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REVIEW

The Emergence of Biosimilar Insulin Preparations—A Cause for Concern?

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Abstract

Several biopharmaceuticals, including insulin and insulin analogs, are, or shortly will be, off-patent, thereby providing an opportunity for companies to attempt to manufacture "copies" commonly referred to as biosimilars and also known as follow-on biologics. Reassurance that such copy biologics are equally safe and effective as the conventional products is essential. It is important for the clinician to consider what information is therefore necessary for such assurances. Biopharmaceuticals, produced from living organisms and manufactured by complex processes, differ in many respects from chemically derived drugs. The biological source materials and manufacturing processes for non-innovator biologics may differ considerably from those used for producing the innovator substance. Differences between innovator and non-innovator products can be identified analytically (e.g., batch-to-batch consistency, product stability along side clinical safety). This provides a strong argument for caution before automatic substitution of conventional products (e.g., insulin by biosimilars). Several non-innovator insulins, including insulin analogs (while still patent-protected), are already available in many countries. Many of these lack rigorous regulations for biosimilar approval and pharmacovigilance. Recently an application for a biosimilar recombinant human insulin was withdrawn by the European Medicines Agency because of safety and efficacy concerns. Therefore, every biosimilar insulin and insulin analog should be assessed by well-defined globally harmonized preclinical and clinical studies followed by post-marketing pharmacovigilance programs, in the interest of people with diabetes worldwide.

Introduction

Pharmaceutical preparations are usually chemistry based, whereas biopharmaceuticals, such as recombinant human insulin or insulin analogs, are peptides or proteins produced by, or isolated from, biological sources. Characteristically, biopharmaceuticals have much higher molecular weights and are intrinsically far more complex as a result of having distinct primary, secondary, tertiary, and quaternary structures. The manufacturing of biopharmaceuticals is inherently a sophisticated, multistep process that involves culturing the cell line derived from the expression system.[1,2] Each host cell introduces a specific "fingerprint" of the master cell on the final product. Furthermore, purification and formulation of the final product can potentially add additional variability. The final product will be reliant upon its primary and three-dimensional protein structure and any posttranslational modifications, isoforms, aggregates, and impurities as well as excipients, and also any stabilizers used in the final pharmaceutical formulation.[3] Any differences in the manufacturing process of biopharmaceuticals can therefore result in different products, one example of which was the case of epoetin alfa (Eprex®; Janssen-Cilag Ltd., Saunderton, High Wycombe, United Kingdom), resulting in a spontaneous increase in the incidence of pure red-cell aplasia.[4] Several suggestions were offered[5]; however, the only explanation consistent with available data is that a small change in formulation decreased protein stability, leading to increased aggregate formation. This case has raised awareness that even minor process changes in the production of biopharmaceuticals can lead to serious clinical consequences. Generic drugs are required by regulatory authorities to possess the exact same chemical structure of the active ingredient and dosage formulation and to utilize the same route of administration as the innovator product and finally to demonstrate bioequivalence. If bioequivalence is demonstrated, a clinical study is deemed

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unnecessary.[6] The approach developed for the authorization of small-molecule drugs is not, however, appropriate for biopharmaceutical products in which both the protein structure and folding pattern need to be similar to the innovator product.[2] The European Medicines Agency (EMA) defines biosimilars as a copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy, and safety, and authorization is based on a comprehensive comparability exercise to the innovator product.[7,8] In contrast to biopharmaceutical innovator products, which are licensed by the National Regulatory Authorities on the basis of a full registration dossier (including stringent quality, efficacy, and safety data for the approved indications), biosimilars are granted market access based on an abbreviated submission required only to demonstrate physicochemical, preclinical, and clinical properties comparable to those of the innovator drugs.[9] In general, investigating the equivalence of a biosimilar to an innovator product is in itself a challenge as current laboratory and analytical methodologies are limited in their ability to determine biological properties and predict potential immunogenicity. The lack of standardization further increases the difficulty when comparing results from different clinical studies, making interpretation difficult and potentially unsafe.

To date, biosimilars for recombinant human insulin and certain insulin analogs (e.g., insulin glargine) have been granted market access in several countries, such as China, India, Pakistan, Peru, Thailand, and Mexico, where current biosimilar regulations are relatively lax. In such a situation, in which a biological medicinal product has been developed and/or not directly compared and analyzed against a licensed reference biological product according to more comprehensive biosimilar regulations, a more appropriate terminology for such products could be "non-innovator copy biologics," rather than biosimilars.[10] The manufacture of recombinant human insulin and insulin analogs requires highly sophisticated production and purification procedures, and thus complete interchangeability with innovator biopharmaceuticals is debatable.[11,12] This review focuses on the present position relating to recombinant human insulins and certain insulin analogs. Clinical and safety aspects, manufacturing processes, as well as current regulatory requirements for their marketing authorization, will be discussed.

Clinical and Safety Challenges with Biosimilar Insulins

Clinical efficacy

Clinical efficacy of biosimilar insulins may also be influenced by factors such as physical stability, formulation, or batch-to-batch variability. Despite the administration of identical units of biosimilar insulin, unpredictable differences in glycemic effects can occur if substantial batch-to-batch variability arises during manufacture or by accelerated loss of activity due to variations in physical stability. Exposure to extremes in climatic conditions (e.g., temperature, humidity) could also have an adverse impact on quality. Furthermore, if two products demonstrate different potencies, different doses may be required for equivalent glycemic control. Finally, differences in formulation may lead to various adverse reactions (e.g., local reactions at the injection site). The use of validated and safe devices are also key elements in ensuring accurate dosing of insulin to the patient.[3]

Immunogenicity

Potential immunogenicity is a safety issue largely unique to biopharmaceuticals that may be severe and potentially cause loss of efficacy. The classic immune response to foreign proteins is observed for biopharmaceuticals of bacterial or plant origin.[13] A second mechanism, which is normally directed to self-antigens, is based on breaking immune tolerance, which leads to antibody formation to human homologs.[14] In either case, the activation of antibody-secreting B cells may lead to severe adverse events (AEs).[15,16] Several factors, including protein peptide sequence, impurities such as endotoxins, formulation, denatured and aggregated proteins, route of administration, dose–response effects, disease type and genetic background of the patient, treatment duration, and other as yet unknown factors play a role in immunogenicity.[17] Evidence supports the theory that aggregation of biopharmaceutical proteins is the primary factor that initiates breaking of antibody-secreting B cell tolerance.[18,19] As biosimilars are produced by manufacturing processes that may well differ from that of innovator products, their formulation and stability may also differ and may therefore lead to higher levels of degradation and denaturation, leading to aggregation of proteins that are potentially immunogenic. Although the incidence and severity of general immune effects, such as local hypersensitivity and anaphylactic reactions, with insulin therapy have decreased with the use of highly purified formulations, potential immunogenicity remains a concern.[17]

Recombinant Human Insulin and Insulin Analog Manufacturing Processes

All steps in the manufacture and purification of human insulin and insulin analogs, such as insulin glargine, can potentially introduce heterogeneities that may influence their biological and clinical properties.[1] Therefore the choice of expression system used is a key element. The bacterium, *Escherichia coli*, and the yeast, *Saccharomyces cerevisiae*, are the hosts of choice and differ with respect to handling of the recombinant protein. In *E. coli*, the recombinant insulin proteins accumulate as inclusion bodies, whereas in *S. cerevisiae* they are secreted into the culture medium. As a consequence, isolation and purification processes are different for each process. In order for the yeast to be amplified exo-enzymes are produced, which must be inactivated, and protein-folding processes are necessary for production involving *E. coli*. Cleavage of the pre-pro-insulin may lead to the accumulation of impurities or the formation of new product-related compounds, which must also be removed. Posttranslational modifications are also necessary if the different insulin chains are produced independently. Additionally, cultivation conditions, nutrient composition, and equipment design can all affect by-product formation.

Process-scale separation of recombinant insulin proteins is a multistep process and includes ion exchange, reversed-phase, and size-exclusion chromatography.[20] Materials such as excipients are also added to the final product, and protein aggregation may occur at any stage of the process.[18,19]

The manufacture of the insulin analog, insulin glargine, results in the formation of characteristic insulin-related substances (IRS) that can be analytically identified using reverse-phase (RP) high-performance liquid chromatography (HPLC) separation.[21,22] For European markets, a maximum of 1.0% IRS is tolerated, as specified in the draft monograph of insulin glargine.[21] A comparison of IRS levels of commercially available copies of glargine (Basalog® [Biocon Ltd., Bangalore, India], Glaritus® [Wockhardt Ltd., Maharashtra, India], Basalin® [Gan & Lee, Beijing, China]) reveals that the overall amounts of insulin glargine-related by-products are low (<1.5%) and all within the required ranges specified in the draft monograph.[21] However, the impurity profiles of the glargine copies indicate small but characteristic differences in the nature detected by RP-HPLC compared with Lantus® (sanofi-aventis, Paris, France) (Fig. 1). The obtained IRS profiles reflect the individuality of the production process used for each glargine preparation. Potential factors that contribute to the uniqueness of IRS profiles include the use of various expression hosts, upstream, as well as downstream processing conditions and degradation reactions, which may be influenced by the drug product's composition.

The expression of insulin glargine in the yeast *Pichia pastoris* results in the formation of glycosylated by-products.[23] These by-products are also present in the final pharmaceutical formulation and contribute to the characteristic impurity profile of Basalog, also produced in *P. pastoris*, as shown (Fig. 1C). Major by-products present in the Basalin (expressed in *E. coli*) HPLC profile have been previously analyzed and described.[24] These result from the enzymatic steps in the manufacturing process due to trypsin-related miscleavages. Details of Wockhardt Ltd.'s manufacturing process for Glaritus (expressed in *E. coli*) and the resulting insulin glargine-related by-products have not yet been published. Nevertheless, the IRS profile is a fingerprint of Glaritus reflecting the different production processes. Despite the fact that characteristic impurity profiles of insulin glargine copies can be detected that are different from that of Lantus, the clinical relevance of such small differences remains unknown.

Pharmacovigilance Aspects

Manufacturers are requested to submit safety specifications and a pharmacovigilance post-marketing strategy along with the marketing authorization application. Most currently established guidelines note that AEs arising from immunogenicity may be too rare to be detected in the relatively small and short-term studies required for authorization; thus post-marketing product safety monitoring is vital. Both the European Union (EU)[25] and World Health Organization (WHO)[9] guidelines recommend that a benefit–risk assessment be conducted on a continuous basis after post-marketing authorization. Post-marketing safety reports should include scientifically evaluated data on product tolerability, including evaluation of the frequency and causality of AEs. National Regulatory Authorities are expected to provide a legal framework for pharmacovigilance surveillance and ensure the ability to identify an AE-related biopharmaceutical marketed in their region.[9]

One of the main challenges today is that in countries where biosimilar guidance does not exist, pharmacovigilance programs are also not available.

Regulatory Aspects of Biosimilar Insulins and Insulin Analogs

EMA

The Committee for Medicinal Products for Human Use (CHMP) of the EMA first established an overarching guideline on biosimilars, which clearly stipulated that biosimilars are not generic medicinal products.[7] Biosimilarity between an innovator product and a potential biosimilar is to be ensured in its entirety through stringent clinical and nonclinical data.[8] In addition, EMA issued product class-specific annexes, including one for human soluble insulin.[25] The annex to the EMA biosimilar guideline outlines clinical and nonclinical requirements for recombinant human soluble insulin products applying for designation as a biosimilar.[1,25] As insulin is administered chronically, the key safety concern is immunogenicity. Thus, the EMA requires that clinical studies of at least 12 months' duration using subcutaneous administration are conducted to collect safety and immunogenicity data, with the incorporation of a comparative phase (≥6 months' duration) to be completed prior to market authorization.[26]

Specific clinical studies are also required for human soluble insulin biosimilars, including a pharmacokinetic study with a single subcutaneous dose crossover design comparing biosimilar and innovator, preferably in type 1 diabetes mellitus (T1DM). Pharmacodynamic studies are also key to demonstrate comparability: these include a time–action profile of hypoglycemic response supported by a double-blind, crossover, hyperinsulinemic, euglycemic clamp study. Provided that clinical comparability can be demonstrated for both pharmacokinetic and pharmacodynamic data, the EMA does not require clinical trial efficacy studies to be conducted. Dossiers also require data to be included from nonclinical studies such as in vitro pharmacodynamic and toxicological studies. The EMA does not assess the interchangeability or substitutability of a biosimilar when granting marketing authorization, and substitution decisions may be taken at a national level. The Working Party of the CHMP has recently issued a concept paper for revision of the current guidance to include insulin analogs and long-acting human insulin preparations.[27] Furthermore, the concept paper recommends further clarification on whether the pharmacokinetic study can be combined with the pharmacodynamic study, the most suitable patient population, and size of the clinical safety study needed. The proposed guideline will replace the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: clinical and non-clinical issues.[8] The concept paper was released for consultation in October 2011 and closed December 31, 2011. Insulin analogs are currently not covered in the EMA guidelines,[11] although insulin analogs represent a growing therapy segment for the insulin-requiring diabetes population.

Recombinant Human Insulin: Non-Innovator Copy Biologics

The first licensed drug generated using recombinant DNA technology was human insulin, which was approved for clinical use in 1982.[28] In recent years, several companies have started to manufacture non-innovator recombinant human insulin formulations in countries where little or no regulatory procedures are in place (Table 1).

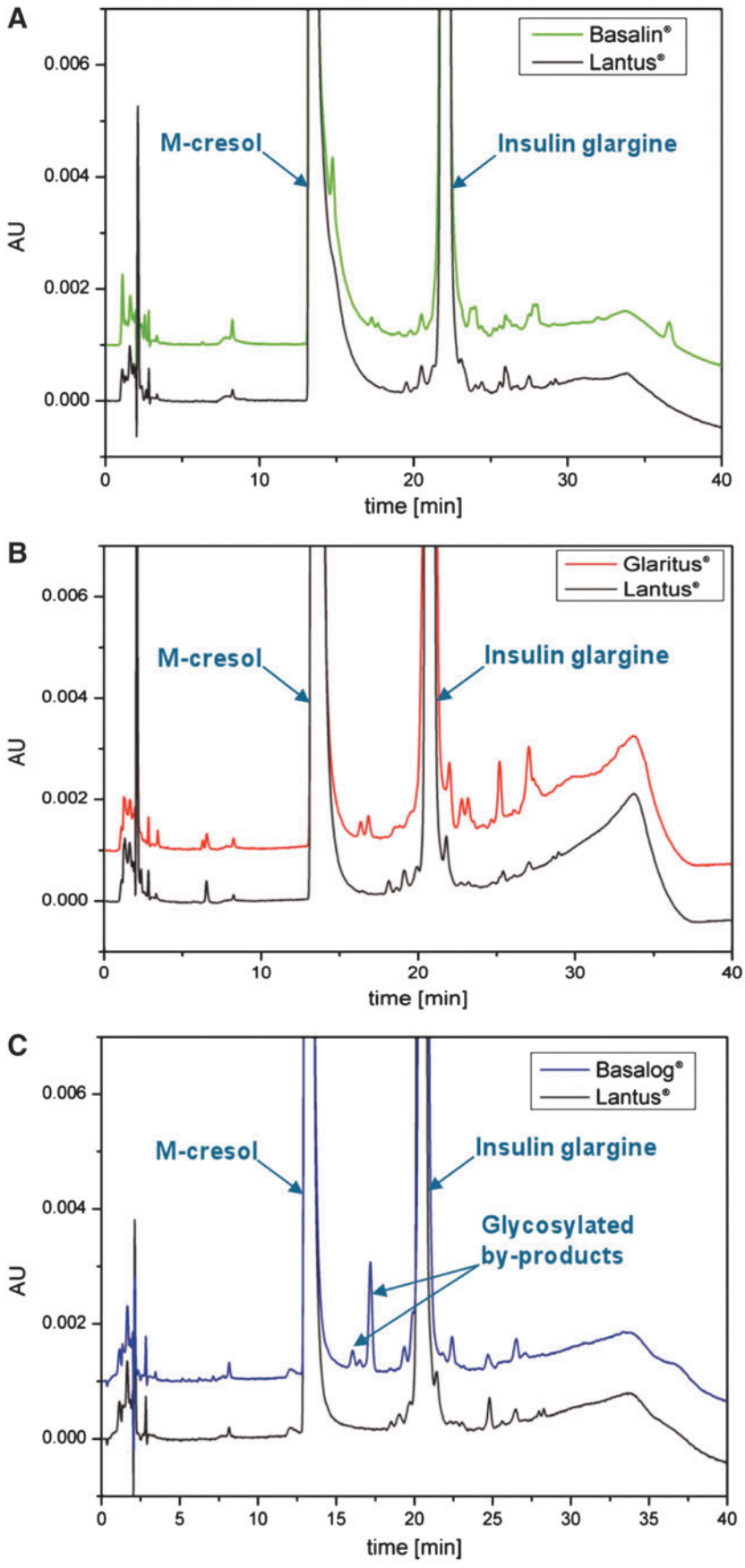

FIG. 1. Analytical comparison of the insulin glargine copies **(A)** Basalin®, **(B)** Glaritus®, and **(C)** Basalog® with the innovator product Lantus® using reverse-phase high-performance liquid chromatography.[21] As each glargine manufacturer has its own unique manufacturing process, the individual biotechnological production process leads to a specific analytical fingerprint of the final product that can be identified by the formation of characteristic insulin-related substances upon reverse-phase high-performance liquid chromatography separation. Total insulin-related substances detected in each chromatogram is below 1.5%, and each single insulin-related substance is below 1% of the total glargine amount. AU, absorption units.

Table 1. Marketed Biosimilar Recombinant Human Insulins in Poland and India

Brand name	*Company (manufacturer)*	*Clinical studies (Phase I, II, III)*
Gensulin®	Bioton, Poland	NA
Biosulin® R, N, 30/70, L	MJ Biopharm Pvt. Ltd., India (Marvel Lifesciences)	NA
Wosulin®	Wockhardt Ltd., India	NCT00596063 (I, completed) NCT00772265 (I, completed) NCT00752180 (I, completed) NCT00719108 (I, completed) NCT01308437 (III, recruiting)
Insugen® R	Biocon, India	CTRI/2010/091/000627 (III, not yet recruiting)

30/70, premixed insulin; CTRI, Clinical Trials Registry India (http://ctri.nic.in/Clinicaltrials/advsearch.php); L, lente insulin; N, NPH insulin; NA, no information available; NCT, National Institutes of Health clinical trials registry (United States) (www.clinicaltrials.gov); R, regular soluble insulin.

Gensulin® (Bioton S.A., Warsaw, Poland) was introduced to the Polish market in 2001 under local regulations prior to Poland becoming a member state of the EU (2004). Insugen® (Biocon Ltd.) has been available in India since 2004 and more recently (2010) in Nigeria. A Phase III study (CTRI/2010/091/000627) is being conducted to assess the safety and efficacy of Insugen® R and Insugen N with Actrapid® (Novo Nordisk, Bagsvaerd, Denmark) and Insulatard® (Novo Nordisk), respectively, in persons with T1DM. Wosulin® (Wockhardt Ltd.) has been marketed in India since 2003, and four Phase I clinical studies (NCT00772265, NCT00752180, NCT00596063, and NCT00719108) have been conducted to date. In addition, a Phase III study (NCT01308437) is being conducted to test the immunogenic safety of Wosulin R (regular, soluble insulin of recombinant DNA origin), Wosulin N (isophane insulin human of recombinant DNA origin), and Wosulin 70/30 (a mixture of insulin human regular injection 30% with isophane insulin human suspension 70%) in patients with T1DM.

Insulin Glargine: Non-Innovator Copy Biologics

Insulin analogs with a delayed and prolonged action, such as insulin glargine and detemir, are well accepted as basal insulin therapy.[29] Insulin glargine (Lantus) was approved in 2000 for medical use in T1DM and type 2 diabetes mellitus. Non-innovator copy biologicals of insulin glargine are being marketed or registered in China, Mexico, India, Pakistan, Peru, and Thailand where there are currently no biosimilar regulatory processes in place (Table 2).

Wockhardt Ltd. intend to test the immunogenicity and safety of its recombinant insulin analog, Glaritus, using Lantus as a comparator, in a Phase III open-label, randomized, clinical trial to be conducted in patients with T1DM (NCT01352663). In addition, a Phase I comparative glucose clamp study to determine bioequivalence of Glaritus with Lantus (NCT01357603) is currently underway. In China, the efficacy and bioequivalence of Basalin, referred to as a "national" insulin glargine biosimilar, and Lantus, referred to as "imported" glargine, were compared with those of NPH insulin (Novolin® N; Novo Nordisk) following subcutaneous administration in healthy volunteers using euglycemic clamp methodology.[30] Basalin and Lantus preparations were found to be bioequivalent. Another study in type 2 diabetes mellitus on the control of fasting and postprandial hyperglycemia using a "national" non-innovator glargine versus "imported" glargine combined with an oral hypoglycemic agent found similar therapeutic efficacy with the two insulin glargines.[31] In Colombia, a dossier for Basalin submitted by a local company (LaFranCol, Cali, Colombia) was rejected in August 2009 on the basis that no immunogenicity studies had been conducted.[33] In China, Gan & Lee has established a partnership with LG Life Sciences (Seoul, Korea) in 2006 for the commercialization of Basalin.[34] Basalog is an insulin glargine non-innovator copy biologic manufactured by Biocon Ltd. in India and marketed there since 2009. A multicenter, randomized, open-label Phase III study comparing Basalog with Lantus in patients with T1DM found that the two basal insulin preparations exerted comparable glycemic control.[32] Therefore, non-innovator biologicals with little or minimal supporting scientific data are being marketed widely in some countries where there is an absence of strict biosimilar regulation and requirement for long-term pharmacovigilance. This could potentially have an adverse impact on the efficacy and safety of treatment in patients with diabetes exposed to such unregulated preparations.

The Marvel Experience

Marvel Lifesciences Private Ltd. (Mumbai, India) developed recombinant insulin in *E. coli* and in March 2007 submitted to the EMA the first European application for authorization of three "biosimilar" insulin formulations: a soluble rapid-acting insulin (Marvel Rapid), a long-acting isophane insulin (Marvel Long), and a 30:70 mixture (30% soluble, 70% insulin) of the two (Marvel Mix). However, Marvel later officially withdrew its application.[35–38] Extrapolating from the CHMP's comments, the product submission was considered as inadequate as reviewed in detail elsewhere,[11,12] which referred to the quality of the research and that biosimilarity to the innovator product was not demonstrated adequately. The production process was not detailed adequately, and the drug product specifications was lacking. Good Manufacturing Practice and Chemistry, Manufacturing, and Control processes were also deemed insufficient. In addition, the dose-delivery properties of vials and cartridges had neither been thoroughly tested nor validated.

This recent example highlights the stringent regulatory requirements for biosimilar insulins in the EU. However, Marvel's insulins, marketed as Biosulin R, N, 30/70, and L, are available elsewhere (e.g., India) (Table 1).

Regulatory Aspects: Food and Drug Administration and Other Authorities

In March 2010, as part of the U.S. healthcare reform bill, the U.S. Food and Drug Administration (FDA) enacted legal authority through the Biologics Price Competition and

Table 2. Marketed Insulin Glargine Copies (Biosimilars)

Status, brand name	*Injectible form (U100/mL)*	*Company (manufacturer)*	*Country (year)*	*Clinical studies, comments*
Marketed				
Basalin®	3-mL cartridges 10-mL vials	Gan & Lee	China (2005)	Cheng et al.[30] (2010) Zhu et al.[31] (2009) CTRI/2010/091/000012 Phase I
	3-mL cartridges 10-mL vials	East West Pharmaceutical (Gan & Lee)	Pakistan (2009)	
Bonglixan®	3-mL cartridges 10-mL vials	Landsteiner Scientific (Gan & Lee)	Mexico (November 2008)	NA
Glaritus®	3-mL cartridges	Wockhardt Ltd.	India (February 2009)	NCT01357603 Phase I NCT01352663 Phase III
Basalog®	3- and 10-mL vials	Biocon	India (June 2009)	CTRI/2008/091/000226 Phase III Verma et al.[32] (2011)
Registered				
Glaritus	3-mL cartridges Disposable pen (DispoPen)	Pharmaris Peru	Peru (August 2010)	NA
Submission				
Glargin®	10-mL vials 3-mL cartridges	Belmedpreparaty (Gan & Lee)	Belarus (June 2011)	NA
Rejected				
Basalin®	Injectible solution	LaFranCol	Colombia (August 2009)	INVIMA[33] (2009) Dossier rejected: lacking immunogenicity studies

CTRI, Clinical Trials Registry India (http://ctri.nic.in/Clinicaltrials/advsearch.php); INVIMA, Instituto Nacionalde Vigilanciade Medicamentosy Alimentos; NA, no information available; NCT, U.S. National Institutes of Health (United States) clinical trials registry (www.clinicaltrials.gov/).

Innovation Act to approve biosimilars and to authorize the interchangeability of biosimilars with their innovator biologic.[39,40] Section 351(k) of the U.S. Public Health Service Act, amended by the Biologics Price Competition and Innovation Act, outlines an abbreviated approval pathway that was created for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed innovator product. The majority of biologics have been regulated under the U.S. Public Health Service Act. However, a few biological products, such as insulin and human growth hormone, were regulated and approved as drugs under New Drug Applications in Section 505 of the Food, Drug and Cosmetic Act.[39,40] The U.S. Congress recognized the historical anomaly of biologics that have been approved as drugs and required the FDA to transition these products, over a 10-year period after enactment, to the effect that all biologics should eventually be regulated under the U.S. Public Health Service Act.

The WHO finalized its guideline in 2010, aimed at providing globally acceptable principles for licensing biotherapeutic products, particularly in countries lacking regulation.[9] The guideline "can be adopted as a whole, or partially, by NRAs [National Regulatory Authorities] worldwide, or used as a basis for establishing national regulatory frameworks for licensure."[9] The WHO guideline generally follows those established in the EU and, in scope, encompasses well-established and characterized biotherapeutic products such as recombinant DNA-derived proteins. Issues of interchangeability and substitution are left up to regional authorities to define. In the EU, substitution is not allowed in France, Germany, Greece, Italy, Slovenia, Spain, Sweden, and the United Kingdom.[42] The Czech Republic requires that physicians actively prohibit substitution, while Austria obliges physicians to prescribe by brand name. Some countries, such as Denmark, Finland, Hungary, Norway, and Slovakia, publish official lists of products that cannot be substituted. A recent article has outlined the issue of interchangeability in the FDA's approval pathway: "A biologic will be considered interchangeable with a reference (innovator) product if the developer demonstrates that it can be expected to produce the same clinical result in any given patient and that the risk associated with alternating or switching between the two products is not greater than that involved in continuing to use the reference product. The FDA will carefully consider what data will be necessary for this purpose and translate that assessment into effective regulatory standards."[42]

Biosimilar guidelines are in effect in Canada, Australia, Turkey, Mexico, Saudi Arabia, Japan, Taiwan, Singapore, and Kazakhstan, as well as Malaysia, where no substitution is allowed.[43] India, Thailand, Colombia, Chile, and Peru have draft guidance, but regulation in many other parts of Asia, including China, is lacking. Brazil was one of the first countries in Latin America to issue guidelines, followed by

Argentina and Venezuela. In South Africa the final guidance included insulins. However, many countries worldwide still do not have any biosimilar regulation in place. Nevertheless, physicians around the globe realize evermore the need for the establishment and implementation of stringent guidelines for the evaluation of biosimilars. In India, where enforced withdrawals of biosimilar batches and a lack of pharmacovigilance have been reported, along with a court case awarding compensation to a victim of a biosimilar insulin "accident," in the interest of their patients' safety, physicians are calling for stringent biosimilar guidelines to be put in place.[44,45]

Outlook

As patent protection of human insulin and insulin-analog innovator products either has already or is soon to expire, several non-innovator biopharmaceuticals, typically called biosimilars, are being developed and marketed in countries where there are no strict regulations. Biosimilar insulins and insulin analogs are not identical copies of innovator products, but are products of their manufacturing processes, raising potential clinical efficacy and safety challenges. Biopharmaceuticals are produced in living systems and may therefore have the potential to induce inappropriate immune responses and potentially lead to immunogenicity, sometimes with serious consequences. Current evidence suggests that the regulation of biosimilar recombinant insulin and insulin analogs should be reevaluated and harmonized worldwide. There are at present no such regulations for biosimilars of insulin analogs.

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