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A REVIEW STUDY ON BIOSIMILARS AND BIOBETTERS

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ABSTRACT

As the patents for several innovator biologicals expire, Pharmaceutical/biopharmaceutical companies are taking the opportunity to develop more reasonable forms creating a rapidly booming biosimilars market. However, as the field of biosimilars develops, challenges in immunogenicity studies, securing market share, exclusivity and regulations still persist. The attractiveness of the biosimilar regulatory pathway is threatened by so-called biobetters. This paper provides brief information and an overview of recent developments. Biobetters or biosuperiors are new biologic entities that are better versions of an innovative biologic. The variation from the original biologic may be in the form of improved efficacy/potency, safety, immunogenicity or a change in the route of delivery or dosing frequency or improvements in manufacturing processes. Certain biobetters may find use in different or broader patient groups. Their amino acid sequences very closely resemble the original biologic, but are slightly modified. The modification is achieved using platform technologies such as chemical modification, protein fusion, altered amino acid sequence, humanization of the glycosylation pattern, or innovative delivery to create a product with superior characteristics. Biobetters, thus, can be considered as hybrids which straddle the space between biosimilars and classical new biologic entities (NBEs), although they are regulated as innovative drugs. The development of biobetters is a key threat to companies pursuing biosimilars of the original biologic. A biobetter with improved efficacy over the original biologic could pose significant challenges to the uptake of a biosimilar. Biobetters create value for physicians and patients by providing meaningful improvements over the original biologic, and for pharmaceutical manufacturers by providing another potential source of "branded" product revenue and risk modification.

Key words: Biosimilars, Biobetters, FDA, EMA, RNA, (NBEs), rDNA.

INTRODUCTION

Definition of Bio similar?

Biosimilars – are products that are "highly similar" to the biologic reference product(s) regarding quality, biological activity, safety and efficacy.

- The Biologics price competition and innovation Act of 2009 (BCPI Act) signed into law March 23, 2010
- BPCI Act creates an abbreviated licensure pathway for the biological products shown to be "highly similar" to and/or "interchangeable" to an FDA licensed reference product
- Biosimilars are not generics – due to complex nature and produced in living systems it can never duplicate the originator
- Do not follow the same regulatory pathway as a generic 351(K) Vs 505(j) (Generic/ANDA)
- Perceived to be a lower business risk Vs original biologic
- Follows stringent legal and regulatory pathways across the globe
- No exclusivity granted for the "higher similar" status / 1 year Exclusivity granted for "interchangeability" status
- Approval across all indications for the reference biologic is possible
- Must wait for the Innovator's patent to expire prior to submitting to FDA for approval

Definition of biobetter?

Biobetter – is a biological that has been structurally and/or functionally altered to achieve an improved or different clinical performance (eg, altered structure, compared to an already approved biologic product)

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- Chemical modification (PEGylation, Glycosylation), New formulation (Novel ROA, modified released)
- Longer half-life, less immunogenic, better efficacy, better safety, less frequent dosing, better purity, longer shelf-life etc.

- The term "biobetter" surfaced in context to biologics price competition and innovation Act
(BCPI Act 2010 – "Biosimilars Act")
- Given the stringent regulatory requirements of highly similar and interchangeability
required for a biosimilar, sponsors turned their interest to biobetters.
- 351(a) – BLA same as the originator regulatory pathway
- Perceived to be a lower business risk Vs original biologic
- Exclusivity (eg, 12 years) and patentable.

FDA Guidance for Biobetters

Meetings and guidance would follow standard practice for new BLAs

Type A meetings- a meeting requested to help an otherwise stalled product development program to proceed

- Dispute resolution, clinical holds, SPA
- Type A meetings should be scheduled within 30 days of the date of the written request

Type B Meetings –

- PIND, EOP1, EOP2, Pre-Phase 3, Pre – BLA
- Occur within 60 days of FDA written receipt of a meeting request

Type C Meetings

- Any other meeting that does not fall under Type A or Type B
- Occurs 75 days receipt of written request

The term biobetter refers to a recombinant protein drug that is in the same class as an existing biopharmaceutical but is not identical; it is improved over the original. Biobetters build on the success of existing, approved biologics but are considered less of a commercial risk than developing a brand new class of biologic.

- Biobetters are not entirely new drugs and they aren't generic versions of drugs, either.
- While many consider biosimilars to be generic versions of biotech drugs, it isn't possible to create a generic biologic drug. That's because biopharmaceuticals are produced in living organisms - such as animals or bacteria - and cannot be copied exactly.
- Congress has authorized the US Food and Drug Administration (FDA) to develop a regulatory approval pathway biosimilars, but the process is a complicated one which must address many concerns, and the pathway has not yet finalized.
- Rather than wait for the process to be completed, some drug manufacturers are opting to invest in the development of biobetters.
- Advantages of Skipping Biosimilar Development in Favor of Developing a Biobetter
- First generation biologics -- such as insulin and early recombinant forms of human growth hormone - are generally immediate-release drugs that are delivered via infusion or subcutaneously. Biobetters are being developed using protein or glyco-engineering which, experts say, reduces the risk of immunogenicity, makes the drug safer and more effective, and requires lower dosing.
- A biobetter has the same target as the original biological, but its effect on the target lasts for an extended period of time.
- Because a biobetter is a new drug, it will enjoy 12 years of market protection in the US and other markets, unlike a biosimilar. In addition, biobetters tend to have lower R and D costs.
- Many of the first generation biologics are going off-patent and will face competition from biosimilars.
- It remains to be seen if biobetters will be competitive.

Companies Developing Biobetters

- Novo Nordisk, Merck & Co, Roche Group, Biogen Idec, Amgen, Sanofi-Aventis, Eli Lilly and GlaxoSmithKline have all expressed interest in the development of biobetter drugs. Several are acquiring smaller, innovative bio-pharmaceutical companies that have promising pipelines.
- For example, British pharma AstraZeneca purchased the biotech company MedImmune which intends to focus on biobetter R&D.
- The Edmonton, Alberta, company Compass Biotechnologies, Inc., announced in late December 2011 that it is focusing on development of improved biosimilar proteins such as EPO and G-CSF.
- Compass also has an agreement to source recombinant protein biosimilars manufactured in "CHO" cells from PanGen Biotech of Seoul, South Korea, and an agreement with Arecor Ltd. of Cambridge, England, to develop a biobetter, heat-stable formulation of the commercial hepatitis B vaccine.
- K. Srinivas Sashidhar, a research analyst with Frost & Sullivan, wrote that "Biobetters will be the next big opportunity for biopharmaceutical companies and CROs.
- Market participants may look forward to collaborations with these companies in order to develop the improved versions of biologics. Organisations well known for innovation and experience with generics might be best positioned to achieve success with biobetters."
- Some of the biggest challenges facing researchers involved in the development of biobetters are to achieve similarity to the originator molecule and obtaining access to originating company's data, according to Sashidhar.

FDA Guidance for Biosimilars

- **Biosimilar initial Advisory Meeting**

- General discussion regarding feasibility of licensure of particular product under PHS Act
- **BPD Type 1 Meeting**
- Dispute resolution, Clinical holds, SPA, Important safety issue
- Type 1 Meetings should be scheduled within 30 days of the date of the written request
- **BPD Type 2 Meeting**
- Specific Issue: Study design/endpoints and can involve review of substantive data
- **BPD Type 3 Meeting**
- In depth data review and advice meeting –extensive data package
- Analytical similarity data/future proposed clinical trials
- **BPD Type 4 Meeting**
- Discuss the format and content of Biosimilar biological product application

Biobetters versus biosimilars

Biobetters and biosimilars are both follow-on biologics, meaning they are developed with reference to an originator biologic. Biosimilars are designed to be as effective as the originator as possible, while also offering a lower price. Notably, the market uptake of many biosimilars has been a struggle, such that biosimilar developers have been required to rely on discount schemes to get their products in formularies and special contracts.

Many payers are searching for the most affordable treatment option available, which raises the concern of whether they will allow access for biobetters that may cost much more than biosimilars. Dr Merron argues that biosimilars are appealing to payers precisely because of the significant cost savings they offer, but they do not provide clinical advantages, whereas biobetters do. While cost is a major component of most prescription decisions, for some disease areas, demonstrating significantly improved efficacy is a more important element. "In oncology, if a new biologic demonstrates significant and clinically meaningful improvements in efficacy, then despite a marginally higher cost, it will be prescribed," he says. Certainly, the entrance of biobetters will in some way affect the market share of certain biosimilars and originator biologics, but from Dr Merron's perspective, the presence of improved biologics will not diminish the value that biosimilars offer. He explains that the impact of biobetters on biosimilars, and vice versa, will vary depending on a number of factors. Some of these factors are:

- The magnitude of benefit the biobetter demonstrates over the originator
- The cost of the biobetter
- The number of indications the biobetter secures compared with the number of

Indications the originator has secured

- The price discount of the biosimilar
- The biosimilar manufacturer

Table1. Overview: Comparison Biosimilars and Biobetters

Biosimilar	Biobetter
Biosimilars have limitations with respect to structure i.e. they must be similar active compound as that of reference products.	Biobetters do not have structural limitations, it may include molecular/chemical modifications, and would therefore considered to have a different 'active compound' when compared to the originator product.
Biosimilars should have somewhat similar safety and efficacy profiles	Biobetters should have which has improved safety and/or efficacy profiles.
Biosimilars are very similar to innovator products.	Biobetters are modified versions of innovator products.
Biosimilars are supposed to be approved after demonstrating similarity between biosimilar and reference product i.e. through comparability data	Biobetters are like new drugs and supposed to travel through full new drug application or hybrid product application with all necessary clinical/non clinical trials data.
Biosimilars are not entitled to have patent protection or data exclusivity.	Biobetters may obtain patent or data exclusivity based on how innovative they are.

Table 2. FDA guidelines on the data required to satisfy regulatory requirements

Outcome of analytical data	Next steps
'Not similar'	Further development through the 351(k) regulatory pathway is not recommended.
'Similar'	Further analytical information is needed to determine if the product is sufficiently similar to the originator.
'Highly similar'	The biosimilar candidate meets the statutory standard for analytical similarity, meaning pre-clinical and clinical studies are warranted to resolve residual uncertainty and support a demonstration of biosimilarity.
'Highly similar with fingerprint-like similarity'	The biosimilar candidate meets the statutory standard for analytical similarity based on extremely sensitive methods and the sponsor can consider using a more targeted and selective approach to conducting pre-clinical and clinical studies.

Table 3. Market uptake and financial impact of biosimilars in Europe

Biologic	Australia	Canada	European Union	Japan	South Korea	United States
Adalimumab			1			1
Calcitonin						1*
Enoxaparin sodium			2			
Epoetin alpha			3	1		
Epoetin lambda	3					
Epoetin zeta			2			
Etanercept	1	1	1		2	1
Filgrastim (G-CSF)	3	1	9	3		1
Follitropin alpha (FSH)			2			
Glucagon						1*
Hyaluronidase						1*
Infliximab	1	2	3	1	1	1
Insulin glargine	1	1	2	2		1*
Rituximab			1		1	
Somatropin	2	1	2	1	1	1*
Teriparatide			2			
Trastuzumab					1	
Total	**11**	**6**	30†	**8**	**6**	**9**

Figure 1. FDA Approval Pathways

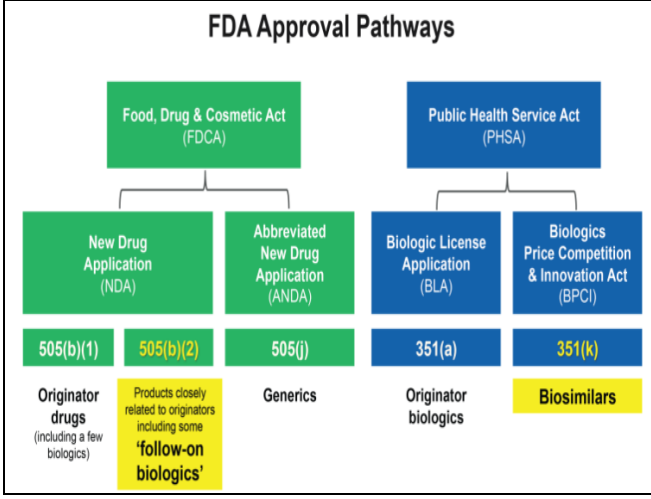
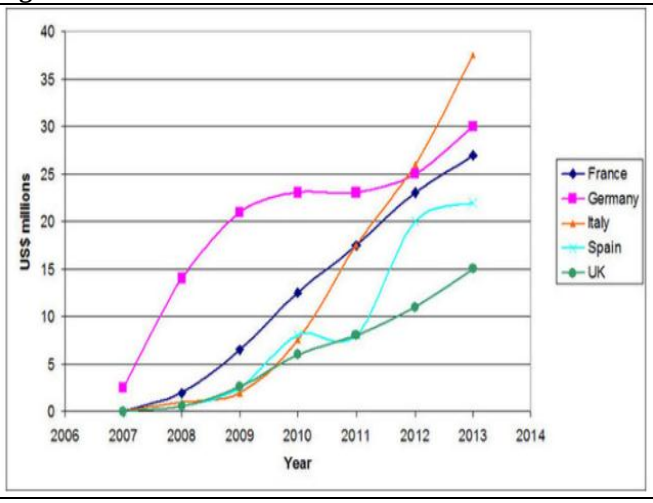


Figure 2. Biosimilar sales across the EU5



Advantage of Biobetters and Biosimilars [1,2]

While biosimilars are supposed to have equal efficacy as that of the originator drug at a reduced price, biobetters will be improved version of originator with some molecular or chemical modification and possibly a reduced side-effect profile. Biobetters are bound to have a higher success rate than originator biologics due to a validated target for the biologic, but an improved biologic is far from certain and may require significant experimentation. Biobetters can also be developed by understanding the protein folding mechanism and its effect on the drug, whereas biosimilars are replica of the originator. Biobetters are based on well-known target theory thus have lower early-stage R&D costs. Biobetters do not have specific regulatory route as there is for biosimilars. A biobetter follows in the footsteps of a drug that has already been shown to be a therapeutic and commercial success; the risk of failure is probably to be fewer than that with most new drugs. A biobetter does not have to wait until a patent expires on the originator product before the product can be launched in the market. Greater potential to avoid infringing patents or at least lower litigation costs since it is not claiming similarity to the originator product. Biobetters have an advantage over biosimilars as they constitute an improvement over the originator and any biosimilar competitors, and should therefore be patentable. A biobetter can command a price premium, as it has a clinical advantage over the originator product. Biobetters should be less cost sensitive when compared to a biosimilar because they are in essence a new compound. As a new chemical entity a biobetter will be given data exclusivity for 12 years in the US and 10 years in the EU.

Intellectual Property Rights

Biobetters/Biosimilars are considered as new biologics and the development process involves extensive clinical/ non clinical study. They may become entitled to enjoy patent protection and marketing exclusivity. It may involve any process which will be a new invention hence become patentable. Patent grants to biobetter vary from country to country based on patent rules [10].

Pharmaceutical companies can opt for strategies of simply improving their own products and coming up with "biobetters" to extend their existing intellectual property rights and get "more mileage out of their chartbuster drugs." There is a problem with this approach though, as "the improvements they make are often incremental in nature. The patent office may oppose this strategy, so the need of hour is to explore other strategies to get biobetters patented [3].

DISCUSSION

Cloning of human genetic material and development of in vitro biological production systems has allowed the production of virtually any recombinant DNA based biological substance for eventual development of a drug. Monoclonal antibody technology combined with recombinant DNA technology has paved the way for tailor-made and targeted medicines. Gene- and cell-based therapies are emerging as new approaches.

Recombinant therapeutic proteins are of a complex nature (composed of a long chain of amino acids, modified amino acids, derivatized by sugar moieties, folded by complex mechanisms). These proteins are made in living cells (bacteria, yeast, animal or human cell lines). The ultimate characteristics of a drug containing a recombinant therapeutic protein are to a large part determined by the process through which they are produced: choice of the cell type, development of the genetically modified cell for production, production process, purification process, formulation of the therapeutic protein into a drug. After the expiry of the patent of approved recombinant drugs (e.g., insulin, human growth hormone, interferons, erythropoietin, monoclonal antibodies and more) any other biotech company can develop and market these biologics (thus called biosimilars). Every biological (or biopharmaceutical products) displays a certain degree of variability, even between different batches of the same product, which is due to the inherent variability of the biological expression system and the manufacturing process. Any kind of reference product has undergone numerous changes in its manufacturing processes, and such changes in the manufacturing process (ranging from a change in the supplier of cell culture media to new purification methods or new manufacturing sites) was substantiated with appropriate data and was approved by the EMA. In contrast, it is mandatory for biosimilars to take a both non-clinical and clinical test that the most sensitive clinical models are asked to show to enable detection of differences between the two products in terms of human pharmacokinetics (PK) and pharmacodynamics (PD), efficacy, safety, and immunogenicity.

The current concept of development of biosimilar mAbs follows the principle that an extensive state of the art physicochemical, analytical and functional comparison of the molecules is complemented by comparative non-clinical and clinical data that establish equivalent efficacy and safety in a clinical "model" indication that is most sensitive to detect any minor differences (if these exist) between biosimilar and its reference mAb also at the clinical level. The European Medicines Agency (EMA) has recognized this fact, which has resulted in the establishment of the term "biosimilar" in recognition that, whilst biosimilar products are similar to the original product, they are not exactly the same. Every biological displays a certain degree of variability. However, provided that structure and function(s), pharmacokinetic profiles and pharmacodynamic effect(s) and/or efficacy can be shown to be comparable for the biosimilar and the reference product, those adverse drug reactions which are related to exaggerated pharmacological effects can also be expected at similar frequencies.

Originally the complexity of biological molecules led to requests for substantial efficacy and safety data for a biosimilar approval. This has been progressively replaced with a greater dependence on assays, from quality through to clinical, that show assay sensitivity sufficient to detect any significant difference in dose. However, the safe application of biologics depends on an informed and appropriate use by healthcare professionals and patients. Introduction of biosimilars also requires a specifically designed pharmacovigilance plan. It is difficult and costly to recreate biologics because the complex proteins are derived from living organisms that are genetically modified. In contrast, small molecule drugs made up of a chemically based compound can be easily replicated and are considerably less expensive to reproduce. In order to be released to the public, biosimilars must be shown to be as close to identical to the parent innovator biologic product based on data compiled through clinical, animal, analytical studies and conformational status.

Generally, once a drug is released in the market by FDA, it has to be re-evaluated for its safety and efficacy once every six months for the first and second years. Afterward, re-evaluations are conducted yearly, and the result of the assessment should be reported to authorities such as FDA. Biosimilars are required to undergo pharmacovigilance (PVG) regulations as its reference product. Thus biosimilars approved by EMEA (European Medicines Agency) are required to submit a risk management plan (RMP) along with the marketing application and have to provide regular safety update reports after the product is in the market. The RMP includes the safety profile of the drug and proposes the prospective pharmacovigilance studies. Several PK studies, such as studies conducted by Committee for Medicinal Products for Human Use (CHMP), have been conducted under various ranges of conditions; Antibodies from an originator's product versus antibodies from an biosimilar; combination therapy and monotherapy; various

diseases, etc. on the purpose to verify comparability in pharmacokinetics of the biosimilar with the reference medicinal product in a sufficiently sensitive and homogeneous population. Importantly, provided that structure and function(s), pharmacokinetic profiles and pharmacodynamic effect(s) and/or efficacy can be shown to be comparable for the biosimilar and the reference product, those adverse drug reactions which are related to exaggerated pharmacological effects can also be expected at similar frequencies. The Patient Protection and Affordable Care Act (Affordable Care Act), signed into law by President Obama on March 23, 2010, amends the Public Health Service Act (PHS Act) to create an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product. These statutory provisions also may be referred to as the *Biologics Price Competition and Innovation Act of 2009* (BPCI Act) [4,5].

To have a product reviewed as a biosimilar or interchangeable, manufacturers must submit a 351(k) biologics license application (BLA) that includes, among other things, information demonstrating Biosimilarity based upon:

- Analytical studies demonstrating that the biological product is "highly similar" to the reference product notwithstanding minor differences in clinically inactive components;
- Animal studies (including the assessment of toxicity); and
- A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD)) sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and for which licensure is sought for the biosimilar product.

FDA may determine, in its discretion, that an element described above is unnecessary in a 351(k) BLA. Therefore, we encourage manufactures to contact the appropriate review division to obtain input on a proposed development program. For a product to be reviewed as an interchangeable product, manufacturers must include information demonstrating Biosimilarity, and include information to show that the proposed interchangeable product is expected to produce the same clinical result as the reference product in any given patient. In addition, for a biological product that is administered more than once to an individual, a sponsor must include information to demonstrate that the risk in terms of safety or diminished efficacy of alternating or switching between use of the proposed interchangeable product and the reference product is not greater than the risk of using the reference product without such alternating or switching.

For any additional questions about the implementation of the BCPI Act and how it relates to an application, please contact:

- The Division of Drug Information in the Center for Drug Evaluation and Research's (CDER) Office of Communications at 855-543-3784, 301-796-3400 or by email to druginfo@fda.hhs.gov , if the reference product for your proposed biosimilar biological product is regulated by CDER.
- The Office of Communication, Outreach and Development (OCOD) at 800-835-4709 or 301-827-1800 or by email to ocod@fda.hhs.gov. If the reference product for a proposed biosimilar product is regulated by the Center for Biologics Evaluation and Research (CBER).

Investing in biosimilars

Biological medicines are revolutionizing healthcare, offering lifesaving treatments, often where none previously exist. Biological medicines have extended the lives of cancer patients, reduced disability for patients with rheumatoid arthritis and provided life-saving replacement proteins for patients with certain rare genetic diseases. However, these medicines are often very expensive, frequently making them unaffordable for patients who might have benefitted from them. But as patents for branded biological medicines approach expiration, bio pharma companies are finding new opportunities in developing biosimilars, or more affordable versions of these lifesaving drugs [6]. The biosimilars field is one of the fastest growing industries globally, largely because many blockbuster biologics will reach patent expiration in the next few years. By the end of 2018, more than 30 innovator biologics with global sales of over $79 billion will have lost patent protection. Growing numbers of biopharmaceutical companies are eager to take advantage of the opportunity presented by biosimilars, and third party capital providers are anxious to support them. But creating a biosimilar isn't easy. While it is relatively simple to reverse-engineer a generic version of a small-molecule drug, the complexity of innovator biological products means that it is impossible to reproduce them exactly. To successful develop a biosimilar and bring it to market takes careful planning and keen understanding the challenges they will face along the way.

Challenge 1: Manufacturing

As mentioned previously, biologics are created from living organisms, and manufacturers can only approximate the complex proprietary process used by the manufacturers of originator biologics. While the primary amino acid backbone of a biosimilar will be identical to that of the originator, any post-translational modifications can affect the purity, safety and efficacy of the product. Even minor batch-to-batch variation in biological products or minor changes to existing manufacturing lines must be monitored carefully as it may affect biological activity, safety and immunogenicity. Capital providers also need to consider the suitability of the proposed formulation with regard to potency, stability and compatibility with excipients, diluents and packaging materials. For these reasons, only a select number of companies have access to the appropriate manufacturing expertise and the Good Manufacturing Practice (GMP) facilities required to produce biosimilars of the standard demanded by

regulators. Such expertise must be taken into account when investment decisions are being made.

Challenge Two: Immunogenicity as part of safety requirements

In the late 1990s, a manufacturing site change of an originator erythropoietin product coupled with a change in the stoppers used for certain containers caused an immune response that dramatically increased the frequency of pure red cell aplasia cases, forcing some patients to need blood transfusions and dialysis. The problem was subsequently resolved, but this salutary lesson is an example of why the European Medicines Agency (EMA), and the US Food and Drug Administration (FDA) established rules for the similarity of both structure and functional activity of biosimilars to those of the innovator/reference product. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) currently offers a guideline on the comparability assessment required when a sponsor of an approved biologic envisions making manufacturing changes. This guideline can help investors and developers understand the evidence they need to gather to prove that the manufacturing process changes will not have an adverse impact on the quality, safety and efficacy of the drug product. It can also help them calculate the added time and expense that such changes will add to their development lifecycle.

Challenge Three: PK/PD and Clinical Trial Design and Execution

The EMA and FDA have published several guidance documents detailing regulatory expectations and specific biosimilar product testing strategies for manufacturing, quality, nonclinical and clinical efficacy, safety, and immunogenicity comparability assessments. Both FDA and EMA recommend a strategic, stepwise development that should result in a targeted approach to nonclinical and clinical studies on a case-per-case basis. These include the need for comparative human pharmacokinetic (PK) -- and relevant pharmacodynamics (PD) studies if they are available, with the U.S. or EU-licensed reference product; and a crossover design for PK/PD studies of products with a short half-life (i.e. less than five days) and for products with a low immunogenic response. Investors and developers should note that clinical development requirements for biosimilars are complex and extensive, particularly if a PD marker is not available. A partner with suitable credentials needs to be identified to run the Phase 1 PK/PD work as well as the Phase 3 clinical trials. With more clinical trials being conducted globally, CROs with a global footprint will usually be better placed as partners for the development of biosimilars than smaller CROs.

Challenge Four: Capital

Due to the potential risks associated with biosimilar development, including the cost of litigation when originator manufacturers fight to protect their franchises, third-party capital providers are proceeding cautiously. This caution is likely to continue in the near term, although as more clinical experience is gained with biosimilars, more originator products come off patent, and more regulatory approvals for biosimilars are granted the perceived risks are likely to diminish. In the interim, most deals have a return structure related to milestones (e.g., regulatory approval or successful completion of a Phase 3 trial), or royalties from the sale of the biosimilar once marketed, to help them manage the commercial risk.

In order to leverage capital to pursue biosimilars programs, investors may focus on dedicated manufacturing capabilities, single products or portfolios of products. If a single source of capital is insufficient for a particular deal, syndication can be considered. It is highly advantageous to partner with a service company with the geographical scope needed to execute all clinically related work (PK/PD and clinical trials) required for regulatory submission. In addition, market exclusivity and interchangeability considerations need to be built into investment models and strategies because these pathways have the potential to change in the future.

Challenge Five: Exclusivity and IP

With the FDA's Biologics Price Competition and Innovation Act (BPCI Act) of 2010, the biotechnology industry won its long fight to preserve a lengthy period of exclusivity for innovator products, but this decision may now be in question. New innovator biologics are currently granted 12 years of market exclusivity in the US, whereas small-molecule drugs normally receive only three to five years. However, in an effort to drive prices down, debate continues about reducing the biologic exclusivity period from 12 to seven years – more in line with other countries (e.g., Europe and South Korea provide eight years' exclusivity; Japan and Canada each provide six years; and Australia provides five).

Another factor to consider is that originator biologic manufacturers are implementing sophisticated lifecycle plans, including filing for new patents to protect their branded products from biosimilar competition. In the U.S., four biosimilar products achieved FDA approval at the time of writing, and all have faced patent challenges that caused their launches to be delayed. Biosimilar sponsors will need to budget for defense against legal actions by originator companies as their patent protection comes to an end.

Challenge Six: Commercialization

Biosimilars are still relatively unfamiliar to physicians, payers and patients, so when these products are launched, biosimilar companies will be forced to market their products using commercial strategies and tactics that closely resemble those for late entrant "me-too" products or branded generics. One key strategy will be naming biosimilar products to distinguish them from competitors. Other strategies include creating meaningful differentiation, price discounts, educating healthcare stakeholders about their safety and efficacy, and creating patient support programs to address reimbursement

challenges. These strategies and tactics will require a significant short- and long-term investment to drive market share.

None of these challenges are insurmountable, but biopharma companies and investors need to take the time to do their due diligence and work with strong partners to best position themselves for success.

Companies Developing Biobetters

Novo Nordisk, Merck & Co, Roche Group, Biogen Idec, Amgen, Sanofi-Aventis, Eli Lilly and GlaxoSmithKline have all expressed interest in the development of biobetter drugs. Several are acquiring smaller, innovative bio-pharmaceutical companies that have promising pipelines. For example, British pharma AstraZeneca purchased the biotech company MedImmune which intends to focus on biobetter R&D. The Edmonton, Alberta, company Compass Biotechnologies, Inc., announced in late December 2011 that it is focusing on development of improved biosimilar proteins such as EPO and G-CSF. Compass also has an agreement to source recombinant protein biosimilars manufactured in "CHO" cells from PanGen Biotech of Seoul, South Korea, and an agreement with Arecor Ltd. of Cambridge, England, to develop a biobetter, heat-stable formulation of the commercial hepatitis B vaccine. K. Srinivas Sashidhar, a research analyst with Frost & Sullivan, wrote that "Biobetters will be the next big opportunity for biopharmaceutical companies and CROs. Market participants may look forward to collaborations with these companies in order to develop the improved versions of biologics. Organisations well known for innovation and experience with generics might be best positioned to achieve success with biobetters." Some of the biggest challenges facing researchers involved in the development of biobetters are to achieve similarity to the originator molecule and obtaining access to originating company's data, according to Sashidhar.

Is there a future for biobetters?

Biobetters are improved versions of originator biologics. Although there are varying interpretations of the term biobetter, according to Andrew Merron, therapy lead in oncology and biosimilars at healthcare research and consulting company Decision Resources Group, the improvements in these products often lie in efficacy, safety, or delivery. "The benefit of an improved biologic agent over existing biologic drugs is clear: better outcomes for patients," he says. The advantage for pharmaceutical companies is also evident in terms of commercial potential. Due to a lack of formal recognition of the term biobetter from regulatory bodies, "biobetters, for all practical purposes, are considered as new products as per current regulatory guidelines," says Durgaprasad Annavajjula, director of scientific affairs at India's Stelis Biopharma. This means that biobetter developers can apply for patent protection. Compared to originator products, biobetters constitute lower costs and developmental risks since the development process depends on pre-existing scientific data from the reference biologic. "Biobetters can be a comparatively easier way for innovator companies to build on what they have, extending a franchise, rather than letting it fade away to biosimilars and other competitors," says an unnamed pharma source who has experience in the development of biobetters. Ideally, biobetter makers have the capacity to command a price premium, but with payers seeking to lower costs and increasingly preferring the most affordable treatment options available, is there really room for biobetters in the healthcare market?

Securing the future of biobetters

The commercial opportunities for biobetter development are within reach. However, besides demonstrating the added value that biobetters offer, developers must also engage regulators, healthcare providers (HCPs), and key opinion leaders. Dr Annavajjula says: "It is highly advisable to interact with regulatory authorities prior to executing the development plans because of the highly dynamic environment of regulatory guidelines. This is critical to develop the quality product that meets the requirements at low cost and minimum risk." Maximizing adoption of improved biologics will also require educating physicians of the specific benefits the biobetter offers. Dr Merron says: "Of particular importance will be driving uptake and securing a positive perception of the drug among key physician influencers or those physicians that help to influence the prescribing behavior of large HCP networks." Overall, Dr Merron believes that there is a future for biobetters since developing enhanced biologics that supersede current clinical standards represents the framework for drug development efforts in therapeutic areas like oncology. Despite the higher costs compared to biosimilars, the significant clinical benefits biobetters can provide will drive market uptake. As long as the benefit is significantly high for patients, biobetters can flourish and even co-exist with biosimilars.[7]

Drug Master File Requirements for the Registration of Biosimilars/Biobetters

Guide for Registration Requirements

1. Administrative information

1.1 Cover letter

1.2 Trade name

1.3 Generic name

1.4 Expiry date

1.5 Other trade names of the similar product

1.6 Pharmaceutical form

1.7 Name of manufacturing company

1.7.1 Name of active substance manufacturer (if different from above)

1.8 Status of the company in Specific Country (currently registered or not Registered)

1.9 Agent in Specific Country

1.9.1 Name

1.9.2 Address

1.10 Marketing status at country of origin and other countries

1.11 Similar products registered in Specific Country
1.12 Reasons for production
1.13 Advantages over other similar drugs (if any)
1.14 Reference medicinal product (RMP) – The innovator
(In addition to 2.9 and 3.6)
1.14.1 Name
1.14.2 Approval at SFDA and/or EMEA
1.14.3 Company
2. Active pharmaceutical ingredient (drug substance)
2.1 General Information
2.1.1 Nomenclature
2.1.2 Structure
2.1.3 General Properties
2.2 Manufacturing
2.2.1 Manufacturer(s)
2.2.2 Description of manufacturing process and process specifications
2.3 Control of materials
2.3.1 Control of source and starting materials
2.3.2 Source, history, and generation of the cell substrate
2.3.3 Generation of cell substrate
2.3.4 Cell banking
2.4 Controls of critical steps and intermediates
2.4.1 Critical steps
2.4.2 Intermediates
2.5 Process validation and verification
2.6 Manufacturing process development
2.7 Comparability data of the structure elucidation and other quality characteristics
of the molecule against a reference medicinal product
2.7.1 Characterization: Elucidation of structure and other characteristics
2.7.2 Impurities
2.8. Control of drug substance
2.8.1 Specification
2.8.2 Analytical procedures
2.8.3 Validation of analytical procedures
2.8.4 Batch analyses
2.8.5 Justification of specification
2.9 Reference standards or materials
2.10 Container Closure System
2.11 Stability
2.11.1 Stability summary and conclusions
2.11.2 Post-approval stability protocol and stability commitment
2.11.3 Stability data
3. Drug product
3.1 Description and composition of the drug product
3.2 Pharmaceutical Development
3.2.1 Components of the drug product
3.2.2 Drug Product
3.2.3 Manufacturing process development
3.2.4 Container closure system
3.2.5 Microbiological attributes
3.2.6 Compatibility
3.3 Manufacturing
3.3.1 Manufacturer(s)
3.3.2 Batch formula
3.3.3 Description of manufacturing process and process controls
3.3.4 Controls of critical steps and intermediates
3.3.5 Process validation and/or evaluation
3.4 Control of excipients
3.4.1 Specifications
3.4.2 Analytical procedures (name, dosage form)
3.4.3 Validation of analytical procedures
3.4.4 Justification of specifications
3.4.5 Excipients of human or animal origin
3.4.6 Novel excipient
3.5 Control of drug product
3.5.1 Specification(s)
3.5.2 Analytical procedures
3.5.3 Validation of analytical procedures
3.5.4 Batch analyses
3.5.5 Characterization of impurities
3.5.6 Justification of specification(s)
3.6 Reference standards or materials
3.7 Packaging materials
3.7.1. Container closure system.
3.7.2. Product package insert/product leaflet.
3.8 Stability
3.8.1 Stability summary and conclusion
3.8.2 Post-approval stability protocol and stability commitment
3.8.3 Stability data
3.9 Appendices
3.9.1 Changes reporting
3.9.2 Facilities and equipment
3.9.3 Adventitious agents' safety evaluation
3.9.3.1 For non-viral adventitious agents
3.9.3.2 For viral adventitious agents
3.9.4 Materials of biological origin
3.9.5 Testing at appropriate stages of production
3.9.6 Viral testing of unprocessed bulk
3.9.7 Viral clearance studies
3.10 List of used excipients
3.10.1 Regional information
3.10.2 Literature references
4. Pre-Clinical comparative study with the RMP
4.1 Preclinical testing
4.1.1. Selected relevant animal species (number/gender)
4.1.2. Delivery, dose and route of administration
4.2 Pharmacology/pharmacodynamics
4.3 Pharmacokinetics
4.4 Toxicological studies
4.4.1. Single dose toxicity
4.4.2. Repeated dose toxicity studies
4.4.3. Local tolerance
4.5 Immunogenicity profile
5. Clinical comparative study with the RMP
5.1 Protocol
5.2 Recruitment details
5.3 Eligibility criteria
5.4 Clinical studies reports
5.4.1 Reports on biopharmaceutical studies
5.4.2 Reports of studies pertinent to pharmacokinetics using human

Biomaterials
5.4.3 Reports on pharmacokinetics (PK)
5.4.4 Reports on pharmacodynamic (PD)
5.4.5 Reports on efficacy and safety
5.5 Immunogenicity findings
5.6 Statistics *(justification of statistical method used)*
5.7 Literature references
6. Pharmacovigilance plan
6.1 Pharmacovigilance plan (track and trace)
6.2 Recall plan
6.3 Plan for adverse reactions (ADR) reports
6.4 Plan to ensure quality of the product (defect, final formulation package)
6.5 Bar-coding method
6.6 Post approval stability protocol and stability commitments
7. Certified Documents
7.1 Good manufacturing practice (GMP) certificates
7.2 Each raw material
7.3 Product analysis
7.4 Product composition
7.5 Diluents and coloring materials
7.6 Absence of alcohol content in the finished product
7.7 Absence of animal materials in the finished product
7.8 Package inserts approval at country of origin
7.9 Registration and marketing at country of origin and other countries
7.10 Pricing at country of origin
7.11 Company from which raw material(s) was obtained
8. Other necessary activities
Site visit to the manufacturing facility, line of production and the raw material source(s) manufacturers (if different from the drug manufacturer) is mandatory

EXPLANATION OF SOME REQUIREMENTS
2. Active Pharmaceutical Ingredient (drug substance)
2.1 General Information
2.1.1 Nomenclature
2.1.2 Structure
2.1.3 General Properties:
A. Physicochemical properties
B. Immunochemical properties
C. Biological activity
D. Purity
E. Carbohydrate content
F. Pyrogeneicity
G. Bioburden and sterility tests
H. Test for dimers and multimers
2.2 Manufacturing
2.2.1 Manufacturer(s):
2.2.2 Description of manufacturing process and process specifications
A. Description of manufacturing process and process controls
B. Batch (es) and scale definition
C. Cell culture and harvest:
D. Purification and modification reactions
F. Filling, storage and transportation (shipping)
2.3 Control of materials
2.3.1 Control of source and starting materials
2.3.2 Source, history, and generation of the cell substrate
2.3.3 Generation of cell substrate
2.3.4 Cell banking
(A) Cell banking system
(B) Cell banking procedures
(C) General principles of characterization and testing of cell banks
(E) Virus detection test (as per ICH guideline Q5A)
(F) Cell substrate stability:
(G) Characterization of expression constructs (ICH Q5B)
(H) End of Production Cell Bank (EPCB)
2.4 Controls of critical steps and intermediates
2.4.1 Critical steps
Cell culture process monitoring:
2.4.2 Intermediates
2.5 Process validation and verification
2.6 Manufacturing process development
2.7 Comparability data of the structure elucidation and other quality characteristics of the molecule against a reference product
2.7.1 Characterization
2.7.2 Impurities
2.8. Control of Drug Substance
2.8.1 Specification
2.8.2 Analytical Procedures
2.8.3 Validation of Analytical Procedures
2.8.4 Batch Analyses
2.8.5 Justification of Specification
2.9 Reference standards or materials
2.10 Container Closure System
2.11 Stability
2.11.1 Stability Summary and Conclusions
2.11.2 Post-approval stability protocol and stability commitment
2.11.3 Stability Data
3. Drug product
3.1 Description and composition of the drug product
3.2 Pharmaceutical Development
3.2.1 Components of the drug product
(A) Drug Substance
(B) Excipients
3.2.2 Drug Product
(A) Formulation Development
(B) Overages
(C) Physicochemical and Biological Properties
3.2.3 Manufacturing process development
3.2.4 Container closure system
3.2.5 Microbiological attributes
3.2.6 Compatibility
3.3 Manufacturing
3.3.1 Manufacturer(s)
3.3.2 Batch formula
3.3.3 Description of manufacturing process and process controls
3.3.4 Controls of critical steps and intermediates
(A) Critical Steps

(B) Intermediates
3.3.5 Process validation and/or evaluation
3.4 Control of excipients
3.4.1 Specifications
3.4.2 Analytical procedures (name, dosage form)
3.4.3 Validation of analytical procedures
3.4.4 Justification of specifications
3.4.5 Excipients of human or animal origin
3.4.6 Novel excipient
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3.5.1 Specification(s)
3.5.2 Analytical procedures
3.5.3 Validation of analytical procedures
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3.5.5 Characterization of impurities
3.5.6 Justification of specification(s)
3.6 Reference standards or materials
3.7 Packaging material
3.7.1 Container closure system
3.7.2 Product package insert/product leaflet:
3.8 Stability
3.8.1 Stability summary and conclusion
3.8.2 Post-approval stability protocol and stability commitment
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3.9.4 Materials of biological origin
3.9.5 Testing at appropriate stages of production
3.9.6 Viral testing of unprocessed bulk.
3.9.7 Viral clearance studies
3.10 List of used excipients
3.10.1 Regional information
3.10.2 Literature references
4. Pre-Clinical comparative study with RMP
4.1 Preclinical testing should mention
4.1.1 Selected relevant animal species (number/gender)
4.1.2 Delivery, dose and route of administration
4.2. Pharmacology/pharmacodynamics
4.2.1 *In vitro* studies used to assess any alterations in reactivity
4.2.2 *In vitro* cell lines derived from mammalian cells, used to predict specific
Aspects of *in vivo* activity
4.2.3 Studies designed to determine receptor occupancy, receptor affinity
4.2.4 *In vivo* studies that assess pharmacological activity
4.3 Pharmacokinetics
4.4 Toxicological studies
4.4.1 Single dose toxicity
4.4.2 Repeated dose toxicity studies
4.4.3 Local tolerance
4.5 Immunogenicity profile
5. Clinical comparative study with RMP
5.1 Protocol
5.2 Recruitment details
5.2.1 Informed consent document(s)
5.2.1 Clinical trial site information
5.3 Eligibility criteria
5.4 Clinical studies reports
5.4.1 Reports on biopharmaceutical studies
5.4.2 Reports of studies pertinent to pharmacokinetics using human biomaterials
5.4.3 Reports on pharmacokinetics (PK)
5.4.4 Reports on pharmacodynamic (PD)
5.4.5 Reports on efficacy and safety
5.5 Statistics *(justification of statistical method used)*
5.6 Reports of post-marketing experience
5.6. Testing of immunogenicity
5.7 Literature references

Biologics by Region (US and EU)
United States

The United States is the world's largest pharmaceutical market and Americans pay higher prices for prescription drugs than any other nation. While federal law in the US does not permit payers to consider drug cost as part of decision-making, the mounting expense of cancer drugs and other innovative biologics is taking its toll on insurers (including the government-funded programs Medicare and Medicaid), and above all on patients who typically share in the cost of medications. Those diagnosed with life-threatening or serious chronic diseases often face significant financial hardships in order to afford modern biologics or may be forced to forego optimal treatment. In 2010, the 351(k) regulatory pathway was established for approval of biosimilars and on 6 March 2015, a biosimilar of filgrastim became the first product to be approved by the FDA via this route, a pivotal event that prompted a significant escalation in biosimilar development activity.

Current access to originator biologics in the United States

On its own, the United States (USA) accounts for one-third of the global spend on drugs per year.1 Pharmaceutical prices are higher in the USA than elsewhere in the world and, in contrast to many other developed countries, cost-effectiveness has so far not been accepted as a legitimate consideration in choice of treatment. Although the Affordable Care Act created a body to compare the effectiveness of treatments, Congress barred it from considering cost. However:

- In 2013 it was reported that cancer drug prices in the USA had doubled in the past decade, from an average of USD $5,000 per month to more than $10,000.
- Eleven of the 12 cancer drugs the FDA approved in 2012 were priced at more than $100,000 per year, double the average annual household income.
- The top-tier cancer drugs cost twice as much in the USA as they do in Canada and in many EU countries.

The most expensive treatments in cancer, as in many other fields, are biologics. US spending on biologics has been increasing by as much as 15–20% each year. The price of biologic disease-modifying anti-rheumatic drugs

(DMARDs) used in rheumatoid arthritis and other chronic autoimmune conditions rose by more than 45% in 5 years (2008–2012). Some US clinicians are very concerned about the cost of biologics and have publicly (and sometimes collectively) confirmed that this influences their prescribing decisions. US insurers increasingly consider cost-effectiveness when deciding whether to cover a drug and how much of its cost patients themselves should fund ('co-pays'). A 2014 survey of more than 100 American rheumatologists found that 80% encounter moderate-to-strong control by payers when prescribing biologics for rheumatoid arthritis. There are also state-by-state variations in these policies, which has created regional inconsistencies.

The impact of rising drug costs is notable:

- Medical insurance premiums have more than doubled since 1999.
- One in five families affected by cancer use up their personal savings paying for treatment.
- Applications by patients for charitable aid to fund their treatments are increasingly common.
- One in six of all US bankruptcies is due to medical expenses.
- Up to 10% of patients with chronic myeloid leukemia discontinue a biologic treatment – which is widely recognized to be life-saving – because of its cost.
- For a patient with a terminal illness, assessment of drug cost-effectiveness is a very personal matter. For some, living to see a child's graduation or a spouse's landmark birthday may be worth every penny. However, some patients may be choosing financial ruin on the basis of a misunderstanding of likely treatment benefit. A study published in the New England Journal of Medicine in 201211 reported that 81% of patients with advanced colon cancer and 69% of patients with advanced lung cancer did not understand that their drug treatment was unlikely to cure them.
- The US government-funded insurance programs Medicare and Medicaid are legally obliged to pay for FDA-approved treatments. But – as with private insurers – expensive new drugs have unsurprisingly taken their toll on these cash-strapped programs.

Regulatory Guidelines in the United States

- Perhaps nowhere are the challenges and uncertainties of the new biosimilar era more evident than in the USA, which is ultimately expected to be the largest market for these products. The Biologics Price Competition and Innovation Act, which created an abbreviated approval pathway for biosimilars – known as 351(k) – became law in March 2010, and the FDA released a set of much-anticipated draft guidance documents on biosimilar development in February 2012.
- However, the first biosimilar application in the USA was not accepted for review by the FDA until 2014. It was for a biosimilar of filgrastim, intended to treat neutropenia.
- On 7 January 2015, the FDA's Oncologic Drugs Advisory Committee (ODAC) concluded that the candidate biosimilar was highly similar to the originator product and unanimously recommended its approval. On 6 March 2015, this product was approved by the FDA – the first US biosimilar licensed via the 351(k) pathway.

It is important to note that there are currently two distinct FDA approval pathways in use for biologics. Some have been approved under the Federal Food Drug and Cosmetic Act as 'drugs', while others have been approved as 'biologics' under the Public Health Service Act. By March 2020, all biologics will be reviewed under the Public Health Service Act.

For now, if the originator biologic product was originally approved as a 'drug', then a new version of that product (i.e. a product which depends at least in part on the data of the originator) is known as a 'follow-on biologic' or 'follow-on protein' as opposed to a biosimilar. The diagram below shows the different FDA drug approval pathways. 'Follow-on biologics' approved via the 505(b)(2) pathway between 1998 and 2006 comprise versions of recombinant glucagon, hyaluronidase, calcitonin salmon and somatropin. The newest product to be approved via the 505(b)(2) pathway (in January 2016) was a follow-on version of insulin glargine. FDA guidelines on the data required to satisfy regulatory requirements for biosimilarity via 351(k) were finalized in early 2017. The guidance states that the degree of similarity between a biosimilar candidate and its originator – as shown by the analytical data – should determine a sponsor's next steps. The FDA advises biosimilar sponsors to use state-of-the-art analytics to detect potential differences between originators and biosimilar candidates, and to engage with regulators early on to discuss their plans for data generation. Some experts regarded filgrastim as a relatively 'low-risk' product and warned that monoclonal antibody biosimilars, for example, may face tougher regulatory hurdles in the USA than they had in Europe.13 However, the first biosimilar monoclonal antibody (a biosimilar of infliximab) was approved by the FDA in April 2016 and was followed a few months later by approvals for biosimilars of etanercept and adalimumab.

Key US regulatory areas include

- **Requirements for extrapolation:** The biosimilars approved by the FDA have generally had their licenses 'extrapolated' to include all the licensed indications of the originators. However, extrapolation is by no means inevitable for all biosimilar candidates and is expected to be evaluated on a case-by-case basis.
- **Requirements for interchangeability:** The FDA intends to approve biosimilars as 'non-interchangeable' or 'interchangeable,' meaning that the biosimilar may or may not be substituted for the originator at the pharmacy level without approval of the prescribing physician. In order for a product to be declared interchangeable by the FDA, it is 'expected to produce the same clinical result as the reference product in any given patient.' The risk in terms

of safety and efficacy cannot be greater than using the reference product without switching. Basically, the FDA expects to see no increase in risk in terms of reduction in efficacy or increase in safety concerns between the two products upon multiple alternating or switching cycles. For simple protein products, the FDA may be able to grant an interchangeability designation at time of approval, but for more complex biologics such as monoclonal antibodies, the FDA may require post-marketing data in addition to clinical study switching data prior to granting an interchangeability designation. The FDA released full draft guidance for demonstrating interchangeability in early 2017.

- **State legislation on pharmacist substitution:** Even if a biosimilar is granted an FDA interchangeability designation, individual state legislation may govern whether pharmacy-level biosimilar substitution for a prescribed branded product is permissible. However, it is possible that state laws may not carry much weight once interchangeability has been FDA-approved. An up-to-date record of state legislation on pharmacist substitution of biosimilars is available here.
- **Product naming:** In September 2015, the FDA issued provisional naming guidance for biosimilars, which proposed that originator biologics and biosimilars are given the same non-proprietary name, but with a unique four-letter suffix for all biologics, including originators. The proposed naming convention seeks to prevent inadvertent substitution of biologic products that are not deemed interchangeable by the FDA, as well as to support safety monitoring by making it easier to accurately track product usage. The FDA's naming guidance was finalized in early 2017, when it was also announced that each suffix should be devoid of meaning rather than signifying the manufacturer's name as originally proposed.
- **Product labelling:** As of April 2016, the FDA requires biosimilars to be identified as such on product labels. However the clinical data cited on the label should be that of the originator [8].

Biosimilar approvals in the United States

An up-to-date record of FDA-approved biosimilars can be found here.

- The FDA began approving 'follow-on biologics' (a general term for less expensive versions of off-patent originator biologics) as far back as 1998 and – over the subsequent 8 years – follow-on biologics of recombinant glucagon, hyaluronidase, calcitonin salmon, and somatropin were granted licenses. However, these were approved via the 505(b)(2) pathway, which pre-dated the establishment of the dedicated biosimilars approval pathway, 351(k). As such, these early products are not given the term 'biosimilar' in the US. See Regulatory guidelines in the United States.
- The events which followed the licensing of Sandoz's Zarxio®, the first FDA-approved biosimilar, illustrate the legal and commercial complexities of the US market. Zarxio was launched in the US on September 3, 2015, approximately 6 months after it received approval. The delay was caused by a patent infringement lawsuit initiated by Amgen, manufacturer of the originator filgrastim, Neupogen®.The dispute focused on whether Sandoz had violated the law by not informing Amgen about its application to the FDA for approval of Zarxio® or revealing its plans to manufacture a biosimilar of filgrastim in the first place (this communication of information between biosimilar and originator companies is informally known as the 'patent dance'). The outcome of the lawsuit was that biosimilar manufacturers are not obliged to share their plans with originators, but do have to give them 180 days' notice of their intention to market their product, which can only be done once FDA approval is secured. Sandoz has appealed the 180-day notice ruling and, as at February 2017, this issue has been escalated to the US Supreme Court, which is considering its ruling.
- Zarxio (which has the non-proprietary name filgrastim-bflm) is being marketed at a wholesale price 15% lower than that of Neupogen. For Medicare, this amounts to a relatively small saving, but biosimilar discounts typically evolve over time and the price of Zarxio may decrease later, as seen in the EU, where it is currently 20–30% cheaper than Neupogen. The American Society for Oncology (ASCO) announced in its 2015 guidelines that substitution of biosimilar filgrastim for the originator in clinical practice is appropriate. In August 2016, CVS Heath Corp., which administers drug-benefit plans for employers and insurers, announced that – from January 1, 2017 – it will drop coverage of Neupogen and instead cover only Zarxio, for which it has negotiated an additional discount.
- FDA decision-makers have grown in confidence since the early days of reviewing biosimilar applications and, in 2016, they approved biosimilars of infliximab, etanercept, and adalimumab, with unanimous votes in the case of the latter two. The approvals included extrapolation of the biosimilar licenses to other licensed indications of the respective originators. However, as before, lawsuits swiftly followed and – in the case of adalimumab – AbbVie (the manufacturer of the originator Humira®) may succeed in preventing the launch of the biosimilar competitor (Amgen's Amjevita®) for several years due to Humira's complex, multi-layered patents.
- NOTE: Eli Lilly's Basaglar®, a follow-on biologic of insulin glargine, has also been approved and launched in the US; however this was not via the FDA's 351(k) pathway but instead via the 505(b)(2) pathway, which officially classifies Basaglar as a 'follow-on biologic' rather than a biosimilar (see Regulatory guidelines in the United States). As with filgrastim, CVS Health Corp. has decided to drop coverage of the originator, Lantus®, in favor of Basaglar.

The future of biosimilars in the United States

- Because of the need for comparative clinical trials, savings from biosimilars cannot match those achievable with small-molecule generics, which are estimated to have saved US consumers approximately $1 trillion in the decade 2002–2012.
- Nonetheless, because of the high unit cost of biologics, and the growing need for them in clinical practice, biosimilars are still expected to achieve substantial savings. There is no consensus on the scale of the savings and they may be influenced by numerous factors, including the timing of FDA approvals, whether indication extrapolation is approved, the granting of interchangeability licenses, prescriber attitudes, competition between biosimilar versions of the same originator, and many other variables. However, a number of authoritative stakeholders have made predictions regarding potential savings in the US. For example:

➢ The Rand Corporation estimates that the introduction of biosimilars may reduce direct spending on biologics in the USA by $44.2 billion from 2014–2024.

➢ Express Scripts, the nation's largest manager of pharmacy benefits, has gone so far as to suggest that biosimilar competition for the top 11 biologics could save as much as $250 billion over the same decade.

➢ A January 2017 forecast report from QuintilesIMS predicts savings of $27 to $58 billion from the use of biosimilars in the US over the next 5 years.

- In March 2015, the Centers for Medicare and Medicaid Services (CMS) removed an incentive for physicians to prescribe more expensive Medicare Part B originator drugs in a move to encourage preferential biosimilar prescribing. They also opened the door to formulary exclusions of originator drugs under Medicare Part D, which is required to offer at least two distinct drugs in each class.
- One point of contention is that, although US payers will undoubtedly benefit from the introduction of biosimilars, it remains unclear to what extent patients will reap the benefits of the savings.

Despite the long wait for the 351(k) pathway to be successfully put into practice, the US biotechnology industry has been highly active in this field for many years and brand-name biologic manufacturers themselves are pursuing biosimilars. Now that the first biosimilars have received FDA approval and are coming to market, biosimilar development programs in the US have gained new momentum [9].

EUROPE

Many European healthcare systems have struggled to fund biologic therapies for the numerous patients who need them, and cost containment in this area has been recognized as a priority by the European Commission (EC). The European Medicines Agency (EMA) has led the world in the development of regulatory guidelines for the development and assessment of biosimilars, establishing key principles of comparability that have been adopted by many other regions around the world. 2016 marked the tenth anniversary of the launch of the first biosimilar in Europe and Medicines for Europe claimed:

Across Europe, nearly 90% of doctors now know what biosimilar medicines are and nearly 60% have already prescribed them.

- Since the first biosimilar medicine was launched in 2006, European Union (EU)-approved biosimilars have generated more than 400 million patient days of positive clinical experience. No untoward effects or unexpected adverse events have been reported.
- Between 2006 and 2014, biosimilar medicines have increased patient access by 44% overall within the EU-5 countries.

Current access to originator biologics in Europe

The European biologic market is growing at an annual rate of approximately 5.5%. By comparison, the total pharmaceutical market growth in Europe between 2012 and 2013 was 1.9%. By late 2014, biologic medicines accounted for 27% of pharmaceutical sales in Europe. Although biologics have transformed clinical outcomes for patients throughout Europe, their high cost has put a heavy strain on European healthcare systems. The European Commission has stated that the cost of biologics compared with small-molecule medicines is a challenge for most payers. For example:

- In more than 50% of European countries the annual cost of a biologic disease-modifying anti-rheumatic drug (DMARD) for rheumatoid arthritis can exceed the per capita GDP by as much as 11 times.
- In France, the cost of cancer therapies has been doubling every 4 years.
- Public hospitals in Portugal are experiencing difficulties in the approval of prescriptions of biologics for patients with rheumatoid arthritis because of the high cost of biologics and the tough budget constraints they face.
- The cost of insulins contributes markedly to overall healthcare expenditure for patients with diabetes who make up approximately 8.5% of the adult European population (2010 estimate).7 The prevalence of diabetes ranges from 2.1% in Iceland to 12.0% in Germany, and is predicted to grow significantly in coming years.

The cost of biologics has put them beyond the reach of many patients in Europe, in particular those who have to contribute a major portion of their treatment costs because of lack of state funding or inadequate private insurance coverage. Patients with chronic conditions are most vulnerable.

- An employee in Europe receiving the national minimum wage has to work 1038 days (on average) to pay for a month of treatment with a biologic DMARD, compared with only 19 days to fund a non-biologic DMARD. Overall, approximately 40% of the total European population has severely restricted access to this therapies.

- In Central and Eastern Europe, reimbursement disparities mean that less than 5% of all patients with rheumatoid arthritis are treated with biologics, compared with Western Europe where the average usage is 11–12%.9, Similar discrepancies between Eastern and Western Europe in terms of access to expensive cancer biologics were recently reported by the European Society of Medical Oncology (ESMO).
- In the UK, at least eight breast cancer biologics with proven overall survival benefit have been rejected between 2011 and 2014 by the National Institute for Health and Care Excellence (NICE) for reimbursement on the National Health Service (NHS) because of cost.

Regulatory guidelines in Europe

The European Medicines Agency (EMA) has led the way in the development of regulatory guidelines for the development and assessment of biosimilars. Their initial overarching biosimilar guidelines were originally issued in 2005 and updated in 2014.

- Most non-EU countries have adopted a large proportion of the EU biosimilar guidelines, for example Australia, New Zealand, Canada, Japan, Korea, Singapore, South Africa and Switzerland. In addition, the World Health Organization (WHO) has used the principles contained in the 2005 EMA guidance as the basis for its own guidelines for Similar Biotherapeutic Products (SBPs).
- In addition to the overarching biosimilar guidelines, the EMA has also pioneered a range of product-specific guidelines to aid the development of specific classes of biosimilar products, including recombinant follicle-stimulating hormone (FSH), interferon beta, erythropoietins, low-molecular-weight heparins, interferon alpha, filgrastim (G-CSF), somatropin, human insulin and insulin analogues, and monoclonal antibodies.
- To gain marketing authorization in the EU, biosimilars need to demonstrate similar quality, safety, and efficacy to their reference medicinal product already approved in the EU. Biosimilar product approval does not include any recommendation regarding interchangeability or substitution with their originator product, as these remain the decision of national regulatory authorities across Europe.
- From February 2017, the EMA is launching a pilot project to test the added value and feasibility of offering tailored scientific advice to individual biosimilar developers. Through this new initiative, the EMA aims to advise developers on the specific studies/tests they should be conducting in light of the data they already have and how robust these data are [10].

Biosimilars approvals in Europe

The EMA approved its first biosimilar – a biosimilar of somatropin (growth hormone) – in 2006 and has accumulated over a decade of real-world experience with biosimilars. As of 2017, the EU remains significantly ahead of other highly regulated markets in terms of the total number of biosimilar products approved, although this total does include several biosimilar versions of the same originator (e.g. filgrastim) in some cases.15 An up-to-date record of EMA-approved biosimilars can be found in the below table. European experience with biosimilars since they were first introduced in 2006 has revealed no reports of untoward effects or unexpected adverse events compared with the originator biologics. Biosimilars are now in clinical use across almost all EU member states. Uptake was fairly slow initially due to their unfamiliarity but has since begun to accelerate.

- In mid-2016, it was revealed that, between 2006 and 2014, biosimilar medicines increased patient access by 44% overall in the European Union 5 countries (EU5: France, Germany, Italy, Spain, and the UK).
- By 2013, biosimilars made up approximately a quarter of all sales of biologics for which EU patents had expired.
- As of September 2015, the biosimilars market in the EU5 stood at US $490 million, a massive increase since 2007 when the market was just being established. Filgrastim biosimilars are leading the way when it comes to market penetration, reaching market shares of 60–80% across the EU.
- Germany is leading the uptake of biosimilars, followed by the UK and France. Italy and Spain showed initial cultural resistance but are now catching up (Figure).

Current differences in the use of biosimilars and competition dynamics across European markets mainly reflect local adoption of treatment practices and guidelines influenced by funding decisions and payer actions.

- With regard to cost savings, mean price discounts of 15–40% (compared with originators) have been seen with biosimilar products introduced into the European market, including somatropin, epoetin, and filgrastim.
- However, a discount of 45% for an infliximab biosimilar was negotiated in France by a major hospital group, while in Norway and Denmark, biosimilars of infliximab are available at a 70% discount. Physicians in Danish and Norwegian hospitals can now treat a patient for 3 years with biosimilar infliximab for the same price as 1 year with the originator.
- In Germany, the use of biosimilar erythropoietin, between 2007 and 2011, led to over €600 million in savings.
- Market competition is already at work; in Germany, price reductions of 30–40% have been seen for originator epoetin and filgrastim since the introduction of biosimilar competitors at significantly lower market prices.25–27 In the UK, the price of originator infliximab was lowered by approximately 25% in 2015, in the face of competitive pressure from two biosimilars.

The future of biosimilars in Europe

- According to recent estimates, the introduction of biosimilars could save eight European countries (Germany, France, Italy, UK, Spain, Sweden, Poland and Romania) up to €33.4 billion by 2020. The largest savings are anticipated for France, Germany and the UK.
- Biosimilar monoclonal antibodies are expected to produce the greatest savings – up to €20.4 billion by 2020. Projections for biosimilar erythropoietins over the same time period range from €9.4–11.2 billion, and for granulocyte colony-stimulating factors from €0.7–1.8 billion.
- A 2014 forecast estimated that the introduction of biosimilar infliximab within six central and eastern European countries could allow 1,205 additional patients with rheumatoid arthritis (RA) to receive biologic therapy and up to 1,790 if interchangeability is permitted.
- A similar forecast in 2015 looking at the use of biosimilar infliximab for inflammatory autoimmune conditions in EU countries suggested that 2,602 additional patients could be treated per year in Germany (based on a 30% discount).
- Rheumatologists in five EU countries have predicted at least 30% of new RA patients eligible for biologics will receive biosimilars. Measures to mandate use of RA biosimilars for new patients in the EU appear likely, but switching from originators is expected to be optional for now.
- The UK's National Institute for Health and Care Excellence (NICE) has recommended that infliximab biosimilars, Remsima and Inflectra, should be used ahead of the originator Remicade. NICE has also published a new resource to support the introduction of Inflectra and Remsima into clinical use

The European Commission expects several new classes of biosimilar medicines to be submitted for approval in Europe in the coming years. A number of 'blockbuster' biologics are expected to lose their EU patents before 2020, including leading treatments for breast cancer, diabetes, multiple sclerosis and rheumatoid arthritis. The opportunities for clinical investigators in biosimilar research are expected to escalate throughout Europe.[11]

Biosimilars By Disease

- **Abatacept**

Rheumatoid arthritis (EU & USA)

- **Adalimumab***

Rheumatoid arthritis (EU & USA)
Psoriasis (EU & USA)
Juvenile idiopathic arthritis (EU & USA)
Psoriatic arthritis (EU & USA)
Ankylosing spondylitis (EU & USA)
Crohn's disease (EU & USA)
Ulcerative colitis (EU & USA)

- **Darbepoetin alfa**

Symptomatic anemia associated with chronic renal failure (EU & USA)
Symptomatic anemia in adults with non-myeloid malignancies receiving chemotherapy (EU & USA)

- **Eculizumab**

Paroxysmal nocturnal hemoglobinuria (PNH) (EU & USA)
Atypical hemolytic uremic syndrome (aHUS) (EU & USA)

- **Golimumab**

Rheumatoid arthritis (EU & USA)
Psoriatic arthritis (EU & USA)
Ankylosing spondylitis (EU & USA)
Ulcerative colitis (EU & USA)

- **Insulin aspart**

Type 1 and 2 diabetes mellitus (adults and children) (EU & USA)

- **Natalizumab**

Relapsing-remitting multiple sclerosis (EU & USA)
Crohn's disease (USA)

- **Omalizumab**

Severe persistent allergic asthma (EU & USA) Chronic idiopathic/spontaneous urticaria (EU & USA)

- **Pegfilgrastim**

Neutropenia in cancer patients receiving chemotherapy (EU & USA)

- **Ranibizumab**

Wet age-related macular degeneration (wAMD) (EU & USA)
Macular edema following retinal vein occlusion (RVO) (EU & USA)
Diabetic macular edema (DME) (EU & USA)
Choroidal neovascularization secondary to pathologic myopia (EU)

- **Ustekinumab**

Plaque psoriasis (EU & USA)
Psoriatic arthritis (EU & USA)

CONCLUSION

Biosimilars have been approved in the EU including a monoclonal antibody (Infliximab). Getting a biosimilar in the market has been harder than expected, especially in the US, and the cost higher than originally predicted. The future of biobetters is difficult to predict, but many analysts believe that biobetters with their improved characteristics, are a more exciting and favorable proposition than biosimilars, and will offer a medical advantage along with a better price. A biosimilar is a biological medicine highly similar to another already approved biological medicine (the 'reference medicine'). Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines. The respective health Agency is responsible for evaluating the majority of applications to market biosimilars in the particular country. Biological medicines contain active substances from a biological source, such as living cells or organisms. Most biological medicines in current clinical use contain active substances made of proteins. These can differ in size and structural complexity, from simple proteins like insulin or growth hormone to more complex ones such as coagulation factors or monoclonal antibodies. Often

produced by cutting-edge biotechnology, biological medicines offer treatment options for patients with chronic and often disabling conditions such as diabetes, autoimmune diseases and cancers. The respective country has pioneered the regulation of biosimilar medicines by establishing a solid framework for their approval and by shaping biosimilar development globally. The evidence acquired over 10 years of clinical experience shows that biosimilars approved through EMA can be used as safely and effectively in all their approved indications as other biological medicines.

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