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Regulatory Guidelines For The Development Of Biologics In Us And Europe

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Abstract

In terms of the definition of a biologic and the technical specifications for approval, the United States and the European Union have different but overlapping regulatory frameworks for biologics. The term "biological product" has been used in the United States for a long time, and its understanding is still influenced by historical background. Biologics are primarily categorised in the European Union based on the components that make them up and the processes used to make them. Notwithstanding these differences, both jurisdictions agree that biologics require particular handling due to their unique qualities, such as their complicated structures and vulnerability to change during manufacturing. Biologics are subject to the general approval process in the EU as well as a few unique restrictions, in contrast to the US, where Congress passed a special statute for them. There is significant overlap in the standards imposed by both regions despite the fact that US and EU authorities have made steps to harmonise some technical requirements for biologics applications. An overview of the regulatory frameworks in the US and the EU is given in this chapter, covering everything from nonclinical trials to clinical trials and approval. The article then goes through approval and rejections in the us and Europe

Keywords:- FDA ,EU ,Biologics , Regulatory Frameworks ,Approvals, Rejections.

INTRODUCTION

Biologics

The term "biologics" refers to a class of medications that are produced using massive cell cultures of bacteria, yeast, plant, or animal cells before being purified. Monoclonal antibodies, growth factors, immune modulators, vaccinations, and items made from human blood and plasma all fall within the broad category of biological medicines. The main difference between biologicals and other medications is that biologicals are typically proteins that have been extracted from blood or living culture systems, whereas other medications are thought of as "small molecules" and are either produced synthetically or extracted from plants.

Due to the differences in their nature and how they are produced, biological therapeutics are regulated, tested, and controlled differently than other medicines. To help ensure their quality, safety, and efficacy, each batch of a biological therapeutic product must be tested extensively at each stage of production in order to ensure

consistency with prior batches. [World health organization, ,Biologicals. available at https://www.who.int/health-topics/biologicals#tab=tab_1

It is like the difference between a lightning bug and a bolt of lightning: "The difference between the almost right word and the right word is truly a significant deal." The three little letters are important, as Mark Twain once said, and this is also true of the distinctions between drugs that are developed chemically and physiologically. But, the three letters this time are DNA.

From fibrinogen coagulant factors to natural protein sutures, protein-based biologics and devices are utilised to treat everything from wrinkles to rattlesnake stings. Prophylactic drugs, in vivo diagnostic equipment, and therapeutic goods are all examples of biotechnological applications in healthcare. For the detection of a variety of health issues, from elevated LDL levels to drug-resistant HIV strains, biotechnology offers imaging agents and molecular diagnostic assays. For the detection of a variety of health issues, from elevated LDL levels to drug-resistant HIV strains, biotechnology offers imaging agents and molecular diagnostic assays.
This field's advancements are fast deconstructing Western medicine. Biotechnological medicine begins with the identification of a genetic variation and relies on therapies that manipulate it as opposed to beginning with a sickness and looking for its cause. By expanding on the idea, it has the potential to forecast health condition and take appropriate action — the fundamental idea of prevention around which managed care was based.
Yet, none of this is cheap, which raises serious questions about how to spend resources and choose patients wisely. Hence, in order to purchase and use biologic drugs efficiently, one must have an understanding of their mysterious activity and structure, the uniqueness of their action, and how they differ from conventional therapeutic agents.

WHAT THEY DO

A gene or a protein is always a biologic's therapeutic target. Humans can examine the function of genes in worms or zebra fish because genetic information is decoded uniformly across all cells, independent of species. Recombinant DNA is produced by separating a DNA segment from human cells, maybe altering it, inserting it into bacteria or a mammalian cell, and then inducing the bacteria or cell to express the DNA segment. Finding the genes that code for proteins, cloning the genes, generating the proteins linked to the genes, figuring out how the proteins affect the illness process, and finally developing a therapeutic treatment are all steps in the development process.
All newly discovered proteins go through a series of cell-based experiments that reveal how a particular protein alters a biological process. In order to assess potency, bioassays use biological markers from live things or tissues. They may comprise antisense or antibody technology, cell-based tissue cultures, microarray expression technology, knockout animal models, transgenic animal models, and transgenic animal models (e.g., diagnostic antibody characterization).
Biologic medications have a higher risk of immunological responses than chemical ones. Chemical medication molecules are typically not detected as "invaders" by the immune system because they are too tiny to be categorised as immunogenic. With biologics, the human immune system can swiftly recognise the molecule and then create an immune response to remove a big molecule that it perceives as a foreign substance, depending on the medicine. This may reduce the action of the biopharmaceutical or, in rare circumstances, increase it.
Virtually all biologics have the ability to trigger the creation of antibodies, however the majority of antibodies have favourable clinical outcomes. Small contaminant pieces, interaction with the patient's serum, or post-dose enzymatic cascades can all contribute to the development of antibodies.

DIFFICULT PRODUCTION

Because living cells that create biologics are sensitive and biological macromolecules are brittle, rigorous manufacturing requirements for fermentation, aseptic processing, storage, and testing are necessary. For biologics, the active ingredient frequently consists of a small fragment of a big macromolecule, whereas the active ingredient of a chemical pharmaceutical is typically a singular molecule subject to well-established analytical assays. The initial protein or polypeptide, as well as other potentially poorly defined biological molecules, are modified into that macromolecule. Variable complexes, or entities with varying numbers of identical components, can be seen in protein and polypeptide products.

Because biologics are often heterogeneous in the molecules and/or polypeptides present, they have an impurity profile that depends on — and can vary with — the techniques employed to create and test each batch. In the case of biologics, the protein mixture must be specified, and the active ingredient and any auxiliary substances must be identified. In other words, if the biologic operates through a molecular group, the result does not need to be homogeneous. For instance, blood is a biologic that isn't made up of just one kind of molecule, as defined by the U.S. Food and Drug Administration.
This is not to imply that there are inadequate quality-control procedures used in the production of biologics; just the opposite is true. 40 to 50 crucial tests may be included in a normal chemical medication manufacturing procedure. A biologic may go through 250 steps or more. Specialized procedures are used in biologic production, and these procedures are not always similar to the facilities, apparatus, or equipment used to make chemical medications. Building and validation of new facilities is disproportionately expensive and also time consuming. This explains both the cost difference between biologic and chemical medications as well as the global shortage of biomanufacturing capacity.

Chemical medications often present less barriers to changing a manufacturing process than biologics would. Without the thorough characterization and rigorous testing necessary for biologics, chemical drug batches are discharged in accordance with the specifications for the drug substance and the finished product.

DOSE AND ALLOCATION

Biologics can cost thousands of dollars per month and need specialised handling because they are frequently less stable than medications made from chemicals. They also need to be protected from jarring when they are in liquid form and from regulated temperature and light. For instance, many big proteins cannot be reconstituted by shaking because shaking can alter the structure of the protein. There may not be more than 1,000 people in the US for some extremely rare diseases, such Gaucher's disease. A small target population and the high cost of product development and marketing result in a high per-patient cost. Frequently, patients are treated at specialised clinics and/or given these medications.
Chemical drugs come in a wide range of dosage forms, and concentrations are typically simple to calculate. However, biologic molecules are typically administered via injection or infusion because they are too large to be swallowed orally without being broken down before entering the bloodstream. Moreover, monitoring is an important part of early therapy and potency is harder to evaluate for biologic medicines.
It is being researched to use new delivery methods, such as food that is directly or indirectly transgenic. The latter is illustrated by goat milk, which makes a chemical that is anti-malarial. Investigations into transdermally delivered vaccines are also ongoing.
New delivery mechanisms, such as food that is directly or indirectly transgenic, are being studied. Goat milk, which produces a substance that is anti-malarial, serves as an example of the latter. Studies into vaccines administered transdermally are also ongoing.

REGULATORY ISSUES

The FDA defines biologic treatments and devices specifically for regulatory purposes. The intended purpose of a product may decide its categorization; for example, an in vitro diagnostic kit may satisfy the basic definition of a medical device but may still be classified as a biologic because it is used to test and release a licenced biological product such as blood. Due to its purpose in diagnosing human disease, a similar kit used to test blood samples for diseases like rubella or to monitor disease progression may fall under medical device laws.
The manufacturing procedure for biologic products is covered by a patent and requires regulatory permission. New clinical trials are required as a result of process modifications, increasing development expenses. A post approval comparability protocol has been developed by the FDA's Center for Biologics Evaluation and Research (CBER) in part to address this issue. This protocol will enable businesses to combine multiple manufacturing changes into a single, condensed post approval application when they alter their process. If a manufacturer can demonstrate that a change in drug production is bioequivalent and doesn't result in any new adverse responses, companies are not required to repeat clinical studies.
CBER has approved a large number of biologic goods, including several vaccines, gene treatments, antitoxins, blood, and some in vitro diagnostics, to name a few. The Center for Drug Evaluation and Research is in charge of the remaining categories, which include monoclonal antibodies, growth factors, enzymes,

immunomodulators, and thrombolytics (CDER). Biologics that are generic (or, more precisely, follow-on) are illegal in the US, and there is no regulatory road for their approval.
Large clinical investigations could be rendered obsolete by genetic testing before therapy. Traditional clinical trials extrapolate results to bigger populations in order to forecast medical outcomes in much larger populations; however, biologics have not yet been designed to target broad, heterogeneous populations, therefore performing large trials is inefficient. Also, the risk/benefit ratio of a medicine for an illness that might otherwise be deadly is tilted in favour of efficacy over safety. This is not the case with a typical medication for a chronic illness, like hypertension, for which there are numerous, generally safe therapy options.

EVALUATING VALUE AND COSTS

Health care providers and payers typically believe biologics are worth their cost, despite being significantly more expensive than chemical entities, as long as the right patients receive them and achieve the required clinical outcomes. Individuals who have not responded to conventional medicines or for whom there are no alternative treatment options are ideal candidates for biologics. Assays help in patient selection for various medications. The net value must take into account the price of DNA-based testing as well as the cost of teaching practitioners on how to utilize them.

BRIGHT FUTURE

Future technology developments are in various levels of preparedness and each has significant implications. Better understanding of a particular gene's or DNA fragment's function is made possible via RNA interference. Little pieces of DNA or RNA called antisense molecules stop the creation of the protein that is encoded in the blocked DNA or RNA, thereby "knocking out" the gene. The function of a particular gene in lab animals is also determined using the knockout technique. The relevant human genes can subsequently be determined using this knowledge.
The physical manifestation of a trait or disease typically results from a series of steps involving a protein-to-protein chain reaction, beginning with gene expression and progressing through a series of minor incidents in which a molecule is altered by one enzyme and then transferred to another enzyme for additional alteration.
By inhibiting gene expression and analysing the subsequent biological or observable changes, scientists are able to better understand the link between genes, characteristics, and proteins. Future medications can be more precisely targeted with the knowledge gathered. One area of research is replacement gene therapy, which aims to treat disorders like haemophilia brought on by protein deficiencies. The secrets of human DNA are being progressively revealed by science. The medical field is catching up. [Access at September 2004] [Thomas morrow ,MD etal, and Linda HULL Felcone et.al, , Defining the difference: What Makes Biologics Unique available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3564302/

MATERIALS AND METHODS

This is study, where effort has been made to study, about the regulatory guidelines for the development of biologics in US and Europe
In the comparative study ,primary and secondary sources of data have been referred to which include the following
a. Journal articles
b. Websites of various regulatory agencies and organizations
c.Guidelines and guidance documents issued by the regulatory authorities of the countries included in the study

AIM&OBJECTIVE

Aim: The aim of this work is to determine the regulatory guidelines for the development of biologics in Europe and United states

Objective:
The main objective of this work is To explore the basic regulatory guidelines for the development of biologics in united states and Europe

To study the regulatory issues while developing the biologics
To study the approval process of biologics by respective regulatory bodies in united states in Europe
To study the newly release biologics in market with approvals and rejections in united states and Europe

RESULTS AND DISCUSSION

Table :1 Comparision of Regulatory Requirements Between USA & EUROPE

S.NO	PARAMETER	US		EUROPE		
1. 1.	**Regulatory authority**	United State Food & Drug Administration (USFDA) (CBER		European Medicines Agency (EMA)		
2.	**Regulatory authority Flag**					
3.	**Regulated under name**	Vaccines, Blood & Biologics		Human regulatory (Biosimilars)		
4.	**Registration process**	One registration process		Multiple registration process 1.National Authorization Procedure 2.Decentralized Procedure 3.Mutual Recognition Procedure 4.Centralized Procedure		
1. 5	**Dossier Format/ Presentation**	ICH CTD		ICH CTD		
6.	**Presentation**	eCTD & Paper		eCTD		
7.	**Dossier Language**	English		English (centralized, decentralized and mutual recognition procedure) Regional language (national authorization procedure)		
8.	**Manufacturing license**	Required		Required		
9.	**Classification**	NA		NA		
10.	**Application Type**	NDA & BLA		MAA		
11.	**Approval Time line (months)**	~18		~10		
12.	**Fees**	FY 2022 ,2023	Clinical trial required	$3,117,218 $3,242,026	Variation type	Work sharing fee for one centralized marketing authorization
					Type IA minor variation	3900 EURO
				$369,413	Type IB minor variation	8600 EURO
		FY 2022,2023	No clinical trial required	$1,558,609 $1,621,013	Type II (level 1)major variation	103800 EURO
					Type II (Level 2)	77900 EURO
				$393,933	Type III(Level III)	26200 EURO
13.	**Clinical Trials**	Required		Required		

DISCUSSION

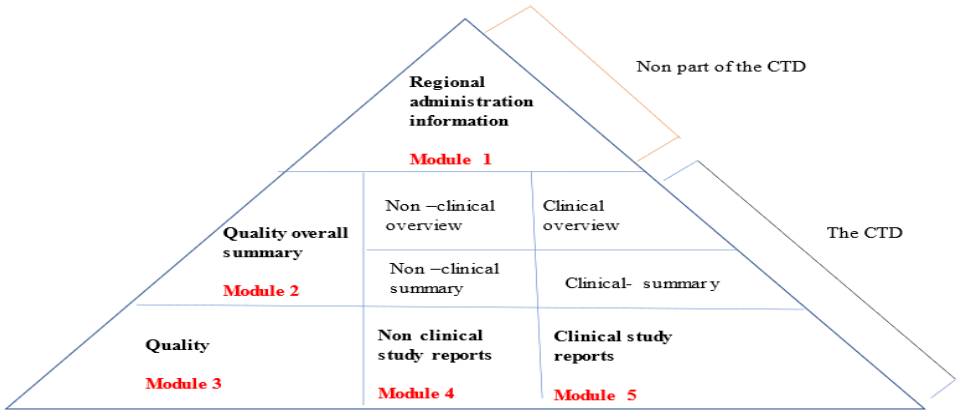

Fig.1. Common Technical Document

The Common Technical Document (CTD) was created to offer a standard format for technical documentation submitted with an application for the registration of a human pharmaceutical product in Europe, United States

There are five primary modules in the CTD dossier: Administration and prescribing information are covered in Module 1, overviews and summaries are covered in Module 2, quality is covered in Module 3, pharmacological documentation is included in Module 4, and clinical study results are covered in Module 5. (clinical trials). The content of each module is described in detail in the guidelines, and the majority of submissions must now use the CTD format for submission dossiers ICH ,CTD Triangle Available at https://admin.ich.org/sites/default/files/2021-02/CTD_triangle_color_Proofread.pdf

Table :- 2 FDA Approved Biosimilar List

BIOSIMILAR NAME	APPROVAL DATE	REFERENCE PRODUCT	MORE INFORMATION
Idacio (adalimumab-aacf)	December 2022	Humira (adalimumab)	Idacio Information
Vegzelma (bevacizumab-adcd)	September 2022	Avastin (bevacizumab)	Vegelma Information
Stimufend (pegfilgrastim-fpgk)	September 2022	Neulasta (pegfilgrastim)	Stimufend Information
Cimerli (ranibizumab-eqrn	August 2022	Lucentis (ranibizumab)	Cimerli Information
Fylnetra (pegfilgrastim-pbbk)	May 2022	Neulasta (pegfilgrastim)	Fylnetra Information
Alymsys (bevacizumab-maly)	April 2022	Avastin (bevacizumab)	Alymsys Information
Releuko (filgrastim-ayow)	February 2022	Neupogen (filgrastim)	
Yusimry (adalimumab-aqvh)	December 2021	Humira (adalimumab)	Yusimry Information
Rezvoglar (insulin glargine-aglr)	December 2021	Lantus (insulin glargine)	Rezvoglar
Byooviz (ranibizumab-nuna)	September 2021	Lucentis (ranibizumab)	Byooviz Information Press Release: FDA Approves First Biosimilar to Treat Macular Degeneration Disease and Other Eye Conditions
Semglee (Insulin glargine-yfgn)	July 2021	Lantus (Insulin glargine)	Semglee Information Press Release: FDA Approves First Interchangeable Biosimilar Insulin Product for Treatment of Diabetes
Riabni (rituximab-arrx)	December 2020	Rituxan (rituximab)	Riabni Information
Hulio (adalimumab-fkjp)	July 2020	Humira (adalimumab)	Hulio Information
Nyvepria (pegfilgrastim-apgf)	June 2020	Neulasta (pegfilgrastim)	Nyvepria Information
Avsola (infliximab-axxq)	December 2019	Remicade (infliximab)	Avsola Information
Abrilada (adalimumab-afzb)	November 2019	Humira (adalimumab)	Abrilada Information
Ziextenzo (pegfilgrastim-bmez)	November 2019	Neulasta (pegfilgrastim)	Ziextenzo Information
Hadlima (adalimumab-bwwd)	July 2019	Humira (adalimumab)	Hadlima Information
Ruxience (rituximab-pvvr)	July 2019	Rituxan (rituximab)	Ruxience Information
Zirabev (bevacizumab-bvzr)	June 2019	Avastin (bevacizumab)	Zirabev Information
Kanjinti (trastuzumab-anns)	June 2019	Herceptin (trastuzumab)	Kanjinti Information
Eticovo (etanercept-ykro)	April 2019	Enbrel (etanercept)	Eticovo Information
Trazimera (trastuzumab-qyyp)	March 2019	Herceptin (trastuzumab)	Trazimera Information

Table :- 3 EMA Approved Biosimilar List

PRODUCT NAME	ACTIVE SUBSTANCE	THERAPEUTIC AREA	AUTHORIZATION DATE	MANUFACTURER/ COMPANY NAME
Abevmy	bevacizumab	Breast cancer Carcinoma of the cervix Colon cancer Fallopian tube cancer Non-small-cell lung carcinoma Ovarian cancer Peritoneal cancer Renal cell cancer	21 Apr 2021	Mylan (now Viatris)
Alymsys	bevacizumab	Breast cancer Carcinoma of the cervix Colon cancer Fallopian tube cancer Non-small-cell lung carcinoma Ovarian cancer Peritoneal cancer Renal cell cancer	26 Mar 2021	Pfizer
Amsparity	adalimumab	Ankylosing spondylitis Hidradenitis Suppurativa Crohn's disease Juvenile rheumatoid arthritis Psoriasis Psoriatic arthritis Rheumatoid arthritis Ulcerative colitis Uvetis	13 Feb 2020	Pfizer
Aybintio	bevacizumab	Breast neoplasms Colorectal neoplasms Fallopian tube neoplasms Non-small-cell lung carcinoma Ovarian neoplasms Peritoneal neoplasms Renal cell	19 Aug 2020	Samsung Bioepis

		carcinoma Uterine cervical neoplasms		
Byooviz	ranibizumab	Degenerative myopia Diabetic retinopathy Macular edema Wet macular degeneration	18 Aug 2021	Samsung Bioepis
Cegfila (previously Pegfilgrastim Mundipharma)	pegfilgrastim	Neutropenia	19 Dec 2019	Mundipharma Biologics
Grasustek	pegfilgrastim	Neutropenia	20 Jun 2019	Juta Pharma (USV
Hukyndra	adalimumab	Ankylosing spondylitis Crohn's Disease Hidradenitis suppurativa Psoriasis Psoriatic arthritis Rheumatoid arthritis Ulcerative Colitis Uveitis	15 Nov 2021	Alvotech/Stada Artnimettel
Idacio	adalimumab	Ankylosing spondylitis Arthritis Crohn's Disease Hidradenitis suppurativa Psoriatic arthritis Psoriasis Rheumatoid arthritis Ulcerative colitis Uveitis	2 Apr 2019	Fresenius Kabi
Insulin aspart Sanofi	insulin aspart	Diabetes mellitus	25 Jun 2020	Sanofi-Aventis
Kirsty (previously Kixelle)	insulin aspart	Diabetes mellitus	5 February 2021	Mylan (now Viatris)/ Biocon
Libmyris	adalimumab	Ankylosing spondylitis Crohn's Disease Hidradenitis suppurativa Psoriasis Psoriatic arthritis Rheumatoid arthritis Ulcerative Colitis Uveitis	12 Nov 2021	Alvotech/Stada Artnimettel
Livogiva	teriparatide	Osteoporosis	27 Aug 2020	Theramex Ireland
Nepexto	etanercept	Ankylosing spondylitis Juvenile rheumatoid arthritis Psoriasis Psoriatic arthritis Rheumatoid arthritis Spondylarthropathies	25 May 2020	Mylan
Nyvepria	pegfilgrastim	Neutropenia	18 Nov 2020	Pfizer
Ogivri	trastuzumab	Early breast cancer Metastatic breast cancer Metastatic gastric cancer	12 Dec 2018	Biocon/Mylan
Onbevzi	bevacizumab	Breast neoplasms Colorectal neoplasms Fallopian tube neoplasms Non-small-cell lung carcinoma Ovarian neoplasms Peritoneal neoplasms Renal cell carcinoma Uterine Cervical Neoplasms	11 Jan 2021	Samsung Bioepis
Oyavas	bevacizumab	Breast cancer Carcinoma of the cervix Colon cancer Fallopian tube cancer Non-small-cell lung carcinoma Ovarian cancer Peritoneal cancer Renal cell cancer	26 Mar 2021	Stada Arzneimittel
Ruxience	rituximab	Chronic lymphocytic leukaemia Granulomatosis with polyangiitis Microscopic polyangiitis Non-Hodgkin Lymphoma Rheumatoid arthritis Pemphigus vulgaris	1 Apr 2020	Pfizer
Sondelbay	teriparatide	Osteoporosis	CHMP positive opinion 27 Jan 2022	Accord Healthcare
Stimufend	pegfilgrastim	Neutropenia	CHMP positive opinion 27 Jan 2022	Fresenius Kabi
Vegzelma	bevacizumab	Breast neoplasms Colorectal neoplasms Non-small-cell lung carcinoma Ovarian neoplasms Renal cell carcinoma	CHMP positive opinion 24 Jun 2022	Celltrion Healthcare

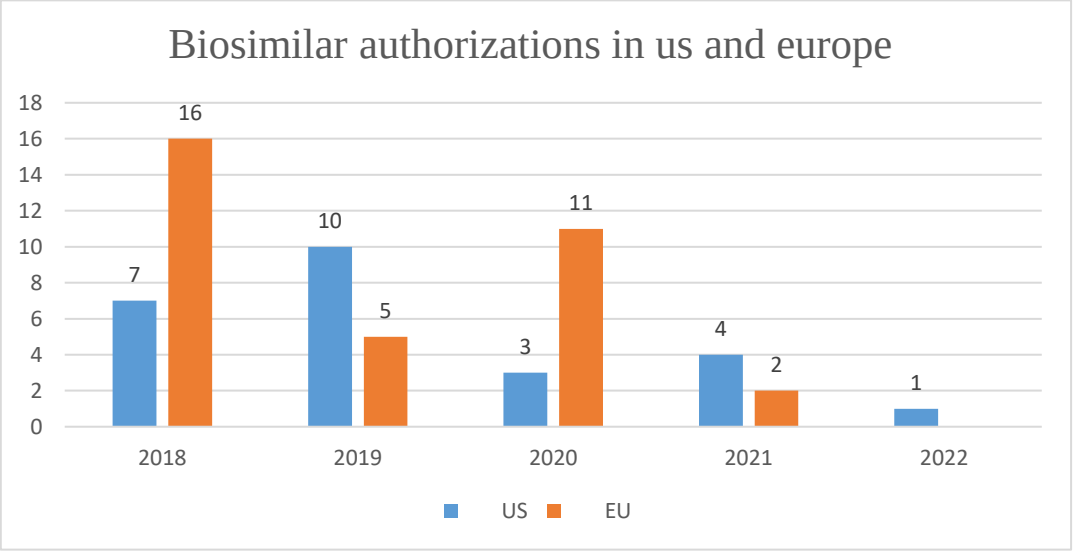

Fig. 2 . Biosimilar authorizations in US and Europe

According to a recent review of U.S. biosimilar approvals, clinical trials necessary for originator drugs tend to be smaller, shorter, and less expensive than most comparative efficacy trials done to achieve FDA approval for a biosimilar. Additionally, the EMA does not require animal trials for the approval of a biologic product, but the FDA does. Additionally, there seem to be fewer biosimilar BLAs than in 2017–2019 given the challenging patent litigation and competitive landscapes, and the FDA-approved adalimumab and rituximab biosimilars' releases are delayed as a result of patent litigation settlements. Therefore, regulatory obstacles and expenses faced by applicants for biosimilar products, in addition to the patent litigation environment, prevent or postpone the introduction of biosimilar products to the U.S. market.

- The EMA is currently considering fourteen biosimilar petitions for marketing approval. The number of applications for shortened biologics licences is rising along with the number of patents on popular biologic medications that are set to expire. In the United States, biosimilars for more than 28 different original biologics are either in the last stages of development or are currently navigating biosimilar paths.
- As shown in the following graph, the EU's relative higher approval rate in recent years has increased its lead over the United States, despite the U.S. FDA reversing that trend in 2019 with ten approvals. Previously, the EU's significant head start had caused an imbalance in the number of biosimilar drugs available in the respective markets. Compared to previous years, significantly fewer biosimilars have received FDA and EMA approval thus far in 2022 and 2021. Four EMA-authorized biosimilar drugs were discontinued in 2021 as a result of the growing rivalry among biosimilar manufacturers in Europe.
- Additional biosimilar versions of Humira® (adalimumab) have been given FDA and EMA approval.
- The third biosimilar variant of Neupogen® (filgrastim) has also received FDA approval.
- In 2022, the EMA did not approve any new biosimilars, although it did suggest the approval of the biosimilars Sondelbay for teriparatide and Stimufend for pegfilgrastim.
- The FDA authorised Coherus' adalimumab YusimryTM biosimilar on December 20, 2021. According to Paul Reider, Chief Commercial Officer of Coherus, "YUSIMRY represents an enormous commercial opportunity for Coherus as we continue our mission to increase patient access to critical biologic medicines while at the same time lowering the cost of care." With 2020 net sales exceeding $16 billion, Humira is the most popular medication in the US. There is a huge demand for a Humira biosimilar that is less priced throughout the healthcare ecosystem. All stakeholders will receive a compelling value proposition from us, and we eagerly anticipate the 2023 launch of YUSIMRY. The FDA gave Amneal and Kashiv's filgrastim ReleukoTM biosimilar the nod on February 28, 2022.
- "The U.S. approval of our first biosimilar is a very important turning point for Amneal. The next step in ensuring Americans have access to reasonably priced medications is represented by biosimilars. By utilising partner assets to get started and then our own critical skills over time, we are developing a worldwide biosimilars business. The co-chief executive officers of the company, Chirag and Chintu Patel, stated that their aim was to become a significant long-term player in the biosimilars market. Aydin H.Harston, et.al, How the U.S. Compares to Europe on Biosimilar Approvals and Products In the Pipeline Available at https://www.biosimilarsip.com/2021/03/08/how-the-u-s-compares-to-europe-on-biosimilar-approvals-and-products-in-the-pipeline-6/

Table :- 4 Rejections of biologics in USA

S.NO	REJECTIONS	REASON
1.	FDA Rejects Pfizer's epoetin alfa biosimilar	The warning letter was issued following a routine FDA inspection of a Hospira facility in McPherson, Kansas, USA in 2016, which listed significant good manufacturing practice (GMP) violations for finished pharmaceuticals. US pharma giant Pfizer announced on 22 June 2017 that the US Food and Drug Administration (FDA) had rejected its application for approval of its epoetin alfa biosimilar.
2.	FDA rejects emergency use authorization for Bharat Biotech's Covaxin jab	Ocugen's rejection of emergency authorization is because the company submitted partial data from the Covaxin trial only in March this year, but the USFDA last month came out with a revised guideline for covid vaccine approval that said it will no longer grant emergency authorization to new applications. Despite this revised guideline from FDA, Ocugen in a statement to investors on 26 May said that the company will be eligible to submit its EUA in June.
3.	FDA rejects trastuzumab and rituximab biosimilars	US pharma giant Pfizer announced on 23 April 2018 that the US Food and Drug Administration (FDA) had rejected its application for approval of its trastuzumab biosimilar. Then Sandoz, part of Novartis, announced on 2 May 2018 that its biosimilar rituximab application had also been rejected .Pfizer received a Complete Response Letter (CRL) regarding the company's Biologics License Application (BLA) for its trastuzumab biosimilar. In the CRL, says Pfizer, FDA highlighted the need for additional technical information.
4.	FDA Issues CRL for Biocon Biologics, Viatris Avastin Biosimilar Feb 14, 2023	Biocon Biologics and Viatris have taken another blow from the FDA after receiving a complete response letter (CRL) for their bevacizumab biosimilar referencing Avastin. Biocon Biologics announced the news in a statement for its investors. The letter represents the second CRL in 2023 for the partners following the one sent concerning their recombinant human insulin biosimilar. Unlike the CRL for the recombinant human insulin biosimilar, which requested additional data to be submitted, the CRL for the bevacizumab candidate cited a failed manufacturing facility inspection.
5	FDA Rejects Romosozumab Biologics License Application, Requests More Data	The FDA rejected the Biologics License Application (BLA) yesterday for romosozumab (Evenity) for the treatment of postmenopausal women withosteoporosis The BLA included data from the pivotal phase 3, placebo-controlled FRAME study. The FDA issued a Complete Response Letter requesting that safety and efficacy data from the phase 3 active-comparator ARCH study be integrated into the application.

Table :- 5 Biologics Rejections in europe

S.NO	REJECTIONS	REASON
1	Refusal of the marketing authorisation for Ipique (bevacizumab) Re-examination confirms refusal 24 February 2022	After re-examining its initial opinion, the European Medicines Agency has confirmed its recommendation to refuse marketing authorisation for the medicine Ipique. The medicine was intended for the treatment of neovascular (wet) age-related macular degeneration (AMD). The Agency issued its opinion after re-examination on 24 February 2022. The Agency had issued its initial opinion on 11 November 2021. The company that applied for authorisation of Ipique is Rotterdam Biologics B.V. At the time of the initial evaluation, the Agency was concerned that the literature review was only based on data obtained with other bevacizumab-containing medicines and that no evidence had been submitted comparing Ipique with another bevacizumab medicine when used intravitreally. Therefore, the Agency was not able to draw conclusions on whether known or unknown differences between Ipique and these medicines might affect the effectiveness and safety of Ipique when used to treat AMD. These concerns did not change after re-examination of the data provided, and the Agency's opinion therefore remained that the safety and effectiveness of Ipique had not been properly demonstrated. The Agency therefore considered that the risks of Ipique outweighed its benefits and it recommended refusing marketing authorisation. The company informed the Agency that there are no ongoing clinical trials with Ipique in the EU.
2	Refusal of the marketing authorisation for Raylumis (tanezumab)17 September 2021	The European Medicines Agency has recommended the refusal of the marketing authorisation for Raylumis, a medicine intended for the treatment of pain associated with osteoarthritis. The Agency issued its opinion on 16 September 2021. The company that applied for authorisation, Pfizer Europe MA EEIG, may ask for re-examination of the opinion within 15 days of receiving the opinion.Although Raylumis showed better pain relief and improved physical functioning in patients with osteoarthritis affecting the hip or knee compared with placebo, the difference was small. In addition, there was no improvement in pain relief and physical functioning when compared with NSAIDs. In terms of safety, patients on Raylumis

		were at an increased risk of side effects, such as rapid progressive osteoarthritis and joint replacement, compared with patients receiving placebo or NSAIDs. Therefore, the Agency's opinion was that the benefits of Raylumis in patients with an insufficient response to NSAIDs or opioids were unclear and did not outweigh its risks and recommended refusing marketing authorisation. The company informed the Agency that there are no consequences for patients in clinical trials with Raylumis.
3	Refusal of the marketing authorisation for Hopveus (sodium oxybate) Re-examination confirms refusal 30 April 2020	After re-examining its initial opinion, the European Medicines Agency has confirmed its recommendation to refuse marketing authorisation for the medicine Hopveus. The medicine was intended for the treatment of alcohol dependence. The Agency issued its opinion after re-examination on 30 April 2020. The Agency had issued its initial opinion on 17 October 2019. The company that applied for authorisation of Hopveus is D&A Pharma. Although some of the studies presented suggested that the medicine could be effective, this was not conclusively demonstrated, and the Agency had concerns about several drawbacks in the design and analysis of these studies that could have affected the results. As the data were insufficient to establish the effectiveness of Hopveus, the Agency's opinion was that the benefits of Hopveus did not outweigh its risks and it recommended refusing marketing authorisation. The Agency's concerns on Hopveus' effectiveness could not be addressed by further restricting the use of Hopveus as the company proposed. The refusal was therefore confirmed after re-examination. The company informed the Agency that there is no impact on patients in clinical trials with Hopveus.
4	Refusal of the marketing authorisation for the medicinal product **Eladynos,7-1-2019**	On 22 March 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Eladynos, intended for the treatment of osteoporosis (a disease that makes bones fragile). The company that applied for authorisation is Radius International Ltd. The company requested a re-examination of the initial opinion. After considering the grounds for this request, the CHMP re-examined the opinion, and confirmed the refusal of the marketing authorisation on 26 July 2018.Eladynos is a medicine that contains the active substance abaloparatide. It was to be available as a solution for injection under the skin.The CHMP considered that the main study did not satisfactorily show that Eladynos is effective at preventing non-vertebral fractures in women who have been through the menopause. The data from two of the study sites were not reliable and had to be excluded as the study had not been conducted in compliance with 'good clinical practice' (GCP) at those sites. From a safety point of view, the CHMP was concerned about the medicine's effects on the heart, such as increases in heart rate and palpitations. Because most post-menopausal women are at an increased risk of heart problems, the CHMP could not identify a group of patients in whom the benefits would outweigh the risks. Therefore, at that point in time, the Committee was of the opinion that the benefits of Eladynos did not outweigh its risks and recommended that the medicine be refused marketing authorisation. The CHMP refusal was confirmed after re-examination.
5	Refusal of the marketing authorisation for Dexxience (betrixaban) Outcome of re-examination 27 July 2018	On 22 March 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Dexxience, intended for the prevention of venous thromboembolism. The company that applied for authorisation is Portola Pharma UK Limited. The company requested a re-examination of the initial opinion. After considering the grounds for this request, the CHMP re-examined the opinion and confirmed the refusal of the marketing authorisation on 26 July 2018. Dexxience was expected to be used to prevent venous thromboembolism (formation of blood clots in veins). It was to be used in adults admitted to hospital for the treatment of a recent medical illness. These patients may be at high risk of blood clots because of reduced mobility during their hospital treatment as well as other underlying conditions that increase the risk.The CHMP considered that the main study did not satisfactorily show Dexxience's effectiveness when used for preventing blood clots in patients admitted to hospital for recent medical illness. Also, patients treated with Dexxience had more episodes of bleeding than those treated with the comparator medicine. This was considered an important concern given that the medicine was expected to be used in

		patients with serious underlying conditions for whom any episode of bleeding could have serious consequences, and Dexxience's long persistence in the body could complicate management of bleeding. Therefore, at that point in time, the CHMP was of the opinion that the benefits of Dexxience did not outweigh its risks and recommended that it be refused marketing authorisation. The CHMP refusal was confirmed after re-examination

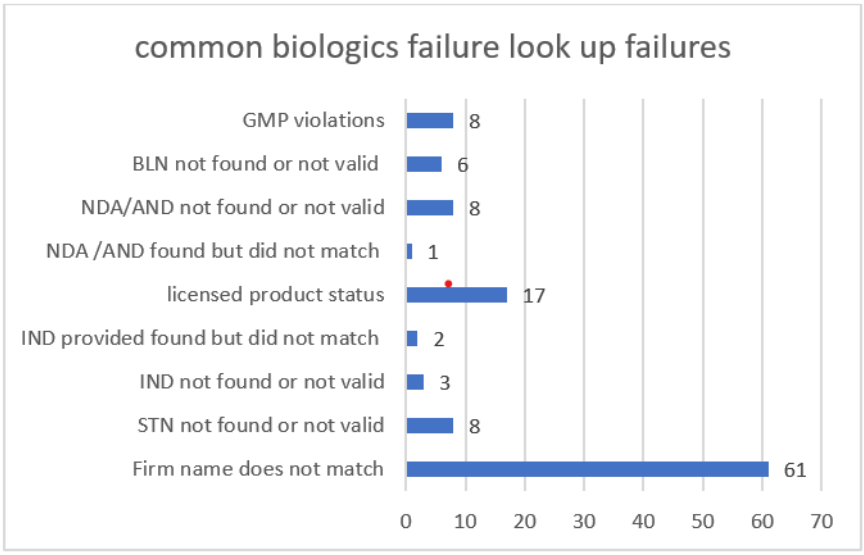

Fig.3.:- Common entry Failure of biologics

CONCLUSION

Despite evident variations in the US and EU regulatory regimes for biologics—for example, with respect to the definitional frameworks for biologics—the systems have a number of similarities. One can confidently infer that both regimes clearly recognise the unique character of biologics and take appropriate efforts to handle any potential concerns that may arise from it because both apply specific harmonised scientific testing standards. Due to basic structural disparities in their medicine authorization regimes and diverse historical developments in both systems, the regions have unique regulatory approval processes. Overall, there are more similarities than differences between the regulatory frameworks in the US and EU for biologics.
We have seen many rejections when we submit the BLA application, including GMP violations, IND not found or not matched and firm name does not match, Biologics licence number not found or not valid, IND/AND are not valid, etc. When the entry data provided is incomplete and/or inaccurate, the entry line may be subject to processing delays. GMP violations, company names that don't match, and licenced product number status are the most frequent ones we see. Therefore, an organisation should be mindful of all of these elements while sending the biologics licence applications to help them bounce back from rejections.

CONFLICT OF INTEREST: None

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