the BRICS-TM agencies for comparative non-clinical studies.

Table 4.6 Comparative non-clinical attributes across BRICS-TM agencies

Non-clinical	ANVISA	Russia MoH	CDSCO	NMPA	SAHPRA	TITCK	COFEPRIS
In vitro							
Assay type	n/d	n/d	Cell based assay	n/d	Comparative binding and binding assays	Comparative binding and binding assays	n/d
In vivo							
PKPD	Mandatory	n/d	n/d	Comparative PKPD	n/d	Dose concentration response assessment	n/d
Toxicity	Repeat dose	n/d	Repeat dose (1X HED)	Single and Repeat dose	Repeat dose	Repeat dose (flexible approach if non-human primate); Unspecific (for relevant species)	n/d
Immunogenicity	n/d	n/d	Comparative Ab response	n/d	Comparative bioactivity	Non predictive in human, use for PKTK evaluation	n/d
Safety	n/d	n/d	n/d	Comparative safety data	Comparative toxicity	n/d	n/d
Local tolerance	n/d	n/d	Performed	n/d	n/d	For novel excipients	n/d

n/d: Not defined, PK: Pharmacokinetics, TK: Toxicokinetics, Ab: Antibody, HED: Human effective dose

Clinical studies

The comparative clinical studies include pharmacokinetics (PK), pharmacodynamics (PD), clinical efficacy and clinical safety studies. The different regulatory requirements for comparative clinical studies from the BRICS-TM agencies are detailed as below;

ANVISA – The agency accepts combined comparative PK/PD studies, however, there is no detailed information available in Resolution RDC nº 55/2010. Similarly, the agency mandates the conduct of comparative clinical studies for proving safety and efficacy with no detail in the guidelines (ANVISA, 2010).

Russia MoH - The biologic specific information is unavailable in the Russian guideline (Russian federation, 2014a).

CDSCO - The PK study requirements are aligned with those of the WHO. A comparative, parallel/cross-over, healthy volunteers/patients, PD study is recommended if at least one PD marker is linked with efficacy, which is well characterised for the reference biologic. If a PK study can be done in patients and PD marker is not available, then PK and PD studies can be combined in a phase III clinical trial. Confirmatory safety and efficacy are mandatory for similar biologics with clinical design expectations of equivalence, non-inferiority or comparability phase III clinical trials to be conducted. Trial population size can be reduced if a similar biologic is indicated for rare diseases. Comparative safety study to be performed based on adverse events, nature, severity and frequency. It is stated that immunogenicity data should be obtained in PK/PD studies, if a phase III trial is waived. No further details were available for immunogenicity studies. Pre and post approval safety assessment data are required. If safety and immunogenicity studies are performed in more than 100 patients during pre-approval, phase IV studies, patient numbers can be reduced accordingly (CDSCO, 2016).

The CDSCO has upgraded regulatory norms for clinical trials via the New Drug Clinical Trials Rule 2019 (MoHFW, 2019). In India, Schedule Y of Drugs and Cosmetics Act and Rules defined the requirement for clinical trials of new drugs and investigational new drugs for manufacturing and import prior to the New Drug Clinical Trial Rules (NDCTR) 2019 came into effect. The revised comprehensive NDCTR closes some of the gaps existing in Schedule Y in terms of number of subjects, nature and timing of

non-clinical studies, content of the proposed protocol for performing clinical trials etc. As part of the first schedule, General Principles and Practices for Clinical Trial section (3) (2)(c) (iii), pertaining to new drugs approved outside India, the phase III study may need to be performed in India. It explicitly states that Phase III studies need to be carried out if scientifically and ethically justified to establish data for safety and efficacy of drugs in Indian patients. It further states that PK studies may be required by the Central Licensing Authority (CLA) in Indian patients. Table 4.7 reflects differences between Schedule Y of Drugs and Cosmetic Act with revised Clinical trial requirement as per NDCTR 2019 (MoHFW, 2019).

Table 4.7 Revised non-clinical and clinical expectations as per NDCTR 2019, CDSCO, India

Criteria	Schedule Y	NDCTR 2019
Non-clinical study expectations		
Nature and timing of conduct of non-clinical studies	n/d	(i) characteristics of the new drug or investigational new drug; (ii) disease of conditions for which the new drug or investigational new drug is intended to be indicated; (iii) duration and exposure in clinical trial subject; (iv) route of administration. **Reference- Chapter XIII: Miscellaneous - First Schedule (3)(a)(i)**
Content of the proposed protocol for conducting clinical trials	n/d	Contents required are specified in detail. **Reference- Chapter XIII: Miscellaneous - Third Schedule Conduct of clinical trial - Table 2**
Single-dose toxicity studies	n/d	Carried out in 2 rodent species (mice and rats) using the same route as intended unless intravenous for humans. If possible, the target organ of toxicity should also be determined. The dose causing severe toxic manifestations or death should be defined in the case of cytotoxic anticancer agents, and the post-dosing observation period should be up to 14 days. **Reference- Chapter XIII: Miscellaneous Second Schedule (2)(1)(1.1)(1.1.1)**
Repeated-dose systemic toxicity studies	Repeat dose (1X HED)	Should be carried out in at least two mammalian species, of which one should be a non-rodent. Dose ranging studies should precede the 14-, 28-, 90- or 180- day toxicity studies. **Reference- Chapter XIII: Miscellaneous Second Schedule (2)(1)(1.1)(1.1.2)**
Male fertility study	n/d	Should be done in one rodent species (rat preferred). **Reference- Chapter XIII: Miscellaneous Second Schedule (2)(1)(1.2)**
Female fertility study	n/d	Should be done in one rodent species (rat preferred).

Criteria	Schedule Y	NDCTR 2019
		Reference- Chapter XIII: Miscellaneous Second Schedule (2)(1)(1.3)(1.3.1)
Teratogenicity study	n/d	One rodent (preferably rat) and one non-rodent (rabbit) species are to be used. **Reference- Chapter XIII: Miscellaneous Second Schedule (2)(1)(1.3)(1.3.2)**
Local toxicity	Repeat dose (1X HED)	Study designs should include three dose levels and untreated or vehicle control, preferably use of two species, and increasing group size with increase in duration of treatment. **Reference- Chapter XIII: Miscellaneous Second Schedule (2)(1)(1.4)**
Dermal toxicity study	n/d	Study may be done in rabbit and rat. The initial toxicity study shall be carried out by non-animal alternative tests. **Reference- Chapter XIII: Miscellaneous Second Schedule (2)(1)(1.4)(i)**
Photo-allergy or dermal photo-toxicity	n/d	It should be tested by Armstrong or Harber test in guinea pig. This test should be done if the drug or a metabolite is related to an agent causing photosensitivity. **Reference- Chapter XIII: Miscellaneous Second Schedule (2)(1)(1.4)(ii)**
Vaginal toxicity test	n/d	Study is to be done in rabbit or dog. **Reference- Chapter XIII: Miscellaneous Second Schedule (2)(1)(1.4)(iii)**
Rectal tolerance test	n/d	Study may be performed in rabbits or dogs. **Reference- Chapter XIII: Miscellaneous Second Schedule (2)(1)(1.4)(iv)**
Ocular toxicity studies	n/d	These studies should be carried out in two species albino rabbit. **Reference- Chapter XIII: Miscellaneous Second Schedule (2)(1)(1.4)(vi)**
Inhalation toxicity studies	n/d	The studies are to be undertaken in one rodent and one non-rodent species. **Reference- Chapter XIII: Miscellaneous Second Schedule (2)(1)(1.4)(vii)**
Clinical study expectations		
Number of subjects	n/d	Depending on the nature and objective of the clinical trial. **Reference- Chapter XIII: Miscellaneous - First Schedule (2)(d)**
New drugs approved outside India	n/d	Phase III studies may need to be carried out if scientifically and ethically justified, primarily to generate evidence of efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information. Prior to conduct of Phase III studies in Indian subjects, Central Licencing Authority may require pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad. **Reference- Chapter XIII: Miscellaneous - First Schedule (3)(2)(c)(iii)**
Therapeutic dose is	Prefer lowest therapeutic dose. Higher	Maximum tolerated dose

Criteria	Schedule Y	NDCTR 2019
essential for PK studies	dose for mAb clearance characteristics	**Reference- Chapter XIII: Miscellaneous - First Schedule (3)(2)(a)(a)**
Requirement of clinical efficacy study in pediatric and elderly population for proving comparability of proposed biosimilar application	n/d	If the new drug is intended to treat serious or life-threatening diseases, occurring in both adults and paediatric patients, If the new drug has a potential for use in paediatric patients – paediatric studies should be conducted. **Reference- Chapter XIII: Miscellaneous - First Schedule (3)(3)(B)(iii)**

n/d- Not defined

NMPA – As per the agency guidelines for PK studies, healthy volunteers or patients, design of the study, single/multiple dose study and equivalence design with inclusion of elimination characteristics are required, however details pertaining to similarity criteria, dose selection, sampling parameters are unavailable. Comparative PD studies and PD biomarker usage are indicated with no further detailed information. Comparative efficacy trial study must be performed if clinical study material of the proposed product is different from the commercially available product. The PK/PD requirements are aligned with the WHO. Only common adverse reactions are to be compared and tested, whereas information pertaining to unknown safety parameters is not defined. Comparative clinical immunogenicity studies can be conducted as part of PK/PD and/or efficacy trials and considered for detecting antibodies linked to process-related impurities (CFDA, 2014).

SAHPRA – The agency recommends PK study requirements similar to EMA guideline on the clinical investigation of pharmacokinetics of therapeutic proteins. It recommends combined PK/PD studies, PD marker determination, selection of design and duration, all based on justification. Comparative PD studies in a justified population are acceptable. Comparative PK/PD studies may be sufficient for clinical comparability if predefined conditions are met. Comparable clinical efficacy trials should be conducted. If a clinical comparability trial design is not feasible, other designs should be explored. Safety and immunogenicity need to be sufficiently characterised. Pre-registration of safety data has to be performed in a sufficient number of patients. The basic principle for performing immunogenicity studies is in line with EMA and the WHO guidelines (MCC, 2014).

TITCK - The requirements are defined as in line with EMA's overarching biosimilar guideline for clinical studies (TITCK, 2017).

COFEPRIS - PK/PD, Clinical criteria are not defined; however, PV information needs to be submitted in line with the Mexican standard (COFEPRIS, 2014).

Table 4.8 illustrates the comparative clinical study requirements across BRICS-TM agencies.

Table 4.8 Comparative clinical attributes across BRICS-TM agencies

Clinical attributes	ANVISA	Russia MoH	CDSCO	NMPA	SAHPRA	TITCK	COFEPRIS
Pharmacokinetics							
Dose	n/d	n/a	Prefer lowest therapeutic dose. Higher dose for mAb clearance characteristics	n/d	Lowest therapeutic dose	Lowest therapeutic dose	n/d
ROA	n/d	n/a	Subcutaneous routes	n/d	Subcutaneous routes	Subcutaneous routes	n/d
Sampling	n/d	n/a	Single dose: Till last quantifiable concentration; Multi dose: First dose and steady state	n/d	Single-dose: First and last administration; Multiple-dose: Steady state	Single-dose: First and last administration; Multiple-dose: Steady state	n/d
Design	n/d	n/a	Single-dose crossover for late elimination phase; Parallel group for long half-life	Single/multiple dose	Single-dose crossover for late elimination phase; Parallel group for long half-life	Single-dose crossover for late elimination phase; Parallel group for long half-life	n/d
Primary parameter	n/d	n/a	n/d	n/d	Single dose: $AUC_{(0\text{-}inf)}$, Multiple dose: C_{max} and C_{trough}	Single dose: $AUC_{(0\text{-}inf)}$ Multiple dose: C_{max} and C_{trough}	n/d
Secondary parameter	n/d	n/d	n/d	n/d	Single dose: C_{max}, T_{max}, V_{ss}, $t_{1/2}$; Multiple dose:	Single dose: C_{max}, T_{max}, V_{ss}, $t_{1/2}$; Multiple dose:	n/d

Clinical attributes	ANVISA	Russia MoH	CDSCO	NMPA	SAHPRA	TITCK	COFEPRIS
					$AUC_{(0-t)}$, steady state AUC	$AUC_{(0-t)}$, steady state AUC	
Acceptable range	n/d	n/a	Clinically justified	n/d	Clinical judgment	Clinical judgment	n/d
Pharmacodynamics							
Combined PKPD	Possible if PD marker available	n/a	Comparative, parallel/cross-over, healthy volunteers/ patient if PD marker available	Possible if PD marker available	Possible if PD marker available	n/d	n/d
Fingerprinting approach	n/d	n/a	n/d	n/d	n/d	n/d	n/d
Clinical efficacy							
Study type	Required but no detailed guideline	n/a	Randomised, parallel group, blinded	Parallel design, random, double-blind	n/d	n/d	n/d
Population	n/d	n/a	n/d	Patient for approved therapeutic indication	n/d	n/d	n/d
Design	n/d	n/a	Equivalence, non-inferiority/ comparability phase III clinical trial	Equivalent efficacy design trial	Clinical comparability trial	n/d	n/d
Endpoints	n/d	n/a	n/d	Secondary endpoints	n/d	n/d	n/d

Clinical attributes	ANVISA	Russia MoH	CDSCO	NMPA	SAHPRA	TITCK	COFEPRIS
Comparability margin	n/d	n/a	n/d	Justified by considering assay sensitivity	n/d	n/d	n/d
Pediatric population	n/d	n/a	n/d	n/d	n/d	n/d	n/d
Clinical Safety							
Immunogenicity	n/d	n/a	Obtained in PK/PD studies	Required but no detailed guideline	Required but no detailed guideline	n/d	n/d
Comparative safety data	Required but no detailed guideline	n/a	Obtained in PKPD studies if phase III trial is waived	Adverse reaction comparison to be done with reference drug	In line with EMA	n/d	n/d
Follow-up duration	n/d	n/a	n/d	n/d	In line with EMA	n/d	n/d

n/d: Not defined, n/a: Not available

Part IV – Post-marketing requirements (Interchangeability, switching and substitution, extrapolation of indications, pharmacovigilance and risk management plan)

Interchangeability

Comparability studies for post-approval changes and interchangeability awaits clarifications from BRIC agencies. The Resolution RDC nº 55/2010 of ANVISA does not address the question of interchangeability (Castaneda-Hernández et al., 2014). SAHPRA disallows interchangeability/switching whereas, TITCK leaves the decision with medical practitioners. This contrasts with the EU, where interchangeability, switching and substitution remains the prerogative of individual member states. The TGA and Swissmedic leave it to the decision of the prescribing physician. However, the USFDA allows a biological product to be substituted for the reference product without intervention of a healthcare provider or prescriber, subject to approval by the agency.

Extrapolation of indications

In the case of established agencies such as the EMA and USFDA and other aligned agencies i.e. TGA and Swissmedic, the agency may examine and approve biosimilar applications for extrapolation of indications supported by scientific justification. Such criteria is not clearly defined by some of the BRICS-TM agencies. As per ANVISA, extrapolation to other indications is possible if the product is registered through the route of development (and not through individual route of development), however further detail is not specified (ANVISA, 2010). With respect to CDSCO, based on one specific clinical indication comparability data, extrapolation can be done to other indications subject to the same mechanism of action and receptors for all indications. New indications of the innovator can be approved by separate application (CDSCO, 2016). The CFDA allows extrapolation of indications based on scientific justification (CFDA, 2014). The SAHPRA states extrapolation to other indications is possible subject to presentation of non-inferiority comparability studies in one indication (MCC, 2014). The Mexican regulations do not permit extrapolation between indications (Castaneda-Hernández et al., 2014).

Pharmacovigilance (PV) and Risk Management Plan (RMP)

The PV and RMP expectations of EMA and WHO are aligned based on the ICH E2E for PV planning and along with USFDA, expects a risk management plan defining all known and potential unknown risks to be monitored post authorisation of the product. Among the BRICS-TM agencies, RDC nº 55/2010 does not specify detailed requirements on PV and RMP, however, it refers to health legislation in effect (ANVISA, 2010). As per PV plan for CDSCO, periodic safety update reports (PSURs) to be submitted every six months for initial periods post approval of similar biologics. Annual PSURs to be submitted for the subsequent two years (CDSCO, 2016). For CFDA, PV and RMP (safety and immunogenicity) have to be submitted and evaluated as per national regulations (CFDA, 2014). The SAHPRA require that PV has to be based on MCC guidelines and RMP should be presented or planned at the time of marketing authorisation application (MCC, 2014).

Paediatric studies

Paediatric research or regulations for extrapolation of efficacy in a paediatric population is defined by the US authority, whereas the guidance for paediatric research is at a very primitive stage across the BRICS-TM.

COVID-19 pandemic and regulatory flexibilities in BRICS-TM

Positive steps on regulatory flexibility on product and GMP approvals during the COVID-19 pandemic, were undertaken by the BRICS-TM agencies (DBT, 2020; Regapharm, 2020; SAHPRA, 2020; Sharma, 2020; Kilic & Ünal, 2021). ANVISA, RDC no 346/2020, (ANVISA, 2020a) to expedite the development of medicinal products for health emergency.

DISCUSSION

Table 4.9 summarises the key differences between mature regulatory agencies and the BRICS-TM regulatory agencies.

Table 4.9 Summary of differences in biosimilar criteria between mature regulatory agencies and BRICS-TM regulatory agencies

Biosimilar criteria		Mature regulatory agencies	BRICS-TM regulatory agencies
Part I - Biosimilarity principles	Terminology	**EMA**- Similar biological medicinal product **WHO**- Similar biological product **USFDA, TGA, BRDD, Swissmedic**- Biosimilars **BRDD**- Similar biologic product	**ANVISA**- Biological product **Russian MoH, SAHPRA**- Biosimilar **CDSCO**- Similar biologic **NMPA**- Therapeutic biological product **TITCK**- Similar biological medicinal product **COFEPRIS**- Biocomparable biotechnological medications
	Development Approach	Stepwise approach **(All agencies)**	**CDSCO**- Sequential process **NMPA**- Gradual progressive sequence **TITCK**- Stepwise approach **SAHPRA**- Stepwise approach **ANVISA, Russian MoH, COFEPRIS**- n/d
Part II - Reference product selection	Acceptance of non-authorised RBP	**EMA**- ICH countries **WHO**- Well-established market **USFDA, TGA**- ICH countries **BRDD**- ICH or Canada aligned countries **Swissmedic**- Swissmedic recognized countries Can be used in non-clinical and clinical studies (with justification or prior consultation with agency – All agencies)	**ANVISA**- From countries having similarity with ANVISA and access to full dossier **CDSCO**- ICH countries **SAHPRA-** SAHPRA aligned countries **COFEPRIS**- Should have valid registration issued by COFEPRIS, commercially available in Mexico **Russian MoH, NMPA, TITCK**- n/d
	Bridging studies	**EMA, USFDA, TGA, BRDD, Swissmedic**- Required if non license comparator product is used. **WHO**- n/d	**ANVISA, Russian MoH, CDSCO, NMPA, COFEPRIS**- Not specified **TITCK**- Not required

	Biosimilar criteria	Mature regulatory agencies	BRICS-TM regulatory agencies
	Sameness of RBP	**EMA, WHO, USFDA, TGA, BRDD, Swissmedic**- Non local authorized RBP in nonclinical and clinical studies	**ANVISA, CDSCO, NMPA, TITCK**- Same reference product throughout the comparability exercise **Russian MoH, SAHPRA, COFEPRIS**- n/d
Part III - Comparability studies (quality, non-clinical and clinical studies)	Quality	**EMA**- Quantity determined based on physicochemical and/or immunochemical assays OR only biological assay subject to correlation with quantity **WHO**- Quantity determined based on biological activity and expression system **USFDA**- Potency determined based on assay(s) **BRDD**- n/d	
	Non-clinical	**EMA, WHO, TGA**- *in vitro* studies required, *in vivo* not mandatory **USFDA, BRDD**- *in vitro* and *in vivo* studies are required	**ANVISA, Russian MoH, NMPA, SAHPRA, COFEPRIS**- *in vitro* and *in vivo* are mandatory but specific requirements not defined **CDSCO**- *in vitro* and *in vivo* are required and requirements defined **TITCK**- *in vitro* studies required, *in vivo* not mandatory
	Clinical	**Phase 1- PK/PD (All agencies)** **PK:** Single-dose crossover for late elimination phase; Parallel group for long half-life **PD:** Combined PKPD permitted if PD marker available **Phase 3 – Clinical efficacy (All agencies)** Confirmatory efficacy studies required along with immunogenicity studies, Equivalence efficacy design	**Phase 1- PK/PD** **PK: (CDSCO, NMPA, SAHPRA, TITCK):** Single-dose crossover for late elimination phase; Parallel group for long half-life **ANVISA, Russian MoH, COFEPRIS**- not defined PKPD requirements **PD:** Combined PKPD, if PD marker available **(ANVISA, CDSCO, NMPA, SAHPRA)** **Russian MoH**, **TITCK, COFEPRIS**- n/d

Biosimilar criteria		Mature regulatory agencies	BRICS-TM regulatory agencies
			Phase 3 – Clinical efficacy (All agencies) Confirmatory efficacy studies required along with immunogenicity studies, Equivalence efficacy design Local clinical studies required **(CDSCO, COFEPRIS)** **Russian MoH:** Local clinical studies or Russian population as part of the global studies
Part IV - Post-marketing requirements, extrapolation to other indications, including interchangeability, switching and substitution, pharmacovigilance, and risk management plan	**Extrapolation**	**EMA, TGA, BRDD Swissmedic**- Based on scientific justification. **WHO**- Based on usage of sensitive clinical model **USFDA-** if approved for RBP	**ANVISA**- Allow if RBP approved through development route. **CDSCO**- Allowed if same MOA and receptor. **NMPA**- based on scientifically justification **SAHPRA**- based on non-inferiority comparability studies in one indication **TITCK-** Scientific justification **COFEPRIS**- not allowed
	Interchangeability	**EMA, BRDD -** decision with member state. **USFDA**- Suggest 2-arm switching studies. **TGA**, **Swissmedic**- decision with prescriber	**ANVISA, Russian MoH, CDSCO, NMPA**- Required, but not defined **SAHPRA**- not allowed **TITCK-** decided by medical practitioners **COFEPRIS**- not allowed
	PV & RMP	Required **(All agencies)**	Required **(All agencies)**

Mature regulatory agencies- EMA, WHO, USFDA, TGA, BRDD, Swissmedic; MOA- Mechanism of action; PV-Pharmacovigilance ; RMP- Risk Management Plan; n/d- Not defined

The biosimilar regulatory framework of the BRICS-TM is gradually aligning with the regulated markets; however, the regulatory pathways are still in an evolving stage (The Economist, 2019). Some of the parameters' i.e., simplified approach is yet to be clarified by Brazil (ANVISA), China (CFDA), Russia MoH and Mexico (COFEPRIS) among the BRICS-TM countries. Also, the parameters such as improved efficacy/safety, comparability studies for post-approval changes and interchangeability awaits clarifications from the BRIC agencies. The SAHPRA disallow interchangeability/ switching whereas TMMDA leaves the decisions with medical practitioners. The guidance for paediatric research is at a very primitive stage across the BRICS-TM. The criteria for non-authorised reference product are not specified in Russia and China whereas Turkey does not allow non-authorised reference product for characterisation. The rest of BRICS-TM agencies allow selection from the ICH/own aligning countries. None of the emerging market agencies specify bridging data requirements.

Most of the similar biologic guidelines of BRICS-TM agencies are based on WHO, hence presence/absence of data requirements are similar to WHO. Therefore, with few exceptions, the expectations on comparative characterisation studies of proposed biologics with the reference product are mostly consistent with that of the WHO. The requirements pertaining to manufacturing process, overages and compatibility characterisation are not covered in the BRICS-TM guidelines except for a reference to WHO or the ICH Q5A. The comparative non-clinical studies for *in vitro* assays (binding and functional activity/viability studies) are specifically defined by the WHO whereas reference guidelines of BRICS-TM markets (except India), does not specify its need. The repeat-dose toxicity, local tolerance, safety pharmacology, reproductive toxicity, carcinogenicity *in vivo* toxicity studies are aligned with EMA, WHO, Turkey and South Africa. Russia and Mexico do not specify detailed requirements whereas South Africa and India are equivalent to that of the WHO. The immunogenicity toxicity studies are essential for South Africa whereas EMA and WHO recommend withdrawal of samples for PK/TK interpretation. Other agencies are silent on immunogenicity.

While the established agencies define the specifics of PK/PD study requirements, there are no specific PK criteria defined for Brazil, Russia and Mexico. India is aligned with WHO and Turkey with EMA. Comparative clinical safety or efficacy could be sufficient, subject to PD marker being incorporated in PK/PD studies, with EMA, WHO, India, Turkey, China and South Africa. As indicated earlier, Russia, and Mexico do not

specify detailed PD requirements. The efficacy trial design and type remain the same for EMA, WHO, Turkey and China. No detailed information is available for Brazil, Russia, and Mexico. Confirmatory Phase III clinical safety and efficacy are mandatory for India whereas South Africa allows trial design to be explored in case of a comparative clinical trial not being feasible. Comparative clinical safety data need to be obtained before authorisation and follow-up data to be submitted post authorisation across stated agencies in this article except Brazil, Russia, and Mexico. The extrapolation of one indication to others is acceptable based on scientific justification except with Mexico. Interchangeability, switching and substitution of biosimilars is not defined in BRIC whereas South Africa restrict as per section 22F (Generis substitution) Act 101 of 1965. The TMMDA leaves interchangeability decision to practitioners. Pharmacovigilance and RMP data need to be submitted across agencies. Though there are no remarkable changes in biosimilar guidelines in the BRICS-TM during the study period, the CDSCO, India, released its “New Drug Clinical Trial Regulation (NDCTR) 2019” expressing its view on pre-clinical and clinical studies. The NDCTR has replaced previous Schedule Y for clinical trials and covers all requirement comprehensively in one document. With regards to the biosimilar data assessment and authorization processes, the literature search reveals fixed approaches followed by mature agencies for biosimilars, unlike the BRICS-TM countries. The regulatory environment in the emerging economies is evolving and are designed around the WHO regulatory framework. The regulatory processes are gradually moving towards alignment with the mature agencies such as EMA, USFDA, TGA, BRDD, HSA and Swissmedic in terms of data assessment by verification process on case-by-case basis by some agencies such as COFEPRIS and ANVISA. The drug approval process from regulatory authorities for different categories of pharmaceutical products provides a perspective on the development of overall regulatory process followed by the agencies. However, the data obtained was majorly for the NAS and not sufficient information available for the biosimilar products. Hence this needs to be studied further as part of the research. Therefore, an extensive study to gain knowledge of precise and detailed regulatory requirements for MAA of biosimilars, resource allocation, review and approval process, to establish a suitable regulatory strategy is required and needs to be explored further.

SUMMARY AND CONCLUSION

The regulatory frameworks for the market authorisation of biosimilars pose multiple challenges to the companies in the emerging countries (Gautam, 2017). It is evident from the critical evaluation and comparison of the emerging agencies guidelines that there are differences between the BRICS-TM expectations and those of mature agencies. The differences are mainly in biosimilarity approach, comparability criteria in terms of quality, non-clinical and clinical studies as well as post-marketing challenges.

- Most of the NRAs in emerging markets are modelled over similar biologic guideline based on those of the WHO, hence presence/absence of data requirements are similar to the ones of the WHO, and hence do not meet the regulatory standards of EMA or USFDA.
- Non-authorised reference product selection criteria are not defined by some of the BRICS-TM agencies (Russia MoH, NMPA (China)) and not accepted by others for characterisation (TITCK (Turkey)). The rest of the BRICS-TM agencies allow selection from the ICH/own aligning countries while Mexico allows biosimilar product to be used as the reference product. There is no information from the agencies related to bridging data requirement.
- The parameters such as improved efficacy/safety, comparability studies for post-approval changes and interchangeability await clarifications from BRIC agencies.
- The reference guidelines for comparative *in vitro* assays in BRICS-TM markets (except India) are not defined. The *in vivo* toxicity study requirements are aligned with EMA (South Africa and Turkey) and WHO (India and South Africa) but without any details in the rest of the agencies.
- The detailed guidance for immunogenicity is awaited from the agencies (except South Africa)
- The PK/PD requirements are largely aligned with WHO/EMA guidelines. The efficacy trial design and type remain the same for EMA, WHO, Canada, Turkey and China. No detailed information is available for Brazil, Russia, and Mexico.
- Confirmatory Phase III clinical safety and efficacy are mandatory for India, whereas South Africa allows trial design to be explored in case a comparative clinical trial is not feasible. Comparative clinical safety data need to be obtained before

authorisation and follow-up data to be submitted post authorisation across agencies, except Brazil, Russia, and Mexico.

- The resource allocation within the agency, data assessment and approval processes for biosimilars in the BRICS-TM are not clear and needs to be investigated and studied further.

Although the current Russian federation law FZ-61 (released in December 2014) has incorporated a definition for biologics/biosimilars, the roles of the experts are to be determined by concerned federal authorities, resulting in an unfamiliar regulatory framework (Lozda, 2016). The regulatory pathway would need clinical trial requirements based on the complexity of the molecule (Lucio, 2018). Mexico (COFEPRIS) is yet to come up with detailed clarification for characterisation, non-clinical and clinical comparability criteria. Though there are gaps in biosimilar regulatory guidelines in emerging markets, the agencies are working hard to align regulatory norms in line with well-established agencies.

Based on the above gaps identified with the BRICS-TM agencies, the plan for the next study was to connect with these agencies through primary research to validate gaps and propose a standardised model for efficient development and approval of biosimilars. The details of the outcomes of primary research on the BRICS-TM regulatory agencies will be presented in Chapter 5.

CHAPTER 5

Evaluation of the Regulatory Review Process and Assessment Criteria for Biosimilar Development in the BRICS-TM Countries

INTRODUCTION

The pharmaceutical industry is expanding into developing countries at a rapid pace. Emerging economies represent 70% of the world population accounting for a 31% share of global Gross domestic product (GDP) and more than 30% of pharmaceutical spending (Leintz & Dedhia, 2015). In addition, they account for one-third of the global growth in drug demand, with a global, compound annual growth rate of 5-8 % (IQVIA, 2019a). Biosimilars, which account for 28% of the global pharmaceutical market have the potential to boost significantly treatment options and hence are expected to play an important role in the pharmaceutical market (Kabir et al., 2019). Emerging economies with low biologic-treatment rates and affordability barriers present attractive opportunities for biosimilars (McKinsey & Company, 2019). They have been a cradle for biologic alternatives in the broader sense, which includes copies of biologics that have not been subject to a dedicated biosimilar comparability pathway. More than 70 such products are marketed in India, and more than 40 are marketed in China. Being part of the BRICS market (comprising the developing markets of Brazil, Russia, India, China and South Africa) together with Turkey and Mexico, which are all deemed to be at a similar stage of newly advanced economic development, they form the biggest and fastest growing sector of pharmerging markets. However, marketing authorisations of these much-needed products are often delayed as manufacturers face challenges of multiple regulatory requirements to register products in different countries (WHO, 2016a; WHO, 2019b). It is encouraging to note that the regulatory approval pathways for biosimilars applied by the major regulatory agencies worldwide are, to a broad degree, scientifically aligned (Krishnan et al., 2015). However, owing to regional differences in healthcare priorities, policies, and resources, some important regulatory inconsistencies are evident in emerging economies. Some of these challenges such as lack of step wise approach, difference in selection and sourcing of Reference Biological Product (RBP), regulatory expectations of clinical efficacy trial design and lack of transparency towards interchangeability, switching and substitution norms, have been identified (Rahalkar et al., 2018). Inevitably, lack of standardised regulatory processes would hamper the growth of biosimilars in these countries (The Economist, 2019). Thus, it is of paramount importance to evaluate the framework for biosimilar development and approval processes in these emerging economies. The emerging economies including the BRICS (Brazil, Russia, India, China, and South

Africa) and MIST (Mexico, Indonesia, South Korea, and Turkey) may provide the best future opportunity for manufacturers of biosimilars (Limaye, 2016). With millions of people in these developing countries, and unmet medical needs, the uptake of biosimilars is expected to be tremendous.

Brazil - The Brazilian national regulatory agency (ANVISA—Agência Nacional de Vigilância Sanitária) issued its first guideline on biosimilar submissions in 2010 (RDC 55-2010) (ANVISA, 2010). This document states the basis of the regulatory process for biologics and biosimilars in Brazil. Most of the main issues addressed are in concordance with the EMA (European Medicines Agency) and WHO (World Health Organisation). However, the regulatory timeline in ANVISA is known to be longer when compared to other agencies. For instance, when compared to FDA, approvals in Brazil are, on average, 8.6 months longer (Debiasi et al., 2017). There are 2 regulatory pathways in Brazil; firstly, the comparative pathway which is based on the WHO recommendations, and products licensed via this route are considered to be biosimilars. The second or individual pathway does not require comparisons with the innovator product and the manufacturer is not allowed to apply for extrapolation of therapeutic indications (Azevedo et al., 2019).

Russia - In Russia, a substantial number of biosimilars have been approved for clinical use as a result of the low registration barriers. Two of the most popular biosimilars of filgrastim in the Russian market, Neupomax® and Leucostim received marketing approval based on limited clinical experience. In the last few years, the medical community, in cooperation with patient advocacy groups and the Russian Ministry of Health have worked together to align with the existing and most developed regulatory standards and pathway, produced by the EMA. The final guideline document was approved on December 23, 2014 (on approval of rules for conducting research for biological medicines of the Eurasian Economic Union) and included the definition of biologic products and biosimilars, as well as the differences between biosimilars and generic products and the requirement of preclinical and clinical studies to prove similarity of the biosimilar and originator. Yet, the Russian government is yet to act on these changes (Lopes, 2016).

India - The “Guideline on Similar Biologics: Regulatory Requirements Marketing Authorisation in India for Biosimilar Drugs” was released by the Department of

Biotechnology (DBT) and the Central Drugs Standard Control Organisation (CDSCO) to streamline the approval process and ensure delivery of high-quality biologics. These guidelines were developed with reference to the ICH guidelines so that products developed in and imported to India will be on par with global regulatory standards (Lopes, 2016).

China - In 2015, China created a standardised regulation for the development and evaluation of biosimilars, which clarified the definition of biosimilars and set standards for preclinical research and development, clinical trials, and manufacturing processes. China has just 9 biosimilars approved compared to 29 in the United States. However, fundamental regulatory reforms in China have established a framework for biosimilar development and approval that will encourage robust competition in that market (Wu & Yip, 2021).

South Africa - The South African biosimilars guideline is essentially based on the corresponding guidelines of the EMA and WHO. Although the extent of clinical and non-clinical studies required for the registration of biosimilars would be less than for innovator medicines, it will to a large degree be dependent on how well the active ingredient has been characterised and its similarity to that of the reference drug substance. Upon review, none of those candidates had complied with the registration requirements for a biosimilar medicine. However, this may be changing. In October 2019, a global report by the International Generic and Biosimilar Medicines Association identified two biosimilars approved in South Africa (filgrastim-Teva in 2018 and Biocon and Mylan's trastuzumab Ogivri in 2019), compared to 54 and 23 in Europe and United States, respectively (Pategou, 2020).

Turkey - According to McKinsey & Company, the annual growth rate of the biosimilars market in Turkey between 2018 and 2025 will be 10 to 15% (McKinsey & Company, 2019). Turkey is deemed to be the most advanced developing market from a technical and scientific perspective, which leaves them well-equipped to handle the more complicated regulatory requirements stipulated by the EMA (Welch, 2019a).

Mexico – The Mexican Federal Commission for the Protection against Sanitary Risks (COFEPRIS) issued its guidelines for "biocomparable medicines" in April 2012, at the time when numerous non-innovator biologics were already on the market. COFEPRIS also issued rules for non-innovator biologicals registered prior to October 19, 2011

(when the guidelines for biocomparable medicines were first published), mandating that companies marketing these products conduct clinical trials to establish biosimilarity and submit their data to the commission (GaBI, 2015).

OBJECTIVES

In the last two decades, the mature regulatory agencies, in particular, in the ICH jurisdictions, have made significant progress towards establishing, revising, and updating biosimilar guidelines to match the constant innovation in biotechnology. Yet there remains scope for improvement in establishing regional standardisation for regulatory requirements of biosimilar development and approval process.

The main objectives of the study were to:

- Evaluate and compare technical capabilities of the BRICS-TM regulatory agencies in the area of biosimilars,
- Identify similarities and differences in regulatory requirements of biosimilar development criteria i.e., biosimilarity principles, comparative studies including physicochemical characterisation, non-clinical and clinical studies,
- Evaluate and compare “must submit documents” as part of biosimilar application for marketing authorisation in the BRICS-TM countries,
- Map the biosimilar marketing authorisation approval pathway specifically for key milestones, scientific advice meetings, clinical trial mandates and backlogs.

This study is a part of a larger research project covering regulatory agencies, industry, physicians and patients to validate findings of earlier secondary research published in the review article “Quality, non-clinical and clinical considerations for biosimilar monoclonal antibody development: EU, WHO, USA, Canada and BRICS-TM regulatory guidelines” (Rahalkar et al., 2018).

METHODS

Study Participants

The regulatory authorities included in this study were those which are part of the BRICS-TM grouping. This refers to the countries of Brazil, Russia, India, China, South Africa, Turkey and Mexico deemed to be developing countries at a similar stage of

newly advanced economic development, on their way to becoming developed countries and also known for their significant influence on regional affairs. It was initially developed as BRICS and since 2009, their governments have met annually at formal summits. Russia hosted the most recent, 12th BRICS-TM summit on 17 November 2020, virtually due to the COVID-19 pandemic (BRICS Information portal, 2020; Chaudhury, 2020; Hindustan Times, 2020). Therefore, the regulatory authorities of all seven countries were invited to take part in the study.

The potential study participants were identified via each respective authority's general email addresses obtained from agency websites, LinkedIn, the research team's personal contacts, ex-employee and local leading regulatory consultants for each authority. They were selected based on their work experience in the biologic or biosimilar division of the authority, having held a position as a general manager or above or a leading regulatory consultant with a close working relationship with the relevant authority in the biosimilar space. They were sent an electronic mail with brief information about the project and the questionnaire, the objective of the study, the number of authorities to be included and requesting their agreement to participate in the study.

Responses and conditions of acceptance were different across all seven authorities. It took approximately 18 months to receive agreement from two agencies i.e., Agência Nacional de Vigilância Sanitária (ANVISA), the Brazilian Health Regulatory Agency, Brazil and the South African Health Products Regulatory Agency (SAHPRA). The respondents from the Central Drug Standards Control Organisation (CDSCO), India agreed to participate on anonymity and the Türkiye İlaç ve Tıbbi Cihaz Kurumu (TITCK), Turkish Medicines and Medical Device Agency data was gathered from public sources of the Agency such as Activity report, official website and Agency's publicity manual. Two agencies including the Russian MoH and Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS), the Federal Commission for the Protection Against Sanitary Risks, Mexico did not respond to the letter of invitation. Consequently, local senior regulatory consultants were engaged as proxy for Russia and Mexico. Despite tremendous efforts to establish direct contact with the National Medical Products Administration (NMPA) of China or via local Chinese regulatory consultants, the outcome was unsuccessful.

On receipt of agreement to participate from the recruited six countries, the self-administered Biosimilar Development, Evaluation and Authorisation (BDEA) (Appendix 1) questionnaire was sent via email for completion by the respective authorities. This was followed up by a face-to-face or virtual meetings after receipt of the completed questionnaire. Such meetings were arranged to understand and further interpret the respective agency's view and to verify the validity of the responses to the questionnaire. In addition, copies of the relevant guidelines were requested as part of the questionnaire to verify the responses and to correlate the actual regulatory requirements. This phase of data collection period took place between March and October 2020.

Measurement Tool

A semi-quantitative questionnaire, Biosimilar Development, Evaluation and Authorisation (BDEA) was developed (in English) (Appendix 1). This was based on slight modification of the Centre for Innovation in Regulatory Science (CIRS) questionnaire (McAuslane et al., 2009) and information from secondary research in order to map the regulatory processes existing within agencies (Rahalkar et al., 2018). In addition, expert inputs were received, and the initial drafts were prepared based on inputs from Biologic and Radiopharmaceutical Drugs Directorate (BRDD) – Health Canada, Turkish Medicines and Medical Device Agency (TITCK) and CIRS. Since the questionnaire was initially developed for small molecules, the modifications were introduced to make it biosimilar-specific. The BDEA was further improved based on pilot validation performed by the Regulatory Authority of Medicines, Equipment and Medical Device (CECMED), Cuba.

Data Collection

Data for the comparator authorities was collected in 2019-2020. The BDEA questionnaire which standardises the review process allowing key milestones, activities and practices of the seven regulatory authorities to be identified was completed by a senior member of the biosimilar licensing division and validated by the head of the division/authority. The final version of the BDEA questionnaire dated March 2020, consists of 35 pages and the questions are grouped under 22 categories and grouped into three major sections as follows:

Part I - Organisation of the agency - This part of the BDEA questionnaire consist of current agency structure, resources in the biosimilar domain and types of review models i.e. review models employed for scientific assessment (Table 5.1), level of data required, and extent of assessment of the data as well as reliance on other authorities, if applicable.

Part II – Agency's view on biosimilar development criteria - This part covers questions pertaining to biosimilarity principle, selection of RBP, comprehensive comparability criteria including physico-chemical, non-clinical and clinical studies and "must submit" documents as part of a biosimilar marketing authorisation application.

Part III – Marketing authorisation approval pathway - This part presents questions with regards to key milestones i.e, the process of assessment starting from receipt of the dossier, validation/screening, the number of cycles of scientific assessments including the questions to the sponsor/applicant, expert registration committee meetings to the final decision on approval or refusal of a biosimilar for registration. A standardised process map, developed based on the experience of studying established and regulatory agencies of the emerging economies, was embedded in the questionnaire.

Data processing and analysis

Data processing and analysis was carried out using Microsoft excel; descriptive statistics was used for quantitative data and content analysis was employed to generate themes and sub-themes for qualitative data.

Ethics Approval

The study has been approved by the Health, Science, Engineering and Technology ECDA, University of Hertfordshire [Reference Protocol number: aLMS/PGR/UH/03332(1)].

Table 5.1 Models of regulatory review

Type	Title	Definition
I	Verification of Marketing Authorisation Approval Application	• Importing agency 'verifies' that the product intended for local sale has been duly registered as declared in the application. • Used to reduce duplication of efforts by agreeing that the importing country will allow certain products to be marketed locally once they have been authorised by one or more reference agencies, elsewhere. • Product characteristics and prescribing information for local marketing conforms to that agreed in the reference authorisation.
II	Abridged review of Marketing Authorisation Approval Application	• Conserves resources by not re-assessing all scientific supporting data that has been reviewed and accepted by reference agency but includes an 'abridged' independent review of the product in terms of its use taking into consideration local cultural and environmental factors. • Includes a review of the biopharmaceutical (CMC) data in relation to climatic conditions and a benefit-risk assessment in relation to use in the local ethnic population, medical practice/culture and patterns of disease. • Approval by a reference agency is a prerequisite before the local authorisation can be granted.
III	Full review of Marketing Authorisation Approval Application	• Suitable resources available including access to appropriate internal and external experts, to carry out a 'full' review and evaluation of the supporting scientific data (quality, non-clinical, clinical) for a major application.

CMC: Chemistry, Manufacturing and Control

RESULTS

The results have been presented in three parts:

Part I – Organisation of agency;

Part II – Biosimilar development criteria; and

Part III – Marketing authorisation process.

Demographic characteristics of the study participants

Out of the seven regulatory agencies invited to take part in the study, four agencies, ANVISA (Brazil), SAHPRA (South Africa), CDSCO (India) and TITCK (Turkey) agreed to take part and completed the questionnaire. Leading regulatory consultants working closely with the agencies for biosimilar medicines from Russia and Mexico also participated in the study. However, multiple efforts to reach NMPA (China) either directly or via regulatory experts were unsuccessful. The individuals who completed

the questionnaire held senior positions (general manager or above) within the biologic divisions of their regulatory authority. The regulatory consultants were Chief Executive Officers (CEO) of their respective consulting firms.

Part I - Organisation of Agency

This provided information on agency size and the strength of the biological division including the number of internal assessors with their minimum qualifications and details on support obtained from external assessors or committees (Table 5.2).

ANVISA - The capacity of the biological department was around 1.6% in comparison with the total size of the agency. The agency did not engage with external assessors, and the applications were reviewed by qualified internal assessors all of whom hold a PhD as their qualification. The agency relied on type III data assessment (full review of the marketing authorisation application) for most of the applications.

Russian MoH - There was no distinction between internal assessors for the review of biological or non-biological marketing authorisation applications, resulting in the same assessors reviewing both types of applications. Product approval was based solely on self-assessment by internal assessors applying the type III review model.

CDSCO - The capacity of the biological division within CDSCO was 2% representing common internal assessors for the review of all new biological and biosimilar applications. The agency mandated a master's degree in pharmacy as the minimum qualification for internal assessors and took expert advice from external assessors for the review of both non-clinical and clinical parts of the dossier. The agency had several bodies with different responsibilities including: Subject Expert Committee (SEC) for clinical review which comprises external physicians and regulators; the Review Committee for Genetic Manipulation (RCGM) for non-clinical data; and the Department of Biotechnology (DBT) for developing and defining regulatory guidelines. The agency followed the type II (abridged) review if the biosimilar had been approved by at least one recognised reference agency and waived the non-clinical studies if the product was already approved by more than one agency, including China and South Korea subject to positive review outcomes. The reference agencies defined for the type II review model were EMA, MHRA, USFDA, TGA and BRDD. In addition, the agency

also carries out type III (full review) review but does not mention a verification review model.

SAHPRA - The overall size of the agency was more than 200 personnel. There was a total of 5 reviewers for biological applications with MSc as minimum qualification (Table 5.2). The agency outsourced CMC, non-clinical and clinical data evaluation to external evaluators and only allowed a Type III full dossier review.

TITCK - The agency followed the Type III review model and took advice from external assessors also for CMC, non-clinical and clinical review.

COFEPRIS - The biological division represented 1% of the overall size of the agency with a bachelor's degree as the minimum qualification for internal assessors. The agency relied more on external experts under both the committees, the SEPB (Sub-committee on evaluation of Biotech Products) and the NMC (New Molecule Committee) headed by COFEPRIS. The COFEPRIS was the only agency regulatory agencies of the emerging economies following the type I data assessment model relying on other reference agencies' evaluation including the EMA, USFDA and TGA. In addition, the agency also conducts type III full dossier evaluation for biosimilars.

It is evident from Table 5.2 that CDSCO, SAHPRA, TITCK and COFEPRIS agencies used the support of external assessors for review of applications despite having an internal biologic division. This reflected a shortage of resources related to internal biologic reviewers. In addition, allocation of common assessors for biologic and non-biologic applications such as that practised by the Russian MoH may lead to insignificant subject matter expertise. All the agencies followed 'Type III - Full review of the marketing authorisation application' data assessment model. In addition, CDSCO followed 'Type II - Abridged review' and COFEPRIS followed 'Type I – Verification review of marketing authorisation application'. This indicated that the reliance of these regulatory agencies of emerging economies on Type I and Type II models was less prevalent.

Table 5.2 Organisation of six regulatory agencies of BRICS-TM

	ANVISA (Brazil)	Russian MoH	CDSCO (India)	SAHPRA (South Africa)	TITCK (Turkey)	COFEPRIS (Mexico)
Total agency staff	1500	930	1500	>200	1172	2000
Resource allocation in biologic/biosimilar division						
Total staff	24	Not defined*	30	10	No information available	20
Number of reviewers	24	Not defined*	8	5	No information available	13
Capacity (%)	1.6%	Not applicable	2%	5%	Not applicable	1%
Internal assessors						
Qualification	Ph.D.	M.Sc. to Ph.D.	M. Pharm[#]	4-year degree to Masters	Experienced, M.Sc, PhD	Bachelor's degree
Segregation by expertise	CMC, Non-clinical, Clinical, Other scientists	No information available	CMC, Non-clinical, Clinical, Microbiologist, Statistician, Assistant Drug Controllers	CMC, Clinical, Microbiologist	CMC, Non-clinical, Clinical, Microbiologist, Other scientists, Project manager	CMC, Non-clinical, Clinical, Project manager
External assessors						
Support received	No	No information available	Yes	Yes	Yes	Yes
Area of expertise	Not applicable	Not applicable	Non-clinical, Clinical	CMC, Non-clinical, Clinical	CMC, Non-clinical, Clinical	CMC, Non-clinical, Clinical
Biosimilar advisory committee	No	No information available	SEC, RCGM DBT	Biological Medicine Expert Advisory Committee	No	SEPB, NMC
Data Assessment						
Data Assessment type	Type III	Type III	Type II, III	Type III	Type III	Type I, III
Recognised reference agencies	Not specified	Not specified	EMA, USFDA, BGTD, MHRA, TGA	Not specified	Not specified	EMA, USFDA, TGA

**No separate biologic division; [#]RCGM and SEC committee details excluded; CMC: Chemistry, Manufacturing and Control; SEC: Subject Expert Committee; RCGM: Review Committee on Genetic Manipulation; DBT: Department of Biotechnology; SEPB: Sub-committee on evaluation of Biotech Products; NMC: New Molecule Committee*

Part II - Biosimilar development criteria

Establishing biosimilarity to the reference biologic product revolved around several steps starting from *in vitro* analytical testing and quality characterisation, non-clinical comparative pharmacology testing to toxicology, PK/PD studies and clinical trials (clinical safety and efficacy) (Markus et al., 2017). Although it was evident, that the regulatory standards of BRICS-TM countries were mostly aligned and largely modelled on the WHO guidelines (WHO, 2013), there was a lack of homogeneity in dossier requirements across these agencies posing a challenge to global development programmes. Such differences as presented by the regulatory agencies were analysed and have been presented here.

Biosimilarity

All the six regulatory agencies of these emerging economies expect the sponsor to demonstrate biosimilarity of the proposed biosimilar product with the reference product. This included proving satisfactory physicochemical and biological characterisation with *in vitro* non-clinical PK/PD studies and literature based clinical performance evaluation, additional *in vivo* safety data plus confirmatory clinical safety and efficacy trial. However, expectations for local or global clinical studies varied among the agencies. ANVISA, SAHPRA and TITCK accepted clinical studies performed in any country globally, while CDSCO and COFEPRIS mandated a local study. The Russian MoH accepted global studies if the trial included Russian patients. In addition, extrapolation of indications was allowed subject to fulfilment of conditions defined by each agency.

Furthermore, these regulatory agencies of the emerging economies (except Russian MoH and TITCK) did not regulate interchangeability by law and allowed a prescriber to decide based on a patient’s need. However, in Russia, biosimilar products can be interchangeable with the reference product by law whereas in Turkey, the reimbursement institution authorised interchangeability.

Comparative quality characterisation

Reference Biologic Product (RBP) selection

Selection criteria: In response to questions on the RBP selection, the agencies mostly indicated mandatory requirements for locally authorised reference product (based on a full dossier submission including quality, safety and efficacy) for comparability studies (Table 5.3).

Primary and alternate source of RBP: Flexibility in terms of sourcing the RBP from other ICH/reference countries existed in CDSCO, TITCK and COFEPRIS, in the event of non–availability of locally authorised reference products. In addition, TITCK also accommodated use of a non-locally authorized RBP as well as locally sourced reference products for certain clinical safety studies (PK/PD study in humans), non-clinical studies (*in vivo*) and development studies such as “quality target product profile” (QTPP) which is a summary of the quality characteristics of the respective biosimilar. These quality characteristics are essential to ensure that the finished product meets the required standard of quality.

Use of RBP authorised in emerging countries: None of the agencies accepted authorised reference products from other emerging countries, except CDSCO which may then only consider this in emergency situations such as the COVID-19 pandemic.

Criteria of RBP batches: Unlike the Russian MoH and COFEPRIS, the regulatory agencies of Brazil, India, South Africa and Turkey also mandate the use of multiple batches of RBP with varied expiry dates. However, ANVISA, has provisions for the changeover of RBP during development and comparability studies.

Bridging study requirement: All the six regulatory agencies of BRICS-TM did not specify the bridging study requirements.

Data sharing arrangements: ANVISA established data sharing arrangements with advanced regulatory agencies such as EMA, USFDA, PMDA and MHRA. CDSCO also holds a data sharing agreement with EMA and USFDA. In contrast, COFEPRIS does not have a data sharing arrangement with other advanced regulatory agencies and expects a full dossier submission for products approved by a foreign agency (Table 5.3). Such arrangements of sharing of information about the product among the

regulatory agencies would help the agency to understand if the RBP batch used for the development process has been made in the same facility or same process or same cell line and if the same information has been submitted to both the agencies. With evaluation of such shared data, the agency can waive the additional requirements on the RBP required for submission or waive the bridging studies. This type of data-sharing agreements would greatly decrease costs of biosimilar development.

The varied expectations for RBP sourcing from these agencies demonstrate the challenge in procuring multiple lots of RBP and the non-convergence in regulatory requirements, thereby limiting the opportunity for multi-country development.

Analytical specification and method

The similarity of physicochemical and biological properties of biosimilar and reference product was demonstrated using two or more orthogonal analytical methods (Kabir et al., 2019). In keeping with this, the current assessment underlined the need for orthogonal methods for purity, impurity and contaminants characterisation as indicated by the responses from all six emerging economies. Furthermore, as specified clearly in the WHO SBP guidelines (WHO, 2013), specifications for a Similar Biotherapeutic Product (SBP) will not be the same as for the RBP due to the difference in manufacturing process and analytical procedures followed by the manufacturer. Hence, specifications should be set based on the manufacturer's experience with the SBP (e.g., manufacturing history; assay capability; safety and efficacy profile of the product) and the experimental results obtained by testing and comparing the SBP and RBP. However, the regulatory agencies of these emerging economies' consideration for determining specifications and analytical methods for proposed biosimilar product varied across agencies.

The ANVISA and TITCK preferred analysis of multiple RBP lots with varied age along with the SBP. The COFEPRIS required a minimum of 3 batches of RBP. The Russian MoH predominantly expected specifications to be designed exactly the same as the RBP whereas CDSCO, SAHPRA and COFEPRIS defined specifications based on manufacturer's experience of the SBP and RBP, consistent with WHO guidelines.

Table 5.3 RBP selection criteria for six regulatory agencies of BRICS-TM

Regulatory agency	Selection criteria	Primary source of RBP	Alternate source of RBP	Use of RBP authorised in emerging countries	Criteria of RBP batches	Bridging study required
ANVISA	Approved based on full registration dossier with ANVISA	Locally authorised RBP	First innovator or biosimilar product authorised locally	Not accepted	Multiple batches of RBP with varied expiry dates	Not specified
Russian MoH	Approved based on full registration dossier with Russian Federation	Locally authorised RBP	First innovator product authorised locally	Not accepted	Singe batch of RBP	Not specified
CDSCO	Approved based on full registration dossier with CDSCO	Locally authorised RBP	ICH countries	Not accepted	Multiple batches (minimum 3 batches) of RBP with varied expiry dates	Not specified
SAHPRA	Approved based on full registration dossier with SAHPRA	Locally authorised RBP	First innovator product authorised locally	Not accepted	Multiple batches of RBP with varied expiry dates (draft stage; but followed in practice)	Not specified
TITCK*	Approved based on full registration dossier with TITCK	Globally authorised RBP	EMA, USFDA, BGTD, TGA, PMDA, MHRA, BfArM	Not accepted	Multiple batches of RBP with varied expiry dates (draft stage; but followed in practise)	Not specified
COFEPRIS	Approved based on full registration dossier with COFEPRIS	Locally authorised RBP	EMA, USFDA, TGA, PMDA	Not accepted	Minimum 3 batches	Not specified

** The TITCK agency did not declare acceptable agencies, theoretically all countries are acceptable, extra data can be requested case by case*

Comparative stability studies

Four of the six regulatory agencies of these emerging economies (i.e., Brazil, Russia, South Africa, Mexico) indicated the need for comparative accelerated and stress stability studies, along with real time, real condition stability studies conducted in their respective climatic zone to support the shelf-life. CDSCO (India) did not require comparative studies and TITCK (Turkey) considers it only as supportive data for biosimilar development. Comparative stability data was essential for '*totality-of-the evidence'* to determine biosimilarity (TOPRA, 2019) and is an integral part of any biosimilarity assessment (EMA, 2014a). As was evident from the responses, all the six regulatory agencies of these emerging economies were aligned with global standards in this aspect. However, CDSCO in practice, might consider an application even in the absence of side-by-side accelerated and stress stability studies though mandated as per the Guidance on Similar Biologics (CDSCO, 2016).

Non-clinical studies

The six regulatory agencies of the emerging economies state that *in vitro* comparative functional assays such as biological assays, binding assays, and enzyme kinetics; *in vivo* pharmacokinetics, pharmacodynamics and immunogenicity studies; and *in vivo* comparative repeat dose toxicity studies were requisite for non-clinical studies. In addition, local tolerance studies and other toxicological studies were expected by CDSCO, TITCK and COFEPRIS. Safety pharmacology studies were required by SAHPRA. In TITCK, the evaluation and acceptability were on a case-by-case basis.

For *in vivo* studies, the Russian MoH advised the use of transgenic animal/ transplant models in a GLP setting while CDSCO suggested toxicity studies in rodent and non-rodent animals for proving statistical difference and advised to submit scientific justification for the choice of animal model. If a relevant non-rodent model was not available in India, then non-rodent studies could be waived by the RCGM. The TITCK reported that the evaluation and acceptability of non-clinical studies was solely on a case-by-case basis in alignment with EU and ICH guidelines (ICH, 2009; EMA, 2014b). The rest of the six emerging agencies' responses were incomplete regarding the type and minimum sample size of each species for the study.

Clinical Studies

Table 5.4 presents the clinical trial requirements for biosimilar development in the six emerging economies.

Applicants needed to submit PK/PD and clinical safety and efficacy studies data as part of a biosimilar application in all the six regulatory agencies of these emerging economies.

Table 5.4. Clinical trial requirements for biosimilar development in emerging economies

Criteria	ANVISA (Brazil)	Russian MoH	CDSCO (India)	SAHPRA (South Africa)	TITCK (Turkey)	COFEPRIS (Mexico)
PK/PD studies (Phase I)						
Combined PK/PD study	✓	✓	✓	✓	✓	✓
Requirement of immunogenicity studies	✓ (Data can be obtained in PK/PD)	X	✓ (Data can be obtained in PK/PD OR Phase III)	✓	✓	✓ (Data can be obtained in PKPD)
Efficacy studies (Phase III)						
Study design randomized, parallel group, double-blind, adequately powered using efficacy endpoints	✓	✓	✓	✓	✓	✓
Clinical study design acceptance Equivalence design Non-inferiority design	✓ ✓	✓ X	✓ ✓	✓ X	✓ X	✓ ✓
Local clinical studies	X	✓	✓	X	X	✓
Required in pediatric and elderly population	X	✓	✓ (for extrapolated condition)	n/d	X	X
Inclusion of third countries patients	✓	n/d	X	n/d	✓ (if any genetic differences)	✓

n/d: Not defined; PK/PD: Pharmacokinetic/Pharmacodynamic; ✓: Required; X: Not required

PK/PD

The PK/PD requirement in terms of design, endpoints, fingerprinting approach and combining PK and PD studies were uniform across these emerging economies and closely aligned with the standards to norms set by the EMA (EMA, 2014b).

Immunogenicity

The responses from the agencies indicated the need for comparative immunogenicity as part of a biosimilar application, except for the Russian MoH. The CDSCO accepted that immunogenicity data could be obtained either from PK/PD or Phase III efficacy studies. Furthermore, all the agencies considered the extrapolation of immunogenicity studies to other indications, subject to the approved indications of the RBP. The expectations for such studies were defined in the Biosimilar Guidance 2016 (CDSCO, 2016) in the case of CDSCO, however such clarity was yet to be defined by the other regulatory agencies of these emerging economies.

Comparative clinical efficacy studies

Clinical study design: In general, all the regulatory agencies of these emerging economies studied expected a randomised, parallel group, double-blind, adequately powered clinical study using efficacy endpoints. Furthermore, ANVISA and COFEPRIS consented to both non-inferiority and equivalence design for clinical studies. The Russian MoH preferred an equivalence design, while CDSCO accepted a non-inferiority design. In addition, the Russian MoH and CDSCO expected clinical comparability studies in paediatric and elderly populations in cases of extrapolated indications.

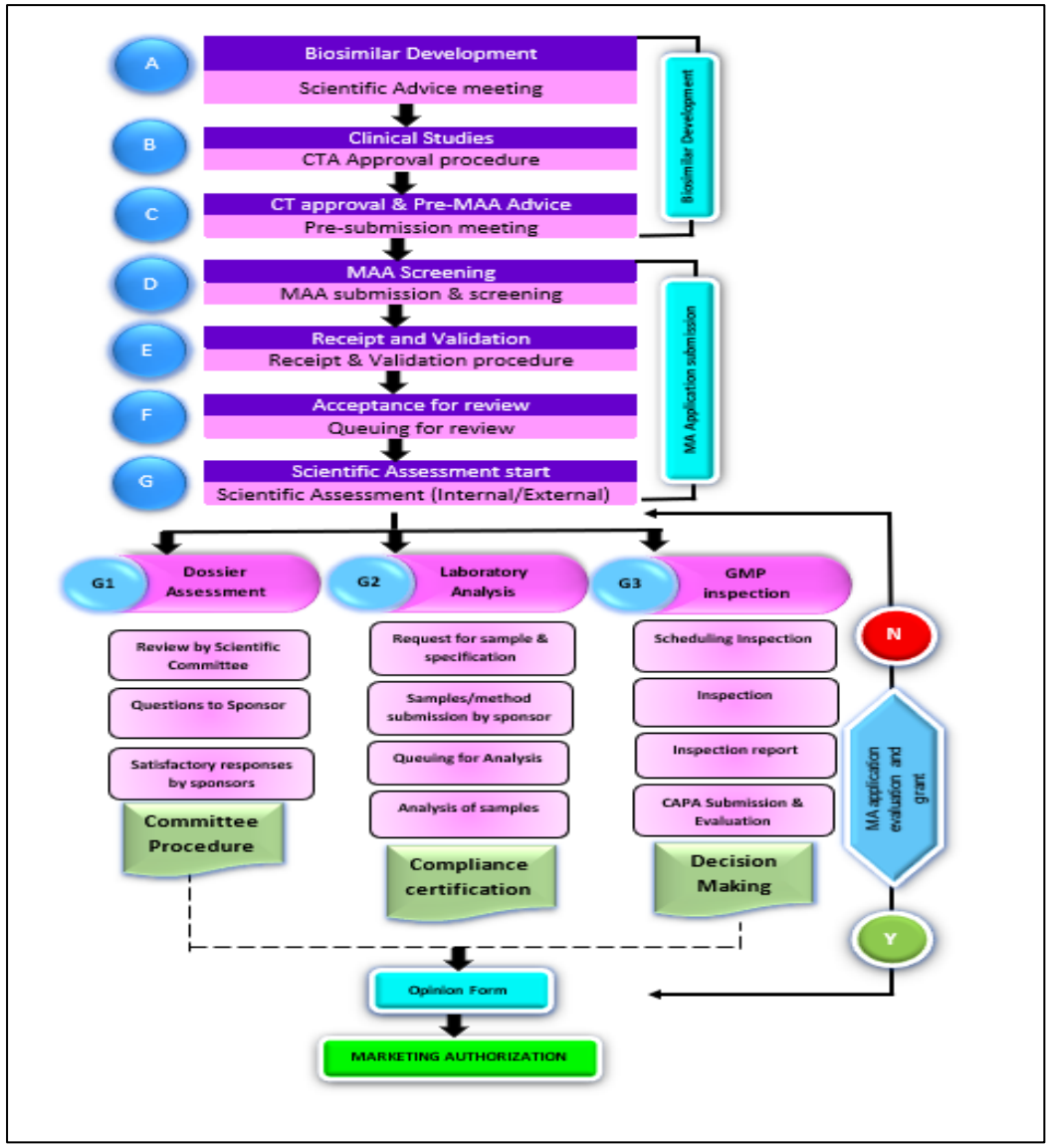
Local clinical studies: The ANVISA did not mandate performance of a local clinical study. However, for a global study, the agency mandated advice on regulatory expectations for clinical studies prior to protocol development, which was legally binding. Further, the foreign patient data was accepted by the agency as part of the biosimilar application if there are no foreseen genetic differences between the population studies and Brazilians. The TITCK has a similar requirement to that of ANVISA for acceptance of foreign patient data. The Russian MoH required local clinical studies for Phase III and mandates the inclusion of Russian patients when using global

studies. Similarly, CDSCO required local Phase III clinical trials in India. The sample size defined by CDSCO was a minimum of 100 patients in each arm. Usually, non-legally binding pre-submission advice was provided by the agency before the start of clinical trials. The agency did not accept foreign patient data as part of a biosimilar application. As for COFEPRIS, the local clinical study requirement depended on the demonstration of comparability at CMC and non-clinical stages, as well as the robustness of the already performed clinical studies. The agency was open for inclusion of foreign patients in clinical efficacy studies for proving biosimilarity.

Part III - Marketing authorisation approval pathway

The biosimilar application approval process includes the following steps: scientific advice, clinical trial application (CTA) approval process; and dossier review process including validation of application, queuing, scientific assessment, sample analysis, GMP certification, product approval (Figure 5.1)

Figure 5.1 Model Marketing Authorization Approval Pathway and Milestones



Notes

A Scientific advise meeting may include discussion and agreement with agency for biosimilar development plan.

B CTA approval procedure may cover submission of clinical trial application, IRB review and Ethics Committee (EC) approval.

C Pre submission meeting may cover discussion about clinical trial (safety and efficacy) results and targeted submission for MAA.

D&E MAA submission screening, receipt and validation may include administrative registration (reference number) and checks on legal requirements, status of company, local agent, manufacturer etc. as well as a 'checklist' validation of the application content (e.g., technical sections, CPP status).

F Queuing for review: *Administrative time* is a measure of the 'backlog' time (if any) while valid applications wait for action to begin.

G Scientific Assessment is a measure of 'review time'. In some systems the 'clock' stops when questions are asked and **Sponsor *time*** can be measured and deducted from the agency review time.

G1 Review by scientific committee may cover review of CTD dossier (m1 to m5) and discrepancies/questions sent to sponsor for clarification/additional data. Upon submission of satisfactory data, agency may conclude review of dossier with positive note.

G2 Laboratory analysis may include biosimilar sample submission to agency assigned laboratory for analysis. Upon compliant result with specification, agency may issue certificate of analysis indicating compliance.

G3 Product specific GMP inspection may involve scheduling of agency inspection at site of manufacturing of biosimilar. It may further result into inspection report expressing critical major minor observations. The manufacturer may submit CAPA and based on that agency may issue GMP certification.

Approval procedure may be extended by pricing negotiation of biosimilar.

Scientific Advice

Throughout the development process of biosimilars, developers need the respective agency's advice. This can include reference product selection and overall development strategy; evaluation and discussion post physicochemical and biological characterisation with *in vitro* non-clinical data; *in vivo* clinical data and justification of differences and clinical safety and efficacy trial protocol design and approval; and overall dossier content. The advanced agencies such as the USFDA (CDER & CBER, 2018b) and the EMA (EMA, 2020a) offer biosimilar developers, formal meetings for scientific advice to perform appropriate tests and studies, so that no major objections regarding the design of the tests are likely to be raised during the review of the marketing authorisation application. This approach supports the timely and sound development of high-quality, effective and safe medicines for the benefit of patients and also helps to avoid patient studies that will not produce useful evidence.

Three of the six agencies (i.e., ANVISA, CDSCO and SAHPRA) offered pre-submission advice for the biosimilar developers. The advice from ANVISA could be obtained through face-to-face meetings, electronic mails, or written correspondence whereas CDSCO and SAHPRA preferred face-to-face meetings. The expert advice received through such meetings were not legally binding on both parties, however, agencies did expect compliance to their comments during development of the biosimilar. The Russian MoH, TITCK and COFEPRIS were yet to establish any formal meeting procedures.

The absence of scientific advisory meetings in TITCK had also been highlighted in an earlier study (Mashaki Ceyhan et al., 2018) where the importance of such interaction with agency had been emphasised. In Russia, face-to-face interaction between the government and a biosimilar manufacturer was not allowed and all regulatory communications must be carried out in writing (Welch, 2017).

Clinical Trial Application (CTA) approval process

The CTA is evaluated and approved by specific committees designated by the agencies such as: Coordenação de Pesquisa Clínica (ANVISA); Subject Expert Committee (CDSCO); and Clinical Trials Committee (SAHPRA). The Russian MoH and TITCK assigned internal assessors to review the application. No clarity on this topic was received from COFEPRIS. An integral part of the CTA is the Ethics

Committee (EC) approval letter, which was to be obtained from the Institutional Review Board of hospitals or institutions where the clinical trial was intended to be performed. The Russian MoH and COFEPRIS require an EC letter as part of the initial application, whereas the rest of the agencies were flexible and would accept such letter during the review process or post approval of the CTA. All the regulatory agencies had varied timelines for CTA approval as shown in Table 5.5.

Table 5.5 Timelines for biosimilar review and approval process

	ANVISA	Russian MoH	CDSCO	SAHPRA	TITCK	COFEPRIS
CTA review	90 days	45 days	90 days	Less than 70 days*	30 days	45 days
Validation	Not applicable	5-15 days	No specific step	15 days	30 days	No information available
Queuing	60-180 days	No information available	14-56 days	≤ 28 days	60-180 days	180-365 days
Scientific Committee review	30 days	30-90 days	No information available	60 days	No information available	90 days
Decision via committee meeting	Not applicable	30 days	Not applicable	≤ 240 days	Not applicable	90 days
Issuance of Marketing Authorisation	Less than 30 days	Less than 30 days	90 days	Less than 30 days	Less than 30 days	90-180 days

** There are cases where this turnaround time might be prolonged i.e., an unfamiliar investigational product which may be referred to external reviewers or other committees of SAHPRA for input for new applications.*

Note: ANVISA, Russian MoH, SAHPRA, TITCK follows calendar days; CDSCO and COFEPRIS follows working days

Dossier review and approval process

Dossier content

The six regulatory agencies accepted electronic CTD dossiers as the format for marketing authorisation applications (MAA) for biosimilar products. The Certificate of Pharmaceutical Product (CPP) was a mandatory document as part of the initial dossier by the Russian MoH and CDSCO, for acceptance of the application by the agency. The ANVISA, COFEPRIS and TITCK provided relaxation for the CPP submission before granting a marketing authorisation. In addition, TITCK also accepted any

marketing authorisation certificate and published approvals from the relevant agencies' official websites. Post submission by the sponsor, the product dossier passed through different stages such as screening against a checklist, acceptance for further review, queuing for review and scientific assessment resulting in approval or non-approval of the application by the agency.

Screening and validation

As part of the screening or validation process, all the agencies verified applications against a standard checklist and requested additional data (except CDSCO) if some documents were missing. In case of CDSCO, submission would not be uploaded on the SUGAM online portal if the dossier were inadequate. Further, all the information pertaining to 'milestone' dates were recorded during the review process into an electronic tracking/recording system maintained by the agencies, i.e., DATAVISA (ANVISA), GRLS (Russian MoH), SUGAM (CDSCO). In the case of SAHPRA and COFEPRIS, there was no specific system in place, whereas no information was available from TITCK on this topic.

Queuing

The queue time for dossiers awaiting review ranged from four weeks to one year as displayed in Table 5.5. All agencies, except the Russian MoH and COFEPRIS, confirmed that priority products including biosimilars were not required to be in a queue for review.

Scientific assessment

Scientific assessment of the biosimilar application depends on the outcome of the dossier review, sample analysis and GMP certification. For dossier review, CDSCO and SAHPRA used external assessors, however, there was no contractual agreement defining the timelines for review of the technical data. ANVISA and TITCK issued an emergency letter to sponsors in the case of a sudden unforeseen crisis as and when they reviewed different sections of the dossier while the rest of the agencies collated quality, safety, and efficacy deficiencies in one batch and sent it to the applicant. The obligatory time for developers to respond to queries varied between 3 to 6 months and referred to as 'clock stop'. Failure to meet the stipulated time, led to rejection of the application with forfeiting of the fees with ANVISA, the Russian MoH, CDSCO and

COFEPRIS. The TITCK sent official letters for rejection to the sponsor, but the company could object to the same however there was no predetermined deadline in this aspect, while SAHPRA allowed for extensions. Further, in case of a negative opinion from the scientific committee, CDSCO had provisions for sponsors to approach the technical committee and apex committee for their intervention and decision. The Russian MoH and ANVISA had no such additional provision and there was also no clarity received in this regard from COFEPRIS. The defined target timeline for scientific review by each of the regulatory agencies also varied as detailed in Table 5.5.

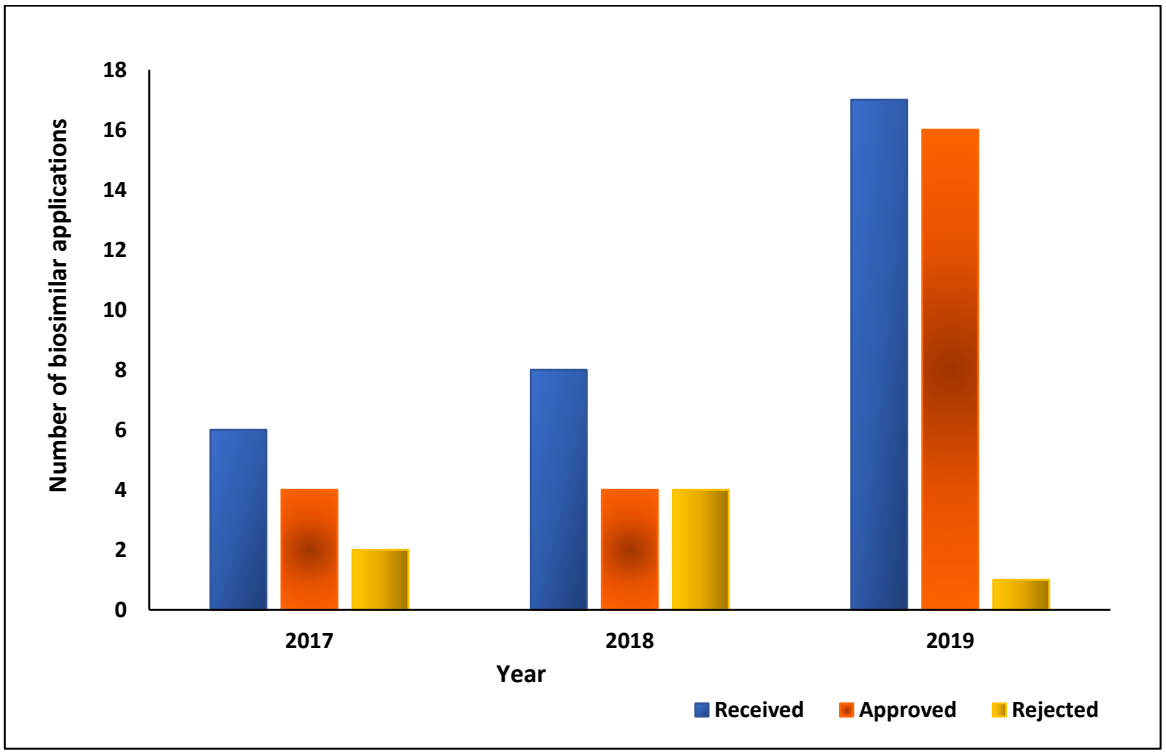
Sample analysis: Most of the regulatory agencies of these emerging economies expressed a requirement of sample analysis at specified approved quality control laboratories as part of the dossier approval process. ANVISA and SAHPRA relied only on technical documentation for biosimilar products and did not require sample analysis. The Russian MoH, TITCK and CDSCO expected sponsors to submit samples along with analytical specifications and methods, reference/working standards and analytical columns. The CDSCO additionally required an analytical validation package. The maximum time to analyse samples is 110 calendar days as defined by FGBU (Russia) while no such deadlines were specified by other agencies.

GMP inspection: These six regulatory agencies of emerging economies also mandated on-site GMP inspections for biological substances and biosimilar product manufacturing sites. Generally, each agency (except CDSCO) performed inspection during the dossier evaluation process, whereas CDSCO inspected site/s after completion of the dossier assessment. For TITCK, separate site GMP application were required, and the agency conducted inspection before scientific assessment of dossier, unless there were priority products. Also, CDSCO and SAHPRA accepted GMP certification from reference agencies i.e., EMA (EU), BGTD (Canada), MHRA (UK), USFDA (USA) instead of on-site inspections. In addition, CDSCO accepted TGA (Australia) certification whereas COFEPRIS accepted EMA (EU), TGA (Australia) and USFDA (USA) certification. The TITCK did not accept foreign agencies' GMP inspections. Across these emerging economies, the final decision maker on the marketing authorisation was the head of the agency.

Public Assessment Reports (PARs) and Approval metrics

Except for ANVISA, the regulatory agencies of these emerging economies are yet to establish procedures for the issuance of a public assessment report or clarifying the basis for approval for the product. In such scenarios, measuring real approval timelines for biosimilars becomes arduous. The biosimilar approval metrics for the duration of 2017-2019 for ANVISA is presented in Figure 5.2.

Figure 5.2 Biosimilar Approval metrics of ANVISA – 2017 to 2019



Number of applications	2017	2018	2019
Received	6	8	17
Approved	4	4	16
Rejected	2	4	1
Approval timeline (calendar days)	789	963	760

DISCUSSION

Biosimilar products are complex molecules produced using highly complex manufacturing processes. Due to the complexity of the biosimilar products, regulatory requirements for analytical comparability, non-clinical and clinical studies vary with the geographies (Rahalkar et al., 2021b), particularly in emerging economies such as the BRICS-TM, as evident from the secondary research (Rahalkar et al., 2018).

Furthermore, with multiple prospective manufacturers on the horizon, the need arises for a streamlined regulatory guideline in emerging economies that ensure biosimilarity, comparability, and interchangeability with respect to safety and efficacy of the product (Rahalkar et al., 2021b). Although substantial progress has been made in regulatory frameworks for chemical drugs, progress is less robust in developing countries, and implementing regulatory frameworks for biologic medicines, particularly biosimilar medicines (Aitken, 2020). The recent studies reported in the literature suggest that the regulatory challenges in biosimilar space continue to be a topic of interest and deserves further debate. However, our study, in comparison to existing knowledge in the area, provides insight about TITCK (Turkey) and COFEPRIS (Mexico) agencies pertaining to biosimilar development challenges, in addition to the 20 countries included in the WHO survey reported by Kang et al., 2021. The findings reposted by Garcia et al., 2016 of Latin America are complemented by this study for challenges pertaining to biosimilar approval pathway. Furthermore, Sharma et al., 2020 discuss global regulatory requirements on biosimilars and their difference amongst generics based on ophthalmic perspective while Cohen et al., 2017 focuses on clinical practices specific for the treatment of psoriasis. However, our study reported here provides insight about biosimilar regulations irrespective of therapeutic areas.

Regarding the type of dossier assessment and allocation of resources for the dossier evaluation by the regulatory agencies, external evaluators are involved for review of applications by SAHPRA, TITCK, CDSCO and COFEPRIS, while Russian MoH has common assessors for biologic and non-biologic applications. All the six emerging agencies follow ‘Type III - Full review of the marketing authorisation application’ data assessment model. In addition, CDSCO follows ‘Type II - Abridged review’ and COFEPRIS follows ‘Type I – Verification of marketing authorisation application, with a clear indication of less prevalence of Type I and Type II review models among these countries. It has been commonly cited that building capacity and expertise in a national regulatory authority is a long-term process and quick resolutions lie in relying on information from other regulatory authorities or a shared or abridged review models (Ferreri, 2020). The study results reveal non-transparency and limited co-operation amongst the agencies for biosimilar medicinal product regulatory review. The outcome of this study may benefit these agencies by highlighting the need for adopting shared review or reliance review models for scientific assessment of biosimilar applications.

Evidence of shared review by SAHPRA (South Africa) with the national regulatory authorities of the member countries of the ZaZiBoNa work sharing initiative (SAHPRA, 2019b) such as Zambia, Zimbabwe, Botswana, Namibia offers an opportunity for an efficient and effective regulatory process for biosimilar evaluation in countries with limited resources. Brazil and Mexico are part of the PAHO (PAHO, 2021) region, and Mexico uses the reliance model with authorities of regional reference, which includes the USA and Canada, thus using Type I review model for scientific assessment depending on the product. However, ANVISA, Brazil do not recognize any reference agencies for the dossier review and carry out full review (Type III). Although Brazil and Mexico are recognized as regional reference agencies in the America, the products authorised in these countries are neither recognised nor the data relied upon by other emerging economies within these regions.

The common expectations on demonstration of biosimilarity to the RBP across these emerging agencies includes satisfactory physicochemical and biological characterisation, in vitro non-clinical studies, additional in vivo safety data along with confirmatory clinical safety and efficacy data. While ANVISA, SAHPRA, TITCK accept global clinical studies, Russian MoH, CDSCO and COFEPRIS mandates conduct of clinical efficacy trials in the local population. The non-acceptance of global clinical data and repetition of clinical studies mandatorily in local population by these regulatory agencies adds to unnecessary development costs (Rahalkar et al., 2021b). Such duplication of studies further is likely to impact the overall biosimilar development process and approval timelines in these countries (Kang et al., 2021).

With regards to the selection criteria for RBP and its procurement, these emerging agencies mandated locally authorised reference product (based on a full dossier including quality, safety and efficacy) for comparability studies. While few agencies like CDSCO, TITCK and COFEPRIS provide flexibilities for sourcing RBP from ICH/ reference countries, ANVISA, Russian MoH and SAHPRA have stringent regulation on using only the locally licensed RBP. In Russia, a comparator product cannot be sourced from another regulatory jurisdiction since it is only allowed to use a reference comparator drug that has Russian marketing authorisation (Pharmaboardroom, 2020a). Further, although most agencies expect multiple batches of RBP with varied expiry dates, the exact number of RBP batches required for comparability studies was not clearly defined by the agencies. Also, reference products authorised by other

emerging countries are not accepted by these agencies, excepting in emergency situations, in case of CDSCO. There is seemingly a non-convergence in the regulatory requirements among these agencies with regards to RBP selection criteria. Acceptance of a non-locally licensed/sourced RBP by few countries and others that require a locally licensed reference product without any leverages, also demonstrates the challenge in procuring multiple lots of RBP, thereby posing a potential barrier for the biosimilar development process in these countries. It has been suggested by WHO, that exchange of information with other national regulatory authorities by accepting sourcing of non-locally licensed reference products, and avoiding unnecessary bridge studies (Ferreri, 2020) can circumvent such challenges in RBP sourcing.

In general, *in vitro* comparative functional assays are required by all the six emerging agencies along with *in vivo* pharmacokinetics, pharmacodynamics and immunogenicity studies. There is a mandatory requirement for *in vivo* repeat dose toxicity studies from all the countries; with TITCK evaluation in accordance with EU and ICH guidelines, on a case-by-case basis. Further, CDSCO expects non-clinical studies in rodent and non-rodent animal and Russian MoH in transgenic animal/ transplant models to be conducted. However, there is no clarity on the type of study or species or other requirements from other agencies. The study clearly shows the lack of consistency in the regulations on non-clinical aspects from these countries. Also, such mandatory requirements for non-clinical studies demonstrates a lack of scientific approach towards the assessment of data indicating lack of full implementation of a ‘step-wise approach’ for proving biosimilarity (Aitken, 2020).

These six regulatory agencies of the emerging economies mandate PK/PD studies (regulations being similar to EMA), clinical safety and efficacy studies along with comparative immunogenicity data as part of a biosimilar application. However, the Russian MoH does not provide clarity on expectations on immunogenicity studies nor for extrapolation of immunogenicity data to other indications in most of the agencies. Further, as discussed earlier, the acceptance of clinical efficacy data from foreign patient data is not supported by all the agencies. Such a mandate on confirmatory clinical efficacy studies shows the agencies lack in science-based approach for review of dossier. It is apparent that the understanding by these agencies on the importance of comprehensive analytical comparability studies and the evaluation of comparability data for any structural and functional differences is inadequate. Further, non-

recognition and non-acceptance of global data leading to duplication of studies, impacts on development costs and delays in approval of the biosimilar product (Ball et al., 2016). Emphasis on recognising data from other reference countries and the relevance of advanced analytical science to prove comparability in place of confirmatory clinical data has also been focussed by IGBA in their policy paper (IGBA, 2020).

Scientific advice helps to ensure that developers perform the appropriate tests and studies, so that no major objections regarding the design of the tests are likely to be raised during the evaluation of the marketing authorisation application. This also helps avoid patients taking part in studies that will not produce useful evidence. Such pre-submission advice for biosimilar developers to get agencies' opinions on the biosimilar development process is only offered by a few of these emerging agencies like ANVISA, CDSCO and SAHPRA. These advisory meetings are through face-to-face meetings, electronic mail or written responses. However, there are no set procedures for any formal meeting in the rest of these emerging agencies. The absence of a communication channel between the biosimilar developer and the national health authority greatly impacts the overall development process. With an increasing number of biosimilar developers across the globe, the scientific advice requests to developed agencies like EMA is expanding. EMA has also launched a pilot project in 2017 (EMA, 2016a) for 'tailored scientific advice' for the development path for biosimilar medicines, to test the added value and feasibility of the project. Implementation of scientific advisory meetings by these six regulatory agencies of emerging economies, similar to those by established regulatory authorities would support the potential manufacturers to have better clarity on the regional regulations and incorporate them in their global biosimilar development program.

The dossier content requirements for biosimilar Marketing Authorisation Application (MAA) are similar within these regulatory agencies of emerging economies. All these agencies accept electronic CTD and mandate CPP as part of the dossier, however the flexibility over time of the submission of such administrative documents (initial dossier or post approval of dossier) varies. Relaxation in terms of provision of other published approvals and authorisation documents in lieu of CPP by few agencies, exists. The dossier screening and validation process against a standard checklist is uniform across all the six emerging agencies, however the acceptance of the MAA with insufficient

data differs with the agencies. The queueing time for dossier review varies from 4 weeks to 1 year, with almost all the agencies discounting the priority products (except the Russian MoH and COFEPRIS). The biosimilar application is considered for scientific assessment based on the outcome of the dossier review, sample analysis and GMP certification. Although most of the agencies evaluate the dossier internally, a few opt for external evaluators for dossier evaluation. This is partly due to the full review of dossier (Type III data assessment model) by the agencies. Joint or shared review of the dossiers will ease the resource constraint or the dossier review process among these agencies (Kang et al., 2021). Further, such joint review can have a positive impact on the query response timelines, by allowing the sponsors to address the deficiencies in a single window rather than responding to the same query multiple times to different agencies. Such provisions might further minimise the number of dossier rejections within the agency, thereby allowing more biosimilars to penetrate into these emerging markets.

Despite the technical dossier, the requirement for samples by all these emerging agencies (except ANVISA and SAHPRA) along with reference standard/working standards for testing at qualified laboratories for the biosimilar approval process extends the overall biosimilar approval timelines. Additionally, each of these agencies mandate on-site GMP inspections for biological substances and biosimilar product manufacturing sites. Though inspection of the manufacturing site is essential for ensuring compliance to global manufacturing standards and assuring the quality of the product, individual or separate inspections by each of the emerging agencies leads to duplication. Instead, acceptance of reference agency GMP certification (including EU, PIC/S), as permitted by CDSCO, SAHPRA and COFEPRIS will improve the process efficiency of the agencies (National Academies of Sciences, Engineering, and Medicine, 2020). Also, collaboration, reliance or joint inspections among these regulatory agencies will minimise the resources and efforts required by developers, resulting in increased regulatory performance (National Academies of Sciences, Engineering, and Medicine, 2020; Welch, 2016b; PIC/S 2018).

The biosimilar therapy in emerging economies is still in the infancy stage with little or no presence but expected to show strong growth (McKinsey & Company, 2019) remains scope for improving transparency in the national regulatory frameworks and aligning regulatory standards among the emerging economies. In the light of the

current global regulatory environment and the pandemic challenges, it was prudent for both regional and National Regulatory Authorities (NRAs) to re-evaluate regulatory requirement for development and approval of biosimilars taking into account the challenges faced by different stakeholders.

Although there were no remarkable changes in biosimilar guidelines in the six emerging economies between 2018-20, there have been progress towards relaxing few guidelines with regards to conduct of clinical trials and GMP inspections. For instance, ANVISA, Brazil, has introduced certain relaxation of clinical trial procedure and allowed sponsors to modify or amend protocol without ANVISA's authorisation. In addition, if clinical study is related to COVID-19 then clinical trial consent can be obtained immediately upon formal submission of the protocol. As per the resolution of the Collegiate Board of ANVISA, RDC no 346/2020 of March 13th, ANVISA has adopted an alternative route for GMP certification of Active Pharmaceutical Ingredient (API), drugs and health products, based on remote inspection or reliance from other health authorities. If the manufacturer is accredited by PIC/s GMP certification, then ANVISA can process a faster GMP certification (ANVISA, 2020a). RDC no 348/2020 of March 17th allows flexibility in evidence and prioritization in analysis if the product has the therapeutic indication for treatment or prevention of the pandemic disease (ANVISA, 2020b). Similarly, the Russian agency has taken step to have remote GMP inspections for foreign manufacturers (Regapharm, 2020).

The CDSCO has upgraded regulatory standards for clinical trials via the New Drug Clinical Trials Rule 2019 (MoHFW, 2019). In India, Schedule Y of Drugs and Cosmetics Act and Rules defined the requirement for clinical trials of new drugs and investigational new drugs for manufacturing and import prior to the New Drug Clinical Trial Rules (MoHFW, 2019) came into effect. The revised comprehensive NDCTR closes some of the gaps existing in Schedule Y in terms of number of subjects, nature and timing of non-clinical studies, content of the proposed protocol for performing clinical trials. As part of the first schedule, General Principles and Practices for Clinical Trial section (3) (2)(c) (iii), pertaining to new drugs approved outside India, the phase III study may need to be performed in India. It explicitly states that Phase III studies need to be carried out if scientifically and ethically justified to establish data for safety and efficacy of drugs in Indian patients. It further states that PK studies may be required

by the Central Licensing Authority (CLA) in Indian patients. The CDSCO, India, has also developed rapid response framework for COVID-19 vaccines. Accordingly, the agency is open to considering pre-clinical or clinical data generated outside the country and shorten development requirements to reduce the time for approval (DBT, 2020). In addition, WHO GMP/ Certificate of Pharmaceutical Product (CoPP) extension of an additional 6 months has been provided and special permission has been granted to import drugs with less than 60% of remaining shelf life, up to October 2020. Similarly, the SAHPRA, South Africa, has issued policy documents for conducting clinical trials, based on the FDA's guidance on conduct of clinical trials of medicinal product during the COVID-19 pandemic (SAHPRA, 2020).

Furthermore, The TITCK, Turkey, announced some flexibility due to COVID-19 such as postponing marketing authorisation certificate's annotation process, online stakeholder meetings regarding marketing authorisation activities, accepting CPP or similar certificate without apostille, readability test waiving until end of 2021, extension of GMP validity period to end of 2021 (Kilic & Unal, 2021).

SUMMARY AND CONCLUSION

The key outcomes from this study for an effective biosimilar development and approval process among these emerging agencies can be summarised as follows:

- This study emphasises the need to foster effective collaboration between regulators and developers in six emerging agencies in order to streamline the development strategies and approval pathways for biosimilar products.
- A formal approach to regular, appropriate and tailored scientific advice from regulatory agencies to developers will help to align expectations on both sides and support step-by-step development, thereby reducing the need for certain studies i.e. *in vivo* non-clinical studies. This may also help to shorten the overall review and approval timeline.
- Significant challenges in sourcing RBP for comparative studies necessitates regulatory flexibility in norms for sourcing the comparator. Allowing RBP from other emerging countries will also facilitate the use of common biosimilar development programs.

- While appropriate resource allocation and upskilling of regulators need to be considered, adoption of an alternative regulatory framework such as abridged review models might help in optimising the use of resources within the biosimilar departments of these six emerging agencies.

To conclude, many medical treatments and medicines now lay in Biotechnology, where understanding of the patient's physiology and cell make up is the key to treatment. Biological drugs bring that value in the treatment of many disabling and life-threatening chronic diseases, including inflammatory arthritis, certain types of cancer, diabetes, inflammatory bowel disease, Crohn's disease, psoriasis and COVID-19. Biosimilars can help the public gain access to health through affordability, and that is where the need for the regulatory guidelines of biosimilars can contribute through harmonisation and simplification. The research undertaken presents an effort in that direction. This study has, for the first time, evaluated the regulatory requirement for approval and development of biosimilars in these six emerging economies and has identified a lack of alignment in certain areas that would benefit from standardisation. There remains scope for improving transparency in the national regulatory frameworks and aligning regulatory standards among these six emerging economies. This would impact the overall review and approval process as well as enabling a common development programme across these countries. Further, a future study could focus on developing proposals for an improved regulatory model for approval and development of biosimilars in these emerging economies. Integration of regulatory standards across emerging economies would also enable streamlined biosimilar development programmes and expedited licensing processes, thereby facilitating improvements in patient care and access to these life-saving medicines.

CHAPTER 6

Comparative Evaluation of Practices in the Mature (ACSS) and Emerging (BRICS-TM) Agencies for Type of data assessment, Criteria for Biosimilar Development and Pathway for Marketing Authorisation Approval

INTRODUCTION

The trend towards globalisation of therapeutic products industries and the rapid emergence of new technologies have created an increased need for regulatory bodies to communicate with each other routinely. This maximises the use of up-to-date technical expertise, and ensures a consistent, contemporary approach to assess the benefits and risks associated with the use of therapeutic products (TGA, 2020). Developing economies account for one-third of global growth in drug demand, with an overall annual growth rate of 5-8 % (IQVIA, 2019a). The BRIC (Brazil, Russia, India, China) nations alone account for roughly 30% of GDP globally (Mminele, 2016) along with other emerging markets such as Mexico, Turkey and South Africa (MSCI, 2020).

Opportunities exist for biosimilars in the emerging economies (Boccia et al., 2017), due to low treatment rates with biologics and constraints of affordability. However, a strong and clear regulatory framework is required to unlock the potential of biosimilars in these markets. Despite the BRICS-TM agencies basing their guidelines on a common regulatory framework for Similar Biotherapeutic Products (SBPs) as established by the WHO (WHO, 2013), the biosimilar regulatory requirements, structure and processes are still significantly different. It is therefore challenging to develop biosimilar medicines for simultaneous submission to all the regulatory authorities (Jain et al., 2017). Comparisons of the requirements of regulatory agencies among countries will assist in facilitating improvements in the integration of regulatory processes. Thus, agencies from jurisdictions with emerging pharmaceutical markets might compare themselves with other similarly sized mature regulatory authorities which are associated with an ICH member through a legally-binding, mutual recognition agreement, before October 23, 2015 (WHO, 2021). Also, comparisons between regulatory authorities of similar size, regulatory mandates, structures, resource characteristics and regulatory challenges would be more beneficial than comparisons between authorities with vastly different characteristics and competencies (Mashaki Ceyhan et al., 2018).

Studies have been performed to compare the South African Health Products Regulatory Authority (Keyter et al., 2019), Turkish Medicines and Medical Devices Agency (Mashaki Ceyhan et al., 2018), the Saudi Food and Drug Authority (Hashan et al., 2016) and the Jordan Food and Drug Administration (Haqaish et al., 2017) with the regulatory authorities of Australia, Canada, Singapore

and Switzerland, focusing on the area of small molecules. The aim of this study therefore was to identify, compare and evaluate the biosimilar regulatory strategy of BRICS-TM agencies with that of Australia Canada Singapore Switzerland (ACSS Consortium), in an effort to identify and replicate best practices in biosimilar development and their authorisation processes.

Australia - Australia first introduced the biosimilar guidelines in August 2008 when it adopted a number of guidelines from the EU on similar biological medicinal products (GaBI, 2018). To date, the TGA has approved 27 biosimilars within the product classes of human growth hormone (HGH), granulocyte colony-stimulating factor (G-CSF), insulin, erythropoietin (EPO), follicle stimulating hormone (FSH), monoclonal antibody and tumour necrosis factor (TNF)-inhibitor, for use in Australia (GaBI, 2021b). The TGA assesses each biosimilar based on the totality of available data, comparing it to the reference product in terms of its physicochemical structure, biological activity, preclinical data (pharmacokinetic and pharmacodynamic data) and clinical trials data (efficacy, safety and immunogenicity). Regulatory approval for a biosimilar requires that no clinically meaningful differences exist and that the biosimilar molecule is therapeutically equivalent to the reference medicine (TGA, 2018). In general, a Phase III clinical trial for a single indication will be sufficient to confirm biosimilarity (together with preclinical and physiochemical data). Once biosimilarity is established, it may be possible for a biosimilar to be approved for other indications by so-called ‘indication extrapolation’ from the reference product’s data (TGA, 2018).

Canada - Health Canada unveiled its regulatory guidelines for the entry of biosimilars into the Canadian market in 2010, which were then revised in November 2016. In February 2018, Canadian Agency for Drugs and Technologies in Health (CADTH) streamlined the biosimilar review process, reducing the number of submission requirements and shortening the review period (Lungu, 2019). Notably, Health Canada harmonised its guidance for the authorisation of biosimilars with the European Medicines Agency (EMA). While biosimilar products first appeared in Canada in 2009 with the approval of Omnitrope (somatropin), uptake has been slow and to date Health Canada has approved fewer than a dozen biosimilars (White et al., 2019).

Singapore - The Health Sciences Authority’s (HSA) published the “Guidance on Registration of Similar Biological Products in Singapore” in 2009, which is mainly

adapted from the EMA's biosimilar guidelines. The biosimilar medicine is subject to the same regulatory framework as all other therapeutic products in Singapore, i.e., the Health Products Act 2016 and the Health Products (Therapeutic Products) Regulations 2016 (Cap 122D). However, the application for a biosimilar product differs from that of other therapeutic products as it can only be registered for as a biosimilar if it is similar to an existing biological product registered in Singapore in terms of physicochemical characteristics, biological activity, safety and efficacy. It is to be submitted as a new drug application (NDA) via the abridged evaluation route, either through NDA-2, for the first strength of a biosimilar product with the same dosage form and route of administration as the Singapore reference biological product, or NDA-3, for subsequent strengths of a biosimilar product that has been registered or submitted as an NDA-2. The administrative requirements are as per those required for an NDA via the abridged evaluation route. There must also have been a comprehensive comparability exercise done with the reference product (Pharmaboardroom, 2020b). Singapore has 7 approved biosimilars (Kang et al., 2020).

Switzerland - The Swiss guidance for approval of biosimilars is also largely based on the EMA guidelines. Swissmedic guidance documentation on biosimilars requires that an applicant product is sufficiently similar with respect to structure, biological activity, efficacy, safety and immunogenicity in order to rule out relevant clinical differences with sufficient reliability (Swissmedic,2020b). CT-P13 (manufactured by Celltrion, South Korea) was the first infliximab biosimilar to be approved by Swissmedic, the Swiss Regulatory Agency for Therapeutic Products (Burri et al., 2019).

OBJECTIVES

The objectives of this study were to:

- Identify regulatory framework of the ACSS agencies:
  - identify resources of the agencies in the biosimilar domain and type of data assessment,
  - identify biosimilar development criteria i.e., biosimilarity principle, comparative studies including physicochemical characterisation, non-clinical and clinical studies,
  - identify the biosimilar marketing authorisation approval pathway specifically for key milestones, validation time, queuing time, backlogs, requirement for sample

analysis, conduct of GMP inspections, issuance of Public Assessment Reports (PARs), scientific guidance meetings and clinical trial mandates.

- Comparative evaluation of above parameters of BRICS-TM with ACSS agencies
- Identify challenges and areas for improvement.

METHODS

A semi-quantitative questionnaire was developed for the BRICS-TM agencies based on an already established questionnaire developed by the Centre for Innovation in Regulatory Science (CIRS) (McAuslane et al., 2009) and relevant literature. It was then decided to name this as the: Biosimilar Development, Evaluation and Authorisation (BDEA) questionnaire. For the purpose of this comparison study, it was slightly modified to reflect organisational differences in the regulatory frameworks of Australia, Canada, Singapore and Switzerland regulatory agencies. ACSS agencies were selected in the study due to its like-minded approach and promote work sharing for greater regulatory collaboration and alignment of regulatory requirements. Each of these agencies leverages each country's strengths, addresses gaps in science, knowledge and expertise and resources to expedite risk assessment, while maintaining or raising quality and safety standards, thereby allowing for rapid assessments to facilitate the market approval of the products (Kühler, 2020). Due to similarity in regulatory systems between these agencies, the ACSS consortium was established in 2007 and now renamed as ACCESS consortium in October 2020 with addition of new agency of MHRA, UK. The Consortium builds on international networks, initiatives and mechanisms to advance work- and information-sharing throughout the life cycles of health products (WHO, 2020).

The content validity of the BDEA including its relevance was carried out by a medium sized independent regulatory agency, the Regulatory Authority of Medicines, Equipment and Medical Device (CECMED), Cuba. Post validation, the questionnaire was further modified by removal of duplication of questions and restructured to make a 35-page long questionnaire.

The BDEA (Appendix 2) consists of three parts: Part I – organisation of the agency; Part II – agency's guidelines/views on biosimilar development criteria; and Part III – marketing authorisation approval pathway.

Part I - Organisation of the agency - This part of the BDEA questionnaire consist of current agency structure, resources in the biosimilar domain and types of regulatory review models (Type I- Verification review, Type II- Abridged review and Type III- Full review) employed for scientific assessment, level of data required, and extent of data assessment of the data including reliance on other authorities, if applicable. The rationale for including this section was to assess the capacity, strengths and weaknesses.

Part II – Agency's guidelines/views on biosimilar development criteria - This part includes questions related to biosimilarity principle, selection of Reference Biological Product (RBP), comprehensive comparability criteria including physico-chemical, non-clinical and clinical studies and "must submit" documents that are required for a biosimilar marketing authorisation application. The rationale for inclusion of this section was to determine the extent of the regulatory requirements for biosimilar development and approval.

Part III – Marketing authorisation approval pathway - This part covers questions with regards to key milestones i.e, the assessment process starting from receipt of the dossier, validation/screening, the number of cycles of scientific assessments including the questions to the sponsor/applicant, expert registration committee meetings to the final decision on approval or rejection of a biosimilar for registration. A standardised process map, developed based on the experience of studying established and emerging regulatory authorities, was embedded in the questionnaire. The rationale for inclusion of this section was to evaluate different stages of the review process and timelines for each milestone.

Eleven regulatory agencies from BRICS-TM (i.e., Brazil, Russia, India, China, South Africa, Turkey and Mexico) and ACSS (Therapeutic Goods Administration (TGA) Australia, Biologic and Radiopharmaceutical Drugs Directorate (BRDD) Canada, Health Science Authority (HSA) Singapore and Swissmedic, Switzerland) countries were invited to take part in this comparative study. The study protocol was shared with the 11 agencies together with the electronic self-administered BDEA questionnaire and the supporting instruction for completion. The data collection took place between August to November 2020. The potential study participants were identified via each respective agency's general email addresses obtained from agency websites,

LinkedIn, the research team's personal contacts, ex-employee and local leading regulatory consultants for each authority. They were selected based on their work experience in the biologic or biosimilar division of the authority, having held a position as a general manager or above (senior management) or a leading regulatory consultant with a close working relationship with the relevant authority in the biosimilar domain. They were sent an electronic mail with brief information about project and the questionnaire, the objective of the study, the number of authorities to be included and requesting their agreement to participate in the study. The questionnaire was completed by a member of the biologic team and approved by the section head. This was followed up by a face-to-face or virtual meetings after receipt of the completed questionnaire with each agency of the BRICS-TM and ACSS countries. Such meetings were arranged to verify the validity of the responses to the questionnaire. Also, copies of the relevant guidelines were requested as part of the questionnaire to verify the responses and to correlate the actual regulatory requirements. In addition, data received from the agency pertaining to number of applications received and reviewed by agencies in reference (ACSS) and test (BRICS-TM) group were assessed.

The therapeutics product branch of HSA (Singapore) was unable to participate due to stretched resources and higher priorities in other areas due to the COVID-19 pandemic. The second-best option of approaching leading regulatory consultant in Singapore was used. However, the participant was unable to provide the necessary information due to a lack of time and difficulty in obtaining clarity from HSA on certain areas of the questionnaire. Figure 6.1 is the CONSORT diagram for enrollment of participants in this study.

Data processing and analysis

Data processing and analysis were carried out using Microsoft Excel. The questionnaire (BDEA) is a mixture of qualitative and quantitative questions. Therefore, both quantitative and qualitative analyses were carried out. The descriptive statistics were applied to the quantitative questions of the questionnaire. For example, in Table 6.2, we have used mean values for calculating the number of applications received by the agencies for the period 2017-2019 and percentage values for staff-workload ratio. The analysis for qualitative data was carried out using content analysis and inductive

coding in order to generate themes and subthemes (Corbin & Strauss, 1990; Boyatzis, 1998; Thomas, 2006).

Ethics Approval

The study has been approved by the Health, Science, Engineering and Technology ECDA, University of Hertfordshire [Reference Protocol number: aLMS/PGR/UH/03332(1)].

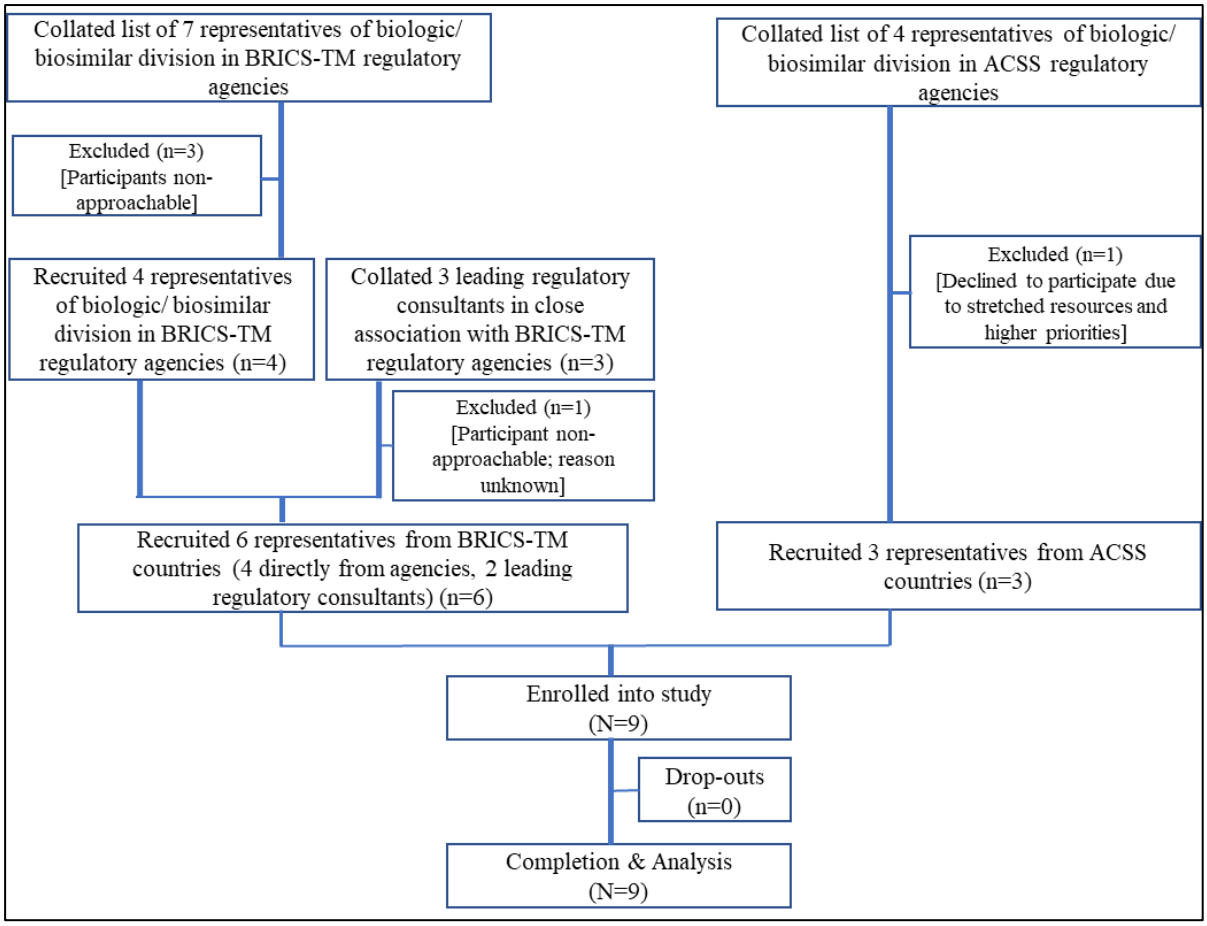


Figure 6.1 CONSORT Diagram

RESULTS

The results are presented in three parts:

Part I – Organisation of the agency;
Part II – Biosimilar development criteria; and
Part III – Marketing authorisation process.

Demographic status of the study participants

Out of 11 regulatory agencies (i.e., seven BRICS-TM and four ACSS countries), four BRICS-TM (Agência Nacional de Vigilância Sanitária - ANVISA), Brazil; Central Drug Standards Control Organisation - CDSCO, India; South African Health Products Regulatory Agency - SAHPRA; and Türkiye İlaç ve Tıbbi Cihaz Kurumu-TITCK) and three ACSS (TGA, BRDD, Swissmedic) agencies agreed to participate in the study. The questionnaire was completed by a member of the biologic team and approved by the section head. Since access to two agencies, Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS), Mexico and the Russian Ministry of Health were experiencing resource constraints, a leading regulatory consultant, experienced in working closely with these agencies and having biosimilar expertise was recruited in each country. The respondents from the consulting firms were either the Chief Executive Officer or equivalent. The consultants used for Mexico and Russia were closely associated with the respective agencies regarding registration of biosimilar products, engaged with the agencies for reviewing clinical study protocols and acting as external assessors for the agency relating to biosimilar products. The remaining two agencies i.e., National Medical Product Administration (NMPA), China and Health Science Agency (HSA), Singapore were not able to complete questionnaire on time due to lack of resources.

Part I - Organization of Agency

TGA (Australia) - Though the agency did not have an established dedicated biologic division, the strength of the assigned biologic staff was 3.7% of the total. In addition to qualified internal assessors with B.Sc. to PhD degrees, external evaluators were engaged for the review of clinical data. Of the three review models, ‘Type II- (Abridged)

and ‘Type III – (Full review) of marketing authorisation applications assessments were frequently carried out by the TGA (Table 6.1).

BRDD (Canada) - The strength of the biological division within the agency was 2.08% in comparison with the total staff of the agency. The agency restricted use of external assessors and had qualified biological assessors with B.Sc. to PhD degrees. The marketing authorisation applications were reviewed using Type III - Full review model with little or no scope for relying on ‘Type I (Verification) or Type II (Abridged review) models (Table 6.1). Instead, the agency reviewed applications through the ACSS consortium, based on a work-sharing model.

Swissmedic (Switzerland) - There was no distinct biological division within the agency and hence, with the exception of CMC reviewers, there were common reviewers for reviewing both biologic and non-biologic applications. The minimum qualification of the internal assessors was PhD, PharmD or MD degree. The agency relied on ‘Type I (Verification)’ and ‘Type III (Full review)’ models for biosimilar marketing authorisation applications’ data assessment.

Comparison of BRICS-TM with ACSS

The strength of biosimilar assessors across BRICS-TM and ACSS was between 1 to 5%, reflecting no large variance in nine agencies’ resources. Most of the BRICS-TM agencies (except ANVISA and Russian MoH) appointed external assessors to review CMC, non-clinical and clinical data, as compared to ACSS agencies, which could be an indication of probable insignificant expertise. The ACSS agencies follow the ‘Type III’ model for the majority of the applications and have flexibilities to follow ‘Type I’ (Swissmedic) and ‘Type II’ (TGA) as well. In addition to reliance model, these agencies have formed ACSS Consortium to enhance efficiency through work-sharing model. Some of the BRICS-TM agencies for example India and Mexico partly aligned with the ACSS countries regarding review model, but largely resort to applying Type III (full review) review model. Thus, this indicates that the BRICS-TM countries should not only strive to achieve greater reliance on reviews performed by agencies in their respective region, also to do the same with the established mature agencies.

Part II - Biosimilar development criteria

Biosimilarity

The ACSS agencies expected the sponsor to demonstrate biosimilarity of the proposed biosimilar product with its reference product by proving satisfactory physicochemical and biological characterisation with in vitro non-clinical PK/PD studies and literature-based clinical performance evaluation, additional in vivo safety data plus confirmatory clinical safety and efficacy trials. The TGA, BRDD and Swissmedic accepted clinical data for the Phase III (clinical efficacy) study from reference countries and do not mandate applicant to carry out clinical trials in the local population.

Further, interchangeability is not regulated by law in Switzerland, allowing the prescriber to decide on switching based on patients' needs. In the case of TGA, interchangeability policy is under the jurisdiction of the Department of Health and funded through the Pharmaceutical Benefits Scheme (PBS). The pharmacists of each province in Canada are charged with the authority to declare two products interchangeable according to its own rules and regulations, without the intervention of the prescriber.

The biosimilarity principles of BRICS-TM agencies are aligned with the expectations of ACSS in terms of different types of studies. The interchangeability decision in BRICS-TM countries lies with the prescriber, except in Russia (where it is regulated by the agency), whereas ACSS follows varied paths. The major challenge with a few of the BRICS-TM agencies is that they require the clinical studies to be conducted locally (Rahalkar et al., 2021a), i.e., they do not accept foreign generated clinical data unlike the ACSS agencies (Table 6.2).

Table 6.1 Comparison of organisational structure and data review model

Criteria	ANVISA	Russian MoH	CDSCO	SAHPRA	TITCK	COFEPRIS	TGA	BRDD	Swissmedic
Total agency staff	1600	930	1500	>200	1172	2000	666	>10,000	435
Resource allocation in Biologic/Biosimilar division									
Total staff in biologic/ biosimilar division	24	Not defined	30	10	No information available	20	No biologic division	375	No such division
Number of biologic/ biosimilar reviewers	24	Not defined	8	5	No information available	13	25	208	49
Mean of Applications received (2017-2019)	10	Not specified	Not specified	Not specified	21	2	6	Not specified	13*
Staff-Workload ratio	41.7%	NA	NA	NA	Can't be defined	15.4%	24.0%	Can't be defined	26.5%
External assessors									
Support required	No	Not specified	Yes	Yes	Yes	Yes	Yes	No	No
Expertise	NA	NA	Non-clinical, Clinical	CMC, Non-clinical, Clinical	CMC, Non-clinical, Clinical	CMC, Non-clinical, Clinical	Clinical	NA	NA
Data Assessment									
Review model	Type III	Type III	Type II, III	Type III	Type III	Type I, III	Type II, III	Type III	Type I, III
Recognised reference agencies	Not specified	Not specified	EMA, USFDA, BRDD, MHRA, TGA	Not specified	Not specified	EMA, USFDA, TGA	EMA, USFDA, BRDD, HSA, Swissmedic, MHRA, PMDA	NA	EMA, USFDA

BRICS-TM: *ANVISA (Brazil), Russian MoH (Russia), CDSCO (India), NMPA (China), SAHPRA (South Africa), TITCK (Turkey), COFEPRIS (Mexico); NA: Not Applicable.*
**Number of applications received in 2019-data for 2017 and 2018 not specified by the respondent.*

Table 6.2. Comparison of biosimilar development criteria of BRICS-TM with ACSS agencies

Criteria	BRICS-TM agencies	TGA	BRDD	Swissmedic
Biosimilarity Physicochemical and biological characterisation with *in vitro* non-clinical PK/PD studies and literature-based clinical performance evaluation, additional *in vivo* safety data plus confirmatory clinical safety and efficacy trials	✓	✓	✓	✓
Interchangeability decision by:				
Agency	X[*]	X[#]	X	X
Prescriber/physician	✓	X	X	✓
Pharmacist	X	X	✓	X
Comparative quality characterisation				
RBP selection Must be locally authorised	✓	✓	✓	✓
Acceptance of non-locally authorised markets	EU, US, Canada, Australia, Japan, UK, Germany[$@α]	EU, US	EU, US, UK	EU, US
Bridging studies	Not specified	Required	Required	Not required
Analytical specification and method	ICH Q6B (Except Russian MoH, specification same as RBP)	ICH Q6B	ICH Q6B	ICH Q6B

Criteria	BRICS-TM agencies	TGA	BRDD	Swissmedic
Requirement of comparative stability studies				
Mandatory	✓ (ANVISA, Russian MoH, SAHPRA, COFEPRIS)	X	✓	X
Not mandatory	✓ (CDSCO)	✓	X	X
Supportive	✓ (TITCK)	X	X	✓
Non-clinical studies				
***In vitro* studies**	✓	✓	✓	✓
***In vivo* studies**	✓	X (if addressed *in vitro*)	Case-by-case basis	✓ (as per EMA guideline)
Clinical Studies				
PK/PD Combined PK/PD study, fingerprinting approach	✓	✓	Not responded	✓
Requirement of immunogenicity studies	✓ (except Russian MoH)	✓	✓	✓
Comparative clinical efficacy studies				
Clinical study design acceptance				
Equivalence design	✓	✓	✓	✓
Non-inferiority design	✓ (ANVISA, CDSCO, COFEPRIS)	✓	X	X
Local clinical studies	✓ (Russian MoH, CDSCO, COFEPRIS)	X	X	X

BRICS-TM: *ANVISA (Brazil), Russian MoH (Russia), CDSCO (India), NMPA (China), SAHPRA (South Africa), TITCK (Turkey), COFEPRIS (Mexico)*

[*]Regulated by agency in Russia; [#]Department of Health; [$]TITCK, [@]COFEPRIS except UK, Germany; [a]No recognized reference agencies by Brazil, Russia, South Africa

Comparative quality characterisation

Reference Biologic Product (RBP) selection

The TGA, BRDD and Swissmedic mandated locally authorised reference products (based on a full dossier including quality, safety and efficacy) that have been marketed for substantial periods of time in their country. They also allowed applicants to use non-authorised reference products as part of the development, in the absence of a locally approved reference product. The TGA and Swissmedic accepted use or sourcing of EU or US licensed reference products (TGA, 2020), whereas BRDD additionally accepted UK licensed reference products. The evidence of bridging studies to prove sameness of a foreign reference product with the reference product authorised in respective countries was an essential part of the submission for applications to TGA and BRDD. While both agencies required multiple lots of RBP with varied shelf-life for comparability studies, they did not allow change in the reference product during development and comparability studies. The most notable difference was observed with Swissmedic where the requirement for bridging studies had been removed.

While ACSS agencies were flexible for using non-locally authorised reference products, ANVISA and Russian MoH preferred to have locally authorised reference products as part of the development. Although silence on bridging studies (Rahalkar et al., 2018) by each of the BRICS-TM agencies, leads to uncertainty among biosimilar developers, bridging studies could be an unnecessary burden given that if the reference product is the same innovator company. It could be deduced that lack of information on bridging studies is in line with good regulatory practices, unless its omission is in contravention of international best practice.

Analytical specification and method

The TGA, BRDD and Swissmedic followed the ICH Q6B (ICH, 1999) for setting the specification considering manufacturer’s experience on SBP and RBP.

The BRICS-TM and ACSS agencies were broadly aligned on this parameter as mentioned in the WHO guidelines (WHO, 2013), except Russian MoH indicating the same specifications for the proposed biosimilar product as those of the RBP by discounting the manufacturer’s experience.

Comparative stability studies

The TGA recognised the limitations of the biosimilar applicant in matching the age of the proposed biosimilar products with the innovator product and hence did not mandate these studies as part of the application. Swissmedic accepted comparative stability studies as supportive data while BRDD required it as part of the application.

In general, comparability study expectations of BRICS-TM regulatory agencies were similar to those required by the ACSS countries.

Non-clinical studies

The TGA did not require *in vivo* toxicity studies if comparability between the biosimilar and the reference product had been sufficiently addressed by *in vitro* studies. Swissmedic followed EMEA/CHMP/BMWP/42832/2005 Rev1 (EMA 2014b) and product-specific guidelines, wherein *in vivo* toxicity studies were required on a case-by-case basis. The requirements for BRDD were unclear.

Unlike TGA and Swissmedic, *in vivo* toxicity study data was essential requirement for the BRICS-TM agencies.

Clinical Studies

PK/PD

The TGA and Swissmedic both accepted a combined PK/PD study along with a fingerprinting approach. The design, endpoints and fingerprinting approach of BRICS-TM agencies was broadly aligned with ACSS countries.

Immunogenicity

All the ACSS agencies indicated the need for comparative immunogenicity as part of the biosimilar application. The data could be obtained from PK/PD studies. The extrapolation of immunogenicity studies to other indications depends on similarity with the RBP or on case-to-case basis. Agencies advised applicants to refer to the EMA immunogenicity guidelines (EMA, 2017) for clarification.

Comparative clinical efficacy studies

Clinical study design - The TGA, Swissmedic and BRDD expected randomised, parallel group, double-blind Phase III clinical trials which are adequately powered using efficacy endpoints unless there are surrogate markers. Equivalence design for the comparative clinical efficacy studies is expected by all the agencies. In addition, TGA also accepted non-inferiority design for the clinical efficacy trials. The clinical study design followed by BRICS-TM agencies was mostly aligned with ACSS countries, with preference over equivalence design. Additionally, ANVISA, CDSCO and COFEPRIS also accepts non-inferiority design for clinical studies.

None of the agencies mandated the clinical studies to be conducted in paediatric or elderly populations for proving comparability of the proposed biosimilar product.

Local clinical studies - The ACSS agencies did not mandate clinical trials to be conducted locally in their respective countries.

The PK/PD, immunogenicity and clinical efficacy requirements of BRICS-TM agencies were aligned with ACSS, however the requirement for local clinical studies were unique to Russian MoH, CDSCO and COFEPRIS.

Part III - Marketing authorisation process

Scientific Advice

The TGA provided pre-submission advice for the biosimilar application however refrained from providing the same for the development process. Swissmedic and BRDD offered advice during the development of the biosimilar via face-to-face meetings, electronic mail or written responses. The agency advice was not legally binding. While ANVISA, CDSCO and SAHPRA were aligned with the process of scientific advice, Russian MoH, COFEPRIS and TITCK had yet to develop such communication channels.

Clinical Trial Application (CTA) approval

Swissmedic reviewed the CTA through internal assessors within 30 days and extended it to 60 days if there was a change in the manufacturing process of the biosimilar. Flexibility around the Ethical Committee (EC) letter of submission during evaluation of

the protocol existed with Swissmedic. Prior to initiating a clinical trial or implementing an amendment to a clinical trial at a site, BRDD required the proposed trial protocol and Informed Consent Form (ICF) to be reviewed and approved by a Research Ethics Committee (REC) as defined in the regulations. The TGA did not provide any clarity on the CTA approval process or timelines. Both ACSS and BRICS-TM countries required an Ethical Committee letter submitted during clinical trials.

Dossier Review and approval

The Certificate of Pharmaceutical Product (CPP) in the technical dossier was not required as part of the application by ACSS agencies. The validation of the application and target time to request additional data was in place as one of the milestones. The total review time including queue duration with BRDD is 300 calendar days whereas such information was unavailable for the TGA and Swissmedic. External experts for clinical opinion were contractually engaged by the TGA and Swissmedic. The deficiencies in the dossier were presented to the applicant in one single lot from all different sections of the dossier. Sample analysis was performed as part of the market release post approval of the product in Australia and Switzerland. The GMP inspection was mandated by all the ACSS agencies. For TGA, the GMP inspection could be either on-site or document-based verification and the inspection was conducted concurrently along with the assessment of the product dossier. However, Swissmedic accepted document-based verification for GMP certification of the manufacturing site. The BRDD relied on on-site evaluation for certifying the manufacturer for process and own inspection or pursuant to Memorandum of Understandings (MOUs) for GMP purposes (Table 6.3). The on-site evaluation was part of the review process and intended to determine whether a sponsor was ‘in control’ of their manufacturing processes and had suitable QA processes. It was a risk-driven process.

The BRICS-TM agencies (except TITCK) were yet to implement a GMP verification process through off-site review of documents based on a reference agency approval. TITCK issued GMP certificate after paper-based evaluation of the GMP submission.

Table 6.3 Comparison of dossier review and approval process in BRICS-TM with ACSS agencies

	BRICS-TM agencies	TGA	BRDD	Swissmedic
CPP requirement	Required	Not required	Not required	Not required
Queue time	28-365 days*#	No information#	300 days*@	No information*
Support from external experts	Yes	Yes	No information	Yes
Sharing of queries on dossier to sponsor	As they arise during the assessment** (or) Collated into a single batch$	Collated into a single batch	No information	Collated into a single batch
Sample analysis	Before approval	Part of market release	No information	Post approval market surveillance##
GMP inspection	On-site (except TITCK)	On-site or document-based verification	On-site evaluation	Document-based verification

BRICS-TM: *ANVISA (Brazil), Russian MoH (Russia), CDSCO (India), NMPA (China), SAHPRA (South Africa), TITCK (Turkey), COFEPRIS (Mexico)*

**ANVISA, Russian MoH, SAHPRA, TITCK, BRDD, Swissmedic follows calendar days; #CDSCO, COFEPRIS, TGA follows working days; **ANVISA, TITCK; $Russian MoH, CDSCO, SAHPRA, COFEPRIS; @Total review time including submission waiting in queue; ##On case-by-case basis, possible before approval if any concern regarding quality of the product.*

Public Assessment Report (PAR)

Public assessment reports are issued by TGA, Australia (AusPAR) and BRDD, Canada for biosimilar products. Currently, PAR from Swissmedic (SwissPAR) is issued only for new active substances and is available upon request for biosimilars. However, among the BRICS-TM countries, only ANVISA publishes equivalent document on their website. Publication of PARs by ACSS agencies thus ensures transparency, by providing access to information by pharmaceutical industry, other health authorities, healthcare professionals and patients (Papathanasiou et al., 2016), on the approved biosimilar product.

Although the organisation is contextual and country-specific often based on country's legal system, the results for the ACSS countries showed a great similarity (including biosimilarity criteria, RBP selection, setting up specification, non-clinical studies and clinical study requirements). In terms of regulatory requirements being non-contextual,

the results confirmed this notion by showing a large degree of similarity. It could be postulated that we could have simply used the acceptable international best practices for purpose of comparison, however, given the dynamic nature of biosimilar development and its expansion, it was envisaged that prospective up-to-date data collection would provide more accurate head-to-head comparison.

DISCUSSION

Biosimilars offer patients in the emerging economies the opportunity to receive key biologic therapies that would otherwise be denied to them due to costs and, therefore, they offer a great growth potential in such economies. However, optimal access to biosimilars depends on collaboration between the relevant stakeholders including policy-makers, regulators, physicians and the industry. In this context, the most important role is played by the regulatory authorities as they provide the regulatory oversight of biosimilars throughout their product life-cycle to ensure only high-quality, safe and effective biosimilars are available in the market (WHO, 2017a). However, the regulatory framework for biosimilar development varies in different jurisdictions (Mintz, 2013). In such cases, companies are often required to conduct similar but distinct studies and submit multiple applications for a given product to agencies in different countries (Institute of Medicine, 2013). Duplication of such efforts could have negative impacts on both manufacturers and National Regulatory Agencies (NRAs) (Ball et al., 2016) and this in turn increases the time and cost it takes to bring new drugs to market. Aligning the regulatory strategy across many countries (regulatory harmonisation) could potentially enhance efficiency (WHO, 2017a). This will save time and financial resources for drug developers, resulting in earlier access for patients to life saving medicines (Elvidge, 2013).

Comparison of regulatory systems from different countries is one of the methods to gain insights on the limitations of regulatory processes, and thereby to overcome some of these challenges. This study of the guidelines and processes for biosimilar development and authorisation by regulatory agencies in BRICS-TM countries in comparison with the ACSS consortium presents various opportunities to build efficiencies in their respective regulatory frameworks.

Effective implementation of a step-wise approach for demonstration of biosimilarity thereby reducing the need for studies like *in vivo* non-clinical studies and repetition of

confirmatory clinical trials in the local population are required (Rahalkar et al., 2021a). A policy paper by IGBA (IGBA, 2020) has also emphasized the use of strong analytical science and human pharmacokinetic data for proving quality, safety and efficacy, in-lieu of confirmatory comparative efficacy clinical trials. This science-based evaluation and waiving of comparative efficacy trial has been updated by MHRA, United Kingdom (part of Access consortium) in its updated guidance on the licensing of biosimilar product (MHRA, 2021).

The BRICS-TM agencies might have to consider flexibility for using non-authorised reference product from other emerging countries and reference agencies to simplify RBP sourcing. The sourcing of product batches of different ages from different markets for development purposes may present significant difficulties and incur costs (Webster & Woollett, 2017; Rahalkar et al., 2021a). In 2009, the World Health Organisation (WHO) Expert Committee on Biological Standardization created a set of recommendations and guidelines to help its member states implement regulation of biologics and biosimilars. However, member states still face regulatory challenges, based on a 2019-2020 WHO survey of participants in 20 countries (Kang et al., 2021) more specifically related to reference biologics, including limited access to information on the reference biologic, financial constraints due to the price of the reference biologic, and difficulty of obtaining reference biologic samples to assess comparability. The authors noted some countries accept reference biologics that are foreign-licensed and -sourced, whereas others require a domestically licensed reference product or bridge studies for a foreign-sourced reference product, which are costly and often result in unnecessary duplication of studies (Rahalkar et al., 2021a). Exchanging information with other national regulatory authorities, accepting foreign-sourced reference products, and avoiding unnecessary bridge studies were few of the proposed solutions to address these challenges.

Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by the regulatory authorities as conditions of approval (ICH, 1999). It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. They are linked to the manufacturing process and gives an assurance that the quality is safe and efficacious over its shelf-life. Most of the BRICS-TM agencies are aligned with ICH Q6B, except Russian MoH which expects

the specification to of the biosimilar to be same as the reference biologic product. Hence, aligning with the international regulatory standards on setting up specifications based on the manufacturer's experience with RBP and the proposed biosimilar product becomes an essential aspect to be considered by the agency.

The WHO Certification Scheme was initially implemented to accelerate the availability of new drugs in developing countries by providing evidence of the quality of products through the use of the Certificate of Pharmaceutical Product (CPP) (WHO, 1995; Withing, 2012). However, combined with increased data requirements and review practices of National Regulatory Authority (NRAs), along with the requirement to submit CPP at the time of submission, has delayed the review and approval process and thereby delaying access to patients (Rodier et al., 2020). Also, in a white paper by EFPIA (EFPIA, 2017) on reliance and expedited registration pathways in emerging markets, one of the key points was avoiding non-essential documentation like the request for CPP before approval instead of at time of submission, or to waive the requirement completely. Hence, using alternative data sources such as agency websites for marketing authorisation confirmation instead of requiring CPP as part of the submission needs to be considered by the regulatory agencies of emerging economies like BRICS-TM.

Scientific advice (SA) allows early communication between the companies and the regulators. With SA, companies can seek the regulator's opinion on quality, nonclinical, and various clinical aspects (e.g., study design, choice of endpoint, indication) of drug development (Broz et al., 2020; EMA, 2021a). Seeking SA on time can support the development of safe and efficacious medicines and ensure that the patients get access to effective treatments in time (EMA, 2021a). SA promotes the efficient use of resources as companies receive feedback on viable strategies and methodologies for product development. Companies can plan and design better trials and choose the best endpoints (Dallman, 2017). By refining the trial design and other aspects as per the SA, companies can save valuable time on prospective queries which may arise during the Clinical Trial Application (CTA) or Marketing Authorisation Application (MAA) (Broz et al., 2020). By fostering scientific collaboration, SA facilitates a working relationship between the company and the regulatory authority. When incorporated into the drug development program, SA can add significant value to the marketing authorisation application. This can significantly enhance the chances of bringing a

medicinal product to market (Alsager, 2015; Dokumeds, 2021). Allowing applicants to have pre-submission meetings to present the companies' product portfolio and discuss overall filing strategies are very much welcomed, especially to discuss products addressing unmet medical need has also been acknowledged by The European Federation of Pharmaceutical Industries and Associations (EFPIA) (EFPIA, 2017).

The BRICS-TM agencies should consider acceptance of off-site GMP audit in the GMP accreditation process to reduce delays caused by physical GMP inspections. For instance, the Pharmaceutical Inspection Co-operation Scheme (PIC/S) (PIC/S, 2014) aims at facilitating cooperation and networking between competent authorities, regional and international organisations, thus increasing mutual confidence regarding inspections. Reliance is also an important aspect for conducting desktop assessment of compliance with relevant good practice guidelines and requirements, as described in the respective WHO guidance (WHO, 2018b). PIC/S has also issued a guidance on inspection reliance, which outlines a process for the desk-top assessment of GMP compliance (PIC/S, 2018).

SUMMARY AND CONCLUSION

Like the ACSS agencies, the emerging economies of BRICS-TM need to move towards reliance and collaboration with other regulatory agencies. A shared or joint review approach for the assessment of dossier in the marketing authorisation application with other comparable agencies and a verification review for products that have been approved by two or more reference agencies and an abridged review for medicines approved by one or more agencies, with a full review only employed for those products that have not been reviewed elsewhere by a reference agency can be considered for reviewing of the product dossier. The WHO supports the implementation of reliance on other regulators' work as a general principle in order to make the best use of available resources and expertise. This principle enables leveraging the output of others whenever possible while placing a greater focus at the national level on value added regulatory activities that cannot be undertaken by other authorities, such as, but not limited to, in-country vigilance and market surveillance and control activities and oversight of local manufacturing and distribution. Reliance approaches facilitate timely access to safe, effective and quality-assured medical products and can help in regulatory preparedness and response, particularly during public health emergencies (WHO, 2020).

CHAPTER 7

Challenges Faced by Biopharmaceutical Industry in the BRICS-TM Countries

INTRODUCTION

Biosimilar development offers low-cost medicines as compared to originator biologics thereby reducing economic stress on manufacturer, but not as compared to generic medicines (Simoens et al., 2017). Despite the high cost of therapy, the clinical efficacy and safety profile of biologic medicines has propelled huge growth of these treatments across the world (Davies, 2017). Today, biologics are one of the largest and fastest growing sectors of the prescription product market with the market share of biologics growing steadily relative to small molecules. The new product pipelines of leading companies suggest that this growth dynamic will continue and be broad-based across various therapeutic areas (Aitken, 2020). However, the high cost of therapy with original biologics puts them out of reach for many across the world. Biosimilar medicines are usually made available at a significant discount to original biologics, and therefore have the potential of improving access and creating valuable savings for patients and healthcare systems (Centers for Medicare and Medicaid Services, 2019). Biosimilars are products that are similar to a reference biologic product (RBP) and according to the United States Food and Drug Administration (USFDA), need to be highly similar to the approved reference product without any clinically meaningful differences in terms of safety, purity and potency (USFDA, 2017).

When the concept of biosimilars first emerged, it generated high expectations from the access and cost savings potential that the medicines could bring to patients globally. However, due to several roadblocks, healthcare systems are yet to realize the full benefits of biosimilars (Biosimilar Council, 2019). Significant challenges persist from the perspective of all key stakeholders involved i.e., regulators, industry, physicians and patients.

The biosimilar industry faces multiple challenges to develop and market these complex products (Kent et al., 2017). Compared with the well-established approval process for new chemical entities (NCEs) and small-molecule generics, the framework for approval of new biological entities (NBEs) and biosimilar products is in evolving stages across most of the developing countries. Biosimilar developers face obstacles in receiving appropriate advice which leads to delays in product launches and late returns on investments (Kent et al., 2017). In addition, most of the emerging market agencies

have unclear regulatory processes with little global convergence. This makes global or multi-country developments expensive, lengthy and risky.

The cost to develop and gain approval for a biosimilar medicine in the US ranges between US$100 million to US$200 million (Wroblewski et al., 2009). This is significantly different from the cost of developing a small molecule generic which typically ranges from US$1 million to US$5 million (Wroblewski et al., 2009). Biosimilar development costs are high due to greater clinical trial requirements and a need for sophisticated manufacturing facilities and cutting-edge technologies. Additionally, there is a requirement for investment in more technically skilled and competent manpower resources alongside direct promotional activities aimed at physicians and patients. Due to the inherent variability of biologics, the reproducibility of biosimilars is a big challenge and thus they are more complex to develop and manufacture (Wroblewski et al., 2009). The timelines for development and approval of biosimilars is also much longer than that of the small molecule generics. A United States Federal Trade Commission Report states that it takes between eight to ten years to develop a biosimilar compared to between three to five years for a small molecule generic (Wroblewski et al., 2009).

Overall, challenges faced by the industry in manufacturing complexity, costs, time-to-market and regulatory pathway for development and approval have resulted in a significant entry barrier for new players in this space. This, in turn, has led to insignificant patient access to biosimilars (Kabir et al., 2019).

The aim of this exploratory study was to specifically identify the challenges faced by the industry in Brazil, Russia, India, China, South Africa, Turkey and Mexico (BRICS-TM) pertaining to biosimilar development and the regulatory processes, including concerns on pricing and market access.

OBJECTIVES

The main objectives of this chapter were:

- To identify the challenges faced by the industry in the biosimilar development, manufacturing and regulatory process in their respective countries
- To understand concerns on pricing and market access

- To evaluate the perception of the companies regarding the effectiveness and efficiency of current regulatory process
- To gather suggestions on potential improvements in the Biosimilar development and approval process in their respective countries and make recommendations for moving forward.

METHODS

A semi-quantitative questionnaire was compiled (in English), targeting various topics of concern for the biopharmaceutical industry based on information from the literature, entitled Biosimilar Development, Submission and Review (BDSR) (Appendix 3). The BDSR questionnaire consists of four parts: general information on biosimilar experience of the company; challenges pertaining to regulatory approval process and development criteria, pricing and access and suggestions on area of improvement. The BDSR underwent several refinement processes including content validation by two industry experts, in order to produce the final version.

Two target groups across the BRICS-TM countries were selected: active industry personnel with experience of over 15 years in the biosimilar space; and representatives from the pharmaceutical trade associations who have member companies with marketed biosimilar products. Recent estimates of companies marketing and developing biosimilar medicines range between 100 -182 (Visiongain, 2016; MP Team, 2019). Most of these companies are based in high-income, developed countries (Gautam, 2017), with fewer active industry players in the developing countries. Also, the expertise and knowledge level of most of the industry personnel in developing countries are lower. Those who declined to take part in the study offered reasons of confidentiality issues and time constraint. Industry personnel could be contacted relatively easily in India as the researcher was from the same country and had prior contacts and hence could reach the industry personnel. However, similar network of industry personnel in the other countries was difficult to establish and therefore this could have impacted recruitment of participants from these countries. Efforts were made to improve the response rate by carrying out three follow-ups with the non-responders.

A secondary online search was performed using search terms such as biosimilar developer; biosimilar marketer; biopharmaceutical company; biosimilar approvals;

trade associations; monoclonal antibodies and specific biological molecules. Sources included review articles, correspondence, meeting reports, opinions and abstracts obtained from Google scholar, websites of BRICS-TM health agencies, library of University of Hertfordshire and regulatory focus journals. The online secondary search was conducted from January 2020 to March 2020, resulting in a list of 41 biopharmaceutical companies marketing or developing biosimilars in BRICS-TM countries as well as 14 active trade associations within these countries which included manufacturers and marketers of biosimilars.

The trade associations identified were Pharmaceutical Research Industry Association, Brazil; Pro Genericos - Associacao Brasileira das Industrias de Medicamentos Genericos, Brazil; Association of International Pharmaceutical Manufacturers, Russia; Association of Biotechnology Led Enterprises (ABLE), India; Indian Pharmaceutical Association (IPA); China Pharmaceutical Industry Association; Chinese Pharmaceutical Association; South Africa Association of Pharmacists in Industry; The Innovative Pharmaceutical Association South Africa (IPASA); International Generic and Biosimilar Medicines Association (IGBA) South Africa; Turkey International Trade Association; İlaç Endüstrisi İşverenler Sendikası (İEİS) (Pharmaceuticals Manufacturers Association of Turkey); Mexican Association of Pharmaceutical Research Industries; and International Generic and Biosimilar Medicines Association (IGBA), Mexico.

A total of 93 industry personnel working within the identified companies and representatives from all 14 trade associations were invited to take part in the study. Contact details of industry personnel and trade associations were obtained through company websites, trade association websites, LinkedIn pages and through industry contacts of the authors. The study was based on electronic questionnaire and following completion, the participants were interviewed face-to-face (average of 45 minutes duration) using online platform in order to verify their responses, expand on their views and minimise bias due to misinterpretation. Confidentiality issues were cited by 14 industry personnel as a reason for non-participation and 46 did not respond at all. None of the 14 trade associations responded. In order to minimise bias arising from differences between responders and non-responders, three follow ups were carried out to try and maximise the response rate. However, this did not lead to an improved response rate (Figure 7.1). Affirmative responses were received from 33 industry

personnel who completed a web-based questionnaire. Subsequently, interviews were conducted with the 33 study participants via phone call or web meetings to verify their responses, fill the gaps and provide additional comments based on their level of experience. This was carried out between March and October 2020.

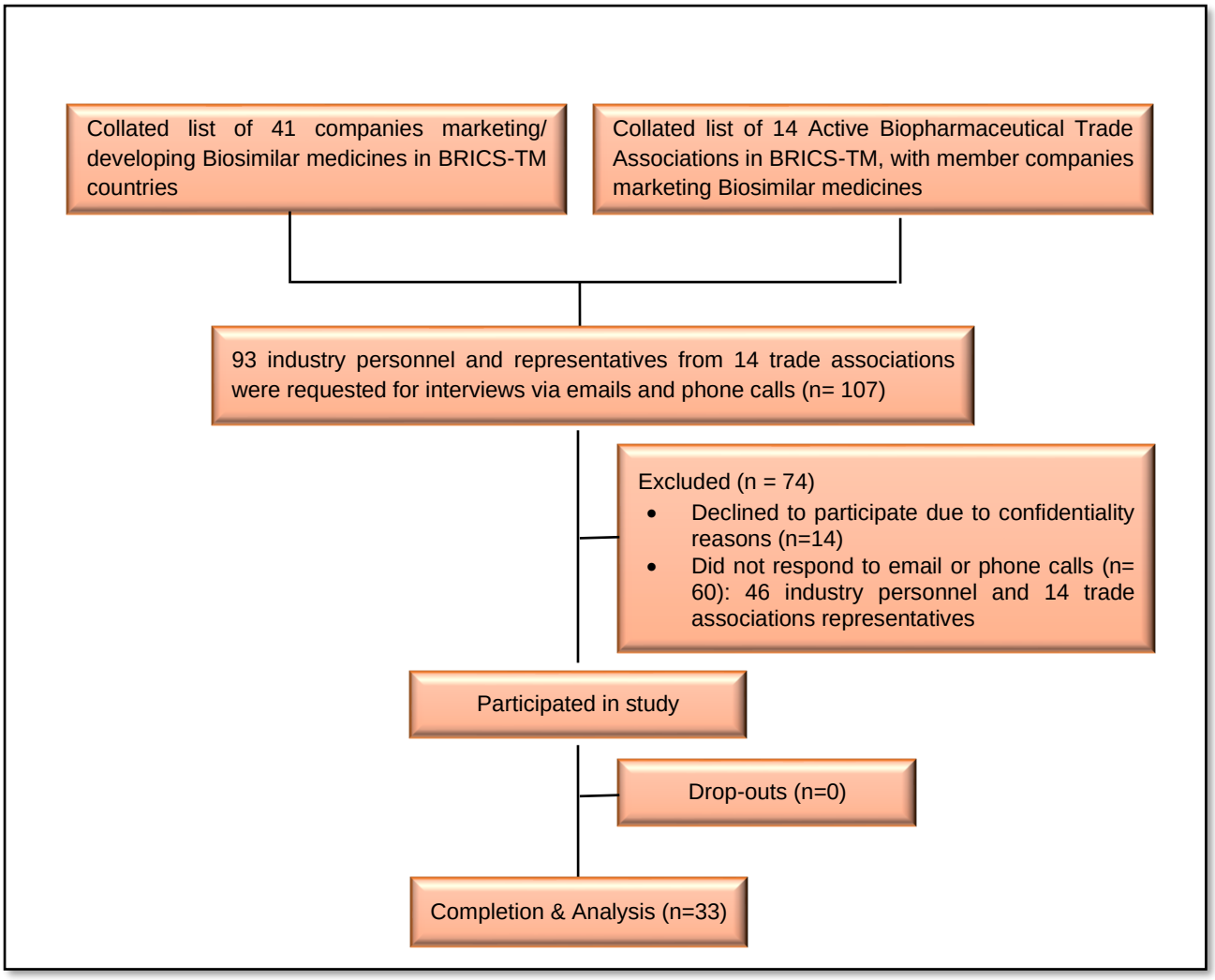
Data processing and analysis

This was an exploratory study attempting to generate a hypothesis; therefore, no sample size calculation was carried out. However, the sample size may not be adequate in generalising the results and bias could have been introduced as a result of purposive sampling. Since no statistical test was applied to the data, this removed the possibility of bias due to such tests. Data processing and analysis was carried out using Microsoft excel and the Statistical Product and Service Solutions (SPSS) analytical software; descriptive statistics (i.e. mean, standard deviation, median, range and mode) were used for quantitative data and content analysis was employed to generate themes and sub-themes for qualitative data.

Ethics Approval

The study has been approved by the Health, Science, Engineering and Technology ECDA, University of Hertfordshire. Protocol number for the same is - aLMS/PGR/UH/03332(1).

Figure 7.1 CONSORT Diagram



RESULTS

The results obtained from the study are presented in three parts: Part I - Bio-pharmaceutical Industry of BRICS-TM; Part II - Biosimilar Guidelines and Approval Process; and Part III - Development Parameters.

Demographic Characteristics of the Study Participants

Out of the 107 personnel from the biopharmaceutical industry and representatives from trade associations invited to take part in the study, 33 agreed. Of those who completed the study, 6 were from Brazil, 4 from Russia, 15 from India, 1 from China, 1 from South Africa, 1 from Turkey and 5 from Mexico. The respondents were senior level executives with a designation of Vice President and above, representing Research and Development, Regulatory, Manufacturing and Marketing divisions of biopharmaceutical companies. The demographic characteristics of the study participants are presented in Table 7.1.

Table 7.1 Demographic characteristics of the study participants

Function	BD	Technical Operations*	Regulatory	R&D
Brazil (Total number of respondents: 6)				
Age group (years)	**40 - 49**	NA	**33 - 40**	NA
Number of respondents	**3**	NA	**3**	NA
Males	**3**	NA	**2**	NA
Females	**0**	NA	**1**	NA
Russia (Total number of respondents: 4)				
Age group (years)	NA	**36 - 60**	**45**	NA
Number of respondents	NA	**2**	**2**	NA
Males	NA	**2**	**2**	NA
Females	NA	**0**	**0**	NA
India (Total number of respondents: 15)				
Age group (years)	**45 - 48**	**48**	**39 - 55**	**61**
Number of respondents	**5**	**1**	**8**	**1**
Males	**5**	**1**	**8**	**1**
Females	**0**	**0**	**0**	**0**
China (Total number of respondents: 1)				
Age group (years)	**49**	NA	NA	NA
Number of respondents	**1**	NA	NA	NA
Males	**1**	NA	NA	NA
Females	**0**	NA	NA	NA

Function	BD	Technical Operations*	Regulatory	R&D
South Africa (Total number of respondents: 1)				
Age group (years)	NA	NA	**40**	NA
Number of respondents	NA	NA	**1**	NA
Males	NA	NA	**1**	NA
Females	NA	NA	**0**	NA
Turkey (Total number of respondents: 1)				
Age group (years)	NA	NA	**45**	NA
Number of respondents	NA	NA	**1**	NA
Males	NA	NA	**1**	NA
Females	NA	NA	**0**	NA
Mexico (Total number of respondents: 5)				
Age group (years)	NA	**47 & 58**	**58**	**36 & 52**
Number of respondents	NA	**2**	**1**	**2**
Males	NA	**2**	**1**	**2**
Females	NA	0	**0**	0

BD: Business Development; R&D: Research and Development; NA: Not applicable
**Technical Operations includes respondents who are Chief Scientific Officers or working in Manufacturing, Operations, and Quality Control departments.*

Part I - Biopharmaceutical Industry of BRICS-TM

The study participants had varied experience in the area of biosimilars. More than 58% of the participants belonged to BRICS-TM companies which had been involved in biosimilar development for more than a decade (11 years and above), while 35% of these were engaged in biosimilar development for between 6-10 years. There were only 6% of respondents whose companies had experience of less than 5 years.

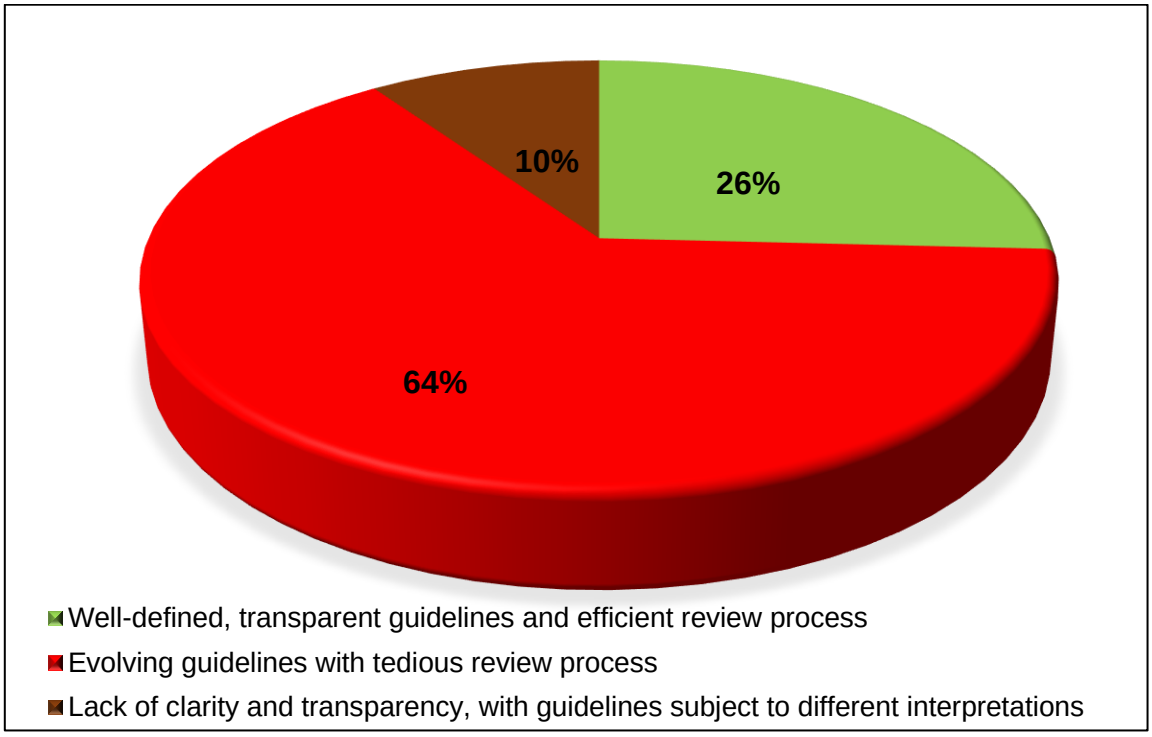
Thirty (90%) of the participating companies were marketing biosimilars. Of these only 11 (37%) were marketing less than 3 biosimilar molecules, while most had commercialised between 3-10 molecules. Four (13%) of companies were marketing more than 10 biosimilars in these emerging markets; 59% of these companies were developing products for commercialising in other emerging markets and 78% had an in-house biologics manufacturing facility. Therefore, the nature and characteristics of the companies which took part in this study confirmed their suitability for continuing the interview for the other parts of the questionnaire involving the challenges of biosimilar development and regulatory processes.

Part II - Biosimilar Guidelines and Approval Process

Guidelines, Evaluation and Approval process

In response to a question on the guidelines and approval process for biosimilars, only 26% considered the guidelines to be well-defined and transparent with an efficient review process. The guidelines were considered to be evolving with a tedious review process by 64% of respondents and the remaining 10% felt that there was a lack of clarity and transparency with guidelines subject to different interpretation (Figure 7.2).

Figure 7.2 Industry feedback on guidelines and approval process



**all percentages have been rounded off to nearest whole number*

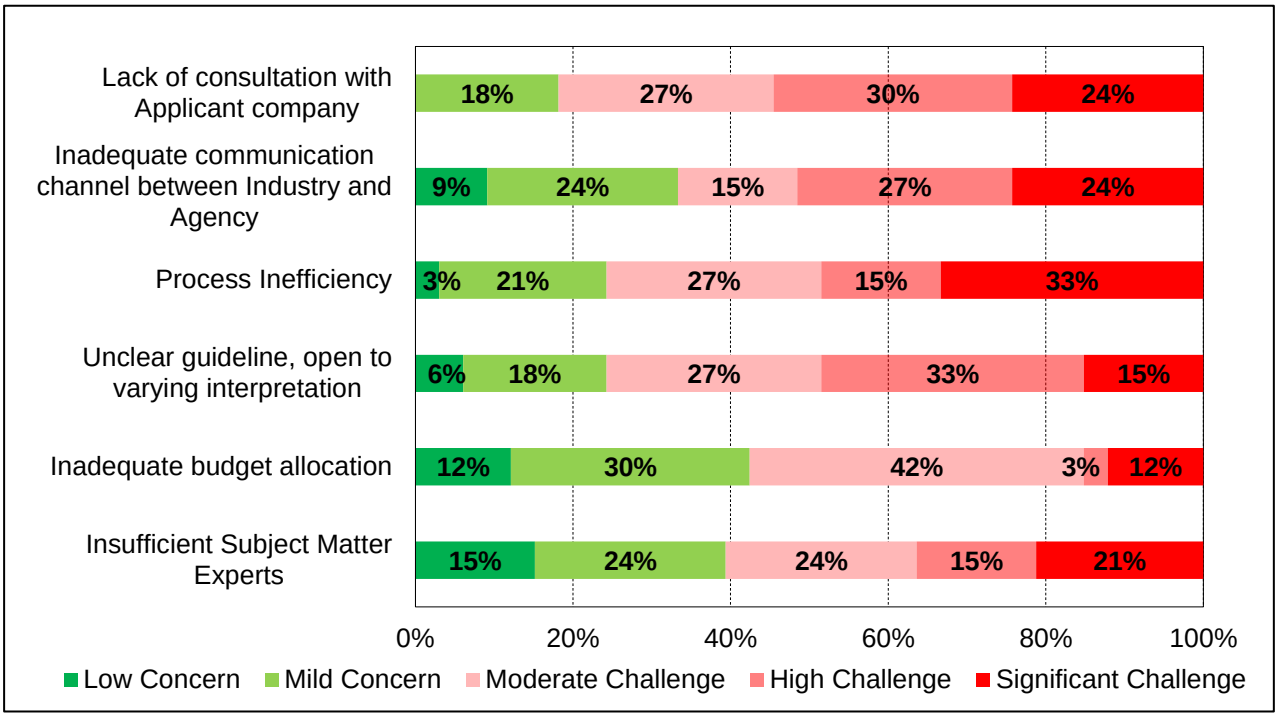
In India, 13 out of 15 respondents indicated an evolving and tedious regulatory process. Participants noted that the coordination between two government bodies separately reviewing non-clinical (Department of Biotechnology - DBT) and clinical data (Central Drugs Standard Control Organisation - CDSCO) has much scope for improvement. In Mexico too, 3 out of 5 respondents indicated on the evolving guidelines and tedious regulatory process for biosimilars. Notably in Brazil, 4 out of 6 respondents indicated that there were well defined, transparent guidelines and an efficient review process. This could, in part, be attributed to the fact that all meetings

between industry and the Agência Nacional de Vigilância Sanitária (ANVISA - the Brazil National Health Surveillance Agency) are recorded and can be retrieved and referred to. With regards to the transparency of the regulatory review process for biosimilars, 43% of BRICS-TM respondents stated that the review process was generally transparent on the main milestones but the decision-making process for each milestone was non-transparent. However, 24% of BRICS-TM reported that the review process was non-transparent.

The participants were asked to rate (on a 5-point scale where 1 = low concern and 5 = significant challenge) the key challenges in the review and evaluation of biosimilar dossiers by the respective country's regulatory agency**.** It is notable that all the identified challenges were rated 3 (moderate challenge) and above indicating that these were all significant issues across the countries (Figure 7.3). 'Process Inefficiency' emerged as the single highest concern with a median rating of 4 and a mode value of 5. 'Inadequate communication channel between the industry and the agency' and 'Lack of consultation with applicant company' emerged as the second biggest concern with a median rating of 3.5 and a mode value of 4 for both parameters.

Some of these challenges could be mitigated by the timely provision of appropriate scientific advice from the agency to the company. However, in response to a question on this matter, it appeared that about 60% of respondents across BRICS-TM either did not receive advice or received advice that was inadequate. This concern was more pressing in Russia where there was no possibility of interaction with the Ministry of Health (MoH) on this subject. Notably, all respondents from Brazil confirmed provision of adequacy of scientific advice from ANVISA.

Figure 7.3 Challenges in review and evaluation of biosimilar dossier



**all percentages have been rounded off to nearest whole number*

Effectiveness and Efficiency of Approval Process

The approval timelines of biosimilar applications did not emerge as a significant challenge with the BRICS-TM agencies. Most regulatory agencies had an average timeline of 24 months with CDSCO India and Russian MoH having a shorter timeline of 6-12 months. In Mexico, the average approval timelines by Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS) was reported as 9 -12 months by the respondents. In India specifically, the most frequent timeline was reported as being 6 months. The expected optimal approval timelines by companies were reported to be in the range of 9-12 months across the BRICS-TM countries with 9 months being the most frequently reported. The largest gap between the agency practice and the industry expectation occurred in Brazil (12 months). The study participants representing the BRICS-TM countries highlighted an absence of an abridged review pathway, although in Mexico, 80% of respondents indicated abridged review pathway being followed by their agency. In response to a question on fast-track approvals of biosimilars, 55% of respondents reported that such procedures exist. However very few have had success in availing of such approvals, except in the case of orphan drugs and recently in the case of medicines for the treatment of COVID-19 [e.g., Itolizumab was approved by CDSCO India for restricted emergency use in Acute Respiratory

Distress Syndrome (ARDS) caused by COVID-19, in July 2020. This monoclonal antibody was approved in India in 2013, and additional indication was approved via a fast-track procedure]. Most countries required pricing approval for biosimilars before commercialisation. This process was not unduly long with timelines ranging from 2-6 months.

Part III - Development Parameters

Reference Biologic Product (RBP) Selection

The BRICS-TM agencies provide clarity in terms of the RBP to be used for each biosimilar development and the list of countries from which sourcing of a foreign acceptable comparator (FAC) was admissible. While the industry might have clarity around the reference product and the country from which it was expected to be sourced, sourcing of the RBP remained a key challenge.

Multiple lots of RBP- In order to meet the requirement for statistical justification of analytical similarity of the biosimilar with the original biologic, multiple lots of the reference product needed to be sourced, as reported by 29 (88%) of the participants. The exact number of batches were often not specified and might vary from case to case, and open to industry interpretation. Individual responses from within countries varied widely but the frequency analysis revealed a mode of 3-10 batches of different ageing except South Africa, where it was indicated there was no expectation for multiple batches. The sourcing of multiple batches of the RBP was a significant challenge for the industry, as indicated by 70% of the companies. Content analysis of the participants' comments showed that concurrent availability of multiple lots of the RBP in the market at any given point of time was a key hurdle.

Quantity of RBP- Even if available, the quantity of product required per batch for various tests and studies (characterisations, comparability studies, clinical studies) could be difficult to source. Large quantities of RBP required to perform comparative clinical safety and efficacy studies increased the overall cost of development.

RBP from a single drug substance- The innovator usually manufactured drug substance on a large scale. Therefore, multiple product batches could come from a single drug substance, which complicated the efforts of biosimilar developers to get

drug product batches from different drug substances. Sourcing multiple batches of the same biological substance led to limited variation in analytical results which in turn complicated the justification for product specifications with the regulator. In order to remedy such a situation, the biosimilar manufacturer often had to set up stringent analytical specifications, which subsequently resulted in manufacturing difficulties, such as non-compliance to stringent standards.

Change in manufacturing process of RBP- If the innovator decided to change the manufacturing process and obtained approval for the same, a fresh development process with new batches needed to be initiated by the biosimilar manufacturer.

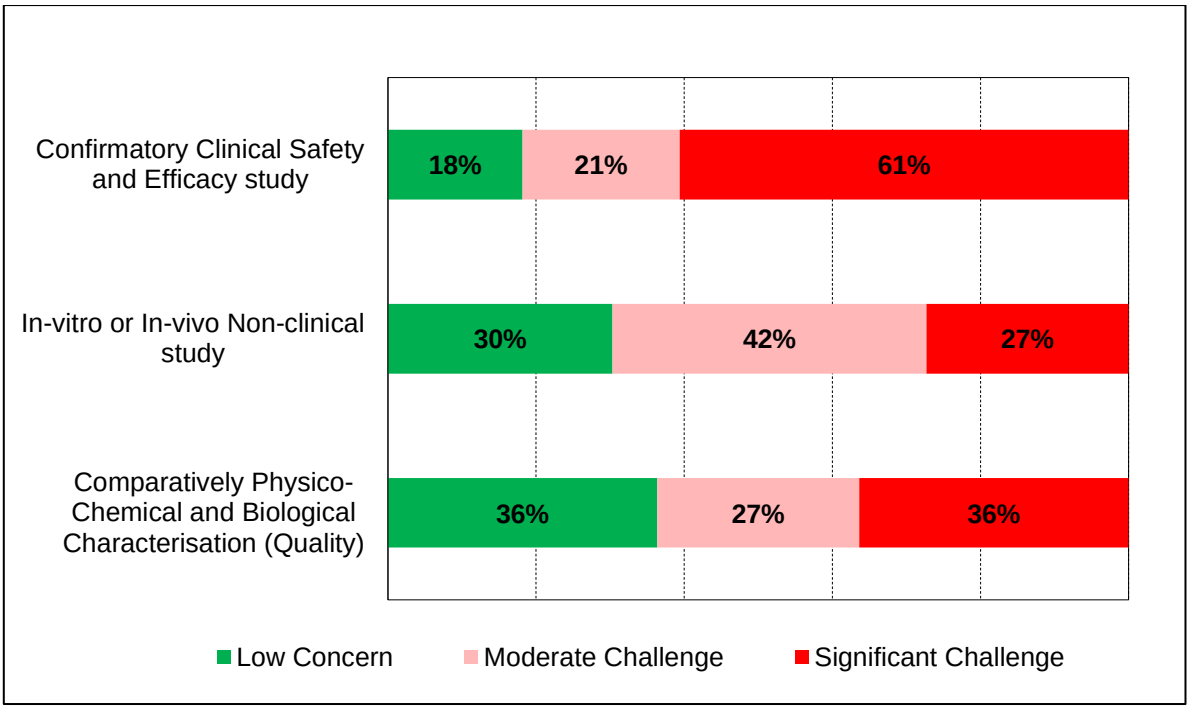
RBP non-availability in open market- In Russia, a specific issue was that all biologics were procured directly by the government from the distributors, resulting in unavailability of the product in the open market for procurement. Consequently, all these factors resulted in sizable time and cost escalation for the companies developing biosimilars.

Criteria for biosimilarity

Criteria for biosimilarity encompasses comparative physico-chemical and biological characterisation, *in vitro* non-clinical studies, *in vivo* safety data, confirmatory clinical safety and efficacy studies.

In response to a question on challenges to prove biosimilarity, the study participants from BRICS-TM rated ‘confirmatory clinical safety and efficacy study’ as their highest concern with a mean rating of 2.4 on a scale of 1 to 3. The most frequent rating value was 3 with 22 of 33 respondents rating this as a ‘significant challenge’. The mean rating of other parameters included: comparative physico-chemical and biological characterisation (quality); and *in vitro* or *in vivo* non-clinical study, which were rated as 2 (i.e., moderate challenge), but not as high as ‘confirmatory clinical safety and efficacy study’ (Figure 7.4).

Figure 7.4 Challenges in demonstrating biosimilarity



**all percentages have been rounded off to nearest whole number*

In terms of efficacy and safety studies, the study participants reported that the cost of trials, large sample size for trials, lead time for patient recruitment and significant drop out rates were some of the major operational issues in conducting clinical studies for biosimilars. Companies also faced lack of expertise to develop in-house bioassay methods for biosimilars.

Naming of Biosimilars

The BRICS-TM regulatory agencies mandated the same international non-proprietary name (INN) for biosimilars as the RBP, as reported by 30 (90%) of the companies participating in the study. This is different from the approach followed by USFDA expecting the nomenclature in accordance with 'Guiding Principles for Coining United States Adopted Names for Drugs' (USP convention, 2016) for each biologic and biosimilar (CDER & CBER, 2017) (Table 7.2).

Table 7.2 International Non-proprietary Name (INN) system adopted for biosimilars

Regulatory Agencies	INN system
USFDA	The FDA appends a unique, 4-letter suffix as per USAN to the INN for each biologic and biosimilar.
EMA	The EU requires a proprietary name (brand name or company name plus INN), accepts the same INN as the RBP, and for AE reporting, the product name and batch number are to be given; bar code is required.
TGA	Mandatory use of the brand name and Australian ABN for the active ingredient; considering adopting a bar-code system.
BRICS-TM Agencies	Biosimilar INN is the same as the RBP across BRICS-TM countries.

ABN: Approved Biological Name; AE: Adverse events; BRICS-TM: Brazil, Russia, India, China, South Africa, Turkey, Mexico; EMA; European Medicines Agency; EU: European Union; RBP: Reference Biologic Product; TGA: Therapeutic Goods Administration; USAN: United States Adopted Names

Non-Clinical Studies

As reported earlier in this study, non-clinical studies for biosimilars were not rated as a significant challenge by the study participants from the BRICS-TM countries. Further details from the responses indicated that though non-clinical studies data were mandatory as part of the application, no regulatory agency mandates studies were to be performed locally. Content analysis of the free text comments proposed that the regulatory agencies should move towards a step-wise approach to development and mandate non-clinical data only if absolutely required.

Clinical Studies

As part of the biosimilar application, most agencies expected data from Phase I Study (comparative clinical PK/PD or combined PK-PD), (Pharmacokinetics Pharmacodynamics) Phase III Study (comparative clinical safety and efficacy) and Phase IV Post Marketing Surveillance Study (including follow up study for immunogenicity). A comparative confirmatory clinical study (Phase III) was one of the most important requirements to be fulfilled as part of the marketing authorisation of the application. In the section describing criteria for demonstrating biosimilarity, it was reported that the companies taking part in this study rated ‘confirmatory clinical safety and efficacy study’ as the highest concern for them in the development of a biosimilar product.

Mandatory local studies

This study needed to be performed locally in India, Mexico, Russia and China and should be comparative in nature, the reference drug needed to be used throughout the study to prove comparative efficacy of the respective biosimilar. Mostly biosimilar applicant companies combined the confirmatory clinical and immunogenicity study.

Lack of clarity on study design

There existed lack of clarity on certain aspects of these studies, e.g., study types, population, end points, design, pediatric population, safety pharmacology expectations and follow-up period.

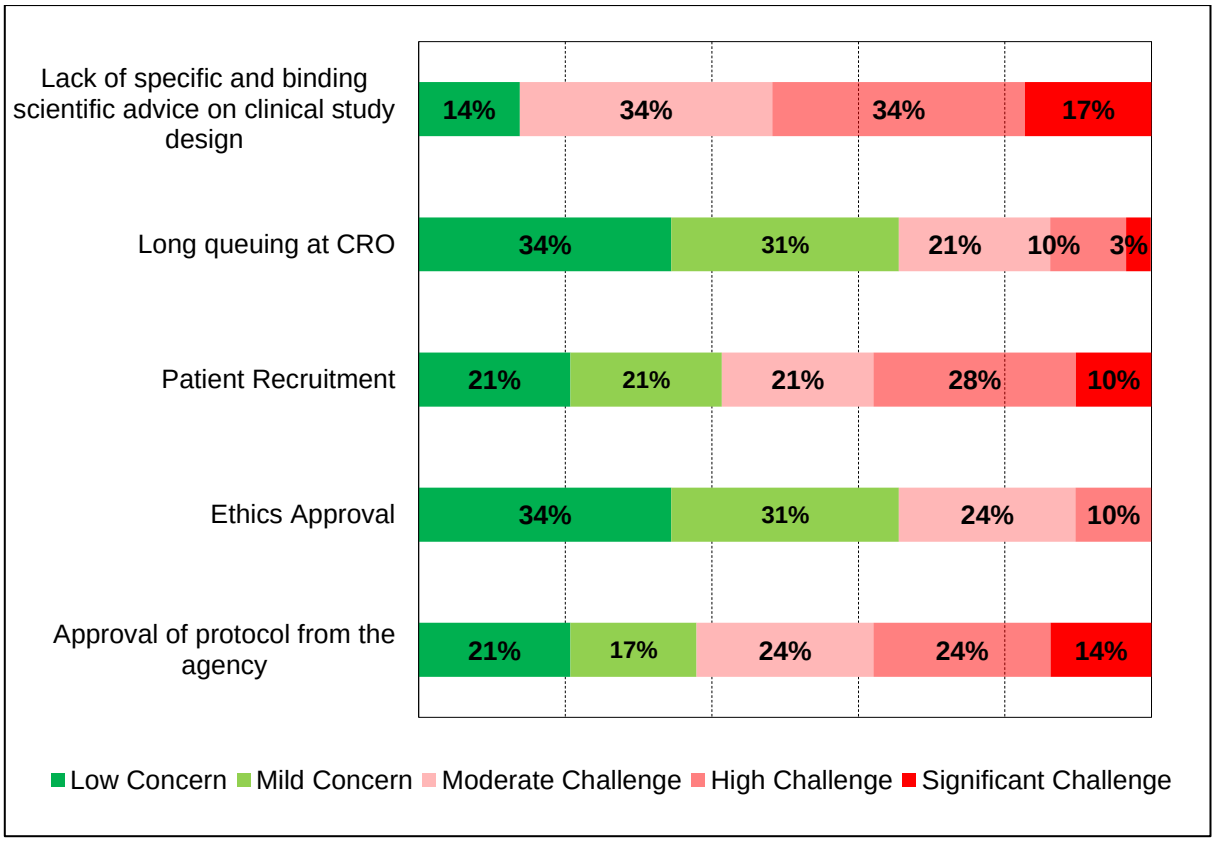
Other factors

The industry also faced challenges in the following areas:

- Approval of clinical trial protocol by the regulatory agency
- Ethics approval
- Patient recruitment
- Availability of a Clinical Research Organisation (CRO)
- Lack of specific and binding scientific advice on clinical studies

These factors were rated by the company participants (Figure 7.5) across the BRICS-TM which showed ‘Lack of specific and binding scientific advice on clinical study design’ to be the single biggest challenge with a mean value of 3.5 and a mode value of 4 (high challenge)’. ‘Approval of protocol by the agency’ and ‘Patient Recruitment’ were rated as the next biggest obstacles. This outcome further validated earlier reported data on inadequacy of scientific advice.

Figure 7.5 Challenges in clinical study



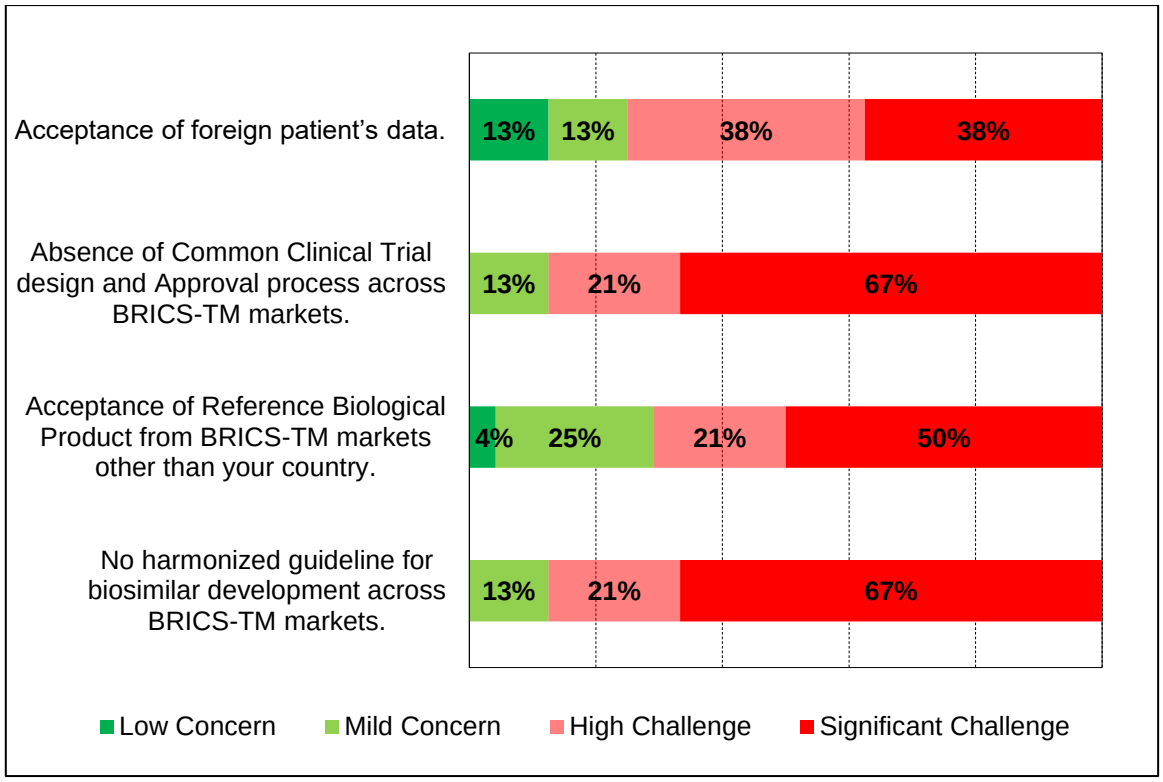
**all percentages have been rounded off to nearest whole number*

Sample Size for Clinical Studies - The BRICS-TM (ANVISA, 2010; CFDA, 2014; COFEPRIS, 2014; MCC, 2014; Russian federation, 2014a; CDSCO, 2016; TITCK, 2017) agencies required confirmatory clinical studies to be performed in two arms with patient ratio as 1:1 for the test and reference product. The response from the countries was markedly variable, however it was reported that the minimum expectation from the regulatory agencies was 100-200 patients per arm, or based on statistical powering of trial, whichever was the highest.

Multi-Country Development

Considering the time and cost involved in developing and marketing biosimilars, the companies active in this space were those which had overcome steep entry barriers and were therefore typically large multi-national players. Despite this, industry players found it difficult to develop a global regulatory strategy for biosimilars covering the emerging markets, due to several hurdles. While 69% of companies indicated that they were pursuing multi-country biosimilar developments including for BRICS-TM countries, they faced obstacles on several fronts (Figure 7.6).

Figure 7.6 Development challenges in BRICS-TM market



**all percentages have been rounded off to nearest whole number*

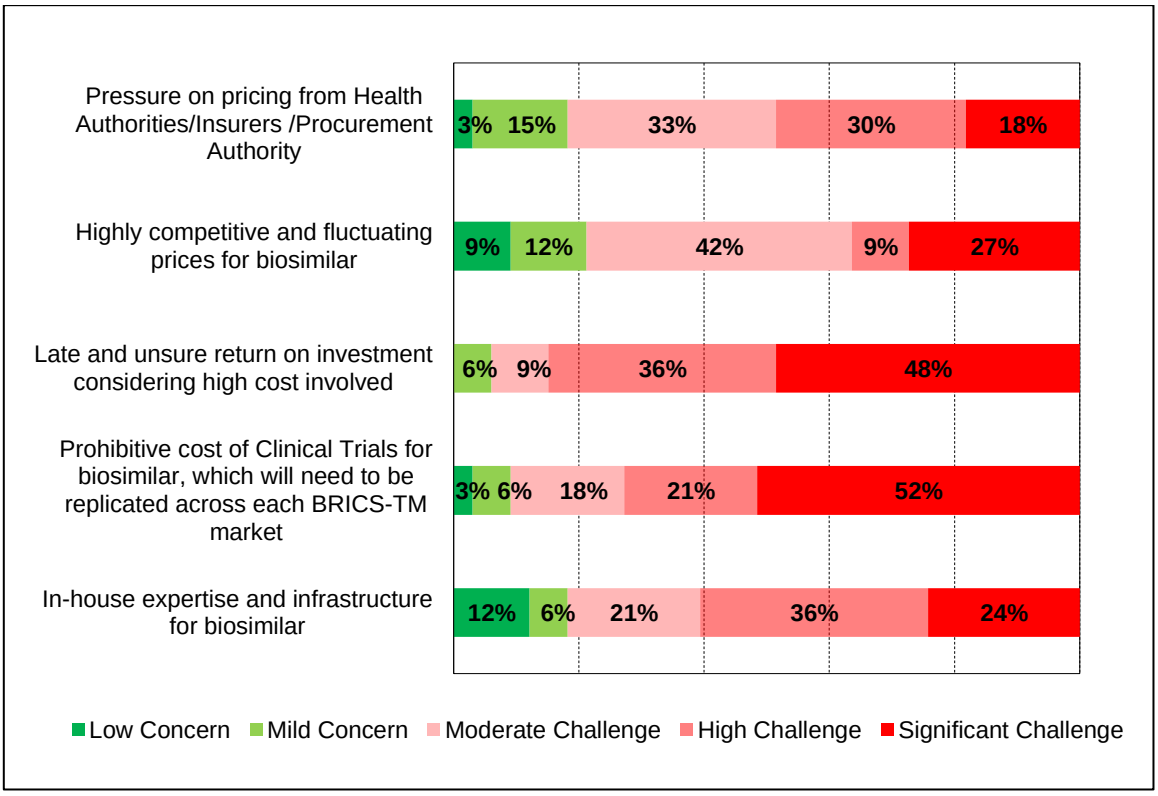
In response to a question on these challenges, the participants rated 'Lack of harmonised guideline for biosimilar development across BRICS-TM' and 'Absence of common clinical trial design and approval process across BRICS-TM' as the highest concerns, with a mean of 3.5 on a scale of 1 - 4 and a mode value of 4 for both. Other issues such as 'Acceptance of reference biological product across BRICS-TM' and 'Acceptance of foreign patients' data' also were rated as a 'significant challenge' with 4 being the most prevalent rating, signifying all four criteria as critical barriers.

Pricing and Market Access Concern

A Quintiles and IMS Health (IQVIA) article on biosimilars and biobetters published in September 2020 (Arias, 2020), reported that the rest of the world (RoW) countries accounted for US$0.1 billion sales for follow-on-biologics (FOBs) including biocomparables vs. US$15 billion global sales, as of second quarter 2020. It was concluded that there is an overall low coverage of biologics, and "Follow-on-Biologics" (FOBs) were an emerging sector where sales remain low. Further, on their own, RoW countries are unable to justify the cost of development for biosimilar projects (Arias, 2020).

This study delved into the reasons for limited access for patients and entry barriers for the industry. 'Innovator patent term and strategy' and 'Higher cost of therapy of biosimilars as compared to small molecule medicines' were rated as the highest barriers to access with a mean rating of 3.6 and 3.4, respectively. The next biggest obstacles were rated to be 'Challenges pertaining to regulatory framework for development and approval of Biosimilars' and 'less numbers of active industry players in biosimilar segment'. Apart from the concerns on patent terms of original biologics, the other three challenges could be substantially mitigated by facilitating ease of development and approval of global biosimilars and enabling more competition in this space. Related to this, companies were asked about specific issues that acted as entry barriers into this space. 'Late and unsure return on investment considering high cost involved' and 'prohibitive cost of clinical trials for biosimilars' were rated as the highest challenges with a median rating of 4.3 and 4.1, respectively. 'Lack of in-house expertise and infrastructure in biosimilars' and 'Pressure on pricing from health authorities/insurers/procurement authority' were rated as the second highest barriers with median rating of 3.5 and 3.4, respectively (Figure 7.7).

Figure 7.7 Entry barriers for industry players to be active in biosimilar space



**all percentages have been rounded off to nearest whole number*

DISCUSSION

The biopharmaceutical industry faces several challenges in the development and registration of biosimilars in the BRICS-TM countries. The result of this exploratory research has highlighted key issues, which are summarised in Table 7.3.

Table 7.3 Summary of critical challenges identified based on primary research

Aspects	Critical Challenges identified
Guidelines, evaluation and approval process	• Evolving guidelines with tedious review process • Process inefficiency • Inadequate communication channel with agency
Process effectiveness	• Absence of abridged review pathway
Development parameters	• Reference Biologic Product – Sourcing of multiple lots within stipulated timeframe – Sourcing acceptable from limited countries – Large quantity required for characterisation and clinical study. – Availability of RBP from different drug-substance lots. – Cost of RBP • Non-clinical studies – Mandatory in-vitro/ in-vivo studies, often not justified. • Confirmatory clinical safety and efficacy studies – Lack of specific and binding scientific advice – Lack of harmonised guideline for biosimilar development across BRICS-TM – Absence of common Clinical Trial design and Approval process across BRICS-TM
Market access and pricing	• Late and unsure return on investment considering high cost involved • Prohibitive cost of Clinical Trials for biosimilars • Pressure on pricing from Health Authorities/ Insurers / Procurement Authority'

RBP: Reference Biological Product; BRICS-TM: Brazil, Russia, India, China, South Africa, Turkey, Mexico.

Clearly, the results indicate that across the BRICS-TM countries, the different functions were mostly aligned in their perception on the specific challenges faced by them (Table 7.4).

Table 7.4 Breakdown of challenges in biosimilar development and approval process in BRICS-TM according to functions of the study participants

Identified challenges	Country	Prevalence of responses (%)	Level of concordance of the responses
Regulatory Affairs (RA)			
Evolving guidelines with tedious review process	Brazil	33.3	Low concern
	Russia	50	High concern
	India	60	High concern
	China	NA	NA
	South Africa	100	High concern
	Turkey	0	No concern
	Mexico	100	High concern
Confirmatory clinical safety and efficacy studies	Brazil	66.67	High concern
	Russia	100	High concern
	India	80	High concern
	China	NA	NA
	South Africa	100	High concern
	Turkey	100	High concern
	Mexico	0	No concern
Reliance and absence of abridged review pathway	Brazil	33.33	Low concern
	Russia	50	High concern
	India	100	High concern
	China	NA	NA
	South Africa	0	No concern
	Turkey	0	No concern
	Mexico	0	No concern
Research & Development (R&D)			
Mandatory non-clinical studies (*in vitro* and *in vivo* studies)	Brazil	NA	NA
	Russia	NA	NA
	India	100	High concern
	China	NA	NA
	South Africa	NA	NA
	Turkey	NA	NA
	Mexico	100	High concern
Lack of specific and binding scientific advice	Brazil	NA	NA
	Russia	NA	NA
	India	100	High concern
	China	NA	NA
	South Africa	NA	NA
	Turkey	NA	NA
	Mexico	100	High concern
Lack of harmonised guideline for biosimilar development across BRICS-TM	Brazil	NA	NA
	Russia	NA	NA
	India	100	High concern
	China	NA	NA

Identified challenges	Country	Prevalence of responses (%)	Level of concordance of the responses
	South Africa	NA	NA
	Turkey	NA	NA
	Mexico	100	High concern
Business Development (BD)			
Late and unsure return on investment considering high cost involved	Brazil	100	High concern
	Russia	NA	NA
	India	100	High concern
	China	100	High concern
	South Africa	NA	NA
	Turkey	NA	NA
	Mexico	NA	NA
Pressure on pricing from Health Authorities/Insurers/Procurement Authority	Brazil	100	High concern
	Russia	NA	NA
	India	80	High concern
	China	0	No concern
	South Africa	NA	NA
	Turkey	NA	NA
	Mexico	NA	NA
Sourcing of multiple RBP lots	Brazil	100	High concern
	Russia	NA	NA
	India	60	High concern
	China	100	High concern
	South Africa	NA	NA
	Turkey	NA	NA
	Mexico	NA	NA
Technical Operations			
In house expertise and infrastructure	Brazil	NA	NA
	Russia	50	High concern
	India	100	High concern
	China	NA	NA
	South Africa	NA	NA
	Turkey	NA	NA
	Mexico	NA	NA
Submission & commercialisation of three batches of validation	Brazil	NA	NA
	Russia	50	High concern
	India	75	High concern
	China	NA	NA
	South Africa	NA	NA
	Turkey	NA	NA
	Mexico	50	High concern

BRICS-TM: Brazil, Russia, India, China, South Africa, Turkey, Mexico; RBP: Reference Biologic Product
Note: If % Outcome of respondents is; ≥50 = High concern, Less than 50=Low concern, 0 = No concern, NA= Not Applicable

Biosimilar regulations vary widely across the regulatory agencies in emerging economies, with a patchwork of applicable rules (Singh et al., 2013). In this research, only 26% percent of respondents found the available guidelines transparent, and the majority felt that communication between the industry and regulatory agency were inadequate and unreliable. Process inefficiencies can often be attributed to the lack of expert resources within the biologics departments of the regulatory agencies (Welch, 2016a). However, building capacity and expertise in a national regulatory authority was a long-term process and quick resolutions lie in relying on information from other regulatory authorities or a joint or abridged review models (McKinsey & Company, 2018). Also, transparency in the regulatory evaluation process would greatly contribute to establishing confidence within the industry and the recording and retrieval of meetings as followed by ANVISA is an example of 'good review practice' that can be emulated.

The RBP sourcing comes across as a major hurdle for most companies (McKinsey & Company, 2018). A greatly simplified basis for selecting a reference comparator, that does not require conducting new bridging studies, has been proposed and justified based on the relevant scientific data in an opinion paper (Webster & Woollett, 2017). In an article on 'The importance of Global Regulatory Harmonisation for Biosimilar Medicines' by International Generic and Biosimilars Association (IGBA) (IGBA, 2019), use of a global comparator product and waiving of bridging studies is highlighted as a key proposal to enable multi-country development. A WHO survey result of 20 countries also reiterated these challenges (Ferreri, 2020). A common approach to the RBP definition, harmonised expectations for number of batches to be used for analytical similarity, acceptance to source RBP across BRICS-TM countries and establishment of an independent agency to supply RBP with varied drug substance lots would in the absence of the product in the open market, will enable multi-country development.

A key improvement area for regulatory agencies in the emerging economies could be adoption of a 'step-wise' approach for biosimilar development (Welch, 2016a). This will reduce the unnecessary non-clinical studies in cases where there was proven similarity in physicochemical characterisation between the test and reference product. Further in the development cycle, companies have singled out that the confirmatory clinical

safety and efficacy study as a major concern. A McKinsey report on biosimilars has reiterated that discussion around lowering development costs via innovation was essential to ensure a sustainable future (McKinsey & Company 2018). Therapeutic equivalence trials account for at least 75% of total development costs (McKinsey & Company, 2018). Secondary research on biosimilar approvals has revealed that usually no submission gets rejected following a full review due to a finding of clinical inequivalence between the biosimilar and its RBP if the two products have been found to be highly similar in analytical and PK studies (Webster et al., 2019). Hence, powered efficacy studies of these biosimilar candidates are of questionable value (Webster et al., 2019). Moreover, repetition of these studies across countries and non-acceptance of foreign patients' data leads to escalation of cost and timelines, jeopardising the return on investment for the developer. A policy paper from IGBA (IGBA, 2020) has also reiterated the higher relevance of advanced analytical science to prove comparability in place of confirmatory clinical data. In addition, WHO is also well positioned on this subject in its 'Guidelines on evaluation of similar biotherapeutic products (SBPs)' (WHO, 2009), based on which other regional guidelines for biosimilars have been modelled into. The WHO (WHO, 2009) clearly notes that the demonstration of comparability of an SBP to its RBP in terms of quality (comparability exercise) is a prerequisite for the reduction of the nonclinical and clinical data set required for licensure. The guidance further elaborates its stand on abbreviated clinical development programs for biosimilar products, citing the advancement in the development of analytical methodology for characterising the complex biotherapeutic products including monoclonal antibodies.

These barriers in the biosimilar space in emerging markets have led to relatively low patients' access to biologic medicines when compared to developed markets (Kent et al., 2017). Patients in these markets stand to gain the greatest increase in access as a result of biosimilar competition. There has been a marked push for high quality biosimilars (Kent et al., 2017) but a real change will only be seen once the regulatory agencies take concrete steps towards improving efficiency and transparency of the processes, standardisation of RBP requirement, establishing abridged review pathways, following a step-wise approach and accepting advanced analytical comparability data in lieu of confirmatory clinical studies.

Regulators are conservative by inclination and incentivisation, and would not mind to lead progressive change, even though it may lead to improvements for patients. It is, therefore, for industry, which invented the products and their associated scientific underpinnings in the first place, to educate regulators on efficient review pathways. It is evident from this paper that many of the regulators essentially consider biosimilars to require only a slight variation of the traditional innovator's drug review pathway, which is to deny completely the science and logic of biosimilarity and the benefits that it can confer. Requirements for approval of biosimilars based upon a good scientific understanding will find no place for studies in animals, no place for local clinical studies, few reasons to "bridge" a local version of the reference to a version approved in another jurisdiction and no reason to require clinical equivalence studies routinely, but it is for industry to bring these understandings to patients, payers, regulators and physicians alike.

Hypothesis to be tested in future studies

- Removal of mandatory compliance with confirmatory clinical safety and efficacy studies would improve patients' access to biosimilars
- Adoption of verification and abridged regulatory review models would reduce the approval timelines
- Establishment of harmonised biosimilar regulatory guidelines for the BRICS-TM countries will enhance development and approval timelines
- Flexibilities in sourcing of RBP will result in development of a common biosimilar development programme.

SUMMARY AND CONCLUSION

This study delves into the understanding and perception of the respondents regarding the effectiveness and efficiency of current regulatory processes for biosimilar products and gathers suggestions on potential improvements in this area. The study was based on the experience and expertise of those involved in the research and development of biosimilars and provides a unique insight into the success and challenges faced by the biosimilar industry at large. The findings suggested that the BRICS-TM industry faces significant challenges related to cost of development, efficiency and transparency of processes, standardisation of RBP requirement, availability of clear scientific advice

and acceptance of advanced analytical comparability data in lieu of confirmatory clinical studies. Despite availability of the Similar Biotherapeutic Product (SBP) guidelines issued by the WHO (WHO, 2009; WHO, 2017b; WHO, 2017c), findings of this study indicate that the guidelines are only partially implemented by the National Regulatory Authority (NRAs) of BRICS-TM countries, leaving their review practices open to interpretation. Hence, continued efforts towards a globally consistent approach to biosimilar development and approval processes considering the regional differences in regulations appears to be essential. This can be ensured by following the concept of 'step-wise approach' and 'head-to-head' biosimilarity, which is the core of the regulatory guidelines of mature agencies such as EMA, FDA and WHO (Cazap et al., 2018). Such global adoption of regulatory guidelines modelled over existing templates could further expedite approval and facilitate patients' access to these medicines. To achieve this, and to gain the trust and acceptance of biosimilars globally, education plays a crucial role (Cazap et al., 2018). Moreover, the role of biopharmaceutical industry is very significant in balancing the need to account for regulatory variations against the costs of the studies required to seek biosimilar approvals in all geographic regions (McCamish & Woollett, 2011). An in-depth knowledge of each region, early strategic planning, and effective communication with regulatory agencies would be advantageous in achieving this (Gupta et al., 2017). Further, the understanding by new inexperienced manufacturers developing biosimilar products requires great care and attention regarding the development and production of these biological products and adhering to GMP is essential. Also, the role of National Regulatory Authorities (NRAs) in overseeing these developments through GMP inspections is critical (Griffiths, 2020). Thus, there is an immediate need to create a culture of quality within the organisation to meet the challenges posed by the complex biosimilar molecules (Sia et al., 2020). This would enable manufacturer's ability to provide consistent production and quality control, thereby preventing drift from the required specifications over time and would greatly influence the acceptance of biosimilars and their integration into daily practice (Vulto & Jaquez, 2017).

The findings of this study have led to a number of recommendations that is hoped to be considered by the BRICS-TM regulatory agencies:

- The regulatory agencies in the BRICS-TM countries should consider timely provision of appropriate tailor-made and binding scientific advice to companies

engaged in biosimilar development. This should also be extended to clinical studies, if applicable

- The regulatory agencies should consider adopting shared evaluation, reliance and abridged regulatory review models for biosimilars
- The regulatory agencies should consider moving towards a step-wise approach to development and mandate non-clinical data only in the cases where it is fundamentally required
- The regulatory agencies should consider accepting advanced analytical comparability data in lieu of confirmatory clinical studies
- Regulatory agencies should consider accepting RBP sourcing from BRICS-TM countries other than their own, with a waiver of bridging studies to ease availability of multiple RBP lots and in order to facilitate common development programmes
- Regulatory agencies should consider standardising the number of RBP lots for development and establish an agency for the timely supply of RBP with varied drug substance lots.

CHAPTER 8

Evaluation of Physicians' and Patients' Views About Biosimilar Access in the BRICS-TM Countries

INTRODUCTION

Biosimilars can be regarded as means of new access to life-saving medicines for millions of patients. Since the time of their introduction into the pharmaceutical space, biosimilar medicines have been proclaimed as a crucial step towards improving access and affordability of biological therapies for patients suffering from serious medical conditions. However, as novel biologics enjoy two protection mechanism i.e., patents and market exclusivity, granting marketing authorisation to biosimilar does not mean allow market entry easily (Halimi et al., 2020). As already discussed in Chapter 1, the biologic medicines have made their mark as targeted, highly effective therapies for a wide variety of severe disease conditions, but high costs have left most patients deprived of their advantages (McKinsey & Company, 2018). Due to the high cost of biological medicines coupled with the fact that patents of many of these medicines are on the verge of expiration, manufacturers are exploring the production of biosimilars. The introduction of biosimilars has the capacity to increase competition among manufacturers, reduce prices, and improve patient access to these medicines (Okoro, 2021).

Biosimilar medicines, similar but not identical to the original biologics, were expected to bridge the access gap and make these drugs affordable to a larger group of patients, much like the impact of small molecule generics. However, the complex nature of these large molecules, the cutting-edge manufacturing technologies, evolving and tedious guidelines for development and approval, and pricing pressures across countries led to significant escalation in costs and less than desired return on investment for the companies, more so in developing countries (Otto et al., 2014). This in turn has limited the number of players entering this space, hence limiting the treatment options for physicians and patients. Some of these challenges for the development of biosimilars faced by the biopharmaceutical industries has already been studied and presented in the earlier Chapter 7.

Biosimilar market depends both on physicians/patients and manufacturers. Overall, there are three decision makers which facilitates the uptake of biosimilars that are the payers, prescriber and patients (Horn et al., 2021). Patients continue to reap the benefits of significant advances in specialty biological medicines with longer and healthier lives. However, the cost of these products continues on an unsustainable

upward trajectory (Biosimilar Council, 2018). The relative price difference between innovator product and biosimilar is significant and depends on country's pricing system. Despite price difference its market entry is slow because more time is required by authority for its approval, price negotiation and most importantly, the patient (Horn et al., 2021). Further, physicians' reluctance to prescribe biosimilars may restrict potential savings in medical costs that could enable biologic treatment of larger patient populations and provide more cost-effective treatment, as similar benefits could be gained by using less expensive treatments (Sarnola et al., 2020).

Hence, the prescriber and patient confidence are crucial to the adoption of these innovative medicines. The potential patient access and savings benefits resulting from biosimilars cannot be realized without significant buy-in from these key stakeholders. Education on the value, safety and efficacy of biosimilar medicines is an integral piece of the market development puzzle. A broad range of health care professionals are engaged in biosimilars prescribing, dispensing and utilization. This includes doctors, physician assistants, nurses and pharmacists, and education tailored to each role is important. Similarly, collaboration with patient advocacy groups and disease-specific organizations to improve understanding is essential to acceptance of biosimilars. It is unlikely that absence of provider and patient acceptance can foster market adoption (Biosimilar Council, 2018).

Further, prescribers are often subject to misinformation or insufficient information about these critical medicines. Such misinformation regarding biosimilars' safety and efficacy threatens to slow biosimilar uptake leading to regulatory, policy and legal roadblocks to competition and thereby impacting the health of the patients who stand to benefit most from these treatments. The resultant knowledge gap impacts the adoption of biosimilars as first line treatment or as a switch from the Reference Biologic Product (D'Ambrosio & Ivashko, 2013; Chavez, 2013; Camacho et al., 2014; Cohen et al., 2016).

When patients are prescribed biosimilars, they are unaware of the implications of this treatment. Often, patients are not provided with a complete explanation of the choice of therapy selected for their conditions and treatments (Okoro, 2021). Many patients feel that interchanging to biosimilar treatment without their consent would introduce unacceptable uncertainties into that decision-making process (Skingle, 2015).

Adequate patient education and counselling when initiating therapy or switching to a biosimilar are critical. Without appropriate pharmaceutical care (patient-centered education and guidance), most patients may have a perception that a biosimilar is less effective than the innovator product (Okoro, 2021). To ensure that the patients are being prescribed the safest and most efficacious treatment possible, the physicians (prescribers) will need to understand the complexities of biosimilars and take decisions that will be in the patient's interests. Acceptance and use of biosimilars hinge on the comfort level of the physicians after evaluating comparative data (Li & Hoffman, 2013). A survey suggests that 86.7% of Asian gastroenterologists is against automatic substitution at the pharmacy level. Asian gastroenterologist is more concerned on extrapolation to other indication and less confident about their use in clinical practice (Park et al., 2019). Approved biosimilars in India are not liable to pass interchangeability test to allow pharmacist to switch with originator product and biosimilars are substituted at pharmacy level without physician consent (Jeremias, 2020).

According to a report, majorly oncologists from Brazil, Russia, Turkey and Mexico would be prepared to prescribe trastuzumab (an anti-HER2 targeted therapy) to more patients if the cost of the monoclonal antibody was lower (Debiasi, et al., 2017). In India, government suggests going for alternative low-price product (Jeremias, 2020). More number of biologics/biosimilar manufacture in South Africa is due to improvement in molecular diagnostic machines. In South Africa, biosimilar price depends on Single Exit Price (SEP) which is agreed between pricing committee of the department of health and applicant (Bassil et al., 2020). Turkey is considered as a low middle-income country and one of the top countries in healthcare system because of physician experience and expertise due to its high population density with varied medical conditions. Many biosimilar companies have invested in Turkey and GCC countries for production but still limit number of biosimilars are in the market (Hamzi, 2019). It is reported that more than 90% of pharmaceutical spending in Mexico is on generics and similar biologics because of their low price as compared to original biologics (Rios, 2020). A survey suggests that in Mexico the expected discount for payers is 5% minimum whereas it ranges from 10-30% in Brazil. Physicians and patients require safety and efficacy to be proved through head-to-head comparison of biosimilarity to originator product and is looking to regulators for sufficient evidence before prescribing

biosimilars to the patients (Sandorff et al., 2015). Although biosimilars have the capacity to reduce healthcare costs in chronic disease management, they face uptake challenges. Despite the growing number of biosimilars approved for patient care, physicians' comfort in prescribing reference products against biosimilars, biosimilar interchangeability, patient caution, and hesitation to switch from a reference product to a biosimilar, and payer considerations are major factors responsible for biosimilar current low utilization (Grabowski et al., 2014; Hobbs & Crawford 2019; Ramzan, 2020).

OBJECTIVES

The aims of this study were to explore the perceptions of physicians and patients towards prescribing and access to biosimilar medicines and identify what actions they perceive would be needed to increase their adoption of biosimilars in their practice. Therefore, the key objectives of the study were to:

- understand the biosimilar prescribing habits of physicians and the measures driving their choice of product
- to learn about their views on biosimilar interchangeability, switching and substitution
- gauge their perception of safety and efficacy of a biosimilar compared to the original biologic
- identify their insights pertaining to biosimilars, including access and affordability for patients.

METHODS

Assessment tools

Physician questionnaire

A semi-quantitative self-administered Biosimilar Physician Questionnaire (BPQ) was developed in English, Spanish and Russian languages and was based on information from the literature and expert opinion. The introduction part of the BPQ covers “participants information sheet” and a “consent form” followed by 44 items grouped into three parts (Part I = physicians’ perspective of their practice – 32 items including 3 relating to reimbursement using 2-7 Likert scale response options; Part II =

physicians' views of patients' perspective – 8 items using 3-7 Likert scale response options; and Part III = barriers and solutions to patients' access to biosimilars – 4 items free text asking to list 3 most important improvements for better access to biosimilars in respective country and 3 most important barriers and their solutions to patients' access to biosimilars). Other parts of the BPQ include a comment box, definition of terms and abbreviations.

The BPQ underwent a number of draft iterations and then a pilot study was carried out involving face-to-face interviews with two physicians to test its applicability, practicality, relevance (using cognitive debriefing) and content validity. The final version of the BPQ (Appendix 4) emerged following its refinement as a result of psychometric testing. Oncologists, rheumatologists, gastroenterologists and dermatologists (Halimi et al., 2020) who reported to be engaged in biosimilar prescribing were recruited into the study. The BPQ was administered through both online physician groups and individual e-mails through direct contact across BRICS-TM countries.

The independent physicians were contacted directly via their emails and 19 medical associations were approached for recruitment of physicians including: Federação Brasileira De Gastroenterologia; Brazilian Society of Surgical Oncology (SBCO); Russian Gastroenterological Association; Russian Society of Clinical Oncology; Russian Association of Oncological Mammalogy; FSBI National Medical Research Center of Oncology; State Scientific Proctology Center Moscow Russia; Gastroenterological Scientific Society of Russia; Moscow Regional Oncological Dispensary; Chinese Society of Clinical Oncology; China Anti-Cancer Association (CACA); South Africa Gastroenterology society (SAGES); Turkish Society of Medical Oncology; Turkish Medical Association; Turkish Scientists And Physicians Association (TUSPA); International Society of Geriatric Oncology; Centro Médico ABC; Oncology Doctors (Residents & Specialists); The Dermatology Group, BD Rheumatologist; and Fibro and Chronic Pain Support and Association of Women in Rheumatology across BRICS-TM countries. Data collection occurred from January 2020 to September 2020.

Patient questionnaire

A semi-quantitative, self-administered Biosimilar Patients' Access Questionnaire (BPAQ) was developed based on information from the literature and discussion with patient support organisations. The BPAQ was developed in English and further translated to Spanish and Russian languages. The translation of English questionnaire to Russian and the responses from Russian to English was performed by physician located in Russia. Similarly, the translation of English questionnaire to Spanish was also performed by local physicians; however, there were no responses received. The introduction part of the BPAQ covers an invitation to potential participants, "participants' information sheet" and followed by 14 items (consent, 1 item; demographics, 3 items – country, gender and age; biosimilar access challenges, 6 items; and reimbursement/affordability, 4 items) with 3/4-item Likert scale tick-box response options. The final version of the BPAQ was produced following a pilot study involving 15 patients to test its applicability, practicality, relevance and content validity.

The BPAQ was intended for use on social media platforms of the patient organisations across BRICS-TM countries. Twenty-nine patient support organisations in the areas of hemato-oncology and rheumatology were invited to collaborate including: Brazilian Lymphoma and Leukaemia Association, Eurasian Federation of Oncology (EAFO); Russian Patients Association; RosOncoWeb; PARE (Patients with Arthritis); IOO "DOVERIE" patients with Inflammatory Bowel Disease Network from St. Petersburg; Cancer Patients Aid Association; Zenonco; ELLE Breast Cancer Campaign (India); Nargis Dutt Foundation; Mission Arthritis India; All India Patients welfare association; Lymphoma Support Group India; Cancer Foundation of China; Chinese Organisation for Rare Disorders (CORD); Cancer Association of South Africa (CANSA); Childhood Cancer (CHOC) Foundation SA; Turkish Association for Cancer Research and Control (TACRC); Turkish Society of Lung Cancer; Help Those With Cancer Association; European Society for Medical Oncology; Cáncer Warriors de México A.C.; Asociación Mexicana contra el Cancer de Mama AC "Fundación Cima"; Asociación Mexicana de Lucha Contra el Cáncer A.C.; Asociación Mexicana de Ayuda a Niños con Cáncer; IAP (AMANC), Hepatobiliary, Liver, Pancreatic and GI cancer group; Cancer Support group; Cancer Survivors and Supporters; Support for family and friends of cancer patients.

The BPAQ (Appendix 5) was uploaded on the social media platform of those patient support organisations which agreed to collaborate, and their members were invited to participate using the SurveyMonkey online platform (https://www.surveymonkey.com/) as part of the survey. The link remained active for 30 days. Patients or guardians of patients who had been receiving biosimilar treatments at any point during their medical condition were eligible to take part in the study. All participants agreeing to take part in the study were asked (as part of the BPAQ introduction) to read the "patient information sheet" and then consent. Data collection occurred from January 2020 to August 2020.

Data Processing and Analysis

This was an exploratory study attempting to generate hypothesis. Data processing and analysis was carried out using Microsoft excel and the SPSS software was applied to employ descriptive statistics for analysis of quantitative data. Content analysis was employed to generate themes and sub-themes for qualitative data.

Ethics Approval

The study has been approved by the Health, Science, Engineering and Technology ECDA, University of Hertfordshire. Protocol number for the same is - aLMS/PGR/UH/03332(1).

RESULTS

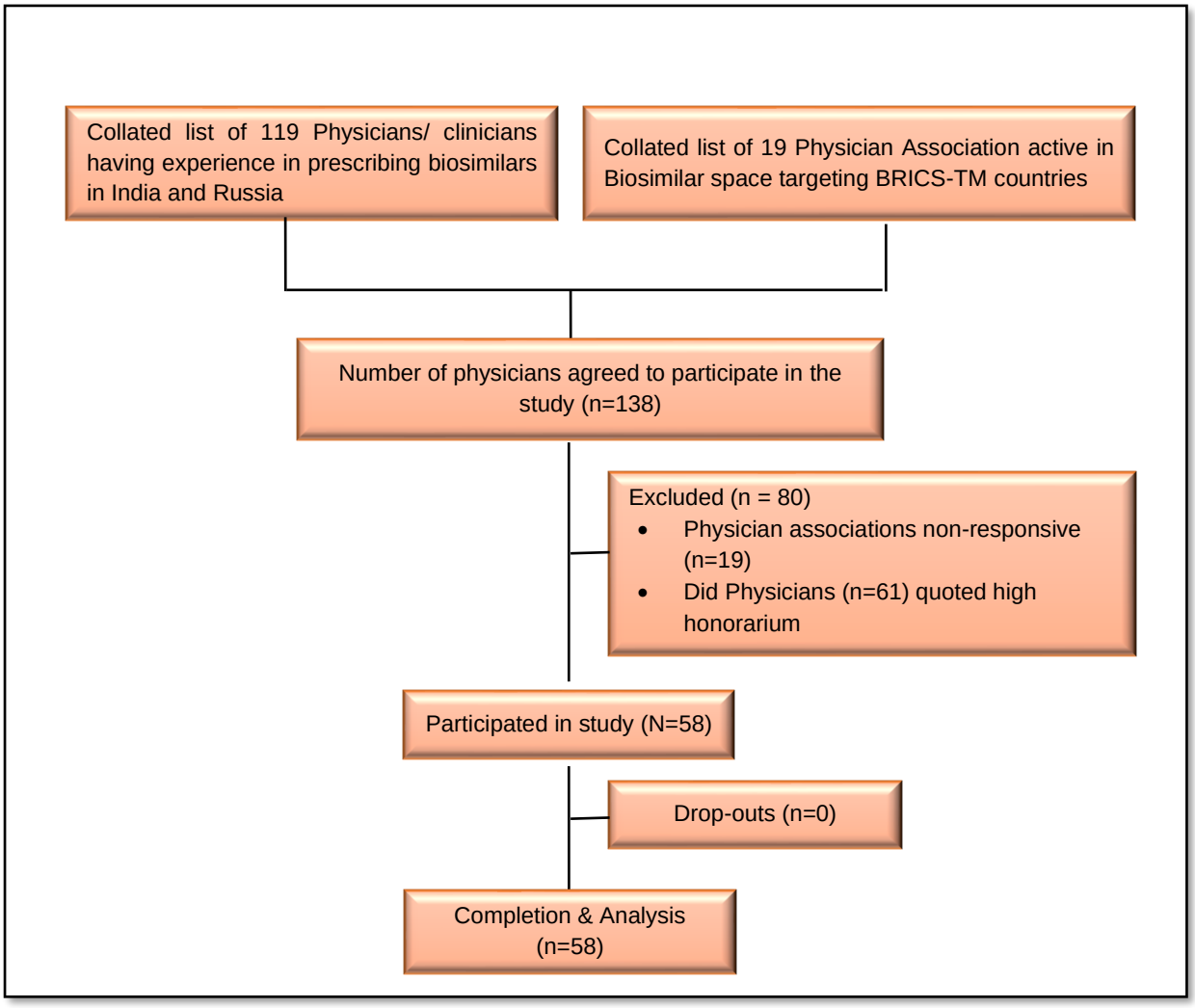
For the purpose of clarity, the results are presented in two parts: Part I – Physicians' Perspectives; and Part II – Patients' Perspectives.

Part I - Physicians' Perspectives

Socio-demographic characteristics of the study participants

A total of 119 independent physicians and 19 medical associations were invited to participate in the study. Fifty-eight physicians agreed to participate and completed the BPQ, and the remainder declined to participate due to lack of time. No response was received from any of the physician associations invited to participate and none offered any reasons for their non-response. Of the 58 physicians who were enrolled into the study and completed the questionnaire (Figure 8.1), 50 were from India and 8 from Russia including 7 dermatologists, 8 gastroenterologists, 16 rheumatologists and 27 oncologists.

Figure 8.1 CONSORT Diagram for enrolment of physicians



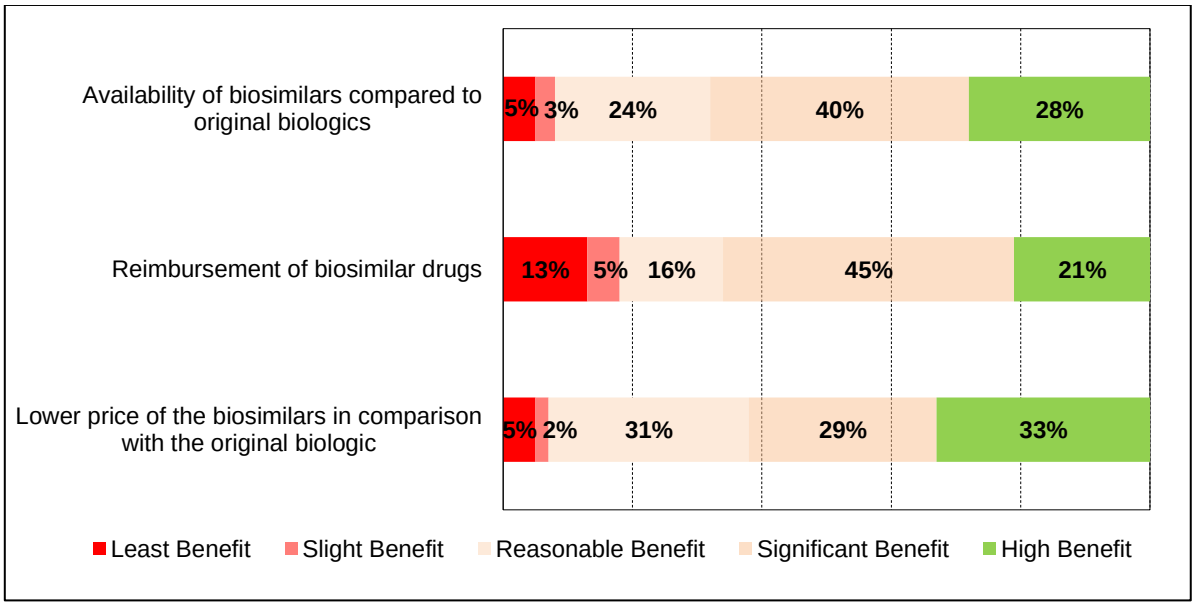
Experience of the study participants with biosimilar medicines

Majority (86%) of the physicians reported experience of over 3 years, 12% less than a year and 2% less than 6 months with prescribing biosimilar medicines. In terms of frequency of prescribing biosimilars, 27 (47%) prescribed biosimilars daily, 13 (23%) at least once a week, 13 (23%) once a month, 2 (5%) one a year and one (2%) prescribed only once. This suggests that the study participants were true representative of those with relevant experience.

Challenges and opportunities experienced by physicians

The physicians reported several benefits in prescribing biosimilars in place of the original biologic therapy. Some key benefits were lower price hence better affordability and likely candidate for reimbursement (Figure 8.2).

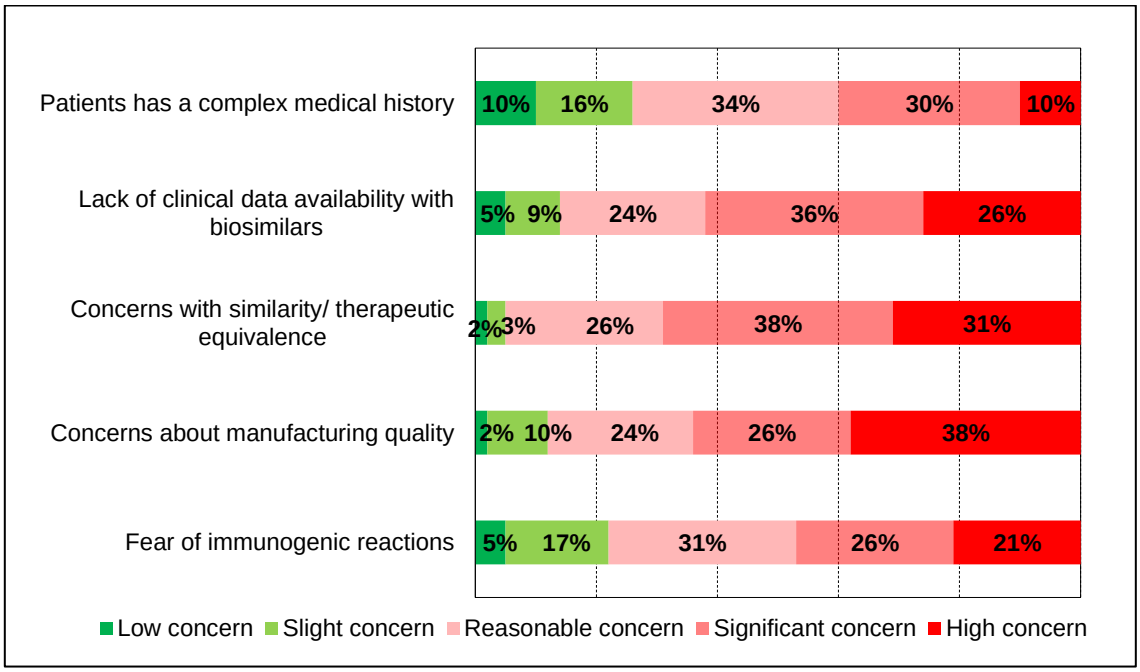
Figure 8.2 Benefits of switching original biologic to biosimilar



**all percentages have been rounded off to the nearest whole number*

However, while taking the decision to prescribe biosimilars, the physicians had high concerns in several areas including similarity or therapeutic equivalence of biosimilars to the Reference Biologic Product (RBP) (69%); and manufacturing quality of biosimilars (64%) (Figure 8.3). In addition, lack of clinical data availability with biosimilars was another area highlighted by most physicians.

Figure 8.3 Concerns faced by physicians in prescribing biosimilar

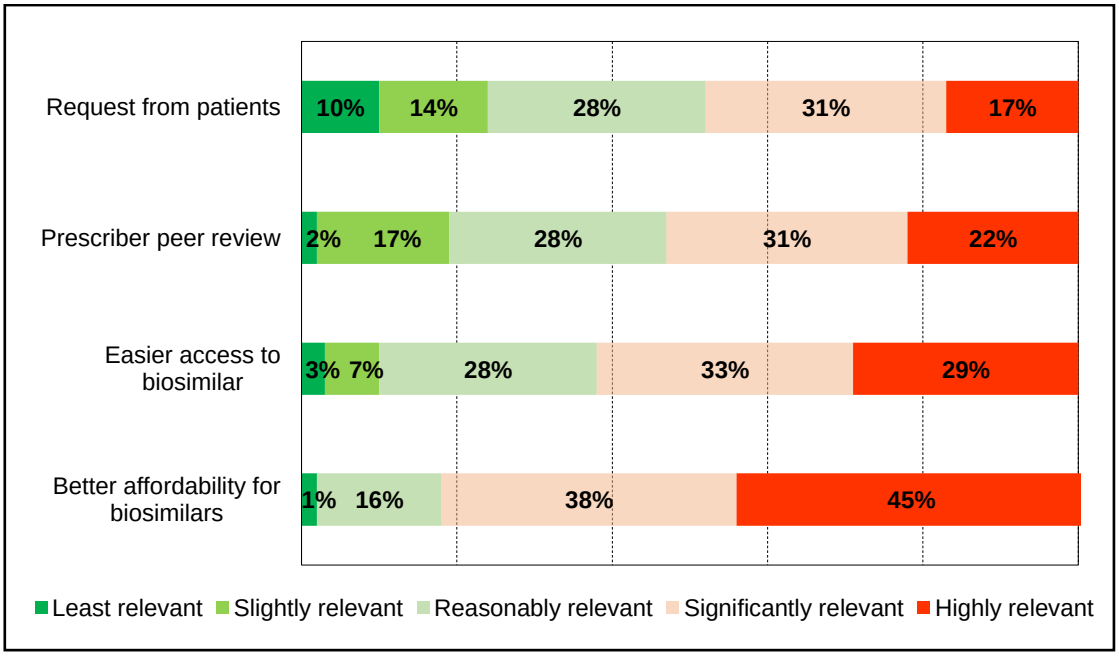


**all percentages have been rounded off to the nearest whole number*

Despite the highlighted concerns with biosimilars, physicians often made the decision to switch from the RBP to a biosimilar for their patients, being influenced by several factors including: better affordability with biosimilars being overwhelmingly influential factor (99%); followed by easier access to biosimilars as the second most influential factor (Figure 8.4). Furthermore, physicians also relied on peer review for confidence on the efficacy and safety of biosimilar medicines and this was rated as a highly relevant factor in their decision making (81%).

However, a great majority of them (95%) reported that they would prefer robust evidence of safety and efficacy guide their biosimilar prescribing and similarly specific information on the product's quality attributes (72%). In a question on how regulatory authorities in the country could encourage or assist adoption of biosimilars by physicians, they specified the need for developing clear guidelines for biosimilars (76%) and a reduction in their cost to improve affordability leading to improved patients' access to such products (72%).

Figure 8.4 Criteria influencing decision to switch from RBP to biosimilar



**all percentages have been rounded off to nearest whole number*

Interchangeability: Switching and Substitution

There was no clear trend with the responses to the question: Does the National Regulatory Authority (NRA) allow interchangeability designation for biosimilars? This meant that 35% responded 'yes', 8% 'no', 16% reported that this was only available

for certain biosimilars and the remaining 41% were not aware of such provision. Similarly, there was no clear trend with the responses to the question: Does the country encourage switching or allows automatic substitution at pharmacy levels if the NRA has designated a biosimilar as 'interchangeable'? This was translated to 31% responding 'yes', 33% 'no' and the remaining 36% felt that this would depend on other factors such as availability. The mixed responses could be a reflection of the lack of clarity on the part of policies relating to interchangeability including switching and substitution.

Physicians' views of patients' perception of biosimilars

According to a majority (93%) of the physicians, patients are comfortable with being prescribed biosimilar medicines. This was confirmed in the patients' survey where 85% of the respondents confirmed their comfort with this category of medicines.

Solutions offered by the physicians

The physicians in this study offered a number of solutions to their perceived hurdles in the free text comment box. The results of the content analysis of the comments revealed that four areas were frequently mentioned namely, affordability, efficacy, safety and quality (Table 8.1). This suggests that the successful uptake of biosimilars would largely depend on the confidence physicians will have in these medicines.

Table 8.1 Key areas of improvement suggested by Physicians for better access to biosimilars

Improvement areas	Suggestions
Affordability	Reduction in cost of biosimilar therapy for patients
Efficacy	Ensure access to clinical data / therapeutic equivalence data; Continuous Medical Education (CMEs) for physicians
Safety	Ensure access to safety data of biosimilars through relevant clinical & non-clinical studies; Establish effective Pharmacovigilance systems
Quality	Regulatory guidelines to ensure that biosimilars are manufactured within strict quality parameters similar to the RBP

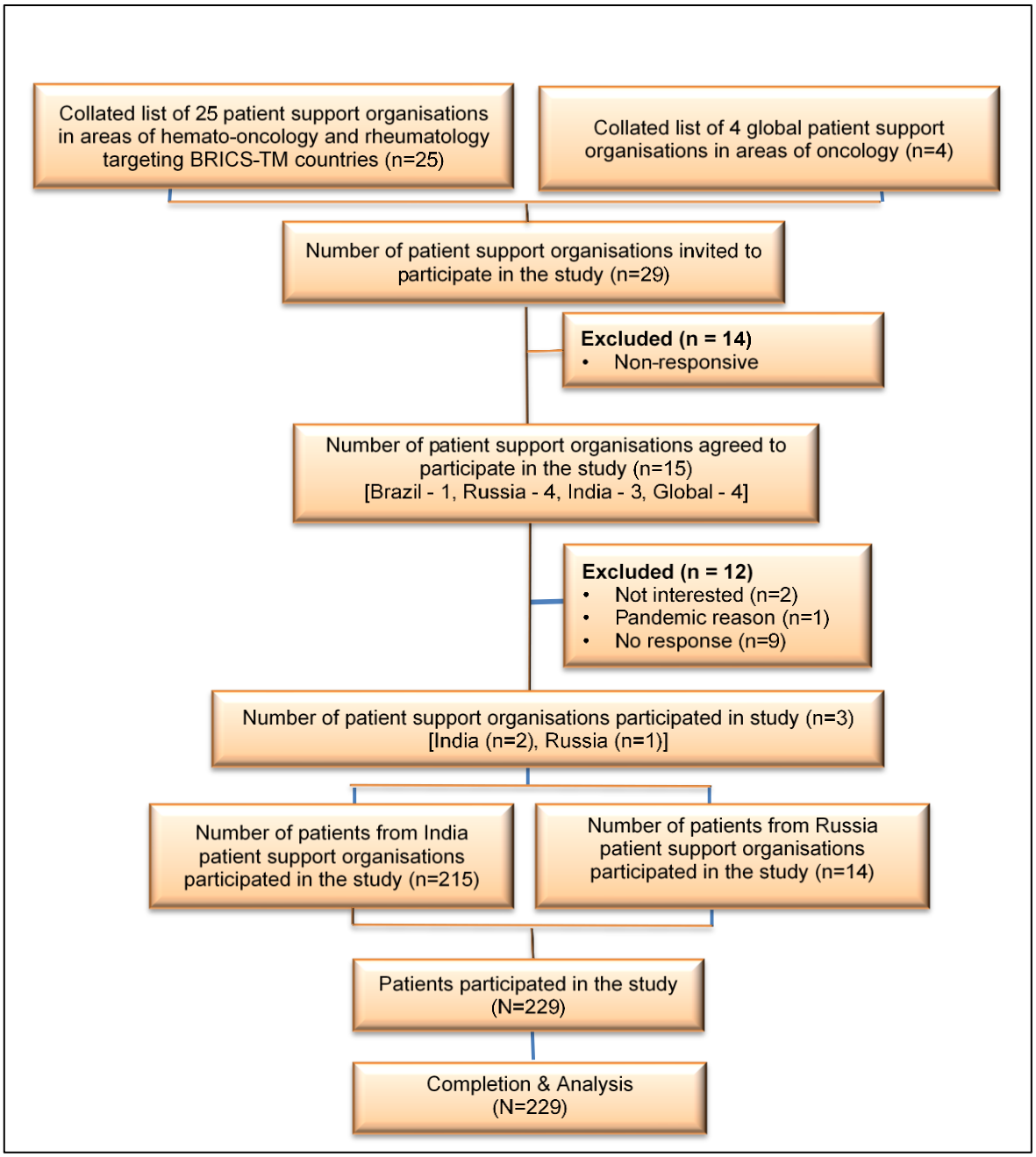
CME: Continuous Medical Education; RBP: Reference Biologic Products

Part II – Patients Perspectives

Socio-demographic characteristics of the study participants

A total of 29 patient support organisations were invited to participate in the study out of which 15 agreed to collaborate. However, members of only three of these patient groups took part in the study (two from India and one from Russia). A total of 229 patients (males=132, females = 97, mean age = 24.4 years, median= 20 years, age range= 10 – 80 years) of which 215 were from India and 14 from Russia completed the BPAQ. Out of 229 patients who took part in the study and completed the BPAQ, only 101 were evaluable (male=58, females = 43, mean age=26.1 years, median age=23 years, age range=12-57 years) (Figure 8.5) comprising of 91 evaluable responses from India and 10 from Russia (Q1 [n=229], Q2 [n=229], Q3 [n=229], Q4[n=123], Q5 [n=204], Q6 [n=87], Q7 [n=93], Q8 [n=98], Q9 [n=84], Q10 [n=88], Q11 [n=80], Q12[n=83], Q13 [n=76], Q14 [n=7]). Majority of the incorrectly completed questionnaires were by patients with cancer who were expected to have been exposed to biological therapies. This suggests provision of poor-quality information to patients leading to low levels of their understanding of these medicines despite their frequent in-clinic use.

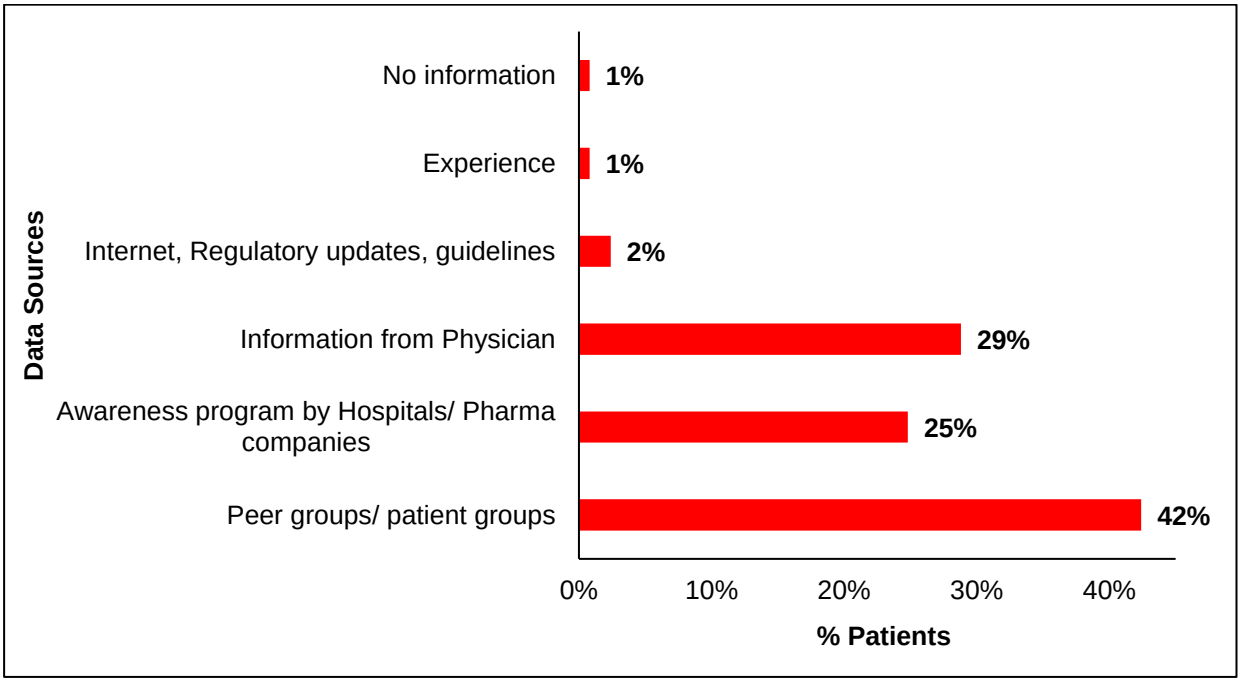
Figure 8.5 CONSORT Diagram for enrolment of patients



Patient's perspective on Biosimilar medicines

For the questions related to patient's experience on use of biosimilar medicines prescribed by their physicians, the duration of use of biosimilar and sources of information on the prescribed biosimilar, 89% of total patients responded. Majority (79%) of the patients responded to be using biosimilar medicines prescribed by their physicians. The duration of usage of biosimilar medicines varied among the patients with 36 (41%) used 'less than a year', 16 (18%) 'between 1 to 2 years', 20 (23%) 'between 2-3 years' and 15 (17%) 'more than 3 years'. The major source of information on biosimilar medicines as responded by the patients were, 'peer groups or patient groups' (42%). Some of the patients claimed to have gathered information on the biosimilar from other sources including awareness programs conducted by hospitals and biopharma companies, information from the physicians and internet sources including guidelines and regulatory updates as illustrated in Figure 8.6. Only 1% of patients asserted to have prior knowledge on biosimilar medicines, and an equal strength of the patients (1%) declared to have been using the prescribed biosimilar medicine without any knowledge or information.

Figure 8.6 Biosimilar source of information for patients

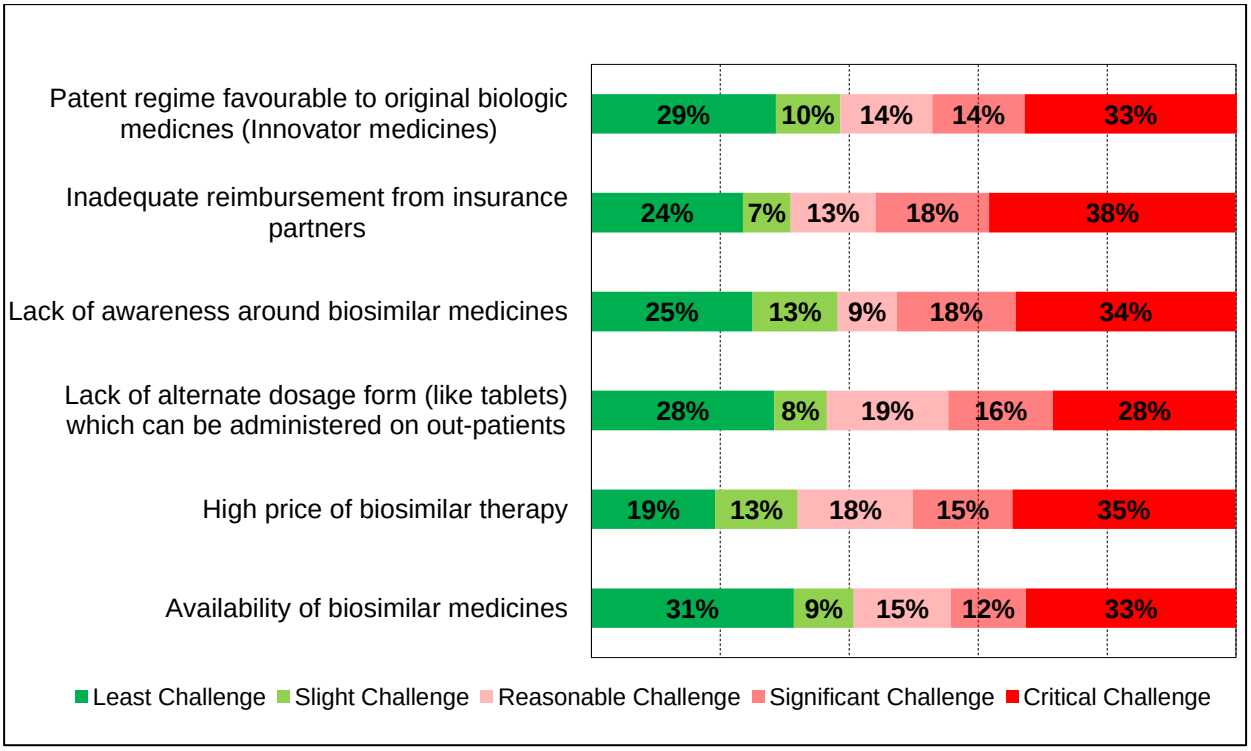


**all percentages have been rounded off to nearest whole number*

Challenges in accessing biosimilars

In response to the question on the key challenges faced by patients, high price of biosimilar therapy and inadequate reimbursement from insurance partners emerged as the biggest issue with 68% and 69% of the patients rating these as reasonable to critical challenge. Although majority of the patients (85%) claimed to be comfortable in using biosimilar medicines prescribed to them, 30% of the patients expressed difficulties related to the availability of biosimilar medicines during treatment. Despite the apparent willingness of patients and their comfort with biosimilar medicines, uptake was limited by challenges expanded upon in Figure 8.7.

Figure 8.7 Key challenges faced by patients in area of biosimilar therapy



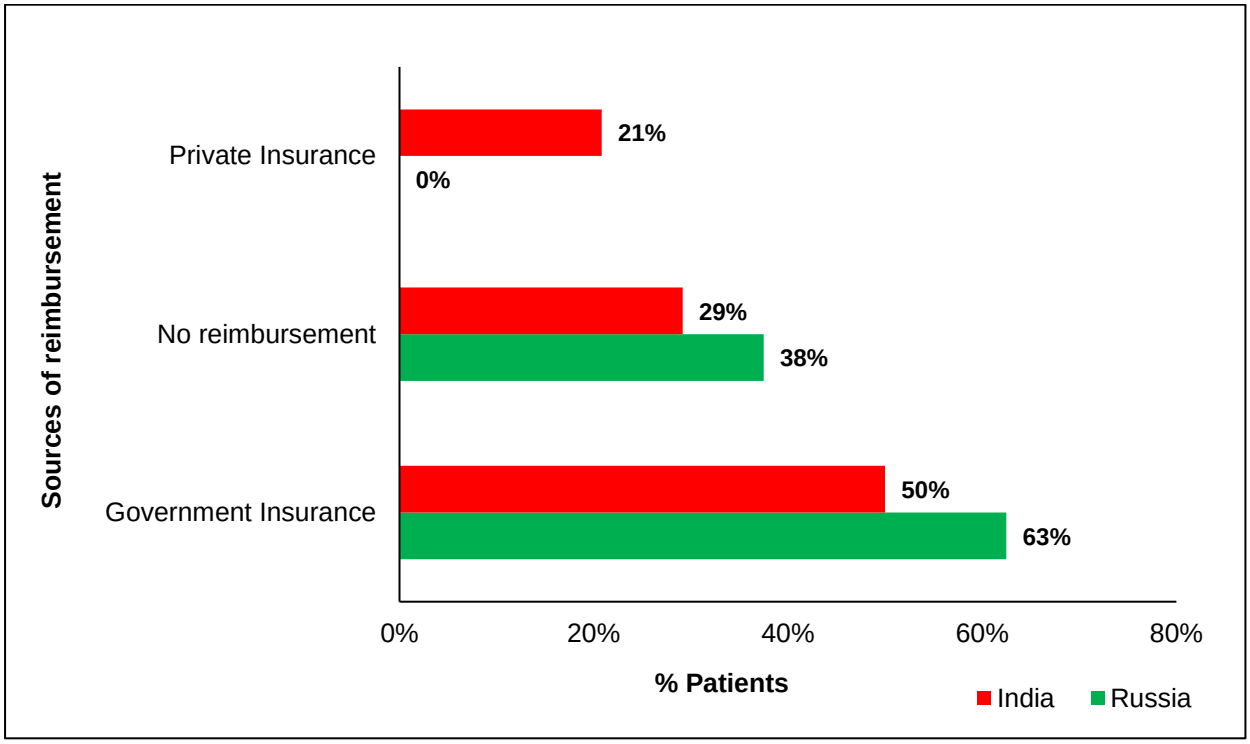
**all percentages have been rounded off to nearest whole number*

Reimbursement and affordability of biosimilars

Affordability of biosimilar medicines was the biggest concern (45%) as revealed from the patient responses, specifically among Indian patients (48%). The Russian patients (78%) admitted that they were able to afford the biosimilar medicines, despite their concern over the high price of biosimilars. Accordingly, majority of the patients undergoing biosimilar therapy reimbursed the cost of treatment through Government Insurance in both India (50%) and Russia (63%). Besides reimbursement from

Government, private insurance also played a pivotal role in reimbursement with 21% Indian patients opting for the same. However, in Russia, there seemed to be no role of private insurance (Figure 8.8) for reimbursing the cost of biosimilar medicines, thus posing a concern for the Russian patients of no alternative reimbursement policies. This is also evident from the patients' satisfaction index with Indian patients (39%) rating the current reimbursement system in their country as 'Excellent', whereas 50% of the surveyed Russian patients, declaring it as 'Not Satisfied'.

Figure 8.8 Sources of reimbursement



**all percentages have been rounded off to nearest whole number*

Solutions offered by the patients

The patients enrolled in this study provided a number of suggestions to overcome the challenges for the uptake of biosimilars. The key suggestions as revealed from the content analysis of patients' feedback in free comments section were related to improving affordability, better reimbursement policies and creating awareness on biosimilars through education (Table 8.2) for the better uptake of biosimilars by patients.

Table 8.2 Key areas of improvement suggested by patients for better access to biosimilars

Improvement areas	Suggestions
Affordability	Reduction in cost of biosimilar therapy for patients
Reimbursement policy	Ensuring implementation of appropriate reimbursement plans/ policies
Knowledge upgradation	Educating/ creating awareness on biosimilars among patients to enhance their knowledge on biosimilars

DISCUSSION

This study has provided a unique insight into the perception of physicians and patient about the prescribing behaviours of biosimilars as well as their acceptability by patients, albeit only from two of the BRICS-TM countries (India and Russia). This study demonstrates that while doctors in India and Russia understand the benefit of and need for biosimilars, there exists a significant knowledge gap. In a study conducted on relevant specialists in Russia, it was found that a significant proportion of Russian physicians across specialties such as rheumatology, gastroenterology, haematology and oncology lack confidence in prescribing biologic therapies for their patients (Karateev & Belokoneva, 2019). The position of the Association of Rheumatologists of Russia regarding the use of biosimilars is to avoid unreasonable switching and/or auto-replacement of the original drug for biosimilar or from one biosimilar to another, especially in so-called stable patients, who have achieved remission of the disease or a stable clinical response to therapy.

Similarity or therapeutic equivalence of biosimilars to the Reference Biotherapeutic Product (RBP) and concerns about manufacturing quality of biosimilars emerged as the major concerns highlighted by prescribers. This is corroborated by an earlier study involving 206 Russian specialists, which reported that the majority of study population felt that availability of clinical study reports should be mandatory for biosimilars and that biosimilars should be subject to rigorous post-marketing surveillance (Karateev & Belokoneva, 2019). This further underpins the clinicians' expectation of gaining complete confidence in the quality, efficacy, safety and immunogenicity of biosimilars (Karateev & Belokoneva, 2019). The role of clinical practitioners should not be overlooked as they introduce biosimilar medicines to patients. It was impressive that

while prescribing biosimilars, they not only focus on pharmacotherapy but also all aspect of pharmaceutical care. Hence while studying pharmacovigilance, practitioners should hold important position in study (Okoro, 2021).

However, global regulatory authorities are moving towards simplifying their approach towards the development and approval of biosimilars (Dalgaard et al., 2013). The 'Step-wise approach' reduces the need for unnecessary studies in cases where there is proven similarity in physicochemical characterisation between the test and reference product (Markenson et al., 2017). Extensive research has been carried out to study the immunogenicity concerns of biosimilars, if switched for the RBP. Several papers have been published on this topic confirming that the risk of immunogenicity is not greater on switching between the RBP and a biosimilar than that of switching between different batches of the RBP itself (Cohen et al., 2018; McKinnon et al., 2018). Further, limited utility of phase III comparative clinical trials for biosimilars has been reiterated in the United Kingdom MHRA's updated guidance on biosimilars (2021) which states that "in most cases, a comparative efficacy trial is not considered necessary" (MHRA, 2021). The gap between regulatory policy making and physicians' expectations further demonstrate the lack of clarity on these products at the prescriber level. Clear local regulatory guidelines establishing the rationale for biosimilar approval would help in establishing the confidence of physicians in these medicines. A uniform standardised guideline tailored stakeholder's communication, once established, will also help with removing patients' concerns about quality, safety and efficacy of these products (Giuliani et al., 2019).

Interchangeability of biosimilars is another key parameter which, if streamlined, can provide significant impetus to the adoption of biosimilars. Interchangeability is a product characteristic which indicates that a medicine can be interchanged for another with no difference in the therapeutic outcomes (Ebbers & Schellekens, 2019). Switching is the exchange of one medicine with another by the prescriber, while substitution is practiced (legally) at the dispensing level of a medicine, designated as interchangeable with another medicine, by the pharmacist without a need for consultation with the prescribing physician (USFDA, 2018b). The non-uniform responses from physicians across both countries indicates the lack of clarity on the concept and guidelines around interchangeability at the local level. While serving as a hurdle to wider adoption of biosimilars, it could act as a safeguard to safety concerns

in situations where improper medicines may be switched or substituted. While the FDA guidance on interchangeability (CDER & CBER, 2019b), outlines the need for dedicated studies to support the interchangeability designation, the EU does not require such trials (EMA, 2019). The regulatory agencies in developing countries will benefit from modeling their policies against the European guidelines, which provide interchangeability designation based on data provided for proving biosimilarity, further supplemented by Good Pharmacovigilance Practices (GVP) for monitoring any safety concerns in the marketplace (Kurki et al., 2017). The Russian national regulatory agency has already established a policy of interchangeability in-line with the EU guidelines without any requirement for post-marketing data (Russian Federation, 2014a).

Majority of the patient group respondents do not have prior knowledge on biosimilars and depend largely on other sources for information. This indicates an overall low awareness level about biosimilars among the patients showing the great need for patient education about biosimilars. An international cross-sectional survey of patient attitudes and understanding about biosimilars among 3198 patients from US and EU also resulted in similar outcome (Jacobs et al., 2016). Less knowledge on biosimilars might create gaps in patients' perceptions on the willingness for the prescribed biosimilar treatment. Patient education to be imparted with some basic information about the regulatory requirements for demonstration of similar efficacy and safety of biosimilars compared with the originator biologic, so that they understand there is no clinically meaningful difference in efficacy or safety between the two treatments and hence can switch to a biosimilar treatment (Jørgensen et al., 2017; Goll et al., 2019).

Biosimilars play a significant role in bringing affordable treatments to market for the access of patients. However, the current study revealed affordability combined with inadequate reimbursement policies and plans as one of the biggest concerns by the patients. The key to lowering drug prices for patients is by increasing competition through more access to safe, affordable biosimilars. The R&D costs for developing biosimilars are significantly high and time for development is extremely long to meet the varying regulatory expectations from different countries. Creating a smarter regulatory pathway not only cuts down the cost of development but also 'time to market' (Chandavarkar, 2016). Implementation of step-wise approach for biosimilar development with science based evaluation would enable a faster and effective

development pathway for the biosimilar developers, with reduced cost and quick launch of products in the market (IGBA, 2020). In addition, reports also show that an understanding of their development and of the regulatory assessment, including requirements for extrapolation of indications (Curigliano et al., 2016) has the potential to reduce the development costs, and thereby increasing access to biosimilars. These strategies are likely to encourage biosimilar developers to bring more biosimilars into the market, leading to competition driven cost reduction of the biosimilars (Patel et al., 2018; Giuliani et al., 2019). Establishing these strategies requires concerted efforts by global regulators and healthcare professionals to minimise development costs through greater harmonisation, mutual recognition and abridged clinical development. Also, increasing effective tender systems that reduce the cost and lead to improved accessibility for patients to be implemented in developing countries, which ultimately will benefit their health and the overall health care system (Kvien, 2020). The hard-hit groups by high prices are the uninsured patients who pay the list price. Implementing effective policies for incentives and reimbursement plans will improve the availability and sustainability of biosimilars in the market (Lexchin, 2020).

SUMMARY AND CONCLUSION

Biosimilars have emerged as the highly effective life-saving drugs for several chronic diseases. However, access to biologic therapies is limited by the cost of biologic medicines, insurance coverage, reimbursement etc. pushing them out of access by patients particularly in developing countries, thereby making them unaffordable. The findings of this study indicate that there is a knowledge and confidence gap in the area of biosimilars amongst prescribers and patients in developing countries. Physicians expect to gain complete confidence in the quality, efficacy, safety and immunogenicity of biosimilars before making the clinical decision to prescribe. Also, there is lack of confidence among the prescribers over switching from original biologic to biosimilar medicine. On the patients front, the biggest challenge appeared to be increased cost of the biosimilars and inadequate insurance and reimbursement policies, limiting the access of these medicines to the patients in developing countries. Establishing simplified and streamlined regulatory guidelines and education campaigns for physicians and patients will help to reassure them of the safety and efficacy of these products. This might lead to faster development of biosimilars at reasonable costs

which in turn will result in price reductions and substantial increase in availability and access of affordable medicines by patients. Broader patient access to biosimilars will contribute to long-term cost savings, enabling resources to fund other treatments and address other healthcare priorities. Therefore, it is important that all stakeholders – manufacturers, regulators, payers, physicians and patients - understand the benefits of having such medicines available on the market. Further studies should examine whether such initiatives would lead to more players entering the biosimilar space with a positive impact on affordability and patients' access.

The key recommendations to the BRICS-TM agencies from this study are:

- National regulatory agencies in BRICS-TM countries should establish platforms for communication with physicians, patients and public in order to instill confidence in the quality, safety and efficacy of biosimilar medicines approved in their respective country
- Healthcare professionals or prescribers should upgrade their knowledge on the biosimilar development and regulatory assessment and approval processes, for better understanding on the concept of interchangeability of biosimilars, thereby impacting the increased availability of biosimilars for the patients to access
- Developers of biosimilars should consider non-commercial education and training such as Continuous Medical Education (CME) to support physicians to build trust in the quality of their products
- Biopharmaceutical industry together with physicians and their professional associations should engage with patient support organisations to enhance awareness of biosimilars among their members, to lead to better acceptance and use of biosimilars among patients
- Professional medical associations should engage in the development of guideline for the appropriate use and application of biosimilars to support their members in their treatment decision-making
- Patient education programs should be developed in partnership with advocacy groups to provide patients with the necessary information to make informed decisions about the use of biosimilars
- Biosimilar regulatory guidelines should be updated across the agencies to consider post-marketing clinical studies for all biosimilars, which would build confidence among the patients and physicians on the use of biosimilars.

CHAPTER 9

Proposed Standardised Model for Improved Regulatory Processes in the BRICS-TM Markets for Biosimilar Approval

INTRODUCTION

The overall global pharmaceutical market is expected to exceed $1.5 trillion by 2023 growing at a compounded annual growth rate of 3–6% over the next five years. In particular, the global biologics market was expected to reach an annual growth rate of 7% over the next 7 years (Coherent Market Insights, 2020a). However, high cost of therapy with original biologics, loss of exclusivity and patent expiries for commonly used biologics have provided the opportunity to develop biosimilars. A 2019 Report from IQVIA Institute of Data Science indicates that by 2023, biosimilar competition in the biologics market will be nearly three-times larger than it is today (IQVIA, 2019a). The biosimilar market is fast-moving and evolving rapidly, with an ever-changing regulatory landscape in both emerging and developed economies. The global biosimilars market was approximately $382 million in 2010 Brice and Toscano (2012) and is expected to reach to $ 55 billion by 2025 (PR Newswire, 2020d). The global biosimilars market share can be broken down into Europe, (45%) the US (15%), and the Rest-of- World (40%) (PR Newswire, 2020d). The uptake of biosimilars in emerging economies is expected to be substantial due to the tremendous unmet medical need of millions of people in these countries (Leintz & Dedhia, 2015). However, this perception might not always be straightforward, as is evident from the data in countries like the Central and Eastern European countries (Kostic M et al., 2017; Pentek M et al., 2017; Baumgart et al., 2019) where the limited price differences between originators and biosimilars in practice limited the uptake of biosimilars or when there is little evidence of switching from originator to its biosimilar (Troein, 2019; Harsanyi, 2020). Also, the different uptake rates for biosimilar might also be impacted by the price reductions by originator company matching biosimilars or concerns with the efficacy/safety of biosimilars and switching promotion to a more concentrated formulation enhancing patient convenience (Godman et al., 2021).

Challenges in uptake of biosimilars

Due to several roadblocks, the global health care system is yet to realize the true benefits of biosimilars. There are significant challenges that persist from the perspective of all the key stakeholders including – industry, regulators, patients and physicians. The biosimilar industry faces multiple challenges to develop and market these complex products (Kent et al., 2017). The manufacturing processes of biologics

is complex and requires specialised expertise and a highly controlled environment. Owing to the need for sophisticated manufacturing facilities, cutting-edge technologies and greater clinical trial requirements, the cost to develop and gain approval for a biosimilar medicine in the United States (US) ranges between $100 to $200 million, as against $1 to $5 million for small molecule generics (Wroblewski et al., 2009). In addition, scientific, legal and regulatory challenges related to biosimilar manufacturing and development explains the cost issues facing biosimilar medicine (Tsiftsoglou et al., 2013; Moorkens et al., 2016). Alongside this, major concerns from clinicians relate to their quality, safety (especially immunogenicity), efficacy (particularly in extrapolated indications), and interchangeability with the originator product (Cohen et al., 2016), although there is a plethora of studies showing similar effectiveness and safety between the originators and the respective biosimilars and the demand for enhanced use of biosimilars (Jørgensen et al., 2017; Godman et al., 2019). Such studies also assist in reducing the Nocebo effects of biosimilar from physicians to patients as discussed in Colloca et al. (Colloca et al., 2019). Further, the innovator company aggressively discounts the originator biologic even upto 89%, for example Abbvie discounting Humira in Netherland (Sagonowsky, 2019) to hold off the biosimilar competitors, making them pull off from the market because of the discounts, thereby retaining market share for its original biologic. Thus, there are multiple facets to create an optimal environment for access to biologic medicines: product development and approval, market authorisation and launch, competitive dynamics and uptake. Different stakeholders play critical roles, and a collaborative action is needed to streamline policies across the spectrum of biosimilar development, approval, commercialisation and use, to maximise the potential of biosimilar medicines and improve health equity for patients at large (IGBA, 2020). Therefore, establishing an efficient regulatory framework is crucial for appropriate evaluation and marketing authorisation of biosimilars (EMA, 2015).

To make full utilization of their availability, effective demand-side and supply-side measures are to be implemented. Limited price reductions by the biosimilar developer can be easily matched by the innovator company and coupled with limited demand side measures can lead to restricted use in practise (Kim et al., 2020; Vandenplas et al., 2021). In contrast, the multiple measures in Italy (Godman et al., 2020) and in Denmark where there was aggressive contracting with biosimilars in the hospitals,

produced significant use and savings (Jensen et al., 2020) and multiple activities in the UK including encouraging new patients to be prescribed biosimilars coupled with procurement activities have resulted in considerable use and savings (Davio, 2018; Tyer, 2019). In higher income countries, savings can also be used to fund more healthcare professionals, to manage patients (Dutta et al., 2020; Vandenplas et al., 2021).

Evolving biosimilar regulations

The European Union (EU) was the pioneer for developing and establishing regulatory requirements for biosimilars in 2005 (EMA, 2005). Following European Medicines Agency's (EMA's) general guideline, World Health Organisation (WHO) guidelines on similar biotherapeutic products (SBPs) published in 2009 (WHO, 2009), represented an important step for harmonisation of the evaluation and regulation of biosimilars, which several countries adopted to elaborate their own guidelines. Later, the US Food and Drug Administration (FDA) published a series of guidance from 2012 to help implement the Biologics Price Competition and Innovation (BPCI) Act. This was an abbreviated pathway to approve biosimilars by demonstration of biosimilarity or interchangeability with the reference product. The agency uses *Totality-of-the-Evidence* (ToE) approach to evaluate the biosimilarity data (CDER & CBER, 2016). Figure 1.5 (Chapter 1) depicts the evolution of biosimilar guidelines across various countries. Most health authorities have subsequently revised and updated biosimilar regulatory norms based on the evolving body of experience.

The developed agencies such as EMA, have clarified many aspects around the regulatory legislation for biosimilars. Also, a majority of emerging economies have regulatory pathways for biosimilars based around the structure and framework established by the WHO (Tsuruta et al., 2015). However, marketing authorisations of these much needed products are often delayed as researchers and manufacturers must work through multiple regulatory requirements to register products across different countries (WHO, 2016a).

Biosimilar regulatory framework in BRICS-TM countries

Emerging economies with low biologic-treatment rates and affordability barriers present attractive opportunities for biosimilars (McKinsey & Company, 2019). The

BRIC (Brazil, Russia, India, China) nations alone account for roughly 30% of production globally (Mminele, 2016). Due to a lack of uniform legal-regulatory standards and processes, biosimilar companies have to develop tailored plans to prove biosimilarity in each country (Tannoury & Attieh, 2017). Variations in regulatory standards also hamper the growth of biosimilars in these countries (The Economist, 2019). To overcome this problem, a regulatory approach is needed to facilitate the requirements for proving quality, safety and efficacy of a biosimilar product. This will also reduce duplication of regulatory efforts of different agencies and lead to a greater access worldwide of more affordable biologics for all patients (IGBA, 2020). Initiatives like 'Prequalification program' by WHO helps to stimulate competition for biosimilars (including those for insulins) (WHO, 2019c) to help lower prices and enhance the use. Also, biosimilar companies are opening up new factories in LMICs to help enhance local/ regional use of biosimilars (Singh, 2019; Godman et al., 2021).

WHO Global Benchmarking Tool (GBT)

The Global Benchmarking Tool (GBT) represents the primary means by which the World Health Organisation (WHO) objectively evaluates regulatory systems, as mandated by World Health Assembly (WHA) Resolution 67.20 (World Health Assembly, 2014) on Regulatory System Strengthening for medical products. The tool facilitates regulatory reliance and harmonisation, which helps to improve timely access to quality-assured medicines (WHO, 2018d; WHO, 2020). The WHO estimates that only 30% of National Regulatory Authorities (NRAs) of its member states have the capacity to effectively and efficiently regulate medical products in their countries (WHO, 2018a). Legal and regulatory frameworks are lacking or fragmented in many low to middle-income countries, which means that the respective NRA may not have the mandate and authority to perform all regulatory functions (Ndomondo-Sigonda et al., 2017). In these countries, when manufacturers of medical products want to bring their products to market, they face a landscape of disparate regulations, unclear regulatory pathways, frequent delays in accessing essential medicines and limited transparency. For instance, Agência Nacional de Vigilância Sanitária (ANVISA, Brazil) biosimilar guideline is based on the WHO and EMA guidelines (Chauhan & Malik, 2016). Russian MoH biosimilar guideline is similar to EMA and USFDA guidelines (Welch, 2017). The Central Drugs Standard Control Organisation (CDSCO, India)

similar biologics guideline is based on the WHO, EMA and USFDA guidelines (Jois et al., 2020). The South African Health Products Regulatory Authority (SAHPRA, South Africa) biosimilar guideline is in line with WHO and EMA (Leng et al., 2015). The Türkiye İlaç ve Tıbbi Cihaz Kurumu (TITCK, Turkey) biosimilar guideline follows EMA practice and directive (Ucer et al., 2021). The Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS, Mexico) biocomparable guideline is partially aligned with ICH and WHO (Lopez-Morales et al., 2018). The WHOs GBT will serve as a global standard for assessing and strengthening the NRAs.

OBJECTIVES

The aim of this study is to conceptualise, design and propose a standard regulatory model for biosimilars development and approval, to be adapted by BRICS-TM agencies for simplifying the biosimilar regulatory framework. The development of the proposed model was based on the evaluation of the outcomes and recommendations from five studies (Chapter 3, 4, 5, 6, 7, 8) conducted by the authors during the past four years.

METHODS

In order to get a detailed understanding of the challenges and opportunities associated with the biosimilars regulatory framework in BRICS-TM countries, five studies were carried out as follows:

Study 1 - The aim of this study was to identify, critically evaluate and compare the current biosimilar development guidelines between mature agencies (EMA, Europe; WHO; USFDA, USA; BRDD, Canada; TGA, Australia; Swissmedic, Switzerland) and emerging regulatory agencies (BRICS-TM) to identify gaps. The current valid guidelines of EMA, WHO, USFDA, HC/BRDD (Biologic and Radiopharmaceuticals Drugs Directorate, Health Canada), ICH, TGA (Therapeutic Goods Administration, Australia), Swissmedic and BRICS-TM (Brazil, ANVISA; Russia, MoH; India, CDSCO; China, NMPA; South Africa, SAHPRA; Turkey, TITCK; Mexico, COFEPRIS) were obtained from their official websites and a comparative qualitative review was performed. The reviewed guidelines were those published between November 1995

and December 2020. Further details on the methods can be found in Chapter 3 and 4 (Rahalkar et al., 2018).

Study 2 - The aim of this study was to identify, interpret and compare the current perspectives of regulatory agencies in BRICS-TM (Brazil, Russia, India, China, South Africa, Turkey, Mexico) countries on the different criteria used for biosimilar development and authorisation processes. A semi-quantitative questionnaire (Biosimilar Development, Evaluation and Authorisation - BDEA) was developed covering organisation of the agency, the agency's approach on biosimilar development and the authorisation process. Seven regulatory agencies covering the BRICS-TM countries were invited to take part and enrolled into the study. The complete details on the methods used for the study can be found in Chapter 5 (Rahalkar et al., 2021c).

Study 3 - The aim of this study was to compare and evaluate the viewpoints of regulatory agencies in BRICS-TM and ACSS (Australia, Canada, Switzerland and Singapore) countries on various aspects of biosimilar development and authorisation processes. This comparative study was performed to benchmark best practices and identify key areas for improvement in the regulatory processes followed by BRICS-TM agencies and serve as a basis for standardisation of regulatory norms. A semi-quantitative questionnaire (a modified version of the BDEA) was developed based on published literature covering different criteria for the biosimilar development and authorisation process. Eleven regulatory agencies (seven BRICS-TM and four ACSS countries were considered for this comparative study. The details of the study can be found in Chapter 6 (Rahalkar et al., 2021b).

Study 4 - In this study, exploratory research was carried out to identify challenges faced by the biopharmaceutical industry in the BRICS-TM countries relating to biosimilar development and the regulatory approval process. A semi-quantitative questionnaire was designed based on published literature - Biosimilar Development, Submission and Review (BDSR). The BDSR questionnaire consists of four parts: general information on biosimilar experience of the company; challenges with regulatory review/approval process and suggestions on areas for improvement; challenges related to biosimilar development and suggestions on areas of improvement; and concerns faced by the industry in the area of biosimilar pricing and access. A total of 93 industry personnel and representatives from 14 trade associations

from the BRICS-TM countries were identified and invited to take part in the questionnaire-based study. Upon completion of the questionnaire, the respondents were interviewed face-to-face and the responses were recorded verbatim. Such interviews were conducted to verify the validity of the responses to the questionnaire. Following validation of the responses, the data processing and analysis was carried out. Further details on the methods can be found in Chapter 7 (Rahalkar et al., 2021a).

Study 5 - This study was carried out to identify barriers to the uptake of biosimilar medicines by physicians(prescribers) and patients in developing countries. The aims of this study were to understand the biosimilar prescribing habits of physicians and the factors driving their choice of product; to learn about their views on biosimilar interchangeability, switching and substitution; to gauge their perception of the safety and efficacy of a biosimilar compared to the original biologic and identify the challenges pertaining to biosimilars, including access and affordability for patients. A self - administered Biosimilar Physician Questionnaire (BPQ) was developed for BRICS-TM countries. The BPQ was administered through both online physician groups and individual e-mails through direct contact across BRICS-TM countries. A total of 119 independent physicians or clinicians were contacted directly, and 19 medical associations were approached. In addition, a short, self-administered and patient-friendly Biosimilar Patients' Access Questionnaire (BPAQ) was developed based on information from the literature. The BPAQ was intended for use on social media platforms and was also sent to patient organizations across BRICS-TM countries. Further details are in Chapter 8.

Data processing and analysis

Data processing and analysis was carried out using Microsoft excel and the Statistical Product and Service Solutions (SPSS) analytical software; descriptive statistics (i.e. mean, standard deviation, median, range and mode) were used for quantitative data. For qualitative data (for instance, content of the interview transcripts), thematic analysis was applied to generate common themes (i.e. topics, ideas and patterns of meaning) and sub-themes.

RESULTS

For the purpose of clarity, the results from the five studies are presented in two parts: Part I – Overall study results; and Part II- Critical outcomes of the five studies.

Part I - Overall study results

Study 1 – This secondary research on the identification and evaluation of gaps and comparison of regulatory guidelines of advanced regulatory agencies such as EMA, USFDA, WHO, BRDD, TGA and Swissmedic Switzerland and emerging agencies (BRICS-TM) indicated a need for primary research to verify the gaps and provide the basis for a proposed standardized model for implementation across BRICS-TM agencies for biosimilar development and approval. The complete results are available in Chapter 3 and 4 (Rahalkar et al., 2018).

Study 2 – This study emphasized the need for joint review model for data assessment to foster effective collaboration between regulators and developers in BRICS-TM countries. There was a lack of standard approach across the agencies for sourcing of reference biological product. The study also revealed the need for step-wise approach and tailored scientific advice from the regulatory agencies to reduce unnecessary studies such as *in vivo* non-clinical studies. The mandatory requirement on clinical efficacy studies by all the agencies revealed the lack of science-based assessment of the product. The detailed results can be found in Chapter 5 (Rahalkar et al., 2021c).

Study 3 - This comparative study revealed preference of locally sourced RBP over foreign reference products by most of the BRICS-TM agencies without any flexibility in regulatory norms for sourcing the RBP from other emerging countries. All these regulatory agencies expected clinical study data as part of the biosimilar application, with some agencies also mandating data from the local population. There was lack of scientific approach for the assessment of biosimilar application for a tailored clinical development programme based on advanced analytical science to avoid conducting confirmatory clinical trials in the local population. Most of the BRICS-TM agencies opted for a full review of marketing authorisation applications with few exceptions, leading to duplication of efforts. In comparison with the mature agencies of ACSS consortium, agency interaction by the biosimilar developers through scientific advice was lacking. Physical GMP inspection of the biosimilar manufacturing facilities was a

prerequisite for approval of biosimilars in the emerging countries unlike the desktop or remote audit in mature agencies of ACSS. The detailed results are as described in Chapter 6 (Rahalkar et al., 2021b).

Study 4 - The industry participants reported several challenges in the biosimilar development process such as expectations on sourcing of RBP and confirmatory clinical trials, lack of a transparent implementation of a stepwise approach, unnecessary toxicity studies, absence of abridged review pathway as key hurdles for biosimilar development. It was also perceived that the biosimilar guidelines and review processes as being protracted and in a state of evolution. The complete details of the results are as described in Chapter 7 (Rahalkar et al., 2021a).

Study 5 - This questionnaire-based study consisting of 58 physicians and 229 patients from India and Russia demonstrated that while doctors in India and Russia understand the benefit of and need for biosimilars, there exists a significant knowledge gap in the area of biosimilar medicines. While they understand the importance of improving patients' access to biological therapies, they expect to gain complete confidence in the quality, efficacy, safety, and immunogenicity of these medicines to underpin their decision to prescribe them. Similarity or therapeutic equivalence of biosimilars to the RBP and concerns about manufacturing quality of biosimilars emerged as the major concerns highlighted by prescribers. The non-uniform responses from physicians across both countries indicates the lack of clarity on the concept and guidelines around interchangeability at the local level. The results from the patient cohort showed that increased affordability of these medicines is the single biggest factor that would greatly influence their higher uptake. Majority of the patient group respondents did not have prior knowledge on biosimilars and depended largely on other sources for information, indicating an overall low awareness level about biosimilars among the patients showing the great need for patient education about biosimilars. The complete details of the results are as described in Chapter 8.

The summary of the five studies and their results are provided in Table 9.1.

Table 9.1 Summary of the studies and recommendations used for the development of a proposed standardized regulatory model

Study Number	Study objective	Method used	Study outcome	Study Recommendations	Study impact
Study 1 (Rahalkar et al., 2018)	Identify, critically review and compare current regulatory guidelines pertaining to biosimilar development between mature agencies (EMA, Europe; WHO; USFDA, USA; BRDD, Canada; TGA Australia; Swissmedic Switzerland) and emerging agencies (BRICS-TM) to identify gaps.	Retrieval of current and valid regulatory guidelines including questions and answers documents from the official websites of the respective regulatory agencies.	• BRICS-TM agencies partially implement WHO SBP guidelines whereas TGA and Swissmedic guidelines primarily follow EMA. • Non-reference authorized product selection is limited to ICH /own aligning countries with no clarity on bridging studies in BRICS-TM countries whereas such transparency exists with TGA and Swissmedic. • Non-clinical studies including immunogenicity toxicity studies need explicit clarity in BRICS TM countries. • Confirmatory Phase III clinical safety and efficacy trials are mandatory in some of the BRICS-TM countries.	The outcome from Study 1 indicates a need for primary research to verify the gaps and provide the basis for a proposed standardized model for implementation across BRICS-TM agencies for biosimilar development and approval.	Likely to aid in identification of differing regulatory requirements for biosimilars in emerging agencies and may serve as a platform for further research.
Study 2 (Rahalkar et al., 2021c)	• Evaluate and compare technical capabilities of the BRICS-TM regulatory agencies in the area of biosimilars,	A semi-quantitative questionnaire, Biosimilar Development, Evaluation and Authorization (BDEA) was developed, comprising three sections: Part I-Organization of Agency, Part II - Agency's view on biosimilar development	• Inadequate resources and subject matter expertise • Full review model of MAA was the most prevalent and less reliance on Type I (i.e., verification) and Type II model (i.e., abridged)	• Employing abridged review or verification review • Establishing scientific advisory meetings to avoid duplication of work.	• This study emphasizes the need to foster effective collaboration between regulators and developers in BRICS-TM countries in order to streamline

Study Number	Study objective	Method used	Study outcome	Study Recommendations	Study impact
	• Identify similarities and differences in regulatory requirements of biosimilar development criteria i.e., biosimilarity principles, comparative studies including physicochemical characterization, non-clinical and clinical studies, • Evaluate and compare "must submit documents" as part of biosimilar application for marketing authorization in BRICS-TM countries, • Map the biosimilar marketing authorization approval pathway specifically for the key milestones, scientific advice meetings, clinical trial mandates and backlogs.	criteria, Part III - Marketing authorization approval pathway. The study participants were representatives from the BRICS-TM regulatory authorities. The electronic self - administered BDEA was completed by all study participants and followed up by a face-to-face or virtual meetings after receipt of the completed questionnaire.	• Varied expectations for local / global clinical efficacy studies • Varied expectation for Reference Biologic Product (RBP) sourcing limited opportunity for multi-country development. • Criteria to define biosimilar analytical specifications were partially aligned with the WHO guidelines.	• Acceptance of RBP from other emerging countries and clarity in guidelines for the specific number of lots to be used for comparability. • Exempting clinical efficacy studies in local population	the development strategies and approval pathways for biosimilar products.

Study Number	Study objective	Method used	Study outcome	Study Recommendations	Study impact
Study 3 (Rahalkar et al., 2021b)	• Identification of regulatory framework for the ACSS regulatory agencies, • To identify resources of the agencies in the biosimilar domain, • To identify biosimilar development criteria i.e., biosimilarity principle, comparative studies including physicochemical characterization, non-clinical and clinical studies, • To identify the biosimilar marketing authorization approval pathway specifically for key milestones, scientific advice meetings, clinical trial mandates, backlogs etc. • Comparative evaluation of the BRICS-TM regulatory frameworks with ACSS to identify challenges and areas for best practices.	A semi-quantitative questionnaire, Biosimilar Development, Evaluation and Authorization (BDEA) used in Study 2 was slightly modified to suit the ACSS agencies. The study participants were representatives from ACSS regulatory authorities. The electronic self -administered BDEA was sent completed by all the study participants and followed up by a face-to-face or virtual meetings after receipt of the completed questionnaire.	• Insignificant subject matter expertise in the BRICS-TM agencies compared to ACSS. • The BRICS-TM agencies are yet to establish international collaboration to enhance efficiency and reliance on review performed by other agencies. • Biosimilarity principle of the BRICS-TM were largely aligned with ACSS, but the key challenge appeared to be the need for local clinical trials, required by some of the BRICS-TM countries. • The ACSS agencies showed flexibility for using non-authorized reference product. ANVISA and Russia MoH preferred to have locally authorized reference product as part of the development. • No clarity on bridging study with each of the BRICS-TM agencies. • In-vivo toxicity studies data was essential for BRICS-TM agencies. • Russia MoH, CDSCO and COFEPRIS expected local clinical studies to be performed.	• Acknowledging joint or shared review for data assessment. • Provision of pre-submission advice to avoid duplication of work. • Acceptance of RBP from other emerging countries and clarity in guidelines for the specific number of lots to be used for comparability. • Reducing or eliminating *in vivo* non-clinical studies and confirmatory clinical efficacy studies in local population. • Provision to use alternative proof for MA confirmation such as agency website, MA certificate etc. instead of CPP. • Flexibility for accepting desktop GMP audit.	This study emphasizes the need for reliance models for joint or shared review process of marketing authorization applications with other comparable agencies on a risk-based approach.

Study Number	Study objective	Method used	Study outcome	Study Recommendations	Study impact
Study 4 (Rahalkar et al., 2021a)	Identify the challenges faced by the biopharmaceutical industries in the BRICS-TM countries pertaining to biosimilar development and the approval processes including concerns for pricing and market access.	A semi-quantitative questionnaire, Biosimilar Development, Submission and Review (BDSR) consisting of four parts was prepared: Part I - General information on biosimilar experience of the company; Part II – Challenges in biosimilar regulatory approval process and suggestions on areas for improvement; Part III - Challenges pertaining to biosimilar development and suggestions on areas for improvement; and Part IV - concerns faced by the industry in the area of biosimilar pricing and access. A total of 93 industry senior staff and representatives from 14 trade associations in the BRICS-TM countries were identified and invited to take part in the questionnaire-based study. Upon completion of the questionnaire, the respondents were interviewed face-to-face and the responses were recorded verbatim. Such interviews were conducted to verify the validity of the responses to the questionnaire. Following validation of the responses, the data processing and analysis was carried out. Further details on the methods	• The industry personnel perceived biosimilar guidelines and approval processes as being protracted and in a state of evolution. • Limited effectiveness of regulatory process due to absence of abridged approval pathway • Expectations on sourcing of RBP and confirmatory clinical trials were reported as key hurdles for development. • The lack of a transparent implementation of a stepwise approach resulted in unnecessary toxicity studies.	• The regulatory agencies in the BRICS-TM countries should consider timely provision of appropriate tailor-made and binding scientific advice to companies engaged in biosimilar development. This should also be extended to clinical studies, if applicable. • The regulatory agencies should consider adopting shared evaluation, reliance and abridged regulatory review models for biosimilars. • The regulatory agencies should consider moving towards a stepwise approach to development and mandate non-clinical data only in the cases where it is fundamentally required. • The regulatory agencies should consider accepting advanced analytical comparability data in lieu of confirmatory clinical studies. • Regulatory agencies should consider accepting RBP sourcing from BRICS-TM	This study delves into the understanding and perception of the experts in the biosimilar industry regarding the efficiency and effectiveness of current regulatory processes for biosimilar products and offers recommendations on potential improvements in this area.

Study Number	Study objective	Method used	Study outcome	Study Recommendations	Study impact
		can be found in Rahalkar et al., 2021a		countries other than their own, with a waiver of bridging studies to ease availability of multiple RBP lots and in order to facilitate common development programmes. • Regulatory agencies should consider standardizing the number of RBP lots for development and establish a source for the timely supply of RBP with varied drug substance lots.	

Study Number	Study objective	Method used	Study outcome	Study Recommendations	Study impact
Study 5	• Understand the biosimilar prescribing habits of physicians and the factors driving their choice of product. • To learn about their views on biosimilar interchangeability, switching and substitution. • Gauge their perception of safety & efficacy of a biosimilar compared to the original biologic. • Identify the challenges pertaining to biosimilars, including access and affordability for patients	A self -administered Biosimilar Physician Questionnaire (BPQ) and a Biosimilar Patients' Access Questionnaire (BPAQ) were developed for the BRICS-TM countries. The BPQ was grouped into three parts (Part I = physicians' perspective of their practice; Part II = physicians' views of patients' perspective; and Part III = barriers and solutions to patients' access to biosimilars). The BPQ was administered through both online physician groups and individual practitioner's e-mails. Completed questionnaires were obtained from 58 physicians. The 14 items Biosimilar Patient Access Questionnaire (BPAQ) was used on social media platforms and also with patient organizations. A total of 220 responses were received from patients.	• Knowledge gap on biosimilars at prescriber level • Lack of clarity on similarity or therapeutic equivalence of biosimilars to the Reference Biologic Product (RBP) • Concerns on quality of biosimilars at physician and patient level • Lack of clarity on the concept and guidelines around interchangeability among physicians • High price of biosimilar therapy and inadequate reimbursement from insurance partners	• Regulatory agencies of the countries studied should establish platforms for communication with physicians in order to instill confidence in the quality, safety and efficacy of approved biosimilar medicines. • Developers should consider non-commercial education and training to support physicians to build trust in the quality of their products. • Biopharmaceutical industry together with physicians should engage with patient support organizations to enhance awareness of biosimilars. • Professional medical associations should engage in the development of guideline for the appropriate use of biosimilars	This research is significant as it specifically provides insights on the barriers faced by physicians and patients in India and Russia, representing developing countries with a large unmet need for these life-saving medicines.

Part II - Critical outcomes from the studies

The following outcomes from the five studies are deemed to be critical for building a regulatory model for an improved biosimilar development and authorization process. The rationale for considering each of these outcomes for developing a proposed model is explained below.

Acceptance of Reference Biologic Product (RBP) from BRICS-TM countries

The Study 2 revealed that the expectations on sourcing multiple lots of RBP with varied expiry dates extends the timeline for biosimilar development. Further, Study 2 showed some agencies accepting RBP that were foreign-licensed and sourced, whereas others required a locally licensed reference product, without any clarity on bridging studies. Such preferences for locally authorized RBP were more prevalent in emerging economies in comparison with mature agencies, as revealed in Study 3. Also, the sourcing of a RBP was identified as a major challenge during a biopharmaceutical industry survey performed between March – October 2020 in BRICS-TM countries (Study 4). Non-leveraging on the use of authorised RBPs (innovator product) sourced from other emerging economies for similarity studies as revealed from the current research, could restrict the overall biosimilar development programme for the emerging economies and likely to impact the time to market.

Elimination of mandatory animal toxicity studies

In Study 2, the *in vivo* non-clinical studies, specifically, repeat dose toxicity study was mandated by all the BRICS-TM agencies for biosimilar development, in addition to analytical comparability and other in vitro functional studies. Such expectations on animal studies were also mandated as necessary as perceived by the biopharmaceutical companies in Study 4. The BRICS-TM agencies expect complete comprehensive comparability data consisting of physicochemical characterization, in vitro and in vivo non-clinical studies and clinical efficacy studies. This indicates a lack of a stepwise approach for demonstrating biosimilarity leading to the unnecessary animal toxicity studies and clinical efficacy studies, thus impacting the overall development cost and timelines.

Science based approach for confirmatory clinical studies

Acceptance of advanced analytical comparability data in lieu of clinical efficacy studies
The Study 2 revealed the clinical efficacy study data as prerequisite by all the BRICS-TM countries despite the provision of comprehensive analytical comparability data to the agencies. This contrasts with the representatives of mature agencies of ACSS as in Study 3. Requirement of such confirmatory clinical trials were reported as key hurdles for biosimilar development by the participants in Study 4.

Removal of requirement for local clinical studies
The acceptance of global clinical data (or foreign patient data) varied with the agencies. Such varying regulatory frameworks on clinical studies across the BRICS-TM agencies is apparent from the outcomes of Study 2 and Study 3. For instance, CDSCO, Russia MoH and COFEPRIS do not accept foreign patient data and mandate the repeat of confirmatory clinical studies in the local population. This kind of duplication of studies and not adopting “reliance” approach is likely to add to unnecessary development costs, restricting the overall biosimilar development process and delaying patients’ access. Substantiating this viewpoint, Study 4 revealed cost implications for conducting clinical studies as one of the key challenges perceived by biosimilar developers.

Adequate scientific advice

Scientific advice supports pharmaceutical developers in facilitating the development of safe and effective new medicinal products. In Study 4, more than 50% of the industry respondents indicated lack of scientific advice or inadequate advice from the agencies during biosimilar development, thus, resulting in inadequate communication channels between the industry and the agency to address such hurdles. Moreover, in Russia, there is no system in place for scientific advice meetings and all interactions of biosimilar manufacturers with the government are through written communications (Tyer, 2019). Also, absence of scientific advisory meetings in Turkey has been highlighted in an earlier study (Chauhan & Malik, 2016) where the importance of implementing such an interaction with the agency was emphasized to improve the agencies’ transparency and communication process.

GMP Verification

The BRICS-TM agencies are aligned with the global approach for following GMP standards, which is clear from the agencies' mandate for on-site inspections as shown in Study 2 and 3. Although CDSCO, SAHPRA and COFEPRIS consider GMP certification from some or all of the reference agencies (EMA, BRDD, MHRA, USFDA, TGA) as acceptable instead of on-site inspection, such flexibility does not exist with ANVISA, Russian MoH and the TITCK. In addition, there is no recognition of the GMP certification of other emerging regulatory agencies. This might result in additional time and resources for repeated inspections, leading to an extended time or delay in approval of products.

Regulatory reliance or joint review models

The absence of a verification review and an abridged review pathway for biosimilar approval in the BRICS-TM countries is evident from Studies 2, 3 and 4. Full review model of marketing authorization application was the most prevalent among these regulatory agencies with less reliance on Type I (i.e., verification) and Type II model (i.e., abridged), as revealed from Study 2. This was also evident from Study 3 which showed that the BRICS-TM agencies are yet to establish international collaboration to enhance efficiency through reliance on review performed by other agencies. Study 4 outcomes revealed the limited effectiveness of regulatory process due to absence of abridged approval pathway among the six regulatory agencies of BRICS-TM.

Enhancing biosimilar education

Study 5 provided a unique insight into the perception of physicians and patients about prescribing behaviours of biosimilars as well as their acceptability by patients, from two of the BRICS-TM countries (i.e., India and Russia). This study demonstrated that while doctors in India and Russia understand the benefit and need for biosimilars, there exists a significant knowledge gap. Further, similarity or therapeutic equivalence of the biosimilar product to the RBP, and concerns on the quality of biosimilars emerged as a major reluctance on the part of the prescribers, which points towards lack of their confidence in the quality, efficacy, safety and immunogenicity of biosimilars. On the other hand, despite patients' willingness to accept biosimilar medicines, the high price

of biosimilar therapy and inadequate reimbursement from insurance partners were perceived as the biggest challenge by the patients.

Issuance of Public Assessment Reports

In an effort to ensure transparency, few National Regulatory Agencies (NRAs) release Public Assessment Report (PAR) specifying scientific consideration for the approval of medicines (Raynor & Bryant, 2013) and such reports are available on the agency website. It covers the widest possible data to be referred by the pharmaceutical industry, other health authorities, healthcare professionals and patients while respecting the privacy of personal data and confidential commercial information (Papathanasiou et al., 2016).

Study 3 revealed that PARs are issued by mature agencies such as TGA (AusPAR) and BRDD, Canada for biosimilar products. Further, PAR from Swissmedic (SwissPAR) (Swissmedic, 2021), though issued only for new active substances, was made available for biosimilars upon request. Hence, PARs are produced by the majority of mature NRAs but are not widely produced by NRAs in emerging economies (IFPMA, 2020). Study 2 revealed that among the BRICS-TM emerging regulatory agencies, only ANVISA, Brazil publishes an equivalent document to PAR on their website. Such assessment reports are planned to be issued by CDSCO, India whereas there is not much clarity with other BRICS-TM agencies.

DISCUSSION

Introduction of biosimilars into the global marketplace becomes more challenging as it involves many stakeholders; regulators, industry, payers, pharmacists, and physicians who need to have adequate knowledge to be effective players in this process (GaBI, 2021c).

A WHO survey results of 20 countries has identified that many of the challenges for performing comparability studies is related to reference biologics. In particular, the challenges included, limited access to information on the reference biologic, financial constraints due to the costs of these, and difficulty of obtaining reference biologic samples to assess comparability (Ferreri, 2020). Challenges in RBP sourcing were also revealed through this study. To mitigate these challenges, the BRICS-TM

agencies might have to consider expanding their list of reference agencies by including other emerging and ACSS countries (where the innovator product is already authorised) in the list to source RBP for biosimilar development. This would ease the RBP sourcing process and would ensure the timely availability of RBP at reasonable cost. Provision of such flexibility in sourcing RBP would also assist the biosimilar developers to significantly improve the efficiency of biosimilar development. A similar approach towards adoption of a “global reference” product for biosimilar development has been suggested earlier (Webster & Woollett, 2017). This is in line with WHOs recommendation on acceptance of foreign-sourced reference products and avoiding unnecessary bridging studies based on information-sharing processes with other regulatory authorities (Ferreri, 2020). Also, the current study recommends agencies to amend the biosimilar guidelines in terms of defining the number of RBP batches required for comparability studies and clarify the requirements on bridging studies which would assist the developers in planning their development studies.

In general, the non-clinical animal studies are considered as an integral part of a biosimilar development programme to demonstrate similarity and safety. The current study also revealed the necessity of conducting animal toxicity studies as part of the biosimilar development. Often companies designing global development programmes are required to be flexible to accommodate differing specifications for non-clinical (*in vitro* and *in vivo*) biosimilarity from different jurisdictions (Welch, 2016a). However, there is an increasing need to re-assess the relevance of *in vivo* animal studies to support regulatory approval of biosimilars. In a study of 23 US biosimilar approvals prior to November 2019 (Moore et al., 2021), there were total of 51 animal studies, using animals such as mice, rats, rabbits, dogs, and macaque monkeys. Although animal studies are required by the Biologics Price Competition and Innovation (BPCI) Act for a biosimilar to receive approval, investigators found that animal studies did not appear to provide useful scientific information given that human data were available both for the reference product and in clinical trials for the biosimilar product (Moore et al., 2021). In contrast, animal studies are not mandated by the European Medicines Agency (EMA) for a biologic to be approved as per Directive 2010/63/EU, effective since January 2013 which anchors the principle of the “Three Rs” to Replace, Reduce and Refine the use of animals, in EU legislation (EMA, 2010). According to this Directive, the use of animals for scientific or educational purposes should only be

considered where a non-animal alternative is unavailable (preamble 12) and Member States shall ensure that, wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, is used instead (Article 4.1). Moreover, non-human primates (NHP) are exempted from use in animal studies whenever possible. This is reflected in Article 8.1(b) as there should be scientific justification that the purpose of the animal study cannot be achieved using species other than NHPs. In contrast to the agency's earlier requirement on a non-clinical package for biosimilar development consisting of comparative studies, including a pharmacodynamic study (bioassay) and a repeated dose toxicology study (van Aerts et al., 2014), this new paradigm of obviating the need for animal studies, in most cases is by a thorough step-wise approach of testing.

The stepwise approach is used to evaluate the unjustified differences or residual uncertainties at each step of development between the proposed biosimilar product and the reference product and address these differences in subsequent development. This approach is prevalent with mature agencies such as EMA, TGA, Swissmedic and BRDD. Considering that animal studies are of low sensitivity for detecting subtle differences between the biosimilar and reference product, species differences between animals and humans limit the suitability of this approach to evaluate biosimilarity. Instead, functional properties of the biosimilar can be tested and compared in vitro, which are generally more sensitive than animal studies. Studies in species other than humans are neither necessary nor definitively informative in the development of biosimilars but are wasteful and involve the use and killing of sentient creatures (van Aerts et al., 2014; van Meer et al., 2015). The 'step-wise approach' has been considered to reduce the need for unnecessary studies such as animal toxicity studies in cases where there is proven similarity in physicochemical characterization between the test and reference product (Markus et al., 2017; Markenson et al., 2017). Therefore, BRICS-TM agencies should consider revising their guidelines to embrace full implementation of step-wise approach and thereby expect animal toxicity studies only when absolutely necessary. In cases, where residual uncertainties exist between the biosimilar and reference product that might cause potential efficacy or toxicity concerns, an informative animal model must be available for such studies to take place (Isaacs et al, 2017). The BRICS-TM agencies should align the regulatory standards of such studies with mature agencies such as EMA which would support a mutually

consented development program. Full implementation of a step-wise approach will enable a faster and effective development pathway for the biosimilar developers, with reduced cost and faster launch of products in the market, improving affordability and patient's access.

The mainstay for the establishment of biosimilarity is the pharmaceutical comparability based on extensive physicochemical and biological characterization (van Aerts et al., 2014). Unlike the small molecules, biosimilars are large and highly complex molecules, easily affected by the changes in the manufacturing process. Hence it is very essential to conduct comprehensive analytical studies to demonstrate that structural and functional characteristics are similar to the innovator product. In contrast to the innovator product, where the emphasis is to demonstrate safety and efficacy in clinical trials, biosimilar development focuses predominantly on in-depth analyses to confirm that the product is identical to the originator in terms of structure, composition, and *in vitro* activity (Carney et al., 2017) to meet the requirements of regulatory agencies. The biosimilar manufacturer must first show that the biosimilar is identical to the innovator product in terms of primary structure followed by more challenging demonstration of identity in terms of higher order (secondary, tertiary, and quaternary) structures. The details on the expectations from regulatory agencies of BRICS-TM on physicochemical characterization as explained in Chapter 5 (Rahalkar et al., 2021c) are presented in Table 9.2.

The parameters listed in Table 9.2 are the critical quality attributes of a biological drug that can affect clinical safety and efficacy (Isaacs, et al., 2017). The purpose of a clinical trial comparing a biosimilar with its innovator is to reduce residual uncertainty following extensive analytical, *in vitro* and pharmacokinetic analyses. Efficacy of the innovator's product had already been proven in the pivotal clinical trials that were conducted to gain regulatory approval and by subsequent experience in clinical practice. Thus, if equivalence of the biosimilar to its innovator can be demonstrated, there is no need to re-establish its clinical benefit (Kay & Isaacs, 2017). The current clinical development model of biosimilars is expensive, and in most cases, large, phase 3 trials do not provide meaningful information on the clinical equivalence of biosimilars and reference compounds. At the same time, the development of state-of-the-art orthogonal analytical methods has enabled a better understanding of the structure and structure–function relationship of biotherapeutics (Frapaise, 2018).

Table 9.2. Summary of Physico-chemical characterization requirements for mAb

	ANVISA	Russian MoH	CDSCO	SAHPRA	TITCK	COFEPRIS
Biological activity (*in-vitro/ in-vivo* assay tests) Binding assays, Enzymatic assays, Cell based assays, Function based assays	✓	✓*	✓	✓	✓	✓
Comparative Characterization of proposed biosimilar structure	✓	✓	✓	✓**	✓	✓
Immunological properties essential for comparative characterisation • Antigen binding assay (including affinity, avidity and immunoreactivity) • Cytotoxic evaluation for unintended target tissue (CDC and ADCC activity) • Cross-reactivity determination • CDR identification • Epitope characterization (including biochemical identification and determination of epitope with bearing molecule • Complementary ability evaluation (Evaluation of binding and activation and/or effector functions)	✓	✓	✓	✓***	✓	✓
• Product effector functions to be characterised • ADCC, Complement binding ability, Cytotoxic properties, Fc-gamma receptor binding activity and neonatal receptor binding activity	✓	✓	✓	✓	✓	✓
• Orthogonal methods • For purity, impurity and contaminants characterisation	✓	✓	✓	✓	✓	✓
• Impurities and other analyses • Purity, Contaminants, Structural heterogeneity, multimers, aggregates and particulate matter, impurity profile and other process related impurities required across countries	✓	✓	✓	✓#	✓	✓

except enzymatic assays; **groups & bridges not defined; * only Ag binding assay and CDC/ADCC considered; #pH, Osmolality also required; CDC: Complement Dependent Cytotoxicity; ADCC: Antibody Dependent Cellular Cytotoxicity; CDR: Complementarity Determining Region*

The higher relevance of advanced analytical science to prove comparability in place of confirmatory clinical data is emphasized in the policy paper from IGBA (IGBA, 2020). Further, this is substantiated by the records of marketing applications for biosimilars in the EU, US, Canada, and Australia, which shows that no biosimilar that has been found to be highly similar to its reference by both analytical and human pharmacokinetic studies has been rejected due to unproven clinical equivalence to its reference product (Webster et al., 2019). For instance, the FDA has licensed 26 biosimilar products, for seven of which multiple clinical efficacy testing was conducted. The FDA has licensed erythropoietin, pegfilgrastim, and filgrastim products without requiring comparative efficacy testing. An examination of the European public assessment report (EPAR) guidance on 84 authorized biosimilars, in which two applications were rejected and 34 withdrawn, convinced the EMA that some biosimilars do not need clinical efficacy testing (e.g., teriparatide, insulins, low-molecular-weight heparins, filgrastim, and pegfilgrastim and other cytokines with PD markers). Some products would not even need safety assessments, such as teriparatide, low-molecular-weight heparin, and insulins (Niazi, 2020a; Niazi, 2020b). This indicates that comparative clinical efficacy studies have limited value in the overall regulatory assessment and decision-making process. Yet, regulators rarely waive the need to conduct these studies. Further, it has been cited that analytical comparability studies provide more sensitive, precise and efficient data in examining directly the quantitative biological effects of differences in composition (such as PKs), than the more diffuse information resulting from statistical manipulation delivered by comparative efficacy studies (Schiestl et al., 2011). Hence, regulatory agencies should rely on analytical science and human pharmacokinetic data and exempt clinical efficacy studies in support of a faster biosimilar development programme. Further, tailored clinical development programmes should be considered to address the residual uncertainty in analytical studies to evaluate the impact of these differences on immunogenicity/ safety. A streamlined approach on the requirements for clinical development programmes based on the scientific data needs to be established. The significance of analytical comparability data as the primary data for biosimilarity instead of clinical efficacy studies has been well described and recommended for an effective biosimilar development programme through the concept of “Confirmation of Sufficient Likeness” (Webster et al., 2019).

There is often a requirement for local clinical studies for biosimilars (Niazi, 2020a) since foreign patient data is not accepted in some jurisdictions. However, implementing clinical studies across countries with varying regulations involves layers of complexity (Navaneethaselvan & Puranik, 2013). In addition, conducting comparative efficacy studies is an expensive and time-consuming effort. If such studies do not contribute useful information, they simply make biosimilar development more expensive and lengthier. The increased cost may deter some potential biosimilar developers, and the extended time to conduct these studies certainly delays approvals which in turns diminishes timely access and cost savings (IGBA, 2020). On a scientific perspective, in biosimilar development, the comparative clinical efficacy study aims to confirm clinical equivalence between a proposed biosimilar and its reference product on the basis of prespecified margins, along with comparable safety and immunogenicity. Such studies do not aim to establish de novo efficacy and safety. Hence, to reflect such differences, comparative clinical studies should be performed in a sensitive population using appropriate end points to allow detection of any clinically meaningful differences between the treatments, if they exist (Stebbing et al., 2020). Thus, the mandate on conducting local clinical studies in another population without a scientific rationale indicate a gap in the understanding of the scientific basis for establishing biosimilarity among the stakeholders in emerging countries. Request for any clinical efficacy study should be based on the scientific assessment of the application and evaluating if such a study will add scientific value. This will prevent unnecessary and unethical enrolment of subjects and patients in local confirmatory comparative efficacy clinical trials (IGBA, 2020).

A high level of advice is generally required for the development of complex medicinal products, especially in small and medium-sized enterprises with limited regulatory experience and resources (Jost et al., 2015). The BRICS-TM agencies should consider establishing a structured process and system for consultation with the stakeholders for providing scientific advice throughout the development and application process, to avoid delays and to align requirements at an early stage of development. A continuous open dialogue would aid in the effective review and approval process. This will save the agency as well as the company significant time and resources that will eventually be reflected in faster approvals and timely access for patients to these medicines. These recommendations are endorsed by the WHO GBT parameter MA05, which

supports approaches within NRAs to promote transparency, accountability, and communication.

The manufacturing process of biosimilar products is complex and challenging due to the inherent complexity of these molecules. In addition, they are sensitive to physical and chemical conditions and hence must be monitored to ensure the product's quality, safety and efficacy. Therefore, it is vital to adopt appropriate GMP guidelines when manufacturing biopharmaceuticals to safeguard public health (Sia et al., 2020). Pre-approval GMP inspections of the manufacturing site can be beneficial, as it will foster trust with the agencies on the quality and safety of the product, thereby triggering the approval of the products. It has been shown that most of the regulatory agencies are moving towards global harmonization of GMP standards enabling access for these products to more people across the globe (Sia et al., 2020). It has been cited that Mutual Recognition Agreements (MRAs) and other reliance arrangements among trusted regulatory authorities (i.e., EU, PIC/S) would allow them to avoid duplicate inspections at sites demonstrating compliant GMP and to focus on sites that have not been inspected or that need re-inspection following noncompliance (National Academies of Sciences Engineering and Medicine, 2020). The BRICS-TM agencies need to initiate a similar mutual recognition programme so that repetitive site inspections can be avoided. With such joint committees in place, one MRA regulatory authority can trust the others to perform an inspection within the other authority's own jurisdiction, the committee could find no reason to doubt the ability of the latter authority to perform a quality inspection outside its own jurisdiction and provides reassurance. Such a programme can provide reassurance that a manufacturing site has been visited and audited by a neighbouring or partnering country (Welch, 2016b). Likewise, implementing procedures to perform an offsite review of GMP documents to issue GMP certification in lieu of an on-site inspection will boost process efficiency in these countries. Such confirmation of GMP compliance through remote (desktop) inspection, where appropriate, without undertaking an onsite inspection is also one of the main objectives of PIC/S. As per PIC/S, this avoids duplication of work between regulatory authorities, reduces regulatory burden on manufacturing sites, and allows more efficient deployment of global inspection resources (PIC/S, 2018). It is worth noting that ANVISA is the PIC/S' 54th participating authority from 1st January 2021 (www.picschem.org) and will now have the international recognition of excellence in

GMP inspection of drugs and pharmaceutical inputs for human use. Hence, acceptance of GMP certification from ANVISA by other BRICS-TM agencies will be a welcome step for the biopharmaceutical industry.

Biosimilar guidelines in the emerging economies may not be fully established, nor are they fully aligned or implemented from one country to another (Welch, 2016b). Such differing regulatory frameworks for biosimilar development among the countries leads to conduct of similar but distinct studies in accordance with the national regulatory requirements, resulting in submission of multiple applications for a given product to agencies in different countries. Moreover, the agencies also conduct separate de novo lengthy and expensive reviews of each biosimilar, without any acknowledgement of the fact that the same product may have been approved already in another highly regulated jurisdiction (Webster et al., 2019). Duplication of studies negatively impacts both manufacturers and National Medical Regulatory Agencies (NMRAs) (Ball et al., 2016) and this in turn increases the time and cost it takes to bring new drugs to market. One of the solutions to address the absence of a verification review and an abridged review pathway for biosimilar approval in the BRICS-TM countries is to create a BRICS-TM consortium for joint review, allowing all types of review models to be followed to rely on reviews performed by other agencies and defining the number of reference agencies by a Memorandum of Understanding (MOU). Agencies can opt for a verification review for products that have been approved by two or more reference agencies and an abridged review for medicines approved by one or more agencies, with a full review only employed for those products that have not been reviewed elsewhere by a reference agency. Employing such a methodology through a risk-stratification approach by the regulatory agencies has been suggested in an earlier study, which can effectively conserve and utilize the constrained resources (Alsager et al., 2015). Further, a survey carried out by the WHO in 2019–2020 (Kang et al., 2020), revealed that relying on information available from other regulatory authorities or joint review of applications for avoiding repetition of studies, assessments/evaluations for products that have already undergone rigorous evaluation in other countries will address the challenges relating to the lack of expertise and limited regulatory resources in the emerging economies. Such quick measures like a joint review process will improve efficiency of biosimilar approvals. The WHO has also published a draft working document on good reliance practices in regulatory decision-making that

describes the high-level principles and recommendations for the implementation of reliance practices (WHO, 2020). Joint work sharing groups like Project Orbis (initiatives by USFDA for concurrent submission and approval of cancer products in US, Australia and Canada) and other types of coordinated review procedures, such as work-sharing under the Access Consortium (previously referred to as “ACSS”) and ZaZiBoNa initiative in Southern Africa (i.e. Zambia, Zimbabawe, Botswana, Namibia) are becoming more routine. The WHO GBT sub-indicator RS03.04 validates these recommendations, which supports reliance on decisions of other mature NRAs through documented policy, procedures and/or mechanisms. Also, the sub-indicator RS09.01 encourages NRAs to participate in a regional and/or global network to promote convergence and harmonization efforts.

Biosimilar market uptake greatly depends on the health care providers or physicians’ willingness to promote, prescribe, and use biosimilars in clinical practice. The results of a survey (Karateev & Belokoneva, 2019) conducted to assess levels of interest, knowledge and perceptions of biosimilars among Russian physicians who prescribe biologics highlight a significant need for evidence-based education about biosimilars for physicians across specialties. The survey revealed that over 80% lack understanding of the difference between biosimilars and generics and 67% were against tender policies limiting therapy choice for patients while 94% support publication of clinical trial results and expressed their willingness to learn more about biosimilars. It also concluded that the majorly of physicians across Russia ranging from rheumatology, gastroenterology, haematology and oncology lack confidence in prescribing biosimilar. This is further underlined by the findings from a systematic review (Lenord et al., 2019), which has indicated that even in the developed and highly regulated markets like the US and Europe, the health care providers still approach biosimilar medicines with caution. The reasons cited as main deterrents for biosimilar use being, limited biosimilar knowledge, low prescribing comfort, and safety and efficacy concerns. Underlying safety (particularly immunogenicity) and efficacy concerns prevented most physicians from switching patients from existing bio-originator therapy to the biosimilar agent (Cohen et al., 2016).

It is common that the originator companies have also changed the manufacturing process for their biologicals multiple times without the need for additional clinical studies - so in effect each successive batch is biosimilar. Hence, it is clear that the

degree of prescriber's knowledge about variability in innovator products due to the change in manufacturing process is not well understood (Jiménez-Pichardo et al., 2018). Such products with manufacturing changes have been authorized by the regulatory agencies such as EMA without the need for additional clinical studies, as in the case of therapeutic monoclonal antibodies (mAbs) and available in the EPAR documents (Vezer et al., 2016). This is important since originator companies do question the effectiveness and safety of biosimilars as a strategy to retain their market share, especially when only limited price differences are expected for biosimilars. Further, a range of policies including education, benchmarking and financial incentives have been implemented by the different Healthcare Organisations (HCOs) in Italy, by assessing the prescribing behaviours in different regions in Italy to increase the use of biosimilars as a way to conserve resources and potential savings generated as well as how the savings generated were used, without compromising the care (Bertolani & Jommi, 2020; Godman et al., 2020). For instance, in a study by Pasina et al. (Pasina et al., 2016), only 22.9% of physicians and 38.8% of pharmacists indicated having complete a training course or have good knowledge about biosimilars. Such concerns among health care providers and patients over biosimilar acceptance can only be addressed through stakeholder education (Limaye, 2016b). A white paper by Omair et al., (Omair et al., 2020), also stressed education as a means for improving the understanding of biosimilars. Further, conducting local real-world studies to gather evidence on biosimilars in naïve and switched patients, with the aim of developing clinical practice guidelines was emphasized. Biosimilar education should address the key areas of providers' concerns including: immunogenicity; clinical trial evidence; extrapolation; and interchangeability. Educating these stakeholders about biosimilar safety and efficacy will likely require cultivating knowledgeable and opinion leaders (AMCP, 2016). Manufacturers have a key role to play in building trust with the key stakeholders (i.e., physicians, patients, and payers) who require balanced and adequate education on the role that biosimilar medicines can play. Physicians need to be provided data and evidence that biosimilar medicines offer a safe and efficacious alternative to original biologics. Patients need to be reassured that biosimilar product are safe and effective. Payers need to be educated about the potential offered by biosimilar medicines in ensuring affordable healthcare (Limaye, 2016). The Academy of Managed Care Pharmacy (AMCP) Forum further recommends developing novel

educational tools (e.g., online webinars) to supplement traditional educational methods (e.g., policy statements, white papers, e-dossiers) (AMCP, 2016).

Within the developed countries, EMA publishes EPAR summaries for all medicines licensed by the Agency. The EPARs are designed to inform members of the general public about how the EMA assess the risks and benefits of a new medicine, before deciding to grant a licence. They are developed with input from patient and consumer organizations. Further, FDA also publishes an Action Package upon approval of a new drug application (NDA) or Biologic License Application (BLA). An “Action Package” includes documents generated by FDA related to review of the application, summary documents with conclusions from all reviewing disciplines about the drug that note any critical issues or disagreements between the applicant and the review team, and more. Specifically excluded from disclosure in the Action Package are trade secret and confidential commercial or financial information (21 U.S. Code § 355). The WHO Public Assessment Report (WHOPAR) is prepared for prequalified products and provides relevant information on the product’s quality, safety and efficacy. The structure and format of the WHOPAR are adapted from the EPAR to serve the requirements of WHO medicines prequalification. The WHO believes that NRAs should share unredacted reports, where possible, to build trust and to optimize reliance on outcomes from other regulators (WHO, 2018c). Such lack of PARs in emerging economies is likely to become an impediment in the future as more NRAs seek to rely on one another’s approvals and the WHO seeks to expand the pool of NRAs who may be relied upon. Like ANVISA, NRAs from emerging economies such as the BRICS-TM should initiate publication of PARs for the reported medicines to improve the process efficiency. A study on standardization of PAR also suggested a harmonized PAR template to support improved regulatory decision-making transparency (Keyter et al., 2020).

A proposed improved regulatory model for biosimilar development

A proposed improved model for a biosimilar development and approval process is displayed in Figure 9.1a and b.

Biosimilar Development

The biosimilar development process starts with the characterization of the reference product to define the target quality profile of the intended biosimilar product. The model

(Figure 9.1a) proposes the use of RBP approved from any reference agency or other emerging regulatory agency for the characterization. In parallel, the manufacturing process is developed, and the proposed biosimilar product is then manufactured to proceed with the analytical comparability exercise. At this stage, scientific advice with the agency is suggested to get clarity on the overall comparability plan, number of batches of RBP to be used and other key parameters. The comprehensive analytical similarity studies comprising structural and functional similarity tests is carried out to prove that there are no differences between the proposed biosimilar product and the reference product. A step-wise approach is recommended at this stage based on scientific evaluation of the analytical similarity data. Based on the assessment on residual uncertainties, the agency can decide if *in vivo* toxicity studies are required, or if they are to be exempted. Further, a second scientific advice for clinical development will have to be considered based on the evaluation of the analytical similarity data. Agencies should avoid the unnecessary conduct of confirmatory efficacy studies if analytical similarity data and the clinical PK/PD results are sufficient to prove the efficacy of the product. Any safety risks anticipated from the data generated can be addressed by conducting immunogenicity studies along with Phase 1 clinical PK/PD studies.

Marketing Authorization process

The regulatory agency should consider a pre-submission advisory meeting prior to the submission of a marketing authorization application (Figure 9.1b) to the agency to confirm the data sufficiency for the review and approval process. The application needs to be assessed for data based on reliance or a joint or shared review process considering abridged or verification review of the dossiers to reduce the review timelines. Further, sample analysis can be avoided as the quality of the product is already established. The site GMP inspection can replaced or waived if the manufacturing site is already certified by reference agencies or other emerging regulatory agencies based on a mutual recognition agreement; alternatively, the agency can opt for an off-site audit. This helps with the earlier initiation of the review process and based on the cumulative assessment of the data, the marketing authorization for the biosimilar product granted by the agency.

Figure 9.1a A Proposed regulatory model for Biosimilar development process

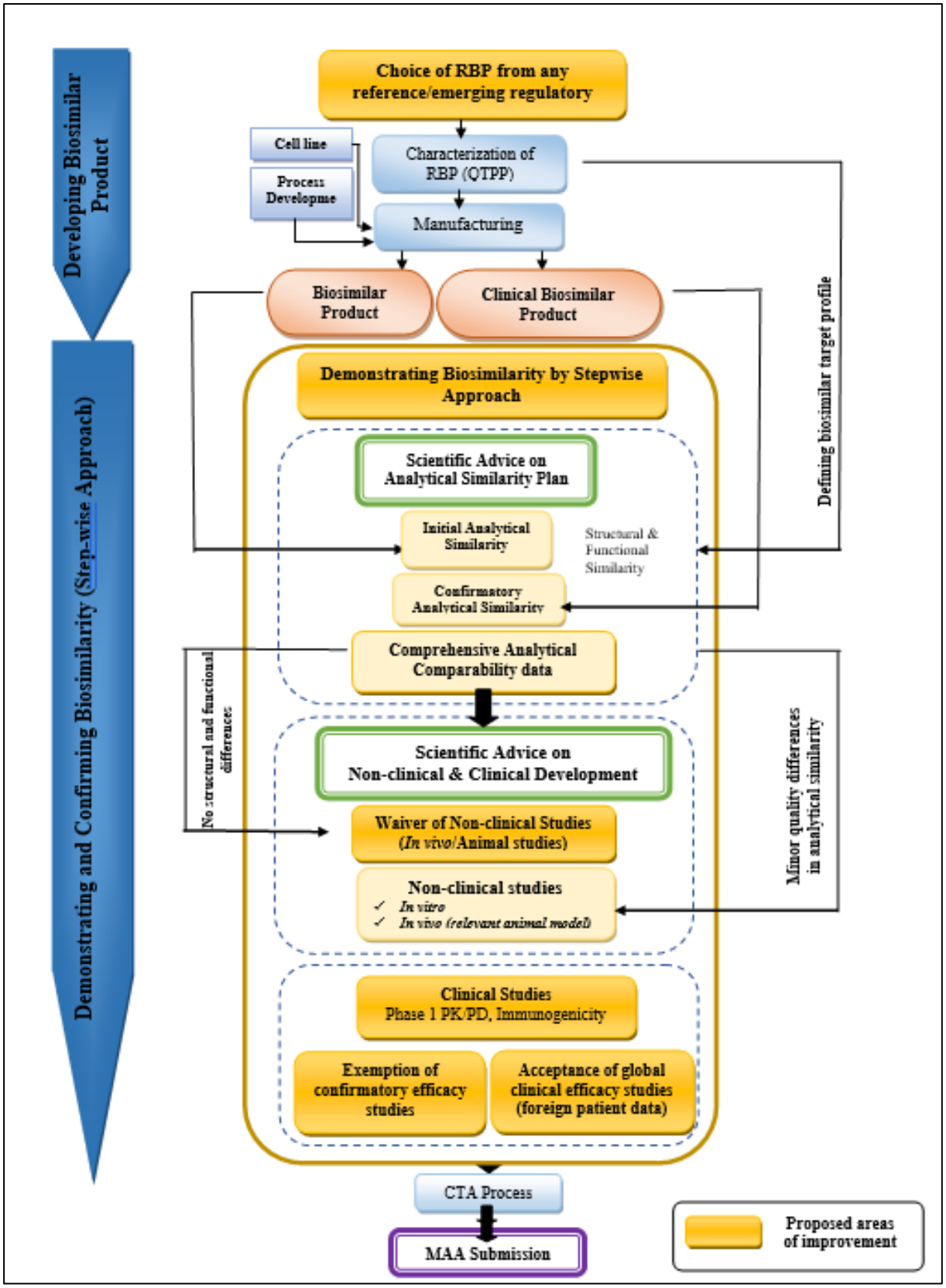
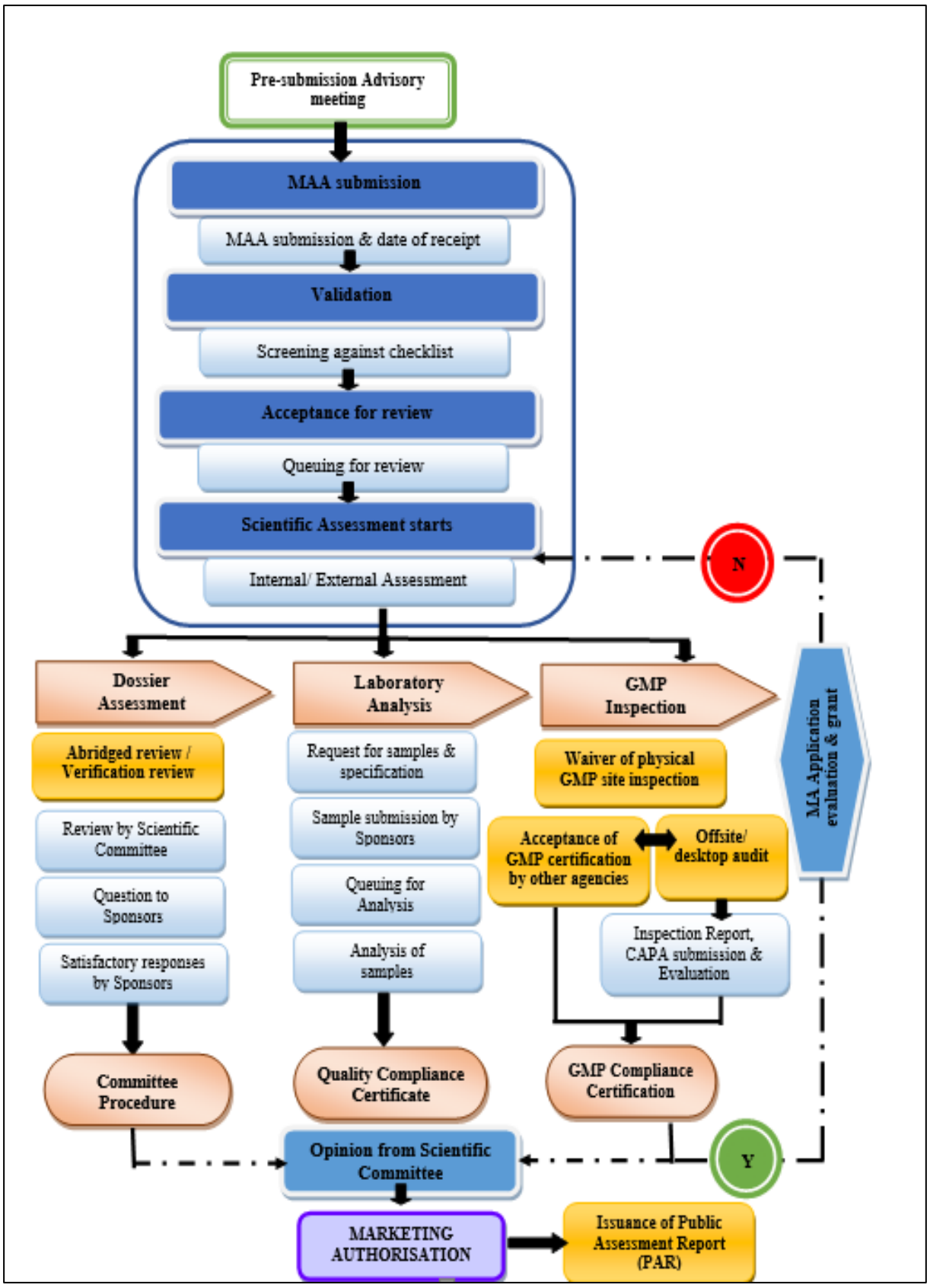


Figure 9.1b A Proposed regulatory model for Biosimilar approval process



SUMMARY AND CONCLUSION

For any biopharmaceutical company manufacturing biosimilars, a simplified biosimilar development pathway is believed to contribute to the sustainable access to biologics. Although, regulators in the emerging economies have taken some significant steps toward establishing a larger biosimilar market within these countries, the lack of homogeneity in dossier requirements across the emerging economies poses a challenge to global development programmes (Welch, 2016a). Implementation of 'step-wise approach' with a tailored scientifically justifiable development process, might release the industry from lengthy biosimilar development processes promoting greater reliance on analytical data and pharmacokinetic and pharmacodynamic (PK/PD) trials, eliminating the current regulatory need to carry out large comparative efficacy studies (Welch, 2019b; IGBA, 2020). Clinician-directed biosimilar education combined with better interaction between regulators, payers, and medicines developers will be imperative to strengthen biosimilar familiarity, to facilitate changes in the prescribing methods for promoting acceptance of biosimilar medications as safe and effective treatment options for patients. Data assessment based on reliance models and joint work sharing groups will further strengthen reliance networks and improve performance. This might be beneficial to establish new global standards to optimize clinical trial design to make them more amenable to simultaneous international review (Mulchan & Guy, 2021).

The success of biosimilars in the market will depend on the strategic choices' that biopharmaceutical firms make. It is hoped that the improved regulatory model resulted from this study and presented here might serve as a basis for strategizing and planning for an efficient, transparent and harmonized or standardized biosimilar development and approval process among the emerging economies. While there are challenges ahead, biosimilars present unique opportunities to bring innovative medicines with an affordable price to patients and enhance the biopharmaceutical industry's performance. It is hoped that biosimilars, along with originator biologics, will be an important part of the healthcare systems in the emerging economies (Leintz & Dedhia, 2015). A joint effort by all the stakeholders can ensure faster delivery of medicines to patients across the globe.

CHAPTER 10

General Discussion

Biologic products are an important treatment option for a wide array of conditions and diseases, primarily cancer, rheumatoid arthritis, and inflammatory bowel disease and many other life-threatening diseases. They have the potential to provide lower cost alternatives and offer greater access to biologics, and thereby allow increased use of biologic therapies (Dutta et al., 2020). Biosimilars are expected to emerge as a rapidly growing segment in the emerging economies due to low treatment rates of biologics and constraints of affordability. Further, emergency public health situations like the COVID-19 (Coronavirus Disease) pandemic have increased demand for monoclonal antibodies such as tocilizumab, sarilumab and Itolizumab for testing on Covid-19 patients. This clearly shows the unprecedented increasing demand for rapid development of biosimilars to assure a consistent and affordable supply for patients in emergency health situations like COVID-19 (Thepharmletter, 2020).

Yet, biosimilar development and licensing remains very complex and requires more investment compared to small molecules. This, in part, might be due to confrontation of biosimilar industries with constantly evolving regulatory environment, ending up with multiple regulatory challenges pertaining to the development and approval pathway of biosimilars. It is evident that the biosimilar regulations have evolved less than two decades ago among the well-established regulatory agencies like EMA and USFDA. While emerging agencies have made efforts to develop biosimilar guidelines keeping in mind the global norms and local requirements, there remain significant areas of improvement. The biosimilar guidelines are not fully established in the emerging economies and differ from country to country unlike developed countries like the EU where all the countries follow the same guidelines established by EMA. The biosimilar companies planning to receive approval for a biosimilar in an emerging market face additional quality, non-clinical, or clinical procedures, depending on the country (Sivabushnam, 2017). This creates challenges to global development programs in the emerging markets. The challenges faced by the biopharmaceutical companies in development, the concerns of the prescribers and patients and the inputs from the regulatory agencies, all have played a role in the constant evolution of regulations in this space and for facilitating and sustaining access to biosimilar medicines for patients.

However, the patients who couldn’t afford medicines in spite of insurance or terminally ill patients who wanted to access drug before being approved by the regulatory

agencies divulge into grey markets or dark web (an online platform where medicines are sold illegally before the drugs are legally approved by the NRAs) for accessing the medicines. A preliminary search was conducted during the research period, on the darknet market to verify the availability of some of the key biosimilar products with high market value (namely Tocilizumab or Acterma, Itolizumab under Alzumab brand, Adalimumab (Amgevita, Mabura), Bevacizumab (Mvasi), Trastuzumab (Zedora), Rituximab (Riximyo, Tuxima), Infliximab (Remsima, Renflexis), Etanercept (Brenzys), Eculizumab, Ranibizumab, Abcixumab (AbcixiRel)). The search revealed negative findings on availability of the above products in the darknet. Such illegal drug distribution requires vigilance and increase in cyber drug regulations to target fraudulent drugs on the dark web to ensure patient safety and to alert the regulatory agencies and scientific community about the potential risks in this chain (Lin, 2018).

Regulatory principles governing biosimilars in emerging economies are still in an evolving stage in emerging countries such as the BRICS-TM (Brazil, Russia, India, China, South Africa, Turkey, Mexico). Integration of regulatory requirements is hence necessary to assist in the common biosimilar development and submission process across these economies. While a common regulatory framework has been proposed by the World Health Organisation (WHO), the developing countries have only partially adopted them. There remains scope for improving transparency in the national regulatory frameworks and aligning regulatory standards among these countries. This would impact the overall review and approval process as well as enabling a common development programme across these countries. Hence, development and marketing of biosimilar product in multiple geographies with varied regulatory expectations would require clear strategy starting from the selection of the appropriate reference product, defining the extent of process and product characterisation and design of non-clinical studies and clinical studies (Batel, 2020).

This research programme was aimed to identify and compare the regulatory framework of the BRICS-TM agencies in terms of resources in biosimilar domain, biosimilar development criteria and biosimilar marketing authorisation approval pathway. It is hoped that the study would facilitate benchmarking best practices leading to convergence of regulatory processes in BRICS-TM countries. The key recommendations stemming from this research have been designed as a proposed improved model for consideration and implementation by the BRICS-TM regulatory

agencies to support a simplified, shortened and cost-effective biosimilar development program, that would enhance regulatory performance and approval of these products facilitating accelerated patients' access to these medicines.

Five studies were conducted as part of this research; these included a review and evaluation of the regulatory guidelines for biosimilar medicine development and marketing authorisation issued by EMA, WHO, USFDA, Health Canada, TGA Health Agencies and comparison of regulatory guidelines in emerging economies against mature agency regulations (Study 1: Chapter 3 and Chapter 4), followed by evaluation of perspectives of key stakeholders involved in biosimilar development and approval process namely; regulators, industries, physicians and patients. The studies included - an evaluation of the regulatory review process and assessment criteria for biosimilar development in BRICS-TM countries (Study 2: Chapter 5), a comparative evaluation of practices followed by mature (ACSS – Australia, Canada, Singapore, Switzerland) and emerging (BRICS-TM) agencies for type of data assessment, criteria for biosimilar development and pathway for marketing authorisation approval (Study 3: Chapter 6), identification and evaluation of challenges faced by bio-pharmaceutical industry in BRICS-TM countries (Study 4: Chapter 7), an evaluation of physicians' and patients' views about biosimilar access in BRICS-TM countries (Study 5: Chapter 8). The data collected from each study were analysed and reviewed individually to facilitate a thorough evaluation of the biosimilar regulatory environment in BRICS-TM countries with a view to improving the development and review process and patients' access to new medicines.

RESEARCH OUTCOMES AND CONTRIBUTIONS

Globally, regulatory expectations for the development and approval of biosimilars are not completely harmonised. Regional and country-specific biosimilar pathway legislation and guidance are at different stages of development and implementation, particularly in emerging economies such as the BRICS-TM countries. The changing regulatory landscape is evident on certain aspects of biosimilar development, including the selection of the reference product, nomenclature, and the design of analytical, non-clinical, or clinical comparative studies, biosimilar product review and authorisation process. Despite most of the BRICS-TM economies are modelled over the WHO regulatory framework for biosimilars, no studies have previously been undertaken to evaluate the biosimilar regulatory requirements in terms of the development, regulatory

review and approval processes. This research programme has for the first time evaluated the biosimilar development, regulatory review and authorisation process of the BRICS-TM regulatory agencies and has provided key recommendations for further improvement.

This research commenced with an in-depth review and evaluation of the biosimilar regulatory environment in developed regulatory agencies such as the USFDA, EMA, Health Canada, TGA (Therapeutic Goods Administration, Australia) and the WHO, as detailed in Chapter 3. Further, the regulatory guidelines in the emerging economies of the BRICS-TM were compared against mature agency regulations (Chapter 4), which is likely to aid in identifying the differing regulatory requirements for biosimilars in the emerging agencies and may serve as a platform for further research. The results from this study indicated that the BRICS-TM agencies partially implemented the WHO SBP guidelines whereas TGA and Swissmedic guidelines primarily followed EMA. The non-authorised reference product selection was limited to the ICH /own aligning countries with no clarity on bridging studies in BRICS-TM countries whereas such transparency existed with TGA and Swissmedic. Further, non-clinical studies including immunogenicity toxicity studies needed explicit clarity in the BRICS-TM countries. Confirmatory Phase III clinical safety and efficacy trials were mandatory in some of the BRICS-TM countries. Thus, the outcome from this study indicated a need for primary research to verify the gaps and propose a standardised model across BRICS-TM agencies for biosimilar development and approval.

The primary research was carried out through evaluation and comparison of technical capabilities of the BRICS-TM regulatory agencies in the area of biosimilars as described in Chapter 5. The research was studied in terms of identification of similarities and differences in regulatory requirements of biosimilar development criteria i.e., biosimilarity principles, comparative studies including physicochemical characterisation, non-clinical and clinical studies, evaluation and comparison of “must submit documents” as part of biosimilar application for marketing authorisation in the BRICS-TM countries, and map the biosimilar marketing authorisation approval pathway specifically for key milestones, scientific guidance meetings, clinical trial mandates and backlogs. The study outcome indicated inadequate resources and insignificant subject matter expertise in the BRICS-TM countries. However, a full review of marketing authorisation application (Type III) was most prevalent rather than

a reliance on Type I (Verification) and Type II review (Abridged review) model. The regulatory expectations for local / global clinical efficacy studies and sourcing of RBP varied across the agencies was a major concern with no provision of use of RBP authorised in other emerging countries. The criteria to define biosimilar analytical specifications were only partially aligned with WHO regulatory norms. The study thus emphasised the need to foster effective collaboration between regulators and developers in the BRICS-TM countries by establishing scientific advisory meetings to avoid duplication of work, and to streamline the development strategies and approval pathways for biosimilar products.

A recent update post the study completion from TITCK, Turkey is that the agency has replaced the draft version of its biosimilar guideline with the final version, published on 14th of September 2021 (TITCK, 2021). The final version currently in force is almost in agreement with the EMA guidelines in terms of quality, non-clinical and clinical comparison studies required for the demonstration of biosimilarity. There is major change in definition of the reference medicinal product together with a new classification, that seems unique to new final version of Turkish guideline. Reference medicinal products are defined as biological medicinal products that are licensed either by Turkish regulatory agency (TİTCK) or by regulatory agencies of ICH founder or regular members. However, the reference medicinal products that are licensed by regulatory agencies of all other countries, i.e., all non-ICH founder or regular members are defined as “The Comparator Medicinal Product”. This is a completely new definition that seems to be unique to Turkish guideline. Further, regarding the choice of the reference medicinal product, final guideline clearly states that “The Comparator Medicinal Product” can be used together with reference medicinal product (local or ICH founder/regular member-sourced) in determination of quality target product profile (QTPP) and also in certain *in vivo* and clinical comparability studies, provided that there is enough bridging data obtained from analytical studies using all three agents (reference, The Comparator Medicinal Product and test). It was also stated that further clinical PK and/or PD bridging data with all three products may also be required depending on the product on a case-by-case basis. This update with regards to the acceptance of reference medicinal product from other emerging countries is a progress from the Turkish agency against the research study outcome.

As a next step, the research was designed to compare the biosimilar regulatory strategy of the BRICS-TM agencies with that of Australia, Canada, Singapore, Switzerland (ACSS Consortium), in an effort to identify and replicate best practices in biosimilar development and their authorisation processes as focussed on Chapter 6. The comparison of regulatory agencies of emerging economies of the BRICS-TM countries and mature regulatory agencies of ACSS was conducted to identify regulatory framework within ACSS health agencies in terms of resource allocation in the biosimilar domain, to identify biosimilar development criteria i.e., biosimilarity principle, comparative studies including physicochemical characterisation, non-clinical and clinical studies and to identify the biosimilar marketing authorisation approval pathway specifically for key milestones, scientific guidance meetings, clinical trial mandates, backlogs etc. Further, the outcome of these studies was used for comparative evaluation of the BRICS-TM regulatory frameworks with ACSS to identify challenges and areas for improvement. The results of this comparative study revealed insignificant subject matter expertise in the BRICS-TM agencies compared to ACSS. As revealed in Chapter 5, it was clear that the BRICS-TM agencies were yet to establish international collaboration to enhance efficiency and reliance on review performed by other agencies, whereas the ACSS regulatory agencies acknowledged joint or shared review for data assessment. The biosimilarity principle of the BRICS-TM were largely aligned with ACSS, but the key challenge was the need for local clinical trials needed by some of the BRICS-TM countries. Unlike some of the BRICS-TM agencies preferring locally authorised reference product (i.e., ANVISA and Russian MoH) ACSS agencies were flexible for using non-authorised reference product as part of development. The study mainly emphasised on the need for reliance models for joint or shared review process of marketing authorisation application with other comparable agencies on a risk-based approach.

In Chapter 7, the specific challenges that were faced by the biopharmaceutical industries in BRICS-TM countries pertaining to biosimilar development and the approval processes, including concerns on pricing and market access has been explored. The perceptions of the biopharmaceutical industries regarding the efficiency and effectiveness of current regulatory processes were identified and evaluated to gather suggestions on potential improvements in the biosimilar development and approval process in their respective countries. The industry personnel perceived

biosimilar guidelines and approval processes as being protracted and in a state of evolution. The industries recognised expectations on sourcing of RBP and confirmatory clinical trials as key hurdles for biosimilar development. The non-comprehensive implementation of a stepwise approach resulting in unnecessary toxicity studies was also a major concern among the industry experts.

In order to explore further the views from other key stakeholders, the attitudes of physicians and patients towards prescribing and access to biosimilar medicines were assessed and the key barriers to adoption of biosimilars were identified to understand the biosimilar prescribing habits of physicians and the factors driving their choice of product. The details of the studies were described in Chapter 8. The study was conducted to understand the knowledge gap on biosimilars at prescriber level, to explore the concerns on quality of biosimilars at physician and patient level, to learn about their views on biosimilar interchangeability, switching, substitution, to gauge their perception of safety and efficacy of a biosimilar compared to the original biologic and to identify the challenges pertaining to biosimilars, including access and affordability for patients. This part of the research was significant as it specifically provided insights on the barriers faced by physicians and patients in India and Russia, representing developing countries with a large unmet need for these life-saving medicines.

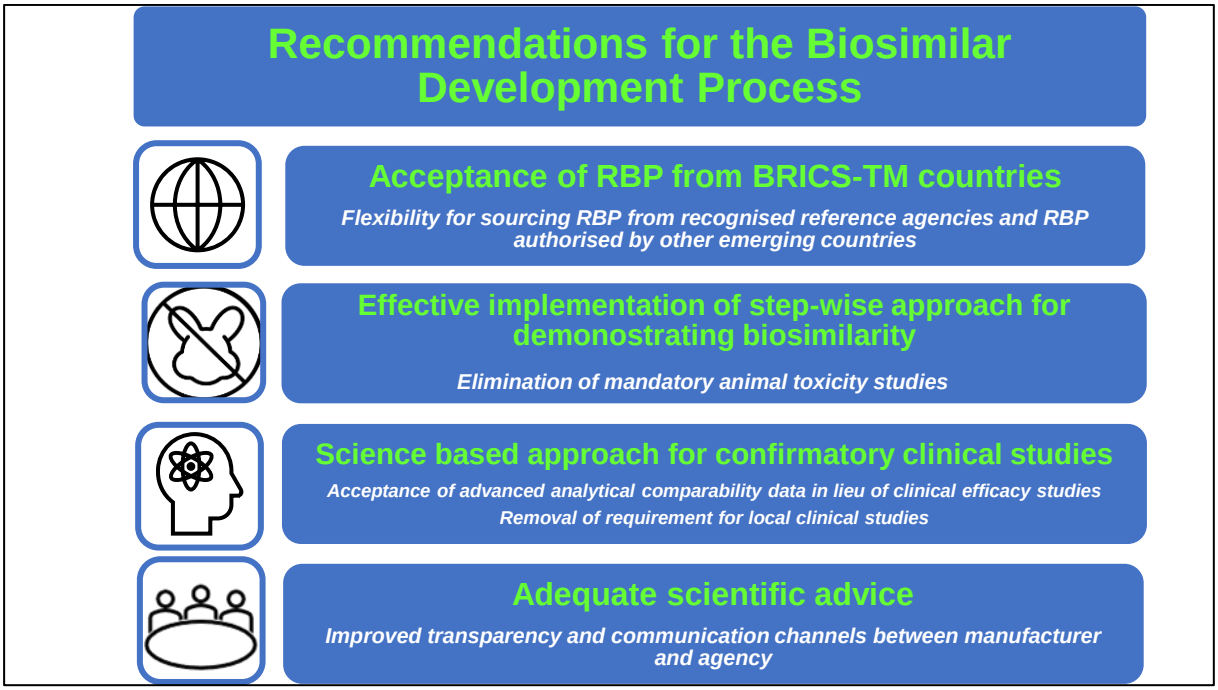
This programme of research culminated in the development of a set of recommendations for a proposed improved regulatory review model for the BRICS-TM countries as detailed in Chapter 9. Five different studies were conducted in the BRICS-TM countries to understand the perspectives of key stakeholders namely the industry, regulators, patient and physicians on the challenges for the development and uptake of biosimilars as described in Chapter 3 to 8. Assessment of biosimilar development criteria, content of the marketing authorisation application and approval pathway were considered for the studies with the goal of conceptualising, designing the outcomes from these studies as the basis of a proposed standardised model for the BRICS-TM countries. This proposed regulatory model is likely to simplify new biosimilar development programmes and pave the way for patients' access to quality and affordable biosimilar medicines.

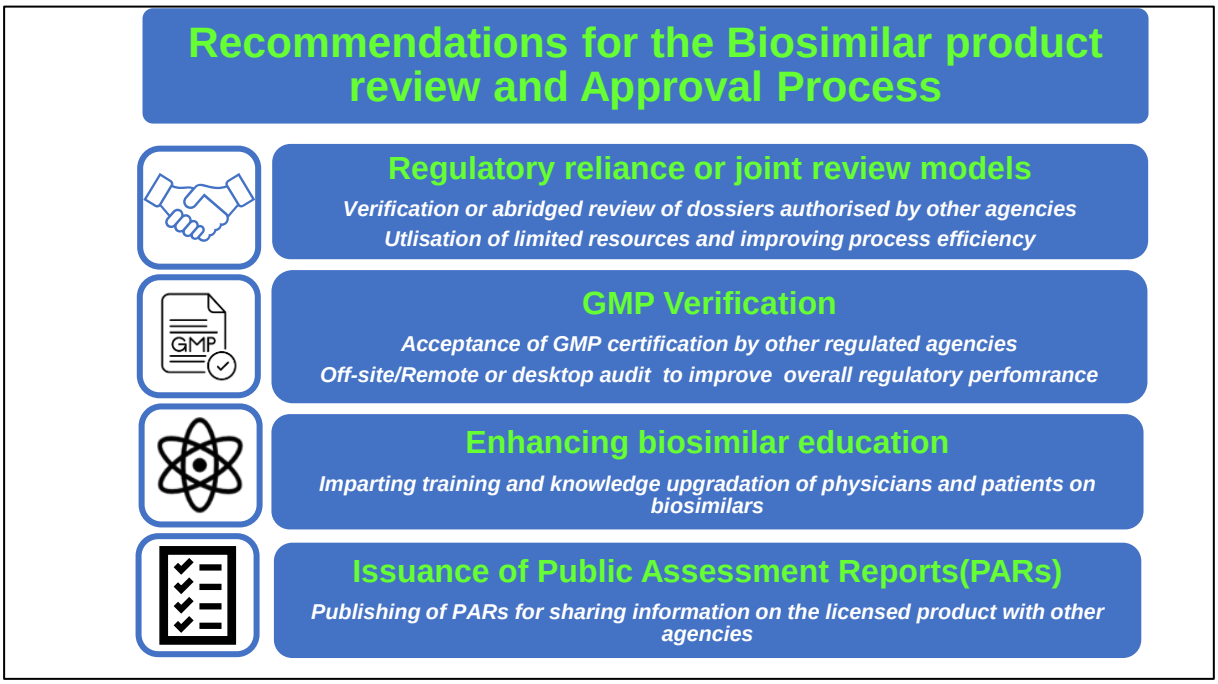
RECOMMENDATIONS FOR AN IMPROVED REGULATORY REVIEW MODEL FOR BRICS-TM COUNTRIES

The studies conducted as part of this research programme have resulted in the identification of key areas for improvement in biosimilar development and approval pathways in the BRICS-TM countries which have formed the basis for development of a model to standardise requirements for biosimilar development and the approval process with a view to improve regulatory performance. The recommendations from these studies are deemed to be critical for building a regulatory model for improved biosimilar development and authorisation process and is presented in Figure 10.1.

The key recommendations include regulatory flexibility in sourcing of the RBP in terms of considering RBP from other markets, which would facilitate common biosimilar development programmes for catering to different regulatory agencies. Further, proposal for a formal approach to regular, appropriate and tailored scientific advice from regulatory agencies to developers would help to align expectations on both sides and support step-by-step development, thereby reducing the need for *in vivo* non-clinical studies. This may also help to shorten the overall review and approval timelines. An improved science based regulatory model for biosimilar development process would also reduce the overall development cost by reducing the clinical confirmatory clinical studies. Further, implementing a reliance mechanism in the review process along with knowledge upgradation would expedite the overall approval process and thereby lead to quick access by the patients.

Figure 10.1 Recommendations for the proposed improved regulatory model for biosimilar development and approval process in the BRICS-TM countries





BRICS-TM: Brazil, Russia, India, China, South Africa, Turkey, Mexico; GMP: Good Manufacturing Practice; PAR: Public Assessment Report; RBP: Reference Biologic Product.

STUDY LIMITATIONS

The current research programme had few study limitations which are explained below.

- Chapter 5 detailed the primary research carried out through evaluation and comparison of technical capabilities of the BRICS-TM regulatory agencies in the area of biosimilars. However, regulatory agency of China did not participate in the study and only the results from 6 out of 7 (85.7%) regulatory agencies were evaluated to arrive at the outcomes. While ANVISA, Russian MoH, CDSCO, SAHPRA, TITCK and COFEPRIS responses were obtained, the multiple efforts to reach NMPA (China) either directly or via regulatory experts were unsuccessful. Though non-participation of China in this study could be considered as a limitation, however the survey (even without China) encompasses a large, diverse and important segment of the world population and pharmaceutical market, so it should provide strategic information to pharma companies, as well as national regulatory authorities and international bodies. So, it may not have influenced the generalisability of the results in terms of identifying areas requiring improvement in the BRICS-TM regulatory review for biosimilars. Further, the response pertaining to biosimilar approval metrics i.e., applications received, applications screened and accepted for further review, biosimilars approved, biosimilars refused and average approval times was received only from ANVISA. The other agencies did not provide complete data on approval metrics which could be considered a limitation as the varied timelines at different stages of marketing authorisation application or review process could not be well correlated with the approval metrics. The response from other agencies would have helped understand the process efficiency and provided benchmark in terms of basis of approval to biopharmaceutical companies.
- Chapter 7 focussed on the challenges faced by the biopharmaceutical industries, across the BRICS-TM countries targeting active industry personnel and representatives from the pharmaceutical trade associations who have member companies with marketed biosimilar products. Despite inviting 107 personnel from the biopharmaceutical industry and representatives from trade associations, only 33 agreed to take part in the study. Those who completed the study were 6 from Brazil, 4 from Russia, 15 from India, 1 from China, 1 from South Africa, 1 from Turkey and 5 from Mexico. Hence, in comparison with the targeted number of study participants, the number of respondents was low. However, 33% response rate for studies of such

nature is considered to be acceptable. Therefore, putting this in the context of the actual fact that the recent estimates of companies marketing and developing biosimilar medicines range between 100-182 (Visiongain, 2016; MP Team, 2019) and most of these companies are situated in high-income, developed countries (Gautam, 2017) with fewer active industry players in the emerging economies, would make it a credible sample size.

- Chapter 8 detailed on the perceptions of physicians and patients on the biosimilar prescription, uptake and access. There were several limitations with this study. The small sample size of both the physicians and patients prevented generalisability of the results. Reasons cited by physicians (n=61) for non-participating in the study included high honorarium, lack of time and interest and national laws restricting to contact the physicians. No response was obtained through any of the physician associations (n=19), reasons for which are unknown. Among the patients' groups invited for the study, non-active active patient organisations (n=12) were non-responsive despite at least three reminders. The small sample size of both the physicians and patients prevents generalisability of the results. However, it does provide a snapshot of the current prescribing and uptake of biosimilars helping to generate hypothesis for further research in similar populations. Similarly, participation of only two of the seven BRICS-TM countries in the study further limited wider understanding of some of the issues raised with practice of biosimilars in other respective countries. Nevertheless, the findings from the two countries could provide a reasonable indication of the scale of the challenges that could exist across the BRICS-TM countries and how a fresh review of the guidelines and policies could overcome the existing hurdles in the wider adoption of biosimilars and patients' access to them. It is therefore hoped that this could move these countries closer to a standardised regulatory requirement.

CHALLENGES FACED DURING RESEARCH AND POTENTIAL SOLUTIONS

The current research focused on proposing a standardized regulatory model on biosimilar development and approval process in the emerging economies of BRICS-TM, which has not been studied earlier. In addition, the research also covered not just the perspectives from different regulatory agencies in these emerging economies, but also the challenges faced by the biopharmaceutical industries in biosimilar development and challenges in the uptake of biosimilars by physicians and patients.

However, like every other research study, there were few challenges experienced during the conduct of the research; some of them are highlighted below together with the strategies used to assist in addressing the challenges mentioned for the attention of the future researchers;

- **Translation:** The present work involved cross-language settings involving non-English speaking countries such as Brazil, Russia, China, Turkey and Mexico. Retrieval of regional biologic/biosimilar guidelines for conducting the secondary research and responses obtained in regional languages for the questionnaire-based studies needed translation of the data collected and different phases of the study. Most of the studies as part of this research were relying on the diverse perspectives of participants and the richness of people's experiences. Thus, maintaining the scientific rigor and accuracy of data collected was challenging and required experienced translators/ interpreters to come up with valid translations followed by validation of all the translated data.

- **Industry Contacts:** The questionnaire-based study involving representatives from biopharmaceutical industries demanded establishing contacts with personnel from biopharmaceutical industries in countries (Brazil, Russia, China, South Africa, Turkey, Mexico) other than the researcher's country of origin (India). This required extensive networking with people from different fields- academia, personal contacts, friends, supervisor, co-researchers etc. and then establishing rapport with these contacts through mails or interactions via calls for making them understand the significance of their participation in the research study. Such challenge could also be tackled by identifying and working with community mobilisers who can support in capacity building and establish contacts in regions where research has not been conducted previously.

- **Physician contacts:** Similar to the industry contacts, obtaining contacts of physicians from different countries to take part in the research study was an arduous task. Besides the personal contacts, various social networking sites including LinkedIn and Facebook were explored to obtain physician contacts for the study.

- **Regulatory Agencies:** In addition to contacts from industries and physicians across the different geographies, connecting with the regulatory agencies of the BRICS-TM countries were exceptionally challenging. Finding right contacts and establishing relationships with the representatives from regulatory agencies took

almost a year but was fruitful. Such networking hurdles were overcome by reaching out to the representatives through industry contacts, regular follow ups with agencies, LinkedIn connects, agreeing on upholding confidentiality/anonymity as well as requesting their support for validation of the draft manuscript before publication.

- **Patient Consent:** Another challenge encountered during the study was obtaining agreement from patient organisations to participate in the survey across the BRICS-TM countries, despite multiple communications with the groups via mails and social networking sites. Although agreement was received from patient organizations in India and Russia, efforts for other countries was ineffective and unsuccessful. Hence, establishing prior contacts with local representatives needs to be well-planned for pursuing the studies with such sensitive population.

- **Communication:** As part of the current research, the questionnaire-based studies also involved one-on-one remote interaction with the study participants using virtual platforms for avoiding any misinterpretation of the responses. Although communicating through voice calls and video calls was difficult, in comparison with face-to-face contacts, regular communication with the study participants helped in building relationships and trust.

FUTURE WORK

- This research programme broadly evaluated the regulatory processes for biosimilar development and approval by the BRICS-TM agencies and has underpinned the major areas of improvement in the processes that supported for designing a proposed improved regulatory review model for the BRICS-TM countries. Effective implementation of this proposed standardised model for biosimilar development will be helpful to;
    - Bridge the gaps in biosimilar regulatory frameworks across the BRICS-TM agencies.
    - Will facilitate an integrated and simplified regulatory pathway for biosimilar development and approval, eliminating unwarranted studies.
- The BRICS-TM & ACSS agencies will be approached for formal presentations on the model. A formal presentation was held through virtual meeting with the Swissmedic regulatory agency on 21st October 2021 (Appendix 9) to discuss the outcomes and study implications of the comparative study on BRICS-TM countries' biosimilar

regulatory frameworks with Australia, Canada and Switzerland to benchmark the best practices (Study 3). From the discussion, it was understood that the agency plans to internally work towards identifying time spent by resources on biological and non-biological application by each reviewer. Further they would discuss internally with their biologics team on the reference product selection, work sharing procedure and then connect with the researcher for supporting further studies, if required. It was also revealed that during pandemic, the Swiss agency has started rolling questions process for new applications and digitalisation tools have been implemented. The agency is also planning to initiate surveys to understand the area for improvement in terms of regulatory process.

- The proposed model will be disseminated widely through presentations, seminars and group discussions to help overcome challenges pertaining to biosimilar access and affordability.
- A web platform will be created to help Industry/ Industry associations access the research outcome.
- In consideration of adding statistical validation of the findings of the studies, it would be valuable to consider a follow-up study through a new online survey to a new population of professionals for them to indicate if they are in agreement or disagreement with the outcomes of the studies presented in this thesis.
- The current studies were exploratory in nature; however future studies with broader objectives would provide deeper insights into the challenges faced by the key stakeholders i.e. biopharmaceutical industries, physicians and patients, which could help with the implementation of regional standardisation of regulatory norms in the developing countries.
- It would be useful to carry out an in-depth study of the regulatory review process of each of the regulatory agencies to reflect on the organisational structure, regulatory review process and evaluate the regulatory performance metrics.
- Extensive research could also be undertaken to explore the dark web for other biosimilars and its impact on the uptake and safety of the patients.
- The application of Artificial Intelligence (AI) technologies in medicines development has significantly increased, having entered in all stages of medicine lifecycle such as target validation, identification of biomarkers, annotation and analysis of clinical data in trials, pharmacovigilance and clinical use optimization. This involvement has raised

many regulatory challenges from algorithm transparency to risk of AI failures to impact on its development (ICMRA, 2021). Studies on the role of AI and the use of other digital technology innovations in the biosimilar space can be considered as part of the future research.

CONCLUSION

The varying regulatory frameworks for biosimilar development in the emerging economies delay the development process, increase cost, and impact the overall approval time and delay patients' access to such vital medicines. In addition, the COVID-19 pandemic meant that both regional as well as the NRAs needed to introduce flexibilities for regulatory requirements and approval. It is hoped that this will continue beyond the pandemic. This study aimed to evaluate the biosimilar regulatory framework of the BRICS-TM countries where the market size for biosimilars is expected to be substantially higher but faces challenges to access these medicines. It is hoped that the standardized regulatory model as proposed in this thesis would be the beginning of initiating the debate for moving the emerging economies such as the BRICS-TM forward towards coming closer together for creating a regional unified regulatory programme. The outcome of this study is hoped to facilitate streamlining of the regulatory standards in these countries, leading to improved patient access to affordable medicines without compromising their quality, efficacy or safety.

REFERENCES

21 U.S. Code § 355 - New drugs US: Legal Information Institute; Washington: Cornell Law School. Retrieved September 14, 2021, from https://www.law.cornell.edu/uscode/text/21/355

ABDI IBRAHIM. (2019). Abdi İbrahim And Alvotech Enter Strategic Partnership In Biotechnology. Retrieved August 20, 2021, from https://www.abdiibrahim.com.tr/en/press/press-releases/abdi-ibrahim-and-alvotech-enter-strategic-partnership-in-biotechnology

Agarwal, S. (2020). Protection gap very high in India even after term insurance available for as low as Rs 1,000/month. Retrieved January 12, 2020, from https://www.cnbctv18.com/finance/protection-gap-very-high-in-india-even-after-term-insurance-available-for-as-low-as-rs-1000month-7014041.htm

Agbogbo, F. K., Ecker, D. M., Farrand, A., Han, K., Khoury, A., et al. (2019). Current perspectives on biosimilars. *Journal of industrial microbiology & biotechnology, 46*(9-10), 1297–1311. doi: https://doi.org/10.1007/s10295-019-02216-z

Aitken. (2020). IGBA Reflection on Regulatory System Strengthening for Biosimilar Medicines. 1-3. Geneva. Retrieved July 29, 2021, from https://www.igbamedicines.org/doc/NAS%20Biosimilars%20Framework%20vF.pdf

Alsager, S., Hashan, H. & Walker, S. (2015). The Saudi Food and Drug Authority: Shaping the Regulatory Environment in the Gulf Region. *Pharmaceutical Medicine*, *29*, 93-103. doi: https://doi.org/10.1007/s40290-015-0089-3

AMCP. (2016). AMCP Partnership Forum: Biosimilars--Ready, Set, Launch. *Journal of managed care & specialty pharmacy, 22*(4), 434–440. doi: https://doi.org/10.18553/jmcp.2016.22.4.434

Anderson, L.A. (2021). What Are Biosimilars? Top Facts You May Not Know. Retrieved September 13, 2021, from https://www.drugs.com/slideshow/biosimilars--1264

ANVISA. (2010). *RESOLUÇÃO DA DIRETORIA COLEGIADA – RDC Nº 55, DE 16 DE DEZEMBRO DE 2010*. Retrieved April 04, 2018, from http://antigo.anvisa.gov.br/documents/10181/2718376/%281%29RDC_55_2010_COMP.pdf/41ebae78-5742-4060-9bec-6ccece9ce262

ANVISA. (2020a). *Brazil-ANVISA Resolution RDC 346/2020 with Alternative GMP Auditing (Good Manufacturing Practice) Requirements Due to COVID-19 Epidemic*. Retrieved March 04, 2021, from https://www.tuv.com/regulations-and-standards/en/brazil-anvisa-resolution-rdc-346-2020-with-alternative-gmp-auditing-(good-manufacturing-practice).html

ANVISA. (2020b). *Brazil-ANVISA Resolution RDC 348/2020 with Alternative Procedures for Registration of Medicines, Biological Products and In Vitro Diagnostic Products Due to COVID-19 Epidemic*. Retrieved March 04, 2021, from https://www.tuv.com/regulations-and-standards/en/brazil-anvisa-resolution-rdc-348-2020-with-alternative-procedures-for-registration-of-medicines.html

Arias, A. (2020). Biosimilars and Biobetters: Market Trends and Future Opportunities. IQVIA European Thought Leadership. Retrieved January 14, 2021, from https://event.on24.com/eventRegistration/EventLobbyServlet?target=reg20.jsp&partnerref=INNSight&eventid=2646086&sessionid=1&key=E57E9B57D61A16E9AE19A38931236B76&regTag=&sourcepage=register&utm_campaign=2020_ArkNewsletterOct_GBU_TC_SD&utm_medium=email&utm_source=Eloqua

Azevedo, V. F., Babini, A. , Caballero-Uribe, C. V. , Castañeda-Hernández, G., Borlenghi, C. & Jones, H. E. (2019). Practical Guidance on Biosimilars, With a Focus on Latin America: What Do Rheumatologists Need to Know? *Journal of Clinical Rheumatology, 25*(2), 91-100. doi: https://doi.org/10.1097/RHU.0000000000000881

Ball H. L. (2019). Conducting Online Surveys. *Journal of human lactation : official journal of International Lactation Consultant Association, 35*(3), 413–417. doi: https://doi.org/10.1177/0890334419848734

Ball, D., Roth, S. & Parry, J. (2016). Better Regulation of Medicines Means Stronger Regional Health Security. *ADB Briefs*, 1-10. Retrieved February 25, 2021, from

https://www.adb.org/sites/default/files/publication/184392/better-regulation-medicine.pdf

Bassil, N., Sasmaz, S., Sayah, M. E. & Akalankam, A. (2020). Realizing Biosimilar Potential in the Middle East & Africa. The Middle East and Africa- Perspective White paper. Retrieved April 20, 2021, from https://www.iqvia.com/-/media/iqvia/pdfs/mea/white-paper/biosimilar_iqvia-whitepaper_final.pdf

Batel, R. (2020). Biosimilar's Growth in Pharmerging Markets: An Analysis of the Regulatory Environments. Thesis: South Africa. Retrieved September 08, 2021, from https://etd.uwc.ac.za/bitstream/handle/11394/8325/Batel_M_Nsc_2021.pdf?sequence=1&isAllowed=y

Baumgart, D. C., Misery, L., Naeyaert, S., & Taylor, P. C. (2019). Biological Therapies in Immune-Mediated Inflammatory Diseases: Can Biosimilars Reduce Access Inequities? *Frontiers in pharmacology, 10*, 279. doi: https://doi.org/10.3389/fphar.2019.00279

Bertolani, A. & Jommi, C. (2020). Local policies on biosimilars: are they designed to optimize use of freed resources? *GaBI. 9*(4),163-70. doi: 10.5639/gabij.2020.0904.027

Bhardwaj, P. (2019). Types of Sampling in Research. *Journal of the Practice of Cardiovascular Sciences, 5*, 157-163. doi: 10.4103/jpcs.jpcs_62_19

Biosimilar Council. (2018). Breaking Through on Biosimilars Delivering More-Affordable, Innovative Medicines to America's Patients, The Biosimilar Council- A Division of AAM. 1-24. Retrieved April 20, 2021, from https://biosimilarscouncil.org/wp-content/uploads/2019/04/Breaking-Through-on-Biosimilars-Biosimilars-Council-White-Paper.pdf

Biosimilar Council. (2019). White Paper- Part 2: Failure to launch: Barriers to Biosimilar Market Adoption. Retrieved January 12, 2021, from https://www.biosimilarscouncil.org/wp-content/uploads/2019/09/AAM-Biosimilars-Council-Failure-to-Launch-2-web.pdf

Biosimilars Council. (2019). Failure to launch: Barriers to Biosimilar Market Adoption. Retrieved January 12, 2020, from https://www.biosimilarscouncil.org/wp-content/uploads/2019/09/AAM-Biosimilars-Council-Failure-to-Launch-2-web.pdf

Biosimilars Resource Center. (2020). What Are Biosimilars? Retrieved February 02, 2021, from https://www.biosimilarsresourcecenter.org/

Blignaut, C. (2020). Amgen launches AMGEVITA™ a biosimilar to adalimumab, in South Africa. Retrieved February 02, 2021, from https://medpharm.co.za/home-featured/amgen-launches-amgevitatm-a-biosimilar-to-adalimumab-in-south-africa/#:~:text=AMGEVITA%E2%84%A2%2C%20which%20is%20available,to%20developing%20high%2Dquality%20biosimilars

Blog, F. (2020). 7 Data Collection Methods & Tools For Research. Retrieved February 04, 2021, from https://www.formpl.us/blog/data-collection-method

Boccia, R., Jacobs, I., Popovian, R. & de Lima Lopes, G. (2017). Can biosimilars help achieve the goals of US health care reform? *Cancer Management and Research, 9*, 197–205. doi: https://doi.org/10.2147/CMAR.S133442

Boyatzis, R.E. (1998). Transforming qualitative information: Thematic analysis and code development. USA: Sage Publications, Incorporated, Thousand Oaks.

BRDD. (2021). Biologic and Radiopharmaceutical Drugs Directorate. Retrieved September 17, 2021, from https://www.canada.ca/en/health-canada/corporate/about-health-canada/branches-agencies/health-products-food-branch/biologic-radiopharmaceutical-drugs-directorate.html

Brice, J. & Toscano, D. (2012). GLOBAL BIOSIMILARS MARKET – Large Opportunity Due to Patent Expiries of Blockbuster Biologics. Retrieved April 29, 2021, from https://drug-dev.com/global-biosimilars-market-large-opportunity-due-to-patent-expiries-of-blockbuster-biologics/

BRICS Information portal. (2020). XII BRICS Summit to Be Held on 17 November 2020 Via Videoconference. Retrieved April 19, 2021, from https://infobrics.org/post/31951

Broz, D.K., Galliverti, G. & Bührer, A. (2020). Scientific advice procedures in the EU–an overview of the regulatory background. *Medical Writing. 29*(3), 1-10.

Retrieved April 14, 2021, from https://journal.emwa.org/eu-regulations/scientific-advice-procedures-in-the-eu-an-overview-ofthe-regulatory-background/

Burri, E., Juillerat, P., Maillard, M. H., Manz, M., Michetti, P., et al. (2019). Position statement on the use of biosimilars in inflammatory bowel disease. *Swiss medical weekly, 149*, w20148. doi: https://doi.org/10.4414/smw.2019.20148

Businesswire. (2019). China NMPA Approves Bio-Thera Solutions' QLETLI® (格乐立®), A Biosimilar To Humira® (Adalimumab). Retrieved April 04, 2021, from https://www.businesswire.com/news/home/20191106006189/en/China-NMPA-Approves-Bio-Thera-Solutions%E2%80%99-QLETLI%C2%AE-%E6%A0%BC%E4%B9%90%E7%AB%8B%C2%AE-A-Biosimilar-To-Humira%C2%AE-Adalimumab

Camacho, L. H., Frost, C. P., Abella, E., Morrow, P. K. & Whittaker, S. (2014). Biosimilars 101: considerations for U.S. oncologists in clinical practice. *Cancer medicine, 3*(4), 889–899. doi: https://doi.org/10.1002/cam4.258

Carney, R.F., Gill, R., Lakos, Z., Synder, J. & Zuluaga, D. (2017). Biosimilars and Their Structural Characterization. Retrieved April 29, 2021, from https://www.americanpharmaceuticalreview.com/Featured-Articles/345863-Biosimilars-and-Their-Structural-Characterization/

Castaneda-Hernández, G., Szekanecz, Z., Mysler, E., Azevedo, V. F., Guzman, R., et al. (2014). Biopharmaceuticals for rheumatic diseases in Latin America, Europe, Russia, and India: innovators, biosimilars, and intended copies. *Joint bone spine, 81*(6), 471–477. doi: https://doi.org/10.1016/j.jbspin.2014.03.019

Cazap, E., Jacobs, I., McBride, A., Popovian, R. & Sikora,K. (2018). Global Acceptance of Biosimilars: Importance of Regulatory Consistency, Education, and Trust. *Oncologist 23*(10), 1188-1198. doi: https://doi.org/10.1634/theoncologist.2017-0671

CBER. (1997). *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use*. Retrieved March 04, 2018, from https://www.fda.gov/media/76798/download

CBER. (2020a). SOPP 8404: Refusal to File Procedures. Retrieved February 04, 2021, from https://www.fda.gov/media/111632/download

CBER. (2020b). SOPP 8408.1: Development of Laboratory Quality Product Testing Plans and Release of Lots as Part of the BLA Approval Process. Retrieved February 04, 2021, from https://www.fda.gov/media/103644/download

CDER & CBER. (2015a). *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product*. Retrieved April 04, 2018, from https://www.fda.gov/media/135612/download

CDER & CBER. (2015b). *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*. Retrieved April 14, 2018, from https://www.fda.gov/media/82647/download

CDER & CBER. (2016). *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product*. Retrieved April 04, 2018, from https://www.fda.gov/media/88622/download

CDER & CBER. (2017). *Nonproprietary Naming of Biological Products- Guidance for Industry*. Retrieved January 12, 2021, from https://www.fda.gov/files/drugs/published/Nonproprietary-Naming-of-Biological-Products-Guidance-for-Industry.pdf

CDER & CBER. (2018a). *Questions and Answers on Biosimilar Development and the BPCI Act: Guidance for Industry*. Retrieved April 04, 2018, from https://www.fda.gov/media/119258/download

CDER & CBER. (2018b). *Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products: Guidance for Industry*. Retrieved April 04, 2018, from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-bsufa-products-guidance-industry#:~:text=The%20Food%20and%20Drug%20Administration,FDA%20and%20sponsors%20or%20applicants

CDER & CBER. (2019a). *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations-*

Guidance for Industry. Retrieved April 04, 2021, from https://www.fda.gov/media/125484/download

CDER & CBER. (2019b). *Considerations in Demonstrating Interchangeability With a Reference Product- Guidance for Industry*. Retrieved April 14, 2021, from https://www.fda.gov/media/124907/download

CDER & CBER. (2020a). *Biosimilarity and Interchangeability: Additional Draft Q&As on Biosimilar Development and the BPCI Act- Guidance for Industry (Draft guidance)*. Retrieved April 04, 2021, from https://www.fda.gov/media/143847/download

CDER & CBER. (2020b). *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans- Guidance for Industry*. Retrieved April 04, 2021, from https://www.fda.gov/media/86340/download

CDSCO. (2016). *Guideline on similar biologics: Regulatory Requirements for Marketing Authorization in India*. New Delhi. Retrieved April 04, 2018, from http://dbtindia.gov.in/sites/default/files/uploadfiles/Guidelines_on_Similar_Biologics%2C2016.pdf

CED. (2017). Regulation & the Economy- The Relationship & How to Improve It. Retrieved September 04, 2021, from https://www.ced.org/reports/regulation-and-the-economy

Centers for Medicare and Medicaid Services. (2019). Medicare Part B Drug Average Sales Price. Retrieved January 12, 2021, from https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice

CFDA. (2014). *Technical Guidelines for R&D and Evaluation of biosimilar*. Retrieved April 04, 2021, from https://gabionline.net/guidelines/China-releases-draft-biosimilars-guidance

Chandavarkar A. (2016). Access and Affordability: Impact of Biosimilars. Retrieved April 12, 2021, from https://bioconblog.com/2016/08/01/access-and-affordability-impact-of-biosimilars-2/

Chaudhury, D. R. (2020). BRICS Summit to be held virtually on November 17. Retrieved April 14, 2021, from https://economictimes.indiatimes.com/news/politics-and-nation/brics-summit-to-be-held-virtually-on-november-17/articleshow/78495022.cms

Chauhan, M. K. & Malik, S. (2016). Regulatory guidelines for approval of biosimilar in India, Europe, Brazil and China: A comprehensive overview. *International Journal of Pharmacy and Pharmaceutical Sciences* *8*(10): 7-11. doi:10.22159/ijpps.2016v8i10.11753

Chavez, S. (2013). CME SURVEY BIOSIMILARS. NACCME. Retrieved April 18, 2021, from https://www.naccme.com/sites/naccme.com/files/biosimilar-survey-results.pdf

Chew, C., Aguiar, M., Bansback, N., Law, M.R. & Harrison, M. (2021). Patient perspectives on the British Columbia Biosimilars Initiative: a qualitative descriptive study. *Rheumatology International*. doi: https://doi.org/10.1007/s00296-021-04874-8

Christl, L. A., Woodcock, J. & Kozlowski, S. (2017). Biosimilars: The US Regulatory Framework. *Annual review of medicine, 68*, 243–254. doi: https://doi.org/10.1146/annurev-med-051215-031022

CIRS. (2017). Questionnaire: Implementing an abridged review: What are the criteria and current practices? Centre for Innovation in Regulatory Science.

COFEPRIS (2019). Medicamentos biotechnologicos biocomparables. Retrieved February 14, 2020, from https://www.gob.mx/cms/uploads/attachment/file/468862/Listado_de_Medicamentos_Biotecnol_gicos_Biocomparables__Versi_n_6__11-06-2019.pdf

COFEPRIS. (2014). Official Mexican Standard NOM-257-SSA1-2014, Biotechnological Medications. Retrieved April 04, 2018, from https://www.mexlaws.com/SALUD/NOM-257-SSA1-2014.htm

Cohen, A.D., Wu, J.J., Puig, L., Chimenti, S., Vender, R., et al. (2017). Biosimilars for psoriasis: worldwide overview of regulatory guidelines, uptake and implications for dermatology clinical practice. *British Journal of Dermatology, 177*(6):1495-1502. doi: https://doi.org/10.1111/bjd.15756

Cohen, H., Beydoun, D., Chien, D., Lessor, T., McCabe, D., et al. (2016). Awareness, Knowledge, and Perceptions of Biosimilars Among Specialty Physicians. *Advance Therapy, 33*, 2160–2172. doi: https://doi.org/10.1007/s12325-016-0431-5

Cohen, H.P. & McCabe, D. (2020). The Importance of Countering Biosimilar Disparagement and Misinformation. *BioDrugs*, *34*, 407-414. doi: https://doi.org/10.1007/s40259-020-00433-y

Cohen, H.P., Blauvelt, A., Rifkin, R.M., Danese, S., Gokhale, S.B. & Woollett, G. (2018). Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes. *Drugs, 78,* 463–478. doi: https://doi.org/10.1007/s40265-018-0881-y

Coherent Market Insights. (2020a). Global Biologics Market to surpass US$ 456.83 Billion by 2027, Says CMI. Retrieved February 03, 2021, from https://www.globenewswire.com/news-release/2020/04/03/2011472/0/en/Global-Biologics-Market-to-surpass-US-456-83-8-Billion-by-2027-Says-CMI.html

Coherent Market Insights. (2020b). Biologics Market – Insights. Retrieved February 03, 2021, from https://www.coherentmarketinsights.com/market-insight/biologics-market-2663

Colloca, L., Panaccione, R. & Murphy, T. K. (2019). The Clinical Implications of Nocebo Effects for Biosimilar Therapy. *Frontiers in pharmacology, 10*, 1372. doi: https://doi.org/10.3389/fphar.2019.01372

Corbin, J. & Strauss, A. (1990). Basics of qualitative research: Techniques and Procedures for Developing Grounded theory. USA: Sage Publications, Incorporated.

Curigliano, G., O'Connor, D. P., Rosenberg, J. A. & Jacobs, I. (2016). Biosimilars: Extrapolation for oncology. *Critical Reviews in Oncology/Hematology. 104*,131-137.doi: https://doi.org/10.1016/j.critrevonc.2016.06.002

D'Ambrosio, J. & Ivashko, A. (2013). Biosimilars are Coming. Are You Ready? Retrieved April 20, 2021 from https://clarkstonconsulting.com/wp-content/uploads/2013/07/INSIGHTS_Biosimilars_2013.pdf

Dalgaard, K., Evers, M. & da Silva J.S. (2013). Biosimilars seven years on: Where are we and what's next? Retrieved April 20, 2021 from https://www.mckinsey.de/~/media/mckinsey/dotcom/client_service/pharma%20and%20medical%20products/pmp%20new/pdfs/biosimilars%20seven%20years%20on_white%20paper.pdf

Dallmann, G. (2017). Scientific Advice in the EU and US: Practical Experience and Rules of the Game on Both Sides of the Atlantic. *Pharmazeutische Medizin*. Retrieved April 12, 2021 from https://static1.squarespace.com/static/57d16156414fb5307d454a1d/t/59b0e99003596ea2cfb9ace4/1504766359114/PM217-92-99-DALLMANN.pdf

Davies, N. (2017). The future of biologics. Retrieved January 12, 2021, from https://www.thepharmaletter.com/article/the-future-of-biologics

Davio K. (2018). After Biosimilar Deals, UK Spending on Adalimumab Will Drop by 75%. Retrieved April 29, 2021, from https://www.centerforbiosimilars.com/news/after-biosimilar-deals-uk-spending-on-adalimumab-will-drop-by-75

Davio, K. (2019). In the Effort to Develop Global Comparator Products, Biosimilars Lead the Way. Retrieved August 27, 2021, from https://www.centerforbiosimilars.com/view/in-the-effort-to-develop-global-comparator-products-biosimilars-lead-the-way

DBT. (2020). Office Memorandum: Rapid response framework for COVID-19 to deal with applications develop for vaccines, diagnostics, prophylatics and therapeutics. Retrieved March 04, 2021, from http://dbtindia.gov.in/sites/default/files/om_covid19.pdf

Debiasi, M. , Pimentel, F. , Pereira, P. & Barrios, C. (2017). Biosimilars in Brazil: The Beginning of an Era of Broader Access. *Journal of Cancer Therapy*, *8*, 814-826. doi: 10.4236/jct.2017.89071

Deloitte. (2020). Next Generation Therapies and related Life Sciences topics. Retrieved February 04, 2021, from https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Finance/gx-finance-next-generation-therapies.pdf

DeRosier, J. (2020). Greater uptake, education needed to realize cost-saving potential of biosimilars. Retrieved February 04, 2021, from https://www.healio.com/news/hematology-oncology/20201009/greater-uptake-education-needed-to-realize-costsaving-potential-of-biosimilars

DiGrande, S. (2018). Rituximab Biosimilar to Launch in Turkish Market. Retrieved February 04, 2019, from https://www.centerforbiosimilars.com/view/rituximab-biosimilar-to-launch-in-turkish-market

Dokumeds. (2021). The Importance of Scientific Advice from the Regulatory Authorities in Clinical Research. Retrieved July 05, 2021, from https://www.dokumeds.com/insights/the-importance-of-scientific-advice-from-the-regulatory-authorities-in-clinical-research

Druedahl, L. C., Almarsdóttir, A. B., Kälvemark Sporrong, S., De Bruin. M. L., Hoogland, H., et al. (2020). A qualitative study of biosimilar manufacturer and regulator perceptions on intellectual property and abbreviated approval pathways. *Nature Biotechnology, 38*, 1253–1256. doi: https://doi.org/10.1038/s41587-020-0717-7

Dutta, B., Huys, I., Vulto, A.G. & Simoens, S. (2020). Identifying Key Benefits in European Off-Patent Biologics and Biosimilar Markets: It is Not Only About Price! *BioDrugs, 34*, 159–170. doi: https://doi.org/10.1007/s40259-019-00395-w

Ebbers, H. C. & Schellekens,H. (2019). Are we ready to close the discussion on the interchangeability of biosimilars? *Drug Discovery Today 24*(10), 1963-1967. doi:10.1016/j.drudis.2019.06.016

EFPIA. (2017). White paper on reliance and expedited registration pathways in emerging markets. Retrieved July 05, 2019, from https://www.efpia.eu/media/288592/white-paper-on-reliance-and-expedited-registration-pathways-in-emerging-markets.docx

Elvidge, S. (2013). Emerging Markets And Your Global Regulatory Strategy. *Pharmaceutical Online*. Retrieved July 05, 2021, from https://www.pharmaceuticalonline.com/doc/emerging-markets-and-your-global-regulatory-strategy-0001

EMA. (2000). *Development Pharmaceutics for Biotechnological and Biological Products. CPMP/BWP/328/99.* London: EMA CHMP. Retrieved April 04, 2018, from https://www.ema.europa.eu/en/documents/scientific-guideline/development-pharmaceutics-biotechnological-biological-products-cpmp/bwp/328/99-annex-note-guidance-development-pharmaceutics-cpmp/qwp/155/96_en.pdf

EMA. (2005). *Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products*. London: EMA CHMP. Retrieved April 20, 2021, from https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF

EMA. (2007). *Guideline on the Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins. CHMP/EWP/89249/2004*. London: EMA CHMP. Retrieved April 04, 2018, from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-pharmacokinetics-therapeutic-proteins_en.pdf

EMA. (2010). *Directive 2010/63/EU of The European Parliment and of the council of 22 September 2010 on the protection of animals used for scientific purposes.* Official Journal of the European Union. London: EMA CHMP. Retrieved April 20, 2021, from https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:en:PDF

EMA. (2013). *Principles for publication of agendas and minutes of EMA scientific committees. EMA/555647/2013.* London: EMA CHMP. Retrieved September 17, 2021, from https://www.ema.europa.eu/en/documents/other/principles-publication-agendas-minutes-ema-scientific-committees_en.pdf

EMA. (2014a). *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. EMA/CHMP/BWP/247713/2012*. London: EMA CHMP. Retrieved April 4, 2018, from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-0.pdf

EMA. (2014b). *Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 Rev1.* 1-13. London: EMA CHMP. Retrieved April 05, 2018, from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf

EMA. (2015). *Guideline on similar biological medicinal products. CHMP/437/04 Rev 1.* London: EMA CHMP. Retrieved April 05, 2018, from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1_en.pdf

EMA. (2016a). *Tailored scientific advice to support step-by-step development of new biosimilars*. London: EMA CHMP. Retrieved March 24, 2021, from https://www.ema.europa.eu/en/news/tailored-scientific-advice-support-step-step-development-new-biosimilars

EMA. (2016b). *Guideline on development, production, characterisation and specification for monoclonal antibodies and related products. EMA/CHMP/BWP/532517/2008*. London: EMA CHMP. Retrieved April 04, 2021, from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-development-production-characterisation-specification-monoclonal-antibodies-related_en.pdf

EMA. (2017). *Guideline on Immunogenicity assessment of therapeutic proteins. EMEA/CHMP/BMWP/14327/2006 Rev 1.* London: EMA CHMP. Retrieved April 04, 2021, from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-immunogenicity-assessment-therapeutic-proteins-revision-1_en.pdf

EMA. (2019). *Biosimilars in the EU: Information guide for healthcare professionals*. London: EMA CHMP. Retrieved April 14, 2021, from https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf

EMA. (2020a). *European Medicines Agency Guidance for Applicants seeking scientific advice and protocol assistance. EMA/4260/2001 Rev. 10.* London: EMA CHMP. Retrieved April 04, 2021, from

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-medicines-agency-guidance-applicants-seeking-scientific-advice-protocol-assistance_en.pdf

EMA. (2020b). *Clinical pharmacology and pharmacokinetics: questions and answers*. London: EMA CHMP. Retrieved April 04, 2021, from https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/clinical-pharmacology-pharmacokinetics-questions-answers

EMA. (2021a). *How scientific Advice works. In: Scientific advice and protocol assistance*. London: EMA CHMP. Retrieved April 04, 2021, from https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance#how-scientific-advice-works-section

EMA. (2021b). How the committees work. Retrieved September 17, 2021, from https://www.ema.europa.eu/en/committees/how-committees-work

EMA. (2021c). Marketing authorisation. Retrieved September 17, 2021, from https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation

EP News Bureau. (2020a). Cadila Pharma launches Cadalimab (adalimumab biosimilar) for India. Retrieved February 04, 2021, from https://www.expresspharma.in/latest-updates/cadila-pharma-launches-cadalimab-adalimumab-biosimilar-for-india/

EP News Bureau. (2020b). Cadila Pharma expands oncology portfolio with biosimilar cancer drug Bevaro. Retrieved February 04, 2021, from https://www.expresspharma.in/latest-updates/cadila-pharmaceuticals-expands-oncology-portfolio-with-biosimilar-cancer-drug-bevaro/

Eurasian Economic Union (2014). Approval of Rules for conducting research of biological medicines of the Eurasian Economic Union (EAEU). Retrieved September 19, 2021, from https://www.rceth.by/Documents/9es10rsN7820161103_e.pdf

European Commission. (2019). 2019 IQVIA Report - The Impact of Biosimilar Competition in Europe. Retrieved Spetember 14, 2021, from https://ec.europa.eu/docsroom/documents/38461

Ferreri, D. (2020). WHO Survey Identifies Global Regulatory Challenges for Biosimilars. *AJMC*. Retrieved January 12, 2021, from https://www.centerforbiosimilars.com/view/who-survey-identifies-global-regulatory-challenges-for-biosimilars

Fidan, E. C. (2019). Turkey life sciences sector outlook. Flanders Investment and Trade: 1-30. Retrieved August 20, 2021, from https://www.flandersinvestmentandtrade.com/export/sites/trade/files/market_studies/Life%20Science%20Market%20Study%20-%20Turkey.pdf

Frantzen, L., Cohen, J. D., Tropé, S., Beck, M., Munos, A., et al. (2019). Patients' information and perspectives on biosimilars in rheumatology: A French nation-wide survey. *Joint bone spine, 86*(4), 491–496. doi: https://doi.org/10.1016/j.jbspin.2019.01.001

Frapaise F. X. (2018). The End of Phase 3 Clinical Trials in Biosimilars Development?. *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy, 32*(4), 319–324. doi: https://doi.org/10.1007/s40259-018-0287-0

GaBI. (2014). Biosimilar infliximab receives approval in Japan and Turkey. Retrieved April 20, 2021, from https://www.gabionline.net/biosimilars/news/Biosimilar-infliximab-receives-approval-in-Japan-and-Turkey#:~:text=South%20Korean%20biotechnology%20company%20Celltrion,in%20Japan%20and%20Turkey%2C%20respectively

GaBI. (2015). Mexico issues rules on biolimbos. Retrieved April 20, 2021, from https://www.gabionline.net/Guidelines/Mexico-issues-rules-on-biolimbos

GaBI. (2016). Dr Reddy's and TRPharm collaborate on biosimilars in Turkey. Retrieved August 20, 2021, from https://www.gabionline.net/pharma-news/Dr-Reddy-s-and-TRPharm-collaborate-on-biosimilars-in-Turkey

GaBI. (2018). Australian guidelines for biosimilars. Retrieved April 10, 2021, from https://www.gabionline.net/Guidelines/Australian-guidelines-for-biosimilars

GaBI. (2019). Bevacizumab ‘similar biologic’ Versavo launched in India. Retrieved April 14, 2019, from https://www.gabionline.net/biosimilars/news/Bevacizumab-similar-biologic-Versavo-launched-in-India#:~:text=India%2Dbased%20generics%20manufacturer%20Dr,is%20a%20humanized%20monoclonal%20antibody

GaBI. (2020a). Cadila Pharmaceuticals launches two similar biologics in India. Retrieved April 14, 2021, from https://www.gabionline.net/biosimilars/news/Cadila-Pharmaceuticals-launches-two-similar-biologics-in-India#:~:text=Indian%20generics%20maker%20Cadila%20Pharmaceuticals,is%20a%20humanized%20monoclonal%20antibody.&text=The%20originator%20product%2C%20Avastin%2C%20is%20sold%20by%20Roche%2FGenentech

GaBI. (2020b). China approves bevacizumab copy biological Ankada. Retrieved April 14, 2021, from https://www.gabionline.net/biosimilars/news/China-approves-bevacizumab-copy-biological-Ankada

GaBI. (2020c). Non-originator biologicals approved in Russia. Retrieved April 14, 2021, from https://www.gabionline.net/biosimilars/general/Non-originator-biologicals-approved-in-Russia

GaBI. (2021a). A new decree modifies several aspects of the regulatory approval system for biosimilars in Mexico. Retrieved August 19, 2021, from https://www.gabionline.net/guidelines/a-new-decree-modifies-several-aspects-of-the-regulatory-approval-system-for-biosimilars-in-mexico

GaBI. (2021b). Biosimilars approved in Australia. Retrieved February 26, 2021, from https://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Australia

GaBI. (2021c). Biosimilars and lack of resources. Retrieved April 13, 2021, from https://www.gabionline.net/Biosimilars/Research/Biosimilars-and-lack-of-resources

Garcia, R. & Araujo, D.V. (2016). The Regulation of Biosimilars in Latin America. *Current Rheumatology Reports, 18*(3),16. doi: https://doi.org/10.1007/s11926-016-0564-1

Gautam, A. (2017). Strategies for biosimilars in emerging markets. *Nature Reviews Drug Discovery, 16*, 520-521. doi: https://doi.org/10.1038/nrd.2017.113

GBR & IEIS. (2020). Turkey Pharmaceuticals and Biopharmaceuticals. Global Business reports- Industry Explorations. Retrieved August 20, 2021, from https://www.gbreports.com/files/pdf/_2020/Turkey_Pharma_2020_-_Web_Version.pdf

Giuliani, R., Tabernero, J., Cardoso, F., McGregor, K. H., Vyas, M. & de Vries, E. (2019). Knowledge and use of biosimilars in oncology: a survey by the European Society for Medical Oncology. *ESMO Open, 4(2)*, e000460. doi: https://doi.org/10.1136/esmoopen-2018-000460

Godman, B., Allocati, E., Moorkens, E. (2019). Ever-Evolving landscape of biosimilars in Canada; findings and implications from a global perspective. *GaBI, 8*(3), 93-97. doi: 10.5639/gabij.2019.0803.012

Godman, B., Allocati, E., Moorkens, E. & Kwon, H. (2020). Can local policies on biosimilars optimize the use of freed resources – experiences from Italy. *GaBI, 9*(4):183-187. doi: 10.5639/gabij.2020.0904.029

Godman, B., Haque, M., Leong, T., Allocati, E., Kumar, S., et al. (2021). The Current Situation Regarding Long-Acting Insulin Analogues Including Biosimilars Among African, Asian, European, and South American Countries; Findings and Implications for the Future. *Frontiers in public health, 9*, 671961. doi: https://doi.org/10.3389/fpubh.2021.671961

Goll, G. L., Jørgensen, K. K., Sexton, J., Olsen, I. C., Bolstad, N., et al. (2019). Long-term efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: open-label extension of the NOR-SWITCH trial. *Journal of Internal Medicine. 285*(6),653-669.doi: https://doi.org/10.1111/joim.12880

Grabowski, H. G., Guha, R. & Salgado, M. (2014). Regulatory and cost barriers are likely to limit biosimilar development and expected savings in the near future. *Health affairs (Project Hope), 33*(6), 1048–1057. doi: https://doi.org/10.1377/hlthaff.2013.0862

Griffiths, E. (2020). Quality standards for biopharmaceuticals: the importance of good manufacturing practice. *GaBI 9*(3), 97-99. doi: https://doi.org/10.5639/gabij. 2020. 0903.017

Gundumogula, M. (2020). Importance of Focus Groups in Qualitative Research. *International Journal of Humanities and Social Science, 8*(11), 299-302. doi: http://dx.doi.org/10.24940/theijhss%2F2020%2Fv8%2Fi11%2FHS2011-082

Gupta, S. K., Chaudhari, P. S. & Nath, R. (2017). Opportunities and Challenges in Biosimilar Development. Retrieved June 14, 2021, from https://bioprocessintl.com/manufacturing/biosimilars/opportunities-challenges-biosimilar-development/

Hagen, T. (2021). China pulls out stops for biosimilar development. *AJMC*. Retrieved September 15, 2021, https://www.centerforbiosimilars.com/view/china-pulls-out-stops-for-biosimilar-development

Halimi, V., Daci, A., Ancevska Netkovska, K., Suturkova, L., Babar, Z. U., & Grozdanova, A. (2020). Clinical and Regulatory Concerns of Biosimilars: A Review of Literature. *International journal of environmental research and public health, 17*(16), 5800. doi: https://doi.org/10.3390/ijerph17165800

Hamzi, T. (2019). Evaluation of biosimilars landscape in the MENA region: what lessons can be learnt from the European experience to improve the biosimilars uptake in the region? The University of Warwick. Thesis. Retrieved April 14, 2021, from https://www.researchgate.net/publication/340314764_Evaluation_of_biosimilars_landscape_in_the_MENA_region_what_lessons_can_be_learnt_from_the_European_experience_to_improve_the_biosimilars_uptake_in_the_region

Haqaish, W., Obeidat, H., Patel, P. & Walker, S. (2017). The Jordan Food and Drug Administration: Comparison of its registration process with Australia, Canada, Saudi Arabia and Singapore. *Pharmaceutical Medicine, 31*, 21-30. doi: https://doi.org/10.1007/s40290-016-0172-4

Harrison, K. (2019). Herceptin (Molecule of the Month for August 2005) – Trastuzumab. Retrieved March 20, 2021, from https://www.3dchem.com/Herceptin-1N8Z.asp#

Harsanyi, A., Csanádi, M., Márky, K., Vinczickzki, Á. Z., Kaló, Z. & Inotai, A. (2020). Influence of biosimilar infliximab launch on the utilization pattern of biological medicines: the case of Hungary. *Expert review of pharmacoeconomics & outcomes research, 20*(6), 653–659. doi: https://doi.org/10.1080/14737167.2019.166723

Hashan, H., Aljuffali, I., Patel, P. & Walker, S. (2016). The Saudi Arabia Food and Drug Authority: An Evaluation of the Registration Process and Good Review Practices in Saudi Arabia in Comparison with Australia, Canada and Singapore. *Pharmaceutical Medicine, 30*, 37–47. doi: https://doi.org/10.1007/s40290-015-0124-4

Health Canada. (2012). *Guidance Document: Conduct and Analysis of Comparative Bioavailability Studies*. Retrieved May 14, 2021, from https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/bioavailability-bioequivalence/conduct-analysis-comparative.pdf

Health Canada. (2016). *Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs*. Retrieved May 06, 2021, from https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/brgtherap/applic-demande/guides/seb-pbu/seb-pbu-2016-eng.pdf

Health Canada. (2017). *Fact Sheet: Biosimilars*. Retrieved May 14, 2018, from https://safebiologics.org/wp-content/uploads/2015/02/biosimilars-biosimilaires-qa-qr-eng.pdf

Health Canada. (2019). *Biosimilar biologic drugs in Canada: Fact Sheet*. Retrieved February 10, 2021, from https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/brgtherap/applic-demande/guides/Fact-Sheet-EN-2019-08-23.pdf

Health Canada. (2021). *Guidance Document: Management of Drug Submissions and Applications*. Retrieved September 17, 2021, from https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/management-drug-submissions/industry/guidance-document-management-drug-submissions-applications.pdf

Higuera, V. (2020). Biologics for AS: What Are Your Options? Retrieved February 04, 2021, from https://www.healthline.com/health/beyond-back-pain-with-as/biologic-options

Hindustan Times. (2020). Virtual BRICS Summit on Nov 17; PM Modi, Xi set for a face-off. Retrieved April 14, 2021, from https://www.hindustantimes.com/india-news/brics-summit-to-be-held-virtually-on-nov-17-cooperation-strengthening-global-stability-on-agenda/story-Io02j2Xpb81KAx03C13O1M.html

Hobbs, A. L. & Crawford, J. P. (2019). Biosimilars and implications for pharmacy practice: Ready or not, here they come! *Pharmacy practice, 17*(3), 1659. doi: https://doi.org/10.18549/PharmPract.2019.3.1659

Horn, S., Berglund, R. & Tavantzis, M. (2021). Barriers to biosimilar market growth. *Alvarez & Marsal Holdings*. Retrieved April 18, 2021, from https://www.alvarezandmarsal.com/insights/barriers-biosimilar-market-growth

ICH. (1999). *Specifications: Test procedures and acceptance criteria for biotechnological/ biological products Q6B*. Geneva. Retrieved April 14, 2021, from https://database.ich.org/sites/default/files/Q6B%20Guideline.pdf

ICH. (2004). Geneva. *Comparability of biotechnological/biological products subject to changes in their manufacturing process Q5E*. Geneva. Retrieved April 04, 2018, from https://database.ich.org/sites/default/files/Q5E%20Guideline.pdf

ICH. (2009). *Guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2).* 1-31. Geneva. Retrieved April 04, 2018, from https://database.ich.org/sites/default/files/M3_R2__Guideline.pdf

ICMRA. (2021). Informal Innovation Network Horizon Scanning Assessment Report – Artificial Intelligence. Retrieved August 26, 2021, from http://www.icmra.info/drupal/sites/default/files/2021-08/horizon_scanning_report_artificial_intelligence.pdf

IFPMA. (2020). What is an 'assessment report' and why are they important for regulatory reliance? Retrieved September 14, 2021, from https://www.ifpma.org/wp-content/uploads/2019/10/Assessment-Reports_FAQs-vFINAL.pdf

IGBA. (2019). The Importance of Global Regulatory Harmonization for Biosimilar Medicines. Retrieved January 12, 2021, from https://www.igbamedicines.org/doc/20191104_SKox_AAM%20conf_FINAL.pdf

IGBA. (2020). Developing a Regulatory Policy Framework Supporting Biosimilar Competition: The Opportunity for Tailored Clinical Biosimilar Development [Policy paper]. Retrieved April 20, 2021, from https://www.igbamedicines.org/doc/IGBA%20Biosimilars%20Clinical%20Trial%20Tailoring%20policy%20paper%20Sept2020%20revision02.pdf

IMF. (2020). GDP, Current prices. Retrieved August 19, 2021, from https://www.imf.org/external/datamapper/NGDPD@WEO/WEOWORLD/BRA/CHN/IND/MEX/ZAF/TUR/RUS

IMF. (2021). GDP, Current prices. Retrieved August 19, 2021, from https://www.imf.org/external/datamapper/NGDPD@WEO/WEOWORLD/BRA/CHN/IND/MEX/ZAF/TUR/RUS

Institute of Medicine (2013). International Regulatory Harmonization Amid Globalization of Drug Development: Workshop Summary. Washington, DC. The National Academies Press. Retrieved April 20, 2021, from https://www.ncbi.nlm.nih.gov/books/NBK153504/ doi: 10.17226/18324

International Network for Natural Sciences. (2020). Types of scientific research. Retrieved February 06, 2021, from https://innspub.net/types-of-scientific-research/

IQVIA. (2019a). The Global Use of Medicine in 2019 and Outlook to 2023: Forecasts and Areas to Watch. Retrieved January 12, 2021, from https://www.iqvia.com/insights/the-iqvia-institute/reports/the-global-use-of-medicine-in-2019-and-outlook-to-2023

IQVIA. (2019b). Medicine Use and Spending in the U.S.: A Review of 2018 and Outlook to 2023. Retrieved April 14, 2021, from https://www.iqvia.com/insights/the-iqvia-institute/reports/medicine-use-and-spending-in-the-us-a-review-of-2018-and-outlook-to-2023

IQVIA. (2020a). Biosimilars in the United States 2020–2024 Competition, Savings, And Sustainability. Retrieved August 16, 2021, from https://www.iqvia.com/-

/media/iqvia/pdfs/institute-reports/iqvia-institute-biosimilars-in-the-united-states.pdf

IQVIA. (2020b). Biologics Market Dynamics: Setting the Stage for Biosimilars. FDA/FTC Workshop on a Competitive Marketplace for Biosimilar. Retrieved January 12, 2021, from https://www.ftc.gov/system/files/documents/public_events/1568297/aitken_-_biologics_market_dynamics_setting_the_stage_for_biosimilars_slides.pdf

Isaacs J, Gonçalves J, Strohal R, Castañeda-Hernández, G., Azevedo, Vet al. (2017). The biosimilar approval process: how different is it? *Considerations in Medicine,1*. doi: 10.1136/conmed-2017-100003

Jacobs, I., Singh, E., Sewell, K. L., Al-Sabbagh, A. & Shane, L. G. (2016). Patient attitudes and understanding about biosimilars: an international cross-sectional survey. *Patient preference and adherence, 10*, 937–948. doi: https://doi.org/10.2147/PPA.S104891

Jacoby, R., Smith, E., & Wilkins, D. (2015). Winning with Biosimilars: Opportunities in global markets. Deloitte Consulting LLP. Retrieved September 19, 2021, from https://www2.deloitte.com/content/dam/Deloitte/us/Documents/life-sciences-health-care/us-lshc-biosimilars-whitepaper-final.pdf

Jain, A., Mollet, A. & Szucs, T.D. (2017). Structural and procedural characteristics of international regulatory authorities. *Nature Reviews Drug Discovery, 16,* 594. doi: https://doi.org/10.1038/nrd.2017.135

Jensen, T. B., Kim, S. C., Jimenez-Solem, E., Bartels, D., Christensen, H. R. & Andersen, J. T. (2020). Shift From Adalimumab Originator to Biosimilars in Denmark. *JAMA internal medicine, 180*(6), 902–903. doi: https://doi.org/10.1001/jamainternmed.2020.0338

Jeremias, S. (2020). Part 2: Modifications Could Help India's Biosimilars Powerhouse. Retrieved April 12, 2021, from https://www.centerforbiosimilars.com/view/part-2-modifications-could-help-indias-biosimilars-powerhouse

Jiménez-Pichardo, L., Gázquez-Pérez, R., & Sierra-Sánchez, J. F. (2018). Degree of prescriber's knowledge about variability in biological drugs "innovators" in

manufacturing process. *European journal of clinical pharmacology, 74*(4), 505–511. doi: https://doi.org/10.1007/s00228-017-2397-x

Jois, R., Mukherjee, S., Rajeswari, S., Rath, P. D., Goyal, V., & Gupta, D. (2020). Similar biologics in India: A story of access or potential for compromise? *The Indian journal of medical research, 152*(5), 456–467. doi: https://doi.org/10.4103/ijmr.IJMR_43_18

Jørgensen K.K., Olsen I.C., Goll G.L., Lorentzen, M., Bolstad, N., et al. (2017). Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet. 389*(10086),2304–2316.doi: https://doi.org/10.1016/S0140-6736(17)30068-5

Jost, N., Schüssler-Lenz, M., Ziegele, B., & Reinhardt, J. (2015). Wissenschaftliche Beratung durch nationale und europäische Zulassungsbehörden bei Arzneimitteln für neuartige Therapien [Scientific advice by the national and European approval authorities concerning advanced therapy medicinal products]. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz, 58*(11-12), 1207–1214. doi: https://doi.org/10.1007/s00103-015-2236-0

Kabir, E.R., Moreino, S.S. & Sharif Siam, M.K. (2019). The Breakthrough of Biosimilars: A Twist in the Narrative of Biological Therapy. *Biomolecules, 9*(9), 410. doi: https://doi.org/10.3390/biom9090410

Kabir, S.M.S. (2016). Methods of Data Collection. In book: Basic Guidelines for Research: An Introductory Approach for All Disciplines. pp.201-275. First Edition. Chapter 9. Book Zone Publication, Bangladesh.

Kang, H. N., Thorpe, R., Knezevic, I., Casas Levano, M., Chilufya, M. B., et al. (2021). Regulatory challenges with biosimilars: an update from 20 countries. *Annals of the New York Academy of Sciences, 1491*(1), 42–59. doi: https://doi.org/10.1111/nyas.14522

Kang, H.N., Thorpe, R., Damas, I. K. C., Blades, R. Z., Levano, M. C., et al. (2020). The regulatory landscape of biosimilars: WHO efforts and progress made from 2009 to 2019. *Biologicals, 65,* 1-9. doi: https://doi.org/10.1016/j.biologicals.2020.02.005

Karateev, D. & Belokoneva, N. (2019). Evaluation of Physicians' Knowledge and Attitudes Towards Biosimilars in Russia and Issues Associated with Their Prescribing. *Biomolecules, 9*(2), 1-14.doi: https://doi.org/10.3390/biom9020057

Kay, J. & Isaacs, J. D. (2017). Clinical trials of biosimilars should become more similar. *Annals of the rheumatic diseases, 76*(1), 4–6. doi: https://doi.org/10.1136/annrheumdis-2015-208113

Kent, D., Rickwood, S. & Biase. S. D. (2017). Disruption and maturity: The next phase of biologics. Retrieved January 12, 2021, from https://www.iqvia.com/-/media/iqvia/pdfs/nemea/uk/disruption_and_maturity_the_next_phase_of_biologics.pdf

Keyter, A., Salek, S., Banoo, S. & Walker, S. (2019). The South African Medicines Control Council: Comparison of Its Registration Process With Australia, Canada, Singapore, and Switzerland. *Frontiers in Pharmacology, 10*. 228. doi: https://doi.org/10.3389/fphar.2019.00228

Keyter, A., Salek, S., Banoo, S. & Walker, S. (2020). Can Standardisation of the Public Assessment Report Improve Benefit Risk Communication? *Frontiers in Pharmacology, 11*(855), 1-13. doi: https://doi.org/10.3389/fphar.2020.00855

Kilic, S. & Unal, N. (2021). COVID-19: Turkey to Extend Measures for GMP Inspections and Certification. Retrieved April 03, 2021, from https://herdem.av.tr/covid-19-turkey-to-extend-measures-for-gmp-inspections-and-certification

Kim, Y., Kwon, H. Y., Godman, B., Moorkens, E., Simoens, S., & Bae, S. (2020). Uptake of Biosimilar Infliximab in the UK, France, Japan, and Korea: Budget Savings or Market Expansion Across Countries? *Frontiers in pharmacology, 11*, 970. doi: https://doi.org/10.3389/fphar.2020.00970

Kos, I. A., Azevedo, V. F., Neto, D. E., & Kowalski, S. C. (2018). The biosimilars journey: current status and ongoing challenges. *Drugs in context, 7*, 212543. https://doi.org/10.7573/dic.212543

Kostic, M., Djakovic, L., Sujic, R., Godman, B. & Jankovic, S. M. (2017). Inflammatory Bowel Diseases (Crohn´s Disease and Ulcerative Colitis): Cost of

Treatment in Serbia and the Implications. *Applied health economics and health policy, 15*(1), 85–93. doi: https://doi.org/10.1007/s40258-016-0272-z

Krishnan, A., Mody, R. & Malhotra, H. (2015). Global regulatory landscape of biosimilars: emerging and established market perspectives. *Biosimilars, 5*, 19—32. doi: https://doi.org/10.2147/BS.S44052

Kuhler, T. (2020). Regulatory Reliance Also Applies to Mature Regulatory Agencies. Retrieved April 12, 2021, from https://globalforum.diaglobal.org/issue/november-2020/regulatory-reliance-also-applies-to-mature-regulatory-agencies/

Kurki, P., van Aerts, L., Wolff-Holz, E., Giezen, T., Skibeli, V. & Weise, M. (2017). Interchangeability of Biosimilars: A European Perspective. *BioDrugs 31*, 83–91. doi: https://doi.org/10.1007/s40259-017-0210-0

Kvien, T.K. (2020). Biosimilars - An effective treatment at a lower cost. Research Outreach. 2020. Retrieved April 12, 2021, from https://researchoutreach.org/articles/biosimilars-effective-treatment-lower-cost/

Leintz, C. J. & Dedhia, R. (2015). Biosimilars and Emerging Markets: Historical and Bioethical Considerations. *Journal of Clinical Research & Bioethics, 6*(5), 1-4. doi: 10.4172/2155-9627.1000243

Leng, H. M., Mutoti, K. P., & Mbelle, N. (2015). Regulatory requirements for the development and registration of biosimilars in South Africa. *GaBI, 4*(3): 150-152. doi: 10.5639/gabij.2015.0403.033

Leonard, E., Wascovich, M., Oskouei, S., Gurz, P., & Carpenter, D. (2019). Factors Affecting Health Care Provider Knowledge and Acceptance of Biosimilar Medicines: A Systematic Review. *Journal of managed care & specialty pharmacy, 25*(1), 102–112. doi: https://doi.org/10.18553/jmcp.2019.25.1.102

Lexchin J. (2020). Affordable Biologics for All. *JAMA Network Open*. *3*(4),e204753. doi: https://doi.org/10.1001/jamanetworkopen.2020.4753

Li, E. & Hoffman, J. M. (2013). Implications of the FDA draft guidance on biosimilars for clinicians: what we know and don't know. Journal of the National Comprehensive *Cancer Network : JNCCN, 11*(4), 368–372. doi: https://doi.org/10.6004/jnccn.2013.0052

Limaye, R. (2016a). Prospects, Analysis and Trends in Global Pharma Industry Expert Panel Submissions. Realizing the Promise of Biosimilars in 2020. Barcelona: CPhI Annual Industry Report.

Limaye, R. (2016b). Overcoming The Barriers To Global Biosimilar Adoption. Retrieved April 04, 2021, from https://www.bioprocessonline.com/doc/overcoming-the-barriers-to-global-biosimilar-adoption-0001

Lin, S. (2018). The Dark Web, An unlimited resource for unregulated drugs. Retrieved September 07, 2021, from https://medium.com/@shenlin2/the-dark-web-an-unlimited-resource-for-unregulated-drugs-7cf2d350d7a1

Lopes, G. (2016). Biosimilars in Emerging Markets: India and Russia. Retrieved April 04, 2021, from https://connection.asco.org/blogs/biosimilars-emerging-markets-india-and-russia

Lopez-Morales, C. A., Tenorio-Calvo, A., Cruz-Rodríguez, R., Sánchez Y Tepoz, J., Belgharbi, L., et al. (2018). Regulatory Pathway for Licensing Biotherapeutics in Mexico. *Frontiers in medicine, 5*, 272. doi: https://doi.org/10.3389/fmed.2018.00272

Lozda R. (2016). Regulatory System Changes in Russia: A Historical Review and Future Perspectives. *Therapeutic innovation & regulatory science, 50*(4), 414–418. doi: https://doi.org/10.1177/2168479015627853

Lucio, S. (2018). The Complexities of Biosimilars and the Regulatory Approval Process. *AJMC*. Retrieved September 13, 2021, from https://www.ajmc.com/view/complexities-biosimilars-regulatory-approval-process

Lungu, E. (2019). Biosimilars in Canada: Current Environment and Future Opportunity. presentation in CADTH. Canada. Retrieved April 14, 2021, from https://cadth.ca/sites/default/files/symp-2019/presentations/april15-2019/B3-presentation-elungu.pdf

Lyman, G.H., Balaban, E., Diaz, M., Ferris, A., Tsao, A., et al. (2018). American Society of Clinical Oncology Statement: Biosimilars in Oncology. *Journal Of Clinical Oncology, 36*(12), 1260-1265. doi: https://doi.org/10.1200/JCO.2017.77.4893

Macdonald, G. (2020). Risks, reforms and rewards: the evolving Russian healthcare market. Retrieved February 14, 2021,

http://www.pmlive.com/pharma_intelligence/Risks,_reforms_and_rewards_the_evolving_Russian_healthcare_market_1338647

Makurvet, F.D. (2021). Biologics vs. small molecules: Drug costs and patient access. *Medicine in Drug Discovery, 9*, 100075. doi: https://doi.org/10.1016/j.medidd.2020.100075

Malakoane, B., Heunis, J. C., Chikobvu, P., Kigozi, N. G. & Kruger, W. H. (2020). Public health system challenges in the Free State, South Africa: a situation appraisal to inform health system strengthening. *BMC Health Services Research, 20*(58), 1-14. doi: https://doi.org/10.1186/s12913-019-4862-y

Marison, I. & Levison, P. (2019). Skills Shortage: Could the Pharmaceutical Industry Be in Trouble? Retrieved September 07, 2021, from https://www.labmanager.com/insights/skills-shortage-could-the-pharmaceutical-industry-be-in-trouble-21301

Markenson, J., Alvarez, D. F., Jacobs, I. & Kirchhoff C. (2017). A practical guide about biosimilar data for health care providers treating inflammatory diseases. *Biologics,11*, 13–21.doi: https://doi.org/10.2147/BTT.S122335

Markus, R., Born, T. , Liu, J. , Kaur, P. Ramchandani, M. & Landa, D. (2017). Developing the Totality of Evidence for Biosimilars: Regulatory Considerations and Building Confidence for the Healthcare Community. *BioDrugs, 31*, 175–187. doi: https://doi.org/10.1007/s40259-017-0218-5

Mashaki Ceyhan, E., Gürsöz, H., Alkan, A., Coskun, H., Koyuncu, O. & Walker, S. (2018). The Turkish Medicines and Medical Devices Agency: Comparison of Its Registration Process with Australia, Canada, Saudi Arabia, and Singapore. *Frontiers in Pharmacology,9,* 1-16. doi: https://doi.org/10.3389/fphar.2018.00009

McAuslane, N., Cone, M., Collins, J. & Walker, S. (2009). Emerging Markets and Emerging Agencies: A Comparative Study of How Key Regulatory Agencies in Asia, Latin America, the Middle East, and Africa are Developing Regulatory Processes and Review Models for New Medicinal Products. *Drug Information Journal, 43,* 349–359. doi: https://doi.org/10.1177/009286150904300314

MCC. (2014). *Biosimilar Medicines Quality, Non-Clinical and Clinical Requirements. 2.30_Biosimilars_Aug14_v3*. South Africa. Retrieved April 04,

2018, from https://www.sahpra.org.za/wp-content/uploads/2020/01/d259816c2.30_Biosimilars_Aug14_v3.pdf

McCamish, M. & Woollett, G. (2011). Worldwide experience with biosimilar development. *mAbs, 3*(2), 209-217.doi: https://doi.org/10.4161/mabs.3.2.15005

McKinnon, R. A., Cook, M., Liauw, W., Marabani, M., Marschner, I. C., et al. (2018). Biosimilarity and Interchangeability: Principles and Evidence: A Systematic Review. *BioDrugs, 32*(1), 27–52.doi: https://doi.org/10.1007/s40259-017-0256-z

McKinsey & Company. (2018). Five things to know about biosimilars right now. Retrieved January 12, 2021, from https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/five-things-to-know-about-biosimilars-right-now

Mckinsey & Company. (2019). What's next for biosimilars in emerging markets? Retrieved April 04, 2021, from https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/whats-next-for-biosimilars-in-emerging-markets

McKinsey & Company. (2020). India Pharma 2020, Propelling access and acceptance, realising true potential. Retrieved June 12, 2021, from https://www.mckinsey.com/~/media/mckinsey/dotcom/client_service/Pharma%20and%20Medical%20Products/PMP%20NEW/PDFs/778886_India_Pharma_2020_Propelling_Access_and_Acceptance_Realising_True_Potential.ashx

Med Ad News (2019). Top 10 pipelines to watch: 2019 Annual report, PharmaLive. Retrieved February 12, 2021, from https://www.pharmalive.com/annual-report-2019-top-10-pipelines-to-watch/

Meher, B. R., Balan, S., Mohanty, R. R., Jena, M. & Das, S. (2019). Biosimilars in India; Current Status and Future Perspectives. *Journal of pharmacy & bioallied sciences, 11*(1), 12–15. doi: https://doi.org/10.4103/jpbs.JPBS_167_18

Melao. (2018). Russia Approves Its Local Company BIOCAD's Infliximab Biosimilar for Ankylosing Spondylitis. Retrieved August 12, 2019, from https://ankylosingspondylitisnews.com/2018/03/19/infliximab-biosimilar-for-ankylosing-spondylitis-approved-in-russia/

MHRA. (2021). *Consultation document: MHRA guidance on the licensing of biosimilar products*. Retrieved May 12, 2021, from https://www.gov.uk/government/consultations/mhra-draft-guidance-on-the-licensing-of-biosimilar-products/consultation-document-mhra-guidance-on-the-licensing-of-biosimilar-products

Miglierini, G. (2019). Emerging trends for the pharmaceutical market. Retrieved February 04, 2021, from https://www.pharmaworldmagazine.com/emerging-trends-for-the-pharmaceutical-market/#:~:text=The%20global%20pharmaceutical%20market%20is,might%20reach%2054%20in%202023

Mikulic, M. (2020). Global chemical drug and biologics market size 2014-2023. Retrieved February 04, 2021, from https://www.statista.com/statistics/1085563/revenue-chemical-drugs-and-biologics-global-pharmaceuticals/#statisticContainer

Mintz, C. (2013). Biosimilars In Emerging Markets. Retrieved April 04, 2021, from https://www.bioprocessonline.com/doc/biosimilars-in-emerging-markets-0001

Mishra, P., Pandey, C. M., Singh, U., Keshri, A. & Sabaretnam, M. (2019). Selection of appropriate statistical methods for data analysis. *Annals of cardiac anaesthesia, 22*(3), 297–301. doi: https://doi.org/10.4103/aca.ACA_248_18

Mminele, D. (2016). The role of BRICS in the global economy. Retrieved April 14, 2021, Retrieved April 04, 2021, from https://www.bis.org/review/r160720c.htm

MoHFW. (2019). *The New Drugs and Clinical Trials Rules, The Gazette of India*. New Delhi. Retrieved April 04, 2021, from https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf

Moore, T. J., Mouslim, M. C., Blunt, J. L., Alexander, G. C., & Shermock, K. M. (2021). Assessment of Availability, Clinical Testing, and US Food and Drug Administration Review of Biosimilar Biologic Products. *JAMA internal medicine, 181*(1), 52–60. doi: https://doi.org/10.1001/jamainternmed.2020.3997

Moorkens, E., Jonker-Exler, C., Huys, I., Declerck, P., Simoens, S., & Vulto, A. G. (2016). Overcoming Barriers to the Market Access of Biosimilars in the European

Union: The Case of Biosimilar Monoclonal Antibodies. *Frontiers in pharmacology, 7*, 193. doi: https://doi.org/10.3389/fphar.2016.00193

Mosegui, G.B.G., Antõnanzas, F., de Mello Vianna, C.M. & Rojas, P. (2021). Drug prices in Latin American countries: the case of rheumatoid arthritis Biosimilars. *Advances in Rheumatology volume, 61*. doi: https://doi.org/10.1186/s42358-021-00172-w

MP Team. (2019). Global Biosimilars Outlook - 2019 & beyond. Retrieved January 12, 2021, from https://mpadvisor.com/tocDocument/MP%20Group%20-%20Global%20Biosimilars%20Outlook%202019.pdf

MSCI (2020). MSCI to Announce 2020 Annual Market Classification Review. Retrieved May 20, 2021, from https://www.msci.com/documents/10199/8f90492a-a6a7-6ed1-e86e-be3e1984458a#:~:text=MSCI%20welcomes%20feedback%20until%20June,Annual%20Market%20Classification%20Review%20announcement.&text=MSCI%20is%20a%20leading%20provider,for%20the%20global%20investment%20community

Mulchan, N. and A. Guy. (2021). Project Orbis: Maximizing patient access to new medicines. Retrieved May 20, 2021, from https://www.raps.org/news-and-articles/news-articles/2021/2/project-orbis-maximizing-patient-access-to-new-med

National Academies of Sciences Engineering and Medicine. (2020). Regulating Medicines in a Globalized World: The Need for Increased Reliance Among Regulators. Washington, DC, The National Academies Press. https://doi.org/10.17226/25594

Navaneethaselvan, D. & Puranik, S.B. (2013). Development Constraints and Regulatory Pathway of Registration of Biosimilar Products in us and Europe. *International Journal of Research in Pharmacy and Science, 3*(4), 18-39.

Ndomondo-Sigonda, M., Miot, J., Naidoo, S., Dodoo, A., & Kaale, E. (2017). Medicines Regulation in Africa: Current State and Opportunities. *Pharmaceutical medicine, 31*(6), 383–397. doi: https://doi.org/10.1007/s40290-017-0210-x

Niazi, S.K. (2020a). Ten Reasons Why Biosimilar Candidates Should Not Be Tested for Clinical Efficacy. Retrieved September 16, 2021, from

https://www.centerforbiosimilars.com/view/ten-reasons-why-biosimilar-products-should-not-be-tested-for-clinical-efficacy

Niazi, S.K. (2020b). Do we need comparative clinical efficacy testing for biosimilars. Retrieved September 16, 2021, from https://www.biosimilardevelopment.com/doc/do-we-need-comparative-clinical-efficacy-testing-for-biosimilars-0001

Okoro, R. N. (2021). Biosimilar medicines uptake: The role of the clinical pharmacist. *Exploratory Research in Clinical and Social Pharmacy, 1*, 1-4. doi: https://doi.org/10.1016/j.rcsop.2021.100008

Omair, M. A., Alhawassi, T., Alwaihibi, M., Aldrees, G., Mosli, M., et al. (2020). Improving the understanding of originator and biosimilar biologics among healthcare providers in Saudi Arabia. *Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society, 28*(12), 1827–1829. doi: https://doi.org/10.1016/j.jsps.2020.11.008

Otto, R., Santagostino, A. & Schrader, U. (2014). Rapid growth in biopharma: Challenges and opportunities. Retrieved April 18, 2021, from https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/rapid-growth-in-biopharma

PAHO. (2021). Collaborating Centres by Member State. Retrieved December 18, 2020, from https://www.paho.org/en/pahowho-collaborating-centres/collaborating-centres-member-state

Papathanasiou, P., Brassart, L. , Blake, P. Hart, A. Whitbread, L., et al. (2016). Transparency in drug regulation: public assessment reports in Europe and Australia. *Drug Discovery Today, 21*(11), 1806-1813. doi: https://doi.org/10.1016/j.drudis.2016.06.025

Park, S. K., Moon, W., Kim, E. S., Park, S. H. & Park, D. I. (2019). Knowledge and Viewpoints on Biosimilar Monoclonal Antibodies among Asian Physicians: Comparison with European Physicians. *The Korean journal of gastroenterology = Taehan Sohwagi Hakhoe chi, 74*(6), 333–340. doi: https://doi.org/10.4166/kjg.2019.74.6.333

Parrish, M. (2020). Global Dose: Focus on South Africa. Retrieved September 17, 2021, from https://www.pharmamanufacturing.com/articles/2020/global-dose-focus-on-south-africa/

Pasina, L., Casadei, G., & Nobili, A. (2016). A survey among hospital specialists and pharmacists about biosimilars. *European journal of internal medicine, 35*, e31–e33. doi: https://doi.org/10.1016/j.ejim.2016.07.010

Pategou, J. (2020). Africa's Biosimilar Landscape: Outlook & Current Challenges. Retrieved April 04, 2021, from https://www.biosimilardevelopment.com/doc/africa-s-biosimilar-landscape-outlook-current-challenges-0001

Pategou, J. (2021). The Opportunities & Challenges Of India's Biologics Market. Retrieved February 12, 2021, from https://www.biosimilardevelopment.com/doc/the-opportunities-challenges-of-india-s-biologics-market-0001

Patel, K. B., Arantes, L. H., Tang, W. Y. & Fung, S. (2018). The role of biosimilars in value-based oncology care. *Cancer management and research, 10*, 4591-602.doi: https://doi.org/10.2147/CMAR.S164201

Patel, P., Cerqueira, D. M., Santos, G., de Lima Soares, R., Sousa, V. D., et al. (2020). A Baseline Analysis of Regulatory Review Timelines for ANVISA: 2013-2016. *Therapeutic innovation & regulatory science, 54*(6), 1428–1435. doi: https://doi.org/10.1007/s43441-020-00169-5

Pedamkar, P. (2020). Types of Research Methodology. Retrieved August 24, 2021, from https://www.educba.com/types-of-research-methodology/

Pentek, M., Lakatos, P. L., Oorsprong, T., Gulácsi, L., Pavlova, M., et al. (2017). Access to biologicals in Crohn's disease in ten European countries. *World journal of gastroenterology, 23*(34), 6294–6305. doi: https://doi.org/10.3748/wjg.v23.i34.6294

Pfizer. (2018). Biosimilars vs. Generics: What's the Difference? Retrieved February 04, 2021, from https://www.pfizer.com/sites/default/files/investors/financial_reports/annual_reports/2018/our-innovation/progressing-our-science/biosimilars-vs-

generics/index.html#:~:text=As%20biologic%20medicines%2C%20biosimilars%20are,manufacture%20than%20small%2Dmolecule%20generics

Pharmaboardroom. (2020a). Biosimilars & Biologics - Russia. Retrieved September 15, 2021, https://pharmaboardroom.com/legal-articles/biosimilars-biologics-russia/

Pharmaboardroom. (2020b). Biosimilars & Biologics. Retrieved April 04, 2021, from https://pharmaboardroom.com/legal-articles/biosimilars-biologics-singapore/

Pharmaboardroom. (2020c). Biosimilars & Biologics. Retrieved September 15, 2021, from https://pharmaboardroom.com/legal-articles/biosimilars-biologics-india/

Pharmaboardroom. (2021). Biosimilars & Biologics. Retreived September 13, 2021, from https://pharmaboardroom.com/legal-articles/biosimilars-biologics-mexico/

PIC/S. (2014). Working Group on Good Clinical and Good Pharmacovigilance Practices. Retrieved April 20, 2021, from https://picscheme.org/en/pia-pic-s-training-expert-circles-training-working-group-on

PIC/S. (2018). *Guidance- GMP Inspection reliance*. PI 048-1. 1-9. Geneva. Retrieved July 28, 2021, from https://picscheme.org/users_uploads/news_news_documents/PI_048_1_Guidance_on_GMP_Inspection_Reliance_1.pdf

PR Newswire. (2019). Amgen Enters Biosimilar Market With Launch Of KANJINTI™ For Breast Cancer And Other Tumors. Retrieved April 04, 2021, from https://www.biosimilardevelopment.com/doc/amgen-enters-biosimilar-market-with-launch-of-kanjinti-for-breast-cancer-and-other-tumors-0001#:~:text=Amgen%20Enters%20Biosimilar%20Market%20With%20Launch%20Of%20KANJINTI%E2%84%A2%20For,treatment%20in%20the%20Brazilian%20market

PR Newswire. (2020a). Henlius Adalimumab Biosimilar Approved by NMPA. Retrieved April 04, 2021, from https://www.henlius.com/en/NewsDetails-2915-26.html

PR Newswire. (2020b). Innovent Announces NMPA Granted Marketing Approval for SULINNO® (Adalimumab Injection) in China. Retrieved April 04, 2021, from

https://www.prnewswire.com/news-releases/innovent-announces-nmpa-granted-marketing-approval-for-sulinno-adalimumab-injection-in-china-301123750.html

PR Newswire. (2020c). Innovent Announces the NMPA Granted Marketing Approval for BYVASDA® (Bevacizumab Biosimilar) in China. Retrieved April 04, 2021, from https://www.prnewswire.com/news-releases/innovent-announces-the-nmpa-granted-marketing-approval-for-byvasda-bevacizumab-biosimilar-in-china-301080076.html

PR Newswire. (2020d). Biosimilar Market The Future For The Generic Pharmaceuticals Industry. Retrieved April 29, 2021, from https://www.biosimilardevelopment.com/doc/biosimilar-market-the-future-for-the-generic-pharmaceuticals-industry-0001#:~:text=The%20reported%20study%20estimated%20the,period%20(2019%2D2025).&text=A%20biosimilar%20is%20a%20biologic,known%20as%20a%20reference%20product

PR Newswire. (2021). Global Biologics Market Opportunities and Strategies Report 2020: COVID-19 Impact and Recovery - Forecast to 2023, 2025 & 2030. Retrieved August 16, 2021 from https://www.prnewswire.com/news-releases/global-biologics-market-opportunities-and-strategies-report-2020-covid-19-impact-and-recovery---forecast-to-2023-2025--2030-301223015.html

PubChem. (2021). Aspirin Molecule. National Library of Medicine. Retrieved August 22, 2021, from https://pubchem.ncbi.nlm.nih.gov/compound/Aspirin

QuestionPro. (2020). Types of Sampling: Sampling Methods with Examples. Retrieved January 12, 2021, from https://www.questionpro.com/blog/types-of-sampling-for-social-research/

QuestionPro. (2021a). Quantitative Data Collection: Best 5 methods. Retrieved August 24, 2021, from https://www.questionpro.com/blog/quantitative-data-collection-methods/

QuestionPro. (2021b). 21 Questionnaire Templates: Examples and Samples. Retrieved August 24, 2021, from https://www.questionpro.com/blog/questionnaire-templates-and-examples/

Rahalkar, H., Cetintas, H.C. & Salek, S. (2018). Quality, Non-clinical and Clinical Considerations for Biosimilar Monoclonal Antibody Development: EU, WHO, USA, Canada, and BRICS-TM Regulatory Guidelines. *Frontiers in Pharmacology, 9*, 1-17. doi: https://doi.org/10.3389/fphar.2018.01079

Rahalkar, H., Sheppard, A., Lopez-Morales, C.A., Lobo, L. & Salek, S. (2021a). Challenges Faced by the Biopharmaceutical Industry in the Development and Marketing Authorization of Biosimilar Medicines in BRICS-TM Countries: An Exploratory Study. *Pharmaceutical Medicine, 35,* 235–251. doi: https://doi.org/10.1007/s40290-021-00395-8

Rahalkar, H., Sheppard, A., Santos, G.M.L., Dasgupta, C., Perez-Tapia, S.M., et al. (2021b). Current Regulatory Requirements for Biosimilars in Six Member Countries of BRICS-TM: Challenges and Opportunities. *Frontier in Medicine. 8*:726660. doi: https://doi.org/10.3389/fmed.2021.726660

Rahalkar, H., Sheppard, A. & Salek, S. (2021c). Comparison of BRICS-TM Countries' Biosimilar Regulatory Frameworks With Australia, Canada and Switzerland: Benchmarking Best Practices. *Frontiers in pharmacology, 12*, 711361. doi: https://doi.org/10.3389/fphar.2021.711361

Ramzan, I. (2020). Interchangeability of biosimilars: a global perspective for pharmacists. *The Pharmaceutical Journal, 305*(7939). doi: 10.1211/PJ.2020.20208123

Raynor, D. K. & Bryant, D. (2013). European Public Assessment Report (EPAR) summaries for the public: are they fit for purpose? A user-testing study. *BMJ open, 3*(9), e003185. doi: https://doi.org/10.1136/bmjopen-2013-003185

Regapharm. (2020). The Russian regulator is developing a remote GMP inspection process in connection with the pandemic. Retrieved April 04, 2021, from http://regapharm.com/the_russian_regulator_is_developing_a_remote_gmp_inspection_process_in_connection_with_the_pandemic

Rifkin, R. & Pourmahram,T. (2020). Biosimilars Bring Value to Health Care. Retrieved April 04, 2021, from https://www.centerforbiosimilars.com/view/biosimilars-bring-value-to-health-care

Rios, A. M. (2020). Pharmaceutical industry in Mexico - Statistics & Facts. Retrieved April 12, 2021, from https://www.statista.com/topics/6074/pharmaceutical-industry-in-mexico/#:~:text=In%20Latin%20America%2C%20Mexico%20has,approximately%207.6%20billion%20U.S.%20dollars

Rodier, C., Bujar, M., McAuslane, N., Patel, P. & Liberti, L. (2020). Use of the Certificate for Pharmaceutical Products (CPP) in 18 Maturing Pharmaceutical Markets: Comparing Agency Guidelines with Company Practice. *Therapeutic Innovation & Regulatory Science, 55,*118-128. doi: https://doi.org/10.1007/s43441-020-00196-2

Roszdravnadzor. Regulatory framework for federal service for surveillance in healthcare. Retrieved September 15, 2021, from https://roszdravnadzor.gov.ru/en

Russian Federation. (2010). *Russian Law Official Document : Federal Law №61, Article 4*. Retrieved September 19, 2021, from https://wipolex-res.wipo.int/edocs/lexdocs/laws/en/ru/ru239en.html

Russian federation. (2014a). *Registration Dossier For Finished Medical Product*.

Russian Federation. (2014b). *Federal Law of April 5, 2013 N 44-FZ. On the contract system in the procurement of goods, works, services to meet state and municipal needs*. Retrieved April 14, 2021, from https://rg.ru/2013/04/12/goszakupki-dok.html

Sagonowsky, E. (2019). AbbVie's massive Humira discounts are stifling Netherlands biosimilars. Retrieved September 14, 2021, from https://www.fiercepharma.com/pharma/abbvie-stifling-humira-biosim-competition-massive-discounting-dutch-report

SAHPRA. (2019a). General Information. 2.01_General information_ Jul19_v10. Retrieved October 14, 2021, from https://www.sahpra.org.za/wp-content/uploads/2020/01/2.01_General-information_-Jul19_v10.pdf

SAHPRA. (2019b). *Expression of interest: SADC medicines regulatory worksharing, Zazibona collaborative process. Zazibona Expression of Interest_Oct19_v1.* Retrieved March 04, 2021, from

https://www.sahpra.org.za/wp-content/uploads/2020/01/2738d027ZazibonaExpressionofInterest_Oct19_v1.pdf

SAHPRA. (2020). *SAHPRA policy on conduct of clinical trials of health products during the current COVID-19 pandemic*. Retrieved April 04, 2021, from http://www.sahpra.org.za/wp-content/uploads/2020/03/SAHPRA-Communication_COVID_19-Final-25032020.pdf

SAHPRA. (2021). Biological medicines evaluation and research unit (BMERU). Retrieved September 02, 2021, from https://www.sahpra.org.za/biological-products/

Sandorff, E., Pinheiro, A.V., Bruni, D. S., Halbert, R. J. & Azevedo, V. F. (2015). Payer and physician evidence and discount requirements for biosimilars in three Latin American countries. *GaBI ,4*(1): 11-16. doi: 10.5639/gabij.2015.0401.005

Santos, L. & de Sousa Campos, G.W. (2015). SUS Brazil: The health region as a way forward. *Health and Society 24*(2), 438-446. doi: https://doi.org/10.1590/S0104-12902015000200004

Sarnola, K., Merikoski, M., Jyrkkä, J. & Hämeen-Anttila, K. (2020). Physicians' perceptions of the uptake of biosimilars: a systematic review. *BMJ Open, 2*, 10:e034183. doi:10.1136/bmjopen-2019-034183

Scheinberg, M., Pineda, C., Castañeda-Hernández, G., Zarbá, J. J., Damião, A., et al. (2018). Biosimilars in oncology and inflammatory diseases: current and future considerations for clinicians in Latin America. *mAbs, 10*(6), 827–842. doi: https://doi.org/10.1080/19420862.2018.1484977

Schiestl, M., Stangler, T., Torella, C., Cepeljnik, T., Toll, H., & Grau, R. (2011). Acceptable changes in quality attributes of glycosylated biopharmaceuticals. *Nature biotechnology, 29*(4), 310–312. doi: https://doi.org/10.1038/nbt.1839

Schiestl, M., Ranganna, G., Watson, K., Jung, B., Roth, K., et al. (2020). The Path Towards a Tailored Clinical Biosimilar Development. *BioDrugs, 34*, 297-306. doi: https://doi.org/10.1007/s40259-020-00422-1

Schneider, P. J. & Reilly, M. S. (2020). Policy recommendations for a sustainable biosimilars market: lessons from Europe. Retrieved February 04, 2021, from http://gabi-journal.net/policy-recommendations-for-a-sustainable-biosimilars-

market-lessons-from-europe.html#:~:text=As%20of%20October%202019%2C%2054,different%20approaches%20to%20biosimilar%20policy

Shanghai Henlius Biotech. (2020a). Henlius Bevacizumab Biosimilar Received NDA Acceptance Notification from NMPA. Retrieved February 04, 2021, from https://www.henlius.com/en/NewsDetails-2733-26.html

Shanghai Henlius Biotech. (2020b). Henlius Received Acceptance Notification for Clinical Trial Application from NMPA for its Denosumab Biosimilar HLX14. Retrieved February 04, 2021, from https://www.henlius.com/en/NewsDetails-2366-26.html

Shanghai Henlius Biotech. (2020c). China's First Trastuzumab Biosimilar 汉曲优®

Approved by NMPA. Retrieved February 04, 2021, from https://www.henlius.com/en/NewsDetails-2690-26.html

Sharma, A., Kumar, N., Kuppermann, B.D., Bandello, F. & Loewenstein, A. (2020). Understanding biosimilars and its regulatory aspects across the globe: an ophthalmology perspective. *British Journal of Ophthalmology, 104*(1), 2-7. doi: https://doi.org/10.1136/bjophthalmol-2019-314443

Sharma, P. (2021). Biosimilars Market Global Scenario, Market Size, Outlook. Retrieved September 07, 2021, from https://www.pinterest.ru/pin/661677370226987902/

Sharma, U. (2020). CDSCO extends WHO-GMP/CoPP validity by six months. Retrieved April 04, 2021, from https://www.expresspharma.in/covid19-updates/cdsco-extends-who-gmp-copp-validity-by-six-months/

Shekhar, R., Hallur, M., Muralidharan, P. & Puranik, S.B. (2020). Regulatory Pathway for Registration of Biosimilars in Russia. *Asian Journal of Pharmaceutical Research and Development, 8*(2), 79-87. doi: http://dx.doi.org/10.22270/ajprd.v8i2.673

Sia, C.H. , Sia, M. K. & Chan, L. W. (2020). Global challenges in the manufacture, regulation and international harmonization of GMP and quality standards for biopharmaceuticals. *GaBI, 9*(2), 52–63. doi: https://doi.org/10.5639/gabij.2020.0902.010

Silva, C. L. (2012). México retoma un liderazgo regulatorio sobre medicamentos biotecnológicos y biocomparables [Mexico recovers leadership on regulation of biosimilar biotech drugs]. *Gaceta Médica de México, 148*(1), 83–90.

Simoens, S., Jacobs, I., Popovian, R., Isakov, L., & Shane, L. G. (2017). Assessing the Value of Biosimilars: A Review of the Role of Budget Impact Analysis. *PharmacoEconomics, 35*(10), 1047–1062. doi: https://doi.org/10.1007/s40273-017-0529-x

Singh S. (2019). Biocon's Malaysia Insulin Glargine Manufacturing Facility Receives EU GMP Certification. Retrieved September 14, 2021, from https://indiamedtoday.com/biocons-malaysia-insulin-glargine-manufacturing-facility-receives-eu-gmp-certification/

Singh, P., Anasari, A. F., Bhamare, B., Vishwasrao, D. S. & Kokil, S. (2013). Developing Biosimilars in Emerging Markets: Regulatory and Clinical Considerations. National Conference on Current Challenges of Biopharmaceuticals, ResearchGate. Pune. Vol.1.2016. Retrieved February 04, 2021, from https://www.researchgate.net/publication/301214317_Developing_Biosimilars_in_Emerging_Markets_Regulatory_and_Clinical_Considerations

Sivabushnam, S. (2017). Emerging markets hold the potential for makers of biosimilars. Beroe Advance Procurement. Retrieved April 14, 2021, from https://www.beroeinc.com/whitepaper/biosimilars-emerging-markets/

Skingle D. (2015). Biosimilars: what do patients need to consider? *RMD open, 1*(1), e000141. doi: https://doi.org/10.1136/rmdopen-2015-000141

Statista. (2021). Biologics share of total pharmaceutical sales in select countries in 2018. Retrieved January 10, 2021, from https://www.statista.com/statistics/1118421/biologic-medicines-share-of-total-pharmaceutical-sales-in-oecd-countries/#:~:text=Biologic%20share%20of%20total%20pharmaceutical%20sales%20in%20select%20countries%202018&text=In%20the%20United%20States%2C%20biologic,developed%20countries%20(OECD)%20in%202018

Staton, T. (2012). Merck gains traction in Brazil with joint venture. Retrieved February 04, 2021, from https://www.fiercepharma.com/pharma/merck-gains-traction-brazil-joint-venture

Stebbing, J., Mainwaring, P. N., Curigliano, G., Pegram, M., Latymer, M., et al. (2020). Understanding the Role of Comparative Clinical Studies in the Development of Oncology Biosimilars. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 38*(10), 1070–1080. doi: https://doi.org/10.1200/JCO.19.02953

Swissmedic. (2020a). *Questions and answers concerning the authorisation of biosimilars*. Geneva. Retrieved February 04, 2021, from https://www.swissmedic.ch/swissmedic/en/home/services/documents/faq_zl_biosimilar.html

Swissmedic. (2020b). *HD-Guidance document Authorisation biosimilar HMV4*. Geneva. Retrieved February 04, 2021, from https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/information/anpassung_wlbiosimilar.html

Swissmedic. (2020c). *Questions and answers on the authorisation of biosimilars*. Retrieved September 17, 2021, from https://www.swissmedic.ch/swissmedic/en/home/services/documents/faq_zl_biosimilar.html

Swissmedic. (2021). Swiss Public Assessment Report (SwissPAR) Switzerland: Swissmedic. Retrieved September 14, 2021, from https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/swisspar.html

Tannoury, M. & Attieh, Z. (2017). The Influence of Emerging Markets on the Pharmaceutical Industry. *Current therapeutic research, clinical and experimental, 86*, 19–22. doi: https://doi.org/10.1016/j.curtheres.2017.04.005

TGA. (2018). *Biosimilar medicines regulation (version 2.2)*. Retrieved February 04, 2021, from https://www.tga.gov.au/sites/default/files/biosimilar-medicines-regulation.pdf

TGA. (2020). Australia-Canada-Singapore-Switzerland-United Kingdom (Access) Consortium. Retrieved April 20, 2020, from https://www.tga.gov.au/australia-canada-singapore-switzerland-united-kingdom-access-consortium

TGA. (2021a). TGA statutory advisory committees. Retrieved September 17, 2021, from https://www.tga.gov.au/tga-statutory-advisory-committees

TGA. (2021b). *Prescription medicines registration process.* Version 2.5. Retrieved September 17, 2021, from https://www.tga.gov.au/sites/default/files/prescription-medicines-registration-process.pdf

The Center for Biosimilars Staff. (2019). Russian Drug Maker Gains World's First Approval for Biosimilar Eculizumab. Retrieved February 14, 2020, from https://www.centerforbiosimilars.com/view/russian-drug-maker-gains-worlds-first-approval-for-biosimilar-eculizumab-

The Economist. (2019). Improving Access and Affordability for Biopharmaceuticals in Emerging Markets. A briefing paper from the Biopharmaceutical Think Tank discussion at the 2019 IFC Global Private Health Care Conference. Retrieved February 20, 2021, from https://www.ifc.org/wps/wcm/connect/e34ce207-a11b-43ad-8b34-b2ba2c73c71b/EIU+Briefing+Paper_Biopharma_FINAL.pdf?MOD=AJPERES&CVID=n3gnsYa

TheHinduBusinessLine. (2018). Zydus to sell biosimilars in Turkey. Retrieved August 20, 2021, from https://www.thehindubusinessline.com/companies/zydus-to-sell-biosimilars-in-turkey/article8732471.ece

Thepharmletter. (2020). Covid presents an opportunity to shape biosimilar landscape; Indian companies want in. Retrieved August 17, 2021 from https://www.thepharmaletter.com/article/covid-presents-an-opportunity-to-shape-biosimilar-landscape-indian-companies-want-in?__cf_chl_jschl_tk__=pmd_vhBu2z_LdJic0dcvi1KLknN9dB1eMinhUfGiH74L0K0-1631102263-0-gqNtZGzNAxCjcnBszQh9

Thomas, D. R. (2006). A General Inductive Approach for Analyzing Qualitative Evaluation Data. *American Journal of Evaluation, 27*(2), 237-246. doi: https://doi.org/10.1177/1098214005283748

TITCK. (2017). *Guideline on biosimilar medicinal products*. Istanbul. Retrieved April 04, 2021, from https://issuu.com/sarfarazniazi/docs/turkishbiosimilarguidances

TITCK. (2021). *Guidance on Biosimilar Medicinal Products*. Istanbul. Retrieved April 04, 2021, from https://www.mondaq.com/turkey/life-sciences-biotechnology-nanotechnology/1121350/guideline-on-biosimilar-medicinal-products-has-been-updated

TOPRA. (2019). Biosimilar Products: Regulatory complexities and challenges of biosimilars. Retrieved April 04, 2021, from https://www.topra.org/topra/topra_member/pdfs/CPD-February-2019-v2.pdf

Troein, P., Newton, M., Patel, J. & Scott, K. (2019). White Paper- The Impact of Biosimilar Competition in Europe. Retrieved September 16, 2021, from https://ec.europa.eu/docsroom/documents/38461

Tsiftsoglou, A. S., Ruiz, S. & Schneider, C. K. (2013). Development and regulation of biosimilars: current status and future challenges. *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy, 27*(3), 203–211. doi: https://doi.org/10.1007/s40259-013-0020-y

Tsuruta, L. R., Lopes dos Santos, M. & Moro, A. M. (2015). Biosimilars advancements: Moving on to the future. *Biotechnology progress, 31*(5), 1139–1149. doi: https://doi.org/10.1002/btpr.2066

Tyer D. (2019). Biosimilars in the UK: where are we now and where does the NHS want to go? Retrieved April 29, 2021, from https://pharmaphorum.com/views-analysis-market-access/biosimilars-in-the-uk/

Ucer, K., Ekim, H. & Yetkin, D. (2021). Medicinal product regulation and product liability in Turkey: overview. Retrieved April 29, 2021, from https://uk.practicallaw.thomsonreuters.com/0-617-2716?transitionType=Default&contextData=(sc.Default)&firstPage=true

USFDA. (2015). *Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*; Draft Guidance for Industry; Availability. Maryland: USFDA. Retrieved September 16, 2021, from https://www.federalregister.gov/documents/2015/05/13/2015-

11528/biosimilars-additional-questions-and-answers-regarding-implementation-of-the-biologics-price

USFDA. (2017). *Biosimilar and Interchangeable Products*. Maryland: USFDA. Retrieved January 12, 2021, from https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products

USFDA. (2018a). *What Are Biologics Questions and Answers*. Maryland: USFDA. Retrieved March 04, 2021, from https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers

USFDA. (2018b). *BIOSIMILARS ACTION PLAN: Balancing Innovation and Competition*. Maryland: USFDA. Retrieved April 04, 2021, from https://www.fda.gov/media/114574/download

USFDA. (2018c). Advisory Committee Laws, Regulations and Guidance. Maryland: USFDA. Retrieved September 17, 2021, from https://www.fda.gov/advisory-committees/about-advisory-committees/advisory-committee-laws-regulations-and-guidance

USFDA. (2018d). Committees and Meeting Materials. Retrieved September 17, 2021, from https://www.fda.gov/advisory-committees/committees-and-meeting-materials

USP convention. (2016). *Guiding Principles for Coining United States Adopted Names for Drugs (2016 USP Dictionary of USAN and International Drug Names).* Retrieved June 14, 2021, from http://www.uspusan.com/usan/pub/index1.html

UW–Madison School of Pharmacy. (2020). The potential and challenge of bringing biosimilars to market. Retrieved February 04, 2021, from https://ce.pharmacy.wisc.edu/blog/the-potential-and-challenge-of-biosimilars/

van Aerts, L. A., De Smet, K., Reichmann, G., van der Laan, J. W., & Schneider, C. K. (2014). Biosimilars entering the clinic without animal studies. A paradigm shift in the European Union. *mAbs, 6*(5), 1155–1162. doi: https://doi.org/10.4161/mabs.29848

van Meer, P. J., Ebbers, H. C., Kooijman, M., Gispen-de Wied, C. C., Silva-Lima, B., et al. (2015). Contribution of animal studies to evaluate the similarity of

biosimilars to reference products. *Drug Discovery Today, 20*(4), 483–490. doi: https://doi.org/10.1016/j.drudis.2014.11.009

Vandenplas, Y., Simoens, S., Van Wilder, P., Vulto, A. G. & Huys, I. (2021). Off-Patent Biological and Biosimilar Medicines in Belgium: A Market Landscape Analysis. *Frontiers in pharmacology, 12*, 644187. doi: https://doi.org/10.3389/fphar.2021.644187

Vezer, B., Buzás, Z., Sebeszta, M. & Zrubka, Z. (2016). Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents. *Current medical research and opinion, 32*(5), 829–834. doi: https://doi.org/10.1185/03007995.2016.1145579

Visiongain. (2016). Pharma Leader Series: 25 Top Biosimilar Drug Manufacturers 2016-2026. Retrieved January 12, 2021, from https://www.visiongain.com/report/pharma-leader-series-25-top-biosimilar-drug-manufacturers-2016-2026/

Vulto, A. G. & Jaquez, O. A. (2017). The process defines the product: what really matters in biosimilar design and production? *Rheumatology,* 56(4), iv14-iv29. doi: https://doi.org/10.1093/rheumatology/kex278

Webster, C. J. & Woollett, G. R. (2017). A 'Global Reference' Comparator for Biosimilar Development. *BioDrugs 31*(4), 279-286. doi: https://doi.org/10.1007/s40259-017-0227-4

Webster, C. J., Wong, A. C. & Woollett, G. R. (2019). An Efficient Development Paradigm for Biosimilars. *BioDrugs, 33,* 603–611. doi: https://doi.org/10.1007/s40259-019-00371-4

Welch, A. R. (2016a). What To Know About Emerging Market Biosimilar Pathways. Retrieved January 12, 2021, from https://www.biosimilardevelopment.com/doc/what-to-know-about-emerging-market-biosimilar-pathways-0001

Welch, A. R. (2016b). 6 Tips For Navigating Emerging Market Biosimilar Regulations. Retrieved April 13, 2021, from https://www.biosimilardevelopment.com/doc/tips-for-navigating-emerging-market-biosimilar-regulations-0001

Welch, A. R. (2017). The Evolution Of Russia's Biosimilar Regulatory Pathway. Retrieved March 16, 2021, from https://www.biosimilardevelopment.com/doc/the-evolution-of-russia-s-biosimilar-regulatory-pathway-0001

Welch, A. R. (2019a). 3 Countries To Watch In The MENA Region. Retrieved April 04, 2021, from https://www.biosimilardevelopment.com/doc/countries-to-watch-in-the-mena-region-0001

Welch, A. R. (2019b). Comparative Biosimilar Clinical Trials: More Questions Than Answers? Retrieved April 13, 2021, from https://www.biosimilardevelopment.com/doc/comparative-biosimilar-clinical-trials-more-questions-than-answers-0002

White, J. B., Lipkus, N. & Maddox, J. (2019). Canada takes major steps toward enhanced biosimilar access. Retrieved April 14, 2021, from https://www.osler.com/en/resources/regulations/2019/canada-takes-major-steps-toward-enhanced-biosimilar-access

WHO. (1995). *Use of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce - EDM Research Series No. 016*. Geneva. Retrieved July 05, 2021, from http://digicollection.org/hss/en/d/Jwhozip43e/11.html

WHO. (2009). *Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)*. In: 60th meeting of the WHO Expert Committee on Biological Standardization, 19-23 October 2009. Geneva. Retrieved April 04, 2021, from https://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

WHO. (2013). *Guidelines on evaluation of similar biotherapeutic products (SBPs)*. In: WHO Expert Committee on Biological Standardization. Sixtieth report. Geneva, World Health Organization, WHO Technical Report Series, No. 977, Annex 2. Retrieved April 04, 2018, from https://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf

WHO. (2016a). Medicines regulation: Comparison of medicines legislation in the East African Community. WHO Drug Information. 30:567. Geneva. Retrieved April

04, 2021, from https://apps.who.int/iris/bitstream/handle/10665/331006/DI304-567-576-eng.pdf?sequence=1&isAllowed=y

WHO. (2016b). *Good regulatory practices: guidelines for national regulatory authorities for medical products. QAS/16.686*. Geneva. Retrieved April 4, 2021, from https://www.who.int/medicines/areas/quality_safety/quality_assurance/GoodRegulatory_PracticesPublicConsult.pdf

WHO. (2017a). *Report on the Expert Consultation on Improving Access to and use of Similar Biotherapeutic Products. WHO/EMP/RHT/TSN/2017.01*. Geneva. Retrieved April 04, 2021, from https://www.who.int/medicines/access/biotherapeutics/FINAL_Report-improving-access-to-and-use-of-biotherapeutics_October2017.pdf

WHO. (2017b). *Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs)*. In: WHO Expert Committee on Biological Standardization. Sixty-seventh report. Geneva, WHO Technical Report Series, No. 1004, 2017, Annex 2. Retrieved April 04, 2021, from https://www.who.int/biologicals/biotherapeutics/WHO_TRS_1004_web_Annex_2.pdf?ua=1

WHO. (2017c). *WHO Questions and Answers: Similar Biotherapeutic Products (Proposed document to implement the WHO guidelines on evaluation of similar biotherapeutic products, Annex 2, WHO TRS No. 977, adopted in 2009). WHO/SBP_Q&A/DRAFT/DEC 2017*. Geneva. Retrieved April 04, 2021, from https://www.who.int/biologicals/QA_for_SBPs_HK_12_Dec_2017_(2).pdf

WHO. (2018a). *WHO essential medicines and health products: annual report 2017: towards access 2030*. Retrieved April 20, 2021, from https://apps.who.int/iris/handle/10665/272972

WHO. (2018b). *Guidance on good practices for desk assessment for compliance with good manufacturing practices, good laboratory practices and good clinical practices for marketing authorization of medical products*. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: Fifty-second report. Geneva; WHO Technical Report Series, No. 1010, Annex 9. Retrieved April 23, 2021, from

https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex9.pdf?ua=1

WHO. (2018c). 18th International Conference of Drug Regulatory Authorities (ICDRA): smart safety surveillance: a life-cycle approach to promoting safety of medical products. Dublin. Retrieved September 14, 2021, from https://apps.who.int/iris/handle/10665/330900

WHO. (2018d). WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems. Retrieved 23 August, 2018, from https://www.who.int/medicines/regulation/benchmarking_tool/en/

WHO. (2019a). WHO launches first-ever insulin prequalification programme to expand access to life-saving treatment for diabetes. Retrieved April 29, 2021, from https://www.who.int/news/item/13-11-2019-who-launches-first-ever-insulin-prequalification-programme-to-expand-access-to-life-saving-treatment-for-diabetes

WHO. (2019b). Essential medicines and health products: Medicines regulatory support. Geneva. Retrieved April 14, 2021, from https://www.who.int/medicines/areas/quality_safety/regulation_legislation/en/#:~:text=Effective%20medicines%20regulation%20promotes%20and,required%20quality%2C%20safety%20and%20efficacy%3B&text=access%20to%20medicines%20is%20not%20hindered%20by%20unjustified%20regulatory%20work

WHO. (2020). *Draft Working Document for Comments: Good Reliance Practices in Regulatory Decision-Making for medical products: high-level principles and considerations. QAS/20.851/Rev.1.* Geneva. Retrieved April 20, 2021, from https://www.who.int/medicines/areas/quality_safety/quality_assurance/QAS20_851_Rev_1_Good_Reliance_Practices.pdf?ua=1

WHO. (2021). List of Stringent Regulatory Authorities (SRAs). Retrieved July 05, 2021, from https://www.who.int/initiatives/who-listed-authority-reg-authorities/SRAs

Wiatr, C. (2011). US biosimilar pathway unlikely to be used: developers will opt for a traditional BLA filing. *BioDrugs, 25*(1), 63-67. doi: https://doi.org/10.2165/11588410-000000000-00000

Withing, E. (2012). How has the evolution of global pharmaceutical market affected the use of WHO Certificates for Pharmaceutical Product (CPP)? *Regulatory Rapporteur, 9*(4),14–16.

Woetzel, J., Madgavkar, A., Seong, J., Manyika, J., Sneader, K., et al. (2018). Outperformers: High-growth emerging economies and the companies that propel them, McKinsey & Company Report. Retrieved September 13, 2021, from https://www.mckinsey.com/featured-insights/innovation-and-growth/outperformers-high-growth-emerging-economies-and-the-companies-that-propel-them

Wonder, M., Backhouse, M. E., & Hornby, E. (2013). Early scientific advice obtained simultaneously from regulators and payers: findings from a pilot study in Australia. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research, 16*(6), 1067–1073. doi: https://doi.org/10.1016/j.jval.2013.07.007

World Bank Group. (2020). GDP (current US$). All Countries and Economies. Retrieved April 06, 2021, from https://data.worldbank.org/indicator/NY.GDP.MKTP.CD.

World Health Assembly. (2014). Regulatory system strengthening for medical products. EB134.R17. Geneva. Retrieved March 12, 2021, from https://apps.who.int/iris/handle/10665/173022

Worldometer. (2020a). World Population. Retrieved August 19, 2021, from https://www.worldometers.info/world-population/

Worldometer. (2020b). Brazil Population. Retrieved April 06, 2021, from https://www.worldometers.info/world-population/brazil-population/#:~:text=The%20current%20population%20of%20Brazil,of%20the%20total%20world%20population

Worldometer. (2020c). Russia Population. Retrieved April 06, 2021, from https://www.worldometers.info/world-population/russia-population/

Worldometer. (2020d). India Population. Retrieved April 06, 2021, from https://www.worldometers.info/world-population/india-population/

Worldometer. (2020e). China Population. Retrieved April 06, 2021, from https://www.worldometers.info/world-population/china-population/

Worldometer. (2020f). South Africa Population. Retrieved April 06, 2021, from https://www.worldometers.info/world-population/south-africa-population/

Worldometer. (2020g). Turkey Population. Retrieved April 06, 2021, from https://www.worldometers.info/world-population/turkey-population/

Worldometer. (2020h). Mexico Population. Retrieved April 06, 2021, from https://www.worldometers.info/world-population/mexico-population/

Wouters, J.J., Sandberg, D.M., Pillay, A., & Kanavos, P.G. (2019). The impact of pharmaceutical tendering on prices and market concentration in South Africa over a 14-year period. *Social Science & Medicine, 220*, 362-370 doi: https://doi.org/10.1016/j.socscimed.2018.11.029

Wroblewski, M., Jex, E.A., Munck, S.D., Garmon, C.J., Michel, S. T., Wantman, A. & Neal, O. L. (2009). Emerging Health Care Issues: Follow-on Biologic Drug Competition. Federal Trade Commission Report. Retrieved January 12, 2021, from https://www.ftc.gov/sites/default/files/documents/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report/p083901biologicsreport.pdf

Wu, H. & Yip, F. (2021). Goodwin Attorneys Discuss How Foreign Companies Can Break Into China's Biosimilar Market. *AJMC*. Retrieved April 04, 2021, from https://www.centerforbiosimilars.com/view/goodwin-attorneys-discuss-how-foreign-companies-can-break-into-china-s-biosimilar-market

Yang, H., Jolivot, L., Tao, X. & Zhao, B. (2019). Executive Insights Biosimilars In China: The Next Frontier. Retrieved February 12, 2021, from https://www.hoganlovells.com/~/media/hogan-lovells/pdf/2019/2019_06_10_executive_insights_biosimilars_in_china_may_2019.pdf

Zolkipli, N.N., Ngah, A. & Deraman, A. (2018). Version Control System: A review. *Procedia Computer Science, 135*, 408-415. doi: 10.1016/j.procs.2018.08.191

PUBLICATIONS AND PRESENTATIONS

Journal Articles

Rahalkar, H., Cetintas, H. C., & Salek, S. (2018). Quality, Non-clinical and Clinical Considerations for Biosimilar Monoclonal Antibody Development: EU, WHO, USA, Canada, and BRICS-TM Regulatory Guidelines. *Frontiers in pharmacology*, *9*, 1079. https://doi.org/10.3389/fphar.2018.01079

Rahalkar, H., Sheppard, A., Lopez-Morales, C. A., Lobo, L., & Salek, S. (2021). Challenges Faced by the Biopharmaceutical Industry in the Development and Marketing Authorization of Biosimilar Medicines in BRICS-TM Countries: An Exploratory Mixed Methods. *Pharmaceutical Medicine*, *35.* https://doi.org/10.1007/s40290-021-00395-8

Rahalkar, H., Sheppard, A. & Salek, S. (2021). Comparison of BRICS-TM Countries' Biosimilar Regulatory Frameworks with Australia, Canada and Switzerland: Benchmarking Best Practices. *Frontiers in pharmacology, 12.* https://doi.org/10.3389/fphar.2021.711361

Rahalkar, H., Sheppard, A., Santos, G.M., Dasgupta, C.Pérez-Tapia, S.M, Lopez-Morales, C.A. & Salek, S. (2021). Current regulatory requirements for biosimilars in six member countries of BRICS-TM: Challenges and opportunities. *Frontiers in Medicine, 8.* https://doi.org/10.3389/fmed.2021.726660

Awaiting publication

Rahalkar, H., Sheppard, A. & Salek, S. (2021). Biosimilar development and review process in the BRICS-TM countries: Proposal for a standardized model to improve regulatory performance (Submitted to Expert Review in Clinical Pharmacology Journal, In press)

Poster Presentations

Rahalkar, H. (2018). Biosimilar in BRICS-TM. Poster presentation at: Drug Information Association (DIA) Global Annual Meeting 2018, 24-27 June 2018, Boston, United States of America **(Appendix 6).**

Rahalkar, H., Cetintas, H. C., & Salek, S. (2018). Comparative evaluation of mAb biosimilar development and licensing regulations in BRICS-TM market. Poster presentation at: The Organisation for Professionals in Regulatory Affairs (TOPRA) Symposium 2018. 1-3 October 2018, London, United Kingdom. **(Appendix 7).**

Rahalkar, H., Sheppard, A., Lima Santos, G.M., Dasgupta, C., Perez-Tapia, S.M., Carlos A Lopez-Morales, C.A., Salek, S.(2021). Current regulatory requirements for biosimilars in BRICS-TM countries: Challenges and opportunities. Poster presentation at: School of Life and Medical Sciences (LMS) Research Conference 2021, 22 June 2021, Hatfield, United Kingdom. **(Appendix 8).**

Powerpoint Presentation

Presentation for virtual meeting with Swissmedic Agency, 22 October 2021 **(Appendix 9).**

APPENDICES

APPENDIX 1:

Questionnaire used to complete Study 2 (Chapter 5)

APPENDIX 2:

Questionnaire used to complete Study 3 (Chapter 6)

APPENDIX 3:

Questionnaire used to complete Study 4 (Chapter 7)

APPENDIX 4:

Questionnaire used to complete Study 5 (Chapter 8)

APPENDIX 5:

Questionnaire used to complete Study 5 (Chapter 8)

APPENDIX 6:

Poster presented at the Drug Information Association (DIA) Global Annual Meeting 2018, 23-27 June 2018, Boston, United States of America

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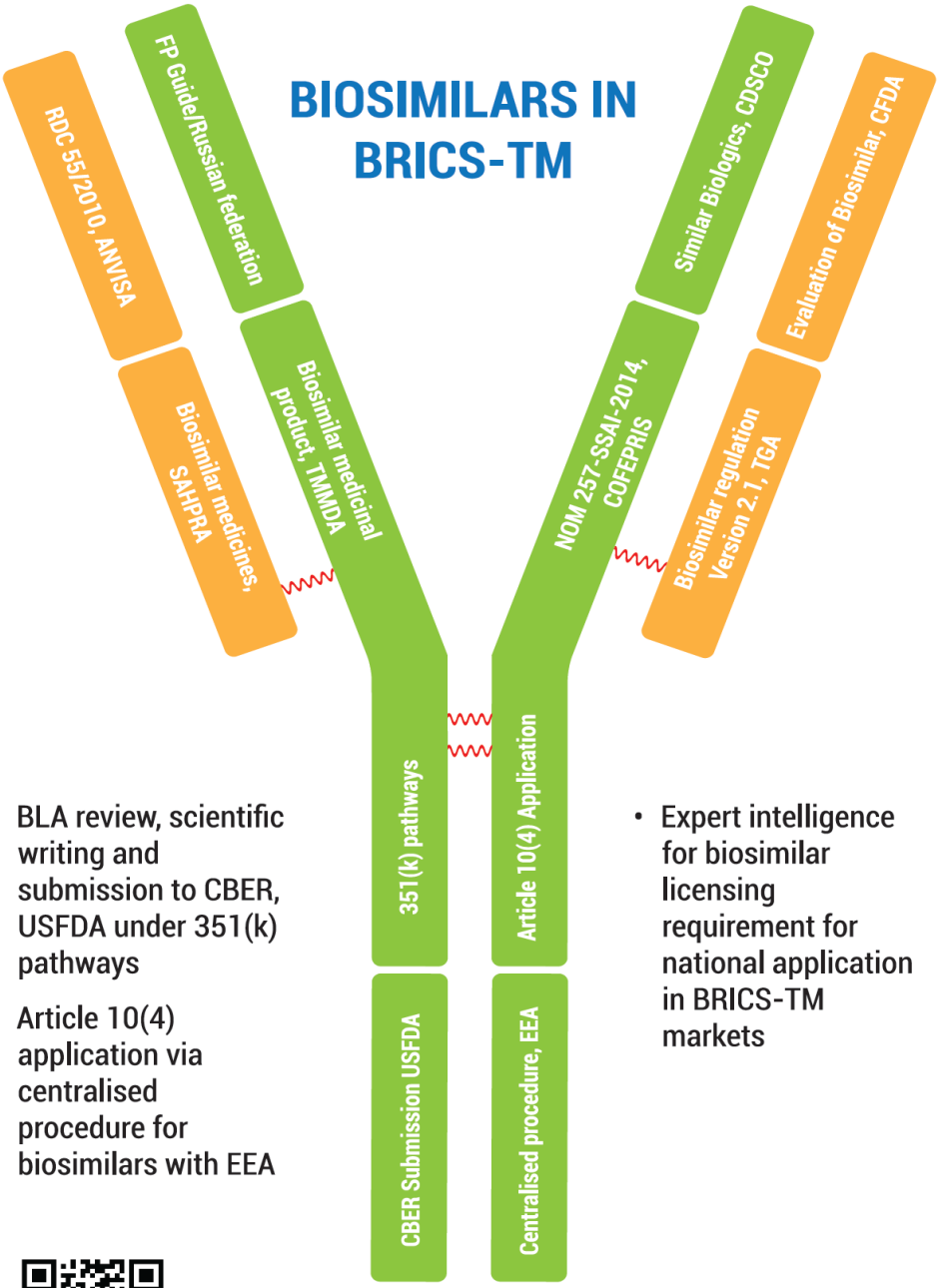
BIOSIMILARS IN BRICS-TM



- BLA review, scientific writing and submission to CBER, USFDA under 351(k) pathways
- Article 10(4) application via centralised procedure for biosimilars with EEA

- Expert intelligence for biosimilar licensing requirement for national application in BRICS-TM markets

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APPENDIX 7:

Poster presented at The Organisation for Professionals in Regulatory Affairs (TOPRA) Symposium 2018, 1-3 October 2018, London, United Kingdom

Comparative evaluation of mAb biosimilar development and licensing regulations in BRICS-TM market

Hasumati Rahalkar[1], [2], Hacer COŞKUN Cetintas[3], Sam Salek[1]

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INTRODUCTION

Biosimilars are biotherapeutic products with identical quality and similar safety and efficacy profiles as the reference biological product. It is essential that the standard of evidence supporting the decisions to grant marketing authorization for biosimilars be sufficient to ensure that the products meet acceptable levels of quality, safety and efficacy for public health purposes.

Although the European Medicines Agency (EMA), the United States Food and Drug Administration (USFDA) and the World Health Organization (WHO) have issued specific guidelines with questions and answer documents clarifying doubts pertaining to development, many other agencies are yet to develop mAb specific regulatory guidance.

AIM

The aim was to evaluate EMA, WHO, USFDA, BGTD/HC mAb biosimilar guidelines for development and licensing and compared with BRICS-TM regulations.

METHODS

The current and valid English-language guidelines including published questions and answers such as the EMA guidelines pertaining to biosimilar medicinal product and mAbs, technical report series (TRS) and pertinent annexes of the WHO, specifically for mAbs, guidance for industry from USFDA, the guidance document and the Fact sheet issued by HC/BGTD, MCC (currently known as SAHPRA) /South Africa guidance document and guidelines on similar biologics from India which were obtained from the official websites of the respective regulatory agencies. The authenticated translated guidelines were referred for Brazil, Russia, China, Turkey and Mexico.

RESULTS

Figure 1: Overview of mAb biosimilar development

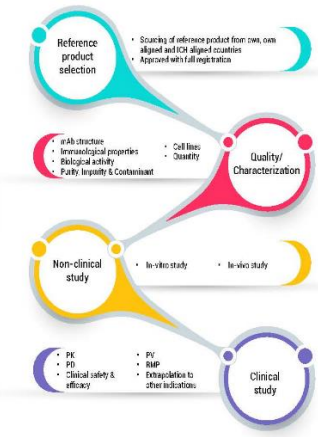
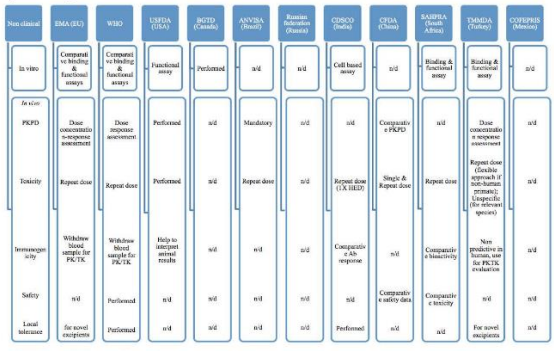


Figure 2: Publication of mAb specific guidelines

Table 1: Comparison of reference product selection in well-established agency and BRICS-TM markets.

Agency	Reference product mandates			
	Licensed in own country	Authorized in ICH countries	Similar or aligned regulatory agency	Bridging data
EMA	✓	✓	×	✓
WHO	×	✓	×	×
USFDA	✓	✓	×	✓
BGTD	✓	×	✓	×
ANVISA	✓	×	✓	×
Russian federation	✓	×	×	×
CDSCO	✓	✓	×	×
CFDA	✓	×	×	×
SAHPRA	✓	×	✓	×
TMMDA	×	×	✓	×
COFEPRIS	✓	×	×	×

Figure 3: Comparative non-clinical attributes across EMA, WHO, USFDA, BGTD and BRICS-TM markets.



n/d: Not define, HED: Human equivalent dose

DISCUSSION

It is evident that mAb biosimilar exclusive guidelines are yet to be published by BRICS-TM agencies. With reference to usage of reference biological medicinal product from ICH or similarly aligned regulatory agencies, the expectations of bridging data is unclear for each of the BRICS-TM market. The necessity of proving biosimilarity post authorization, interchangeability, switching, substitution and pediatric research remains undefined with these emerging agencies. Further non-clinical and clinical mandates with detailed requirements are yet awaited. Though there are gaps in mAb biosimilar regulatory guidelines in emerging markets, we believe that the agencies are working hard to align regulatory norms in line with well-established agencies. The regulator participates in multiple forums, exchanges knowledge and is willing to upgrade. It would be advisable for the companies to approach agencies in advance to obtain biosimilar development advice so that hassle free authorization can be obtained.

ABBREVIATIONS

ANVISA: The Brazilian Health Surveillance Agency, BGTD: Biologics and Genetic Therapies Directorate, BRICS-TM: Brazil Russia India China South Africa- Turkey Mexico, CDR: Complementary Determining Region, CDSCO: Central Drugs Standard Control Organization, CFDA: China Food and Drug Administration, COFEPRIS: The Federal Commission for the Protection against Sanitary Risk, EMA: European Medicines Agency, ICH: International Conference on Harmonisation, mAb: Monoclonal Antibodies, PD: Pharmacodynamics, PK: Pharmacokinetics, RBP: Reference Biological Product, ROA: Route of Administration, SAHPRA: South African Health Products Regulatory Authority, TK: Toxico-kinetics, TMMDA: Turkish Medicines and Medical Devices Agency, USFDA: United States Food and Drug Administration, WHO: World Health Organisation

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DISCLOSURE

Authors of this presentation have nothing to disclose.

Table 2: Differences in biosimilarity principles across well-established agency and BRICS-TM markets.

Biosimilarity Criteria	EMA(EU)	WHO	USFDA (USA)	BGTD (Canada)	ANVISA (Brazil)	Russian federation (Russia)	CDSCO (India)	CFDA (China)	SAHPRA (South Africa)	TMMDA (Turkey)	COFEPRIS (Mexico)
Posology	✓	×	✓	n/d	n/d	n/d	✓	n/d	n/d	✓	n/d
ROA	✓	✓	✓	✓	n/d	n/d	✓	n/d	n/d	✓	n/d
Strength, form, formulation	✓	✓	✓	✓[a]	n/d	n/d	✓[b]	n/d	n/d	✓	n/d
Improved efficacy	NS	NS	n/d	n/d	n/d	n/d	n/d	n/d	n/d	NS	n/d
Improved safety	✓	✓	n/d	✓	n/d	n/d	n/d	n/d	n/d	✓	n/d
Extrapolation of indications	✓	✓	✓	✓	✓	n/d	✓	✓	✓	✓	n/d
Biosimilarity post approval	NR	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d	NR	n/d
Interchangeability, switching, substitution	✓[a]	✓	✓	✓[β]	n/d	n/d	n/d	n/d	✓[c]	✓	n/d
Pediatric research	✓	n/d	✓	n/d	n/d	n/d	n/d	n/d	n/d	n/d	n/d

✓ Indicates the requirements are define in the guidelines, NR: Not required, NS: Not suitable, n/d: Not define, +except formulation, [a]Decision is in hands with member state, [b]Decision is in hands with province/territory, [c]Pharmaceutical form and formulation not define, [β]Substitution is not allowed and interchangeability is possible with practitioner's decision

Table 3: Comparative clinical attributes across EMA, WHO, USFDA, BGTD and BRICS-TM markets.

Clinical	EMA(EU)	WHO	USFDA (USA)	BGTD (Canada)	ANVISA (Brazil)	Russian federation (Russia)	CDSCO (India)	CFDA (China)	SAHPRA (South Africa)	TMMDA (Turkey)	COFEPRIS (Mexico)
Pharmacokinetics											
Lowest therapeutic dose	✓	✓[a]	✓	✓	×	×	✓[a]	×	✓	✓	×
Subcutaneous route	✓	×	✓[c]	×	×	×	✓	×	✓	✓	×
Sampling (Single dose: first & last, Multiple dose: first dose & steady state)	✓[α]	✓[#]	✓[α]	×	×	×	✓[#]	×	✓[α]	✓[α]	×
Design (Single dose cross over, Parallel grou p)	✓[β,ρ]	✓[a]	✓[βρ]	✓	×	×	✓[β,ρ]	✓[β]	✓[β,ρ]	✓[β,ρ]	×
Primary parameter (Single dose: AUC_{0-t} Multiple dose: C_{min} & $C_{max,ss}$)	✓[α]	×	×	×	×	×	×	×	✓	✓	×
Secondary parameter (Single dose: C_{max}, T_{max}, $Vs, t_{1/2}$, Multiple dose , $AUC_{0-\tau,ss}$ steady state AUC)	✓	×	×	×	×	×	×	×	✓[α]	✓[β]	×
Acceptable range (%)	80-125	80-125	80-125	90-125[ψ]	×	×	✓	×	✓	✓	×
Pharmacodynamics											
PD marker for combined PKPD	✓	✓	✓[ε]	✓[α]	✓	×	✓	✓	✓	×	×
Fingerprinting approach (non-surrogate markers)	✓	×	×	Unclear	×	×	×	×	×	×	×
Clinical efficacy											
Study type (Parallel, ranrom, blinded)	✓[#]	✓[#]	✓[#]	✓[α]	✓	×	✓	✓[#]	×	×	×
Patient population for approved indication	✓	✓	×	×	×	×	×	✓	×	×	×
Equivalence design	✓	✓	×	✓	×	×	✓	✓	✓	×	×
Endpoints	✓	✓	×	×	×	×	×	✓	×	×	×
Comparability margin	✓	✓	×	×	×	×	×	✓	×	×	×
Pediatric population	NR	NR	×	×	×	×	×	×	×	×	×
Clinical safety											
Immunogenicity	✓[β]	✓[β]	✓	×[β]	×	×	✓	✓	✓	×	×
Comparative safety data	✓	✓	✓	✓	×	✓	✓	✓	✓	×	×
Follow-up duration (6-12 months)	✓	✓	×	×	×	×	×	×	✓	×	×

✓ Indicates the requirements are define in the guidelines, × Indicates the requirements are not indicated in the guidelines, NR: Not required, [a] Higher dose for mAb clearance characteristics, [α]Steady state sampling for multiple doses, [#]Multifactorial truncated AUC for multiple doses, [ρ]For multiple dose: $AUC_{\tau,ss}$ steady state AUC, [β] Single or Composite marker, [c] Double-blind, parallel analysis, duration minimum 4 weeks, [a]Double-blind, [ψ]Comparative trial, [ε]Single dose for late elimination, [ρ] Parallel group for mAb characteristics, [ρ]Parallel group for long half-life, [a]Only single & multiple doses, [ε]Cross over for short half life, [a] Same as reference product, [α]Study PK/PD relationship, [ρ]Only parallel design, [α]Single dose: Till last quantifiable concentration, [a]equivalence margins for primary parameters

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APPENDIX 8:

Poster presented at School of Life and Medical Sciences (LMS) Research Conference 2021, 22 June 2021, Hatfield, United Kingdom

University of Hertfordshire UH

School of Life and Medical Sciences

Current regulatory requirements for biosimilars in BRICS-TM countries: Challenges and opportunities

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Introduction

Emerging economies represent 70% of the world population accounting for 31% share of global GDP and more than 30% of pharmaceutical spending [1]. Biosimilars, which account for 28% of the global pharmaceutical market have the potential to significantly boost treatment options and hence are expected to play an important role in the pharmaceutical market [2]. Emerging economies with low biologic-treatment rates and affordability barriers present attractive opportunities for biosimilars. However, marketing authorizations of these much-needed products are often delayed as manufacturers face challenges of multiple regulatory requirements to register products in different countries. Inevitably, lack of standardised regulatory processes would hamper the growth of biosimilars in these countries. Thus, it is of paramount importance to evaluate the framework for biosimilar development and approval processes in these emerging economies.

Aims

The aim of this study was to identify, interpret and compare the current perspectives of regulatory agencies in BRICS-TM (Brazil, Russia, India, China, South Africa, Turkey, Mexico) countries on the different criteria used for biosimilar development and marketing authorisation process.

Methods

A semi-quantitative questionnaire was developed covering organization of the agency, the agency's approach to biosimilar development and the marketing authorization process. Seven regulatory agencies covering the BRICS-TM countries were invited to take part and asked to complete the questionnaire. All data was treated in the strictest confidence. Data processing and analysis was carried out using descriptive statistics for the quantitative data and content analysis was employed to generate themes for the qualitative data.

Results

Figure 1. Models of Regulatory review

Table 1. Organisation of BRICS-TM agencies

Criteria	ANVISA (Brazil)	Russia MoH	CDSCO (India)	SAHPRA (South Africa)	TITCK (Turkey)	COFEPRIS (Mexico)
Internal assessors' expertise						
CMC	✓		✓	✓	✓	✓
Non-clinical	✓	n/d	✓	X	✓	✓
Clinical	✓		✓	✓	✓	✓
External assessors' expertise						
CMC			X	✓	✓	✓
Non-clinical	N/A	n/d	✓	✓	✓	✓
Clinical			✓	✓	✓	✓
Data Assessment Type						
Type I	X	X	X	X	X	✓
Type II	X	X	✓	X	X	X
Type III	✓	✓	✓	✓	✓	✓
Recognised reference agencies						
EMA, TGA, USFDA, BRDD, MHRA	n/d	n/d	✓ ✓	n/d	n/d	✓ X

N/A- Not applicable, n/d-Not defined

Table 2. Comparison of biosimilar development criteria of BRICS-TM agencies

Criteria	ANVISA (Brazil)	Russia MoH	CDSCO (India)	SAHPRA (South Africa)	TITCK (Turkey)	COFEPRIS (Mexico)
Biosimilarity						
Physicochemical and biological characterisation with *in vitro* non-clinical PK/PD studies and literature-based clinical performance evaluation, additional *in vivo* safety data plus confirmatory clinical safety and efficacy trials	✓	✓	✓	✓	✓	✓
Interchangeability decision by:						
Prescriber/physician	✓	X	✓	✓	✓	✓
Agency	X	✓	X	X	X	X
Comparative quality characterisation						
RBP selection						
Must be locally authorised	✓	✓	✓	✓	✓	✓
Acceptance of alternate source						
• ICH countries	X	X	✓	X	✓	X
• EMA, USFDA, BRDD, TGA, PMDA	X	X	✓	✓	✓	✓
• BfArM, MHRA	X	X	X	X	✓	X
Bridging studies	n/d	n/d	n/d	n/d	n/d	n/d
Analytical specification and method	ICH Q6B	Same as RBP	ICH Q6B	ICH Q6B	ICH Q6B	ICH Q6B
Requirement of comparative stability studies						
Mandatory	✓	✓	X	✓	X	✓
Not mandatory	X	X	✓	X	✓	X
Supportive	X	X	X	X	✓	X
Non-clinical studies						
In vitro studies	✓	✓	✓	✓	✓	✓
In vivo studies	✓	✓	✓	✓	✓	✓
Clinical Studies						
Combined PK/PD study, fingerprinting approach	✓	✓	✓	✓	✓	✓
Requirement of immunogenicity studies	✓	X	✓	✓	✓	✓
Comparative clinical efficacy studies	✓	✓	✓	✓	✓	✓
Clinical study design acceptance						
Equivalence design	✓	✓	✓	✓	✓	✓
Non-inferiority design	✓	X	✓	X	X	✓
Local clinical studies	X	✓	✓	X	X	✓

Table 3. Timelines for biosimilar review and approval process

Criteria	ANVISA (Brazil)	Russia MoH	CDSCO (India)	SAHPRA (South Africa)	TITCK (Turkey)	COFEPRIS (Mexico)
CTA review	90 days	45 days	90 days	< 70 days*	30 days	45 days
Validation	N/A	5-15 days	No specific step	15 days	30 days	n/d
Queuing	60-180 days	n/d	14-56 days	< 28 days	60-180 days	180-365 days
Scientific Committee review	30 days	30-90 days	n/d	60 days	n/d	90 days
Decision via committee meeting	N/A	30 days	N/A	≤ 240 days*	N/A	90 days
Issuance of Marketing authorisation	< 30 days	< 30 days	90 days	< 30 days	< 30 days	90-180 days

*Turnaround time might be prolonged in few cases, N/A- Not applicable, n/d- Not defined.

Table 1 shows the resource allocation within the agency, types of review models (Figure 1) employed for scientific assessment and reliance on other authorities.

Table 3 shows the varied timelines for biosimilar dossier review and approval processes at different stages of the marketing authorisation application.

Table 2 shows the differences in the regulatory requirements for biosimilar development criteria across the BRICS-TM regulatory agencies.

Discussion

Biosimilars can be an important tool for improving access to biologic medicines, while maintaining quality and clinical effectiveness. The majority of emerging economies have regulatory pathways for biosimilars based around the same structure and framework established by the WHO. The current research underlines the need for an enhanced regulatory reliance amongst the agencies for an effective and timely assessment of biosimilar application. The outcomes of this study also highlight the need for a greater degree of clarity and uniformity in the regulatory framework for RBP sourcing and selection criteria to provide for a cost-effective and faster development process. Thus, integration of regulatory standards across emerging economies would enable streamlined biosimilar development programmes and expedited licensing processes, thereby facilitating improvements in patient care and access to these life-saving medicines.

Disclosure- Authors of this presentation has nothing to disclose.

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References

1. C. J. Leintz and R. Dedhia, 'Biosimilars and Emerging Markets: Historical and Bioethical Considerations', Journal of Clinical Research & Bioethics 6 (2015).
2. E. R. Kabir, S. S. Moreino and M. K. S. Siam, 'The Breakthrough of Biosimilars: A Twist in the Narrative of Biological Therapy', Biomolecules (2019).

APPENDIX 9:

Presentation for virtual meeting with Swissmedic regulatory agency, 22 October 2021

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