OCTAVUS CONSULTING
Intelligence Redefined

ERA OF BIOSIMILARS

CONTENTS

INTRODUCTION

Biologics are derived from the natural resources such as human, animal, or microorganisms and manufactured by various biotechnology methods such as recombinant deoxyribonucleic acid technology, controlled gene expression, and antibody technology. Biologics have benefitted patients with rheumatologic diseases, inflammatory bowel disease, malignant conditions, dermatological conditions, and other connective tissue disorders by halting the disease progression, alleviating the symptoms, and improving the quality of life. Biologics are one of the top selling drugs worldwide as well as in the US, but the major drawback of this drug has been its exorbitant cost, which makes it unaffordable and inaccessible to many patients. Almost 2% of US patients uses biologics and 26% of national prescription drug spending $453B in 2017.[1]

The term "biosimilar" refers to the products that could be marketed after the expiration of BLA patents. They are not identical to the reference product but are biologically similar. Biosimilar medicines are biologic drugs containing one version of existing biologic substances no longer protected by patents. They are biologically tested with the reference product in terms of bio similarity, safety and efficacy, claiming their similar properties to the original biologic products. It is proved that FDA-approved biosimilars have saved patients from $548 to $250B over their first 10 years on the market.[2]

Additionally, it has been reported by 2020 that almost $25B of $100B in biologics sales will be off-patent therapeutics. In 2006, biosimilars were approved and launched in Europe by EMA with issued guidance, making a way for launch of additional 19 biosimilars in EU markets. Global biosimilars sales reached $1.3B in 2013 and is expected for $11B till 2020.

The first biosimilar approved in EU in 2006 is Omnitrope and is followed by the US FDA in 2015 for filgrastim-Sandoz, a biosimilar to filgrastim (granulocyte CSF) and the process continued for the treatment of cancer and other conditions. Hence India is struggling in fields of biosimilars. But India, approved its first biosimilar before EU and the US for Hepatitis B, in 2000 Thymosin Alfa-1 developed by SciClone Pharmaceuticals. Additionally, Dr. Reddy has launched Herceptin's biosimilar in the US for stomach cancer

EMA DEFINITION OF BIOSMILARS – A biosimilar medicine is a biological medicine that is developed to be similar to an existing biological medicine (the "reference medicine"). Biosimilars are not the same as generics, which have simpler chemical structures and are considered to be identical to their reference medicines (ema, 2009)

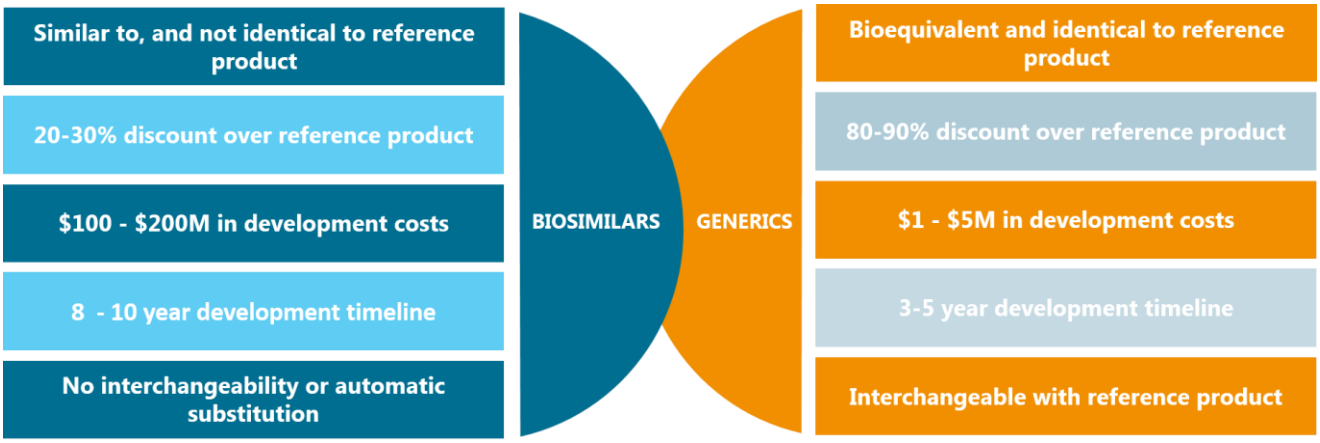
Additionally, in 2013 Biocon and Mylan were first Indian countries receiving Indian regulatory approval for trastuzumab biosimilar.[3]

Most are looking to Europe's track record for lessons learned, but the United States has unique market and regulatory characteristics that creates distinct challenges and opportunities. The most applicable lessons we've learned from Europe are that biosimilar launches are not like generic or branded launches, and product uptake varies widely based on the specific dynamics of the medication, market, and competitive landscape. For example, even with substantial biosimilar discounting; the erythropoietin market in Europe is still dominated by established erythropoiesis-stimulating agent (ESA) brands. On the other hand, the European launch of enoxaparin, a biosimilar anticoagulant to Sanofi's Lovenox, has been more successful, boasting a share differentiation.[4]

DEFINITION ACCORDING TO THE US FDA

A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product

Biologics innovators are already under market pressure from biosimilar market entrants in most global markets. Fortunately for innovators, European market uptake, for example; has been slow and mixed, allowing companies to forge defensive strategies. Also fortunate for innovators is that the discounts for biosimilars have not been nearly as drastic as the 80-90% typically associated with generic pharmaceuticals.[4] Innovators' strategic market planning should focus on employing brand teams and targeted messaging to reinforce any degree of differentiation from biosimilar entrants, which will vary from product to product, well in advance of forecasted competitive launches. Particularly with large, complex monoclonal antibodies, it is important to carefully review safety and efficacy data to thoroughly understand product differences. Additionally, innovators should investigate ways to expand their products' applications by repositioning them for new therapeutic areas. Some examples include devising safer or more patient friendly delivery mechanisms, simplifying dosing, considering portfolio-based approaches to specific customer segments, or developing next-generation versions of existing biologics, otherwise known as "biobetters".[4]



APPROVAL PATHWAY IN THE US FDA

The Biosimilars were previously handed to Biologics Price Competition and Innovation Act of 2009 (BPCI Act) formed by President Obama on Mar 23, 2010. The BPCI act created abbreviated licensure pathway for biological products shown to be biosimilar or interchangeable with the FDA licensed reference product. The biologic product is highly like the reference product, rely on licensure for publicly available information regarding FDA's determination that the product is safe, pure and potent. The pathway then permits the licensing of the biological product under section 351(k) pathways of the Public Health Service Act (PHS Act). The reference product tends to be the product licensed under section 351(a) of PHS act.[5]

General Requirements for 351(k) Pathway:

The 351(k)pathway application must include the following.

- Is biosimilar analogous to a reference product
- Utilizes the same mechanisms of action for the proposed condition
- Condition of use proposed have been previously approved with reference product
- Has same dosage, route of administration, and strength
- Meets safety standards to assure that the biological product continues to be safe, pure, and potent

Additionally, the application also includes some more information demonstrating a bio-similarity data based on analytical study showing that biologic is highly like the reference products, animal

studies including the assessment of toxicity and clinical studies evaluating PK, PD and immunogenicity.[5]

The biosimilars regulations in Japan were issued by Japan's regulatory authority, MHLW in March 2009 and followed the principles of the EU biosimilars regulations. The Korean Food and Drug Administration (KFDA) issued a guideline regarding the regulation of biosimilar products (Guideline on Evaluation of Biosimilar Products) in July 2009. Health Canada finalized its guidelines for subsequent entry biologics (SEBs) in March 2010. While global guidelines on similar biotherapeutic products were adopted by the WHO Expert Committee on Biological Standardization at its 60th meeting in October 2009.[6]

APPROVAL PATHWAY IN EUROPE

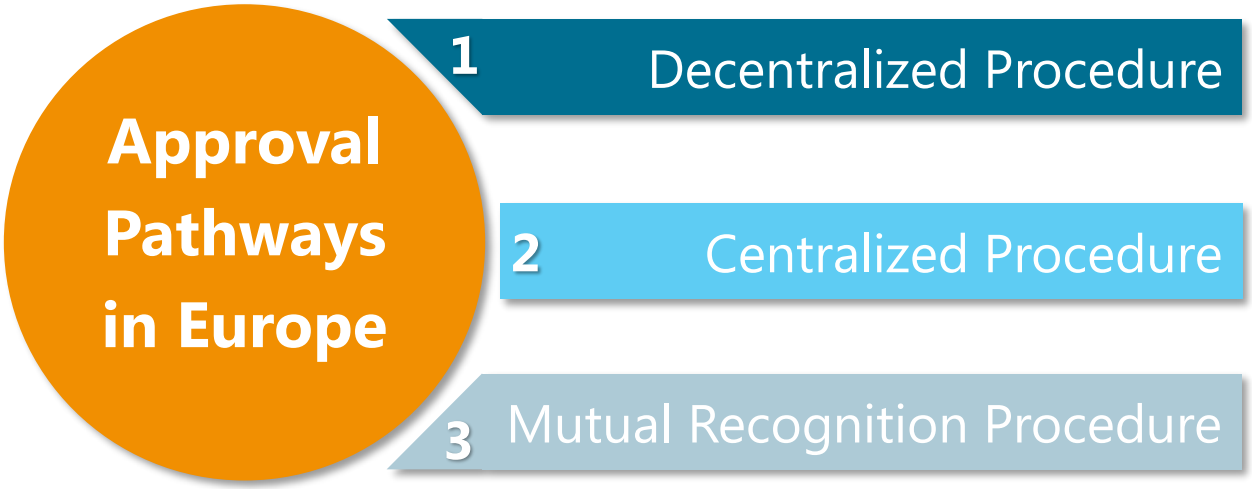
The European Union, consisting of 27 Member States, has continuously worked on improving and streamlining the drug review and marketing authorization processes. The regulatory process forms a legislative and government action barrier. The guidelines for biosimilars developers were proved and ensured in 2012 (EMA 2012b). The similarity is proven between biosimilars and reference product by a combination of experimental analysis and clinical te sting. EMA scientific committee evaluates the quality, safety and efficacy of all biological medicines approved in the EU.

The evaluation of biosimilars is done according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines approved in the EU. The developers need to examine through comparability studies with the 'reference' biological medicines. There should be no clinically meaningful differences between the biosimilar and the reference product in terms of safety, efficacy and quality. The biosimilar authorization is available once the exclusivity period is over of the reference product. In general, this means that the biological reference medicine must have been authorized for at least eight years before another company can apply for approval of a similar biological medicine.

The approval in European countries is far different from the process involved for US FDA. There are currently three different procedures that can be used to submit a medicinal product for marketing approval in the European Union. The European countries has mainly three procedure for approvals involving the:[7]

- **Centralized Procedure (CP)**
- **Decentralized Procedure (DCP)**
- **Mutual Recognition Procedure (MRP)**

The procedure has their own characteristics for following the three different process of approval. The procedure varies from a full application and submission of all data regarding the pharmaceutical, pre-clinical and clinical trials, to bibliographic or a well-established medicinal use application or on another basis, such as a generic application.
If the CP is not in use which is mainly used for orphan medicinal products and medicinal products, which contain new active substances with specific therapeutic indications for AIDS, diabetes or cancer. When a product is not applicable for CP, it falls under the other two categories i.e., MRP and DCP.
The MRP and DCP has a common point that both the method requires a member state to act as a Reference Member State (RMS), while further RMS sends report to CMS where the applicant wants to market the product.



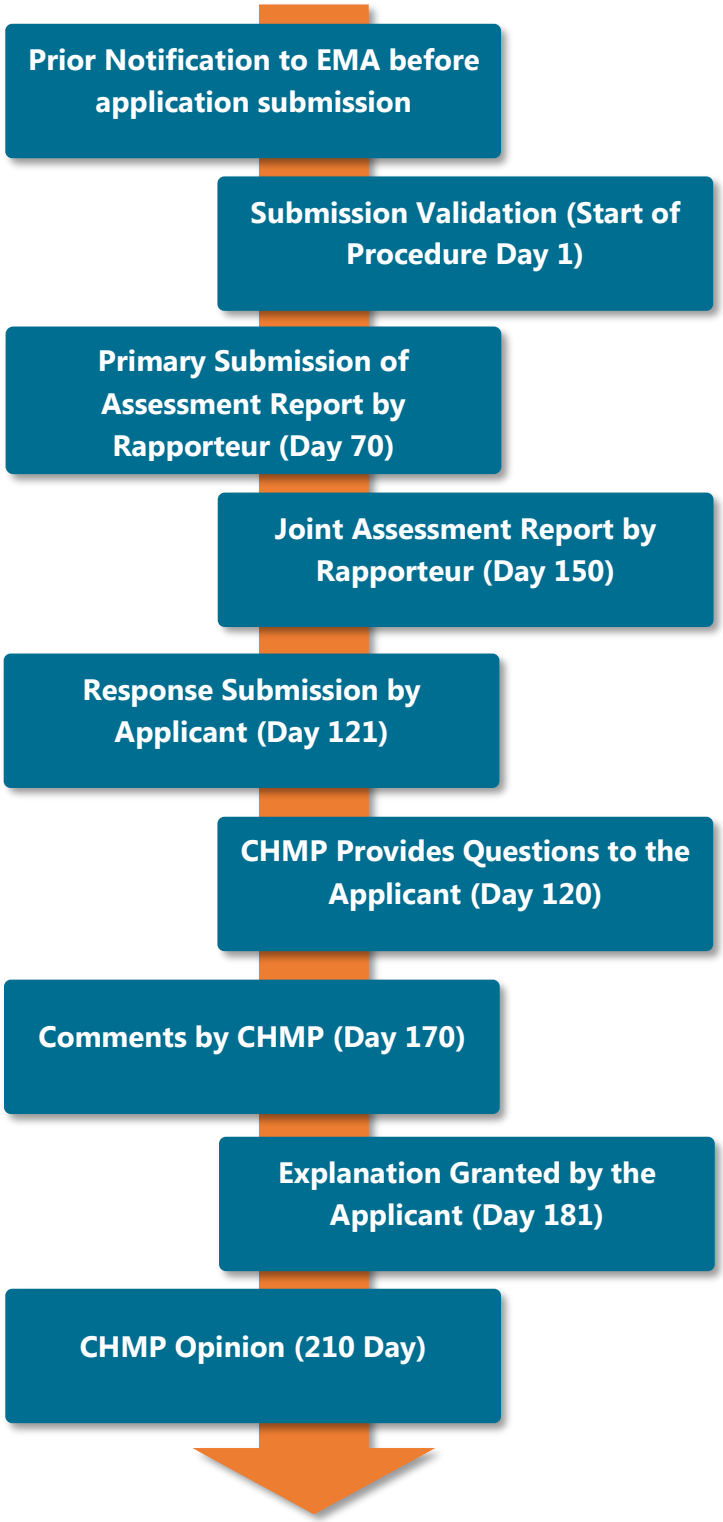
CENTRALIZED PROCEDURE

The Centralized Procedure came into existence in 1995 in European States. The applicant applies to EMEA for the approval which is valid in 27 countries as well as Norway, Iceland and Liechtenstein. With a prior expected period of seven months the applicant should inform EMEA about his submission. The applicant is free to meet the EMEA for any regulatory or general issues. The applicant applies for the CP procedure, and if the product lies under this procedure the CHMP informs the applicant for the same.

Once the application is completed and is validated via Rapporteur; chosen among

CHMP members, the EMEA starts its proceedings. The initial report is sent to the EMEA and CHMP within 80 days. The CHMP members are assigned to conduct a peer review of the Rapporteur/Co-Rapporteur's scientific evaluation, as well as the validity of the scientific/regulatory conclusions reached. The conclusion and list of question is sent to the applicant on day 120 day. The EMEA stops its proceedings to receive the response document form the applicant. The CHMP adopts a timetable to evaluate the responses. The EMEA validates the opinion in 90 days. Post CHMP positive opinion the applicant then serves EMEA with all necessary document in all EU languages.

Finally, with the completion of this procedure the EMEA accepts CHMP procedure in 30 days and with all document and reports the file is transferred to EC, and the Members of the Standing Committee, and to Norway and Iceland. The MAA is granted and is valid in all EU states. The European Public Assessment Report (EPAR) will be published on the EMEA website, once the Commission decision has been issued.



Types of Opinion Granted

- **Positive Opinion**
- **Negative Opinion**
- **Re-examination**

Positive Opinion

The positive opinion is given which, runs from a Monday to Thursday. If the CHMP gives positive opinion recommending the authorization of medicine, summary of opinion is published in CHMP meets and on EMA's pending decision page following the CHMP plenary meet. Post 2 weeks, of the submission of decision the summary moves to the EPAR page, for updated documents are published. The assessment report related to the extension of indication as adopted by the CHMP is also always published under the tab 'Assessment history'. A document called procedural steps taken and scientific information after authorization is also published (under the tab 'Assessment history') or updated if the document was already available. This document provides an overview of all the changes made to the marketing authorization since the medicine's initial authorization.

Negative Opinion

If the opinion is negative on the extension of indication, a refusal Q&A is published in the CHMP meeting highlights and the medicine's EPAR page on the Friday following the CHMP plenary meeting. The refusal document is published in all the languages are published in the medicine's EPAR page in addition to the same page under the tab 'Assessment history'. The procedural steps taken and scientific information after authorization is also published or updated if the document was already available.

Re-examinations

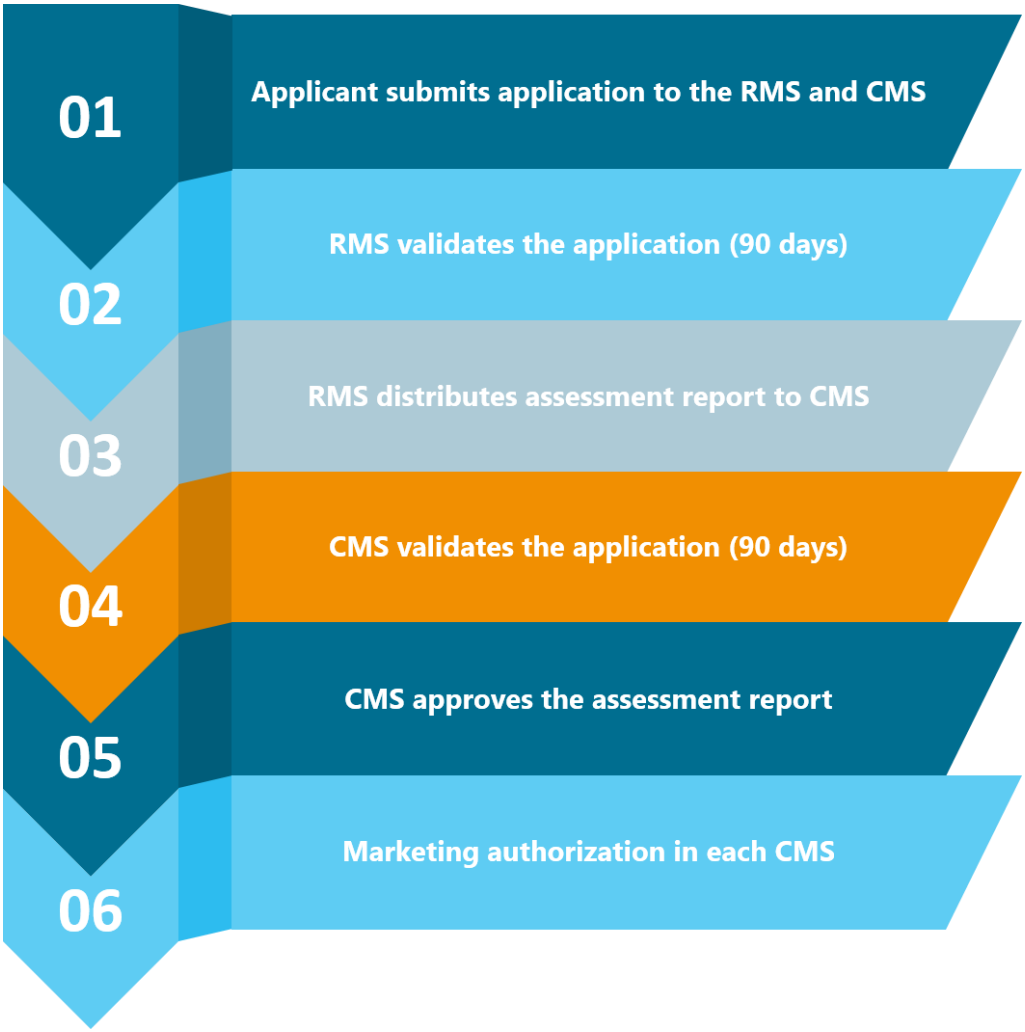
If a negative opinion is filed against the drug the applicant has an option to request for re-examination of CHMP opinion no later than 15 days after receipt of the opinion. Post CHMP re-examination of its original opinion, the Q&A report is being published on Friday in EMA's pending EC decisions page.
If the conclusion of the re-examination is positive, a summary of opinion is posted with re-examined Q&A in CHMP highlights. Post two weeks of the EC's decision, same set of EPAR document is published including refusal Q&A and the re-examination Q&A.

If the conclusion of the re-examination is negative a refusal EPAR is published around 2 wks. after the EC's decision refusing the MAA of the application including both the original refusal Q&A and the re-examination Q&A. Most of the time the re-examination practice is for the negative opinion for which the EMA has not agreed to accept. Sometime the re-examination is also for the positive opinion as the company hasn't agreed on some points which involves the same procedure.[8]

MUTUAL RECOGNITION PROCEDURE (MRP)

The MRP procedure was involved in late 1995 with the objective to obtain marketing authorization in one or several marketing Member states when the product is already approved in at least one country in the EC. The applicant requests for one or more CMS to mutually recognize the authorization granted by RMS. The applicant needs to send the application to authorities of RMS and to each CMS.

Within 90 days of the application the RMS provides the assessment report and if necessary, update it and then send it to CMS and to the applicant. Within 90 days of the trial, the CMS recognize the decision of the RMS and with 30 days post closure of the procedure the competent authorities of CMS adopt a decision and grant marketing authorization for the product.

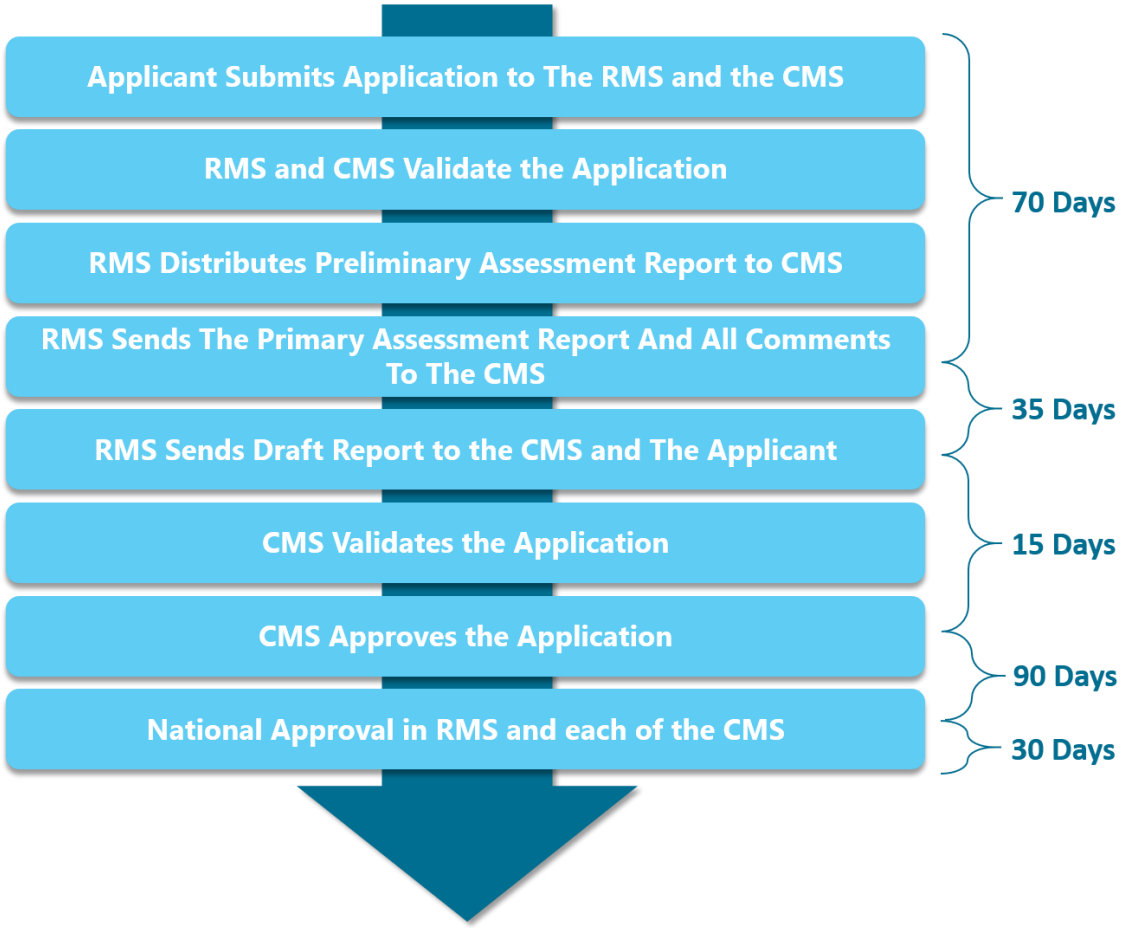


DECENTRALIZED PROCEDURE (DCP)

The DCP procedure was included in 2005 and is applicable when the authorization of product is not approved in none of EU member states. The applicant needs to send the application to one of the member state concluding it or designating it as RMS. The selection of RMS depends on many considerations including workload, previous experience, interests, and acceptance of the dossier by the RMS. The RMS starts the procedure and forwards a preliminary report to the CMS and the applicant with 70 days.

The CMS is asked to send comments on the report and on day 105, the RMS forwards all the comments to the applicant and stops the clock, to gain response from the applicant. Additionally, the CMS has 90 days to approve the procedure. Competent authorities of the

RMS and CMS adopt a decision within 30 days. At the end of the Decentralized Procedure with a positive agreement, a national marketing authorization will be issued in the RMS and each of the CMS(s).



BIOSIMILAR USER FEE ACT

The Biologics Price Competition and Innovation Act (BPCIA) was enacted in 2010 and granted the U.S. Food and Drug Administration (FDA) authority to create an abbreviated approval pathway for biosimilars. The Biosimilar User Fee Act (BsUFA) was introduced in 2012 under section 744G of the Federal Food, Drug, and Cosmetic Act (the FD&C Act).[8] BsUFA includes BPD fees for products in FDA's Biosimilar Biological Product Development (BPD) Program. BPD fees consist of the initial BPD fee, the annual BPD fee, and the reactivation fee. The BPD fee is an annual per-product fee, not a per-meeting or per-review activity fee.

The act authorizes FDA to collect fees for activities in connection with biosimilar biological product development, applications for approval of biosimilar biological products, establishments where such products are manufactured in final dosage form, and biosimilar biological product. The process is effective from Sept 2017, which is expected to collect the necessary revenue to fund 351(k) pathways for biosimilars. The fee includes rates for applications, supplements, establishments and products based on those included in PDUFA (Prescription Drug Use Fee Act).

The Biological Project Development department have multiple types of fees included:

Initial BPD Fee:

The initial BPD fee is a one-time per-product fee due which is 10% of the PDUFA fee given within five calendar days after FDA grants the first BPD meeting for the product, or upon IND submission. Not paying the BPD fee FDA may hold the IND submitted as well as the meeting.

Annual BPD Fee:

In the next fiscal year when the sponsor has already paid initial fee for product, must pay annual BPD fee is to pay each fiscal year unless the sponsor discontinues participation in the BPD program for the product or submits a MAA for it.

Reactivation Fee:

Under this fee if the sponsor has discontinued participation in BPD program and wants to resume it then he/she must pay reactivation fee for the continuation of program. The reactivation fee is 20% of the fee rate established under PDUFA.

Product Fee:

The product fee is assessed annually for eligible products on each applicant in an approved bio-similar biological product application.

BIOSIMILAR 12 YEARS EXCLUSIVITY ACT

The lengthy preclinical and clinical development necessary to bring a biologic to market has often been cited as one of the central reasons why biologics deserve 12 years of market exclusivity, or about five years more exclusivity than their small molecule counterparts. The authors from the Program On Regulation, Therapeutics, And Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, note that "although biologics are often thought to be more time-consuming to develop than small-molecule drugs, development times for biologics are similar to, or possibly somewhat shorter than, for small-molecule drugs". The study found that of the 275 new drugs approved by the US FDA's Center for Drug Evaluation and Research (CDER) between 2007 and 2016 (77% were small-molecule drugs and 23% were biologics), median total development times—from first patent filing to FDA approval: were about 12 years for both types of products.[9]

For both biologics and small-molecule drugs, the European Union provides 10 years of exclusivity, and Australia and New Zealand provide 5 years of exclusivity. By contrast, the United States provides 5 years of guaranteed exclusivity for small molecules that are new chemical entities, although in practice this exclusivity provides closer to 7 years of market protection for small molecules because the FDA cannot begin reviewing applications from generic competitors until the 5 years of data exclusivity have expired. This disparity in exclusivity in the United States—12 years for biologics versus roughly 7 years for small molecules.

Tom DiLenge, president of BIO's advocacy, law & public policy division, told Focus in a statement: "By singularly focusing on time of development, the study unfortunately ignores all of these other factors and issues and thus is not a constructive addition to the public dialogue, which is not all that surprising given the biased source of its funding. "The study was funded by the Laura and John Arnold Foundation, which has spent millions to lower drug prices and increase clinical trial transparency. And the "other factors and issues" DiLenge mentioned were related to "differences in the patent and regulatory

schemes" and manufacturing costs. BIO's comments on Friday come a day after Reps.

Jan Schakowsky (D-IL), Bruce Westerman (R-AR), Rosa DeLauro (D-CT), Angie Craig (D- MN), Lloyd Doggett (D-TX), Andy Levin (D-MI) and Raja Krishnamoorthi (D-IL) and Raja Krishnamoorthi (D-IL) introduced the Price Relief, Innovation, and Competition for Essential Drugs (PRICED) Act to reduce the exclusivity period for biologics from 12 years to five years. In 2017, the Obama Administration Office of Management and Budget estimated that reducing the exclusivity from 12 to 7 years could save almost $7 billion over 10 years.

Reducing the exclusivity period to 5 years would save even more money and aligns biologics with the traditional period guaranteed under the Trade-Related Aspects of Intellectual Property Rights (TRIPS) and with the exclusivity period for small-molecule drugs," the representatives said. The study follows a policy proposal from Pew Health in 2017, which suggested reducing the exclusivity period for biologics, noting that the costs to develop biologics and small-molecule drugs are similar.

NOMENCLATURE AND INTERCHANGEABILITY

NOMENCLATURE

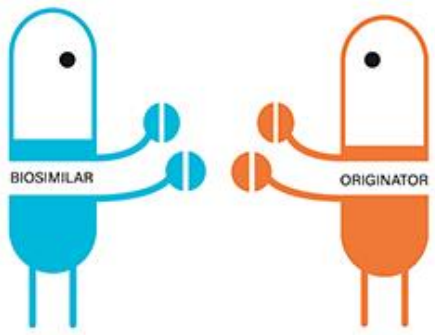
The US FDA has issued several documents regarding the nomenclature, approvals, interchangeability of biosimilars. Biosimilars can't be exact copy of each other so the government decided the ways to preserve patient safety and will help in tracking and tracing these agents via post-marketing surveillance. Additionally, in 2017 FDA drafted guidelines on the nomenclature of biosimilars, named with the nonproprietary name and with included four-letter suffix. The difference will help individuals to facilitates the accuracy of the medical record to evaluate the effect of the drug with distinguishable names and with extreme complexity and large molecular size. The four-letter suffix holds to identify the manufacturer and be easily memorized by prescribers and users of biologics. According to the BPC released findings the SERMO poll denoted that 500+ physicians meaning 80% of the professionals approved for the four-letter suffix that biosimilar manufacturer's name, versus a random four-letter suffix.

Recently, the World Health Organization released its proposal to address biosimilar naming. It suggests adding a voluntary, four-character biological qualifier to the end of the biologic's traditional international nonproprietary name (INN), not as part of the INN, but as an

"additional and independent element used in conjunction with the INN". This biological qualifier would be devoid of meaning, but it would allow practitioners to trace the product back to a specific manufacturer for pharmacovigilance purposes.[10]

INTERCHANGEABILITY

Provisions within BPCIA allows biosimilar to be designated interchangeable if it meets the standards beyond bio similarity. An interchangeable product is one that "can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual.

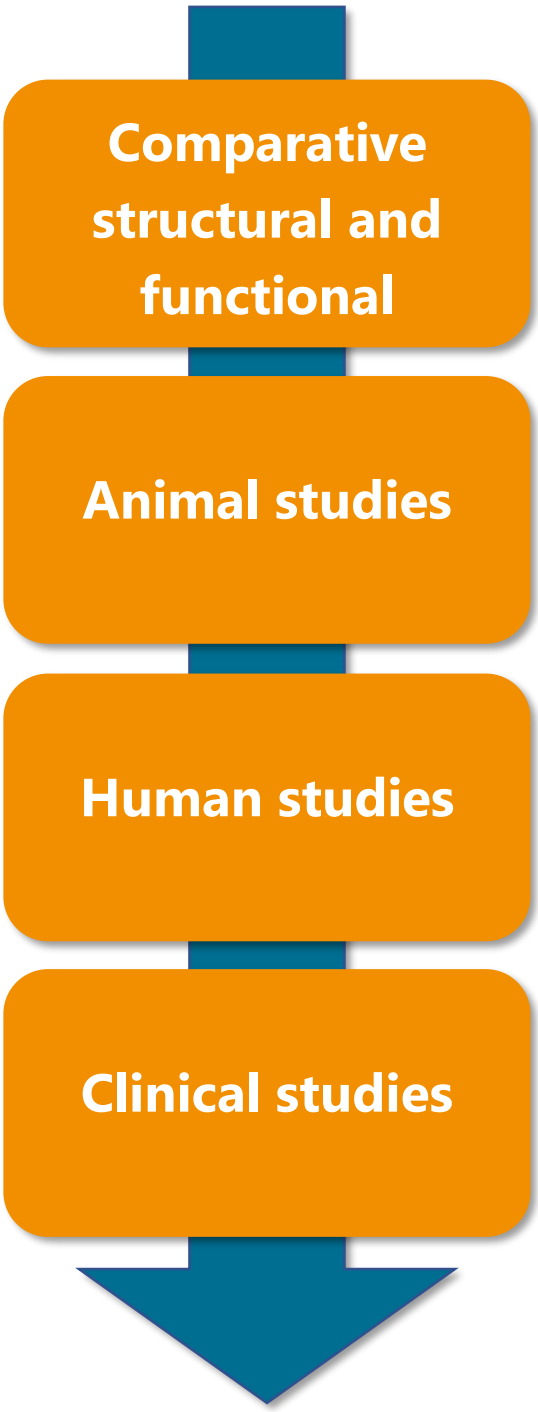


Recently the US FDA has issued guidelines on interchangeability of biologics which can be substituted without the involvement of the prescriber as they provide treatments for diseases like cancer, rheumatoid arthritis, diabetes and multiple sclerosis. The FDA's final guidance on interchangeability will provide clarity for developers who want to demonstrate that their proposed biological product meets the statutory interchangeability standard under the Public Health Service Act (PHS Act). The guidelines demonstrate that once an application or supplement seeking licensure as an interchangeable product is submitted, the FDA will approve the biological product as interchangeable if the information submitted meets applicable statutory standard. To date, the FDA has already licensed 19 biosimilar products, which should help strengthen competition in the biologic market. This, and other work we are undertaking as part of the Biosimilars Action Plan, is building a solid regulatory foundation for the review and approval of biosimilar and interchangeable biologics designed to improve patient access to lower-cost options.[11]

REGULATIONS ON CLINICAL TRIALS

PK and PD studies that demonstrate similarity in humans between the biosimilar and the reference product may provide a scientific basis for a selective and targeted approach to further clinical testing. PK studies determine what the body does to the biologic, while PD studies determine what the biologic does to the body. A range of 80–125% generally is used to demonstrate equivalence at the 90% confidence level for PK/PD evaluations. The PK study assesses exposure to all active components of the reference product as measured by dose (drug input to the body) and various measures of single or integrated drug concentrations in plasma and other biologic fluid, for example, peak concentration (Cmax), lowest concentration measured following dosing (Cmin), concentration prior to the next dose during multiple dosing (Ctrough ss), and area under the plasma/blood concentration–time curve (AUC). PD markers assess response to the reference product. For selecting PD markers, it is important to consider: (1) time of onset of the PD marker relative to dosing, (2) dynamic range of the PD marker over the exposure range to the reference product, (3) sensitivity of the PD marker to differences between the biosimilar and the reference product, (4) relevance of the PD marker to the mechanism of action of the reference product and (5) relationship between changes in the PD marker and clinical outcomes.

For PK as well as PD evaluations, assessing measures known to be clinically relevant to effectiveness can provide strong support to the demonstration of



bio similarity. For PK, a common measure is exposure (e.g., serum concentration over time). For PD, examples of measures include the American College of Rheumatology 20% (ACR 20) response rate and Disease Activity Score 28 (DAS28) in RA, the Crohn's Disease Activity Index, and the Ankylosing Spondylitis Disease Activity Score (ASAS or ASDAS). Although PD end points or assays that are sensitive and clinically important are established for many inflammatory disorders, no direct PD measurements can be attributed to antitumor necrosis factor biologics in patients. When PD end points are not closely related to clinical outcome, use of multiple complementary PD assays may be the most useful. Because the PD assay is highly dependent on the pharmacologic activity of the biosimilar, the approach for assay validation and the characteristics of the assay performance may differ depending on the specific PD assay. Demonstration of specificity, reliability, and robustness remain as guiding principles for choosing PD assays. Discussion with regulatory agencies may be appropriate where end points are not well established. Clinical trials evaluating PK and PD are generally designed based on the selected population and related factors, as well as what is known regarding the intra- and inter-subject variability of human PK and PD for the reference product. Clinical pharmacology studies should be conducted in the subject or patient demographic group most likely to provide a sensitive measure of differences between the biosimilar and reference product. The total number of subjects should provide adequate power for similarity assessment. For many drugs, human PK and PD studies are conducted in healthy volunteers if the product can be administered safely to this population. For biologics, however, there are some key considerations regarding the use of healthy volunteers. First, healthy subjects may have a greater immunogenic response than a population with disease (depending on whether the background standard of care in the population is immunosuppressive and other population factors). Second, healthy subjects are not appropriate if the disease relevant to the indication, or its treatment, is known to alter the PK of the reference product. Differences in PK related to sex, race, renal function, or hepatic function also may require special consideration. Clinical trials of biosimilars used for inflammatory disorders usually are carried out with a parallel design rather than a crossover design. In a parallel design, subjects are randomized to one of the two (or more) treatment groups. While the treatments differ between groups in a parallel design, all subjects are otherwise treated as similarly as possible. In a crossover study, a subject receives one treatment during the first study period and a different treatment during the second study period, with a washout phase between the two periods to allow the body to clear the first treatment. Because the elimination half-life of biologics used for inflammatory disorders is often a week or longer, the washout phase may be weeks or months, making a

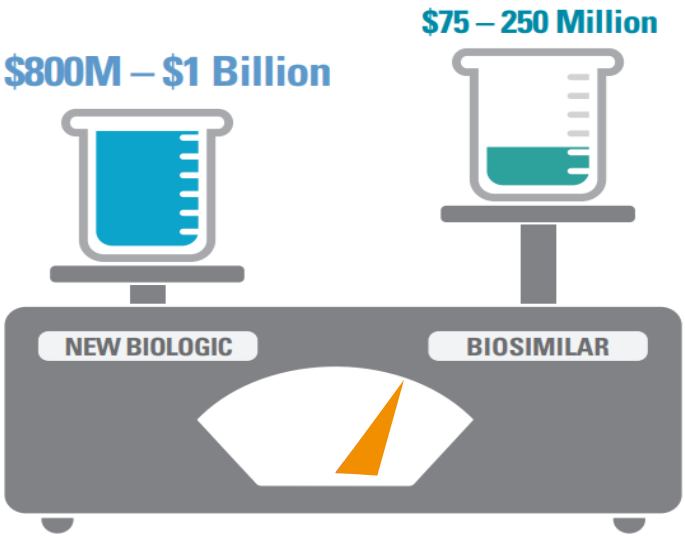
crossover design impractical. Furthermore, a crossover design may not be appropriate if patients do not have stable disease. In addition, the washout period in a crossover design often leads to flare of the inflammatory disease, which can result in an enhanced placebo response as the flare often subsides on its own.

The dose and route of administration should be the same as for the reference product. If the reference product can be administered in several doses or via more than one route, the dose and route of administration to be tested in clinical trials are those determined to be the most sensitive to detect differences in PK and PD between the biosimilar and reference product. Therefore, the dose chosen is the one for which the reference product is indicated and that is on the steepest part of the dose–response curve. Modeling and simulation tools can be useful in the selection of an optimally informative dose or doses for evaluating PD similarity.[12]

COMPETITION OF BIOSIMILARS

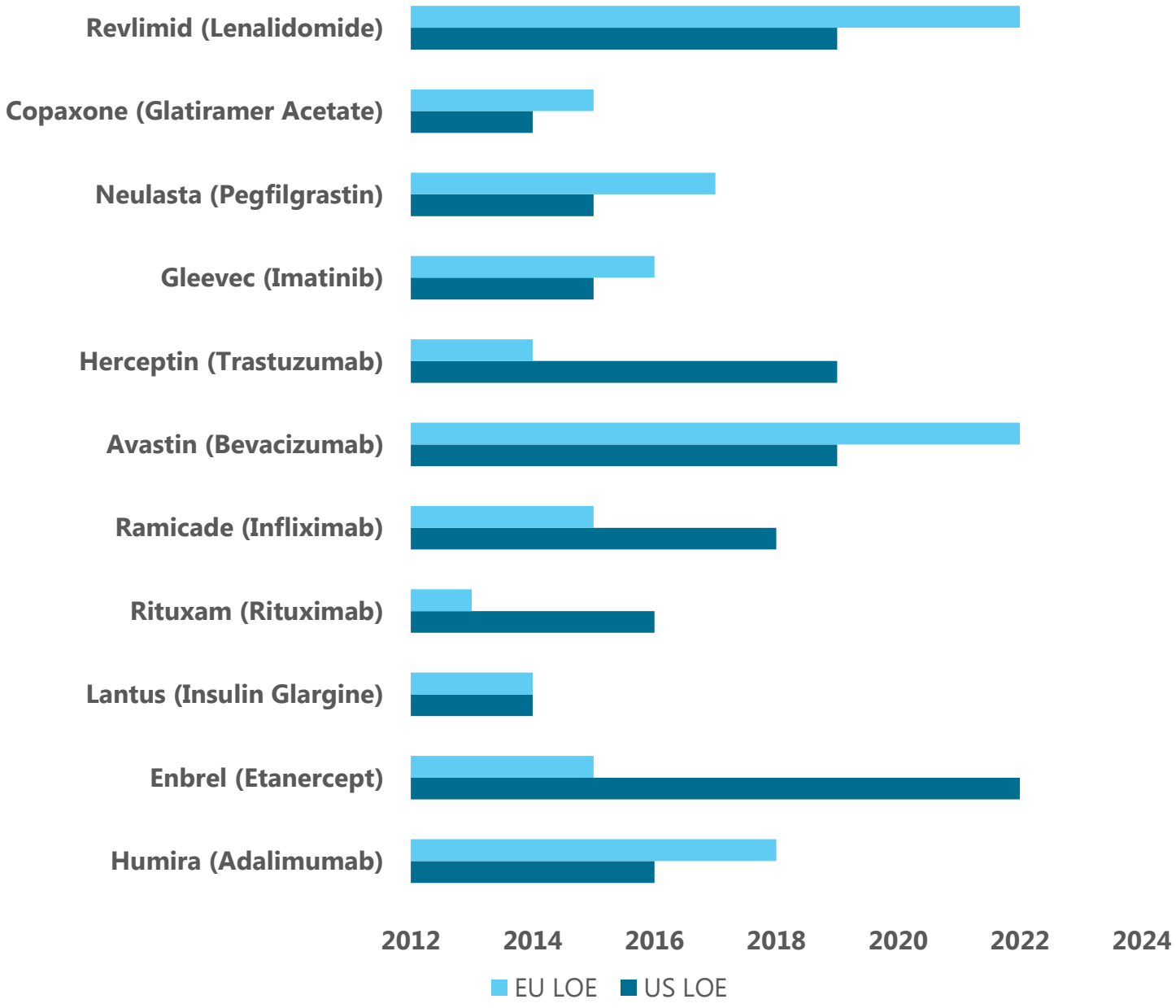
Biosimilars are in trend due to the growing disease in market and high-cost therapies used for treatments. Biosimilars mimic their reference biologics in use, safety, and efficacy. Analysts expect the worldwide biosimilars market to reach $25-$35B by 2020. Since the first biosimilar approval in the European Union (EU) in 2006, there are now more than 700 biosimilars approved (~450) or in the pipeline (~250) globally. Additionally, it is estimated to cost between $75 and 250M to develop a biosimilar. By comparison, it is estimated to cost between $800Mand $1B to develop a new biologic, according to a 2013 BioWorld report.[13] Biosimilars compete against biologic medicines just like generics compete with branded chemically based medicines. The biosimilars market will continue to evolve rapidly and with uncertainty. No matter their strategic objectives, all biopharmaceutical companies in the ecosystem need to be ever-present and in tune with the pulse of this disruptive and rapidly evolving market. The FDA has already approved 19 biosimilars. However, none of those drugs can be substituted—or interchanged by a pharmacist—for the reference biological drug from which they are derived. The new guidelines set testing standards for a biosimilar to be declared interchangeable, allowing pharmacists to replace a branded drug with a generic biologic in the same way they currently do for small-molecule drugs, without having to talk with a doctor first. Both patient advocates and the FDA hope that bringing more biosimilars to market will improve access to these groundbreaking drugs by giving consumers more choices and by lowering prices. In one study of patient costs for biologics to treat autoimmune disorders, annual out-of-pocket costs

ranged from $22,000 to $29,000. The wholesale prices of the biologics examined in the study ranged from about $700 to more than $7,000 per dose.[14]



Recently, Amgen launched to biosimilars Mvasi (biosimilar bevacizumab) and Kanjinti (biosimilar trastuzumab) in the US post approval from the US FDA. The WAC cost of Mvasi and Kanjinti is 15% lower than their reference products i.e., Avastin and Herceptin respectively. Mvasi is available at WAC of $677.40/100 mg and $2,709.60/400 mg single-dose vial and Kanjinti is being made available at a WAC of $3,697.26/420 mg multi-dose vial. During launch Mvasi and Kanjinti will be 12% and 13% respectively lower to average selling price (ASP) of their reference products. Since a biosimilar may cost less than a biologic provider lose money when they prescribe a low-priced biosimilar medicine instead of a higher-priced biologic medicine. There is also the problem of current biologic contracting practices that link insurers' rebates to minimum volume-thresholds or link biologic sales thresholds to rebates on other medical devices. Generics versions are rare in the US and increasing costs of the drug in recent years have led to reports of people with diabetes rationing supplies or skipping doses. Autoimmune diseases segment of biosimilars market exceeded USD 1,387.9 million in the year 2018. Global Biosimilar market is set to grow at $69B in 2025. Several well-known biologics are estimated to lose their patents in the forthcoming years. The US market is estimated to grow at significant rate of 38.1% over the projection period. China dominated the Asia Pacific biosimilars market and was valued at USD 1,498.1M in the year 2018. Presence of several

biosimilar products manufacturing companies in the country along with over 100 biosimilars in development will boost the business growth. Between 2009 and 2017 the Commission also reviewed more than 80 proposed mergers in the pharmaceutical sector and identified competition concerns in 19 of those cases. In those 19 cases, the mergers could go ahead only after the companies involved "offered to address concerns and modify the transaction. Other drivers of AbbVie's revenue this quarter—which totaled more than $8.2B and exceeded expectations—were the oncology drugs ibrutinib (Imbruvica) and venetoclax (Venclexta) as well as risankizumab (Skyrizi), a treatment for plaque psoriasis. The companies are looking for better option and markets for exposure of their products for gaining revenue. Earlier in 2019, Amgen withdrew its MAA application in EU for its ABP 710 (biosimilar, infliximab) as the company wanted better exposure for its biosimilar and was in search of more valuable markets for sales of its biosimilars. ABP 710 is a mAb anti-inflammatory drug targeting RA, Crohn's disease, UC etc.



Patent Expirations of Major Biologics

Sandoz's biosimilar rituximab involved in treatment of previously untreated, advance stage follicular lymphoma and has multiple biosimilars launched in the EU. Presently, multiple biopharma companies focusing on biosimilar development and commercialization are working keenly on biosimilars for their development. Pfizer's Ruxience (biosimilar, rituximab) recently received FDA's approval for cancer and autoimmune disease in addition to Amgen and Allergan's US launch of Mvasi (biosimilar bevacizumab) and Kanjinti (biosimilar trastuzumab). The biosimilar market is constantly in competition for multiple diseases. Additionally, multiple companies are still in clinical trials for the development of biosimilars. Sandoz's Proposed Biosimilar Denosumab study has moved into enrollment of patients in the study for Postmenopausal Osteoporosis. The biosimilar market is widespread in the US, EU including China. Innovent and Lilly's IBI301 (rituximab, biosimilar) received NMPA's acceptance to treat Non-Hodgkin's lymphoma. Additionally, the British Columbia is also thinking for expansion of the biosimilar market with its wide usage. BC decided to switch from reference product to biosimilars within 6 months, for patients suffering from diabetes, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, and rheumatoid arthritis. The British Columbia is also trying to save $96.6B in the first 3 years with the listing of Jardiance and Taltz drug for diabetes and psoriatic arthritis.

CONCLUSION

The Biosimilars can improve the basic idea of living for patients suffering from diseases and will serve as a novel treatment from medical and scientific advancement. We believe that long-term growth of this burgeoning class of drugs will come from emerging markets - and will accelerate as regulatory pathways around the globe are developed. Developed markets, such as the United States, EU5 and Japan, are expected to provide near-term biosimilars growth, aided by governments who are issuing clear regulatory approval guidelines and payers promoting uptake in order to contain health care costs. In these markets, bio-betters, which offer a clinical advantage over existing therapies, may grow more quickly than biosimilars.

The bio-betters which offer may grow more quickly than biosimilars. While biosimilars' growth potential appears bright, winning with biosimilars in emerging markets is not a simple undertaking. One of the most interesting talks about biosimilar is they have distinguishable names so that health care professionals and patients clearly understand which medicine is being administered.

In addition, US and European doctors also switch patients between different brand-name biologics with similar modes of action to treat the same disease. For example, several brand-name biologics attack the tumor necrosis factor pathway to thwart the inflammation seen in diseases like psoriatic arthritis. Evidence from Europe, she says, shows that such substitutions have little cause for concern.[15]

It is also important that the prescribing physician have clear labels describing their safety and the data behind the approval decision so that an informed choice can be made regarding the appropriate medicine for the patient.

Overall, it takes more time and money to reproduce a biologic than it does a small molecule.

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