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Regulatory landscape of biosimilars in Singapore: a critical overview

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ABSTRACT

A Biosimilar medicine is a medicine which is similar to a biological medicine that has already been authorised (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 Medicines 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). Guidance on registration of similar biological products in Singapore was published by the HSA in August 2009. This was added as Appendix 17 to the 'Guidance on Medicinal Product Registration in Singapore' in April 2011. Bio similar 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.

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].

Definition:

A similar biological product is a biological medicinal product referring to an existing registered product, submitted for medicinal product registration by an independent applicant, and is subject to all applicable data protection periods and/or intellectual property rights for the original product [2].

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(s), dosing regimen(s) and Patient group (s) for the Singapore Registered reference product [2].

Data Protection & Exclusivity:

- Sections 19A and 19B were included in the Medicines Act in 1998 to enable Singapore to comply with its obligations under Article 39 of the WTO TRIPS Agreement.
- Section 19D was introduced in July 2004, in order for Singapore to fulfil its obligations under Article 16.8.1 of the US-Singapore FTA [3].

Patent Linkage:

- Medicines Act sections 12A effected in 2004 to comply with United States-Singapore Free Trade Agreement (US – S FTA) Article 16.8.4 (b),(c)
- Medicines Act sections 16 (1B)
- **Medicines Regulations:** Regulation 5B
  6th Schedule, Part I
  6th Schedule, Part II
- **Patent Declaration Categories:** Category A1 Application
  Category A2 Application
  Category A3 Application
  Category B Application
  Sections 12(3) of Medicines Act. [4]
- **Revocation of Product license:** Medicines Act sections 16 (1B)

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"* [2].

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

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regimen and patient population shall be the *same* as that for the NDA-2 [5].

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.

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 *non-refundable* 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 *non-refundable* 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 instalments. 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.

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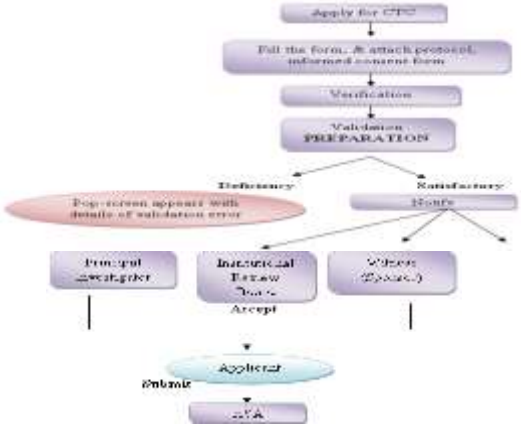
For applicants that had chosen the progressive payment scheme, in the event of an application withdrawal at any point in time during the evaluation stage, any fees that had been charged, but not yet collected, would *still* have to be paid; all evaluation fees that had been paid are non-refundable [6].

Change in evaluation fees:

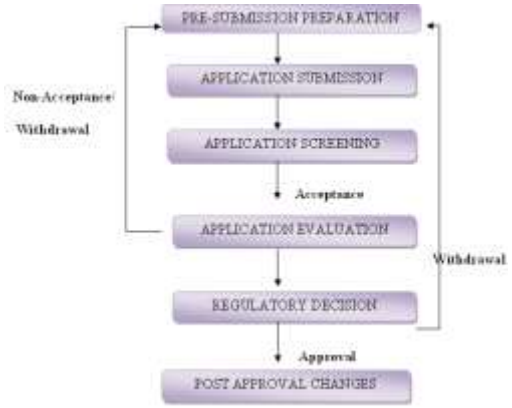
Changes in the evaluation fees may occur if there are changes to the application type:

- Change of Application within the Same Application Type.
- Change of Application between Different Application Types [6].



Registration Process:

Application for a bio similar product is to be submitted as a new drug application (NDA) via the abridged dossier evaluation route [7].



Post Approval Process:

The steps to submit an MAV or MIV is similar to submitting an NDA as seen in the
(Figure -2)

There are two types of variation applications: Major Variation Application (MAV) and

Minor Variation Application (MIV). For similar biological products, MAV-1 is applicable.

Documentary requirements:

Administrative Documents:

- Comprehensive Table of Contents
- Introduction
- Application Form
- Labelling, Package Insert and Patient Information Leaflet
- Approved SPC/PI (Package Insert)/PIL
- Description of Batch Numbering System
- Proof of Approval
- Authorisation 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

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 [8]

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

References:

1. Guideline on Similar biological medicinal products CHMP/437/04 [Internet], Available Online at: http://www.emea.europa.eu/htms/human/humanguidelines/multidiscipline.htm. Accessed 7 January 2012.

2. Guidance on Medicinal product registration in Singapore, Guidance on registration of Similar biological products in Singapore [Internet], Available Online at: http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/western_medicines/guidelines.html. Accessed 29 December 2011.

3. Medicine Act, Chapter 176, Revised Edition 1985 Act 52 of 1975, S156/93 7 of 1998.

4.Guidance on Medicinal Product Registration in Singapore, Chapter A Available Online at: http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/western_medicines/guidelines.html. Accessed 28 December 2011

5. Guidance on Medicinal Product Registration in Singapore, Chapter E Available Online at: http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/western_medicines/guidelines.html. Accessed 28 December 2011

6. Guidance on Medicinal Product Registration in Singapore, Chapter F Available Online at: http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/western_medicines/guidelines.html. Accessed 28 December 2011

7. Guidance on Medicinal Product Registration in Singapore, Chapter B Available Online at: http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/western_medicines/guidelines.html. Accessed 28 December 2011

8. Guidance on Medicinal Product Registration in Singapore, Chapter G Available Online at: http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/western_medicines/guidelines.html. Accessed 28 December 2011

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.

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

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

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 d) Documentation e) Production f) Quality Control g) Contract Manufacture & Analysis h) Distribution, Complaints & Recalls Self-Inspection	Site Mater File should not contains more than 25 to 30 pages
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 corrective actions and time frames for rectification, the audit will be "closed out"

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.

Table-5: Dossier Submission Requirements for MAV-1

Documents	Location in		Module/Part required for
	ICH CTD	ACDT	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