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Development Constraints and Regulatory Pathway of Registration of Biosimailar Products in us and Europe

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ABSTRACT

Biosimilars represent, potentially, an attractive market, although there are significant regulatory and commercial hurdles to overcome. Because of the large and complex nature of biological molecules, biosimilars cannot be guaranteed to be identical to innovator biologics. Establishing a high degree of similarity in quality between the biosimilar product and the original product is a crucial key in the regulatory approval process, because biologicals vary greatly in properties and where even small alterations can lead to unacceptable changes in safety and efficacy. Even minor structural differences (including certain changes in glycosylation patterns) can significantly affect a protein's safety, purity, and/or potency, it is important to evaluate these differences. Protein modifications and higher order structure can be affected by environmental conditions, including formulation, light, temperature, moisture, packaging materials, container closure systems, and delivery device materials. Specific safety or effectiveness concerns regarding the reference product and its class (including history of manufacturing- or source-related adverse events) may warrant more comparative clinical safety and effectiveness data. Assessment of immunogenicity and interchangeability are other important criteria to fulfil the Biosimilar requirements. The rapidly evolving regulatory science in the biosimilar area would benefit from better cooperation, information exchange and collaboration from regulators. It is recommended that the sponsors need to discuss the development strategy with regulators at appropriate stage of development and get their concurrence on the strategy. This will help to ease the regulatory review process and early product approvals.

KEY WORDS: Biosimilar, Similarbiotherapeutic product, Registration

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1. INTRODUCTION:

Biosimilars or follow-on biologics are terms used to describe officially-approved subsequent versions of innovator biopharmaceutical products made by a different sponsor following patent and exclusivity expiry on the innovator product. According to EMA, a biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product(reference medicinal product). A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise[1]. As per FDA definition, Biosimilar or biosimilarity means that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components," and that "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[2].

The term Biosimilar is used by EMA (European Medicines Agency) or versions of marketed therapeutics that, from a regulatory perspective, cannot be considered like simple generic drugs due to their structural complexity. Biosimilars are legally approved subsequent versions of innovator biopharmaceutical products following patent and exclusivity expiry. However, the definition of biosimilars differs among the various regulatory agencies across the world. Internationally, different names are used for Biosimilar; for example, they are known as *"similar biological medicinal products"* by the EMA and KOREA Food & Drug Administration (KFDA), as *"follow-on protein products or follow-on biologics"* by the Foodand Drug Administration (FDA) and PMDA, Japan; Ministry of Health, Labor andWelfare (MHLW) as *"subsequent entry biologics"* by Health Canada; "Similar Biotherapeutic Products" by World Health Organization.

Global biologics sales have grown to more than $100 billion. As an increasing number of biologics face patent expiration, biosimilars offer a major opportunity for drug developers. By 2020, patents will expire on twelve biologics with global sales of more than $67 billion[3].

By 2015, sales of biosimilars are expected to reach between US$1.9-2.6 billion, up from US$378 million for the year to the first half of 2011[4]. Potentially, this market could be the single fastest-growing biologics sector in the next five years – albeit from a small base – spurred by the convergence of major dynamics that will see new biosimilars enter the US market by 2014, bring additional molecules to Europe through 2015, and open up oncology kand autoimmune disease areas to biosimilars for the first time ever.

Biosimilars can be less expensive than the originator biologics and can potentially provide increased access to biologic therapies including monoclonal antibodies and therapeutic proteins that treat life threatening cancers, anemia and immunological diseases.

The changing outlook for biosimilars comes at a time when the global pharmaceutical market is feeling the combined impact of two key events: a period of unprecedented patent expirations on many of the world's largest pharmaceutical brands, and a financial crisis that has required healthcare systems to make significant and sustained cost reductions.

Because of the large and complex nature of biological molecules, biosimilars cannot be guaranteed to be identical to innovator biologics. Therefore, regulators have been concerned that undetected differences in biosimilars may result in reduced efficacy or different adverse reactions. Regulators have been working towards abbreviated licensing pathways to speed up the availability of biosimilars, but efforts have been slowed by complex issues related to demonstrate comparability of biosimilar with the safety and effectiveness of innovator biologics.

The biggest challenges facing biosimilar drug developers is proving the equivalence or similarity of their biological drug to the reference product because of great variation in properties and even small alterations can lead to unacceptable changes in safety and efficacy. So there is a need of class-specific guidelines for various complex molecules of biological. The EMA has developed product class-specific guidelines for erythropoietin's, insulin's, growth hormones, Alfa interferon, granulocyte-colony stimulating factors and low-molecular weight heparins (LMWH), with three more (beta interferons, follicle stimulation hormone, monoclonal antibodies) currently being drafted by EMA.

2. CONSTRAINTS IN DEVELOPMENT OF BIOSIMILAR PRODUCTS:

2.1 Nature of Protein Products and Related Scientific Considerations

As per FDA's definition, "Protein means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size". Unlike small molecule drugs, whose structure can usually be completely defined and entirely reproduced, proteins are typically more complex and are unlikely to be shown to be structurally identical to a reference product. Many potential differences in protein structure can arise. Because even minor structural differences (including certain changes in glycosylation patterns) can significantly affect a protein's safety, purity, and/or potency, it is important to evaluate these differences. In general, proteins can differ in at least three ways:

(1) Primary amino acid sequence

(2) Modification to amino acids, such as sugar moieties (glycosylation) or other side chains

(3) Higher order structure (protein folding and protein-protein interactions).

Modifications to amino acids may lead to heterogeneity and can be difficult to control. Protein modifications and higher order structure can be affected by environmental conditions, including formulation, light, temperature, moisture, packaging materials, container closure systems, and delivery device materials. Additionally, process-related impurities may increase the likelihood and/or the severity of an immune response to a protein product, and certain excipients may limit the ability to characterize the drug substance. Hence it is important that appropriate advance analytical techniques should be used for extensive characterization of test product with respect to their physico-chemical and biological properties, such as higher order structures and functional characteristics.

2.2 Expression system

Therapeutic protein products can be produced by microbial cells (prokaryotic, eukaryotic), cell lines of human or animal origin (e.g., mammalian, avian, insect), or tissues derived from animals or plants. It is expected that the expression construct for a proposed biosimilar product will encode the same primary amino acid sequence as its reference product. However, minor modifications, such as N or C terminal truncations that will not have an effect on safety, purity, or potency, may be justified by the applicant. Differences between the chosen expression system of the proposed biosimilar product and that of the reference product should be carefully considered because the type of expression system and host cell will significantly affect the types of process- and product-related substances and impurities (including potential adventitious agents) that may be present in the protein product. Minimizing differences between the proposed and reference expression systems to the extent possible can enhance the likelihood of producing a highly similar protein product. The characterization of the expression construct, including its genetic stability, should be demonstrated in accordance with principles recommended in ICH Q5B.

2.3 Manufacturing Process Considerations

Different manufacturing processes may alter a protein product in a way that could affect the safety or effectiveness of the product. The differences in biological systems used to manufacture a protein product may cause different post-translational modifications, which in turn may affect the safety or effectiveness of the product. Thus, when the manufacturing process for a marketed protein product is changed, the application holder must assess the effects of the change and demonstrate through appropriate analytical testing, functional assays, and/or in some cases animal and/or clinical studies, that the change does not have an adverse effect on the identity, strength, quality, purity, or potency of

the product as they relate to the safety or effectiveness of the product[5]. Hence it is important that a comprehensive understanding of all steps in the manufacturing process for the proposed biosimilar product should be established during product development. Characterization tests, process controls, and specifications that will emerge from information gained during process development must be specific for the proposed biosimilar product and manufacturing process. The use of Quality-by-Design approaches to pharmaceutical development, along with quality risk management and effective quality systems, will facilitate the consistent manufacturing of a high-quality product.

2.4 Assessment of Physiochemical properties - Structural Analysis

Physicochemical assessment of the proposed biosimilar product and the reference product should consider all relevant characteristics of the protein product (e.g., the primary, secondary, tertiary, and quaternary structure, post-translational modifications, and functional activities).It is important to understand the heterogeneity of the proposed biosimilar product and the reference product (e.g., the nature, location, and levels of glycosylation) and the ranges of variability of different isoforms, including those that result from post-translational modifications. It is expected that appropriate analytical test methods should be selected based on the nature of the protein being characterized and knowledge regarding the structure and heterogeneity of the reference and the proposed biosimilar product, as well as those characteristics that are critical to product performance. To address the full range of physicochemical properties or biological activities adequately, it is often necessary to apply more than one analytical procedure to evaluate the same quality attribute.

In selecting these tests, it is important to consider the characteristics of the protein product, including known and potential impurities. Information regarding the ability of a method to discern relevant differences between a proposed biosimilar product and a reference product should be submitted as part of the comparison. Tests chosen to detect and characterize these post-translational protein modifications should be demonstrated to be of appropriate sensitivity and specificity to provide meaningful information as to whether the proposed biosimilar product and the reference product are highly similar.

2.5 Functional Assays

Functional assays serve multiple purposes in the characterization of protein products. These tests act to complement physicochemical analyses and are a quality measure of the function of the protein product. The pharmacologic activity of protein products can be evaluated by in vitro and/or

in vivo functional assays. These assays may include, but are not limited to, bioassays, biological assays, binding assays, and enzyme kinetics.

A functional evaluation comparing a proposed product to the reference product using these types of assays is also an important part of the foundation that supports a demonstration of biosimilarity and may be used to scientifically justify a selective and targeted approach to animal and/or clinical testing.Functional assays are useful to provide additional evidence that the biologic activity and potency of the proposed product are highly similar to those of the reference product and/or to demonstrate that there are no clinically meaningful differences between the proposed product and the reference product. Also provides an additional data to support results from structural analysis, investigate the consequences of observed structural differences, and explore structureactivity relationships.The available information about these assays, including sensitivity, specificity, and extent of validation, can affect the amount and type of additional animal or clinical data that may be needed to establish biosimilarity.

If a reference product exhibits multiple functional activities, manufacturers should perform a set of relevant assays designed to evaluate the range of activities. The manufacturer should recognize the potential limitations of some types of functional assays, such as high variability, that might preclude detection of small but significant differences between the proposed biosimilar product and the reference product. As a highly variable assay may not provide a meaningful assessment as to whether the proposed biosimilar product is highly similar to the reference product. Thus, these limitations should be taken into account when assessing the robustness of the quality of data supporting biosimilarity and the need for additional information. Finally, functional assays are critical in assessing the occurrence of neutralizing antibodies in nonclinical and clinical studies.

2.5 Receptor Binding and Immunochemical Properties

Binding or immunochemical properties are part of the activity attributed to the protein product, analytical tests should be performed to characterize the product in terms of these specific properties (e.g., if binding to a receptor is inherent in protein function, this property should be measured and used in comparative studies as per ICH Q6B). Various methods such as surface plasmon resonance, microcalorimetry, or classical Scatchard analysis can provide information on the kinetics and thermodynamics of binding. This information can be related to the functional activity and characterization of the proposed biosimilar product's higher order structure. Hence it is important that during biosimilar product development, applicant should study these specific properties with appropriate analytical tools to prove the biosimality with reference product.

2.6 Impurities

The applicant should characterize, identify, and quantify impurities (product- and process-related as defined in ICH Q6B) in the proposed biosimilar product and the reference product. If comparative physicochemical analysis reveals comparable product-related impurities at similar levels between the two products, pharmacological/toxicological studies to characterize potential biological effects of specific impurities may not be necessary. However, if the manufacturing process used to produce the proposed biosimilar product introduces different impurities or higher levels of impurities than those present in the reference product, additional pharmacological/toxicological or other studies may be necessary.

Process-related impurities arising from cell substrates (e.g., host cell DNA, host cell proteins), cell culture components (e.g., antibiotics, media components), and downstream processing steps (e.g., reagents, residual solvents, leachables, endotoxin, bioburden) should be evaluated. The potential impact of differences in the impurity profile upon safety should be addressed and supported by appropriate data. In all cases, the chosen analytical procedures should be adequate to detect, identify, and accurately quantify biologically significant levels of impurities (see ICH Q2B). In particular, the results of the immunological methods used to detect host cell proteins depend on the assay reagents and the cell substrate used. Such assays should be validated using the product cell substrate and orthogonal methodologies to ensure accuracy and sensitivity. This should be done across both products to the extent relevant and feasible. Also adventitious agents or endogenous viral contamination should be ensured by screening critical raw materials and confirmation of robust virus removal and inactivation achieved by the manufacturing process.

2.7 Reference Product and Reference Standards

A thorough physicochemical and biological assessment of the reference product should provide a base of information from which to develop the proposed biosimilar product and justify reliance on certain existing scientific knowledge about the reference product. Sufficient evidence that the proposed biosimilar product is highly similar to the reference product must be demonstrated in an appropriate time frame to support a selective and targeted approach in early product development. An analytical similarity assessment should support the use of lots that demonstrate the biosimilarity of the proposed biosimilar product used in the principal clinical trial to the reference product and the proposed commercial product. The biosimilar application should include a thorough analytical comparison between the proposed biosimilar product and the reference product.

If the drug substance has been extracted from the reference product in order to assess analytical similarity, the applicant should describe the extraction procedure and provide support that the

procedure itself does not alter product quality. This undertaking would include consideration for alteration or loss of the desired products and impurities and relevant product-related substances, and it should include appropriate controls that ensure the relevant product characteristics of the reference product are not significantly altered by the extraction procedure.

If there is a suitable, publicly available and well-established reference standard for the protein, then a physicochemical and/or functional comparison of the proposed biosimilar product with this standard should also be performed. For example, if an international standard for calibration of potency is available, a comparison of the relative potency of the proposed biosimilar product with this potency standard should be performed. Overall, analytical studies carried out to support the approval of a proposed biosimilar product should not focus solely on the characterization of the proposed biosimilar product in isolation. Rather, these studies should be part of a broad comparison that includes, but is not limited to, the proposed biosimilar product, the reference product, applicable reference standards, and consideration of relevant publicly available information.

2.8 Stability

An appropriate physicochemical and functional comparison of the stability of the proposed biosimilar product with that of the reference product should be initiated. Accelerated and stress stability studies, or forced degradation studies, should be used to establish degradation profiles and provide direct comparison of the proposed biosimilar product with the reference product. These comparative studies should be conducted under multiple stress conditions (e.g., high temperature, freeze thaw, light exposure, and agitation) that can cause incremental product degradation over a defined time period. Results of these studies may reveal product differences that warrant additional evaluation and also identify conditions under which additional controls should be employed in manufacturing and storage. Sufficient real time, real condition stability data should be provided to support the proposed shelf life.

2.9 Animal Data

2.9.1 Animal Toxicity Studies

The scope and extent of any animal toxicity studies will depend on the body of information available on the reference product, the proposed product, and the extent of known similarities or differences between the two. If animal toxicity studies are not warranted, additional comparative in vitro testing, using human cells or tissues when appropriate, may be warranted. In general, nonclinical safety pharmacology, reproductive and developmental toxicity, and carcinogenicity studies are not warranted when the proposed product and reference product have been demonstrated

to be highly similar through extensive structural and functional characterization and animal toxicity studies. If there are specific safety concerns based on the clinical use of the reference product, some of or all such additional animal studies with the proposed product may be warranted.

2.9.2 Inclusion of Animal PK and PD Measures

A single-dose study in animals comparing the proposed product and reference product using PK and PD measures may contribute to the totality of evidence that supports a demonstration of biosimilarity. Specifically, applicant can use results from animal studies to support the degree of similarity based on PK and PD profiles of the proposed product and the reference product. PK and PD measures also can be incorporated into a single animal toxicity study, where appropriate. Animal PK and PD assessment will not negate the need for human PK and PD studies.

2.9.3 Animal Immunogenicity Studies

Animal immunogenicity assessments generally do not predict potential immunogenic responses to protein products in humans. However, when differences in manufacturing (e.g., impurities or excipients) between the proposed product and the reference product may result in differences in immunogenicity, measurement of anti-protein antibody responses in animals may provide useful information relevant to patient safety. Additionally, significant differences in the immune response profile in inbred strains of mice, for example, may indicate that the proposed product and the reference product differ in one or more product attributes not captured by other analytical methods. If available, this information is of value in the design of clinical immunogenicity assessment.

2.10 Clinical Studies

2.10.1 Human Pharmacology Data

Human PK and PD studies comparing a proposed product to the reference product generally are fundamental components in supporting a demonstration of biosimilarity. Both PK and PD study (where there is a relevant PD measure) generally will be expected to establish biosimilarity, unless an applicant can scientifically justify that an element is unnecessary.A human PK study that demonstrates similar exposure (e.g., serum concentration over time) with the proposed product and reference product can provide support for a biosimilarity demonstration. A human PD study that demonstrates a similar effect on a clinically relevant PD measure or measures related to effectiveness or specific safety concerns (except for immunogenicity, which is evaluated separately) can also provide strong support for a biosimilarity determination.

Applicants should provide a scientific justification for the selection of the human PK and PD study population (e.g., patients versus healthy subjects) and parameters, taking into consideration the relevance of such population and parameters, the population and parameters studied for the licensure for the reference product, as well as the current knowledge of the intra-subject and inter-subject variability of human PK and PD for the reference product. Also applicants should predefine and justify the criteria for PK and PD parameters for studies included in the application to demonstrate biosimilarity. Establishing a similar human PK and PD profile contributes to the demonstration of biosimilarity and may provide a scientific basis for a selective and targeted approach to subsequent clinical testing.

2.10.2 Immunogenicity assessment

The goal of the clinical immunogenicity assessment is to evaluate potential differences between the proposed product and the reference product in the incidence and severity of human immune responses. Hence, establishing that there are no clinically meaningful differences in immune response between a proposed product and the reference product is a key element in the demonstration of biosimilarity. Structural, functional, and animal dataare generally not adequate to predict immunogenicity in humans. Therefore, at least one clinical study that includes a comparison of the immunogenicity of the proposed product to that of the reference product will generally be expected.

The extent and timing (e.g., premarket testing versus pre- and postmarket testing) of a clinical immunogenicity program will vary depending on a range of factors, including the extent of analytical similarity between the proposed product and the reference product, and the incidence and clinical consequences of immune responses for the reference product. If the immune response to the reference product is rare, two separate studies may be sufficient to evaluate immunogenicity: (1) a premarket study powered to detect major differences in immune responses between the two products and (2) a postmarket study designed to detect more subtle differences in immunogenicity. The applicant should develop assays capable of sensitively detecting immune responses, even in the presence of circulating drug product (proposed product and reference product). The proposed product and reference product should be assessed in the same assay with the same patient sera whenever possible.

2.10.3 Clinical safety and effectiveness

For Biosimilar applications, comparative safety and effectiveness data is 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 PK and PD data,

and clinical immunogenicity assessment. Specific safety or effectiveness concerns regarding the reference product and its class (including history of manufacturing- or source-related adverse events) may warrant more comparative clinical safety and effectiveness data.

Alternatively, if the reference product has a long, relatively safe marketing history and there have been multiple versions of the reference product on the market with no apparent differences in clinical safety and effectiveness profiles, there may be a basis for a selective and targeted approach to the clinical program.

3. REGULATORY PATHWAY:

3.1 Europe submissions:

The European Union (EU) has pioneered in the development of a regulatory system for biosimilar products. The European Medicines Agency (EMA) began formal consideration of scientific issues presented by biosimilar products at least as early as January 2001, when an ad hoc working group discussed the comparability of medicinal products containing biotechnology-derived proteins as active substances[6]. In 2003, the European Commission amended the provisions of the EU secondary legislation governing requirements for marketing authorization applications for medicinal products and established a new category of applications for "similar biological medicinal products"[7]. In 2005, the EMA issued a general guideline on similar biological medicinal products, in order to introduce the concept of similar biological medicinal products, to outline the basic principles to be applied, and to provide applicants with a 'user guide', showing where to find relevant scientific information[8].

Since then, 14 biosimilar products have been approved by EMA under the pathway and two monoclonal antibodies have been recommended for approval in July 2013.

The main regulatory texts for biosimilars in the EU are Directive 2003/63/EC, Directive 2004/27/EC and the following guidelines: Overarching Guideline (Guideline on Similar Biological Medicinal Products (EMEA/CHMP/437/04), Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance, quality issues (EMEA/CHMP/BWP/49348/2005) and the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance, non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005).

Table.1: Approved Biosimilars in Europe[9]

Biosimilar	INN	Company	Approval Year
Omnitrope	Somatropin	Sandoz	2006
Valtropin		Biopartners	
Binocrit	Epoetin Alfa	Sandoz	2007
Epotin Alfa		Hexal	
Abseamed		Medice	
Silapo	Epoetin Zeta	Stada	
Retecrit		Hospira	
FilgrastimRatiopharm	Filgrastim	Ratiopharm	2008
Ratiograstim		Ratiopharm	
Biograstim		CT Arzneimittel	
Tevagrastim		Teva	
FilgrastimHexal		Hexal	2009
Zarzio		Sandoz	
Nivestim		Hospira	2010

Table.2: Recommended by EMA for approval of Biosimilars in Europe[10]

Biosimilar	INN	Company
Inflectra	Infliximab	Hospira
Remsima		Celltrion

The guideline on non-clinical and clinical issues sets out the requirements for pharmaco-toxicological assessment (non-clinical studies), and for studies of pharmacokinetics, pharmacodynamics, efficacy and safety clinical studies and a guideline on immunogenicity. The guidelines describe the issues that biosimilar companies must address, including factors that influence immunogenicity, the design and interpretation of assays to evaluate the immunogenic potential of a biosimilar and its comparability to other products, and the implementation of a risk management plan.

Besides the general guidelines, product-class-specific guidelines have been issued for recombinant erythropoietin, somatropin, human granulocyte colony-stimulating factor, human insulin, recombinant IFN-alfa and low-molecular weight heparins (LMWH).

Table.3: List of EMA's Overarching Biosimilar Guidelines[11]

Topic	Reference number	Publication date	Effective date	Guideline status
Similar biological medicinal products	CHMP/437/04 Rev.1	May 2013	NA	Deadline for comments 31 Oct 2013
	CHMP/437/04	September 2005	October 2005	Adopted
Similar biological medicinal products containing biotechnology derived proteins as active substance: non-clinical and clinical issues	EMEA/CHMP/BMWP /42832/2005 Rev. 1	June 2013	NA	Draft -Deadline for comments 30 Nov 2013
	EMEA/CHMP/BMWP /42832/2005	February 2006	June 2006	Adopted
Similar biological medicinal products containing biotechnology derived proteins as active substance: quality issues	EMA/CHMP/BWP/ 247713/2012	May 2012	NA	Draft - Deadline for comments 30 Nov 2012
	EMEA/CHMP/BWP/ 49348/2005	February 2006	June 2006	Adopted

Table.4: List of EMA's Product specific Biosimilar Guidelines[11]

Topic	Reference number	Guideline status
Similar biological medicinal products containing recombinant follicle stimulation hormone (Publication date March 2013; Effective date September 2013)	CHMP/BMWP/ 671292/2010	Adopted
Similar biological medicinal products containing interferon beta (Publication date March 2013; Effective date September 2013)	CHMP/BMWP/ 652000/20100	Adopted
Similar biological medicinal products containing monoclonal antibodies: non-clinical and clinical issues (Publication date June 2012; Effective date December 2012)	EMA/CHMP/B MWP/403543/2 010	Adopted
Similar biological medicinal products containing recombinant erythropoietins (Publication date April 2010; Effective date September 2010)	EMEA/CHMP/ BMWP/301636/ 08	Adopted
Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - Guidance on similar medicinal products containing recombinant erythropoietins (Publication date March 2006; Effective date July 2006)	EMEA/CHMP/ 945626/2005	Adopted
Non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins (Publication date January 2013)	EMEA/CHMP/ BMWP/118264/ 2007 Rev. 1	Draft - Deadline for comments 31 July 2013
Similar biological medicinal products containing low-molecular-weight heparins (Publication date April 2009; Effective date October 2009)	EMEA/CHMP/ BMWP/118264/ 2007	Adopted
Non-clinical and clinical development of similar medicinal products containing recombinant interferon alpha (Publication date June 2009; Effective date April 2009)	EMEA/CHMP/ BMWP/102046/ 2006	Adopted
Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - Guidance on biosimilar medicinal products containing recombinant granulocyte-colony stimulating factor (Publication date February 2006; Effective date June 2006)	EMEA/CHMP/ BMWP/31329/2 005	Adopted
Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - Guidance on similar medicinal products containing somatropin (Publication date February 2006; Effective date June 2006)	EMEA/CHMP/ BMWP/94528/2 005	Adopted
Revision of the guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (Publication date December 2012)	EMEA/CHMP/ BMWP/32775/2 005	Draft - Deadline for comments 30 June 2013
Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues - Guidance on similar medicinal products containing recombinant human insulin (Publication date February 2006; Effective date June 2006)	EMEA/CHMP/ BMWP/32775/2 005	Adopted

Table.5 List of EMA's other relevant Guidelines for Biosimilars[11]

Topic	Reference number	Guideline status
Immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (Publication date June 2012; Effective date December 2012)	EMA/CHMP/BMWP /86289/2010	Adopted
Comparability of biotechnology-derived medicinal products after a change in the manufacturing process - non-clinical and clinical issues (Publication date July 2007; Effective date November 2007)	EMEA/CHMP/BMW P/101695/2006	Adopted
Immunogenicity assessment of biotechnology-derived therapeutic proteins (Publication date January 2008; Effective date April 2008)	EMEA/CHMP/BMW P/14327/2006	Adopted
Comparability of medicinal products containing biotechnology-derived proteins as active substance - Quality issues (Publication date December 2003; Effective date December 2003)	CPMP/ICH/5721/03	Adopted
Comparability of medicinal products containing biotechnology-derived proteins as drug substance: non-clinical and clinical issues (Publication date December 2003; Effective date June 2004)	EMEA/CPMP/3097/0 2	Adopted
Development of a Committee for Proprietary Medicinal Products guideline on comparability of biotechnology-derived products (Publication date June 1998; Effective date September 2013)	CPMP/BWP/1113/98	Concept paper

Regarding data exclusivity, two regimes coexist in the EU. The old regime, which dates back to 1983, was modified in 2004. The new regime applies to all reference products submitted for approval on and after 30 October 2005.

The data exclusivity period for biologicals, as for other medicines, under the new regime is known as "8+2+1". This means that a (generic) applicant shall not be required to provide the results of pre-clinical tests and clinical trials if he can demonstrate that the medicinal product is a generic version of a reference medicinal product which is or has been authorised for not less than eight years in a Member State or in the Community. However, a generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product. Moreover, the ten year period shall be extended to a maximum of eleven years if, during the first eight of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which are considered to bring significant clinical benefits in comparison with existing therapies.

3.2 United States submissions:

3.2.1 Evolution of guidelines with US FDA:

In the 1980s novel biological medicines produced by recombinant DNA technology appeared on the horizon. FDA began to receive marketing applications for biotechnology-derived protein products, mostly for recombinant DNA-derived versions of a naturally sourced product. FDA established a regulatory approach for the approval of recombinant DNA-derived protein products, which it announced in a policy document published on June 26, 1986, in conjunction with a 1985 document titled "Points to Consider in the Production and Testing of New Drugs and Biologicals Produced by Recombinant DNA Technology".Due to the complexities of protein products, FDA has, as a matter of policy, generally required submission of an NDA in accordance with section 505(b)(1) of the FD&C Act or a BLA in accordance with section 351(a) of the PHS Act containing product-specific full safety and efficacy data for recombinant DNA-derived protein drugs. FDA has recognized, however, that "in some instances complete new applications may not be required".

In 1996, FDA provided recommendations in its FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology Products, which explains how an applicant may demonstrate, through a combination of analytical testing, functional assays (in vitro and/or in vivo), assessment of pharmacokinetics (PK) and/or pharmacodynamics (PD) and toxicity in animals, and clinical testing (clinical pharmacology, safety, and/or efficacy) that a manufacturing change does not adversely affect identity, purity, or potency of its FDA-approved product.

In October 1999, FDA issued a draft guidance for industry on Applications Covered by Section 505(b)(2), which, among other things, stated that FDA may accept an application submitted through the approval pathway described by section 505(b)(2) of the FD&C Act for a drug product containing an active ingredient(s) derived from natural sources or recombinant DNA technology. FDA approved a 505(b)(2) application for a follow-on recombinant DNA-derived human growth hormone product in May 2006.

The BPCI Act was enacted as part of the Affordable Care Act on March 23, 2010. The BPCI Act creates an abbreviated licensure pathway for biological products demonstrated to be biosimilar to, or interchangeable with, a reference product. Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. Section 351(i) of the PHS Act defines biosimilarity to mean that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that 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.For the approval of follow-on biologics in the United States, current regulations depends on whether the biologic product is approved under the United States Food, Drug, and Cosmetic Act (US FD&C) or it is licensed under the United States Public Health Service Act (US PHS). For those biologic drugs marketed under the PHS Act, the BPCI Act passed by the US Congress on March 23, 2010 amends the PHS Act to establish an abbreviated approval pathway for biological products that are highly similar or interchangeable with an FDA-authorized biologic drug, and gives the FDA the authority to approve.

3.2.2 United States Food, Drug, and Cosmetic Act (US FD&C):

Section 505 of the Act describes three types of new drug applications:

1) an application that containsfull reports of investigations of safety and effectiveness (section 505(b)(1))
2) an application thatcontains full reports of investigations of safety and effectiveness but where at least some of theinformation required for approval comes from studies not conducted by or for the applicant and forwhich the applicant has not obtained a right of reference (section 505(b)(2))
3) an application thatcontains information to show that the proposed product is identical in active ingredient, dosage form,strength, route of administration, labeling, quality, performance characteristics, and intended use, amongother things, to a previously approved product (section 505(j)). Note that a supplement to anapplication is a new drug application.

3.2.2.1 Submission through 505(b)(2) pathway:

Section 505(b)(2) was added to the Act by the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments). This provision expressly permits FDA to rely, for approval of an NDA, on data not developed by the applicant. Sections 505(b)(2) and (j) together replaced FDA's paper NDA policy, which had permitted an applicant to rely on studies published in the scientific literature to demonstrate the safety and effectiveness of duplicates of certain post-1962 pioneer drug products.

Enactment of the generic drug approval provision of the Hatch-Waxman Amendments ended the need for approvals of duplicate drugs through the paper NDA process by permitting approval under 505(j) of duplicates of approved drugs (listed drugs) on the basis of chemistry and bioequivalence data, without the need for evidence from literature of effectiveness and safety. Section 505(b)(2) permits approval of applications other than those for duplicate products and permits reliance for such approvals on literature or on an Agency finding of safety and/or effectiveness for an approved drug product.An application for a drug product containing an active ingredient(s) derived from animal or

botanical sources or recombinant technology where clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a listed drug.

3.2.2.2 Submission through 505(j) pathway:

A 505(j) application is an abbreviated new drug application (ANDA) that contains information to show that the proposed product is identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics and intended use, among other things, to a previously approved product - the reference listed drug (RLD).ANDAs do not contain clinical studies as required in NDAs but are required to contain information establishing bioequivalence to the RLD.

In general, the bioequivalence determination allows the ANDA to rely on the Agency's finding of safety and efficacy for the RLD. A drug product that is the subject of an ANDA is referred to as a generic drug. FDA approved the first generic version of Lovenox (enoxaparin sodium injection), an anti-coagulant drug used for multiple indications including prevention of deep vein thrombosis (DVT), a potentially deadly blood clotting condition in July 23, 2010.

3.2.3 Public Health Service Act:

The Biologics Price Competition and Innovation Act (BPCI Act) was passed as part of the Affordable Care Act that President Obama signed into law on March 23, 2010.

BPCI Act creates an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product [section 351(k) of the Public Health Service Act]. Under the BPCI Act, a protein, except any chemically synthesized polypeptide, will be regulated as a biological product[12].

3.2.3.1 Submission through 351(k) pathway:

A 351(k) application must include the following information demonstrating that the biological product:

- Is biosimilar to a reference product;
- Utilizes the same mechanism(s) of action for the proposed condition(s) of use- only to the extent known for the reference product
- Condition(s) of use proposed in labeling have been previously approved for the reference product
- Has the same route of administration, dosage form, and strength as the reference product

- that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
- 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.

To meet the higher standard of "interchangeability," an applicant must provide sufficient information to demonstrate biosimilarity, and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch (see section 351(k)(4) of the PHS Act). Interchangeable products may be substituted for the reference product by a pharmacist without the intervention of the prescribing healthcare provider (see section 351(i)(3) of the PHS Act).

4. DISCUSSION AND CONCLUSION:

Biosimilars represent, potentially, an attractive market, although there are significant regulatoryand commercial hurdles to overcome. Biopharmaceuticals are different from small molecule chemical drugs. Because of the large and complex nature of biological molecules, biosimilars cannot be guaranteed to be identical to innovator biologics. Therefore, regulators have been concerned that undetected differences in biosimilars may result in reduced efficacy or different adverse reactions. Establishing a high degree of similarity in quality between the biosimilar product and the original product is a crucial key in the regulatory approval process, because biologicals vary greatly in properties and where even small alterations can lead to unacceptable changes in safety and efficacy.

As discussed, the biosimilar product development has many constraints and economical barriers. Even minor structural differences (including certain changes in glycosylation patterns) can significantly affect a protein's safety, purity, and/or potency, it is important to evaluate these differences. Protein modifications and higher order structure can be affected by environmental conditions, including formulation, light, temperature, moisture, packaging materials, container closure systems, and delivery device materials. Additionally, process-related impurities may increase the likelihood and/or the severity of an immune response to a protein product, and certain excipients may limit the ability to characterize the drug substance. These issues can be addressed by establishing appropriate target quality profile in the initial stage of the development followed by "Quality by Design" concept. Also appropriate functional assays to be established which provides an additional data to support results from structural analysis, investigate the consequences of observed

structural differences, and explore structure activity relationships. Unlike small generic molecules, biosimilar development needs extensive animal studies and clinical studies including immunogenicity assessment depends upon the molecule. For global development programs, selection of reference product from US or EU and relevant bridging study to be performed with other market reference product.Specific safety or effectiveness concerns regarding the reference product and its class (including history of manufacturing- or source-related adverse events) may warrant more comparative clinical safety and effectiveness data. Regulatory guidelines are evolving worldwide for the last 30 years for biological products and the expectations for each national authority are still to be harmonised. EMA has taken a lead in review and approval of biosimilar products in EU when compared to US and 14 products have been approved so far. Also they have developed many guidelines related to Biosimilar and considering the complexity of the molecules, EMA has developed many molecule specific guidelines. These guidelines indeed help sponsors to develop the product in appropriate manner wherein the complete development package should meet the regulators expectations in terms of physiochemical and clinical aspects. The biosimilar applications can be filed in US using any one of the following path ways (i) section 505(b)(2) new drug application (ii) section 505(j) ANDA application (iii) section 351(k) of PHS act. Assessment of immunogenicity and interchangeability are other important criteria to fulfil the Biosimilar requirements.

Overall, the rapidly evolving regulatory science in the biosimilar area would benefit from better cooperation, information exchange and collaboration from regulators. It is recommended that the sponsors need to discuss the development strategy with regulators at appropriate stage of development and get their concurrence on the strategy. This will help to ease the regulatory review process and early product approvals.

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