CHALLENGES AND OPPORTUNITIES IN REGULATORY AFFAIRS: BIOTHERAPEUTICS, BIOLOGICS, BIOSIMILARS AND BIOBETTERS.

Miss. Mansi M. Durgude[1], Miss. Chandrabhaga D. Gaikwad[2], Miss. Siddhi S. Borhade[3], Miss. Gayatri Korde[4], Miss. Aparna A. Kale[5], Mr Nilesh M. Gorad[6], Miss. Ashwini B. Gaikwad[7.]

Students, Samarth College of Pharmacy, Belhe, Maharashtra, India[1, 2, 3, 4, 5, 6]

Proff, Samarth College of Pharmacy, Belhe, Maharashtra, India[7]

ABSTRACT

A shortened Food and Drug Administration approval process for biosimilar medicines that are more affordable and very comparable to the reference biological product but not identical. Fewer biosimilars are anticipated to enter the biologics industry than generic pharmaceuticals did when they first entered the small-molecule medication market since bringing biosimilars to market currently demands large financial commitments. Furthermore, subject to changing state substitution laws, most biosimilars will likely compete as therapeutic alternatives rather than as therapeutic equivalents due to the high regulatory hurdles to obtaining interchangeability, which would allow pharmacists to substitute a biosimilar for its reference product. In other words, in order to compete with their reference product, biosimilars must offer superior quality, lower prices, and a producer with a solid reputation among medical professionals, insurers, and patient groups. The development of novel biologics in the same therapeutic class, such as "biobetters," which provide minor upgrades over reference medicines like a longer duration of action, will also pose a significant threat to the viability of biosimilars. For the foreseeable future, it seems like there won't be many large cost savings from using biosimilars, but supply and demand-side variables should eventually lead to a rise in their utilisation.

Keywords: *Biologics, skills, challenges, regulatory affairs, Bosimilars, legal, development, agencies, therapeutics.*

1. INTRODUCTION:

The regulatory requirements for therapeutic product marketing authorization are the focus of regulatory affairs. The development, regulation, and value proposition of novel therapeutic goods are all being affected by a variety of influences in this industry. The COVID-19 pandemic has hastened already-in-progress changes due to scientific advancements, technological disruption, a renewed emphasis on the centrality of the patient in all phases of therapeutic product development, and increased cooperation between national regulatory bodies. The increasing integration of real-world evidence will enable medicines to enter the market at an earlier stage of development due to faster clinical trials, and will lead regulators to place a greater emphasis on post-marketing regulation. The rise in patient input into all aspects of drug development, including regulatory review, has also had an impact on medicinal product regulation. As a result, some biologics, biosimilars, and biobetters products will be investigated under regulatory science, which is a crucial component of medicine and is also used to treat conditions including cancer,

diabetes, rheumatoid arthritis, and cancer. By introducing insulin by Bating and Macleod in Canada early in 1923, biological were brought to treatments. The permission of numerous regulatory bodies, including the Central Drug Control Organisation (CDSCO) and Review Committee on Genetic Engineering permission Committee (GEAC), is necessary for the marketing authorisation of a biological product in India.

2. BIOTHERAPEUTICS:

According to the US National Library of Medicine National Institutes of Health, bio therapeutics are "antibody-drug cell therapy products where the active substance is extracted or produced from biological source."

The first biotherapeutic drug created by Genentech Inc. and produced by Eli Lily and Company and authorised for sale in 1982 was recombinant human insulin, also known by the trade name "Humulin" (Walsh, 2004). The biopharma sector has swiftly matured in the 39 years after its initial authorisation. Today, more than 300 of these products are in widespread use, and hundreds more are in the development stage (Reichert, 2006).

The ongoing need for biotherapeutics and its widespread adoption as a therapeutic choice can be attributed to the unmet medical need for which biotherapeutics offers the possibility of extended therapeutic approaches to speciality diseases. These patients' treatment options were limited prior to the discovery of these biotherapeutics. The newest medications, known as bio therapies, provide patients with a great deal of comfort and promise the recovery from many illnesses. Hundreds of biotherapeutics have been created and given FDA (Food and Drug Administration) approval for use in humans since the inception of biotechnology. These innovative drugs provide patients a range of important advantages while also serving as precise instruments for studying the biology of human diseases. As a result, several high-quality clinical studies' accomplishments and failures have provided a wealth of knowledge. Proteins, hormones, cytokines, antibodies, gene cell therapy products, vaccinations, stem cell therapies, and more are examples of biotherapeutic products.

In terms of the materials used, the complexity of the structure, the manufacturing method, and the regulatory requirements, biologics differ from conventional pharmaceuticals. Biologics might occasionally cost more as a result, which for certain patients can be a barrier to access. The main disadvantage of conventional chemical synthesis-based medications is that they frequently cause cellular/organ damage to the liver, kidneys, neurological system, and gastrointestinal tract through a variety of adverse pharmacological reactions. Given that the study actually monitors the blood concentrations, there may be PK/PD evidence for tiny compounds. As the drug is administered in small doses and its action is challenging to correlate with blood concentration, it is not possible in the case of biological drugs. Despite having a specific site of action, they need to be administered throughout the body. Such a reaction is absent from biotherapeutics, which also provides the benefit of delivery with a significant interval between doses. These medications are meant to boost the immune system rather than damage unhealthy areas.

Figure 1: Product Development Overview of Biological/Biotherapeutics.

Table 1: Differences between Bio therapeutics & Biosimilars.

Characteristics	Chemical Drugs (small molecule)	Bio therapeutics (large molecule)
Production	Chemically Synthesized	Living Organism
Composition	Defined	Complex/ Heterogeneous
Molecular Weight	Low	High
Characterization	Low complexity	High complexity
Immunogenicity	Low	High
Stability	High	Low
Manufacturing Risks	Low	High
Cost (to patients)	Low to medium	High to very high
Administration	Parenteral	Oral

2.1. Importance of Bio therapeutics:

Bio therapeutics research is among the fastest-growing segments in the pharmaceutical industry and accounts for nearly one of new drug approvals. Bio therapeutics has become an integral part of modern medicine and is increasingly used to treat and prevent serious diseases, illnesses or infections. They have been highly effective in the treatment of a range of conditions- from cancer to diabetes to rheumatoid arthritis and more.

2.2. Applications of Bio therapeutics:

According to the International Federation of Pharmaceutical Manufacturers & Association, bio therapy medications play a part in the research and development of biomarkers, which in turn serve to forecast the risk of cancer, aid in diagnosis, and inform treatment regimens.

2.3. Drawbacks of Bio therapeutics:

Hypersensitivity responses and immunological activation are two of the biotherapeutics' main downsides. Drugs like these are widely sought-after for the treatment of cancer and other fatal illnesses.

3. BIOLOGICS VS BIOSIMILARS:

3.1. Biologics:

Biologic medications are ones that were produced by living cells or creatures. Gene therapies, transplant tissue, recombinant tissue, recombinant proteins, stem cell therapies, and monoclonal antibodies are a few examples of biologic medications. They are frequently used to treat a variety of serious and sometimes fatal disorders. In terms of material sources, structural complexity, production techniques, and regulatory requirements, biologics differ from conventional pharmaceuticals. Biologics may occasionally be more expensive as a result, which may make them difficult for some patients to obtain.

Biological products have transformed the diagnosis, prevention cure and management of a wide range of serious and chronic diseases. What makes them different from the more traditional, small-molecule drugs (like acetaminophen or acetylsalicylic acid [aspirin]) is that biologic agents are found naturally in your body and may include things like sugars, proteins, nucleic acids, or specific cells or tissues. Biologic medicines are created when different doses or formulations of these naturally occurring agents are used to treat diseases like cancer.

Biologics are developed using a number of different processes, the key is that they all use biological or natural sources produced by or extracted from living organisms including humans, animals (like our transgenic goat), yeast and special microorganisms.

Some examples of biopharmaceutical products and medicines that are made from biological agents include:

• Insulin for diabetes.

• Vaccines to prevent many diseases, like shingles or the flu.

• Hormones for hormone replacement and deficiencies, such as growth hormone disorders.

• Monoclonal antibodies for the treatment of cancers and autoimmune diseases.

• Blood products and transfusions, such as in the treatment of haemophilia.

• Immunomodulators that help to regulate or normalize the immune system, such as beta interferon for multiple sclerosis.

• Enzymes used to remove blood clots.

• Botox has both dermatologic and neurologic uses.

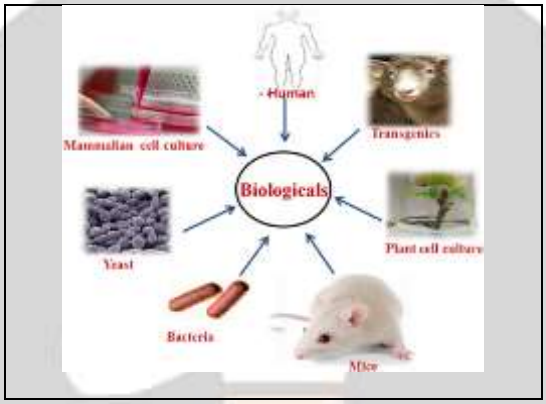

Figure 2: Sources of Biologic Products.

3.2. Biosimilars:

3.2.1. Official Definitions of Biosimilars:

1. The European Medicine Agency: A biosimilar is a biological medicine that is developed to be similar to an existing biological medicine (the 'reference medicine'). When approved, a biosimilar's variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness

2. The United States Food and Drug Administration: A biosimilar is a biological product that is highly similar to a US licensed reference biological product not withstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency of the product.

3. The World Health Organization: A biosimilar is a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

Biosimilars are biotherapeutics that are a second (or subsequent) generation of follow-on- biologics that are similar in terms of quality, efficacy and safety to already licensed reference biologic products.

3.2.2. Need:

- Biosimilars industry can act as a spring board for the pharmaceuticals to innovate, excel and earn profit and the same needs to be promoted at the earliest.

- We need to increase access through affordable pricing and some of the drugs need to be under price control.
- Governments can support growth in production of complex generics and biosimilars by clarifying the regulatory framework for them, which is still evolving in many countries.

Biosimilars are likened just like generic drugs which are second (or subsequent) generation products imitating the originator small-molecule chemical drugs. Although biosimilars and generics are comparable in many aspects (they are both follow-on products to a successful reference product or innovator) a key distinction lies in the definition. Generics drugs are required to have the same active pharmaceutical ingredients (API) as their reference originator product and must possess the same chemical structure as the reference (Alfonso-Cristancho et al., 2015). In contrast, biosimilars are similar but not necessarily chemically identical products (Samrat Sisodia, 2014).

The patent expiry of first-generation biotherapeutics has opened the possibility to the manufactures, for developing generic versions known as 'similar biologics' or 'biosimilars' or 'follow on biologics'. Biosimilar like generic drugs are manufactured after the patent expiry of the original 'innovator' product (van de Vooren et al., 2015). Market authorization of these biosimilars is granted based on the physicochemical and functional demonstration of compatibility to the licensed reference product. However, differences in structural and manufacturing complexities from reference product affect the safety and efficacy profiles, including immunogenicity of the biosimilar. Any alteration in the immunogenicity of the biosimilar with its innovator may influence the benefit-risk profile. Therefore, adequate identification of adverse event profile and unexpected adverse reactions associated with biosimilar is a key interest to regulators and biosimilar manufacturers. Worldwide regulatory authorities for approval of biosimilars require dossier consisting of analytical, pre-clinical and clinical studies to evaluate the efficacy and safety profiles of biosimilars (Bui & Taylor, 2014; Mellstedt et al., 2008). Additionally, not all adverse events are identified during clinical trials, and many of them could cause serious reactions after entry to market (Ahmed et al., 2010).

Figure 3: Top Companies for the Selling of Biosimilars.

4. CONCEPT OF PURPLE BOOK:

4.1. A Reference Biological Agent:

This entity denotes a product defined under section 351(i)(4) of the PHSA as the single biological product licensed by the U.S.FDA under section 351(a) of the PHSA against which the biosimilar biological agent was evaluated in its application submitted under section 351(k) of the PHSA.

4.2. A Biosimilars Agent:

It is a product described under section 351(i)(2) of the PHSA as highly similar to the reference agent. A biosimilar agent that is licensed by the U.S. FDA under section 351(a) of the PHSA has been demonstrated to have no clinical differences between the biosimilar and the reference biological agent with retards to potency, purity or safety.

4.3. An Interchangeable Biological Agent:

It indicates a product defined under section 351(k)(4) of the PHSA (Copyright© 2023 Provincial Health Services Authority) as a product licensed by the U.S. FDA under section 351(k) of the PHSA that is a biosimilar and predictably produces the same clinical outcome as the reference biological agent in a given patient. Additionally, classification of interchangeability indicates that administering the product more than once to the same patient showed a similar efficacy and safety profile that remained unchanged or diminished even when the administration was alternated between the biological agent and the reference product.

The Purple Book provides the information on the approved biologics listed with their BLA numbers and the availability of any interchangeable or bio-similar products. If the biologic product is withdrawn, it is reflected in the Purple Book as well. The exclusivity of the biologics will include the 12-year exclusivity plus paediatric exclusivity if any. The Purple Book will not include information on orphan drug exclusivity, nor will it contain any patent information. Although the U.S. FDA has created the Purple Book for assistance with biosimilar product substitution, many states are passing state-specific laws. These laws outline multiple aspects of the substitution process, including communication with providers and record keeping requirements.

5. REGULATORY AFFAIRS:

Regulatory Affairs in the pharma industry may be defined as "The interface between the pharmaceutical company and the regulatory agencies across the world."

Regulatory Affairs is an attractive career choice for graduate students from a scientific background who enjoy communication and team work, are comfortable with multi-tasking and are eager to expand their knowledge in the wide realms of the Pharmaceutical world.

Regulatory Affairs is a rewarding, intellectually stimulating and highly regarded profession within pharmaceutical companies. It is a unique mix of science and management to achieve a commercially important goal within a drug development organization. Touches everything relating to drugs from the earliest nonclinical studies, through development into routine manufacture and marketing, can add significant impact for patients and drug companies.

Regulatory Affairs profession at its heart is all about Collecting, Analyzing and Communicating the Risks and Benefits of health care products to regulatory agencies and public all over the world. This department is responsible for understanding the regulatory requirements for getting New / Generic products approved.

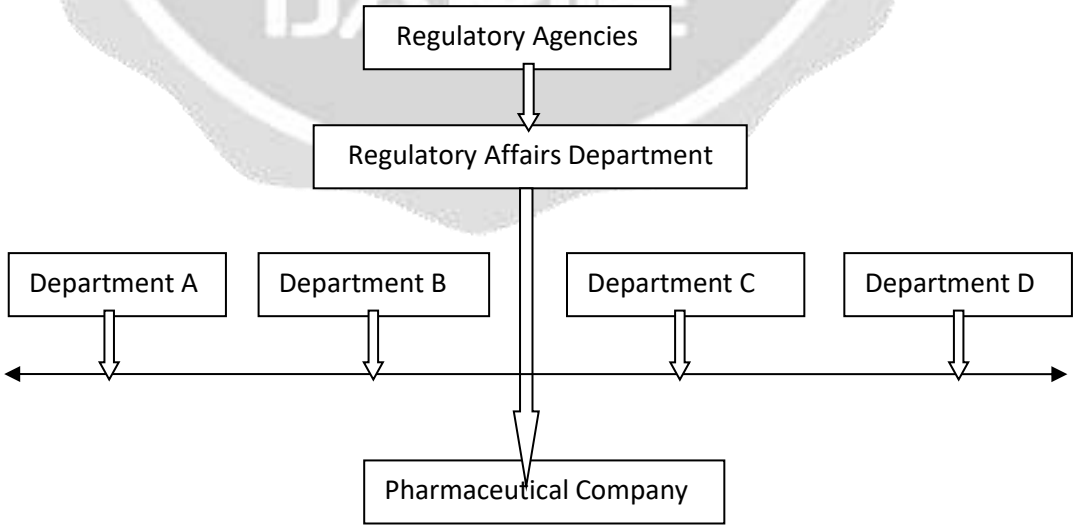

Figure 4: Overview of Regulatory Affairs Department

5.1. Historical Overview Of Regulatory Affairs:

During 1950's, multiple tragedies i.e. sulfanilamide elixir, vaccine tragedy and thalidomide tragedy have resulted in substantial increase of legislations for drug products quality, safety and efficacy. This has also resulted into stricter norms for Marketing Authorization (MA) and Good Manufacturing Practices (GMPs).

5.2. Scope of Regulatory Affairs:

Pharmaceutical Drug Regulatory Affairs.

Regulatory Affairs in Product Management.

Regulatory Affairs in Clinical Trials.

Regulatory Affairs in R&D etc.

5.3. Objectives of Regulatory Affairs:

 How and why the pharmaceutical industry and drug regulations have developed in USA

 Major Regulations of USA

 Framework of EU and its regulatory

 "The Rules Governing Medicinal Products in the European Union"

 Pharmaceutical Legislations of EU

 Indian Pharmaceutical Industry & Drug Regulations development in different Era

 Types of Marketing Authorization Procedure in EU Market

 Major Rules and Act of India

 Roles of Regulatory Affairs Professional in Health Authorities as well as Pharmaceutical Industry

5.4. Need of Regulatory Affairs In Pharmacy Curriculum:

India is growing very rapidly in pharmaceutical sector; there is a need of regulatory affairs professionals to cater the current needs of industries for the global competition. Regulatory affairs professionals are the link between pharmaceutical industries and worldwide regulatory agencies. They are required to be well versed in the laws, regulations, guidelines and guidance of the regulatory agencies. There is a growing need to incorporate the current requirements of pharmaceutical industries in the standard curriculum of pharmacy colleges to prepare the students with the latest developments to serve the industries.

5.5. Future Directions in Regulatory Affairs:

Some of the future trends in the regulatory affairs profession that we have identified include leveraging big data, artificial intelligence (AI) and machine learning (ML) in regulatory processes, which will facilitate real-time regulation, the utilization of real-world evidence and the increasing role of patient.

1. Megatrends.

2. Digital disruption.

3. Evolving therapeutic landscape.

4. The centrality of the patient.

5. Global regulatory harmonization and convergence.

6. Challenges arising from these identified trends.

7. Skills for the future regulatory affairs workplace.

5.6. Regulatory Systems and Processes:

1. Keeping records for Drug Product Submission and Approval Database.
2. Preparing Standard Operating Procedure (SOP) for efficient management of drug regulatory affairs department.
3. Be part of Regulatory forums/ conferences/ webinars/ seminars to exchange regulatory knowledge.

5.7. Regulatory Bodies in the world:

Regulatory bodies such as the Food and Drugs Administration (FDA) in the USA are responsible for approving whether a drug can proceed to clinical trials and whether it should be allowed to come in to the market or not.

These bodies has to evaluate the scientific and clinical data to ensure that the drug can be produced with consistently high purity, better therapeutic results and it does not have unaccepted side effects.It must also approve the labeling of the drug and the directions for its use or we can say regulatory body has taken interested in all aspects of a drug designing and its formulation.

Table 2: Different Regulatory Bodies in the World.

Sr. No.	Country	Name of Regulatory Authority
1.	USA	Food and Drug Administration (FDA)
2.	UK	Medicines and Healthcare Products Regulatory Agency (MHRA)
3.	Australia	Therapeutic Drug Administration (TGA)
4.	India	Central Drug Standard Control Organization (CDSCO)
5.	Canada	Health Canada
6.	Europe	European Medicines agency (EMEA)
7.	Denmark	Danish Medicines Agency
8.	Costa Rica	Ministry of Health
9.	New Zealand	Medsafe – Medicines and Medical Devices Safety Authority.
10.	Sweden	Medical Products Agency
11.	Netherlands	Ministry Of Health, Welfare and Sport Agency, CIBG Farmatec.
12.	Ireland	The Health Products Regulatory Authority
13.	Italy	Italian Medical Agency
14.	Nigeria	National Agency for Food and Drug Administration and Control (NAFDAC)
15.	Ukraine	Ministry of Health
16.	Singapore	Health Sciences Authority (HSA)
17.	Hong Kong	Medical Device Division
18.	Paraguay	Ministry of Health and Social Welfare
19.	Sweden	Medical Products Agency (MPA)
20.	Thailand	Ministry of Public Health
21.	China	National Medical Products Administration (NMPA)
22.	Germany	Federal Institute for Drugs and Medical Devices
23.	Malaysia	Medical Device Authority (MDA)
24.	South Africa	South African Health Products Authority (SAHPRA)
25.	Sri Lanka	National Medicines Regulatory Authority (NMRA)
26.	Switzerland	Swissmedic, Swiss agency for Therapeutic Products
27.	Uganda	National Drug Authority, NDA
28.	Brazil	Agencia Nacional de Vigiloncia Sanitaria (ANVISA)

29.	Japan	Ministry of Health, Labour & Welfare (MHLW)
30.	Columbia	National Food and Drug Surveillance Institute (INVIMA)
31.	Mexico	Comision Federal Para la Protection contra Riesgos Sanitarios (COFEPRIS).

Table 3: Some Examples of Regulatory Agencies

6. GLOBAL CLINICAL TRIAL OPPORTUNITIES:

1. Fast recruitment of subjects.

2. Reduced cost.

3. Research into regional diseases.

7. GLOBAL CLINICAL TRIAL CHALLENGES:

1. Inform consent.

2. Data quality.

3. Differences in the medical practice.

4. Acceptability of foreign data.

5. Ethnic factors.

8. DEVELOPMENT PATHWAY OF BIOLOGICS, BIOBETTERS, BIOSIMILARS:

The development of biologicals, biobetters and biosimilars can be divided into nonclinical studies and clinical studies. The term nonclinical and preclinical are often used interchangeable. The nonclinical studies can be performed at any time during life cycle of the product but it is better to do as early as possible in order to avoid surprises and adversities in the development of the molecules.

The preclinical studies include pharmcodynamics which explores what a medicine does to the body and pharmacokinetics studies about what body does to the medicines. Another objective of preclinical studies is to have information about toxicology of the drug in development before administration in humans.

Non clinical regulatory guidelines mandate to follow standard operating procedure (SOP) in addition to Good Clinical Practices (GCP) provisions. Data are to be presented in the form of Common Technical Documents as prescribed by International Conference on Hormonization (ICH) for registration of pharmaceuticals for human use.

In clinical development of Biosimilars and biobetters there is a big difference than a conventional synthetic drug there is a different in mechanism of action which is supposed to manupulate the immune responces rather than act directly like a synthetic small molecule. Hence, the design of the studies and instruments and advanced technology. Most of the characterization uses molecular biology technique and mass spectroscopy for characterization and qualification.

8.1. CTD (Common Technical Document):

8.1.1. General Principles:

The CTD aimed to provide a common format for the technical documentation that would significantly reduce the time and resources needed to compile applications for registration of pharmaceuticals and to ease the preparation of electronic submissions.

The first set of ICH CTD guidelines were published in 2002. Currently, there are 4 ICH guidelines on the CTD namely; M4, M4Q, M4S, and M4E, along with 4 question and answer documents. In July 2003, the CTD became the mandatory format for NDAs in the EU and Japan, and the strongly recommended format for NDAs submitted to the U.S. FDA. Since the implementation of the CTD format in the EU, USA, and Japan, the CTD has also been adopted by several countries including Canada and Switzerland. The submissions aspaper CTD is now replaced by its electronic counterpart (eCTD). Since 2010 eCTD is mandatory for the centralised procedure in the EU.

8.1.2. Organization of the CTD:

The CTD dossier is divided into five main modules as presented in Fig.5.

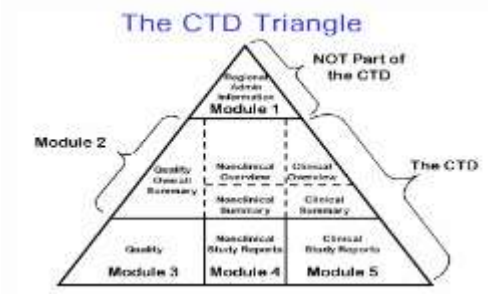

Figure 5: Common Technical Development (CTD) Module.

(1) Module 1: Administrative information and prescribing information.

(2) Module 2: Overviews and Summaries of Module 3-5.

- Module 2.1: Table of Contents.
- Module 2.2: Introduction.
- Module 2.3: Quality Overall Summary.
- Module 2.4: Non-clinical Overview and 2.6: Non-clinical Written and Tabulated Summaries.
- Module 2.5: Clinical Overview and Module 2.7: Clinical Summary.

(3) Module 3: Quality (Pharmaceutical Documentation).

(4) Module 4: Non-clinical Reports (Pharmacology/ Toxicology).

(5) Module 5: Clinical Study Reports (Clinical Trials).

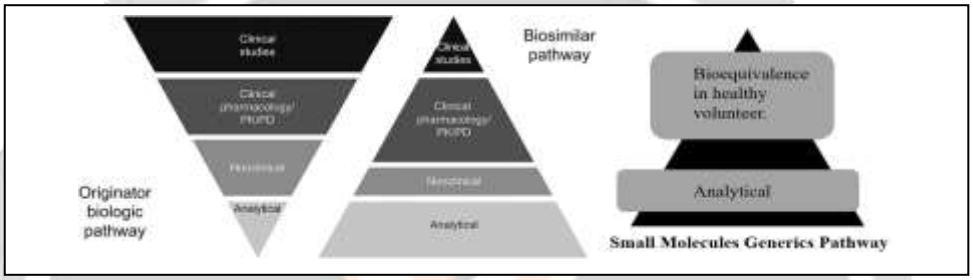

Figure 6: Development pathway of Originator Vs Generic Vs Biosimilar.

9. BIOLOGICS PRICE COMPETITION & INNOVATION ACT OF 2009 (BPCI ACT):

The BPCI Act created an abbreviated licensure pathway in section 351(k) of the Public Health Service Act (PHS Act) for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product (see sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Pub. L. 111–148) (ACA)). FDA believes that guidance for industry that provides answers to commonly asked questions regarding FDA's interpretation of the BPCI Act will enhance transparency and facilitate the development and approval of biosimilar and interchangeable products. In addition, these Q &As respond to questions the Agency has received from applicants regarding the submission of biologics license applications (BLAs) for biosimilar and interchangeable products. FDA may provide additional Q&As through draft guidance as appropriate.

10. FDA RECOMMENDATIONS FOR LABELLINIG OF INTERCHANGABLE BIOSIMILARS:

Interchangeable biosimilars are subject to certain guidelines stated in the industry's Labelling for Biosimilar Products (July 2018) (Biosimilar Labelling Guidance), as described below.

For instance, the Biosimilar Labelling Guidance suggests that biosimilar product labelling incorporate pertinent data and information from the reference product labelling with appropriate adjustments, such those outlined in the guidance. The FDA holds that interchangeable biosimilar labelling, like biosimilar product labelling, should include pertinent facts and information from the reference product labelling, including clinical data that supported the FDA's determination of the safety and efficacy of the reference product.

Additionally, according to the Biosimilar Labelling Guidance, the FDA believes that, generally speaking, the labelling of biosimilar products shouldn't contain information about or results from clinical studies that have been conducted to prove biosimilarity.

In addition, regardless of the format of the reference product labelling, interchangeable biosimilar labelling must

comply with the content and format requirements of the physician labelling rule (PLR) as described in 21 CFR 201.56(d) and 201.57, as required by 21 CFR 201.56(c)(1) and as stated in the Biosimilar Labelling Guidance with respect to biosimilar products. Regardless of whether the reference product must adhere to these standards, interchangeable biosimilar labelling must comply with the content and format requirements of the pregnancy and lactation labelling rule (PLLR) as outlined in 21 CFR 201.57(c)(9)(i) through (iii).

Certain differences between interchangeable biosimilar and reference product labelling may be appropriate. For example, as discussed in the Biosimilar Labelling Guidance with respect to biosimilar products, interchangeable biosimilar product labelling conforming to PLR and/or PLLR may differ from reference product labelling because the reference product labelling may not be required to conform to those requirements at the time of licensure of the interchangeable biosimilar. As an additional example, it may be appropriate for interchangeable biosimilar labelling to deviate from that of the reference product to the extent that an applicant chose to seek licensure of the interchangeable biosimilar for fewer than all of the reference product's licensed conditions of use. As stated in the guidance for industry Considerations in Demonstrating Interchangeability With a Reference Product (May 2019), although a sponsor may seek licensure for a proposed interchangeable product for fewer than all conditions of use for which the reference product is licensed, FDA recommends that a sponsor seek licensure for all of the reference product's licensed conditions of use when possible.

The FDA also thinks interchangeable biosimilars can benefit from the recommendations outlined in sections IV through VII of the Biosimilar Labelling Guidance. On the suggestions on particular biosimilar areas.

CONCLUSION:

The global regulatory environment has changed dramatically over the past several years with a great emphasis on strategic collaborations, harmonization, and convergence between national regulatory authorities and this trend is likely to continue. As these factors begin influencing the work of the regulatory professional, drug development and medical practice, it would be interesting to review their impact in a few years' time.

Despite many challenges, the development of biosimilars, biologics and biobetters continues in earnest. Biosimilarity must be established based on the totality of evidence, from structural and functional assessment through nonclinical and clinical studies, adopting a tailored approach throughout development. It is clear that we must think differently when developing biosimilars, especially when defining CQA's (Critical Quality Attributes) and setting endpoints for nonclinical and clinical studies. The arrival of Biosimilars challenges for healthcare community to learn and understand the scientific basis of similarity to the reference product using a stepwise approach. An increased awareness is needed to understand that clinical studies are a blunt instrument in the development of biosimilars, and that analytical evaluation is a far more sensitive tool in assessing similarity.

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