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Regulatory comparative studies for the registration process of bio similar products in Australia and Singapore

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Abstract
The expiration of patents on many biological medicinal products has prompted the development of these products as similar biological (biosimilar) products. Biosimilar' denotes a biological medicine which is highly similar to an already authorized reference biological medicine and also referred to as Bio therapeutic products, Follow on biologics, Subsequent entry biologics, with respect to different Ministry of health. Depends on type of country regulations, and approval process of generic version of biopharmaceuticals is specified. The standard approach of demonstration of bioequivalence for chemical generic products is scientifically not applicable for biosimilar products. The biosimilar product approach, based on comparability (demonstration of similarity), should be adopted. In view of the impending submissions and to facilitate access of such products at a more affordable price in Singapore, the Regulatory Authority is Health Sciences Authority (HSA). In Australia the regulatory authority Therapeutic Goods Administration (TGA) has adopted the European Union procedure for approving biosimilars, Centralized Procedure is mandatory for Biosimilar and fall within the scope of Regulation EC 726/2004; Food drug & administration is still in the process of developing guidelines regarding these types of products. In Singapore these are approved under NDA-2, NDA-3 process. This paper aims to facilitate the regulatory requirements for the approval process of Biosimilar in Regulated and Emerging markets by establishing the foundation for a harmonized regulatory standard to meet common demands of a regions like Australia & Singapore.

Keywords: bioequivalence, biosimilar, emerging markets, HSA, NDA, TGA

Introduction

A "biosimilar medication" or "biosimilar" is an exceptionally comparative, yet not indistinguishable, version of a unique natural medication (Reference medication) a medication contained enormous complex molecules got somehow or another from a living life form. In this sense, a biosimilar contrast somewhat from a conventional small molecule "Generic" medication, which is generally perceived as a pharmaceutical product that is indistinguishable, at any rate as far as active ingredients, to the first marked "originator" or "innovator" item. As the arrangement and innovation needed to create biological medicines keeps on progressing quickly, they are progressively conspicuous in the Australian and worldwide drug markets [1].

They are biologic clinical items whose dynamic medication substance are made by a living life form or got from a living being by recombinant DNA or controlled gene expression strategies. A biosimilar is a natural medication that is comparable, however not indistinguishable, to an all-around enlisted reference biotherapeutic item as far as quality, safety, and efficacy and expected to have similar mechanism of activity for similar illnesses as the pioneer biopharmaceutical drugs. These medications might be additionally called as biosimilar products follow-on protein Products and subsequent-entry biologics

The worldwide biosimilars market was esteemed at $2,552.0 million of every 2014 and is relied upon to reach $26,551.3 million by 2020, upheld by a compound annual growth rate (CAGR) of 49.1% during the forecast period 2015 to 2020, as per Allied Market Research's Report and this will open a pathway for the drug manufacturers to expand their market share, overall revenues and decrease the clinical consumption of biosimilar products.

The Current State of Biosimilar use in Australia

The Australian administrative system is nearly facilitative to the selection of biosimilars that are 'a-flagged' can be substituted for their reference products by a pharmacist without supervision by the prescribing doctor. The significant expenses related with biologics are foreseen to put an expanding trouble on public medical care spending in Australia except if measures are actualized to viably encourage expanded take-up. In the 2017-18 financial year, five of the best 10 medications by cost to the Australian Government were biologic medicines [2].

The Australian Therapeutic Goods Administration (TGA) has generally adopted the European way to deal with regulatory approval of biosimilars. To acquire TGA approval, each biosimilar should be assessed utilizing clinical, pre-clinical and laboratory-based comparability studies to create proof of comparative quality, safety and efficacy of each new biosimilar. There has been some controversy nationally and globally about appropriate information threshold requirements for biosimilar regulatory approval. Concerns have additionally been communicated with respect to patient exchanging between a reference medication and a biosimilar, due to, for instance, restricted long term efficacy, safety and immunogenicity information [3].

Registration of Medicinal Products in Singapore

The Health Sciences Authority (HSA) is the licensing authority for medicinal products in Singapore. The Health

Products Regulation Group (HPRG) of HSA controls health products in Singapore to guarantee that their quality safety and efficacy satisfy globally benchmarked guidelines. The authorizing of therapeutic product available to be purchased and supply in Singapore, including pharmaceutical and biological medicinal products, is represented by legislative requirements under the Medicines Act (Chapter 176) (1977).

Pre-market assessment is led to decide the danger versus advantage profile of medicinal products before enrolment and HSA adopts a risk-based with approach of current worldwide rules, principles and scientific knowledge. HSA has executed three assessment courses for new medication applications subsequent to contemplating the natural danger of the item and following the certainty based upon earlier endorsements by HSA's reference agencies. The reference organizations for medicinal products are specifically Australia Therapeutic Goods Administration (TGA), European Medicines Agency (EMA), Health Canada, United Kingdom Medicines and Healthcare products Regulation Agency (MHRA), and United States Food and Drug Administration (FDA).

Need for Separate Regulations

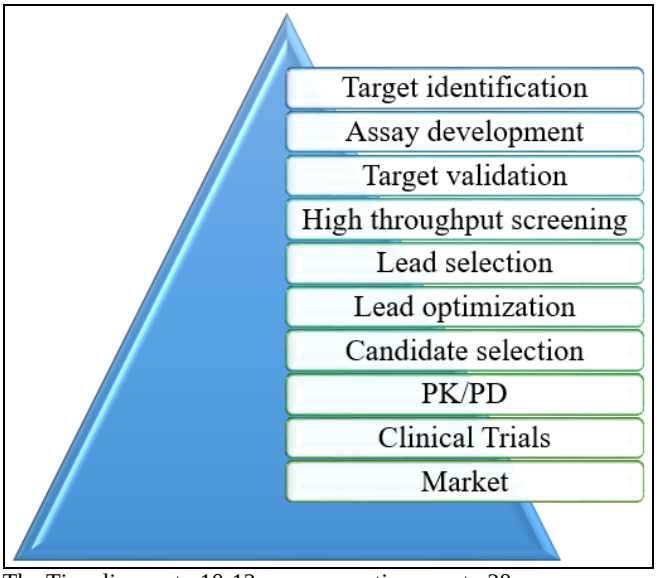
As Biosimilar are immunogenic. This may make antibodies in the patient's body to attack and neutralize the biosimilar and it could have serious consequences. Since the immunogenicity of biologic medications is unusual, even little changes in a molecule could modify the immunogenicity profile. The Safety must be set up by placing the biologic product through clinical testing in patients. Thinking about these imperatives, it is essentially hard to make an indistinguishable generic of a branded Due to this, administrative experts in numerous nations are careful about approvals to biosimilars and prescribe broad clinical trials to be embraced [4].

The current research is fundamentally to arrange all the regulatory requirements for the endorsement process of Biosimilars in Regulated markets which incorporates Australia, and emerging business sectors which includes Singapore. The blueprint of the current investigation is given in (Table 1).

Table 1: Outline of Current study

S.No	Country	Regulatory Body	Reffered AS
1	Australia (Regulated market)	Therapeutic Goods Administration (TGA)	Biosimilar, Similar biological medicinal products
2	Singapore (Emerging market)	Health Science Authority (HSA)	Similar biological product

Drug development is a ‘trial & error’ process from the initial research results to the final market introduction of the new product. The following steps illustrate the general progression and gate points of a product development. The product development of biosimilar are mentioned in (Fig. 1).



The Time line up to 10-12 years, sometimes up to 20 years

Fig 1: The product development of biosimilars

Regulatory Requirements of Biosimilars in Australia

Biosimilar medicines regulation guideline helps sponsors of biosimilar medicine to finish an application to enlist their medication on the Australian Register of Therapeutic Goods (ARTG) and to comprehend their continuous sponsor responsibilities. In Australia, the Therapeutic Good Administration (TGA) responsibility for registration and marketing authorisation of medicines (focusing on safety, efficacy and manufacturing quality) while the Pharmaceutical Benefit Advisory Committee (PBAC) advices the Australian Government on whether supply of a medication ought to be financed (focusing on cost-benefit analysis) just as prompting on brand substitutability and different issue identifying with the PBS.

Choice of Reference Product

The picked reference medicinal product should be a therapeutic product approved in the Community, based on a total dossier as per the arrangements of Article 8 of Directive 2001/83/EC, as changed. The active substance of a similar biological medicinal product should be comparative, in sub-atomic and biological terms, to the active substance of the medicinal product [5].

Submission Procedure and Requirements [6]

Quality Guidelines CHMP/437/04 Rev1

Guideline on similar biological medicinal products. EMA/CHPM/BWP/247713/2012 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1).

Comparability Guidelines

CPMP/ICH/5721/03 ICH Topic Q 5 E: Comparability of Biotechnological/Biological Products Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process.

Clinical and Non-Clinical Data Guidelines

EMEA/CHMP/BMWP/42832/2005 Rev 1: Guideline on similar biological medicinal products Containing Biotechnology-Derived Proteins as Active Substances: Non-Clinical and Clinical Issues. Effective 1 July 2015

CHMP/BMWP/101695/2006: Guideline on Comparability of Biotechnology-Derived Medicinal Products after a change in the Manufacturing Process - Non-Clinical and Clinical Issues.

The technique for Centralized Submission Procedure of product in Australia Standard time table for the evaluation of centralized applicationis clarified asstream graph (Fig.2)

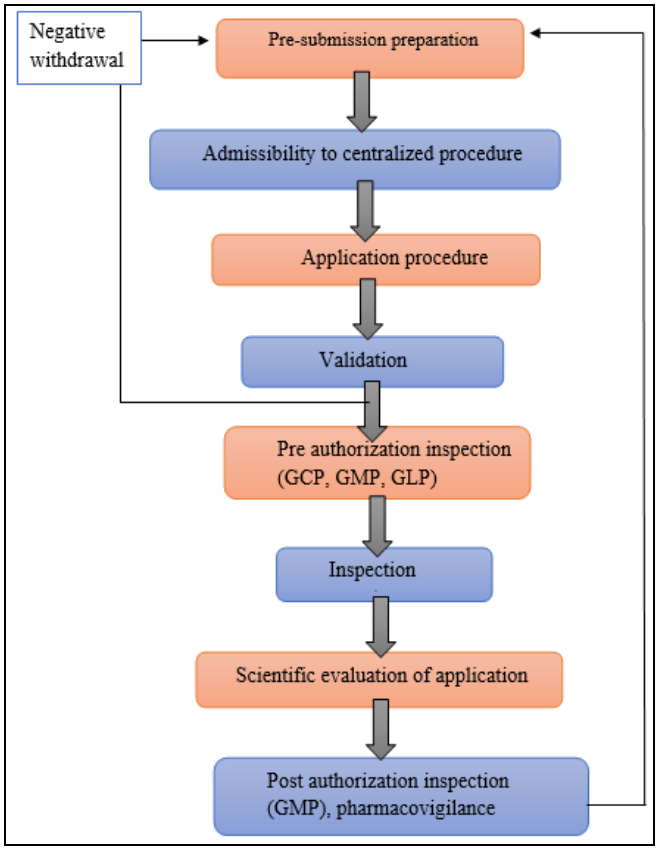


Fig 2: Centralized Submission Procedure of a product in Australia Standard timetable for the evaluation of a centralized application

Documentary requirements

The documents needed by TGA and HSA for accommodation of biosimilars are isolated into 4 classifications:

- Pre submission requirements
- Manufacturing requirements
- Pharmacovigilance requirements
- Post Approval Requirements

TGA Requires from the Applicant

- One full copy of the dossier (modules 1-5 according to the EU-CTD format), including the applicant's part of the Active Substance Master File, if any;
- Two additional copies of Modules 1 and 2 including the draft summary of product characteristics, labeling and package leaflet in English;
- One electronic copy of module 1 and 2 (at least 2.1-2.5) in word.

The pre submission requirements of biosimilars in Australia are sub partitioned into Administrative and quality documents are acutely referenced in (Fig. 3 & 4).

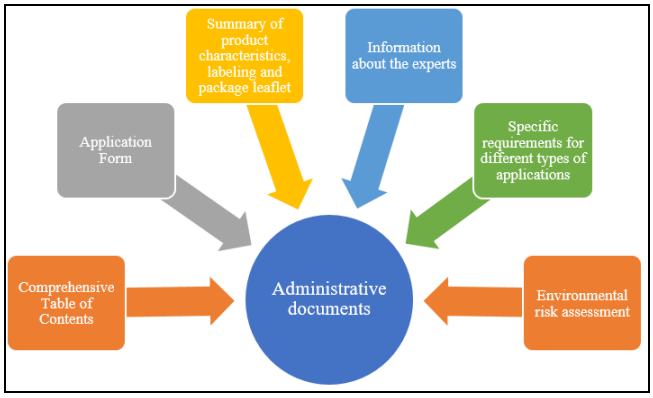


Fig 3: Administrative requirements of Australia

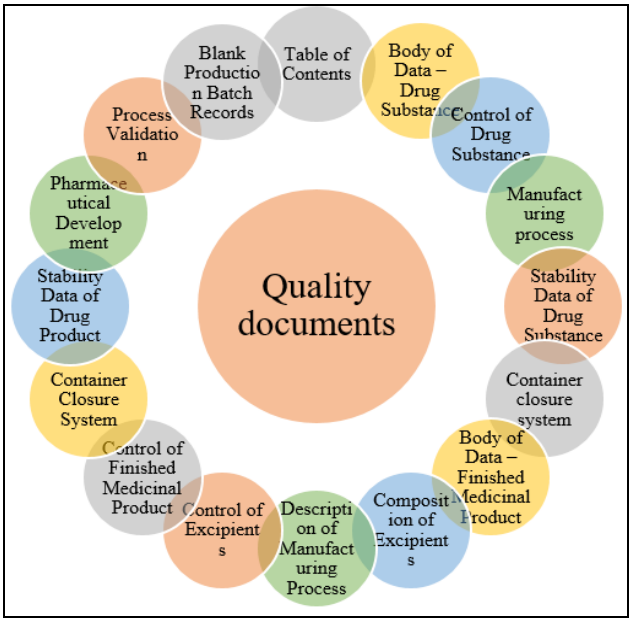


Fig 4: Australia quality documents

a. Manufacturing Requirements

- Genetically modified cell lines
- Complex fermentation process
- Complex purification process
- Formulation
- Complex analytical characterization

b. 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 pharmacodynamic 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.

c. Clinical Documents

- Pharmacokinetic studies
- Pharmacodynamic studies
- Immunogenicity

1. Pharmacovigilance Requirements

- The legal basis is set out in Article 19(1) of the Regulation and Article 111(1) (d) of Directive 2001/83/EC.

2. Post approval requirements

Variations

Type IA - Minimal or no impact at all, on the quality, safety or efficacy of the medicinal product. No prior notification before implementation.

Type IA: Immediate Notification

Type IA: Notification within 12 Months of implementing the change

Approval time: 30 days

Format

EU-Common Technical Document (CTD), Electronic Common Technical Document (eCTD), Applicants have the choice of presenting an (eCTD) in close by the paper CTD, Applicants are prompted that where an eCTD is presented, the paper CTD stays the proper accommodation, and subsequently both paper and electronic entries should go along completely with the Common Technical Document as respects introduction and substance of the dossier. The CTD Filing contemplations in submission of Biosimilar Australia are momentarily refreshed in (Table 2).

Table 2: CTD Filing considerations in submission of Biosimilar Australia

Documents	Location in		Module/Part required for
	ICHCTD	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.
Non clinical documents	Module 4	Part III	Complete Non- clinical module including comparability studies.
Clinical documents	Module 5	Part IV	Complete Clinical module including comparability studies.

Application Procedure

For all biotechnology therapeutic products including biosimilars the Centralized Procedure is obligatory. They fall inside the extent of Regulation EC 726/2004. When utilizing the Centralized Procedure, a solitary Marketing Authorization Application (MAA) must be submitted to the EMEA bringing about one single Marketing Authorization (MA) legitimate all through the EU. The European Federal Trade Association (EFTA) nations will allow public MAs subject to a positive Committee for Medicinal Products for Human Use (CHMP) assessment.

Regulatory Requirements of Biosimilars in Singapore

The Direction on Registration of Similar Biological (Biosimilar) Products in Singapore was created in interview with the business partners and became effective on first August 2009 [7]. The rule depended for the most part on the European Medicines Agency's rules on biosimilar items (CHMP Guideline on Similar Biological Medicinal Products, CHMP Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues, CHMP Guideline on Comparability of Medicinal Products Containing Biotechnology Derived Proteins as Active Substance: Quality Issues, and CHMP Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues), with thought of Singapore's neighbourhood administrative climate [8]. The fundamental standards in the rule are additionally like that in the "WHO Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) [9].

Choice of Reference Product

The picked reference biological product should be registered in Singapore and a biosimilar registered can't be utilized as a kind of reference product. The reference product ought to be of the comparing strength and from a similar medication product manufacturing site as the Singapore reference product. A similar reference product should be utilized all through the equivalence evaluation for quality, safety and efficacy studies concentrates during the advancement of a biosimilar product to permit the age of intelligible information and conclusions. The active substance of the biosimilar product and the reference product ought to be similar in molecular and biological terms. The drug structure and route of administration of the biosimilar product ought to be equivalent to that of the reference product [10].

Submission Procedure and Requirements

The application for a biosimilar product is to be submitted as a new drug application by means of the compressed dossier evaluation route. The pre-necessities for the biosimilar product is that it must be assessed and endorsed as a biosimilar product by in any one of HSA's reference organizations, to be specific, Australia TGA, Health Canada, EMA, and US FDA. General methodology and necessities for submission are similar to that for a new biological product and the details are in the "Guidance on Medicinal Product Registration in Singapore" [11]. Applications for a biosimilar product do not qualify for evaluation via the verification evaluation route. The Overview of the Electronic Application Process for Clinical Trial Certificate (CTC) is given in (Fig. 5).

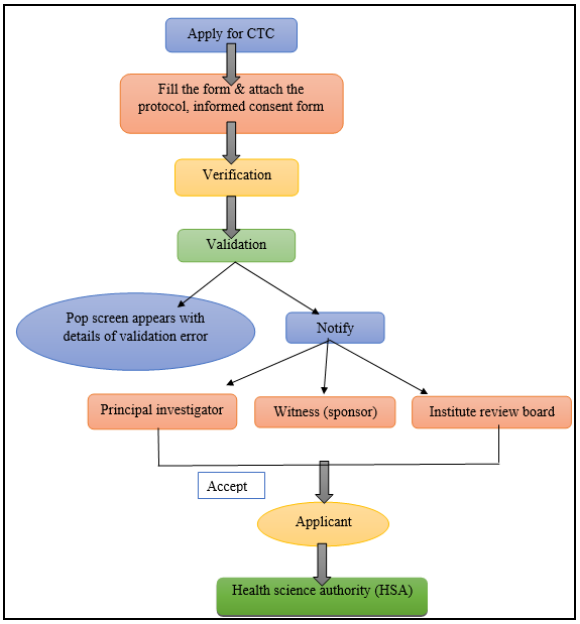


Fig 5: Overview of the Electronic Application Process for Clinical Trial Certificate (CTC)

Registration Process

Application for a bio comparable item is to be submitted as another medication application (NDA) by means of the compressed dossier assessment course [12]. The accommodation method of biosimilars is referenced in (Fig. 6).

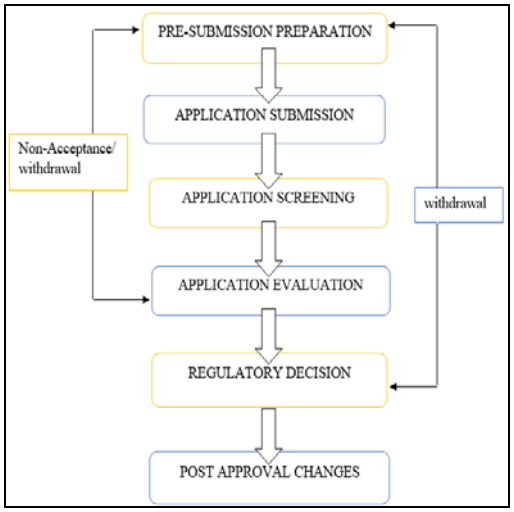


Fig 6: Submission Procedure in Singapore

Application Types

The product more likely than not been affirmed by in any event one of the accompanying reference organizations: EU EMA, Australia TGA (Therapeutic Goods Administration), US FDA (Food Drug Administration) and Health Canada.

Bio similar products are qualified for the (New Drug Application) NDA-2 and NDA-3 application types. While choosing the Product Type in Pharmaceutical Regulatory and Information System (PRISM) area 3.2, select "Biological Drug"

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 strengths of a biosimilar 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 NDA2 [13].

Documentary Requirements

The total quality dossier, including all relevant documents, as needed for new biological product submitted through the abbreviated dossier assessment course ought to be submitted. The biosimilar product will, with respect to the quality information, satisfy all technical content requirements for Module 3 of the ICH CTD or Part 2 of the ACTD, and fulfil the satisfy the technical requirements of the monographs of pharmacopeia and any extra prerequisites, as characterized by HSA and ICH rules. Complete data on the turn of events, manufacture and control of both the active drug substance and the medication product should be given [14].

It is firmly prescribed to create the necessary quality, safety and efficacy data using the biosimilar product manufactured with the commercial manufacturing process (representing the quality profile of the batches to be commercialized) in the comparability exercise for the exhibition of biosimilairty against the reference biological product. The CTD Filing contemplations in accommodation of similar biological product. In Singapore are examined in (Table 3).

Table 3: CTD Filing considerations in submission of similar biological product in Singapore

Documents	Location in		Module/Part required for
	ICHCTD	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.
Non clinical documents	Module 4	Part III	Complete Non- clinical module including comparability studies.
Clinical documents	Module 5	Part IV	Complete Clinical module including comparability studies.

The documents needed for enrolment of biosimilars are sorted into Administrative, Quality, Non-clinical, and Clinical documents, in which the Administrative and Quality report prerequisites are momentarily referenced in (Fig. 7).

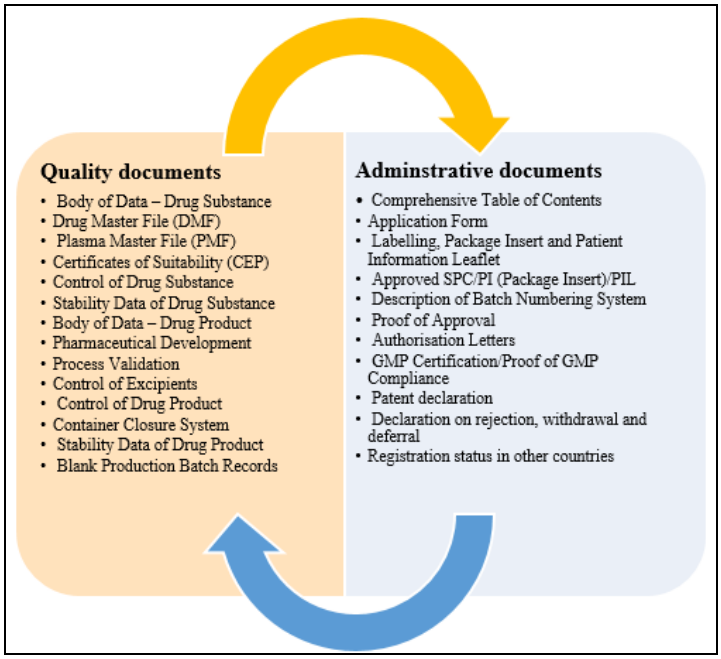


Fig 7: Singapore documentary requirements administrative

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

The clinical documentation necessities are received from the CHMP Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues (CHMP/42832/05).

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

At the time of market endorsement for a medicinal product, data on the security of the product is moderately restricted, and there are some potential risks which might not have been recognized. For biosimilar products, there is likewise the worry on potential immunogenicity issues. Therefore, post-market observing of clinical security for biosimilar product is necessary as with all medicinal products, with focus around the particular worries for biosimilar products. The candidate is required to submit a risk management plan at the time of application for product licensure. The point of the arrangement is to relieve potential risks related with the biosimilar product. The applicant should give extra educational materials to the doctors and patients to furnish them with data on the particular or potential risks of the biosimilar product.

Post Approval Requirements

There are two kinds of variety applications: Major Variation Application (MAV) and Minor Variation Application (MIV). For similar biological products MAV-1 is Applicable.

MAV-1

Any variety to the approved indications, dosing regimens, patient groups and additionally consideration of clinical data expanding the utilization of the product [15].

The Dossier Submission Requirements for MAV-1 are given in (Table 4).

Table 4: Dossier Submission Requirements for MAV-1

Documents	Location in		Module/Part required for
	ICHCTD	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
Non clinical documents	Module 4	Part III	No
Clinical documents	Module 5	Part IV	Study reports of pivotal studies and synopses of all studies (Phase I-IV) relevant to requested indication, dosing and/ or patient group

Biosimilar products would be exposed to a risk-based post approval batch release program. The product permit holder would be needed to submit batch quality reports before import and sale of each batch of biosimilar product for evaluation. The batch release reports incorporate the manufacturer's batch discharge information and certificate of analysis. The licence holder is additionally needed to update HSA on the stability data of the batch of product selected every year to be essential for the stability study program for the drug product. HSA may choose to request extra documents or to do autonomous batch testing of chosen groups, whenever considered significant.

Format: International Common Harmonization Common Technical Document (ICH CTD) or ASEAN Common Technical Document (ACTD) format.

AS the biosimilars in regulated and emerging market sectors have distinctive administrative in approving of a drug product, this article clarifies the contemporary prerequisites of biosimilars in both Australia and Singapore. The significant prerequisite guidelines of the two nations are gathered and referenced in the (Table 5).

Table 5: Comparative Studies of biosimilars between Australia & Singapore

Regulatory Authority	TGA (Therapeutic Goods Administration)	HSA (Health Science Authority)
Submission Format	CTD or eCTD	ACTD
GMP	Directive 2003/94/EC	In steps wise like, pre audit, documentary requirements, site audit & post audit
Data Protection	10 Years	Sections 19A & 19B of Medicines Acts

		under Article 39 of the WTO TRIPS Agreement
Patent Linkage	NO Specific act was mentioned	Medicines Act sections 16 (1B) & 5B
Clinical Issues	Need to be register in Eudra CT System	Electronic application process for CTC through PRISM application
Safety concerns	Article 111 (1) (d) Directive 2001/83/EC.	ADRs should be submitted in CIOMS forms.
Required Timeline for Submission	1. Pre-Submission meeting request- 6-7 months before submission. 2. Submit Pre-submission meeting request form- 6 weeks before the proposed Meeting date. 3. Submit proposed invented name- Latest 4-6 months prior to the planned submission date of the MAA. 4. Inspections Fees will be payable from the date of inspection-45 days. 5. Request for Renewal- Six months before expiry. 6. Opinion on the renewal of the marketing authorization- After 90 (or Maximum 120) days.	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 license holder is required to submit the global PSURs to HSA- 6 months for the first 2 years; Yearly for the following 3 years.
Type of Fees applicable for Biosimilar	**Fee payable at each submission**	Percentage of Evaluation Fee Payable at Each Stage of Submission in Singapore
General fee	It shall be increased by ECU 10000 for each additional strength and or pharmaceutical form of the same medicinal product submitted at the same time as the initial application for authorization- 70000	Application Type- NDA –2
Extension fee	This is the fee for each additional application for a Community authorization to market a product made for strength/ pharmaceutical form after an initial application for authorization has been submitted to the Agency- 40000.	Evaluation Type- Abridged Accepted for Evaluation- 30% fees should be paid.
Inspection fee	This is the flat-rate fee for any inspection within or outside the community- 10000	Active Evaluation- 40% fees should be paid.
Transfer fee	This is the fee for a change in the holder of each marketing authorization to which the transfer relates- 5000.	Midway in Evaluation- 20% fees should be paid.
Renewal fee	This is the fee for review of the new Information- 10000	Evaluation Completed- 10% fees should be paid.

Conclusion

The regulatory prerequisites of biosimilars in both Regulated (Australia) and emerging market sectors (Singapore) were studied momentarily, registration and submission measure were clarified in detail. Gathered all the data that is needed to satisfy in submission process of a product in which, Type of Registration, Format needed for submission, Process Flow, Time lines required and Documents required are the Key regulatory contemplations that was recognized.

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Conflicts of Interest

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

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