Available online on 15 Sept. 2019 at https://ijdra.com/index.php/journal

International Journal of Drug Regulatory Affairs

Published by Diva Enterprises Pvt. Ltd., New Delhi
Associated with Delhi Pharmaceutical Sciences & Research University

Review Article

Regulatory architecture of biosimilars in Singapore: A critical overview

Soundarya Reddy Kalva[a,*], Sahitya Reddy Kalva[b], Sudheer Kumar Gumme[c]

[a]*14535 bld, 112, Bexley Commons Rosedale, Huntersville, NC-28078, USA*
[b]*CropIn Technology Solutions, 3rd Floor, 1021, 16th Main Rd, Tavarekere, Aicobo Nagar, 1st Stage, BTM Layout 1, Bengaluru, Karnataka India 560029*
[c]*ICON plc, 4 Innovation Drive, Dundas, Ontario L9H 7P3, Canada.*

Abstract

A Biosimilar medicine is a medicine which is similar to a biological medicine that has already been authorized (the 'biological reference medicine'). The expiration of the patents on many biological products has prompted the development of these products as similar biological products. The European Medicinal Agency (EMEA) has done a commendable job at creating the regulatory path to facilitate approval of biosimilars. The Health Product Act requires all medicinal products sold in Singapore and manufactured locally for export to be licensed with the Health Products Regulation Group, Health Science Authority (HAS). Biosimilar products are eligible for the New Drug Application (NDA-2 and NDA-3) application types. The Biosimilar product should be evaluated and approved by at least one of HAS's reference agencies namely Australia, Health Canada, Europe, United States. Approved biosimilars must be demonstrated, through extensive characterization and appropriate clinical trials, to be as safe and effective as originators for the benefit of patients.

Keywords: Biosimilars, Health Science Authority (HAS), NDA-2, NDA-3, EMEA, Clinical Trial Certificate (CTC), MAV, MIV

Article Info: Received 05 Aug. 2019; Review Completed 28 Aug. 2019; Accepted 11 Sept. 2019

Cite this article as:
Kalva SR, Kalva SR, Gumme SK. Regulatory architecture of biosimilars in Singapore: A critical overview. International Journal of Drug Regulatory Affairs [Internet]. 15 Sept 2019 [cited 15 Sept 2019]; 7(3):34-39. Available from:
http://ijdra.com/index.php/journal/article/view/341

DOI: 10.22270/ijdra.v7i3.341
*Corresponding author Tel.: +1 9082540678
E-mail address: soundaryareddy.kalva@gmail.com (S. R. Kalva).

1. Introduction

In Singapore, generic version of biopharmaceuticals is specified as "similar biological products". The Central Regulatory Authority in Singapore for approval of a product is Health Science Authority (HAS). The Guidance document for similar biological products is adapted mainly from the EMEA guidelines. (1) Biosimilar products are required to go through a scientifically rigorous pathway based on a stepwise head to head comparability to the RBP in terms of quality of product (physical and chemical characteristics), non-clinical studies (toxicity, functionality) and clinical studies (safety, efficacy & immunogenicity). The comparability is designed to show similarity and demonstrate that there are no clinically meaningful differences between the RBP and biosimilar product.

A biosimilar product may ride on the safety and efficacy of the RBP to obtain approval for one or more indications approved for the RBP without head-to-head comparison in clinical studies for each indications. This is based on the overall evidence taking into account the physicochemical similarity demonstrated through analytical and functional assays (structure, molecular weight, binding assays, etc) that the biosimilar works in the same way as the RBP, as well as clinical studies conducted in the most sensitive clinical setting which allows the bridging of the efficacy and safety to other indications. (2)

Definition

A biosimilar product is a biological therapeutic product demonstrated to be similar, in physicochemical characteristics, biological activity, safety and efficacy to an existing registered biological product. (3)

Reference product

• It must be a Singapore biological reference product.

• The active substance(s) of the bio similar product and reference product should be similar in molecular and biological terms.

• The conditions of use for the bio similar product must fall within the directions for use including Indication, dosing regimen(s) and Patient group (s) for the Singapore Registered reference Product. (3)

Application Types

The product must have been approved by at least one of the following reference agencies: EU EMA, Australia TGA (Therapeutic Goods Administration), US FDA (Food Drug Administration) and Health Canada.

Bio similar products are eligible for the (New Drug Application) NDA-2 and NDA-3 application types. When selecting the Product Type in Pharmaceutical Regulatory & Information System (PRISM) section 3.2, select "Biological Drug". (4)

NDA-2: For the first strength of a bio similar product with the same dosage form and route of administration as the reference biological product.

NDA-3: For subsequent strength(s) of a bio similar product that has been registered or has been submitted as an NDA-2. The product name, pharmaceutical dosage form, indication, dosing regimen and patient population shall be the same as that for the NDA-2. (4)

Format

International Common Harmonization Common Technical Document (ICH CTD) or ASEAN Common Technical Document (ACTD) format. Testing Laboratory: Certificates of analysis from a laboratory in one of HAS's reference agencies or other accredited biologics testing laboratory.

Timelines

Table 1 Timeline requirements in product submission in Singapore

S. No	Requirements	Timeline
1.	The complete dossier should be submitted after the PRISM application submission.	2 working days
2.	Submit full information after issuance of screening query letter	30 calendar days
3.	Reporting of Serious Adverse Drug Reactions (ADR) & non-serious ADRs	15 days
4.	Product licence holder is required to submit the global PSURs to HSA	6 months for the first 2 years; Yearly for the following 3 years.

Fees: The fee structure and quanta are subject to on-going review.

Screening fee: The screening fee per application is payable at the time of PRISM submission. The screening fees are nonrefundable once the application has been successfully submitted via PRISM.

***Evaluation fee*:** Evaluation fees are payable upon acceptance of the dossier for evaluation. The evaluation fees are nonrefundable once the application is accepted, regardless of the final decision by Health Science Authority (HAS). The progressive payment scheme was implemented to allow payment of evaluation fees by installments. This is an optional opt-in payment scheme catered for companies who are under the GIRO payment scheme. It is applicable to similar biological Products.

Table 2 Percentage of Evaluation Fee Payable at Each Stage of submission in Singapore

Percentage of Evaluation Fee Payable at Each Stage					
Application Type	Evaluation Type	**Evaluation Status**			
		Accepted for Evaluation	Active Evaluation	Midway in Evaluation	Evaluation Completed
NDA -2 NDA -3	Abridged	30%	40%	20%	10%

For applicants that had chosen the progressive payment scheme, in the event of an application withdrawal at any point in time during the evaluation stage, any fees that had been charged, but not yet collected, would still have to be paid; all evaluation fees that had been paid are non-refundable. (5)

Change in evaluation fees

Changes in the evaluation fees may occur if there are changes to the application type:

• Change of Application within the Same Application Type.
• Change of Application between Different Application Types. (5)

GMP Audit

Table 3 GMP Audit requirements in Singapore

S. No	Requirements	Remarks
1.	**Pre-Audit:** Updated Site Master File should be sent to HSA for pre-audit assessment. Site Master File describes manufacturing plant and include a) General Information b) Personnel c) Premises & Equipment	Site Mater File should not contains more than 25 to 30 pages

	d) Documentation e) Production f) Quality Control g) Contract Manufacture & Analysis h) Distribution, Complaints & Recalls i) Self-Inspection	
2.	**Site Audit:** Describes purpose of the visit and scope of activities and update the recent changes.	Review past non-conformities
3.	**Documentary review:** Review all batch records, analytical records, GMP training records, validation documents, product complaints, records of self-inspection.	Wrap-up meeting and classify Non-conformities into major or minor etc.
4.	**Post Audit:** A letter should be sent to manufacturer to obtain his response to the non-conformities observed.	If the audit team is satisfied with the CA and time frames for rectification, the audit will be "closed out"

2. Submission Procedure

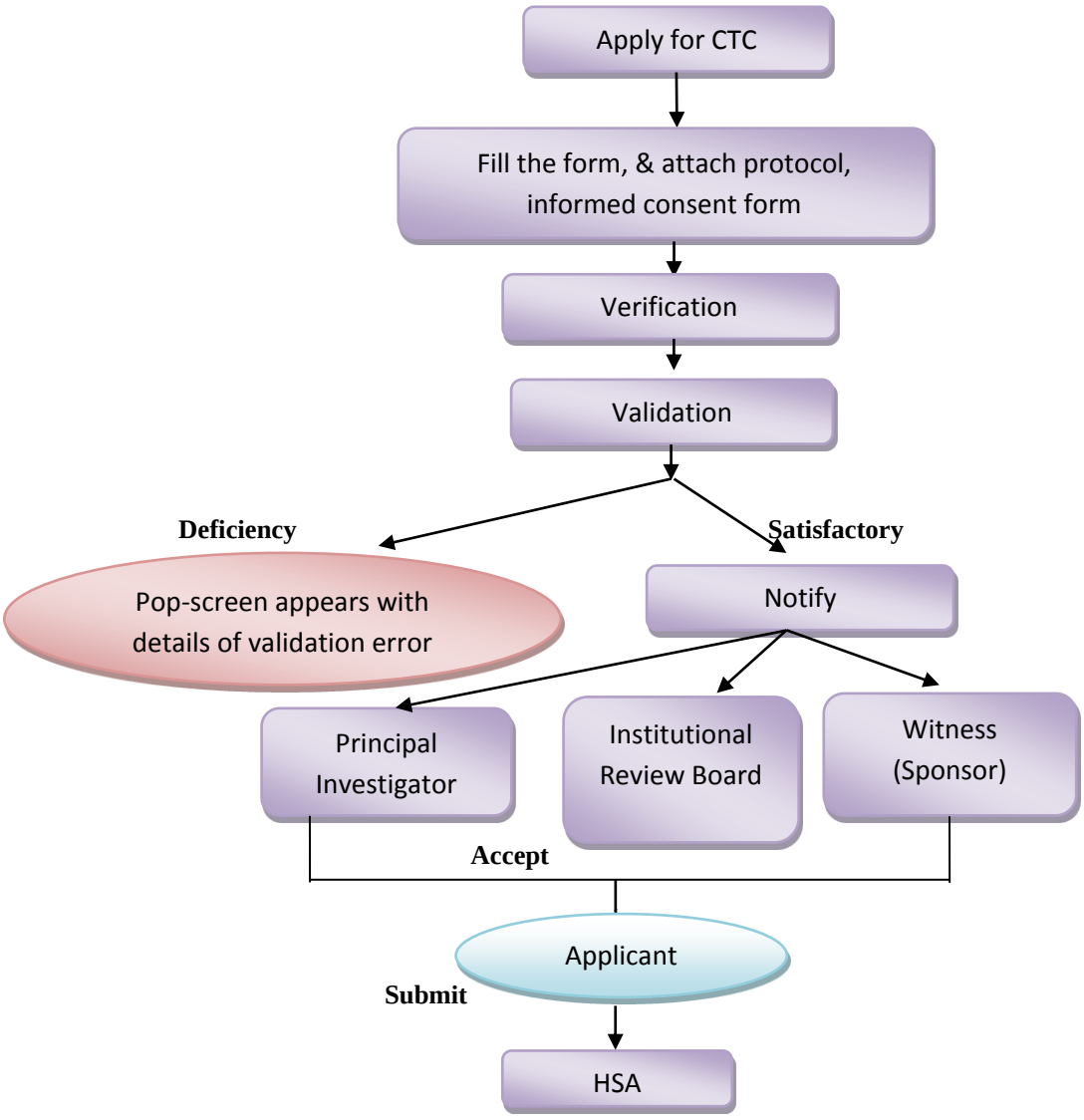

Figure 1. Overview of the Electronic Application Process for Clinical Trial Certificate (CTC)

3. Registration Process (6)**:**

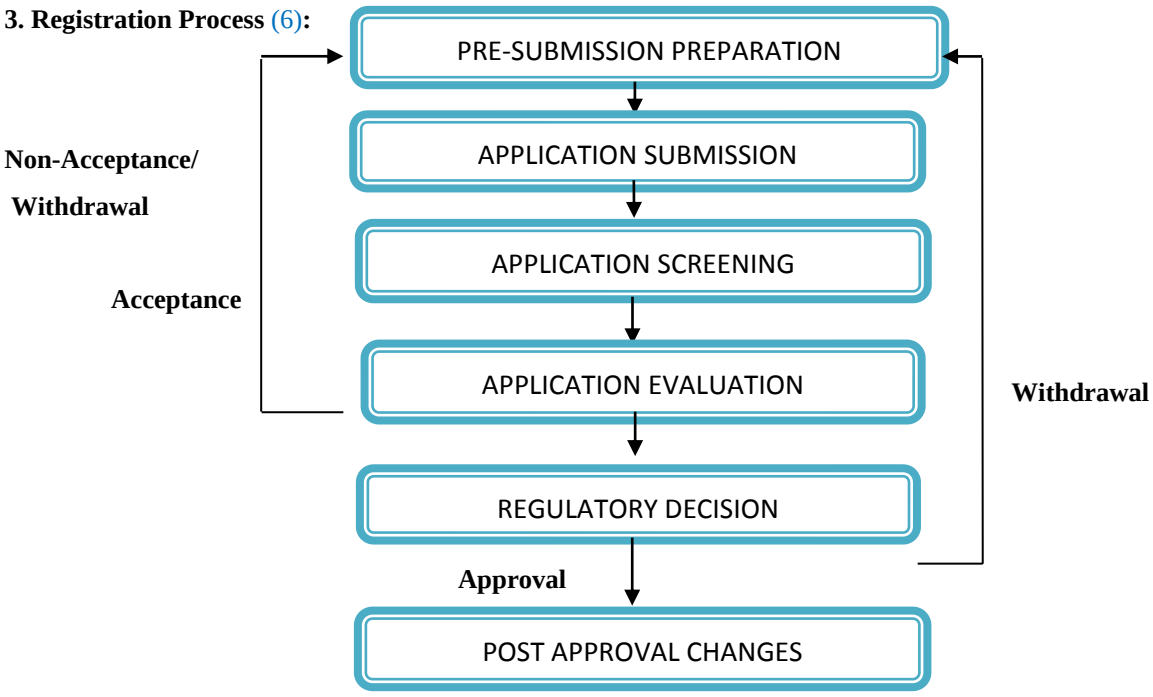

Figure 2. Submission procedure in Singapore

Application for a bio similar product is to be submitted as a new drug application (NDA) via the abridged dossier evaluation route.

Post Approval Process

The steps to submit an MAV or MIV is similar to submitting an NDA as seen in the above figure.

There are two types of variation applications: Major Variation Application (MAV) and Minor Variation Application (MIV). For similar biological products, MAV-1 is applicable.

4. Documentary Requirements (7)**:**

Table 4 CTD Filing considerations in submission of similar biological product in Singapore

Documents	Location in		Module/Part required for
	ICH CTD	ACTD	Bio similar Product
Administrative documents	Module 1	Part 1	Yes
CTD overview & Summaries	Module 2	Incorporated in Part II, III, & IV.	Yes
Quality documents	Module 3	Part II	Complete Quality module including comparability studies.
Nonclinical documents	Module 4	Part III	Complete Non-clinical module including comparability studies.
Clinical documents	Clinical documents	Part IV	Complete Clinical module including comparability studies.

Administrative Documents

- Cover letter (to be attached to Introduction section)
- Comprehensive Table of Contents
- Introduction
- Application Form
- Labelling, Package Insert and Patient Information Leaflet
- Approved SPC/PI (Package Insert)/PIL
- Assessment Report from Reference Agencies
- Description of Batch Numbering System
- Proof of Approval
- Authorization Letters
- GMP Certification/Proof of GMP Compliance
- Patent declaration
- Declaration on rejection, withdrawal and deferral
- Registration status in other countries

Quality documents

- Body of Data – Drug Substance
- Drug Master File (DMF)
- Plasma Master File (PMF)
- Certificates of Suitability (CEP)
- Control of Drug Substance
- Stability Data of Drug Substance
- Body of Data – Drug Product
- Pharmaceutical Development
- Process Validation
- Control of Excipients
- Control of Drug Product

- Container Closure System
- Stability Data of Drug Product
- Blank Production Batch Records

Non-Clinical Documents

- *In vitro Studies* - Assays like receptor-binding studies or cell-based assays should normally be undertaken in order to establish comparability.
- *In vivo Studies* - Animal studies should be performed to investigate pharmacodynamics effect/activity relevant to the clinical application, non-clinical toxicity as determined in at least one repeat dose toxicity study, including toxicokinetic measurements, and specific safety concerns.

Clinical Documents

- Pharmacokinetic studies
- Pharmacodynamics studies
- Confirmatory PK/PD studies
- Immunogenicity

Pharmacovigilance Requirements

- ADR reporting by product license holders
- Reviewing of PSURs for bio similar products
- Serious, Related, and Unexpected Non-Fatal/ Non-Life Threatening Events are reported in CIOMS form.
- Risk management plans for bio similar products
- Educational materials
- Product Sales Data

Post Approval Batch Requirements

Bio similar products are subjected to a risk-based post-approval batch release programme. Prior to import and sale of each batch of the bio similar product, should submit:

- Manufacturer's batch release data and certificate of analysis.
- A letter of commitment to provide yearly stability data on annual stability batch.

Post Approval Requirements

There are two types of variation applications: Major Variation Application (MAV) and Minor Variation Application (MIV). For similar biological products, MAV-1 is applicable.

MAV-1 *(8)*

Any variation to the approved indication(s), dosing regimen(s), patient group(s), and/or inclusion of clinical information extending the usage of the product.

Table 5 Dossier Submission Requirements for MAV-1

Documents	Location in		Module/Part required for
	ICH CTD	ACTD	Bio similar Product
Administrative documents	Module 1	Part 1	Yes
CTD overview & Summaries	Module 2	Incorporated in Part II, III, & IV	Yes
Quality documents	Module 3	Part II	No
Nonclinical documents	Module 4	Part III	No#
Clinical documents	Clinical documents	Part IV	Study report(s) of pivotal studies and synopses of all studies (phase I-IV) relevant to requested indication, dosing and/or patient group

Non-clinical overview only, if applicable

5. Conclusion

As Biosimilar are immunogenic. This may cause antibodies in the patient's body to attack and neutralize the biosimilar and it could have serious consequences. Regulations and laws should address multiple areas, going beyond just the regulatory approval process, pharmacovigilance systems and prescription practices are adapted. Quality, Non-Clinical, Clinical Studies guidelines taken from European Medicine Agency. I Conclude:

- In Singapore, evaluation routes for Biosimilar are through NDA-2 and NDA-3.
- PRISM Application is most needed for any product submission in Singapore.
- Clinical Trial Certification (CTC) is made through Online.
- For Similar Biological products, Major Variation Application (MAV-1) is applicable.

Acknowledgements

I would like to express my gratitude to International Journal of Drug Regulatory Affairs who gave me the opportunity to publish the article.

Financial Disclosure statement: The author received no specific funding for this work.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

References

1. Europe. European Medicines Agency. Guideline on Similar biological medicinal products, CHMP/437/04 Rev 1 [Internet]. EMA; 2014 Oct 23 [cited 2019 Aug 03]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1_en.pdf
2. Health Science Authority. Frequently asked questions: Health Product Regulations, Therapeutic Product Registration [Internet].hsa.gov; 2014 Apr 22 [cited 2019 Aug 3]. Available from:

https://www.hsa.gov.sg/pub/faq/faq/faqcategory/biosimilars.aspx
3. Guidance on registration of Biosimilar Products in Singapore, Appendix 15 [Internet]. hsa.gov; Nov 2016 [cited 2019 Jul 22]. Available from: https://www.hsa.gov.sg/content/dam/HSA/HPRG/Western_Medicine/Overview_Framework_Policies/Guidelines_on_Drug_Registration/DR_Guide_2016/DR%20guide%202016%20final/Appendix%2015_Guidance%20on%20Registration%20of%20Biosimilar%20Products.pdf
4. Guidance on Therapeutic Product Registration in Singapore, Chapter E [Internet]. hsa.gov; 2019 Jan 15 [cited 2019 Jul 29]. Available from: https://www.hsa.gov.sg/content/dam/HSA/HPRG/Western_Medicine/Overview_Framework_Policies/Guidelines_on_Drug_Registration/DR_Guide_update_Jan2019/Guidance%20on%20Therapeutic%20Product%20Registration%20in%20Singapore_Jan2019.pdf
5. Guidance on Therapeutic Product Registration in Singapore, Chapter F [Internet]. hsa.gov; 2019 [cited 2019 Jul 29]. Available from: https://www.hsa.gov.sg/content/dam/HSA/HPRG/Western_Medicine/Overview_Framework_Policies/Guidelines_on_Drug_Registration/DR_Guide_update_Jan2019/Guidance%20on%20Therapeutic%20Product%20Registration%20in%20Singapore_Jan2019.pdf
6. Guidance on Therapeutic Product Registration in Singapore, Chapter B [Internet]. hsa.gov; 2019 Jan 15 [cited 2019 Jul 29]. Available from: https://www.hsa.gov.sg/content/dam/HSA/HPRG/Western_Medicine/Overview_Framework_Policies/Guidelines_on_Drug_Registration/DR_Guide_update_Jan2019/Guidance%20on%20Therapeutic%20Product%20Registration%20in%20Singapore_Jan2019.pdf
7. Guidance on Therapeutic Product Registration in Singapore, Chapter C [Internet]. hsa.gov; 2019 Jan 15 [cited 2019 Jul 29]. Available from: https://www.hsa.gov.sg/content/dam/HSA/HPRG/Western_Medicine/Overview_Framework_Policies/Guidelines_on_Drug_Registration/DR_Guide_update_Jan2019/Guidance%20on%20Therapeutic%20Product%20Registration%20in%20Singapore_Jan2019.pdf
8. Guidance on Therapeutic Product Registration in Singapore, Chapter G [Internet]. hsa.gov; 2019 Jan 15 [cited 2019 Jul 29]. Available from: https://www.hsa.gov.sg/content/dam/HSA/HPRG/Western_Medicine/Overview_Framework_Policies/Guidelines_on_Drug_Registration/DR_Guide_update_Jan2019/Guidance%20on%20Therapeutic%20Product%20Registration%20in%20Singapore_Jan2019.pdf