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Review Article

Biosimilars -New Horizon of the Generic Drugs

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Abstract

Biosimilars (or Biologics) are the fastest growing segment of the pharmaceutical market with about 30 odd branded molecules sales in excess of $50 billion facing patent expirations. However, development of biosimilars is not an easy cake walk and linked with many challenges either due to its complexity in development or regulatory concerns or manufacturing challenges etc. Biosimilars can be expensive to manufacture and fully characterize in comparison with the innovative biomolecule. Furthermore, the complexity involved in carrying out the pharmacology and toxicology studies, design and execution of clinical studies would needless to say involve time and lot of investment. Unlike small molecule generics, the process of developing and commercialization of a biosimilar can take up to 7 years or longer. Years back, when the innovative protein molecule had been developed, product criteria had been spelt out as per one's own requirement. However, when a biosimilar is being developed, the product and process so developed would have to comply with more stringent regulatory requirements. Development of biosimilars would require a lot amount of analytical, physical and clinical evidence to demonstrate high similarity to the innovator drug.

Keywords: Biosimilars, generic, patent, regulatory, comparability

INTRODUCTION

Patents for many branded biologics will expire during the next few years, allowing biosimilars manufacturers to seek FDA approval for generic versions of these agents. The Biologics Price Competition and Innovation Act (BPCIA) of 2009, which was passed as part of the health care reform legislation enacted into law in 2010, authorizes the FDA to establish a long-awaited regulatory pathway for biosimilars. In 2012, the FDA issued draft guidance summarizing the proposed criteria for this path-way; this guidance is yet to be finalized.

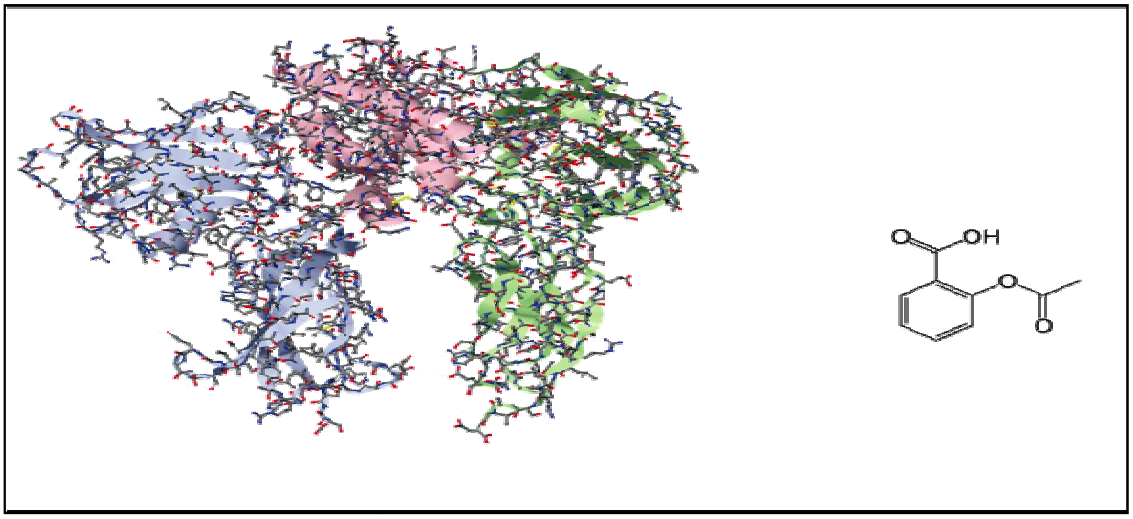
These criteria have inspired debate and the emergence of several critical issues, such as to what extent the biosimilars pathway should be abbreviated, how much clinical data should be required for approval, or when an agent should be designated as comparable or interchangeable with an originator biologic. These parameters will determine the ease and cost for a manufacturer to develop and market a biosimilar and will also ultimately influence the price of these medications.

The availability of biosimilars is eagerly anticipated, because these agents are expected to improve affordability and promote wider and earlier access to critical, often lifesaving therapeutic interventions. Ideally, the FDA's finalized guidelines will establish a regulatory path for biosimilars that will ensure patient safety, control development costs, and encourage innovation by manufacturers.

Definition of Biologics and Biosimilars

According to the U.S. Federal Code of Regulations (CFR), the definition of a biologic is "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of disease or injuries of man." Biologics were first developed in the 1980s using recombinant techniques to copy or improve on naturally occurring complex peptides, proteins, and glycoproteins. Since then, even more complex products, such as monoclonal antibodies, have been produced through the manipulation of the DNA in bacteria, yeast, or mammalian cells to produce therapeutic or diagnostic agents. Biologic therapies available today include enzymes, vaccines, human insulins, interferons,

interleukins, erythropoietins, gonadotropins, granulocyte–colony-stimulating factors (G–CSFs), human growth hormones, monoclonal antibodies, blood coagulation modifiers, and tissue plasminogen activators.Biologics are much more complex than conventional "chemical" drugs because they are larger and have more complicated structures (Figure 1).



Erythropoietin **Aspirin**

Many biologics have become increasingly well characterized, including their mechanisms of action. The structure–function relationships of biologics are very sensitive, because modifications of primary or higher-order (secondary, tertiary, or quaternary) configurations may affect safety, purity, and/or potency. During the manufacturing process for biologics or biosimilars, primary amino acid sequences can become modified through glycosylation, changing the shape of a protein because of alterations in the way it folds. These post-translational modifications are not controlled by the recombinant DNA inserted into the host cell but are affected by the cell line and the environment in which the cell line is grown.

Every manufacturer of biologics or biosimilars uses a unique cell line and a proprietary process to produce a particular biologic agent, so it is impossible to produce biosimilars that are identical to the originator drug. By contrast, conventional chemical drug molecules are much smaller, have a simpler structure, and can be easily manufactured using a controlled and predictable chemical process that generates identical copies.

Conversely, for biologics, even minor modifications in the manufacturing process can result in a different end product. Therefore, the therapeutic efficacy, safety, and quality of a biosimilar could vary from the originator, or "reference," biologic, because the end product is highly dependent on a proprietary manufacturing process that differs for each manufacturer. The inability to produce an exact copy of an originator biologic is the reason for the term "biosimilar" rather than "biogeneric" or "bioidentical".

Nomenclature of Biosimilars:

The complex nature of biological molecules requires specific nomenclature guidelines. Naming biosimilars has further increased this complexity, and to date, several different and inconsistent conventions have been applied around the world. Often, biosimilar and reference products may share the same name. Together with naming inconsistencies, that has led to concern over the strength of the World Health Organization's International Nonproprietary Name (INN) system currently in place.

The FDA defined how biologicals should be named in a January 2017 guidance, which states that each biosimilar must have a proper name made up of a core name hyphenated to a four-

letter suffix representing the developer. For example, Adalimumab-atto (Amjevita) is a biosimilar of AbbVie's Humira drug.

Difference between Biosimilars and Generic drugs

Area	Biosimilars	Generic Chemical Drugs
Chemical structure	The amino acid sequence is the same, but slight differences are expected in terms of protein folding and glycosylation	The active drug is chemically identical to the reference product
Analytical characterization	The final structure cannot be fully defined based on current analytical techniques; therefore, the degree of structural similarity to the reference product is unknown	Current techniques are available to ensure that the active drug in the generic product is identical to the reference product
Manufacturing complexity	Very complex; produced in living cells and involves several stages of purification, production, and validation of the final product	Relatively simple; uses organic medicinal chemistry reactions
Impact of a change in manufacturing process	Small changes in process may alter the final structure and function of the protein	Likely to be negligible because the end product is identical
Legislation approving an abbreviated pathway	The Biologics Price Competition and Innovation. Act of 2009 establishes a framework for an abbreviated approval pathway for biosimilars; final guidance has yet to be released by the FDA	Hatch–Waxman Act allows generics to be approved through an Abbreviated New Drug Application (ANDA)

Names and Definitions of Biologic Copies According to Different Regulatory Agencies

Agency	Naming	Definition
FDA (Food and Drug Administration), USA	Follow-on Biologic or Biosimilar	"A biological product that is highly similar to a U.S.-licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which 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".
EMA (European Medicines Agency)	Biosimilar	"A biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product) in the EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established"
WHO (World Health Organization)	Similar Biotherapeutic Product	"A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product"
PMDA (Pharmaceutical and Medical Devices Agency), Japan	Follow-on Biologic or Biosimilar	"A biotechnological drug product developed by a different company to be comparable to an approved biotechnology-derived product (hereinafter "reference product") of an innovator"
Health Canada	Subsequent Entry Biologic	"A biologic product that is similar to and would enter the market subsequent to an approved innovator biologic product"
ANVISA (Ag^encia de Vigil^ancia Sanitaria), Brazil	Biologic Product	"A biologic medicine with known biologic activity that contains no new molecules, already licensed in Brazil and that has gone through all the production steps (including formulation, vialing, freeze drying, labeling, packaging, storage, quality control and biologic product lot release)"

Regulatory framework in Europe and the United States — differences and similarities between European Medicines Agency (EMA) and Food and Drug Administration (FDA) pathways

Criteria	EMA	FDA
First approved biosimilar	Omnitrope (somatropin), 2006	Zarxio (filgrastim-sndz), 2015
Biosimilar regulatory paradigm	Demonstration that a potential biosimilar is highly similar to its reference product in safety, purity, and potency/efficacy with no clinically meaningful differences	Demonstration that a potential biosimilar is highly similar to its reference product in safety, purity, and potency/efficacy with no clinically meaningful differences
In vivo comparative toxicology studies	Not required routinely, relies more on in vitro evaluation of structure–function relationships	Routinely required, although the agency can waive this
Multistep comparison of a biosimilar to its reference product	Analytical and functional studies; in vivo nonclinical analyses; clinical pharmacokinetic/pharmacodynamic assessments; head-to-head clinical trials in the most sensitive population(s) — safety, efficacy, and immunogenicity studies	Analytical and functional studies; in vivo nonclinical analyses; clinical pharmacokinetic/pharmacodynamic assessments; head-to-head clinical trials in the most sensitive population(s) — safety, efficacy, and immunogenicity studies
Biosimilar review process	Nontherapeutically aligned structure in centralized CHMP reviews	Therapeutically aligned structure with multiple levels of supervision and oversight
Legal pathway	A separate branch of the generic pathway (Directive 2001/83/EC, Article 10.4)	Biologics Price Competition and Innovation Act (BPCI Act) of 2009
Meetings between developers/sponsors and regulatory agencies	Centralized advice procedure by the EU CHMP Scientific Advice Working Party provides mostly written advice; meetings called when regulators disagree with a sponsor's proposed plan. Advice procedures with individual EU country health authorities, usually involving meetings	FDA meeting structure defined by the Biosimilar User Fee Act (BsUFA for biosimilar applications). Biosimilar product development (BPD) meetings enable Biologic License Applications under 351(k) pathway
Interagency meetings	EMA and FDA cluster meetings (closed, regulators-only meetings); EMA/FDA parallel advice (for companies)	EMA and FDA cluster meetings (closed, regulators-only meetings); EMA/FDA parallel advice (for companies)

Those FDA-designated suffixes should prevent inadvertent substitution of products. The agency states that these products thus will be distinguishable so that only products that have been approved as interchangeable biologicals (biosimilars) for a particular indication will replace innovator treatments for that indication. This is intended to prevent accidental alternation between different biological products that share the same core name.

Biosimilars are receiving approval in Europe before receiving it in the United States. However, no naming convention has been established in Europe to date. There, biosimilars share the same INN with innovator products, which can create confusion among healthcare professionals.

Biosimilar Development & Manufacturing

Therapeutic proteins derived through recombinant DNA technology (Figure can vary in their primary amino acid sequence or through modifications made to their amino acid chains (e.g., glycosylation, PEGylation, or addition of other side chains to form a secondary structure) and in their higher-order structure (e.g., folding to form a tertiary structure, more complex interactions to form a quaternary structure). Proprietary biomanufacturing processes and environmental conditions used in development of innovator products usually are difficult for biosimilar manufacturers to replicate. So biosimilars are highly unlikely to be completely identical to comparator products.

First, the DNA sequence that encodes a desired biosimilar is identified, isolated, inserted into a vector, and incorporated into the genome of a suitable host cell (e.g., bacterium or mammalian cell). Bacterial host cells are inexpensive and easy to grow, and they generate high product yields. But they cannot produce large, complex proteins such as MAbs. By contrast, mammalian cells do so, but they are more sensitive and costly, and they generate relatively low product yields. A master cell bank with identical cells that produce a desired protein is established through cell screening and selection. That bank is used to culture additional cells at increasing scale under strictly defined conditions that optimize protein production.

In downstream processing, undesired proteins and other impurities are removed from culture supernatant. Harvested protein is analyzed for uniformity in its three-dimensional structure and potency using a number of analytical methods, including physicochemical and biological tests. Finally, the purified drug substance is formulated with added excipients (e.g., antioxidants, osmotic agents, and buffers), filled into containers and external packaging, then stored and shipped under appropriate environmental conditions.

Biosimilar use of different expression systems from those producing reference drugs can change a protein's posttranslational modifications (e.g., glycosylation profile), which in turn can affect product safety or effectiveness. Modification of any steps in biomanufacturing (e.g., use of a different vector to create host cells, systems for cell screening and selection to establish the master cell bank, culture media, methods for production or purification, and excipients) can alter the effectiveness and safety of a product. Thus, biosimilar manufacturers must assess

the effects of such changes using appropriate analytical methods, functional assays, and animal and clinical studies to ensure that such changes do not adversely affect the identity, quality, purity, potency, safety, or effectiveness of their products. That also is a question addressed by regulatory agencies when they evaluate biosimilars for approval.

Reference Standard Selection:

The EMA has clear guidelines on use of reference standards for similar biological medicinal products. To facilitate the global development of biosimilars and prevent unnecessary repetition of clinical trials, it may be possible for an applicant to compare its biosimilar in certain clinical studies and in vivo non-clinical animal studies with a reference product that is not authorized in the European Economic Area (EEA), but that comparator should be authorized by a regulatory authority with similar scientific and regulatory standards (e.g., signatories to the International Council on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use, ICH).

According to the EMA biosimilar guidelines, if an applicant performs parallel development for Europe and the United States, then inclusion of US reference standards is necessary. Scientifically, the type of bridging data needed always will include data from analytical studies (e.g., structural and functional data) that compare all three products (the proposed biosimilar, the EU reference product, and the US comparator). They may include data from clinical pharmacokinetic (PK) and/or pharmacodynamic (PD) bridging studies for all three products as well.

The Increasing Clinical Use and Cost of Biologics

Biologics were a pivotal innovation by the pharmaceutical industry, because they successfully addressed previously unmet therapeutic needs. Since their introduction, biologics have become increasingly significant in terms of new product development, clinical use, and health care expenditures. In 2010, these agents were the fastest-growing segment of the pharmaceutical market as a result of expanding indications, increased utilization, and a burgeoning biologics development pipeline. During that year, biologics accounted for 32% of the products in drug development, 7.5% of marketed medications, and 10% of pharmaceutical expenditures. In 2011, worldwide biologic sales reached $142 billion, with 37.6% of this amount garnered by the top 10 selling products

The cost of biologics is also rapidly rising. Biologics are much more costly to develop and manufacture than conventional chemical drugs. Biologics firms spend about 30% of their revenues on research and development (R&D), among the highest percentages of any industry in the U.S. On aver-age, the R&D for a biologic agent costs $1.2 billion, compared with $500 to $800 million for a conventional chemical drug.

The investment of time to develop a biologic is also greater, usually between 10 and 15 years, compared with 7 to 10 years for a conventional chemical drug.

Unfortunately, these increased investments by biologics manufacturers also translate into higher costs for consumers. Biologics are much more expensive than conventional chemical drugs. In 2012, the average cost of a branded biologic was estimated to be $34,550 per year and was even higher for some treatments—for example, as much as $200,000 per year for imiglucerase (Cerezyme) to treat Gaucher's disease or $50,000 per year for adalimumab (Humira, Abbott) to treat rheumatoid arthritis or Crohn's disease. The rate at which biologics prices have increased has also far exceeded the overall rate of infla-tion.4 The cost of biologics rose by 14.2% in 2009, by 17.2% in 2010, and by more than 13.6% in 2011, compared with the much smaller changes of –0.4%, 1.6%, and 3.2%, in the Consumer Price Index (CPI) during the corresponding years.

Reasons for the surge in Biosimilars development

The impending expiration of the patents for many branded biologic agents is a significant driver of biosimilars development. Since the 1980s and 1990s, the developers of originator biologics have been awarded patents granting a 20-year period of exclusivity. This exclusivity period has given rise to the "patent cliff," the term used to describe the clustering of numerous branded biologics patent expirations occurring between 2011 and 2019. The expiration of these patents will compel competing manufacturers to develop biosimilars for these biologics, creating a market that is expected to grow at an annual rate of 20% going forward.

Along with the patent cliff, the high cost of branded biologics is also a significant driver of biosimilars development. Cost pressures facing both public and private third-party payers, as well as the desire to improve patient access through decreased drug costs, creates a demand for biosimilars. Biosimilars are expected to be a cost-effective alternative to high-priced branded biologics, offering significant and much needed cost savings to both payers and patients. A 2008 Congressional Budget Office (CBO) report estimated that biosimilars will reduce federal spending for biologic drugs by $25 billion by 2018. Other drivers of biosimilars development include the long-awaited establishment of a new, expedited regulatory pathway for biosimilars by the FDA; advances in manufacturing techniques; and the expansion of biologics indications to include larger patient populations.

Defining a Regulatory Pathway for Biosimilars

The Biologics Price Competition and Innovation Act of 2009

Traditionally in the U.S., biologics are approved under the Public Health Service Act (PHSA), whereas conventional chemical drugs are approved under the Federal Food, Drug, and Cosmetic Act (FDCA). Under the PHSA, originator biologics receive approval through a Biologics License Application (BLA), also known as the "351a pathway." This process requires significant preclinical and clinical data to prove the efficacy, safety, and quality of the agent. In 1984, the Hatch–Waxman Act amended the FDCA to include expedited 505(j) and 505(b) regulatory pathways, which allow generic chemical drugs to be approved through an Abbreviated New Drug Application (ANDA). By contrast, the PHSA does not define an approval process for biosimilars.

Unlike the U.S., the European Medical Agency (EMA) has had a regulatory pathway for the review and approval of biosimilars, which is based on comparability to originator biologics, in place since 2006. The U.S. followed Europe's lead by drafting the BPCIA in 2009. The BPCIA was included as part of the Patient Protection and Affordable Care Act (PPACA), which was enacted into law by Congress in March 2010. The BPCIA amends the PHSA to include an abbreviated 351k pathway for the approval of biosimilars of originator biologics that have previously been licensed through a BLA. This legislation also authorizes the FDA to designate a biosimilar as being either "comparable" or "interchangeable" with the reference product and to establish the evidentiary requirements and process for this purpose. The details regarding these and other requirements for the biosimilars pathway have not yet been finalized by the FDA.

The BPCIA grants 12 years of exclusivity to originator or reference biologics; therefore, by law, the FDA cannot approve a biosimilar until this period has elapsed. The exclusivity period is intended to ensure economic incentives for biologic manufacturers to continue to invest in R&D for new, originator biologics. In exchange for the 12-

year exclusivity period, biosimilar manufacturers are granted access to the 351k path-way, or the abbreviated BLA pathway, which will expedite the approval of biosimilars.

FDA Draft Guidance on the Biosimilars Regulatory Pathway

In February 2012, the FDA issued three draft guidance documents regarding the regulatory requirements for biosimilars:

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product

Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009

These documents clarify the requirements of the BPCIA and discuss the scientific and quality considerations involved in evaluating the comparability of a biosimilar with a reference product. According to these draft documents, when reviewing biosimilars applications, the FDA will take a facts-focused, risk-based approach dependent on product data and clinical experience with the reference drug. Biosimilarity will be demonstrated through the submission of data derived from analytical, animal, and clinical studies. The guidance states that clinical studies must include an assessment of pharmacokinetics, pharmacodynamics, and immunogenicity and should also address one or more indications licensed for the reference product. The FDA will also consider product formulation, complexity, and stability when evaluating biosimilarity. Methods of evaluating safety beyond traditional clinical trials, such as pharmacovigilance, will also be used to monitor a biosimilar after it is on the market.

Despite these statements, the FDA is granted discretion in the amount and type of data that it will require for the approval of biosimilars. After manufacturing changes are made to a branded biologic, the FDA and other regulatory agencies generally require only a "comparability exercise" (analytic data, with preclinical and clinical evidence required only when necessary). This approach acknowledges that a biosimilar is not unlike a product that would result after a change is made to the manufacturing process for a branded biologic. Therefore, the proposed FDA regulatory pathway for biosimilars resembles a comparability exercise rather than a new product-development program. This concept enables the agency to approve a bio-similar without requiring a full complement of clinical trials, which in turn facilitates lower product development costs, expedites regulatory approval, and eases market entry for biosimilars manufacturers.

FDA Draft Guidance on Biosimilarity

The FDA recognizes that a biosimilar cannot be structurally identical to the originator (reference) product because differences in the manufacturing process alter the end product. Rather than requiring that a biosimilar be structurally identical to an originator biologic, the FDA requires that a biosimilar not be "clinically different." According to the BPCIA, a biologic product is deemed biosimilar to the already approved, originator biologic if the available data show that it is highly similar to the reference product, "notwithstanding minor differences in clinically inactive components, and there are no clinically significant differences between the biologic product and the reference product in terms of safety, purity, and potency of the product." Because the efficacy and safety of the reference product have already been demonstrated, a manufacturer must provide evidence only that a biosimilar is not significantly different.

The goal is to use smaller-scale, direct comparisons and extrapolation instead of relying on replicating clinical trials that are presumed unnecessary. This is partially achieved through data derived from analytical studies that demonstrate that the biological product is "highly similar" to the reference product. The draft guidelines also acknowledge that biosimilarity can be demonstrated even though there are "formulation or minor structural differences, provided that the sponsor provides sufficient data and information demonstrating that the differences are not clinically meaningful and the proposed product otherwise meets the statutory criteria for biosimilarity.'' For instance, certain post-translational modifications (such as alterations to C and N terminals) or changes to excipients are not expected to preclude a finding of biosimilarity.

However, structural variability is very subtle and diverse, and currently available analytical techniques can be insufficient in fully characterizing biological products. So the FDA takes what it calls a "totality of evidence" approach, stating that analytical, physicochemical, and biological

characterization should be extensive, utilizing comparisons between the biosimilar and reference product, including structure, function, and animal data, as well as human pharmacokinetics (PK), pharmacodynamics (PD), clinical immunogenicity, efficacy, and safety studies. Clinical studies demonstrating the efficacy and safety of the biosimilar in one or more of the reference product indications for which the biosimilar will be licensed are also required. However, the FDA has the flexibility to determine that some of these studies aren't necessary, allowing the agency to define the best approach for specific biosimilar products and classes.

Characterization of Biosimilars Through Analytical Studies

In the draft guidance provided by the FDA, the agency uses analytical studies to serve as the foundation for establishing comparability to the reference biologic, similar to a comparability exercise that is required for an originator biologic after a manufacturing change. The confidence in biosimilarity, as shown analytically, also provides the basis for the regulatory relief with respect to preclinical and clinical studies, which facilitates an abbreviated biosimilars-approval process. Analytical studies are also useful in determining the type and amount of animal and clinical data that should later be included in the biosimilar-approval application.

However, first the sponsor must show that a candidate product is highly similar to the originator reference product at the analytical level, including structural characteristics. The analytical data required for this purpose could include studies showing the amino acid sequence, higher-order structures, glycosylation, pegylation, and so on, and should also include an analysis of lot-to-lot variability. Structure–function relationships can be analyzed by evaluating pharmacological activity via *in vitro* or *in vivo* experiments, with comparisons being made to the reference product. Sophisticated, high-tech tests such as spectroscopy can be used to measure physiochemical and functional similarity to the originator biologic. Nuclear magnetic resonance or mass spectroscopy can be used to distinguish differences in tertiary and quaternary structures, and gel electrophoresis and reverse-phase, high-performance liquid chromatography (HPLC) can be used to identify disparities in glycosylation patterns, aggregation, and purity. Product-specific colorimetric assays, such as enzyme-linked immuno-sorbent assays (ELISAs) and size exclusion chromatography, can determine the molecular weight and size differences between biosimilars and innovator reference biologics.1

The sponsor company must also perform a detailed analysis of the originator reference product for comparison. Because the originator product will have varied over its lifetime as a result of manufacturing changes (a phenomenon known as "drift"), multiple batches of the reference drug must be acquired, and analyses should be conducted across the shelf life of each of them. These data are then used to create the boundaries, or "goalposts," of acceptable features for the biosimilar.

After the biosimilar product attributes are within these boundaries, the sponsor can conclude that their candidate is "highly similar" to the originator reference product. Any parameter for the biosimilar that is outside the goalposts of the reference product must be demonstrated to have no impact on the clinical attributes of the final product. The draft guidance recommends that the sponsor company describe any differences between the biosimilar and the reference product in detail, explaining how they might potentially affect the safety and purity of the agent.

Validation of Biosimilars through Preclinical and Clinical Studies

The FDA also has the flexibility to decide which, if any, pre-clinical and clinical data are required to support a biosimilar application. When analytical data alone are insufficient to judge whether a biosimilar is comparable to the reference product, the FDA and sponsor company will determine which preclinical and clinical studies are necessary for validation of comparability. The FDA draft guidelines state that "analytical studies and at least one human PK and/or PD study against the reference product licensed under section 351(a) will be required to support a demonstration of biosimilarity." The extent of the preclinical and clinical development program for a biosimilar depends on the degree of comparability that the agent demonstrated analytically.

Comparative clinical efficacy and safety studies also will not always be needed for the approval of a biosimilar. The draft guidelines state that as a scientific matter, comparative safety and effectiveness data will be necessary to support a demonstration of biosimilarity if there are residual uncertainties about the biosimilarity of the

two products based on structural and functional characterization, animal testing, human pharmacokinetic and pharmacodynamic data, and clinical immunogenicity assessment.

The draft guidelines suggest that, in some circumstances, PD data could suffice as evidence of comparable efficacy. However, for many monoclonal antibodies, clinical efficacy trials will likely be required as a rule, because good PD efficacy markers do not exist for these therapies. Comparative clinical efficacy and safety studies will also likely be mandatory for other large, structurally complex, heterogeneous biologics (such as fusion proteins) in order to confirm comparable efficacy and minimize the risk of adverse outcomes.

The FDA draft guidance does explicitly mention the need for sponsor companies to assess immunogenicity in a clinical study unless this requirement is waived by the FDA. Specifically, the draft guidance states that the FDA recognizes that "immunogenicity remains a critical factor when assessing biosimilarity," and the agency provides reassurance that it "will evaluate immunogenicity in a risk-based manner." The biggest concern regarding immunogenicity is that changes in the production process could produce an end product that provokes an immune response in patients. Therefore, when the FDA deems the risk of immunogenicity to be high, large clinical studies will likely be required to assess the risk of the rare life-threatening events associated with this response. However, assessment of immunogenicity could also be achieved through a small pre-submission clinical program, supplemented by postmarketing immunogenicity studies.

Regarding indications, after comparability has been demonstrated, the efficacy and safety of the biosimilar must be justified or demonstrated separately for each indication that has been approved for the originator biologic. Specifically, the FDA draft guidelines state that the potential exists for the proposed product to be licensed for one or more additional conditions of use for which the reference product is licensed. However, the sponsor will need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.

Therefore, the number of approved indications for a bio-similar might be reduced, compared with the reference product. However, in some cases, the FDA does allow data sup-porting biosimilarity in one indication to be extrapolated to support the licensing of a biosimilar for one or more additional indications for which the reference product is approved. This could be accomplished by extrapolating data regarding the mechanism(s) of action, pharmacokinetics and drug distribution, and expected toxicities and immunogenicities, as well as other factors that might affect the efficacy or safety for each indication and for different patient populations. However, extrapolating data from one indication to support another will probably be the exception rather than the rule, even though doing so would eliminate the need for large comparative trials for each indication.

With respect to the off-label use of biologics, whether data demonstrating the efficacy of a biosimilar can be extrapolated to off-label indications is not clear.18 In Europe, such extrapolation is allowed under the premise that if the biosimilar is comparable to the innovator product for one indication, it is likely to be comparable for another.18 However, if the mechanism of action differs between indications, additional clinical data might be needed to assess whether the off-label use of a biosimilar is appropriate

Challenges for Biosimilars from the regulatory perspective

Besides challenges on the biosimilarity demonstration to the reference product and patent hurdles, there are other regulatory challenges for biosimilars. All guidelines require pharmacovigilance and risk management plan (RMP) for biosimilars when the application is submitted. EMA's RMP should provide detailed information on risks and safety concerns. RMP should be proposed by the manufacturer and then submitted to analysis by the regulatory agencies.[38] The RMP for biosimilars should also consider immunogenicity data collection with description of methodology, strategies for monitoring, risk-minimization, and communication.[39] Until now there is no evidence of clinically relevant increase of immunogenicity for approved biosimilars. In the US, pharmacovigilance requirements for biosimilars have not been specified but the post marketing reporting is mandatory considering FDA guidance on Good Pharmacovigilance Practice for products with unknown safety risks.

Other regulatory challenge is related to interchangeability and/or substitution. These terms are often used as synonyms in the US, but not in the EU. According to the European Generic Medicines Association (EGA), interchangeability refers to the prescription of a biosimilar in place of the reference product by prescribers, while substitution means that pharmacists are allowed to dispense a biosimilar. EMA does not guarantee interchangeability and established that these aspects are beyond its competence. Therefore, authorities of each Member State should decide after scientific evaluation performed by CHMP and other data submitted to the regulatory agency on support of the request. Many countries of the EU, such as Italy, Spain, United Kingdom and France, have opposed the automatic substitution by pharmacists. In the US, the determination of interchangeability will be a separate issue from biosimilar's approval and each state will decide on the legislation for substitution, including whether physician or patient would be consulted before pharmacist's dispensation. Overall, due to the intense efforts from originator manufacturers concerning health risks and differences of biosimilars in relation to the reference product, giving uncertainty for prescribers and patients, the application of inter-changeability and/or substitution is limited. The use of biosimilars in the clinic may have a positive impact in the near future, paving the way for adequate decisions.

Extrapolation of indications for biosimilars is another challenge. It is critical to consider that reduced clinical studies conducted by comparability can support extrapolation of indications of biosimilars to other conditions not included in the clinical assessment. The possibility of including approval for all therapeutic indications meant for the original product is one potential advantage to develop biosimilars. The vision of regulatory agencies varies according to the biologic class, and one agency can approve for all indications, while another can approve for few indications. One of the reasons for low acceptance of biosimilars by prescribers is the extrapolation of indications without conduction of specific clinical studies. However, the concept of extrapolation of indications has been practiced by manufactures for a long time through introduction of several minor changes after approval of biologics. EMA has great experience concerning the extrapolation of indications. Filgrastim is indicated for neutropenia induced by chemotherapy and its biosimilar was approved for all indications of the reference product such as transplantation and peripheral blood progenitor cell mobilization. Recently, the filgrastim biosimilar, submitted to FDA in 2014, was unanimously approved for all five indications granted to the reference product Neupogen by Oncologic Drugs Advisory Commitee. A biosimilar for erythropoietin was licensed to renal anemia and the approval for cancer derived anemia was a natural consequence of indication extrapolation. In 2013, EMA approved the first biosimilar mAb (infliximab) with extrapolation of all indications licensed for the reference product. The same mAb was approved at the same condition in Korea and Japan. However, Canada approved biosimilar of infliximab with extrapolation for some indications but not for Crohn's disease and ulcerative colitis indications based on differences found in certain analytical assays.

Remarkable advances have occurred in relation to regulatory requirements for biosimilar application and approval. It is expected that the regulatory agencies become more confident in relation to current challenges and update their guide-lines with more detailed considerations to ensure the benefits of the biosimilars to healthcare providers and mainly to the patients.

The Impact of the Manufacturing Process

To obtain the approval from the regulatory agencies, biosimilars must go through a rigorous development process and demonstrate no clinically significant differences in safety, purity, and potency compared to the reference product. Considering this complex process, it is important to understand how biosimilars are developed. Biosimilars have to follow the same manufacturing process as their reference biologic product, which is very expensive and time-consuming. How-ever, there is a potential time and cost savings when comparing the biosimilar development to that of the reference product because some steps are not necessary in the generation of a similar biologic product. A timeline scheme is presented in Figure 2, representing the general trend for biosimilars development, in which the discovery/research phase and dose finding studies (Phase II clinical trial) are not required, considering that the biosimilar administration regimen uses the same dosing as the reference product. A Phase III study for efficacy equivalence between the biosimilar and its reference product is needed but can be conducted with a smaller

number of patients. The elimination of one phase of the standard clinical trial protocol is not unique to biosimilar development. Recently FDA has issued guidance for expedited clinical program meant to accelerate approval of breakthrough therapies for life threatening indications, with expected reduction in time by approximately 40%. Nonetheless the discovery/research period remains a differential for biosimilar development.

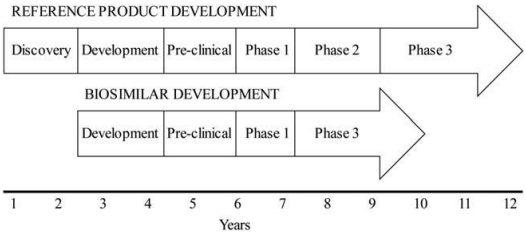


Figure 2.Representative timeline of the steps involved in the development of a biosimilar compared with the reference product (adapted from Hospira website).

Developers of biosimilars usually do not have access to the details of the manufacturing process and active ingredients used for the reference product development. Although following almost the same steps, the inherent variability of the biologic system used and the manufacturing process will not result in a biological product identical to their respective reference product. The only characteristic that will be a copy of the reference product is the amino acid sequence. A comparison of the structural and functional characteristics and the product and process-related impurities of the biosimilar and its reference product will be necessary. Any difference between the products must be justified with regard to the potential impact on the clinical performance of the biosimilar.

Details in the production of biologic products vary from batch to batch and with any manufacturing change that can occur for different reasons, including scaling-up the process to address commercial demand, improving the efficiency of the process, and modernizing the process when major equipment needs to be replaced or updated.

The available comparability protocols allow for these changes to occur, and in the same way, this concept provides support for the biosimilars evolution. The first step in developing a biosimilar is to carefully examine multiple samples of the reference product to determine using analytical techniques how variable this reference is over time and during its shelf life. The biosimilar manufacturers are developing and validating powerful analytical tools to compare their products with the originators. An interesting point is that these improved analytical methods that allow for the detection of even small changes also reveal variability between lots of the reference products currently on the market. The analysis of multiple batches of Aranesp, Rituxan/Mabthera, and Enbrel revealed substantial alterations of the glycosylation profile for all the tested products. In addition, different lots of Rituxan/Mab-thera and Enbrel showed changes in the N- and C-terminal heterogeneity. Rituxan/Mabthera also demonstrated variation in antibody-dependent cell-mediated cytotoxicity (ADCC) activity among the batches tested. The authors of this study concluded that the observed changes were predicted to not result in an altered clinical profile, and therefore all the analyzed products in the tested timeframe are permitted to remain on the market with unaltered labels according to the health authorities.

The use of different expression systems in the development of biosimilars compared with the reference drugs may change the post-translational modifications, such as the glycosylation profile of the protein, which, in turn, could affect the safety or effectiveness of the product. Variations in the glycosylation protein pattern can alter the immunogenicity or clearance of the final product. Moreover, minor modifications in the formulation of biological products that affect inactive ingredients or changes in the primary packaging materials may also alter immunogenicity. This situation can be illustrated by the case of the anti-anemic reference drug EprexVR, in which increased immunogenic responses and elevated rates of pure red cell aplasia were observed following a process change that replaced human serum albumin with polysorbate 80 and glycine as excipients. The mechanism by which EprexVR induced pure red cell aplasia is still not fully understood, but it seems to be the result of an increase in the levels of aggregates during storage, although the levels were not reported to have exceeded the specifications.

The development of biosimilars to replace the biopharmaceuticals for which the patents have expired or are about to expire led to new concepts in manufacturing processes. The produc-

tion facilities relied on the use of relatively inflexible, hard-piped equipment, including large stainless steel bioreactors, and tanks to hold product intermediates and buffers, which are now being substituted for single-use counterparts for the development of biosimilars and also in the development of new products. Some advantages for the adoption of single-use or disposable technologies for the biopharmaceuticals manufacturing are: (1) reduced capital costs for plant construction and commissioning; (2) reduced risk for product cross-contamination in a multiproduct facility; (3) rapid changeover; (4) lower utility costs due to a reduced need for steaming-in-place (SIP); and (5) reduced need for cleaning validation. A case study performed by Paıs-Chanfrau and collaborators (2009) showed that a hybrid plant with significant integration of disposable technology reduced capital costs by up to 40% compared with an exclu-sive stainless steel facility. The need to reduce timelines and initial costs, while relying on multipurpose plants, are all aspects needed for the development of biosimilars. To a great extent, these necessities have helped push the single-use components industry.

Comparability of Biosimilars

Comparability protocols emerged from the FDA's 1996 guidelines and were applied to approved biologics for which sponsors introduced changes to improve the manufacturing process or to implement new equipment or modern analytical assays. There are regulatory requirements to com-pare the similarity of the products before and after the change without having to apply for a new product development program. Based on this FDA guideline, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q5E comparability regulatory guidelines were issued which indicated that the comparability protocol could be adopted also during preclinical and clinical studies. These two guidelines were the basis for the comparability standards that were applied to biosimilar products being submitted for approval by the regulatory agency. These standards indicate that the product of one manufacturer is compared with the reference drug of another manufacturer. Bioprocess manufacturing in the development of biosimilars can promote small changes in the structure of the biologics that can affect their function due to the host cell and the environment in which cells grow. Structural changes occur due to post-translational modifications such as glycosylation patterning. The glycoform profile of biologics is one of most important aspects and should be well characterized due to their potential impact on clinical outcome. In the case of biosimilars, the comparability exercise demonstrates the expected biosimilarity which is verified by a complete analytical characterization of the product in comparison to the reference product. Initially, a detailed characterization of reference product should be performed using orthogonal analytical tools to establish acceptable product attributes, taking into account the multiple batches of the original product. These analytical parameters are the specifications for the biosimilars.

Biomolecular analyses of biologics are performed for the product characterization, and they are very important factors in the bioprocess. The analyses are composed of three categories: physicochemical, immunological, and biological assays. Overall assay development and validation can cost around US $1.5 million. Physicochemical assays are performed from the beginning until the final step of the bioprocess and account for 66–75% of the product characterization. They can take 400–800 work hours to develop and validate. The immunological properties of the biologics should also be characterized. Bioassays provide information about critical characteristics related to the function of the product and its efficacy. These assays require more time to develop and represent 15% of the total number of assays. Further-more, bioassays are used for the selection of the drug-candidate, product release, stability assessment, and comparability studies to support process changes or biosimilarity. In relation to mAb biological functions, special attention is necessary because the effector functions should be evaluated even if the product activity does not require these functions. The same procedure should be performed with the biosimilar and its reference product. However, it is difficult to evaluate the impact on the safety of biologics by bioassays, and regulatory agencies demand clinical trials and post-marketing studies to assure the safety and efficacy of biosimilars.

Biosimilars should be characterized by analytical assays as accurately and thoroughly as possible by comparability studies. Demonstration of the high level of analytical similarity between the biosimilar and the reference product is the first step of these studies. Therefore, all the structural

elements of the protein and all the modifications should be evaluated with the capability to detect differences between the biosimilar and the reference products. Based on the observed characteristics of the reference product, the quality target product profile (QTPP) is defined for the biosimilar, including the variability and impurities found among the reference product lots since the early steps of development. Analytical techniques to release batches of innovator biologics showed little variability when the product was approved in the beginning of 2000s. However, the current advanced technologies avail-able for biosimilars comparability studies reveal differences in batches even of the originator products manufactured on different geographical places or due to manufacturing changes or simply lot to lot variation. Therefore, the question is how best to describe the similarity of these products.

Table 2. Physicochemical and Biological Characterizations from the Comparability Studies of the Biosimilar Remsima

Characteristic	Attribute	Analytical Tool
Primary structure	Amino acid sequence	RP-HPLC, LC-ESI-MS, LC-ESI-MS peptide mapping
Higher order structure	Disulfide structure Free thiol analysis Secondary and tertiary structure Thermal stability	LC-ESI-MS peptide mapping Elman assay CD, FTIR, Antibody conformational array, X-ray crystallography DSC
Purity	Monomer content	SEC-HPLC, SEC-MALS, SV-AUC, CE-SDS
Charge heterogeneity/amino acid modification	Charged isoforms, Deamidation/oxidation/C-terminal variants	IEF, IEC-HPLC, LC-MS peptide mapping
Glycosylation	N-glycan analysis Glycosylation occurrence Oligosaccharide profile Sialic acid analysis Monosaccharide content (fucose, GlcNAc, galactose, and mannose)	LC-MS CE-SDS HPLC HPAEC-PAD HPAEC-PAD
Potency	Antigen and C1q binding FcRn binding Antigen neutralization Apoptosis CDC	ELISA SPR Cell-based neutralization assay Cell-based apoptosis assay Cell-based CDC assay

Abbrevations:
CD, circular dichroism spectroscopy; CE-SDS, capillary sodium dodecyl sulfate gel electrophoresis; DSC, differential scanning calorimetry; ELISA, enzyme-linked immunosorbent assay; FTIR, Fourier transform infrared spectroscopy; GlcNAc, N-acetylglucosamine; HPAEC-PAD, anion exchange chromatography with the pulsed amperometric detection; IEF, isoelectric focusing; IEC-HPLC, ion exchange chromatography; LC-ESI-MS, liquid chroma-tography electrospray ionization mass spectrometry; RP-HPLC, reversed-phase high-performance liquid chromatography; SEC-HPLC, size-exclusion chromatography; SEC-MALS, SEC-multi angle light scattering; SPR, surface plasmon resonance; SV-AUC, sedimentation velocity analytical ultracentrifugation.

The goal is to perform analytical assays that allow for the analysis of both physicochemical and biological functions of the drugs. It is difficult to determine the number of assays required to fully characterize biosimilars, but it should be sufficient to demonstrate biosimilarity. Furthermore,

analytical assays should be developed, qualified, and validated, despite the time-consuming nature of these. A comparability study was performed using standard quality control assays for epoetins (two original products and two biosimilars) and glycosylation profile and potency differences were found among them. Recent advances in analytical tools allow the characterization of biosimilars in accurate and robust ways that were not possible when the reference products were developed and approved. State-of-art liquid chromatography (LC) and mass spectrometry (MS) were used to compare the identity of a biosimilar mAb and its reference product and verify the presence of sequence variants and post-translational modifications (PTMs), such as the glycosy-lation profile.

Structural information of biologics, such as the conformation stability profile, is very important in ensuring their functional properties. These characteristics for higher order protein structure are used for comparability studies at the early and late steps to demonstrate evidence of similarity. Several examples of analytical tools to determine the high order protein structure are 2D NMR ($^{1}H/^{15}N$) fingerprinting, hydrogen-deuterium exchange mass spectroscopy (H/DX-MS), circular dichroism (CD), Fourier transform infra-red (FTIR), and differential scanning calorimetry. 2D NMR fingerprinting is useful to evaluate the integrity of the protein structure by analyzing the spectra of the biologics. H/DX-MS assesses the formulation conditions and reflects the solution conformation of the proteins by identifying flexible and rigid domains. CD and FTIR are known methods used to analyze the secondary protein structure, that is, the alpha and beta sheet content. Differential scanning calorimetry evaluates the thermal stability of biologics by monitoring the conformational stability during heating. The application of the above-mentioned higher-order protein structure analyses gives complementary information about biologics and their reference and can increase the understanding of their mechanisms of action.

Specific guidelines for biosimilar mAbs were issued by the EMA determining that biological activity should be characterized by a comparability study using sensitive immunological methods able to detect differences between a biosimilar and its reference. In vitro assays that need to be performed in the testing include binding efficacy to antigen and Fc gamma receptors, neutralization of antigen, and effector function related to Fc (ADCC; complement-dependent cytotoxicity, CDC). Each mAb has a unique pro-file in relation to these characteristics, and the assays should account for the properties of the mAb in development. Bio-assays usually present great variability, especially when per-formed with human-derived material, making the comparison between the biosimilar and the reference mAb still more difficult. The design space should be defined to account for such variability and simultaneously ensure product quality. Some companies have engineered human cell lines to be used in bioassays and thus avoid the use of human blood cells.

Recently the physicochemical characterization, including state-of the art and higher order structure techniques, of the comparability study for the first biosimilar mAb approved by EMA, Remsima (infliximab), was published. Other studies such as the biological characterization, non-clinical studies, and clinical trials were performed and showed a high similarity to the reference product. Table 2 summarizes the analytical assays used in the comparability studies of Remsima to the reference product. A biosimilar of rituximab (GP2013) was characterized by its physicochemical and bio-logical properties in a comparability study, and it was shown to be highly similar. These extensive studies serve as the basis for mAb biosimilar manufacturers to develop comparability studies that are as comprehensive as the ones that led to Remsima's approval.

In addition to the analytical characterizations of biosimilars, comparability studies should include the non-clinical and clinical studies. The PK evaluation by quantitative assays to measure biosimilar and reference products in the patient serum is mandatory. An overview containing the strategies to demonstrate the PK similarity study using a single analytical method with statistical evaluation was recently described.

QbD approach to Biosimilars

An important aspect of the path to demonstrate biosimilarity depends on bioprocesses parameters. Bioprocesses generally involve many parameters that can be interlinked or independent and introduce additional variability, including changes in the raw materials, operators, facilities, and equipment. Because of the necessity to ensure product quality for pharmaceutical and bio-

pharmaceutical drugs, in addition to providing an in-depth understanding of product and process manufacturing, regulatory agencies such as the FDA implement new approaches based on scientific principles to guarantee quality and understanding of the drug and manufacturing processes. The first initiative for the risk-based approach for current pharmaceutical Good Manufacturing Practices (cGMPs) was introduced by FDA in 2002. Then, the process analytical technology (PAT) Guidance for Indus-try was issued to help in designing, developing, and implementing efficient tools during manufacturing and for quality assurance.

The ICH has published quality guidelines, based on GMP risk management for pharmaceutical and biological products since 2005. Q8 and Q11 are guidelines for the development of products and the manufacturing process, respectively. These documents represent the basis for the application of the modern quality approach known as Quality by Design (QbD). Briefly, QbD is composed of the following steps: define the QTPP and determine the critical quality attributes (CQAs) for the product and process steps, define the parameters of the process to be controlled to guarantee CQAs, determine the operating ranges of such parameters to consistently yield acceptable product, and, finally, define the design space (manufacturing area that ensures CQAs). Q9, the quality risk management guideline, contains important concepts for the successful implementation of QbD. The application of Q9 and sophisticated experimental design, followed by statistical evaluation, allow for the manufacturer to define the critical raw materials and those that have low impact on the process, while also determining critical process parameters to establish the appropriate manufacturing controls. After these studies, it is possible to select the attributes to be monitored and controlled in a design space. Any changes performed inside the design space are acceptable and can be released, but do not request regulatory approval. Q10, the pharmaceutical quality system guideline, complements GMP and plays a critical role in building a robust quality system into the process. The parameters of QbD are integrated in the Q10 approach, allowing for process control. The application of the QbD concepts into bioprocesses of complex biologics has great advantages for innovator and biosimilar manufacturers to provide high product quality standards. Some advantages are previous in-depth knowledge of cell culture characteristics, reduced time to set-up large scale manufacturing, identification of culture batches that do not attend specifications, and a reduction of manufacturing failures. Furthermore, QbD helps to ensure homogeneity and quality of the final product. These properties may have impact on the safety and therapeutic effectiveness.

The overall effect of the bioprocess parameters on the quality of a final drug product is difficult to analyze. The use of statistical design of experiments (DoE) methods in the QbD approach aids in understanding the effects of possible multiple combinations and interactions of various parameters on the final drug quality. The DoE strategy is scientific-based and leads to the determination of a design space and strategies for in-process manufacturing control. The FDA initiated a pilot program regarding QbD for small molecules, and this experience was very useful and led them to issue a pilot program for biologics. In 2009, Genentech and Roche submitted two applications for biologics to the FDA QbD pilot, and both applications obtained approvals in 2013. The expectation of the FDA is that the experience gained by these pilot programs will help in the development of specific guidelines for implementing QbD and the risk-based approach. Another expectation is that the positive experiences of both industry and regulators will facilitate the implementation of these high quality approaches since the early stage-development of biosimilars. Although it necessitates a large investment to develop and implement the project and manage these approaches, when the bioprocess starts working, it will be easier to control or introduce small changes in the manufacturing process because of the previous knowledge of whole product process. This guarantees a time saving, high quality product and, consequently, better efficacy of treatment for the patients.

After the publication of the ICH guidelines, to synchronize and facilitate the implementation of QbD, the FDA and EMA began a pilot program for the parallel assessment of QbD applications for chemical substances in 2011. This effort resulted in two question-and-answer documents, and in April 2014, a 2-year-extension of the program was announced. It is expected that a similar pilot program will be extended to implement QbD for biologics. These pro-grams will bring benefits to both biotechnological industries, in-

cluding biosimilars producers, and regulatory agencies.

Controversies Regarding Biosimilars

While final FDA guidance regarding the biosimilar regulatory pathway is pending, key issues are being debated. Topics of discussion include to what extent the biosimilars regulatory pathway should be abbreviated, how much and which types of clinical and interchangeability data should be required, and even which convention biosimilar product names should follow.

Regulatory authorities and sponsor companies generally agree that if a biosimilar undergoes a comparability exercise showing that it is as close to the originator product as the originator product is to itself after manufacturing changes, then an abbreviated clinical trial program can be justified. However, although the development of a biosimilar may, in theory, resemble a change in manufacturing process for a biologic, these endeavors are in fact quite different.

One important consideration is that the development of a manufacturing process for a biosimilar is performed entirely without full access to the documentation regarding the evolution of the innovator product. Therefore, there is a much greater potential for differences between an innovator biologic and a biosimilar than for a branded biologic after a manufacturing change. The FDA has acknowledged this issue by stating in its draft guidance:

Demonstrating that a proposed product is biosimilar to a reference product typically will be more complex than assessing the comparability of a product before and after manufacturing changes made by the same manufacturer. This is because a manufacturer who modifies its own manufacturing process has extensive knowledge and information about the product and the existing process, including established controls and acceptance parameters. In contrast, the manufacturer of a proposed product will likely have a different manufacturing process (e.g., different cell line, raw materials, equipment, processes, process controls, and acceptance criteria) from that of the reference product and no direct knowledge of the manufacturing process for the reference product. Therefore, in general, more data and information will be needed to establish biosimilarity than would be needed to establish that a manufacturer's post-manufacturing change product is comparable to the pre-manufacturing change product.

Current analytical techniques and abbreviated clinical studies might not be able to detect all of the potential differences in clinical outcomes between a biosimilar and the reference product. One problem with analytic studies is that they measure specific variables and are not able to predict all biological activity in patients, leaving open the possibility of overlooking characteristics of the proposed biosimilar that may signal safety or other problems. For example, even sophisticated *in vivo* models are not able to provide definitive conclusions regarding immunogenicity, because many immune responses are species-specific. There are also published examples in which unexpected clinical findings were observed following a major manufacturing process change for a biologic. Such examples demonstrate the need for clinical studies to assess the efficacy and safety of a biosimilar, especially when analytical studies are insufficient for assessing risks.

Another concern is that the cost-savings accrued by an abbreviated biosimilars approval pathway won't make up for the possible resultant losses in the efficacy, safety, or quality of these agents. However, requiring biosimilars to undergo a full development program (including extensive clinical trials) is not considered to be a viable approach, especially for lower-priced agents. If sponsor companies aren't granted significant regulatory relief regarding submission requirements for preclinical and clinical studies, the biosimilars pathway may reach an impasse. The value offered by the biosimilar regulatory pathway would then be in question, particularly since the sponsor company could achieve 12 years of product exclusivity by instead taking the standard BLA route. Despite concerns regarding potential negative effects of an abbreviated regulatory pathway on product quality, the experience in Europe has been that biosimilars that have undergone the expedited approval process provide cost savings and improved patient access without compromising therapeutic or safety outcomes.

To date, American companies have been hesitant to aggressively pursue a biosimilar pipeline without formal clarification of the data that the FDA will expect to see in 351(k) applications.16 When the FDA finalizes the guidance for the biosimilar regulatory pathway, the approval process will probably take at least 2 years; therefore, the

entry of biosimilars into the U.S. market is also expected to be delayed until 2015 at the earliest

Approval process for biosimilar products

All FDA-approved biological products, including reference products and biosimilar products, undergo a rigorous evaluation so that patients can be assured of the efficacy, safety, and quality of these products.

A reference product is the single biological product, already approved by FDA, against which a proposed biosimilar product is compared. A reference product is approved in a "standalone" application that must contain all data and information necessary to demonstrate its safety and effectiveness. Generally, the data and information necessary to demonstrate the safety and effectiveness of a reference product will include clinical trials for the disease indications being sought by the manufacturer.

A biosimilar is highly similar to, and has no clinically meaningful differences in safety, purity, and potency (safety and effectiveness) from, an existing FDA-approved reference product. The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed biosimilar product and the reference product, not to independently establish the safety and effectiveness of the proposed product. The manufacturer of a proposed biosimilar product generates an array of data comparing the proposed product to the FDA-approved reference product in order to demonstrate biosimilarity. The comparative data are generated and evaluated

When considering licensure of a biosimilar product, FDA reviews the totality of the data and information, including the foundation of detailed analytical (structural and functional) characterization, animal studies if necessary, then moving on to clinical pharmacology studies and, as needed, other comparative clinical studies. In a stepwise fashion that begins with a foundation of detailed analytical (structural and functional) characterization and comparison of the products, moving on to animal studies if necessary and then to comparative clinical studies.

Consequently, rather than generating the same full profile of nonclinical and clinical data as the reference product, a manufacturer that shows its proposed biosimilar product is highly similar to and has no clinically meaningful differences from the FDA-approved reference product may rely in part on FDA's previous determination of safety and effectiveness for the reference product for approval. This generally means that biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products, additional therapeutic options, and reduced costs for patients.

What data are required for approval of a biosimilar or interchangeable product?

A biosimilar product application must include data demonstrating biosimilarity to the reference product. This usually includes data from - Analytical studies demonstrating that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components;

Animal studies, including an assessment of toxicity; and A clinical study or studies sufficient to demonstrate safety, purity, and potency of the proposed biosimilar product in one or more of the indications for which the reference product is licensed. This typically includes assessing immunogenicity, pharmacokinetics (PK), and, in some cases, pharmacodynamics (PD) and may also include a comparative clinical study. In addition to the data listed above, an application for an interchangeable product must also include information or data demonstrating that:

The proposed interchangeable product is expected to produce the same clinical result as the reference product in any given patient; and, For a product administered more than once to an individual, switching between the proposed interchangeable product and the reference product does not increase safety risks or decrease effectiveness compared to using the reference product without such switching between products

Do all biosimilar applications have the same types of data?

The bullets above outline the types of data and information to be included in a biosimilar product application. FDA evaluates each biosimilar product on a case-specific basis to determine what data are needed to demonstrate biosimilarity and which data elements can be waived if deemed scientifically appropriate. This determination may be informed by what is already publicly known about the reference product.

Many factors can help tailor the data requirements for each biosimilar application. Some ex-

amples include:

- The strength and robustness of the comparative analytical studies showing similar structure and function between the proposed biosimilar and the reference product. For example, analytical similarity data showing very few analytical differences may provide strong support that the proposed product is highly similar.How similar the PK and PD profiles are between the biosimilar and reference product.

- Pre-existing information about the safety profile of the reference product. For example, if it is known that patients have the potential to develop immune responses with adverse outcomes to the reference product, FDA will likely require a more rigorous evaluation of immune responses with the biosimilar.

Why do we need an abbreviated approval pathway for biological products?

Biological products are the fastest-growing class of therapeutic products in the United States and account for a substantial and increasing portion of health care costs. Congress, through the Biologics Price Competition and Innovation Act, created an abbreviated approval pathway to provide the public with greater access to safe and effective biological products. This pathway provides more treatment options, potentially lowering health care costs through competition and increasing access to lifesaving medications.

Can a biosimilar be approved for an indication that is approved for the reference product even if the biosimilar is not directly studied in that indication?

Yes, a biosimilar product may be approved for an indication without direct studies of the biosimilar in that indication. If the total evidence in the biosimilar application supports a demonstration of biosimilarity for at least one of the reference product's indications, then it is possible for the biosimilar manufacturer to use data and information to scientifically justify approval for other indications that were not directly studied by the biosimilar manufacturer. This concept is called "extrapolation" and is critical to the goals of an abbreviated pathway—improving access and options at a potentially lower cost.

Extrapolation is based on (1) all available data and information in the biosimilar application, (2) FDA's previous finding of safety and efficacy for other approved indications for the reference product, and (3) knowledge and consideration of various scientific factors for each indication. Extrapolation is not an assumption that the data from one directly studied indication or population alone is sufficient to support approval in a different non-studied indication or population. The biosimilar manufacturer must provide scientific justification to support extrapolation.

These scientific justification factors include knowledge of the mechanism(s) of action, PK, PD, efficacy, safety, and immunogenicity of the reference product in each of its approved indications. FDA evaluates all of the biosimilar product data to assess whether there are differences between the biosimilar and the reference product that may affect these scientific factors in any of the indications or populations not directly studied by the biosimilar manufacturer. If no such differences are identified, approval of the biosimilar for other non-studied indications or populations is generally supported.

FDA works with biosimilar manufacturers during product development to determine what data are needed to support extrapolation. Remember that a reference product manufacturer must show its product is safe and effective for each indication for which approval is sought, most often through indication-specific clinical trials. Since the goals of a biosimilar development program are different from those of a reference product development program (see the first question above), it is generally unnecessary from a scientific perspective to require a biosimilar manufacturer to conduct clinical trials in all the same disease indications for which the reference product was studied and approved.

Concluding Remarks

Biosimilars have been evolving over time; the less complex molecules, some produced in microorganisms, were followed by recombinant mammalian cell derived proteins with varying degrees of complexity until the heavily glycosylated biosimilar of erythropoietin was approved. Now, the time for mAbs has arrived and the market will be boosted by a number of alternatives already in clinical trials. At the same time that the big pharma faces the challenge of losing market exclusiveness, some of these companies are developing biosimilars from other original manufacturers while pursuing new biologics in their development pipeline.

It is clear that the industry of biosimilars brings

benefits for both science and healthcare. Producing copies of a com-parable biological medicine to a reference product that is already in use is not easy, especially reducing the production costs to attain market feasibility. Obtaining cell lines with higher productivity for the manufacturing processes, tight control parameters to avoid heterogeneity beyond the reference product are important especially in the biosimilars industry. Understanding lot to lot variability and space design for QbD implementation is critical in the development of powerful analytical tools. The in-depth analysis of different lots of branded mAbs produced over time has added to the knowledge-base in the biotech and pharma industries. It is important to consider the link between the manufacturing variability and clinical outcome in the differences found in the lots of marketed mAbs, as not necessarily the differences imply in clinical significance.

Many contract manufacturing companies were launched on the premise of pursuing biosimilar development and the need to cut time schedules, together with developing new concepts in manufacturing processes by the adoption of the single-use technology. Biosimilars are here to stay and the biosimilar mAbs are on the cusp to attain approval from quality and safety regulators as well as the confidence of health authorities, doctors, and patients.

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