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Review Article

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A Comparative Study of Biologic Regulation in US, Canada, Australia, Europe and Singapore

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Abstract

Extensive research in chemistry, manufacturing, controls, preclinical science, and clinical trials is required when developing a novel biological medication. Drug reviewers in regulatory bodies throughout the world and all regulatory bodies are entrusted with determining whether research evidence establishes new drug product safety, effectiveness, and quality control in order to protect public health. Among the world every province has its own regulatory organization in charge of enforcing laws and regulations and developing guidelines for drug marketing. There are some particular requirements sets by regulatory authority that must be satisfied when submitting in the particular nation. The world is split into various approval procedures, it is pivotal for manufacturers to carefully assess market interest, expenditures, target zones, and regulatory standards before establishing biologics. Despite the existence and widespread adoption of an ICH-CTD standard format, some limitations are included. This article discusses the comparison considerations used for biological product approval in the United States, Canada, Europe, Australia, and Singapore.

Keywords: Regulatory Authority, Regulation, Biologic Regulation, Biosimilars, DNA sequence, Biologics License Application, (BLA), Subsequent Entry Biologics (SEB), EMA, TGA, CBER

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1. Introduction

1.1 Introduction to Biologics

A biologic (al) medical product, or biologics, is a biopharmaceutical. A biologic is a product made from micro-organism or containing live organism subpart. (1) It includes various products derived from humans, animals, and microorganisms through biotechnology. These could be complicated mixtures of carbohydrates, nucleic acids, proteins or live organisms. (2)

Biologic medications include:

- Vaccines,
- Blood and blood products,
- Cells and tissues
- Allergies, genes, and recombinant proteins.

Biologics treat various diseases, illnesses and build immunogenicity towards viral and bacterial infection. They have also changed the cancer treatment approach and delayed or reversed the progression of immune-related diseases. As a result, biologic medications are sold as infusion powders or injection solutions. (2, 3)

1.2 Biosimilars

A biosimilar drug, often known as a bio similar, is a pharmaceutical that is structurally and functionally comparable to a biologic drug. It's a nearly identical clone of an original product made by a different company that can be manufactured once the patent on the original product expires.(2)

1.3 General manufacturing process of Biological Product

Identifying the DNA sequence that encodes the protein and its cloning into a suitable DNA vector are the first steps in the production of recombinant protein products. The DNA expression vector is subsequently transfected into a specific cell system, which produces the desired quality and quantity of product. To produce an adequate quantity of recombinant cells for commercial reasons, they are cultured in enormous bioreactor containers (like a giant beer factory). A multi-

step-down streaming procedure is then used to purify the target protein of interest.

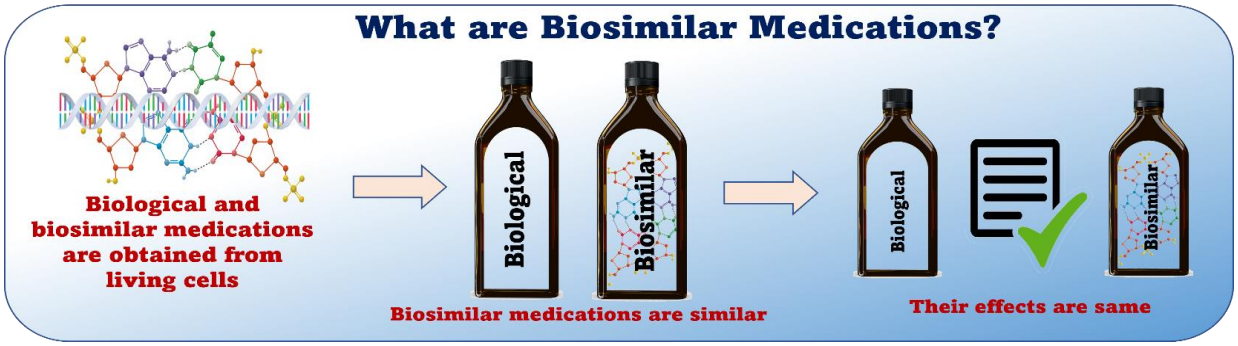

Figure 1. Introduction of Biosimilar Medicines

This protein is then formed into a delivery device that can be transported, stored, and administered to patients. To ensure adequate uniformity of the product, the entire production process must be done under highly controlled, and validated circumstances, as per good manufacturing practise criteria. Changes in cell culture settings, such as fermentation medium or cell culture habitats, can result in variability in amino acid sequences, abnormal glycosylation patterns, and the production of unwanted by-products and cellular wastes. Protein damage can occur due to processes such as denaturation, conformational changes, and aggregation formation that occur during the extraction and purification of proteins. Manufacturing processes, raw material, extraction, and purification procedures influence biological characteristics. (4)

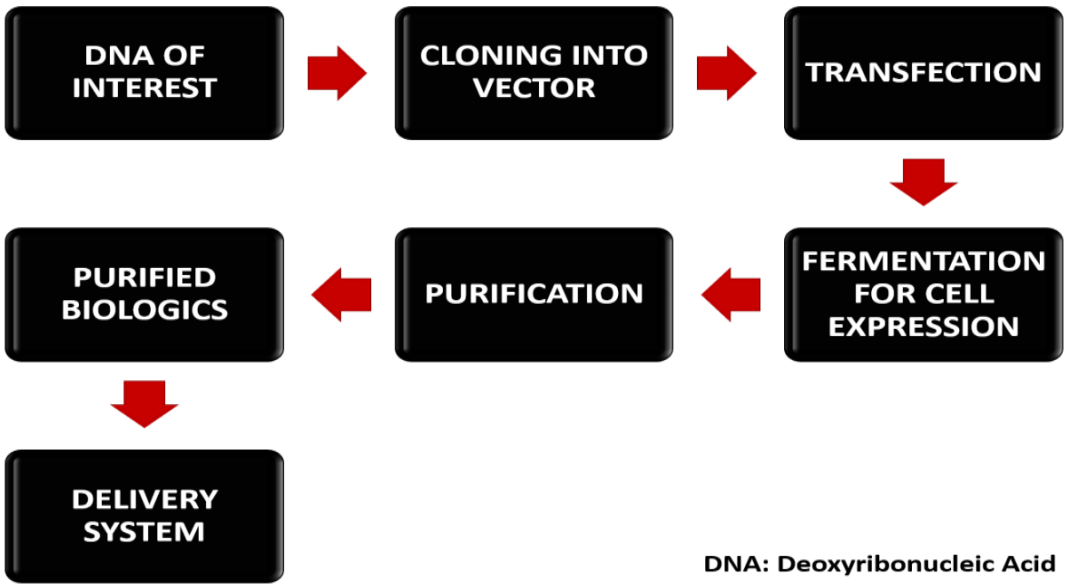

Figure 2. Manufacturing of biological products

2. Regulation of biologicals in different countries

2.1 Regulatory overview for Biologicals in USA

In the United States of America, "biological products" are vulnerable to premarket restrictions and protection of intellectual property from "pharmaceutical products." According to the Biologics License Application, biological goods must have a licence to prove "safe, pure, and legitimate" (BLA). CBER is a department of the F & D Administration in charge of regulating biological products for human consumption under constitutional provisions such as the Public Health Service Act and the Federal FD&C Act. The BLA requests permission to introduce or deliver a biologic product into interstate commerce (21 CFR 601.2). The Biologics License Application (BLA) is governed by the regulations found in 21 CFR 600–680. After an experimental novel medication has been approved, a BLA is submitted. The new biological products will receive 12 years of data protection. (5, 6)

The completion of Form 356h is required to submit a BLA application. It outlines the general specifications for a BLA.

2.2 Regulatory overview for Biologics in Canada

In Canada Following entry biologics, also known as Subsequent Entry Biologics (SEB), may be developed by companies. As biologic drug patents expire, the federal regulatory agency that evaluates the quality, safety, efficacy of drugs available in Canada, acknowledges that manufacturers may be interested in developing SEB drugs. In 2010, Health Canada approved "Guidance for Sponsors: Subsequent Entry Biologics (SEBs)

Information and Submission Requirements." Although the concept of a SEB applies to all biologic medicinal products, additional criteria must be met for the product to be approved as a SEB. The Canadian guidance shares comparable concepts and principles with the WHO's standards. (7, 8)

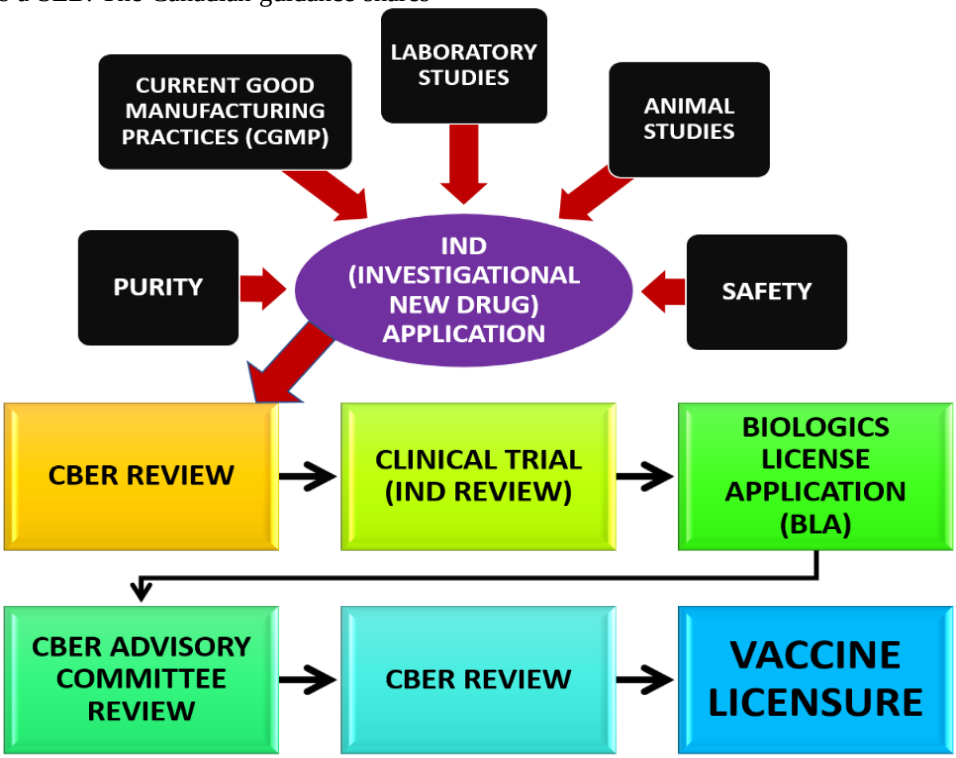

Figure 3. Marketing authorization process of biological product

2.3 Regulatory overview for Biologics in Europe

Biologic products in Europe are registered through the Centralized Procedure, resulting in an EU licence valid in all EU member states. Data is examined by EMA's scientific committees (the CHMP and PRAC), as well as EU professionals on biological drugs and biosimilar specialists, once a business files for marketing authorization at the EMA (Biosimilar Working Party). Following the EMA's examination, the European Commission issues a scientific opinion, which gives an EU-wide marketing authorization. (9)

When the Agency receives the application, it will begin the validation process for the open submission listed on its website. Validation must be completed by the procedure's start date. Suppose the Rapporteur and (Co) Rapporteur have received the dossier after confirmation. In that case, the EMA begins the process at the quarterly beginning date indicated on the EMA website. Applicants must be prepared to respond to any issues raised at this stage within a few days. (9)

The Agency must assure that the CHMP's perspective is provided within 210 days (not including clock stops during the procedure). (9)

2.4 Regulatory overview for Biologics in Australia

The Therapeutic Goods Administration (TGA) has issued the Australian Regulatory Guidelines for Biologics (ARGB), which contains important information for biologics manufacturers, funders, healthcare providers, and the broader population.

All biologics are classified based on risks as in four classes such as Class 1 and Class 2(low risk), Class 3(medium risk), Class 4(High risk). The TGA uses the Therapeutic Goods Act and the Therapeutic Goods Regulations to govern therapeutic goods, including biologicals. Biologicals are covered by Part 3-2A—Biologicals in Chapter 3 of the TG Act.

The TGA regulates biologicals in Australia using a risk-management approach based on the same risk-management principles as pharmaceuticals and medical devices. A risk-management strategy must be implemented to assure product quality and safety while minimizing risk. At all phases of the biological's life, it should assist manufacturers in identifying and analysing hazards and evaluating and controlling them. Furthermore, the wide variety of beginning materials and techniques utilized in the production of biologicals results in varying levels of risk. As a result, in order for a Class 2, Class 3, or Class 4 biological to be approved for inclusion. (10)

2.5 Regulatory overview for Biologics in Singapore

Singapore's Health Science Authority regulates biologics (HSA). The EMA (biosimilars, biologicals: drug substance) and their recommendations on biosimilar goods are mostly followed for biological product guidance. Biological products in Singapore are controlled as therapeutic items and as Singapore Reference Biological Products (SRBP). In Singapore, there are two types of applications for new product registration for therapeutic products: new drug

applications (NDA) and generic drug applications (GDA Biologics (also known as biosimilars) on the other hand, are not eligible for a GDA and must be submitted through an NDA. (11, 12)

The registration process consists of a series of steps described in Figure 5.(12) A new drug application can be submitted in three ways:

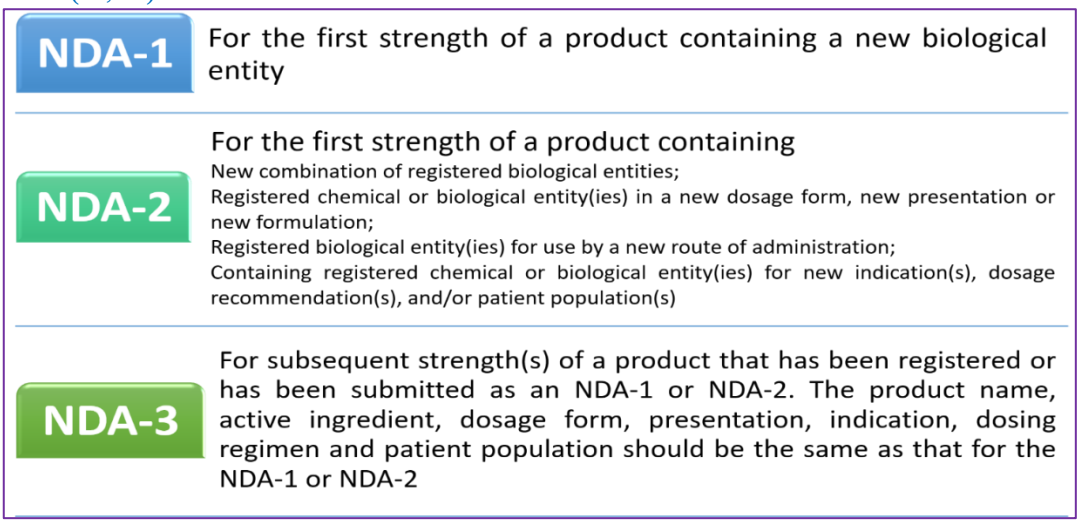

Figure 4. Different pathways for submission

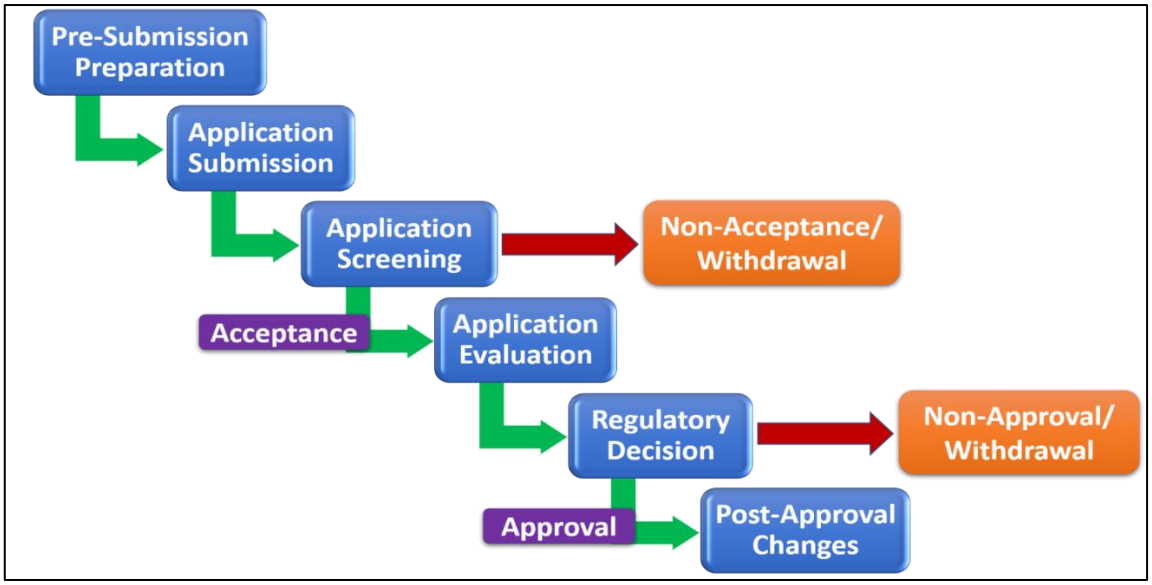

Figure 5. Registration process of therapeutic products (12)

3. Comparison parameters

Following table 1 shows the comparison with respect to different parameters between US, Canada, Europe, Australia & Singapore.

Table 1. Principal differences between US, Canada, Europe, Australia & Singapore (12)

PARAMETERS	US	CANADA	EUROPE	AUSTRALIA	SINGAPORE
Regulatory authority	United State Food & Drug Administration (USFDA) (CBER)	Health Canada	European Medicines Agency (EMA)	Therapeutic Goods Administration (TGA)	Health Science Authority (HAS) (Singapore)
Regulatory authority Flag					

Regulated under name	Vaccines, Blood & Biologics	Drugs and Health products (Biologics)	Human regulatory (Biosimilars)	Biologicals	Therapeutic products (Biosimilars)
Registration process	One registration process	One registration Process	Multiple registration process 1.National Authorization Procedure 2.Decentralized Procedure 3.Mutual Recognition Procedure 4.Centralized Procedure	One registration Process	One registration Process
Dossier Format/ Presentation	ICH CTD	ICH CTD	ICH CTD	ICH CTD	ACTD/ICH CTD
Presentation	eCTD & Paper	eCTD & Paper	eCTD	eCTD & Paper	CD/DVD & Paper
Dossier Language	English	English/French	English (centralized, decentralized and mutual recognition procedure) Regional language (national authorization procedure)	English	English
Manufacturing license	Required	Required	Required	Required	Required
Classification	NA	NA	NA	Risk based classification **Class 1:** low risk and appropriate level of external governance and clinical oversight. **Class 2:** low risk. **Class 3:** medium risk. **Class 4:** high risk.	NA
Application Type	NDA & BLA	NA	MAA	NA	NDA
Approval Timeline (months)	~18	~12	~10	~10-12	~8-9 months
Fees	$5,672	$490,666	$112,200	Class I: $700 Class 2,3 and 4: $6,960	Screening fee- $565 Evaluation fee- $11,200
Clinical Trials	Required	Required	Required	Required	Required for novel product

Following table 2 and 3 represents the comparison of the stability parameters between USA, Canada, Europe, Australia & Singapore, and Market attractiveness scoring and solution respectively.

Table 2. Comparison of Stability Parameters (13-15)

Parameters	USA	CANADA	EUROPE	AUSTALIA	SINGAPORE
Stability Zone	II	I	I	II	IV b
Stability Zone Name	Subtropical Zone	Temperate Zone	Temperate Zone	Subtropical Zone	Higher Humid zone
No. of submission Batches	3	3	3	3	3
Long term stability	25°C ±2°C & 60% RH ± 5% RH	21°C ±2°C & 45% RH ± 5% RH	21°C ±2°C & 45% RH ± 5% RH	25°C ±2°C & 60% RH ± 5% RH	30°C ±2°C & 65% RH ± 5% RH

Table 3. Market attractiveness scoring and solution

Parameters	USA	CANADA	EURPE	AUSTRALIA	SINGAPORE
Cost of R&D/ Production	Unfavourable	Unfavourable	Unfavourable	Unfavourable	favourable
Manufacturing and Clinical Trial Capabilities	Favourable	Favourable	Favourable	Favourable	neutral
Government Support of Industry	neutral	neutral	neutral	neutral	Favourable
Regulatory Rigidity	Unfavourable	Unfavourable	Unfavourable	Unfavourable	neutral

4. Conclusion

A comparison of the marketing authorization requirements for regulated and emerging countries has been described that all countries follow ICH regulation. The prime objective of the rules governing medicative products in the United States, Europe, Canada, Australia, and Singapore is to protect public health. It is the obligation of government regulatory agencies to ensure that pharmaceutical companies follow regulations. There are laws that ensure drugs to be manufactured, evaluated, and scampered in accordance with guidelines to ensure their safety and the well-being of patients.

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Conflict of Interest

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

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