

# Biologics and Biosimilars: An Overview

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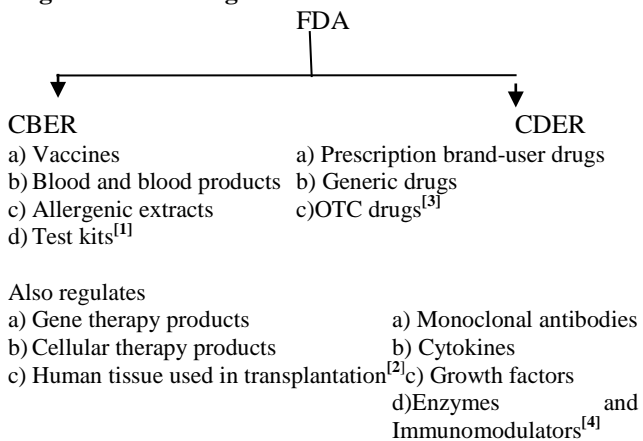
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## INTRODUCTION:

Biologics are the medicinal/therapeutic/preventive preparations composed or derived from living organisms either human, animal or microorganisms. Biologics are large protein based therapeutics. They are made up of proteins, carbohydrates, nucleic acids. It includes serums, vaccines, antitoxins, blood antigens, antibodies, recombinant proteins. Biologics may also be tissues or cells used in transplantation.

A biosimilar is a medicinal drug that is same to biologic product but it is not systematically similar to that of brand biologics. The brand product is also known as the reference product. A generic drug is chemically same to reference or brand-name drug.

### Regulation of biologics:



Biologics and biosimilars have to be held with a particular method such as refrigeration to avoid contamination and it is regulated directly to the blood stream, and this is also called as speciality drugs.<sup>[5]</sup>

### Comparison of biologic drug prices:

s.no	Country	2011	2015	2016
1.	United states	10% increase <sup>[6]</sup>	13% increase	\$105.5 billion <sup>[7]</sup>
		Biologics	2006-2014 increases upto 13.3% <sup>[8]</sup>	
2.	Europe	33% compared with original prices		
3.	Portugal	61% price reduction <sup>[9]</sup>		

### 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.<sup>[10]</sup> The main 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%.<sup>[11]</sup> So this the 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.

### 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.

This Hatch-Waxman act is essential and it gives a pathway for approval of generic drugs under FFDCA and not for the biosimilars under PHSA. Some of the biological products are controlled as drugs under FFDCA preferably than PHSA.<sup>[12]</sup>

When patent of a biological product was about to expire, there was a contest with generics has not fulfilled due to absence of FDA regulatory authority. Later GPhA, Generic Pharmaceutical Association (called as Association for accessible medicines) advocated FDA regulatory system.<sup>[13]</sup>

There were some deficiencies in the pathway to market the biosimilars in Europe because of some barriers. The first biosimilar product marketed in Europe is Omnitrope, which has a human growth hormone.

In the United States, the same omnitrope was declared in June 2006. This drug was approved by pfizer, SANDOZ “claimed that FDA had infringed its statutory commitment”<sup>[14]</sup>. The 505 (b) (2) pathway was helped to improve the drug omnitrope within 180 days.<sup>[15]</sup> When omnitrope was introduced in U.S, FDA indicated, that there was no pathway accepted for drug approval process, including the biologic products.

**Latest Approval pathway for biosimilars:**

In the year 2010 march, a new abbreviated approval process under the section 351 (K) of PHSA to the FDA authority in order to prove that the biologic product are highly similar with an FDA license. This was done under the Biologics Price Competition and Innovation Act (BPCIA) enacted as title VII of the affordable care Act ACA.<sup>[16]</sup>

They also implemented a process, to collect, user fees from industry. According to the BPCI act, a “biosimilar” product is compared to reference product, there should not be any major differences and the active compounds are clinically safe, with pure and potency.

FDA conducted a public meeting on November 2 & 3, 2010 for the approach of new pathway for the biosimilars, At that time FDA delivered the three draft guidance document and the final guidance on April 28, 2015<sup>[17]</sup>

document has been established on the agency website. Based on the 351(K), the company wanted to release their product into the market, and they filed an FDA application which includes the analytical studies, animal studies and a clinical studies.<sup>[18]</sup>

**Biosimilars approved by FDA:**

FDA has agreed with the seven biosimilar products in marketing, it has happened to adverse impact by brand-name manufacturers.

Delayed due to infringement of patent : eg; Erlezi, Amjevita & Cyltezo

Due to sue of Johnson & Johnson : eg; Remicade

Due to exclusionary contract : eg; Inflectra

Due to anticompetitive practice : eg; Renflexis

**BIO-SIMILARS Approved by FDA**

S.NO	Name	Active substance	Manufacturer	Indications	Approved date
1.	Zarixo	filgrastim-sndz	Sandoz	cancer, hematopoietic stem cell transplantation, neutropenia	06/03/2015
2.	Inflectra	infliximab-dyyb	Celltrion/Pfizer	psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, Crohn's disease, psoriasis, ankylosing spondylitis.	05/04/2016
3.	Erlezi	etanercept-szss	Sandoz	rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis	30/08/2016
4.	Renflexis	infliximab-abda	Samsung/Merck	psoriatic arthritis, rheumatoid arthritis, ulcerative colitis	21/04/2017
5.	Cyltezo	adalimumab-adbm	Boehringer Ingelheim	rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease	25/08/2017

**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.Inc .<sup>[19]</sup> Zarixo is similar as of neupogen.

**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-drug.<sup>[20]</sup>

**ERLEZI:**

FDA has released its third bio-similar product in U.S in the year 2016 august namely Erlezi which is a biosimilar of enbrel and that is formulated by Amgen. Based on the sandoz “ the acquaintance as depends upon a entire package of systematic, non-clinical & scientific data to justify the highly biologically similar to that of a licensed reference product.<sup>[21]</sup>

**AMJEVITA:**

FDA has approved its fourth bio-similar product in september 2016, namely Amjevita<sup>[22]</sup> which is a biosimilar of Humira.<sup>[23]</sup>

**FDA Matters on Biosimilars:**

a) Naming:

The drug product should be marketed by its logo name or any proprietary name or any proprietary name of that product.

CDER & CBER has given the “ Purple Book” which contains the lists of biosimilar and biological products that explains the date on which product is being licensed. Other than the proprietary name of a drug product sometimes non-proprietary name can also be utilized in labelling and regulating and controlling, the drug products that helps to identify the active pharmaceutical ingredients.

The FDA's also gives the reason in concerning its naming custom for biosimilars. In case of chemical drugs, the generic name is what we call as non-proprietary name.

The non-proprietary naming can be done in different ways:

FDA= Amalgamation i.e combination of core name + distinctive suffix composed of four lowercase letters<sup>[24]</sup>. eg: Filgrastim-xzwy<sup>[25]</sup>

WHO= Biological qualifier for biosimilar naming (extra & autonomous element used in concurrence with INN separately to differentiate a biological substance to aid in the prescription and dispensing of medicine.

It is formed of Four consonants 2-Letterblocks separated by 2-digit checksum<sup>[26]</sup>

b) Labelling:

The advised drug product should consists of a explained label which explains about the product safety and effectiveness.<sup>[27]</sup> FDA agreed labelling is also known as “Professional Labelling”, “Package insert or package circular”. Label should explain the indications, use, dosage forms, administration route, warnings and precautions, overdose etc..<sup>[28]</sup>

c) 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).<sup>[29]</sup>

d) Interchangeability and substitution:

It is supposed to give the same clinical effect as the mentioned product in any given patient and for a biological product operated more than once. Interchangeable products may be substituted for the reference products.<sup>[30]</sup>

Hatch-Waxman act plays a most important role in replacing a generic drug for a brand-name drug. A generic drug can be sited as interchangeable products for the reference products.<sup>[31]</sup>

EUROPE: EMA does not value about the exchangeable<sup>[32]</sup>. It evaluates the biosimilar products for the authorization purposes.

FDA: Regulates the drug products.<sup>[33]</sup>

Biosimilar User Fee Act (BSUFA)

In 1992, the FDA congress proceeded the Prescription Drug User Fee Act (PDUFA)<sup>[34]</sup>. It is based upon two concepts.

i) Performance goals: Target completion

ii) Use of fees : Only to support the activities of review<sup>[35]</sup>

The user fees were brought into existence up to 43% of FY 2016 FDA budget.<sup>[36]</sup>

BSUFA –I FDA accumulated six different types of fees from industry. The FDA has also generated the new product program called as Biosimilar product development program to generate fee revenue for new program.<sup>[37]</sup>

BSUFA-II enacted on December 18 2015. It agreement on FDA performance goals and procedures for FY018-FY022.<sup>[38]</sup> The product fee is renamed as BsUFA program

fee. The application fee will no longer be reduced by the progressive amount of BPD fees paid by the sponsor to that product.<sup>[39]</sup>

Federal Research & New Drug Development:

There was some therapeutic advancements which lies in between the fundamental and applied research which seems to be significant challenging<sup>[40]</sup>. FDA states origin of truly innovational drugs known as “New Molecular Entities”. These are some of the drugs which have not been approved by FDA previously.<sup>[41]</sup> In some cases, technologies are developed with some fund for study such as

- Recombinant DNA Technology
- Production and Chimerization, methods for antibodies
- Methods for bacterial production<sup>[42]</sup>

**CONCLUSION:**

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 a effective medicinal products as same as referenced biological products. Many biosimilars products has been launched by the FDA agency and if the new implementations has been followed then the products may have a greater safety and efficacy of the forthcoming biosimilar products.

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