Market Authorization Process of Bio-Similar Drugs in the U.S. and Europe

By

Gaurav

Dissertation submitted for the partial fulfillment of the

MBA Pharmaceutical Management

Academic year, 2016-2018

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TO WHOMSOEVER MAY CONCERN

This is to certify that **Gaurav** student of MBA Pharmaceutical Managementfrom The IIHMR University, Jaipur has undergone internship training at PlasmaGen Biosciences (p) Ltd. from **5th February 2018to 4th May 2018**.

The Candidate has successfully carried out the study designated to him during internship training and his approach to the study has been sincere, scientific and analytical.
The Internship is in fulfillment of the course requirements.

Iwish him all success in all his future endeavors.

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TO WHOM SO EVER IT MAY CONCERN

This is to certify that **Mr. Gaurav** has completed his project with **PlasmaGen BioSciences Private Limited, Bangalore** from Feb 05, 2018 to May 04, 2018. He was working on the project titled "**Market Authorization Process of Biosimilar Drugs in the U.S and the Europe**" under my guidance. During the training period his conduct was good.

I wish him success in all his future endeavors.

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15th May,2018

To whomsoever concerned

This is to certify that **Mr. Gaurav** (Employee code – 349) working with PlasmaGen Biosciences (P) Ltd as Executive – Sales & Marketing, has successfully completed his dissertation on the topic **"Market Authorization Process of Biosimilar Drugs in U. S and Europe"** during the period 5th February, 2018 to 4th May, 2018 under the supervision of Mr. Anant Bharne (GM – Sales & Marketing), Mr. Rakin Khan (Product Management Executive), Ms. Payal Shobhwani (Product Executive) and Mr. Soamodyoti Dey (Manager- Regulatory Affairs).

For PlasmaGen Biosciences (P) Ltd.,

M/s. Plasmagen Biosciences Pvt. Ltd. BANGALORE-18

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CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled **Market Authorization of Biosimilar in the U.S and the Europe** and submitted by **Gaurav**, Enrollment No.-0068, under the supervision of **Mr. Abhishek Dadhich** for award of MBA in Pharmaceutical Management of the University carried out during the period from **5st February 2018** to **4st May, 2018** embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other institute or other similar institution of higher learning.

Signature

Acknowledgement

Having been exposed to a fair amount of theoretical concept, I was looking forward to get a firsthand experience of a business organization and try to relate what I am encouraged to do at Institute of Health Management Research, Jaipur.

My Acknowledgement is incomplete without heartful thanks to Dr. Abhishek Dadhich, Internal Project Guide for showing me the right direction in doing this project.

I would like to give very special recognition to the countless other people who have been generous with their time, support & encouragement and have contributed to this project report in their own

Thank you
Gaurav MBAPM-08

Contents

Executive summary

The research is a result of extensive secondary research done over the period of time to throw light on the Authorization process of biosimilar in the United States and Europe . Only these two countries have been considered because they are the major hub of biopharmaceutical market where a lot of research and development is done by big corporations and thus have a well-defined regulatory process exist for approval of pharmaceutical products. The report will examine the status of the regulatory process of biosimilar in these countries .

List of abbreviations

EPO	Erythropoietin
FDA	Food and Drug Administration
BWP	Biological Working Parties
CHMP	Committee for Medicinal Products for human use
DNA	Deoxyribonucleic Acid
EMEA	European Medical Agency
EU	European Union
GMP	Good Manufacturing Practice
IgG	immunoglobulin
INN	International Non-proprietary Name
NCA	National Competent Authorities
Pharma	Pharmaceutical
PhRMA	Pharmaceutical Research and Manufacturers of America
PRCA	Pure Red Cell Aplasia
PTM's	Post Translational Modification
SAG	Scientific Advisory Groups
SBMP	Structural Biology of Membrane Proteins
WHO	World Health Organization
WP	Working Parties

INTRODUCTION

The, first generation of biopharmaceuticals manufactured using recombinant technologies was launched in the 1980s. And patents protecting them are now nearing expiration. Recombinant proteins current command premium pricing due, in part, to the high manufacturing costs associated with their production. Superior safety and efficacy profiles, and limited or absent competition. It has been estimated that by the end of the current decade, over $I0 billion month of biopharmaceuticals will have lost patent protection .

As with small molecule drugs the expiration of patents creates an opportunity for generic biologicals to enter in the market. Since biological product are complex and often heterogeneous, and cannot be replicated in a precise manner (as chemical compounds), the term 'generic' is not entirely appropriate. Instead, a variety of other terms is currently used: in Europe, the EMEA refers to 'biosimilar', whereas in the US, the FDA favours the term 'follow-on biologics'. Since the EMEA is ahead of the FDA in the application of a consistent and continued regulatory pathway for biosimilars, this Report will follow its lead in the use of relevant terminology .

In April 2006, the first two biosimilar proteins were approved by the EMEA. These were both growth hormones; Valtropin from Biopartners and Omnitrope from Sandoz; the latter product was also approved by the FDA .

Human growth hormone is a relatively simple, non-glycosylated protein, but the majority (70%) of approved recombinant proteins are glycoproteins, which require technically complex mammalian cell culture for their production .

Approved in 1989, Amgen's Epogen (epoetin alfa; recombinant human erythropoietin [EPO]) was one of the first recombinant human glycoprotein therapeutics. The EPO drugs, such as Epogen, have become best-sellers due to it their ability to relieve anaemia-related fatigue and they allow kidney patients to forestall regular blood transfusions. In June 2007, a significant milestone was reached in the development of biosimilar when the EMEA recommended three biosimilar versions of epoetin alfa for approval — Sandoz's Binocrit, Hexal Biotech's Epoetin alfa Hexal, and Medice Arzneimittel’s Abseamed .

Every successful biopharmaceutical is likely to face biosimilar competition when it comes off-patent and sooner or later every successful originator company will be involved or competing with biosimilars. The global development of biosimilars therefore represents a

critical part of the future of biotechnology. This Report will examine significant recent developments in the biosimilar market and will arm the reader with strategic information needed to face new opportunities as well as the challenges of the biosimilars revolution .

The role of patents the drug industry

The pharmaceutical industry has always relied on patents to safeguard the vast amount of investment, which is required to bring a drug to market. Patents underpin the modern biopharmaceutical industry and are for many biotechnology companies the key to survival .

Genes and proteins can be patented as composition-of-matter, processes or combinations of both. Processes can involve uses of nucleic acids, proteins or other composition-of-matter in industrial processes, or to predict, detector treat diseases. The gene for erythropoietin (EPO) was one of the first genes patented (it was isolated by working backwards from the protein product). The first patent was issued for isolated EPO protein having in vivo biological activity. There are now more than a dozen patents on EPO for new, novel uses of EPO, including a patent on a variant form of EPO .

The exclusive rights to exploit a patented invention are granted for only a limited period and, once this term has expired, the general public is free to use the invention. The European Patent Convention, which came into force in 1978, set a term of 20 years from the filing date for European patents .

The Patents Act 1977, which came into force on the same day, set the same term for UK national patents; this has become the international standard and is now observed by most countries. In the US, the US Patent Term Guarantee Act, which came into force on March 29th, 2000, ensures that the term of a patent is extended to at least 17 years if the prosecution of patent lasts longer than three years. Under the domestic Publication of Foreign Filed Patent Applications Act, Which took effect on May 29, 2001 US patent applications are now being published 18 months after filing .

A particular problem in the pharmaceutical industry is that the time required for obtaining FDA approval typically reduces the period of exclusivity provided by the patent protection. The 1984 Patent Term Restoration Act provides up to five additional years of patent protection beyond the basic term (i.e. 20 years from filing the application) to alleviate the unintended effects of the FDA approval process. Thus, the term of a patent protecting a drug may be extended for a period calculated based on the time needed for regulatory approval .

However this extended period may not extend the term of the patent to more than 14 years after the approval date. Only one patent may have its term thus extended. It is also, possible to obtain extensions of the standard, tent term in Europe and Japan .

Protein-based biopharmaceuticals

Biopharmaceutical's represent one of the fastest-growing segments of the pharmaceutical industry. There are currently more than 200 biopharmaceuticals on the market. Most are protein-based, although two nucleic acid-based products are now on the US/Europe market. Over 300 biopharmaceuticals are being investigated in clinical trials .

Most of the protein-based biopharmaceuticals currently on the market owe their existence, to the efforts of biotech companies, as opposed to big pharma, which has traditionally focused on small molecule drug candidates. Many protein-based drugs provide effective and safe treatments for chronic conditions and they now include therapeutic monoclonal antibodies as well as the more traditional recombinant proteins and peptides .

Drug delivery presents particular challenges because the products are generally hydrophilic in nature and of high molecular weight. Currently, most marketed therapeutic proteins and peptides are formulated Injectable for immediate release .

Review of literature: -

De Labry et al, 2013: Biosimilars in the European market

This research paper was published in the Generics and Biosimilars Initiative (GaBI) Journal. GaBI is an impartial peer-reviewed scientific journal; however, it should be acknowledged that the mission of GaBI is to raise the scientific status of generic and biosimilar medicines, and as such could be perceived to have a pro-biosimilar outlook. This updated report largely reinforced the Europe-wide trend for increasing biosimilar uptake and decreasing originator use continued into 2010. This suggests that the rate of biosimilar uptake in Europe was in fact accelerating during 2010. Once again, the large variability in individual country biosimilar uptake was commented upon. The market penetration figures for 2010 were claimed to range from the high level. Regardless of these discrepancies it remained evident that large differences exist in biosimilar penetration across countries .

Rovira et al, 2011: The impact of biosimilars' entry in the EU market

Describes the impact of biosimilar, introduction upon the European biological therapeutic, market between 2007 and 2009, The aim of the report was to provide an analysis of the characteristics of biosimilars and the development of the EU's biosimilars market with a view to improving EU Member States' understanding of the biosimilar market, including the likely impact on future pharmaceutical budgets. Information regarding the launch dates, prices per standard unit and sales volumes of biosimilar somatropin, epoetin and Filgrastim in 24 European countries and the United Kingdom. In relative terms, the market of biosimilars was determined to be quite small during this period. The authors reported that large inter-country variability in biologic use and biosimilar penetration was already being observed by 2009. The report concluded that the main appeal for biosimilar development in the European market will be its ability to reduce costs for consumers and payers, and that market penetration will depend on the product characteristics, stakeholder perception and appropriate incentives for doctors and patients .

Research Objective

• Criteria for approval of biosimilars in US and Europe

• Difference in approval process in these countries

Research Methodology

It is a secondary research and all the information has been taken from the published "scientific journals and other technical literature both paid and unpaid". The information is taken only from reliable sources.

Study type – Retrospective

Time duration - 5 Feb to 4 may

Type of data - Secondary data

Collection of data - Secondary data from article and journal (collected from The Impact of the Entry of Biosimilars: Evidence from Europe, International Journal of Drug Development & Research and internet sources (USFDA)

- Published journals
- Company websites
- Research papers

Inclusion criteria: -

- The drugs should be similar to the reference product in both the countries
- Phase III trials of biosimilar drugs should be performed in both the countries.
- Post marketing survey is done by internal and external authorities in both the countries.

Exclusion criteria: -

- Drugs which are not like to the reference product should be discarded.
- If the clinical trials are not performed they are not legally enter into the market.
- Product is not taken in this study only guidelines are explored in both the countries regarding biosimilar.

Analysis

In some diseases, proteins do not work properly, or they may be absent, and the introduction of biological drug (non-recombinant or recombinant) can improve symptoms or pathology. In the case of monoclonal antibodies (which are of the IgG format) and some fusion proteins, the therapeutic effect is obtained either by blocking a target, or by activating immune effector functions .

Proteins play crucial roles in almost every biological process. They are responsible in one form or another for a variety of physiological functions including: binding, transport and storage; enzymatic catalysis; structural support; immune protection; generation and transmission of nerve impulses; molecular switching, which controls cellular processes; control of growth and differentiation; and coordinated motion .

Genes can encode multiple proteins and a single protein can have multiple functions. The key to appreciating, how individual proteins function lies in an understanding of three-dimensional protein structure. Secondary and tertiary structure represents the most thermodynamically stable conformation for the protein molecule in solution, and results from non-covalent interactions between the various amino acid side-chains within the molecule and with the water molecules surrounding it. Different regions of the protein, often with distinct functions, may form structurally-distinct domains. Structurally-related domains are found in different proteins which perform similar functions. The exposed surface of the protein may also be involved in interactions with other molecules, including proteins. Protein-protein interactions, for example between sub-units of enzyme complexes or polymeric structural proteins, result in the highest level of organisation, or quaternary structure .

Post-translational modification of a protein can have a profound effect on its structure, and consequently affect its activity or function. Natural proteins can display a broad range of post-translational modifications (PTMs), but only a subset of these PTMs are associated with currently marketed therapeutic proteins. Glycosylation represents one of the most common but complex PTM modifications. Other PTMs, including carboxylation, hydroxylation, sulfation and amidation, are characteristic of some therapeutic products. Some therapeutic

Proteins may also require proteolytic processing (for example, for the production of biologically active insulin) and disulphide bond formation .

Glycosylation is a complicated, enzyme-directed site-specific process; mammalian cells typically use hundreds of enzymes to glycosylate proteins. Two types of glycosylation exist: N-linked glycosylation to the amide nitrogen of asparagine side chains and 0-linked glycosylation to the hydroxyl oxygen of serine and threonine side chains. N-linked glycosylation is particularly influential in determining protein stability, ligand binding, immunogenicity and serum half-life .

Glycosylation is characterized by heterogeneity, in that several glycoforms are usually generated. Heterogeneity arises from the addition of several oligosaccharides at N- and 0-glycosylation sites, together with heterogeneity of the oligosaccharide attached at any given site. Contributing to heterogeneity is variable-site glycosylation (in which some glycosylation sites remain unoccupied within a proportion of the glycoprotein molecules) and, more commonly, the occurrence of variable monosaccharide chain sequences. The glycoforms profile may differ depending on the tissue in which a particular glycoprotein is expressed in the same organism .

Biosimilars:

Biotechnological drugs have become an essential part of modern pharmacotherapy and are expected to reach a 50% share in the pharmaceutical market in the next few years. The expiry of patent protection for many original biotechnological medicines has led to the development of what are called biosimilars or follow-on biologics. Biosimilars attempt to copy the original technology leading to the production of innovative biotechnological medicines to obtain a product which is similar to the original one. The term `biosimilars' is in use in the European Union but in the US the term `follow-on biologics' is much more popular .

It is important to state that biosimilars are not (bio) generics. Biosimilars are attempted copies of existing biological medicinal products or protein drugs. However, they are made with a different cell line and a different manufacturing and purification process and the final product are not identical .

Biotechnological medicines are medicinal products of biotechnological origin that contain proteins derived from DNA technology, and hybridoma techniques. The biotechnologies use living organism such as plant and animal cells bacteria, viruses and yeasts for the production

of medicines. Biotechnological medicines extend our abilities to fight diseases, including many which in the past had been recognised as incurable. E.g. orphan diseases. Therefore, biotechnological medicines, which often replace or supplement a natural protein produced by the body, satisfy medical need previously unmet by chemical medicines. The rapidly growing class of biotechnological medicines includes such biological factors as cytokines. Hormones, clotting factors, monoclonal antibodies, vaccines and molecules used for cell/tissue based therapies. By definition biotechnological medicines are far more complex with regard to their structure than traditional drugs as is also their mode of action. While chemical agents usually, affect one or a few processes in the living organism .

The biotechnological molecule e.g. recombinant interferons, interacts with nearly 100 genes which makes its exact mode of action really difficult to predict and explore. It is estimated that so far almost 500 million patients worldwide have been helped by biotechnological medicines. By 2010 biopharmaceuticals will represent 50% of the pharmaceutical market, a leap from less than 20% in 2004. According to the recent PhRMA Survey, (2006) in addition to more than 120 now existing, 418 new biopharmaceuticals are being developed in almost all the areas of modern medicine but most in the field of oncology Infectious and autoimmune diseases and respiratory disorders .

Although chemical and biotechnological drugs are pharmaceutical products, they are completely, different in terms of their manufacturing structure and action. Chemical drugs have a well-defined structure whereas the structure of biotechnological medicines is much more complex and heterogeneous. This is reflected by the huge differences in a molecular weight of the molecules. For example the molecular weight of aspirin is 180 Da whereas that of interferon- β is 19,000 Da. Therefore the typical biologic drug molecule is 100-1,000 times larger than that of a conventional (chemical) small molecule drug. The former also possesses a fragile 3-dimensional structure unlike the will-characterised 1-dimensional structure of Chemical agents (chemical formula), which in most cases is easy to reproduce. In contrast the structure of biotechnological medicines is very difficult to characterize because they are products of living cells and usually contain a mixture of different isoforms .

PROPERTIES	GENERICS	BIOSIMILARS
SIZE	Small	Large
MOLECULAR WEIGHT	~150 Daltons	~150,000 Daltons
STRUCTURE	Simple and well-defined	Complex with potential structural variations
MANUFACTURING	Predictable chemical process to make identical copy	Specialized biological process to make similar copy
COMPLEXITY	Easy to fully characterize	Difficult to characterize
STABILITY	Relatively stable	Sensitive to storage and handling conditions
ADVERSE IMMUNE REACTION	Lower potential	Higher potential
APPROVAL REQUIREMENTS	Small clinical trials in healthy volunteers	Large clinical trials in patients

For example recombinant erythropoietin's (epoetin) differ in their carbohydrate structure and the number of sialic acid residues. Chemical drugs are also much more stable where biological drugs are sensitive to changes in physical conditions which require not only strict control of the manufacturing process but also appropriate storage at pharmacies and by the patients. Most chemical drugs are taken orally but almost all biologics are injected or inhaled because, as proteins, they are very sensitive to enzymatic degradation in the gastrointestinal tract .

The manufacturing process leading to the production of a biotechnological medicine is also much more complex. A controlled manufacturing process is intrinsically important to biotechnological medicines. Manufacturing biotechnological medicines is complex, lengthy and expensive. Each manufacturer must make their own unique cell line which is a clone to a single cell. The cell line is constructed using a unique proprietary DNA expression vector. The characteristics of the incorporation of DNA are unique for each cell. The cell line is evaluated for product integrity, activity and overall quality. In addition to product quality, the cell line is chosen based on expected performance in manufacturing such as growth and Viability. It is also clear that even minor variations could produce vastly different products, since the process is extremely sensitive to changes in both manufacturing and production .

Why Biosimilars Are Not (Bio) Generic

Chemical drugs are in most cases relatively easy to reproduce as their structure is precisely defined and expressed by the chemical formula. The unique multi-dimensional structure of the proteins and, in consequence, their complicated mode of action is never fully reproducible. In fact biotechnological medicines, even with the same molecular weight and produced by the same type of cells or microorganisms, can possess different pharmacokinetic and pharmacodynamics properties. This was well shown in the case of various α -epoetin which are manufactured in many Areas of the world breaking the patient-protection laws. Such substances cannot be called biosimilars as they do not meet the regulatory approval standards .

In fact after the expiry of patent protection for original biotechnological products the first biosimilars entered the market in 2006 after having been approved by the European Agency for the Evaluation of Medicinal Products (EMEA). Those first biosimilars were Omnitrope (biosimilar to Genotropin) and Valtropin (biosimilar to Humatrope). It is of note; however, that EMEA has recently rejected the biosimilar Alpheon (interferon- α) due a higher number of side effects and more frequent recurrence of the disease in patients treated with Alpheon than with its reference product Roferon-A, and the lack of appropriate validation of the manufacturing process and the test used to evaluate a potential immunologic response to the drug. Also multiple biosimilar products are under development for the European market and most of them are expected to be approved in the coming years .

For similar biological medicinal products, the so-called biosimilars, clinical trials are required rather than just the bioequivalence studies required to support the registration of a generic small molecule drug product. The EU Directive 2001/83/EC, as amended, stated that where a biological medicinal product which is similar to a reference biological product, does not meet the conditions in the definition of generic medicinal products the results of appropriate pre-clinical tests or clinical trials relating to these conditions must be provided. The challenge is to determine the exact nature of the non-clinical and clinical programme required to gain Regulatory approval. The applicant is encouraged to provide a detailed description of the strategy used to demonstrate the biosimilar and the reference product have similar profiles in terms of quality, safety and efficacy. The extent to which comparability can be proven will have quite an impact on how many non-clinical and clinical studies the biosimilar applicant will be required to conduct . The dossier submitted by the applicant to

the EMEA should cover all aspects of the comparability assessment and must include data on possible unwanted immune reactions to the therapeutic protein. Post-marketing pharmacovigilance plans are also expected to be included in the biosimilar dossier .

Biosimilars — Legal and Regulatory Framework in Europe and the US

The history of the development of regulatory laws in case of biogenerics is an exceptionally short one, but this is due to the fact that the issue virtually did not exist before expiry of patent protection for major biotechnological medicines on the market (i.e. epoetin, interferons, etc.) which took place mainly in the years 2004-2006. In fact the first recommendation for the approval of biogenerics was issued in 2004 by the European Parliament (European Directive 2004 27/EC). So far regulatory requirements for the approval of biosimilars have not been fully established and it is expected that the guidelines issued in 2005 by the EMEA (EMEA/CHMP/42832/2005) will undergo further changes in the near future. Most importantly the guidelines emphasize the problems of the complexity of biotechnological products, the likely consequences of changes in the manufacturing process, and also the issues regarding the quality of the product, its safety and efficacy. Although these regulations are an important step in the right direction there is still uncertainty on the specific issue of the documentation necessary for an approval. Also the specificity of the different biotechnological medicines is not fully recognized. It is interesting that the European Union with its EMEA is a pioneer in the regulations on biosimilars since the agency for drug evaluation in the US, i.e. the Food and Dog Administration (FDA) is still working on the final version of the guidelines on follow-on biologics. In fact many patents for original biotechnological medicines will expire later in the US than in the EU countries (e.g. epoetin-α). Unfortunately, despite the publication of the aforementioned EMEA guidelines there are still no such regulations at the national levels in the member countries of the European Union. The only exception is France where in 2007 Parliament adopted legislation covering biosimilar medicines transposing the European Directive 2004/ 27/EC .

The most important issue of the EMEA guidelines is the notion that biotechnological medicines cannot simply be copied as has been the case with conventional chemical medicines. However the guidelines accept minor differences in the active substance, such as variability in post-translational modifications. This recognition is crucial with respect to the safety of the new biotechnological products which will be approved in the near future .

The overview of the EMEA guidelines on biosimilars is given in figure 2

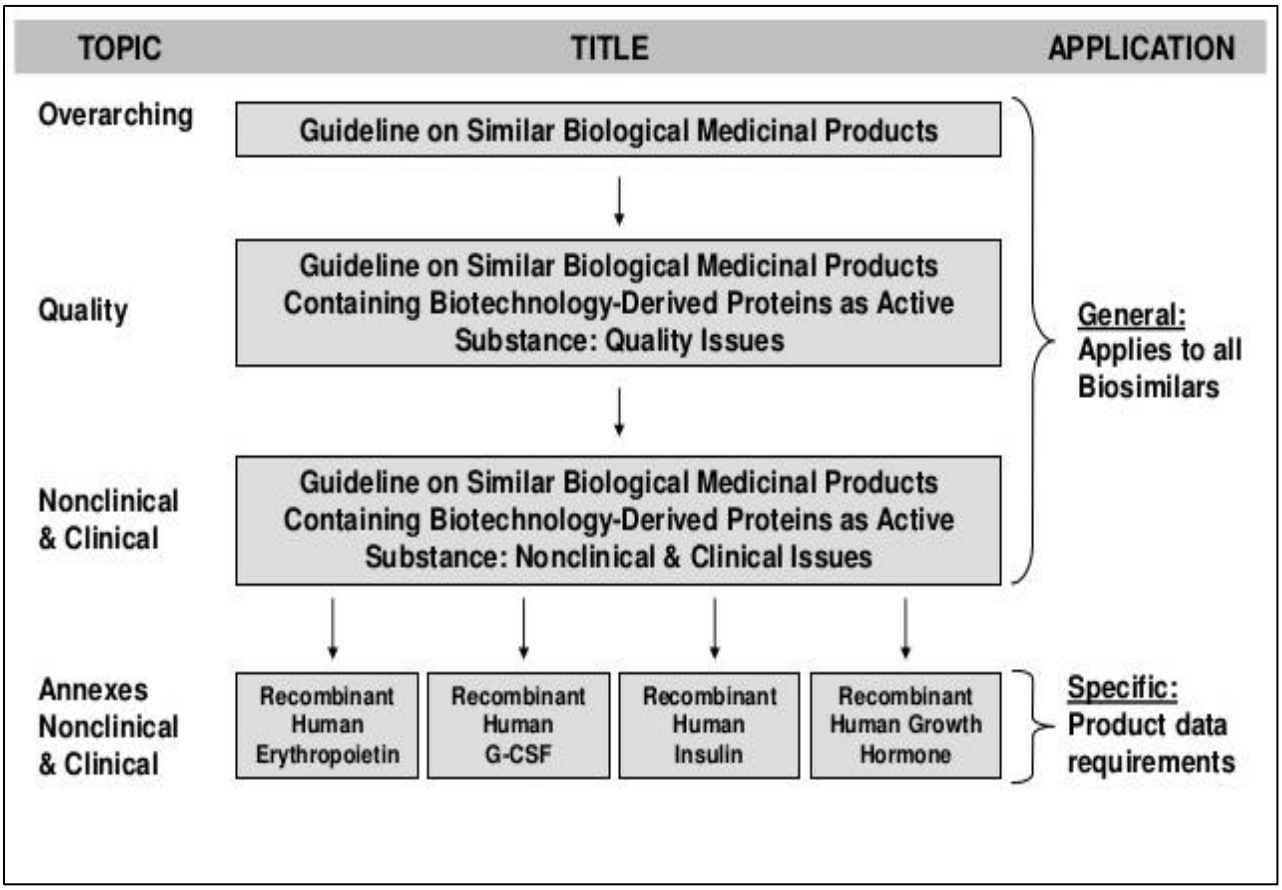


Figure: 2

The other important part of the guidelines indicates that biosimilar manufacturers need to identify a single reference product and conduct tests to demonstrate biophysical similarity. It is also obligatory for the manufacturer to provide sufficient, non-clinical (in vitro and in vivo pharmacodynamics and toxicological studies) and clinical data to demonstrate the clinical similarity to the reference product. In case of the biosimilar recombinant human erythropoietin for the treatment of renal anaemia, the new product will have to be tested in at least two efficacy studies in chronic kidney disease patient including one titration study in epoetin-naive patient (chronic kidney disease patients with subcutaneous administration of the drug) and one maintenance study in patients already treated with erythropoiesis - stimulating agents (chronic dialysis patients with intravenous administration of the product). Also a risk management /pharmacovigilance plan with attention paid to immunogenicity and potential are serious adverse events should be presented before approval. Furthermore an efficacy study with an appropriate indication is required if the reference product has multiple

indications. Biosimilar manufacturers may extrapolate to other indications if the mechanism of action is the same and if appropriately justified .

Identification of Potential Problems with Biosimilars

There are 4 major points to consider about biosimilars, i.e. safety, automatic substitution, naming and labelling/ prescription rules .

By definition biosimilars will only be similar but not identical to the product they seek to copy. In biotechnological medicine, each product has a unique safety profile dependent on its mechanism of action, unique manufacturing process, and composition (including by-products and impurities). The best example to illustrate that the safety profile of the biosimilar will not be identical to that of the reference product is that the recently approved biosimilar growth hormone Valtropin has different precaution and warnings than its reference product Humatrope. This is a likely consequence of the different cell lines used to produce both drugs (yeasts in the Valtropin and Escherichia coli In the case of Humatrope. Immunogenicity is the unique safety issue of biotechnological medicines. All therapeutic proteins have the potential to induce antibody responses. Such a response may include both an initial response to therapeutic protein and later a broad response including endogenous Proteins. In many cases no clinical consequences are found but in rare cases an antibody-related reaction can be serious and even life-threatening. Unfortunately the immunogenicity of biosimilars cannot be fully predicted using preclinical or non-human studies. For this reason clinical immunogenicity studies are required before approval. However, robust pharmacovigilance still remains a critical pan of the process .

There are various potential consequences of immunogenicity such as loss or enhancement of efficacy, neutralization of a native protein and general immune effects (allergy, anaphylaxis, scrum sickness) .The complication of epoetin therapy. I.e. PRCA, well known nephrologist, was caused by the production of neutralizing antibodies directed against recombinant erythropoietin. This complication was manifested by severe epoetin- resistant anemia which required blood transfusions, immunosuppressive treatment and eventually kidney transplantation. The story of PRCA was very instructive not only for nephrologists as its outbreak occurred more than 10 years after the introduction of epoetins on the market and was most likely caused by only a subtle change in the manufacturing process. Taking into consideration the complexity of the action of therapeutic proteins and the fact that most of them are relatively new drugs, it is likely that we are not yet aware of all complications of

their use (especially those that may develop after a long term treatment). As mentioned before, to minimize the risk of such unexpected reactions an appropriate pharmacovigilance is mandatory. The issue of pharmacovigilance is not unique to biosimilars but without any doubt it has been highlighted and exaggerated by their arrival. Pharmacovigilance should ensure the traceability of the products. Companies and regulatory agencies should distinguish one manufacturer's product from another. This is complex if biosimilars have the same international non-proprietary name (INN) as the innovator. Also adverse event reports are often incomplete. This holds especially true in cases of an automatic substitution. Uncontrolled substitution will confound accurate pharmacovigilance although it is obvious that occasional changes are inevitable or necessary in chronic therapy .

Substitution

The introduction of biosimilars raised many discussions whether the common notion of most practicing physicians those medicines with the same molecular structure are the same and therefore can be safely substituted still holds true. In the case of generics of chemical drugs the substances are identical and the risk of substitution is expected to be low. Despite those claims such risk still exists. Most practicing physicians realize that not every patient can tolerate well every medicine based on the same chemical compound. Medical literature provides many reports showing that this holds especially true in the case of drugs with a narrow therapeutic window (e.g. anti-epileptics, anti-arrhythmic or cyclosporine). The principle behind substitution of the traditional chemical drugs is that the original drug and its generic are identical and have the same therapeutic effect. In consequence generics are approved following a demonstration of bioequivalence, thus excluding any clinically significant differences in bioavailability. In the case of biosimilars the same substitution rules cannot be applied since biotechnological medicines are not identical .

The existing and future regulations should prevent inappropriate substitution. Inappropriate substitution could occur in two ways, i.e. the pharmacist overrides the prescription of the physician or the pharmacist chooses a product from the same INN class. In the first case the physician prescribes a brand or a specific generic and the pharmacist overrides with an alternative 'generic' without consultation with the physician. In the second case the physician prescribes by INN but does not specify manufacturer and the pharmacist chooses one of the products with the same INN. In practice such choice is based on the price of the drug or personal experience. In both cases, however, substitution can occur without knowledge or

consent of the physician. If it happened in the case of a biosimilar it would decrease the safety of the therapy. The future regulations regarding biosimilars should ensure the physicians that automatic generic substitution rules should not apply and any decisions to substitute one biotechnological medicine with another should be made with the knowledge and explicit prior consent of the physician .

Naming

The WHO INN system aims at identifying every medicinal product. This system is important for the clear identification, safe prescription and dispensing of medicines to patients, and for communication and exchange of information among health professionals and scientists worldwide. The INN is the 'technical' name for medicinal products. The generic versions of chemical medicines are assigned the same name, as they are identical copies of the reference product. The WHO is currently deciding whether biosimilars should be assigned a different INN to that of the original biotechnological medicine .

Labeling

From all that is written above it is clear that labels of originator and biosimilar products should be different. Physicians, pharmacists and patients should be aware of the clinical data available to support an introduction of a medicine to therapy. A summary of product characteristics should be transparent and clear. Reference products should be defined. Also data for approval should be described. Furthermore unique safety data should be included and substitution advice should be provided .

Agency approving the biosimilars in the US and the Europe

EMEA structure

European guidelines are being generated through consultation both within the EMEA and externally. Internally, the CHMP (Committee for Medicinal Products for Human Use) collaborates with several Working Parties (WP) through scientific advice and peer review. An important WP is the Biological WP (BWP) which operates closely with the Safety WP and Quality WP. The BWP's remit includes developing guidelines on quality and clinical requirements for biologics, and participation in the shaping of ICH guidelines. Externally, the EMEA/CHMP operates within a network including Scientific Advisory Groups (SAGs), the National Competent Authorities (NCAs) of EU Member States, patient groups, universities

and academic societies. Finally, the EMEA welcomes and encourages input from practicing physicians. Together, these groups aim to reach a consensus on medicinal products containing biotechnology-derived active substances .

EMEA biosimilars guidelines

EMEA, Committee for Medicinal Products for Human Use (CHMP) has issued a number of guidelines relevant to biosimilars that detail the requirements for market approval. Biosimilar products will be approvable if they have a reference branded market-approved product at which the data protection period has expired. In the US, the FDA does not have the legal authority to approve most follow-on biologics, and therefore has not yet issued a specific regulatory pathway. The EMEA guidelines advocate pre-clinical and clinical testing of biosimilars to demonstrate safety and efficacy prior to market authorisation, followed by tailored pharmacovigilance plans to monitor potential immunogenicity .

The EMEA guidelines cover a range of issues including manufacturing, measurement of comparability, physicochemical and biological analyses and clinical trial requirements. In addition to the pharmaceutical, chemical and biological data normally required for a generic drug application, applications for the market approval of biosimilar products require additional toxicological and other non-clinical and clinical data. TA goal will be to demonstrate that the biosimilar product is similar to the reference product in terms of quality, safety and efficacy. Products will be dealt with on a case-by-case basis, which reflects the complexity and diversity of the products under review. Updates to the guidelines will be published on the EMEA website (www.emea.europa.eu) EMEA/CHMP issued an overarching biosimilars guideline to set the scene and guidelines for the development of biosimilars covering quality, non-clinical and clinical issues, and immunogenicity for both biosimilars and innovator products that undergo a manufacturing change. In addition, EMEA/CHMP released four product class-specific guidelines or concept papers .

Brief details of the EMEA guidelines

The Guideline on similar biological medicinal products, which came into effect in October 2005, had the purpose of "introducing the concept of similar biological products, outlining the basic principles to be applied and providing applicants with a 'user guide' showing where to find relevant scientific information in the various CHMP guidelines, in order to substantiate the claim of similarity .

The Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues came into effect in June 2006. The aim of this document is to "lay down the quality requirements for a biological medicinal product claiming to be similar to another one already marketed". Importantly, this guideline addresses the requirements regarding manufacturing processes, analytical methods to assess comparability, factors to consider when choosing a reference product, and physicochemical and biological characterization of the SBMP .

***The Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance*:** non-clinical and clinical issues also came into effect in June 2006. This guideline "lays down the non-clinical and clinical requirements fills biological medicinal product claiming to be similar to another one already marketed". The non-clinical section addresses the pharmaco-toxicological assessment. The clinical section addresses the requirements for pharmacokinetic, pharmacodynamic, efficacy and safety studies, with emphasis on the evaluation of immunogenicity of the SBMP .

The Guidelines on immunogenicity assessment of biotechnology-derived therapeutic proteins came into effect in April .8. This guideline provides a broad overview of the immunogenic issues that biopharmaceutical companies must adequately address for the approval of a biosimilar product or when a manufacturing change occurs. The guideline discusses factors that might influence immunogenicity and the potential consequences of immunogenicity; the development, design and interpretation of non-clinical and clinical assays to evaluate the immunogenic potency of a product and its comparability to other products; and the implementation of a risk management plan. Many of the concepts discussed in the guideline will likely need to be adapted on a case-by-case basis .

Four product class-specific guidelines were issued for the development of biosimilars containing recombinant erythropoietin (EPO), somatropin, human insulin and human granulocytes colony-stimulating factor. These documents outline pre-clinical and clinical data requirements for marketing approval, describing the size of the trials required and the best indication for demonstrating equivalence for each product, in comparison with a reference product .

One example of the product-specific guidelines is the EMEA *Annex to the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues; guidance on similar medicinal products*

containing recombinant, erythropoietin. This guideline was effective from July 2006 and "lays down the non-clinical and clinical requirements for EPO-containing medicinal products claiming to be similar to another one already marketed". Interestingly, the regulatory requirements are more stringent for EPO than for the other recombinant proteins, reflecting its greater molecular complexity and clinical history, i.e. antibody (Ab)-mediated pure red cell aplasia (PRCA). Equivalent therapeutic efficiency with the reference product must be demonstrated in at least two randomised, parallel-group clinical trials, which are preferably double-blind. The document also states that patients with renal anaemia would be the best study population and that after an initial titration phase the comparative phase should be at least 12 weeks, followed by a maintenance study of at least three months. Therapeutic equivalence must be demonstrated for pre-dialysis and haemodialysis chronic kidney disease patients, and by both the intravenous and subcutaneous routes of administration. Clinical trials should involve at least 300 patients, and at least 12 months of immunogenicity data should be provided .

Recently, both France and Spain adopted legislation preventing the automatic substitution of a biological medicine for a biosimilar. This decision transposes into French law the European Directive 2004/27/EC governing the definition of generic and biosimilar medicines. Thus, French and Spanish law now forbids the replacement of one biological medicine for another at the pharmacy without the express consent of the prescribing physician .

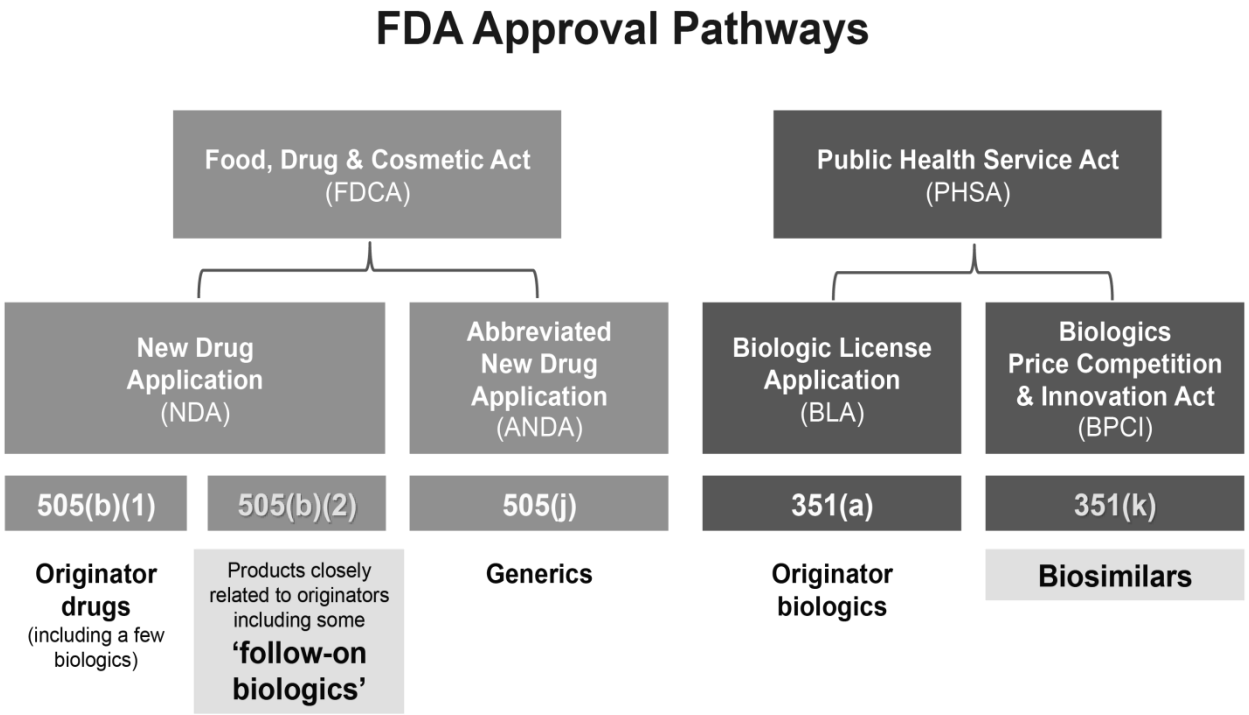
Post-marketing surveillance

The onset and incidence of immunogenicity is unpredictable; therefore, extended post-marketing surveillance (pharmacovigilance) to monitor potential immunogenicity is very important. Biosimilar guidelines from the EMEA state that a pharmacovigilance plan to address immunogenicity and potential rare adverse events should be included in the data package submitted for the product approval. The term “pharmacovigilance” describes the detection, assessment, understanding and prevention of adverse effects after the launch of a product onto the market. As already discussed previously, there are important lessons to be learned from the experience with Eprex and Ab-mediated PRCA. Although the innovator product had been in use for years, it was some time before the link between the relatively small modification in the product formulation and the increase in the number of PRCA cases was established .

Regulatory framework in the U.S

As biological medicinal products are more complex in regards to e.g. structure, stability and manufacturing processes than small molecule drug products, a separate approval pathway was necessary, taking into account the complexity of those molecules. Finally, in 2010 the Public Health Service Act (PHS Act) was amended in section 351 by introducing an abbreviated licensure pathway under section 351(k) for biological products for which at least biosimilarity or even interchangeability is demonstrated in comparison to a biological reference product which has been approved by the FDA under 351(a) of the PHS Act. The Biologics Price Competition and Innovation (BPCI) Act, being part of the Patient Protection and Affordable Care Act (section 7001 - 7003), was enacted on 23rd March 2010 .

The BPCI Act lays down the legal basis for the "Licensure of biological products as biosimilar or interchangeable". In section 351(i) of the PHS Act (42 U.S. Code §262(i)) the terms "biological product", "biosimilarity", "interchangeability", and "reference product" are defined . Biosimilarity" means "that the biological product is highly similar to the reference product not withstanding minor differences in clinically inactive components; and there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product



The overview of the FDA guidelines on biosimilars is given in figure 3.

A biological product can be deemed “interchangeable” to a reference product in case it is determined to be “biosimilar to the reference product; and it can be expected to produce the same clinical result as the reference product in any given patient. [Furthermore,] the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch. [Then,] the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product .

A “reference product” is defined as “the single biological product licensed under subsection 351(a) of the PHS Act against which a biological product is evaluated in an application submitted under subsection (k) .

Section 351(k) of the PHS Act (42 U.S. Code §262(k)) lists the requirements concerning the marketing authorization application (MAA), i.e .

- The required content which can be amended in case the FDA considers certain data to be superfluous for assessment
  - Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components .
  - Animal studies (including the assessment of toxicity); and
  - A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.
- The requirements for determination of interchangeability
- Prerequisites concerning the reference product
- Regulations in terms of data/market exclusivity for the first interchangeable biologic product and for the reference product
- Provisions for preparation of guidance documents by the FDA

Furthermore, section 351(l) of the PHS Act deals with handling of patent issues, including

- Provision and handling of confidential information including timelines

- Provision of lists and descriptions of patents
- Handling patent disputes, infringements, and newly issued or licensed patents
- Notice of commercial marketing and preliminary injunction
- Limitation on declaratory judgment action

In addition, the BPCI Act amends Section 505(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S. Code § 355c - Research into paediatric uses for drugs and biological products) and specifies that a biosimilar biological product shall be considered to have a new active ingredient with regards to the requirement for conducting clinical studies in paediatric populations. In contrast, "an interchangeable biologic product" does not have a new active ingredient and therefore does not require additional studies in paediatric populations. The provisions regarding paediatric studies of biological products including provisions for market exclusivity are specified in section 351(m) of the PHS Act (42 U.S. Code § 262) as amended by the BPCI Act .

The BPCI Act also emphasizes that all biologics have to seek licensure through 351 of the PHS Act as amended. However, exceptions are laid down for products where a biological product of the same product class has previously been licensed under 505 FD&C Act (21 U.S. Code § 355) until the date of enactment of the BPCI Act. For these biological products, the applicant may file an application under 505 FD&C Act within the next 10 years from enactment of the BPCI Act. That does not apply to biological products where a potential reference product had already received licensure under 351(a) of the PHS Act. 10 years after enactment of the BPCI Act, all biologics previously approved under the 505 FD&C Act shall be deemed to be licensed under 351 of the PHS Act (section 7002(e) of the BPCI Act) .

QUALITY ASSURANCE:

Both originator reference products and biosimilar medicines are made under carefully, controlled conditions to ensure the products are consistent and of the required quality. This is known as Good Manufacturing Practice (GMP) .

In the European Union, GMP inspections for all biopharmaceuticals -originator reference Products and biosimilar medicines - are coordinated by the EMA and performed by the national regulatory agencies .

There are three levels :

- Routine GMP inspections of manufacturing sites to ensure that medicines arc produced, safely and correctly .
- Pre-Approval Inspections (PAI) for GMP compliance prior to the approval of new medicines for marketing if there are specific issues identified during the approval process .
- Unannounced inspections .

All European pharmaceutical companies are legally required to monitor the use and effects of all their medicines. They must have systems in place to detect, assess, understand and endeavour to communicate any adverse reactions or any other medicine-related problem. The science and activities of these processes are known as “Pharmacovigilance". As part of the pharmacovigilance process each manufacturer must provide a description of their pharmacovigilance system before its medicine is approved. This system is inspected by the regulatory authorities. As part of the pharmacovigilance process cash manufacturer must provide a description of their pharmacovigilance system before as medicine is approved. This system is inspected by the regulatory authorities .

In addition, for every new medicine, including biosimilar medicines, a Risk Management Plan (RMP) must be submitted and agreed to by the EMA. The RMP describes what is known about the safety of the medicine and outlines how the manufacturer will further monitor and fill any gaps in knowledge as well as any measures needed to minimise any risk from the medicine. This plan must be regularly updated throughout the entire time the medicine is marketed and used”. “Once marketed, pharmaceutical companies must also continuously evaluate the information on the benefits and risks of their medicines

Considerations in Establishing a US Approval Pathway for Biosimilar and Interchangeable Biologicals

on 23, March 2010 the US health care reform legislation, the Patient Protection and Affordable Care Act (PPAC), was signed into law, providing a legal pathway for approval of biosimilar products via the Biologics Price Competition and Innovation Act of 2009 (BPCI). Since that time FDA has been working on implementation .

Overarching Principles

Patient safety is paramount, and the safety of biosimilars can ultimately only be established through clinical trials followed by a post-marketing risk management program. The more

complex question is the extent to which comparative efficacy needs to be established through clinical vials to demonstrate bio-similarity and interchangeability. If the preclinical and phase I programs already demonstrate biosimilarity, there may be no need to repeat the entire original clinical program since the structural and biological similarity would have already been demonstrated to the reference product. Thus, only certain clinical data may be required to confirm similar safety as well as efficacy claims .

A key principle underlying our thinking for streamlining biosimilar development programs is to acknowledge that, unlike when a new biological entity is first developed, much is already known about the structure-function relationships, mechanism of action, and safety and efficacy profile of the innovator product in specific patient populations. In addition, there has been a vast improvement in physico-chemical and biological methodologies such as MS-MS, chemo-luminescence and surface Plasmon resonance, that can be used for characterization of therapeutic proteins and which can accurately detect structural or functional differences between the products. Furthermore this progress continues apace with the developments of methods such as hydrogen/deuterium exchange nuclear magnetic resonance which can monitor dynamically the three dimensional structure of proteins .

Another key concept is the "totality of the data." by this; we mean that physico-chemical and biological characterization, coupled with nonclinical and clinical pharmacological data, Already provided a solid basis for establishing biosimilarity. It is important to balance the value of relevance of these data against the need for clinical safety and efficacy data particularly were minor or modest differences between the biosimilar and reference products are unlikely to translate into meaningful differences in the clinic .

This approach is similar to that applied to comparability testing data from developers of new biological entities following major changes in manufacturing. While for minor process changes the innovator can draw heavily and successfully on previous experience, major changes such as the introduction of new expression construct closely parallel the challenges of developing biosimilar .

Comparison of US and Europe biosimilar Regulation and Litigation

While the biosimilar regime is brand-new and untested in the United States, the Europe community has more than five years' experience with a similar program. We expect the FDA to look to the European Medicines agency (EMA) as it begins to define the requirements for a

"section (k)" abbreviated biosimilar marketing application. Of course, the specifics of the rules and regulations differ between the jurisdictions. The following is a high-level comparison of the regulatory and patriot litigation regimes between the U.S. and Europe .

• Definition of Biosimilar

US; the biological product is highly similar to the reference product not withstanding minor differences in clinically inactive components; and there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product 41 U.S.C. §262(i)(I)

Europe; Biosimilarity is not explicitly defined, but is situational, "whether a medicinal product would be acceptable using the 'similar biological medicinal product' approach depends on the state of the art of analytical procedure, the manufacturing processes employed, as well as clinical and regulatory experiences CHMP/437/04". "Comparability studies are needed to generate evidence substantiating the similar nature, in terms of quality, Safety and efficacy, of the new similar biological medicinal product and the chosen reference product authorise in the community. "CHMP/427/04

•Exclusivity Period for Reference Product

US; A section (k) application may not be filed until 4 years after reference product approval. A biosimilar may not be approved until 12 years after reference product approval, 42 USC 262 (k) (7) .

Europe: "8+2+1." A biosimilar application may not be filed until 8 years after the reference product approval. A biosimilar may not be approved until 10 years after reference approval. The market exclusivity may be extended by an additional year if the reference product sponsor obtains approval fix a second significant new indication during the data exclusivity period .

• Establishing biosimilarity

US: Required data comparing the applicant's biological product to a reference product :

- Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components

- Animal studies (including toxicity)
- A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) those are sufficient to demonstrate safety, purity, and potency
- Identity of mechanism of action, if known. 42 USC §262(k) (2) (a) (1)

Europe: "An appropriate comparability exercise will be required to demonstrate that the similar biological and reference medicinal products have similar profiles in terms of quality, safety and efficacy." EMEA/CHMP/BMWP/42832/2005

Under the relevant guidelines, the comparability exercise will include :

- **PURIFY**. The purity and impurity profiles of the active substance and medicinal product should be assessed both qualitatively and quantitatively by a combination of analytical Procedures for both reference and similar biological medicinal products. Both product and processes-related impurities should be examined. EMEA/CHMP/BWP/49348/2005 .
- **PHYSIOCHEMICAL PROPERTIES**. A physicochemical characterisation program should include a determination of the composition, physical properties, and primary and higher order structures of the active substance of the similar biological medicinal product. An inherent degree of structural heterogeneity occurs in proteins due to the biosynthetic process, therefor, the similar biological medicinal product can contain a mixture of post-translationally modified forms. Appropriate efforts should be made to investigate and identify these forms. EMEA/CHMP/BWP/49348/2005 .
- **BIOLOGICAL ACTIVITY.** The comparability exercise should include an assessment of the biological properties of the similar biological medicinal product and the reference medicinal product. Biological assays using different approaches to measure the biological activity should be considered as appropriate (i.e. depending on the biological properties of the product). EMEA/CHMP/BMWP/49348/2005 .
- **PRECLINCAL.**
  - In vitro studies: Assays like receptor-binding studies or cell-based assays
  - In vivo studies: Animal performed in a species known to be relevant and employ state of the art technology to study: Pharmacodynamic effect and Non-clinical toxicity

o other routine toxicological studies such as safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies are not required for similar biological medicinal products EMEA/CHMP/BWP/42832/2005 .

- **CLINICAL TRIALS** . Usually comparative clinical trials will be necessary to demonstrate clinical comparability between the similar biological and the reference medicinal product. EMEA/CHMP/BMWP/42832/2005
- **IMMUNOGENICITY** . In view of the unpredictability of the onset and incidence of immunogenicity, long term results of antibody monitoring is required EMEA/CHM /BMWP/42832/2005 .
- **Interchangeability**

  US; the biological product may be substituted for the reference product without the mention of the health care provider who prescribed the reference product" §262(i)(3). It is unclear how, this Provision relates to state regulation of generic substitution by pharmacies .

  Europe: No equivalent to the "interchangeable" designation. No automatic substitution for biologics in the EU. Countries by country regulation over pharmacy substitution, for example biologics are excluded from substitution in Spain, no substitution list in Franc .
- **Incentives**

  US: There is no incentive to be the first to file section (k) application as a biosimilar. There is a market exclusivity incentive to be the first to file as art interchangeable product. The exclusivity period varies depending upon the status of any related patent litigation. §262(k) (6)

  Europe: There is no exclusivity incentive for filing a biosimilar marketing authorization application .
- **Guidance's**

  US: The FDA is authorized to issue "general or specific" guidance to industry to define the requirements for proving biosimilarity. §262(K) (8). Guidance's are not required before applications are filed. The FDA may determine that a particular product class (other than recombinant proteins) does not allow approval of an application for a license under the biosimilar pathway. No guidance has been

proposed yet. The FDA held its initial public meeting on guidance in November 2010 .

Europe: The EMA has published to a number of the general and specific guidance document, including :

- Guideline on similar biological medicinal products. CHMP/437/04
- Guideline on similar biological medicinal products combining Biotechnology-derived proteins as active substance: Quality issues. EMEA/CHMP/BWP/49348/2005 .
- Guideline on similar biological medicinal products containing Biotechnology-derived proteins as active substance: Non-clinical and clinical issues EMEA/CHMP/BMWP/42832/2005 .
- Guidelines on specific biologic classes, including
  (I) insulin EMEA/CHMP/BMWP/32775/2005
  (2) Somatropin EMEA/CHMP/BMWP/94528/2005
  (3) Granulocyte-colony stimulating factor EMEA/CHMP/BMWP/31 329/2005
  (4) Erythropoietin EMEA/CHMP/BMWP/301636/2008 .
- Draft guideline on monoclonal antibodies EMEA/CHMP/BMWP/403543/2010 .
- Concept papers on low-molecular weight hepatitis EMEA/CHMP/BMWP/496286/2006, and interferon alfas EMA/CHMP/BMWP/86572/2010

- **Pre-litigation procedure**

US: Special pre-litigation procedure requiring (I) notice of marketing approval application by the biosimilar applicant; (2) disclosure of the biosimilar application to the reference product sponsor; (3) exchange of lists of patents where a claim of patent infringement could reasonably be asserted by the reference product sponsor; (4) exchange of infringement claims and defences; and (5) dispute resolution negotiations before an infringement suit can be filed. Approximately 200-300 days will elapse between acceptance of the biosimilar application by the FDA and filing of any patent infringement lawsuit .

Europe: No special pre-litigation procedure. No notice by biosimilar applicant required to reference product sponsor. But notice is sometimes given by follow-on manufacturers in order to allow patent issues to be addressed and thereby minimizing the chance for an injunction inherent in an at-risk launch .

- **Jurisdiction**

  US: Pre-clinical and clinical investigation in preparation of a regulatory filing is exempt from infringement. 35 U.S.C. 271(e)(1). Filing of a section (k) biosimilar application is a constructive infringement sufficient for U.S. District Court jurisdiction 271(e) (2) (C) .

  Europe: conducting necessary trials or studies for biosimilar approval is not infringement. Article 10(6) of Directive 2004/27/EC ("Bolar exemption"- adopted in various forms by member states).Moreover, unlike the US, filing an application for marketing approval is not a constructive infringement. Declaratory and injunctive relief, however, may be available before actual biosimilar sales .

  Thus, on the regulator side, FDA can and should rely on EMA's experience in comparing proposed biosimilars to reference products. Unfortunately, on the patent side, because of the significant differences in the legal frameworks, US biosimilar litigation is terra incognita .

Selection of Reference Products

In Europe, at the present time, pivotal safety and efficacy of biosimilars need to be demonstrated. Against reference products approved and sourced from within the European Economic Area (EU plus Norway, Iceland and Liechtenstein) as comparator. If the US were to take a similar position and mandate that therapeutic equivalence trials be performed against a US-sourced reference product, this would lead to redundant replication of large phase 3 studies. This, in turn, could raise ethical concerns and would likely have a negative impact on the cost and viability of biosimilars in the US .

Thus, we consider that in cases where it cannot be proven that ex US-sourced reference product and reference product available in the US originate from the same production process and are released to the same specifications, it thought to be quite sufficient to confirm their similarity using state of the art analytical methods to compare both physico- chemical and biological (in vitro and in vivo) properties across these batches. In these circumstances, it thought to be acceptable to support marketing approval using phase 3 safety and efficacy studies against reference products sourced from this ex US source. Where there is the potential for uncertainty, human pharmacokinetic (Pk), Pharmacodynamic (PD) equivalence data should, in general, be adequate to confirm the comparability of reference product derived from international sources with US- sourced reference product .

Certainly, if differences were to exist between the differently sourced reference product , these differences would most likely be detected using the more sensitive physico-chemical and biological test methods, together, where necessary and feasible, with comparative PK/PD assessment in humans, than by the much less sensitive approach of safety and efficacy clinical trials. Therefore, the combination of physico-chemical and biological testing, coupled where, relevant with clinical PK/PD assessments, generally represents the most rigorous way to show comparability between the biosimilar candidate and reference products sourced from regions outside the US .

The data package bridging the biosimilar candidate drug to both h US and ex US-sourced reference products that would result from the above-mentioned combination of in vitro (physico-chemical/biological) and in vivo (human PK/BE) studies is quite similar to what has been required to support non-trivial changes to the manufacturing process that may be introduced late in clinical development or post-approval .

In many cases, the innovator company has not been required to perform even a formal bridging PK equivalence study, due to the perceived strength of the in vitro comparability data .

Extrapolation between Indications

Clinical trials on new biological entities were designed to demonstrate efficacy against placebo; however, placebo trials will often no longer be viable, at least for serious and life-threatening diseases for which there now will exist effective therapies. Therefore, for follow-on biologics, it is necessary to perform non-inferiority or equivalence trials .

In order to ensure adequate retention efficacy of such trials generally need to be several-fold larger than the initial placebo-controlled trials performed by the originator. If equivalence trials were to be performed in each indication, the development program would thus need to be many folds larger than the original program, negating the whole concept of a biosimilar Pathway .

As long as the mechanism of action is relatively well understood across indications, it should be possible to demonstrate comparable safety and efficacy of biosimilar and reference product in one adequately sensitive indication, and then taking into account all prior

nonclinical and clinical comparability data, to conclude therapeutic equivalence for all indications, i.e. extrapolate the results across multiple indications .

By adequately sensitive, we mean a patient population where differences between the biosimilar and reference product, if they exist, are most likely to be detected and that generates a dataset with a relatively low coefficient of variation .

Even in cases where the target indications are highly diverse, for example, as is the case with many approved monoclonal antibody products, Extrapolation should be considered reasonable .

Monoclonal antibodies can theoretically exert multiple effects in vivo, and the relative contributions of these effects might well not be the same across indications. Nevertheless, if all relevant biological effect is understood to be involved in generating a therapeutic effect in the selected target population, trials in this population should be an adequate indicator for general therapeutic equivalence .

Primary Endpoints

For those innovator products where there exists a strong and well defined pharmacodynamic effect, for example, as with insulin and G-CSF, PD markers may trump clinical endpoints in term of precision and could be equally or more relevant .

When using PD endpoints as a surrogate for clinical endpoints, the PD effect needs to be dose-sensitive and correlate to the therapeutic effect. If this correlation can be adequately demonstrated from the literature, then a PD marker will be more sensitive measure of efficacy than a clinical endpoint .

The use of surrogate clinical endpoints can also play a key role in the development of biosimilars. For example, in oncology, overall survival is considered the gold standard, but this is often not a practical endpoint for non-inferiority trials. Moreover, demonstration of survival becomes extremely challenging as new next-line become available to treat disease progression. Progression-free survival is perhaps best endpoint, but can also take many years to demonstrate equivalence. Therefore, a more practical, approach would be to use a response parameter as the primary endpoint, and to include progression-free survival, and where possible, overall survival, as secondary endpoint. There is already regulatory precedence for this, for example, in the approval of liposomal doxorubicin versus doxorubicin .

Equivalence Margin/Non-Inferiority Margin in Therapeutic Trials

The draft FDA guidance for industry on non-inferiority trials states that it "is common in NI trials for the test drug to be pharmacologically similar to the active control. (If they were not pharmacologically similar, an add-on study would usually have been more persuasive and more practical). In that case, the expectation of similar performance (but still requiring conformation in a trial) might make it Possible to accept a single trial and perhaps could also allow less conservative choices in choosing the non-inferiority margin.

Clearly in the case of biosimilars, not only are the pharmacological principles similar, but the molecules are structurally highly similar if not identical. Furthermore, data will have been generated to demonstrate equivalence with respect to receptor binding, biological properties, PK and possibly PD profiles. There will, therefore, often be no scientific reason to expect that comparable efficacy would not be achieved for a biosimilar product, with the possible exception of the effect of enhanced immunogenicity, which cannot be predicted through physico-chemical, biological and single-dose clinical testing and needs to be evaluated in a sensitive patient population. For biosimilars, it is the totality of data that needs to be assessed in order to judge therapeutic equivalence, and a confirmatory clinical trial represents just one element of the biosimilarity program. Thus, acceptance of a less conservative therapeutic equivalence margin should be reasonable, so long as some level of efficacy over putative Placebo is demonstrated and immunogenicity is measured directly with no evidence suggesting a different immunogenicity profile

Non inferiority or Equivalence Design

On the issue of whether to perform a non-inferiority or equivalence trial for demonstration of biosimilarity, where a protein exerts a direct physiological effect and there is a close correlation between dose and therapeutic effect—as is the case for produces such as insulin, G-CSF, epoetin and somatropin—clearly supra-activity will be a safety concern and equivalent trials are likely essential .

However, in the case of monoclonal antibody products clinical effect in inflammatory disease or oncology is generally measured in terms of the proportion of responders and not as a physiological effect. Under these circumstances, it would seem more appropriate to perform non- inferiority trials, since an increase in responders. I.e. crossing the upper bound of the

selected equivalence margin should not in itself be a reason to reject a product as biosimilar, especially given that safety would be monitored independently .

It should be stressed that this does not mean a biosimilar can claim superiority, and, in any case, to conclusively demonstrate superiority between two products, which are ostensibly similar, would require a far larger study program than might be required to show non-inferiority. If there was a trend to superior efficacy, this would at the very least need to be explained; one such possibility is reduced immunogenicity, which is certainly a possibility even for two highly similar molecules, due to aggregation or the contribution of impurities, which can act as adjuvants .

The summary table for the Comparison of US and Europe biosimilar Regulation and Litigation

Approving agencies	**US(FDA)**	**EU(EMA)**
Regulatory system	Biologics price competition and innovation act, 7 guidance	Overarching guidelines, very developed with the product-class specific guidelines
Reference products	Must already be licences in US or in another market and can be proven similar to U.S approved reference products	Must already approved by EMA or a market with proven similar regulation
Safety and efficacy	No “clinically meaningful” difference in the purity , potency and safety from the reference product	Risk base and scientific case-by-case basis, requires “similar efficacy and safety “as the reference products
Interchangeable	biosimilar may substitute from the reference product without interference of the healthcare provider	Interchangeability of the product is left up to the member states of EU, not the EMU
Exclusivity period	12 year of exclusivity to the pioneered product	10 year of exclusivity to the pioneered product

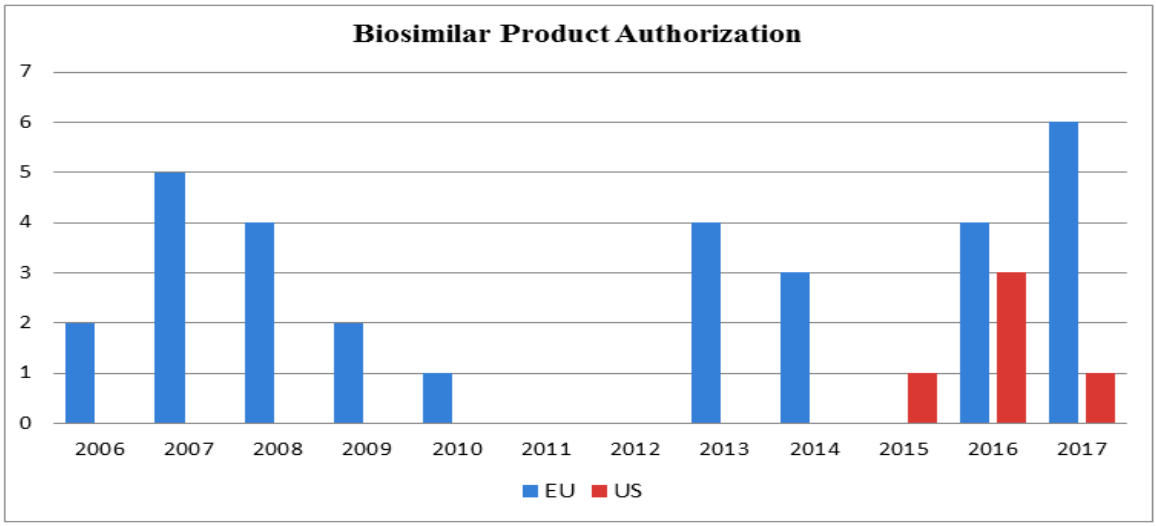
First biosimilar approved	2015	2006
Approving process	Abbreviated, compared with reference product	Abbreviated, compared with reference product
Specific guidance for specific therapeutic biosimilar category	None yet by FDA	Multiple annexes established by EMA
Pharmacovigilance	FDA encourages post-marketing safety monitoring	All product require pharmacovigilance plan that can be identified product name and batch
Naming	Determined by FDA with manufacture (proposed naming convention of INN plus	Same INN ; distinct brand names
Legislation/guidelines	No guidelines yet released by FDA, but BPCI act signed into law in 2010.	EMA has issued both general (overarching)and specific guidelines

How the U.S compares to Europe on Biosimilar Approvals and products in the Pipeline

Since 2005, the biosimilar regulatory framework in Europe has been implemented through the Committee for Medicinal Products for Human Use (CHMP) under the European Medicines Agency (EMA). The CHMP provides initial assessments for marketing authorization of new medicines that are ultimately approved centrally by the EMA. Since Sandoz's somatotropin biosimilar Omnitrope® was first authorized on April 12, 2006, an additional 34 out of 40 applications have been approved in Europe. Three of the authorizations have been withdrawn post-approval by the marketing authorization holders

The U.S. did not implement a regulatory framework for biosimilar evaluation until after enactment of the Biologics Price Competition and Innovation (BPCI) Act of 2009. Given that the first U.S. biosimilar drug was approved almost a decade after the first in Europe, the number of authorized biosimilar drugs in Europe far exceeds the number of biosimilars

approved in the United States. Sandoz's filgrastim biosimilar Zarxio® received the first U.S. approval in 2015, whereas nine filgrastim biosimilars have been approved in Europe dating back to multiple authorizations in 2008. Zarxio® (in the U.S.) and Zarxio® (in Europe) are biosimilar to the reference product Neupogen marketed by Amgen and originally licensed in 1991. Subsequent to Zarxio's approval, only five other biosimilar drugs have gained U.S. approval to date. As illustrated in the following graph, the EU's significant head start led to the existent imbalance in the number of biosimilar drugs available in the respective markets .



Currently, thirteen biosimilar applications are under review by the EMA for marketing authorization.

Drug Product	Reference Product Proprietary Name	Reference Product Sponsor	Number of Applications
Adalimumab	Humira®	AbbVie	2
Bevacizumab	Avastin®	Roche/Genentech	2
Infliximab	Remicade®	Janssen	1
Insulin glargine	Lantus®	Sanofi-Aventis	1
Pegfilgrastim	Neulasta®	Amgen	4
Trastuzumab	Herceptin®	Roche/Genentech	3

As an increasing number of U.S. patents expire on blockbuster biologic drugs, the numbers of abbreviated biologics license applications are also increasing. Biosimilars for at least nine different original biologics are currently navigating the FDA's biosimilar pathway or are in late stage development .

Drug Product	Primary U.S. Patent Expiry
Filgrastim	2013
Infliximab	2018
Adalimumab	2016
Etanercept	2028
Bevacizumab	2019
Trastuzumab	2019
Rituximab	2018
Pegfilgrastim	2015
Epoetin alfa	2013

On August 29, 2017, Boehringer Ingelheim announced (here) that the FDA approved its CyltezoTM biosimilar to AbbVie's Humira®. Boehringer Ingelheim indicated that its adalimumab biosimilar is a pre-filled syringe for the treatment of multiple chronic inflammatory diseases. The CyltezoTM approval marks the second adalimumab biosimilar to clear the FDA's regulatory review following Amgen's Amjevita® approved in September 2016, although no adalimumab biosimilars are commercially available yet in the United States .

Despite the recent FDA approval of CyltezoTM, the European market extended its large lead in biosimilar drug approvals during the summer of 2017. Given biosimilar applicant experience in navigating the EMA process and the EMA's high authorization rate, the FDA will need to continue to provide useful guidance and streamline the approval process in order to reduce the imbalance .

U.S. Food and Drug Administration List of Approved Biosimilar Drugs (CDER list of licensed biologics updated on September 1, 2017)

Drug Product	Company	Reference Product and Sponsor	Marketing Status	FDA Approval Date
Renflexis ® (infliximab-abda)	Samsung Bioepis	Janssen Remicade® (infliximab)	Not Available	Approved 4/21/2017
Amjevita® (adalimumab-atto)	Amgen	AbbVie Humira® (adalimumab)	Not Available	Approved 9/23/2016
Erelzi ® (etanercept-szzs)	Sandoz	Amgen Embrel® (etanercept)	Not Available	Approved 8/30/2016
Inflectra® (infliximab-dyyb)	Celltrion	Janssen Remicade® (infliximab)	Launched Nov. 2016	Approved 4/05/2016
Zarxio® (filgrastim-sndz)	Sandoz	Amgen Neupogen® (filgrastim)	Launched Sept. 2015	Approved 03/06/2015

Discussion

When comparing both authorization processes of biosimilar in Europe and in the U.S., it has to be taken into consideration that it was approved in Europe in 2009 whereas it was licensed in the U.S. six years later in 2015. The development program of both products started many years before the final approval of biosimilar. Both development programs had to be designed on the basis of guidance obtained during an advisory meeting held with the agency because guidance documents were not published yet. When looking at the content of the guidance documents finalized in 2006 in Europe compared to 2015, it seems as if the U.S. and Europe are aligning their views on biosimilar approval which might be a result of the 'biosimilar cluster' which was set up by the FDA and the EMA in 2011 to collaborate and discuss topics regarding regulations of biosimilars and of the experiences gained from the already licensed and marketed biosimilars in Europe. There have not been many differences between U.S. in 2012 and the guidelines published in Europe in 2006 as compared in the Master thesis. When comparing the assessment process and required data for the biosimilar licensed in the U.S. with the respective procedure in Europe, it becomes clear that both agencies basically follow the same ideas. However, this was the biosimilar approval in the U.S .

Conclusion

Europe has been way ahead of the other countries including US in terms of developing biosimilars. Regulatory requirements for the approval of biosimilar products are similar but slightly different in terms of :-

- Definitions of biosimilarity
- The scope of the guidelines
- The choice of the reference product
- The data required for product approval and some other aspects

Summary

Biosimilar Approval Pathways in the US and Europe - Development and approval of biosimilar mABs may face tough regulatory environment as the global market for biosimilar is valued at $243.8m in 2009 and is expected to increase to $4,697m in 2016 at a compound annual growth rate (CAGR) of 52.6%. The market will be driven by increasing pressure on governments to control rising healthcare expenditures and establishment of abbreviated regulatory approval pathway for biosimilars in the US besides patent expiry for major biologic drugs. The market is expected to gather momentum after the launch of biosimilar monoclonal antibodies. Thus, on the regulatory side, FDA can and should rely on EMA's experience in comparing proposed biosimilars to reference products. Unfortunately, on the patent side, because of the significant differences in the legal frameworks, US biosimilar litigation is terra incognita .

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