Original Research

Challenges Faced by the Bio-Pharmaceutical Industry in the Development and Marketing Authorization of Biosimilar Medicines in BRICS-TM Countries: An Exploratory Study

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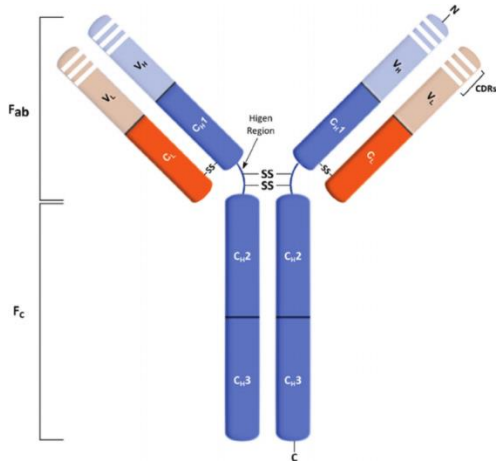
Biosimilar Development, Submission and Review Questionnaire (**BDSR**)



CONFIDENTIAL

Industry's view on Biosimilar in BRICS-TM markets

QUESTIONNAIRE-03

VERSION 010

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Confidentiality

All information collected from individual company or will be kept strictly confidential. No data that will identify an individual company will be reported or made available to any third party. External reports or presentations of the data will include only blinded results and any appropriate analytical interpretations.

STUDY BACKGROUND

This study is intended, primarily, to document procedures and practices that relate to biological medicines that are the subject of **biosimilar** applications.

AIM OF THE STUDY

To identify key challenges faced by bio-pharmaceutical companies in developing, manufacturing and commercializing biosimilar products across BRICS-TM countries.

OUTCOMES

Based on the information collected from the regulatory agencies, physicians and industry representatives across BRICS-TM markets, the key challenges and gaps in the approval pathway and patient access mechanisms will be identified. It is, therefore, hoped that a common biosimilar development strategy and an improved model for regulatory pathways in the BRICS-TM countries will be proposed.

WHO TO CONTACT FOR QUESTIONS OR ADDITIONAL INFORMATION?

If you need any additional information or have questions, please contact either Hasumati Rahalkar at **hr17abj@herts.ac.uk** or Professor Sam Salek at m.s.salek@herts.ac.uk If you would like a summary report of the outcomes of the study, please state your request at the end of the questionnaire with your contact details.

PART I: INFORMATION ON BIOSIMILAR EXPERIENCE

Q1 How many years has your company been involved in the development and commercialization of biosimilars?

☐ 1-5 years ☐ 6-10 years ☐ 11-15 years ☐ More than 15 years

Q2 How many biosimilars are being marketed by your company?

☐ Less than 3 ☐ Between 3-5 ☐ Between 5-10 ☐ More than 10

Q3 How many biosimilars are under development (including partnered) by your company?

☐ 1-3 ☐ 4-5 ☐ 5-10 ☐ More than 10

Q4 Is your company marketing/developing biosimilars for any of BRICS-TM markets, in addition to your country?

☐ Yes ☐ No

If Yes, please specify Country _____

Q5 Does your company have in-house biosimilar manufacturing facility?

☐ Yes ☐ No

If Yes, please specify location _____

PART II: CHALLENGES RELATING TO BIOSIMILAR APPROVAL PROCESS

Q6 How would you rate the current regulatory GUIDELINES for approval process of biosimilars in your country?

☐ Well-defined, transparent guidelines and efficient review process

☐ Evolving guidelines with tedious review process

☐ Lack of clarity and transparency with guidelines subject to different interpretation

☐ Others, please specify

Additional comments:

_____

_____

_____

Q7 How would you evaluate the TRANSPARENCY of the REVIEW PROCESS of biosimilar?

☐ Review process is transparent, and files can be tracked online from submission to final approval

☐ Review process is relatively transparent, files can be tracked online from the agency's letters/Q&A

☐ Review process is generally transparent for the main milestones but the decision-making process within each milestone is not transparent

☐ The review process is not transparent

Q8 What are the key challenges in review and evaluation of biosimilar dossier by your country's agency? *(Please rate here on the scale of 1 to 5, 1 being the least significant challenge and 5 being the most significant challenge)*

List of Challenges	Rate 1 to 5
Insufficient subject matter experts	
Inadequate budget allocation	
Unclear guideline, open to varying interpretation	
Process inefficiency	
Inadequate communication channel between the sponsor and the agency	
Lack of consultation with the sponsor	

Others (please specify) _____
_____
_____

Q9 How would you rate the agency's alignment of the biosimilar regulatory review process with the EMA & USFDA?

☐ Local regulations are fully aligned with EMA
☐ Local regulations are fully aligned with USFDA
☐ Local regulations are partially aligned with EMA
☐ Local regulations are partially aligned with USFDA
☐ Local regulations are not aligned with either EMA or USFDA
☐ If not aligned, please describe with which agency it is aligned:

_____
_____

Q10 How FREQUENTLY are you able to seek scientific advice/regulatory input from the agency for a specific biosimilar product?

☐ As and when required with no upper limit defined
☐ Specific meetings for non-clinical, clinical and pre-submission phase
☐ 1-2 meetings, meeting type/phase not defined
☐ No interaction possible

Q11 Have you ever been provided with a SATISFACTORY scientific advice by an authority prior to filing a biosimilar application?

☐ Adequate advice received ☐ Inadequate advice received
☐ Advice not received

If advice received, whether the scientific advice provided will be LEGALLY binding for both the regulator and the sponsor?

☐ Yes, for both parties ☐ No, for both parties
☐ Yes, only for company ☐ Yes, only for regulator

Q12 What is the CURRENT TIMELINE for evaluation and approval of a biosimilar by the regulatory agency?

☐ 6 months ☐ 9 months ☐ 12 months ☐ 24 months

☐ Others _____

Q13 What should be the OPTIMAL TIMELINE for evaluation and approval of a biosimilar by the regulatory agency in YOUR OPINION?

☐ 6 months ☐ 9 months ☐ 12 months ☐ 24 months

☐ Others _____

Q14 What is the timeline for pricing and listing of a biosimilar post approval with a national product and pricing approval agency?

☐ 1 month ☐ 2 months ☐ 3 months ☐ 6 months

☐ Others _____

Q15 Abridged Review Pathway

a. Does your agency follow abridged review pathway for marketing authorisation applications?

☐ Yes ☐ No

If Yes, have you ever obtained an approval under this pathway?

☐ Yes ☐ No

From which country did you receive first approval _____

b. Did you get waiver for any of these studies under the abridged review pathway?

☐ Pre-clinical study ☐ Clinical Safety study (Immunogenicity)

☐ Clinical Efficacy study (Confirmatory) ☐ Post-marketing Surveillance study

Q16 Does your agency allow priority/fast track application?

☐ Yes ☐ No

If Yes, has your company ever received an approval under this pathway?

☐ Yes ☐ No

If Yes, please specify the biosimilar product _____

Q17 In your country, is IP regime favourable to biosimilar?

☐ Yes, favourable to biosimilars

☐ No, favourable to Originator Biological Product

PART III: CHALLENGES relating TO BIOSIMILAR DEVELOPMENT

Q18 Has your company experienced any challenge relating to the content of a dossier application?

☐ Yes ☐ No

If Yes, please specify _____

_____

Q19 Reference Biological Product Selection

a. Does your agency provide complete clarity on Reference Biological Product selection for biosimilar development?

☐ Yes ☐ No

☐ Others (please specify) _____

b. Does your agency expect to use multiple batches of reference biological product during development stage?

☐ Yes ☐ No

If Yes, how many batches _____

c. have you faced difficulties in sourcing multiple batches of Reference Biological Product?

☐ Yes ☐ No

Define challenges

_____
_____
_____
_____

d. In the case of non-availability/withdrawn of Original Biological Product, does your agency define and allow alternate biological product to be used as a reference product?

☐ Yes ☐ No

If Yes, is this reference product also a BIOSIMILAR?

☐ Yes ☐ No

Q20 In your opinion, in which of the areas listed below, does industry face challenges in demonstrating BIOSIMILARITY? *(Please rate here on the scale of 1 to 3, 1 being the least significan challenge and 3 being the most significant challenge)*

List of Challenges	Rate 1 to 3
Comparatively Physico-Chemical and Biological Characterisation (Quality)	
In-vitro or *In-vivo* Non-clinical study	
Confirmatory clinical safety and efficacy study	

☐ Others (please specify) _____
_____

Q21 Does your company face any challenges in submitting THREE COMMERCIAL SCALE BATCHES validation data as part of a dossier submission?

☐ Yes ☐ No

If Yes, please specify _____
_____
_____
_____

a. Does your agency allow to commercialise product which is manufactured as part of validation study?

☐ Yes ☐ No

☐ Others (please specify) _____

_____

Q22 Has your company ever obtained approval for extrapolated indication (based on reference biological products approved indications) by demonstrating of biosimilarity in one indication?

☐ Yes ☐ No

If No, was there any reason for rejection? Please specify.

_____

_____

Q23 Post-approval challenges

a. Is the INN for a biosimilar the same as that for the original biological product?

☐ Yes ☐ No

If No, please explain the differences _____

_____

b. Does your agency have a separate PV system to report adverse reactions for biosimilars?

☐ Yes ☐ No

If Yes, how do you report adverse reactions in the system?

☐ By INN ☐ By trade name

☐ Others (please specify) _____

_____

c. Has your company experienced a need for demonstration of biosimilarity due to change in the manufacturing process as part of post approval changes for a biosimilar?

☐ Yes ☐ No

If yes, specify changes _____

_____

Q24 In your experience, which of the following NON-CLINICAL study (indicating requirement) is mandatory to be performed as part of biosimilar applications?

Study	Required (Y/N)	Type of animal species	Sample size
1. PKPD *in-vivo*			
2. Toxicity			
• Single dose toxicity study			
• Repeated-dose toxicity study			
• Unspecific toxicity			
• Reproduction toxicology			
• Carcinogenicity			
3. Immunogenicity			
• Comparative Safety pharmacology			

• Local tolerance			
Others, if any			

Q25 In your experience, what is the timeline for approval of a clinical trial application?

☐ 30 days ☐ 45 days

☐ Specify (if different) _____

_____

Q26 In your experience, which of below PK study design were accepted by your agency for an approved biosimilar from your company?

a. Short half-life products

☐ Single dose **CROSS-OVER** with late elimination phase

☐ Single-dose **PARALLEL** with late elimination phase

☐ Others (if any) _____

b. Long half-life products

☐ Single dose **CROSS-OVER** with late elimination phase

☐ Single-dose **PARALLEL** with late elimination phase

☐ Others (if any) _____

Q27 Has your company faced any challenges in clinical PKPD study for a biosimilar?

(Please rate here on the scale of 1 to 5, 1 being the least significant challenge and 5 being the most significant challenge)

List of Challenges	Rate 1 to 5
Approval of protocol from the agency	
Ethics approval	
Patient recruitment	
Availability of time at CRO	
Lack of specific and binding scientific advice on clinical study design	

☐ Others (please specify) _____

_____

Q28 Have you ever performed combined PKPD studies for any of your company's biosimilar application?

☐ Yes ☐ No

☐ Others (if any) _____

_____

If the answer is No, please explain the reason.

_____

_____

Q29 What is the minimum sample size expected by your agency for CLINICAL STUDIES?

List of Studies	Sample Size
Pharmacokinetics (PK)	
Pharmacodynamics (PD)	
Combined PKPD	
Clinical Safety (Immunogenicity study)	
Clinical Efficacy (Confirmatory Clinical Trial)	
Post-marketing Surveillance study	

Q30 Have you ever planned to take your product outside of your country, in BRICS-TM markets?

☐ Yes ☐ No

If Yes, please specify which Country _____

a. While developing biosimilar products for BRICS-TM markets, which of challenges listed below were experienced by your company? *(Please rate here on the scale of 1 to 5, 1 being the least significant challenge and 5 being the most significant challenge)*

List of Challenges	Rate 1 to 4
No harmonised guideline for biosimilar development across BRICS-TM markets.	
Acceptance of a Reference Biological Product from the BRICS-TM markets other than your country.	
Absence of a common clinical trial design and approval process across the BRICS-TM markets.	
Acceptance of foreign patients' data.	

☐ Others (please specify) _____

_____

PART IV: CHALLENGES relating TO PRICING AND ACCESS

Q31 Can patients access biosimilar medicines easily in your country?

☐ Yes ☐ No

Q32 According to you what are the main reasons for limited access of biosimilars to patients? *(Please rate here on the scale of 1 to 5, 1 being the least significant challenge and 5 being the most significant challenge)*

List of Challenges	Rate 1 to 5
Innovator patent term and strategy	
Higher cost of therapy as compare to small molecule medicines	
Challenges pertaining to regulatory framework for development and approval of biosimilars	
Less numbers of active industry players in biosimilar space	
Not on approved list of medicines	

☐ Others (please specify) _____

_____

_____

Q33 In your opinion, what are the biggest entry barriers for industry players to be active in biosimilar space? *(Please rate here on the scale of 1 to 5, 1 being the least significant challenge and 5 being the most significant challenge)*

List of Entry barriers	Rate 1 to 5
In-house expertise and infrastructure for biosimilar	
Prohibitive cost of clinical trials for biosimilars	
Late and unsure return on investment considering high cost involved	
Highly competitive and fluctuating prices for biosimilars	
Pressure on pricing from health authorities/insurers /procurement authority	

☐ Others (please specify) _____

_____

_____

Q34 Concluding Observations

List THREE major improvement areas relating to development and regulatory review process of biosimilars.

1. _____
   _____
2. _____
   _____
3. _____
   _____

Q35 Would you like to receive a summary report of the outcomes of this study?

☐ Yes ☐ No

If yes, please provide your email address: _____

Please provide your details below

Name of the person:			
Company Name:			
Position:			
Age:	**Gender:**	☐ Male	☐ Female
Country:			
Date:	**Place:**		

Glossary of terms and abbreviations

Term	Definition
Abridged review pathway	It conserves resources by not re-assessing scientific supporting data that has been reviewed and accepted elsewhere but includes an 'abridged' independent review of the product in terms of its use under local conditions. This might include a review of the biopharmaceutical (CMC) data in relation to climatic conditions and distribution infrastructure and a benefit-risk assessment in relation to use in the local ethnic population, medical practice/culture and patterns of disease and nutrition.
Clinical efficacy study	The ability to produce a desired effect i.e. appropriate pharmacological activity for a specified indication.
Clinical safety study	It is the pharmacological science relating to the collection, detection, assessment, monitoring and prevention of adverse effects.
INN	International Non-proprietary Names (INN) identify pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property.
IP regime	Intellectual property (IP) is for a technical invention which allows manufacturer to prevent others from using invention for commercial purposes for up to 20 years.
Marketing authorization application (MAA)	Authorization application submitted to a regulatory authority to launch a drug product on the market for which the application has been submitted.
PK study	Comparative pharmacokinetic (PK) studies designed to demonstrate similar PK profile of the biosimilar and the reference medicinal product regarding key PK parameters. The design of a PK study depends on various factors, including clinical context, safety, PK characteristics of the reference product (target-mediated disposition, linear or non-linear PK, time-dependency, half-life, etc.)
PD study	The branch of pharmacology concerned with the effects of drugs and the mechanism of their action.
PV	Pharmacovigilance (PV) is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem after it is in the market place.

Thank You for completing this questionnaire
