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Biosimilars and Generic Biologics: Current Status and Understanding the Difference

Ajinkya Purbe

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ABSTRACT
Biologics are derived from living sources in contrast to most drugs which are chemically synthesized and have a known structure. A biosimilar is a certain type of biologic prepared by a different company to the one which originated the product. The first generation of biopharmaceutical products manufactured using recombinant technologies was launched in the 1980s, and they are now on the way to patent expiration. As a result, research based and generic pharmaceutical companies alike are pursuing the opportunity to develop "generic" substitutes for original biologics, herein referred to as biosimilars. Biologics has introduced many new treatments to life-threatening and rare illnesses. Biologics are produced by cells in culture or whole organisms, which are inherently more variable than chemical synthesis methods. biosimilars are "similar but not the same" or in other words biosimilars are "the twin but not the clone" to the original biologic innovator
Keyword: Biologics,biosimilars,FDA,CDER

I. INTRODUCTIONS

"Biologics" represent one of the fastest growing segments of the pharmaceutical industry.They refer broadly to substances produced by living cells using biotechnology (i.e., recombinant DNA technology, controlled gene expression, or antibody technologies), which have introduced many new treatments to life-threatening and rare illnesses such as cancer, diabetes, anaemia, rheumatoid arthritis and multiple sclerosis. They involve a wide range of substances, including recombinant hormones, growth factors, blood products, monoclonal antibody-based products, recombinant vaccines, and advanced technology products (gene and cell therapy biological products) [1]. Biogeneric are biological products manufactured after expiry of the patent of innovator biopharmaceuticals and these are also called as Biosimilars, Similar biologics, Follow-on biologics, Follow-on protein products and Subsequent entry biologics in different countries [2]. The global biosimilars market is expected to be worth $19.4 billion by 2014, growing at a Compound Annual Growth Rate (CAGR) of 89.1% from 2009 to 2014[3]. Biologic sales now account for about US$92 billion and are expected to worth more than US$167 billion by 2015[4]. The RNCOS study indicated that over 40 biologics are marketed in India and more than half of these, 25 in total are biosimilars. A further 25 biosimilars are in their final stages of development [5].

Q1.1Official Definitions of Biosimilars

- 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 [6].

- 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 [7].

2. Indian Scenario

The RNCOS study indicated that over 40 biologics are marketed in India and more than half of these, 25 in total are biosimilars. A further 25 biosimilars are in their final stages of development [8]. According to statistics released by Data monitor, the Indian biosimilars market, which was $200 million in 2008, is expected to grow to $580 million by 2012[9]. Under the Trade-Related aspects of Intellectual Property Rights (TRIPS) agreement, the pre-1995 product patents do not apply in India and this leaves as many as 48 biologicals that were patented prior to 1995, marketable in India[10].

Furthermore, the innovators have not sought patent protection for some drugs in India, thereby creating a strong opportunity for Indian companies to influence the huge domestic market

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and supply to other countries where these products are not patented [11]. The focus within the biopharmaceutical sector in India is directed more towards development of biosimilars because of much lower developmental costs and risks, reduce spending on research and development, reduced time to market and expertise in reverse engineering drug development process. Over 50 different brands of biosimilars are approved by more than 20 different biopharmaceutical companies and some of these molecules have completed a decade of market presence with several thousand doses already administered [12].

3.Biosimilar Products in India

Table: 1. Biosimilar Products in India

Insulin	Wockhardt Biocon Shreya Life Sciences	Wosulin Insugen Recosulin	2003 2004 2004
Erythropoietin	Hindustan Antibiotics EmcureWockhardt Ranbaxy Intas Pharmaceuticals ShanthaBiotechnics	Hemax Epofer Wepox Ceriton Epeofit&ErykineShanpoiet i	2000 2001 2001 2003 2005 2005
Hepatitis B vaccine	ShanthaBiotechnics Bharat Biotech Panacea BiotecWockhardt Serum Institute of India Biological E	Shanvac B Revac B Enivac HB Biovac-B Gene Vac-B Bevac	1997 1998 2000 2000 2001 2004
Granulocyte colony stimulating factor	Dr Reddy‟s Laboratories Intas Pharmaceuticals	Grastim Neukine	2001 2004
Streptokinase	Bharat Biotech ShanthaBiotechnicsCadila Pharmaceuticals	Indikinase Shankinase STPase	2003 2004 2004
Interferon alpha-2b	ShanthaBiotechnics	Shanferon	2002
Rituximab (Mab)	Dr Reddy‟s Laboratories	Reditux	2007
Anti- Epidermal Growth Factor (MAb)	Biocon	BioMAB-EGFR	2006

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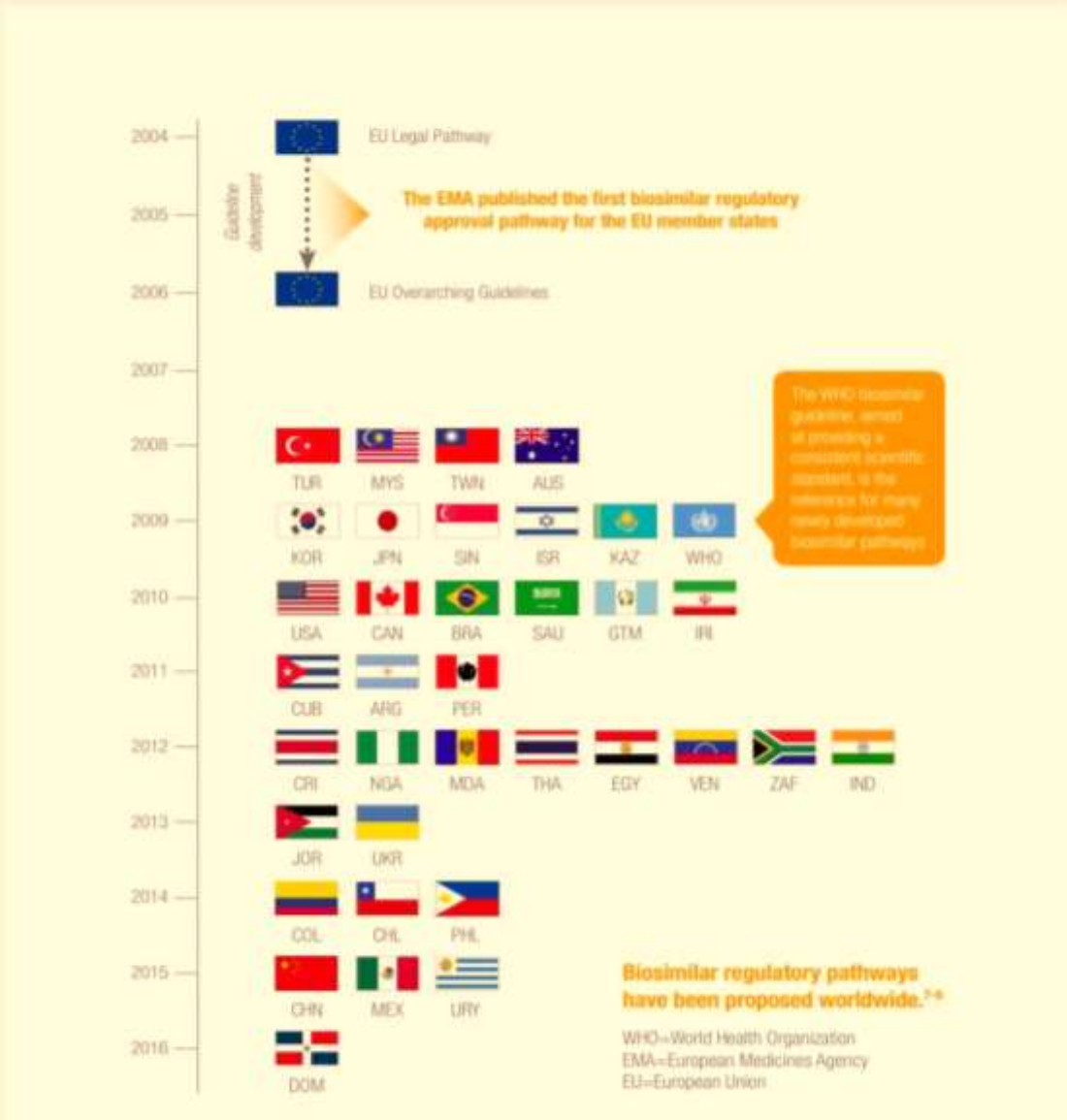

Figure:1. Biosimilar Regulatory Pathways Proposed WorldwideWith Years

4.Difference Between Cost of Manufacture and Price

According to a Bernstein Analysis the resulting difference between manufacturing cost and price is estimated to be on average around 2.3%, with some products having up to 4.4% difference Thus, result a viable product from a profit viewpoint [13].

Table: 2. Difference Between Cost of Manufacture and Price

Product	Price (US$)	Price/g (US$)	Manufacturing cost* (US$/g)	Cost/price difference
Avastin (bevacizumab)	687.5/100mg	6875	188	2.7%
Enbrel (etanercept)	243/25mg	9706	428	4.4%
Humira				

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(adalizumab)	1816/40mg	45400	308	0.7%
Rituxan (rituximab)	675/100mg	6751	188	2.8%
Herceptin (trastuzumab)	3331/440mg	7570	126	1.7%
Erbitux (cetuximab)	600/100mg	6000	188	3.1%
Soliris (eculizumab)	5122/300mg	17073	135	0.8%
Remicade (infliximab)	784/100mg	7839	188	2.4%
Average	1223/100mg	12877	231	2.3%

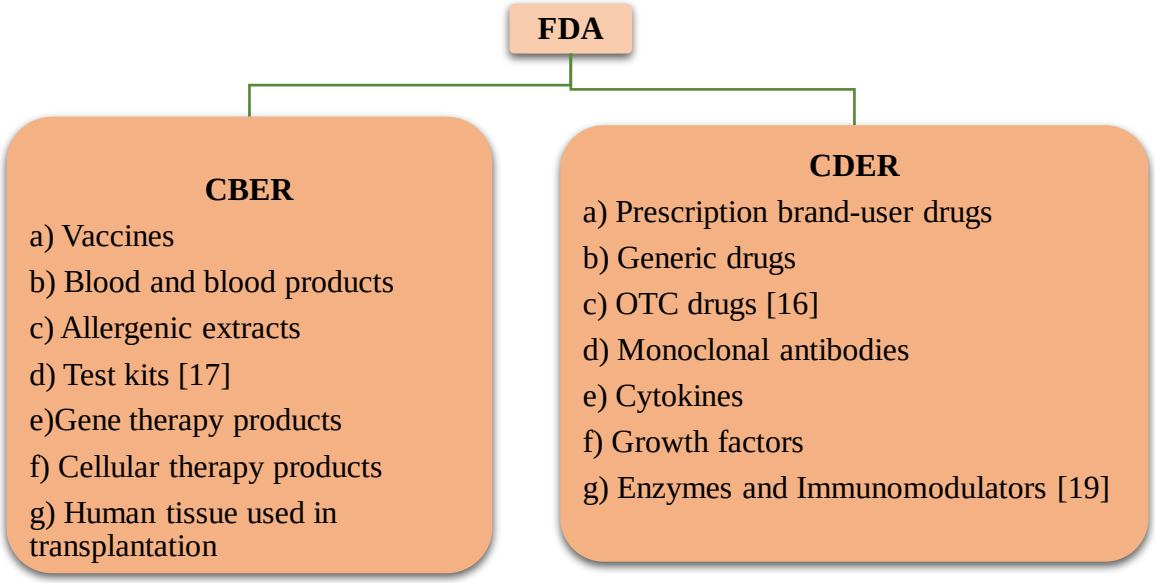
5. The Role of Hospital Pharmacists on Biosimilars

It is of utmost importance that the hospital pharmacist is aware that the innovator products and biosimilars are not interchangeable, because patients must be carefully monitored if their treatment is changed between products. Moreover, patient welfare is foremost and for pharmacists, the knowledge that biosimilars are not generics, and the possible implications for clinical outcomes when products are switched, will help ensure patient safety[14].

Additionally, biosimilars are deemed to contain a new active ingredient, whereas interchangeable products are not. The Eprex example also provides a rationale for not considering a biosimilar to be interchangeable with an innovative product.

FDA has stated that it has not determined how interchangeability can be established for complex proteins[15].

6. Regulation of Biologics:



7.Biosimilars Legislation:

There was an act accepted for the permit of FDA approval of generic chemical drugs. It is known as "DRUG PRICE COMPETITION and PATENT TERM RESTORATION ACT" of 1984 also called as Hatch- Waxman Act [20]. The main

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aim of the act is to low the price of drugs to customers and to make the U.S generic drug industry to grow. According to the survey generic drug decreases price up to 60%-90% [21]. generic drug industry saves their cost by avoiding the expense for clinical trials in order to develop a new drug. In the Hatch-Waxman Act discussion FDA-biotechnology has evolved and allowed the human drug developed by that department namely HUMULIN-R in the year 1982 & Protropin in 1985.The products that are biological which are controlled and authorized for marketing by FDA through BLA (Biologics License Application) under the public Health services Act (PHSA).Those products are really controlled by NDA, ANDA under the FFDCA-Federal Food Drug and Cosmetic Act[21].

7.1 Hatch-Waxman Act of 1984

The Hatch-Waxman Act included newly two pathways for the approval of drugs to the FDA. a) Section 505 (J) b) Section 505 (b)(2) a) Section 505 (j)

It is an ANDA process

Comparison of safety and efficacy for the before now approved drug and with the generic company drug.

Acceptance of most generic chemical drugs b) Section 505 (b) (2)

Utilized to distinguish between brand-name drug to that of drug

Consent of clinical and non-clinical data to prove the safety and the effectiveness of the drug

8. Bio-Similars Approved by FDA

Table: 3.Bio-Similars Approved by FDA

Sr.No.	Name	Active Substance	Manufacturer	Indications	Approved Date
1.	Zarixo	Filgrastim-sndz	Sandoz	Cancer, hematopoietic stem cell transplantation, neutropenia	06/03/2015[22].
2.	Inflectra	Infliximab-dyyb	Celltrion /Pfizer	Psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, Crohn's disease, psoriasis, ankylosing spondylitis	05/04/2016[23].
3.	Erlezi	Etanercept-szzs	Sandoz	Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis	30/08/2016[24].
4.	Renflexis	Infliximab-abda	Samsung/Merck	psoriatic arthritis, rheumatoid arthritis, ulcerative colitis	21/04/2017[25].

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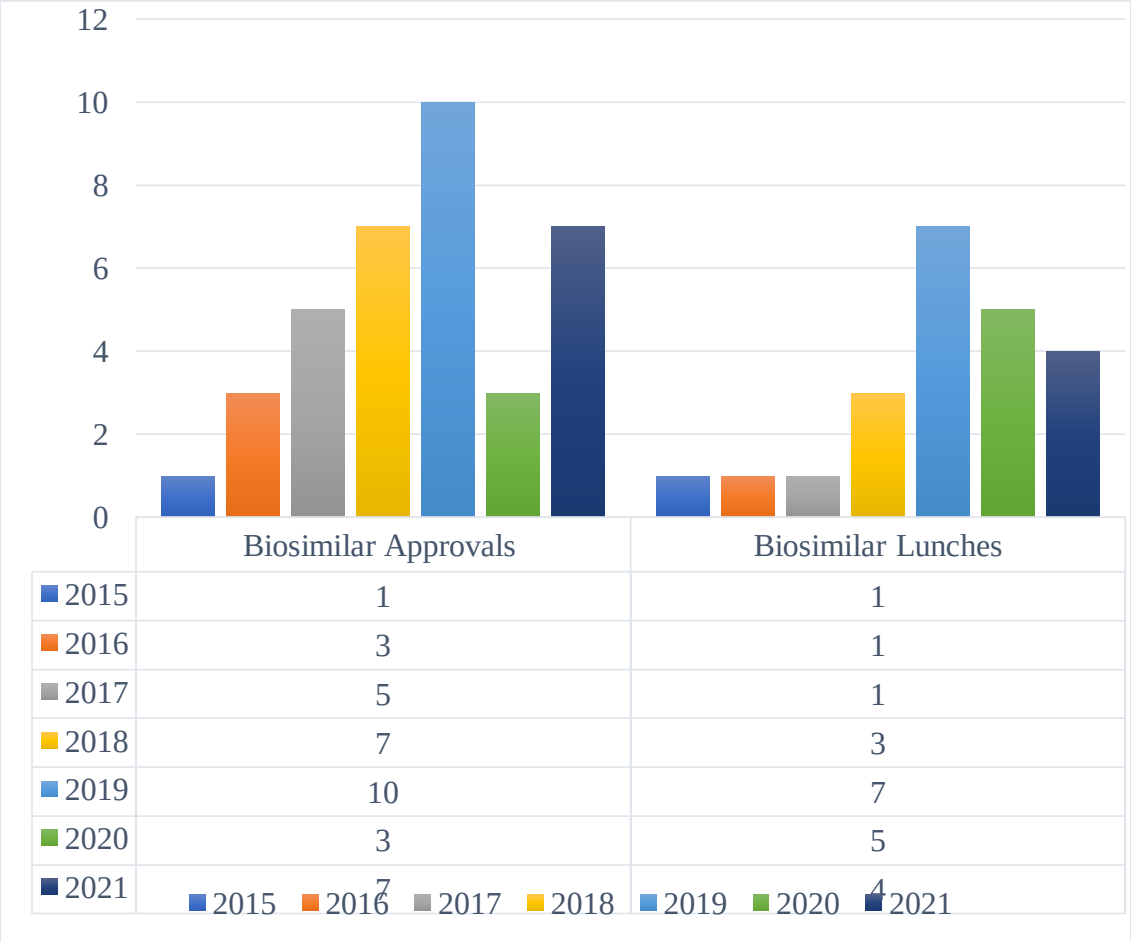
8.1 ZARIXO

FDA has approved the first biosimilar product in the year march 2015 in United States namely zarixo which is biologically similar product of neupogen. It was first traded into market by Amgen.IncZarixo is similar as of neupogen[26].

8.2 INFLECTRA

FDA has announced their second biosimilar product in U.S in the 2016 April named Inflectra which is same biologically similar of Remicade. Later Pfizer started to market the inflectra drug in U.S to 15 % less-price of those brand-drugs [27].



	Biosimilar Approvals	Biosimilar Lunches
2015	1	1
2016	3	1
2017	5	1
2018	7	3
2019	10	7
2020	3	5
2021	7	4

Figure: 2.Biosimilar Approvals and Lunches Review

9. Development of Biosimilars

There are four stages [28].

9.1. Product Development andComparative Analysis

This stage involves the production of protein of interest from cell culture and validates their stability. The product must also demonstrate that it is biosimilar to the innovator product.

9. 2. Process Development, Cale Up andValidation

During this stage, scale up of manufacturing process can be carried out to improve the product yield. This process should be carried out under good manufacturing practices and reproducibility of the manufacturing process needs to be demonstrated.

9.3. Clinical Trials

Clinical trials will be required for almost all biosimilar products in order to demonstrate bioequivalence to innovator product.

9.4. Regulatory (EMEA, WHO and FDA) Review and Approval

10.US FDA Guidance for Biosimilar Nomenclature

The non-proprietary name designated for each originator biological product, related biological product, and Biosimilar product will be a proper name that is a combination of the core name

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and a distinguishing suffix that is devoid of meaning and composed of four lowercase letters. And the random suffixes will not just be for Biosimilars but for newly licensed and previously licensed originator biological products, related biological products and Biosimilars.

"Non-proprietary names that include distinguishing suffixes can serve as a key element to identify specific products in spontaneous adverse event reporting and to reinforce accurate product identification in billing and claims records used for active pharmacovigilance," FDA explains. "Other product specific identifiers, such as proprietary names or NDCs, may not be available or could change over time." The distinguishing suffixes should also help to minimize "inadvertent substitution [29].

FDA suggests the proposed suffix be:

- Be unique
- Be devoid of meaning
- Be four lowercase letters of which at least three are distinct
- Be non-proprietary
- Be attached to the core name with a hyphen
- Be free of legal barriers that would restrict its usage

10.1. FDA, The Proposed Suffix Should Not

• Be false or misleading, such as by making misrepresentations with respect to safety or efficacy

• Include numerals and other symbols aside from the hyphen attaching the suffix to the core name • Include abbreviations commonly used in clinical practice in a manner that may lead the suffix to be misinterpreted as another element on the prescription or order

• Contain or suggest any drug substance name or core name

• Look similar to or be capable of being mistaken for the name of a currently marketed product

11.Manufacturing of Biosimilars

11.1. Principle

The manufacture of biological medicinal products involves certain specific considerations arising from the nature of the products and the processes. The ways in which therapeutic biological products are produced, controlled and administered make some particular precautions necessary.

11.2 Typical Steps In Manufacturing of Biological Product [30]

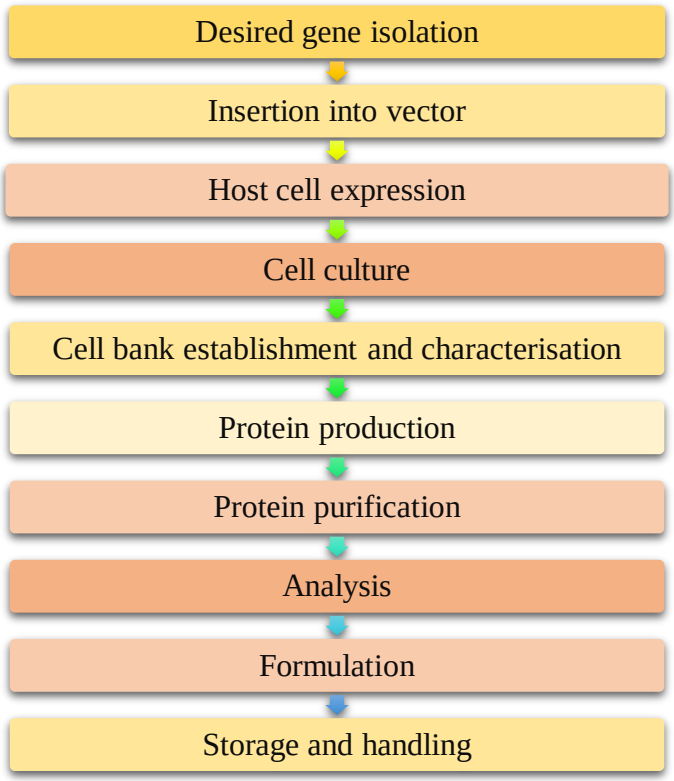

Figure: 3.Typical Steps In Manufacturing of Biological Product

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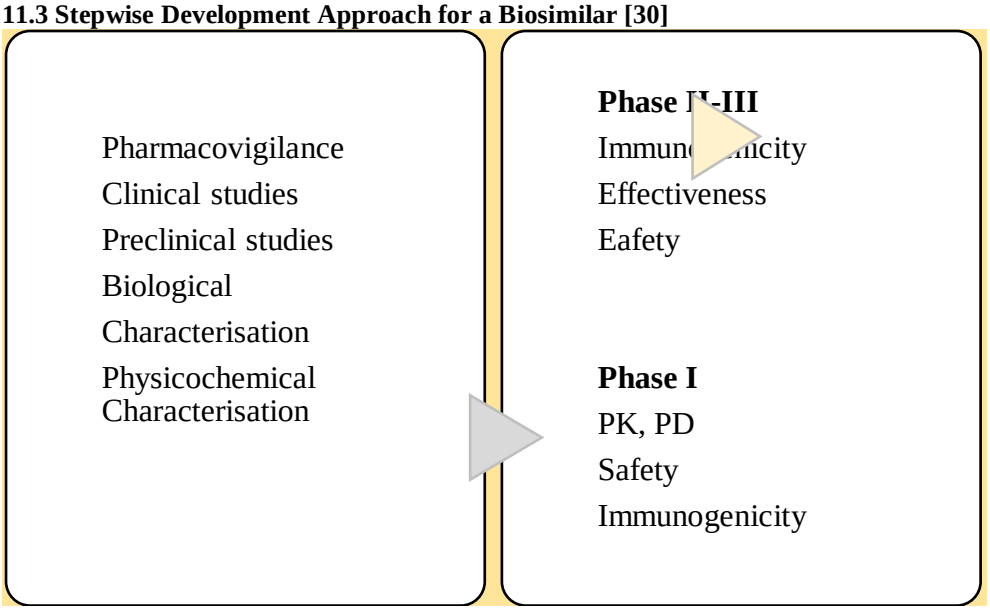
11.3 Stepwise Development Approach for a Biosimilar [30]



11.4 Up Stream Process:

The majority of biological medicines are produced using genetically modified cells. These are cells whose genes have been changed, using recombinant DNA techniques. so that they produce a specific substance or perform a function. Genes for a certain protein are introduced into the genes of a host cell (such as a bacteria or yeast cell or our transgenic goat), which would subsequently produce that protein. Each biological medicine manufacturer has its own host cell bank, producing a unique cell line, and develops its own unique manufacturing process.

The manufacturing of Biologics is a highly demanding process. As we have seen, protein-based therapies have structures are far larger, far more complex, and more variable than the structure of drugs based on chemical compounds. Additionally, biological drugs are made using intricate living systems that require very precise conditions in order to make consistent products.

11.5 Manufacturing Process Consists of These Four Main Steps:

1) Producing the master cell line containing the gene that makes the desired protein.

a) The genetic code (a sequence of DNA) of a selected protein (e.g. a hormone, antibody, blood product) is identified and a functional DNA sequence created.

b) The genetic code is inserted into various host cell lines (e.g. bacteria or yeast), so that the host cells produce this protein

c)The host cell line that produces the protein the most successfully becomes the chosen host cell line.

2. Growing large numbers of cells that produce the protein in machines called bioreactors; this process is called fermentation.

3. Isolating and purifying the protein, separating it out of the bioreactor via a filtration process.

12.6 Down Stream Process

Validity of the downscale is an essential prerequisite for clearance studies for viruses, mycoplasmas and DNA. The acceptance criteria for a valid scale down of the process must be defined. These typically include that the purity and yield of the product obtained from the scale down process is equivalent to that of the full-scale process. Additional criteria may be defined based on the functionality of the specific step under investigation. Where the step to be scaled down is relatively straightforward i.e. inactivation steps such as heat, low pH and solvent/detergent treatments, then Down streaming is relatively straightforward [31].involving a proportional reduction in the volumes for exampleSteps of downstream process:

1. Filtration
2. Ultrafiltration
3. Chromatography

Most purification procedures involve chromatographic steps, which can be divided into three classes [32].

a) Batch/Adsorption/Desorption

b) Isocratic Chromatography

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c) Gradient Method

13. Labelling

The advised drug product should consist of an explained label which explains about the product safety and effectiveness [33]. FDA agreed labelling is also known as "Professional Labelling", "Package insert or package circular". Label should explain the indication's, use, dosage forms, administration route, warnings and precautions, overdosage [34].

- The label on the container should show [35].
- The name of the drug product
- A list of active ingredients and the amount of each present
- The batch or final lot number assigned by the manufacturer
- The expiration dates
- Recommended storage conditions
- Direction for use and warning and precautions that may be necessary
- The name and address of the manufacturer or the company
- Transition

Biologics was agreed as drugs under FFDCA will transformation to biological license under PHSA in march 2020. FFDCA will not at all existed and will be restore BLA under PHSA. The FDA suggests such application be withdrawn (or) resubmitted under PHSA in the section 351(a) (or) 351 (k)

14.Advantages of biosimilars

- Similar drug having same efficacy and safety comes to market
- Development cost and time are relatively less for biosimilars
- It helps in cost reduction of drug
- It also increased access to patients for costly treatments[35].

15. Comparison of Biosimilarsand Biologics

Table: 4. Comparison of Biosimilars and Biologics

Process	Biologic	Biosimilar
Manufacturing	Produced by biological process in first cell lines Sensitive to production process changes – expensive and specialized production facilities Reproducibility difficult to establish	Produced by biological process in host cell lines Sensitive to production process changes – expensive and specialized production facilities Reproducibility difficult to establish
Clinical Development	Extensive clinical studies, including Phase I–III Pharmacovigilance and periodic safety updates needed	Extensive clinical studies, including Phase I–III Pharmacovigilance and periodic safety updates needed
Regulation	Needs to demonstrate "comparability" Regulatory pathway defined by Europe (EMEA) Currently no automatic substitution intended	Needs to demonstrate "similarity" Regulatory pathway defined by Europe (EMEA) No automatic substitution allowed

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16. Indian Guidelines

The New Indian Guidelines "Draft Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India," were announced in June 2012, by Department of Biotechnology (DBT). The Indian guidelines on similar biologics address the pre-marketing and post-marketing regulatory requirement (i.e., "comparability exercise"), and also address the requirements related to manufacturing process and quality control. As such these Indian guidelines on similar biologics are comparable in many respects to biosimilar guidelines of USA and EU. India has adopted a "sequential approach" (like "stepwise approach" - US and EU) to market biosimilar products [36,37].

The review committee on genetic manipulation of the Genetic Engineering Approval Committee (GEAC) with the permission of DCGI, approve clinical trials to be conducted in India related to biosimilar therapeutic products. The biosimilar has to demonstrate comparable data of non-clinical studies viz., pharmacokinetics and toxicology (safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity) and clinical studies (efficacy and tolerability y for each indication) before it gets approval for all indication of the reference medicine[38].

There are about 100 biopharmaceutical companies actively involved in research and development, manufacturing and marketing of biosimilar therapeutic products in India. There were 14 therapeutic drugs (similar biologics) available in 50 brands in 2005; the number has increased to 20 therapeutic drugs in 250 brands in 2011. Biosimilar therapeutic products include insulin, erythropoietin, chorionic gonadotropin, streptokinase, interferon and heparin. The growing biosimilars market offers huge potential for companies involved in manufacturing, research and development [39].

17. Biologics and Biosimilars For theTreatment of Diabetes

Insulin

Figure:4. Insulin

17.1Mechanism of Action andIndications

Insulin initiates its action by binding to a glycoprotein receptor on the surface of the cell. This receptor consists of an alpha-subunit, which binds the hormone, and a beta-subunit, which is an insulin-stimulated, tyrosine-specific protein kinase[40].

17.2 Side Effect

- Sweating.
- Dizziness or light-headedness.
- Shakiness.
- Hunger.
- Fast heart rate.
- Tingling in your hands, feet, lips, or tongue.
- Trouble concentrating or confusion.
- Blurred vision[41].

18. Biologics and Biosimilars In Inflammatory Bowel Disease

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18.1 Adalimumab

Figure: 5. Adalimumab

18.1.1 Mechanism of Action and Indications

Adalimumab is the first fully human monoclonal antibody (MAb) that was approved by the FDA in 2002 for rheumatoid arthritis (RA) [42]. It was initially named as D2E7 marketed by Abbott Laboratories (Chicago, IL, USA) and currently owned by AbbVie (Chicago, IL, USA) [42]. It was initially named as D2E7 marketed by Abbott Laboratories (Chicago, IL, USA) and currently owned by AbbVie (Chicago, IL, USA) [43]. The name Humira stands for human MAb in RA. It is a recombinant human immunoglobulin (Ig)-G1 MAb created using the phage display technology [44]. It inhibits TNF-α, which is a cytokine involved in normal inflammatory and immunological responses, and it inhibits its interaction with p55 and p75 cell surface TNF-alpha receptors. It does not have action on TNF-beta. [44]. It also causes changes in the levels of adhesion molecules that are responsible for leukocyte migration. Adalimumab is indicated for use in moderate-to-severe RA, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, moderate-to-severe CD and UC with inadequate response to conventional therapy, moderate-to-severe chronic plaque psoriasis, hidradenitis suppurativa, uveitis, and Behcet's disease [45]. It is available as a sterile, preservative-free solution in the pen of 80 and 40 mg, the prefilled syringes of 80, 40, 20, and 10 mg, and a single use institutional vial of 40 mg, which are to be given subcutaneously (SC) [42]. The bioavailability of the agent is 64% with a half-life of 2 weeks following linear kinetics of elimination [42].

18.1.2 Side Effects

The most serious adverse reactions encountered in clinical trials were serious infections due to immunosuppression, malignancies, and demyelinating neurological disease [42]. Serious infections include pneumonia, septic arthritis, prosthetic/postsurgical infections, erysipelas, cellulitis, diverticulitis, and pyelonephritis at an incidence rate of 0.04/patient-year (PY) when compared with 0.02/PY in the placebo arm [42]. The most frequently encountered malignancies other than lymphoma and nonmelanoma skin cancers (NMSC) include breast cancer, colon cancer, lung cancer, melanoma, and prostate cancer Some of the common side effects include injection site pain and reaction, hypersensitivity, and gastrointestinal disturbances. In contrast, rare adverse effects result in the reactivation of latent tuberculosis, autoantibody production leading to a lupus-like syndrome, blood

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dyscrasias, congestive cardiac failure, and interstitial lung diseases [47].

Humira comes under category B for its use in pregnancy as animal studies have proven to be safe but controlled studies in humans are lacking [42]. Its use in lactation is based on the benefit–risk ratio as decided by the doctor because it is unknown if adalimumab is excreted in breast milk or absorbed systemically [42]. Its use in children has not been evaluated, and it should be used judiciously in geriatric population as there is already an increased risk of infections and malignancies in elderly [42].

18.2Certolizumab pegol

Figure:6. Certolizumab pegol

18.2.1Mechanism of Action and Indications

Certolizumab pegol is a monoclonal antibody (MAb) manufactured by Union ChimiqueBelge (UCB) Pharmaceuticals (Brussels, Belgium) and subsequently approved by the FDA in April 2008 for CD [48]. Certolizumab pegol is a recombinant antigen-binding fragment (Fab) antibody against TNF-α, which is conjugated to 40 kDa polyethylene glycol, thereby enhancing the bioavailability, drug stability, and plasma half-life [49]. The molecular mass of the Fab antibody fragment alone is 47.8 kDa. It is the only crystallizable fragment (Fc)-free PEGylated TNF-α inhibitor, so it does not fix complement or cause antibody-dependent cell-mediated cytotoxicity [49]. The FDA-approved indications are moderateto-severely active CD or RA, active psoriatic arthropathy, and ankylosing spondylitis [48]. It is available as powdered reconstitution form, which contains 200 mg of sterile, white, lyophilized powder, and as prefilled syringe, which is a single-use, 1 mL prefilled glass syringe with a fixed 25 G 1/2 in thin wall needle, providing a dose of 200 mg/1 mL [48].Upon single SC dose or intravenous (IV) dose, there was a predictable dose-related plasma concentration. There is a linear relationship between the dose given and the maximum plasma concentration (C_{max}) and the area under the curve over time. Though metabolism studies have not been performed in humans, animal studies suggest that polyethylene glycol polymers are excreted unchanged in urine and the terminal plasma half-life is 14 days[48].

18.2.2Side Effects

The common adverse effects include injection site reactions and infections mainly of the respiratory tract and urinary tract; some of which can be very severe due to immune modulation. Similar to the other drugs in the class, reactivation of tuberculosis, hepatitis B, and malignancies have been reported, but hypersensitivity reactions are rare [48]. Some of the other rare adverse effects reported in controlled trials are blood dyscrasias, optic neuritis, hepatitis, alopecia totalis, anxiety, bipolar disorder, suicidal tendencies, nephrotic syndrome, renal failure, menstrual disorders, and dermatitis. [48]. Certolizumab is a category B drug in pregnancy. Animal studies have proven no harm, but controlled human studies are not done [48]. Because of its large molecular weight, it neither crosses the placental barrier nor gets secreted in the

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milk. Even if present in milk, the biologics would get degraded in the intestinal tract, but the local effect in the mucosa is not known [48]. It is not recommended in pediatric use, and caution should be excised regarding its use in elderly due to the risk of malignancy and opportunistic infections.

19. Biologics and Biosimilar Treatment in Cancer

Rituximab

Figure:7. Rituximab

Rituximab is a chimaeric monoclonal antibody that binds the CD20 antigen on the surface of B cells with high affinity. It consists of light and heavy chain variable regions of a murine anti-human CD20 monoclonal antibody fused with human immunoglobulin light chain and 1 heavy chain constant regions [54]. Binding of rituximab to CD20 results in killing of B cells by and activating antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [55,56] and potentially also by inducing apoptosis [57].

19.1 Mode of Action: B Cell Killing Mechanisms

There are three possible mechanisms of action for antiCD20 antibodies that kill B cells

i) ADCC
ii) CDC
iii) induction of apoptosis

Indirect evidence suggests which is most important in vivo. ADCC mediated by FcgR-bearing effector cells (NK cells or monocytes/macrophages) has been demonstrated in animal models and in patients treated with rituximab [58].FcgRIIIa polymorphisms have been associated with increased rituximab binding by NK cells and monocytes and increased killing by ADCC [59]. Such polymorphisms have been shown to influence B cell killing and overall survival after rituximab treatment of patients with NHL [60-62]. A study of 12 patients with SLE suggested that the degree of B cell depletion by rituximab in SLE was also associated with FcgRIIIa genotype [63]. Several lines of evidence support a role for CDC as a mechanism of action of rituximab. The susceptibility of various B cell malignancies to CDC in vitro is consistent with the resistance of each malignancy to rituximab in vivo [64]. C1q deficient mice exhibit impaired B cell killing [64]. Complement consumption has been observed in patients with B-NHL during treatment with rituximab [65].

19.2 Side Effects of Rituxan

- Common side effects of Rituxan include:
- Headache,
- Stomach pain,
- Nausea,
- Heartburn,
- Flushing,
- Night sweats,
- Weakness,
- Muscle or joint pain,
- Back pain, or

20.Biosimilars In Rare Diseases

Orphan drugs are medicines used in the treatment of rare diseases, which are often associated with high treatment costs [50]. These drugs present a series of challenges regarding the development of biosimilars, including (a) the high costs of obtaining the RP for manufacturing purposes; (b) a reduced number of batches in order to determine batch-to-batch variability and to build extensive comparability data; (c) difficulties in obtaining a large enough population size for phase I and III trials; and (d) a heterogeneous population with the condition [51]. There are already some biosimilar orphans in development, ABP 959 and BOW080, which are two eculizumab-intended biosimilars. ABP 959 already has a registered ongoing phase III randomized controlled trial of paroxysmal nocturnal haemoglobinuria to compare the efficacy and safety with the RP and is planned to include 40 subjects [52]. As mentioned earlier,

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CTs are still required by the regulatory agencies to demonstrate biosimilarity. The FDA states that the nature and scope of the clinical study or studies will depend on the nature and extent of residual uncertainty regarding biosimilarity after conducting structural and functional characterization and, where relevant, animal studies [53]. In theory, these studies could not be presented if there is scientific justification that supports it [53]. Even though the initial and most essential step in demonstrating biosimilarity is the preclinical one, until now, all the biosimilar approvals were based on the totality of evidence including CTs.

21.Future Paradigm

Biologics off late as mentioned has become an important modality of treatment in IBD and the mainstay of therapy in patients with fistulizing or perianal CD [66]. However, the available treatment has certain drawbacks, the most important of which is 30% primary nonresponders [67]. Some patients transiently show response but then experience a loss of response (secondary nonresponders) [68]. Besides this, the available agents come with a myriad of serious adverse effects such as antibody formation, malignancies, reactivation of tuberculosis and hepatitis B as mentioned. Therefore, there is a need to develop newer agents that are more effective with fewer side effects and agents with novel targets and novel mechanisms of action. Some of these novel targets include Janus kinase inhibitors (eg, tofacitinib), IL inhibitors, antisense oligonucleotides (e.g. mongersen), sphingosine-1-phosphate (S1P) receptor agonist (eg, ozanimod), anti-integrin inhibitors, and so on [69]. Janus kinase inhibitors interfere with the signaling pathway that is needed for inflammatory process, whereas the antisense oligonucleotides prevent translation process by binding to mRNA from which the protein is usually synthesized [70,71]. S1P receptor agonists decrease the total lymphocyte count in circulation, especially CD4+ CCR7+ and CD8+ CCR7+ T cells [72].

22.Medical Uses for Biologics

Biologic drugs are used for treatment of numerous diseases and conditions, and are the most advanced therapies available. Some biologic drugs are used for the treatment of Crohn's disease, ulcerative colitis, rheumatoid arthritis, and other autoimmune diseases. Available biologics have revolutionized cancer treatment, delayed or reversed the course of immune related conditions, changed the lives of people with rare diseases, and have offered hope for many patients who previously had no effective treatment options for their condition.

Examples of medical uses for biologic drugs include:

- Various cancers
- Rheumatoid arthritis (RA)
- Psoriasis
- Diabetes[73].

23. Side Effects of Biologics

- Side effects of a biologic drug depends on the specific biologic drug, and method of introduction into the body.
- Most biologic drugs have the potential to cause allergic hypersensitivity reactions.
- Since some biologic drugs are given by injection, they also can cause injection site reactions.
- Other biologic drugs are given intravenously and can cause infusion reactions.
- These side effects are compiled from side effects listed for several biologic drugs. Each type of biologic drug has its own specific side effect profile and may or may not cause the side effects listed here.Common side effects of biologic drugs include:
- Allergic reactions
- Injection site reactions
- Weakness
- Diarrhoea[74].

II. CONCLUSION

Biosimilar are not generic; biologics are larger and more complicated than chemical drugs, due to the complexity of biological/biotechnology derived products the generic approach is scientifically not appropriate for biosimilar products. There is need to use well-designed clinical trials to establish bio similarity. The challenge with biosimilars is to know the differences which matter clinically. The specific product given to the patient should be clearly identified. Biosimilars have a very huge market in United States and the FDA agency has initiated many ways in developing the biosimilars and the research is still going on in order to make aneffective medicinal product as same as referenced biological products. Many bio similar products have been launched by the FDA agency and if the new implementations have been followed then the products may have a greater safety and efficacy of the forthcoming biosimilar products. As patents for older insulins will expire, the use of biosimilars will inevitably increase and is expected to have a major informedcomment as name impact

on diabetes care marketing of lower cost biosimilar insulins will probably be associated with better adherence and clinical outcomes, as already shown in other therapeutic.

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