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Review Article

Introduction of biosimilar insulins in Europe

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Abstract

Regulatory approval of the first biosimilar insulin in Europe, LY2963016 insulin glargine (Abasaglar®), in 2014 expanded the treatment options available to people with diabetes. As biosimilar insulin products come to market, it is important to recognize that insulin products are biologicals manufactured through complex biotechnology processes, and thus biosimilar insulins cannot be considered identical to their reference products. Strict regulatory guidelines adopted by authorities in Europe, the USA and some other countries help to ensure that efficacy and safety profiles of biosimilar insulins are not meaningfully different from those of the reference products, preventing entry of biological compounds not meeting quality standards and potentially affecting people's glycaemic outcomes. This review explains the concept of biosimilar medicines and outlines regulatory requirements for registration of biosimilar insulins in Europe, which is illustrated by the successful development of LY2963016 insulin glargine and MK-1293 insulin glargine (Lusduna®). Preclinical and clinical comparative studies of the biosimilar insulin glargine programmes include *in vitro* bioassays for insulin and insulin-like growth factor 1 receptor binding, assessment of *in vitro* biological activity, evaluation of pharmacokinetic/pharmacodynamic profiles in phase I studies and assessment of long-term safety and efficacy in phase III studies. The emergence of biosimilar insulins may help broaden access to modern insulins, increase individualized treatment options and reduce costs of insulin therapy.

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Introduction

The first biosimilar insulin, LY2963016 insulin glargine (LY IGlar) (Abasaglar®), was approved in the European Union (EU) in September 2014 [1]. Currently, other biosimilar insulins have begun to enter the market, and more are likely to enter the market in the years to come. Although 'biosimilars' have been used in Europe for ~ 10 years [2,3] in nephrology, oncology, rheumatology or endocrinology (Fig. 1), the concept of biosimilars is still not well known to many general practitioners, nurses and other specialists caring for large and growing populations of people with diabetes.

Biosimilar insulins are welcomed as additional and potentially less expensive choices of therapies. However, clinicians and people with diabetes may not understand the concept of biosimilarity and how these medications are similar and not identical to their reference products. Preclinical and clinical data of the LY IGlar programme previously were reviewed by Heinemann *et al*. in 2015 [4]; the current review extends and updates the previous report and includes data from the newly approved biosimilar MK-1293 insulin glargine (MK IGlar) (Lusduna®). In this review, we define biosimilar medicines, describe EU regulatory requirements for biosimilar basal insulins, present the development programmes of LY IGlar and MK IGlar, and outline potential benefits and concerns relevant from a clinical perspective.

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Defining biosimilar medicines

'Biosimilar' is a regulatory designation and as such might have different definitions under different jurisdictions. The European Medicines Agency (EMA) defines a biosimilar as 'a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product)' [5]. Similarity should be established in terms of quality characteristics, biological activity, safety and efficacy. For a biological medicine with a protein as the active substance, the amino acid sequence of the biosimilar medicine is expected to be the same as that of the reference product [6].

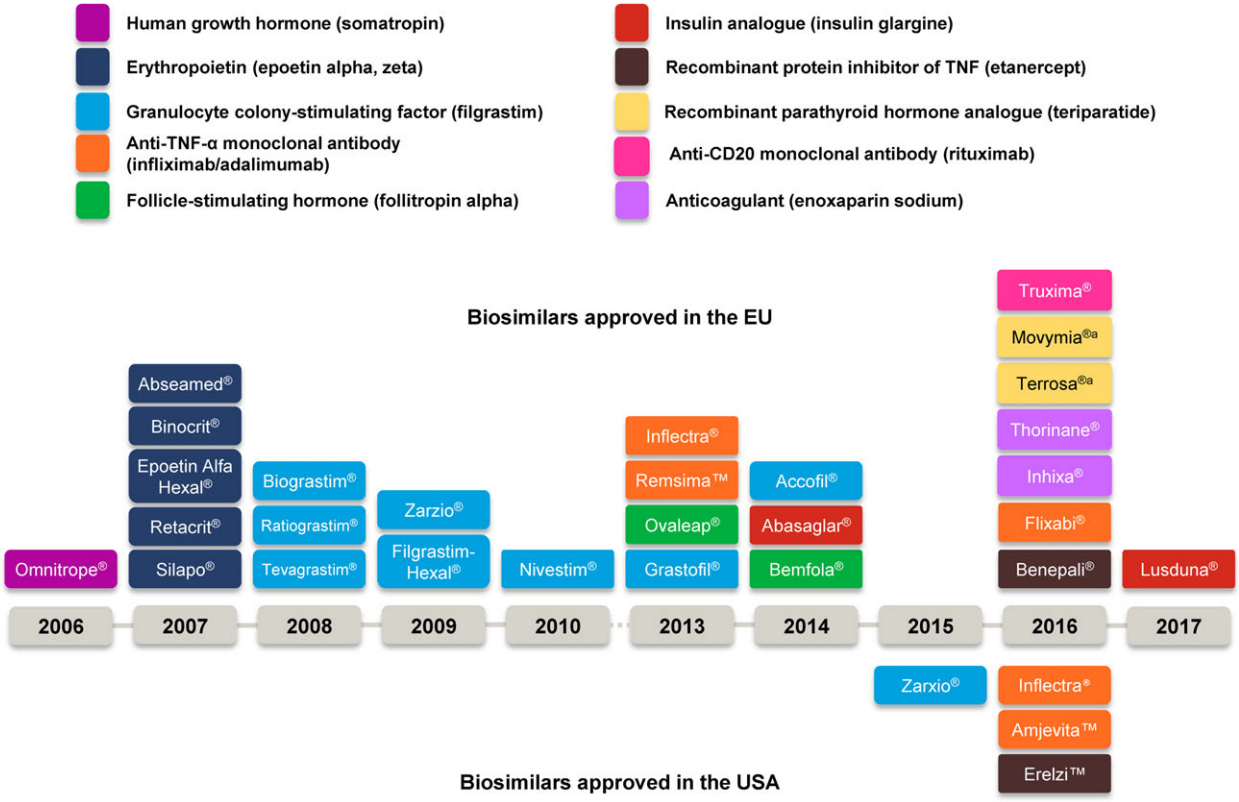
Differences between biosimilar and generic medicines

Generics are copies of innovative small-molecule medicines. The active substance of a generic medicine contains exactly the same molecule as the reference medicine. Biosimilar medicines also attempt to copy innovative biological medicines; however, the molecular structures of biosimilars are far larger and more complex than those of generic medicines [7–9] (Table 1). The active substance of a biosimilar medicine depends on both the primary amino acid sequence and higher order structures such as protein folding and post-translational modifications, which ultimately may affect the safety and efficacy of the medicine.

The higher order molecular structures of biosimilars might be affected by a variety of factors throughout the manufacturing, distribution and storage processes (Fig. 2), which also are complex and might introduce variability in the biosimilar medicines [8,9]. Even minor changes in structure are considered to be potentially associated with altered efficacy and safety profiles, in particular, an altered immunogenicity profile. The larger and the more complex a biological product is, the greater are the concerns for structural differences between the biological product and the reference product [7,8]. Insulin products are not as complex as some larger biologicals such as monoclonal antibodies; however, their development still warrants thorough evaluation in clinical programmes based on the same principles and risks as the larger biologicals (Fig. 3).

Manufacture of biological drugs as source of variability

The typical insulin-manufacturing process consists of gene isolation and insertion into a host cell, such as bacteria (*Escherichia coli*) or yeast, establishment and expansion of cell lines to produce the insulin, isolation, purification, formulation, packaging and distribution through a cold-chain distribution channel [7]. Minor changes to any of the manufacturing steps might affect the properties of the final



[a]Movymia® and Terrosa® have received positive opinions from the European Medicines Agency's Committee for Medicinal Products for Human Use but are not yet authorised for use

FIGURE 1 Biosimilar medicines approved in Europe and the USA since 2006 [3,17–20,61–63].

Table 1 Key distinctions between generic and biosimilar medicines

Generics	Biosimilars
Copies of small-molecule medicinal products derived from chemical manufacturing processes	Similar versions of biological medicinal products derived from biotechnological manufacturing processes
Identical chemical structures to those of already marketed products	Amino acid sequence to be identical to that of the reference product
Low molecular weight	Differences in biotechnological manufacturing processes between companies – biosimilar products cannot be described as identical
Known structure	Higher molecular weight
Stable at room temperature	Complex structure
Different routes of administration	Unstable, sensitive to heat and shear
Organic/chemical synthesis	Mostly parenteral administration
Homogeneous/high purity	Produced from living cells/organisms
Rarely immunogenic	Heterogeneous/difficult to standardize
Not affected by slight changes in environment	Higher immunogenic risk
Simple purification and characterization	Affected by slight changes in environment
Simple detection and purification of contamination	Complex purification and characterization
Reproducible	Difficult detection and purification of contamination
	Reproducibility difficult

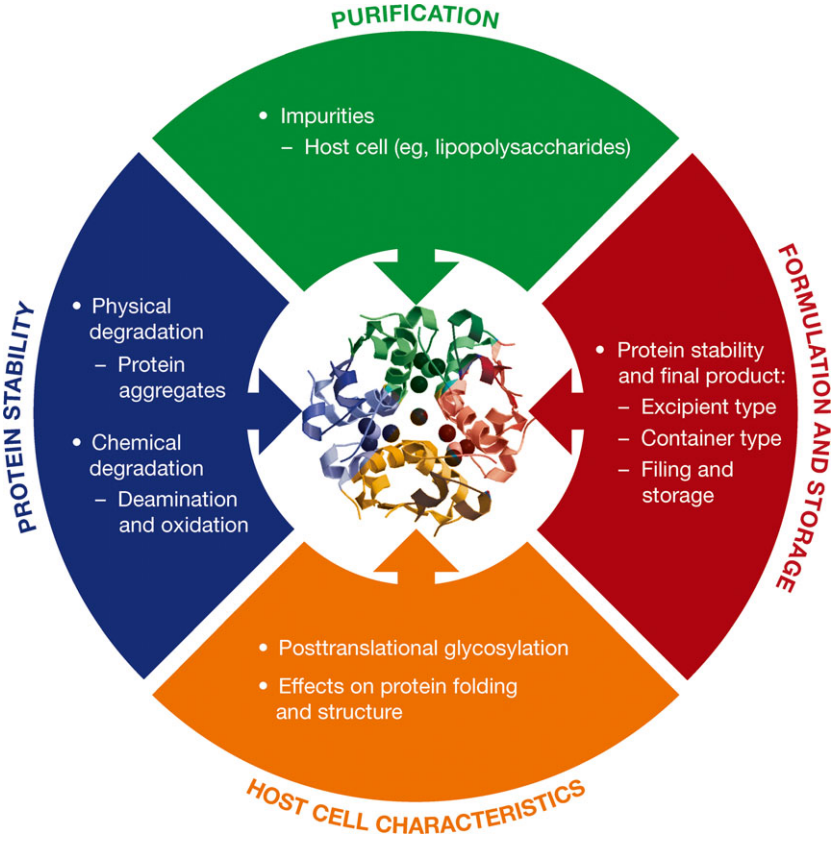


FIGURE 2 Potential influence of the manufacturing process on biosimilar molecules/insulin.

product (Fig. 2). The manufacturing processes are proprietary, and different manufacturers use different processes, increasing the potential for structural differences between biologicals [9,10].

The clinical relevance of how the manufacturing process can affect the properties of a biological medication is illustrated by one of the human erythropoietins used to treat anaemia. Increased incidence of life-threatening pure red cell aplasia was reported as early as 2002 [11,12]. These adverse events were then subsequently linked to an increased immune response to the drug [12,13]. Corrective measures included replacement of the uncoated rubber syringe stoppers with Teflon-coated stoppers, enhancement of product controls, emphasis on appropriate storage

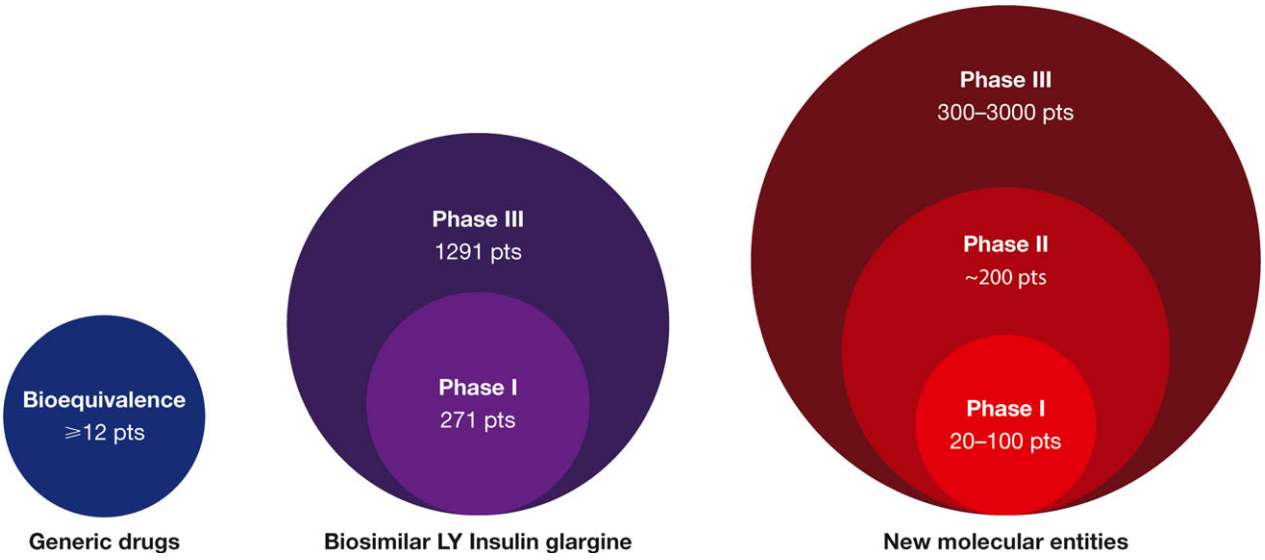


FIGURE 3 Relative magnitudes of clinical studies for generic medicines [64], biosimilar LY insulin glargine [32,35,37,38,41,43] and new molecular entities [65]. The sizes of the circles do not necessarily represent the relative sizes of the trials between categories. Pts, participants.

temperatures and the recommendation to administer the drug intravenously rather than subcutaneously. Subsequently, the incidence of pure red cell aplasia returned to previously reported levels.

Not only does the effect of the manufacturing process on the product characteristics of the biosimilar need to be considered, but batch-to-batch quality standards must also guarantee long-term stability of the product profile, mitigating variability in the product.

EMA requirements for biosimilar insulin

Approximately 10 years ago, the EMA was the first regulatory agency to issue its three guidelines outlining the general principles of biosimilarity, quality, and nonclinical and clinical aspects of biosimilars [5,6,14]. The guidelines create a framework for demonstrating similarity between a biological drug and the reference molecule and include quality characteristics, biological activity, safety and efficacy in a tailored development programme. Annexes to the guidelines describe guidance for specific types of biosimilar medicines, e.g. guidance for products containing recombinant human insulin and insulin analogues [15].

Preclinical evaluation of insulin products begins in the same way as with other biological compounds: evaluation of drug composition, physical properties, primary and higher order structures and purity and impurity characterizations [5,6]. Differences observed between the biosimilar and reference products should be justified and may require further clinical evaluation, especially if the differences could affect immunogenicity. Table 2 summarizes requirements for preclinical and clinical characterizations of similar insulin products.

Requirements in other countries

Outside Europe, the definition of a biosimilar or the criteria to approve a biosimilar might differ. In the USA, an approval pathway was created only recently [16], and only four biosimilar drugs have been approved: the leucocyte growth factor filgrastim-sndz [17], the anti-tumour necrosis factor monoclonal antibody infliximab-dyyb [18], the tumour necrosis factor blocker etanercept-szzs [19] and the anti-tumour necrosis factor monoclonal antibody adalimumab-atto [20].

In some countries, regulatory scrutiny is less rigorous than elsewhere, which could lead to the approval of products that are not supported by robust similarity data [7]. Negative perception of biosimilars may reflect such previous experience with similar products of biological medicines in markets with less-stringent regulatory criteria. If this occurs, the safety or efficacy profiles of such 'biological copies' should not be extrapolated to biosimilars that undergo rigorous scrutiny in regulated markets such as those of the EU and the USA.

Examples of unsuccessful EMA regulatory submissions

Not all submissions for the registration of biosimilar insulin products have met the strict regulatory criteria. One example is the submission by Marvel Lifesciences Ltd of three recombinant human insulin formulations [21].

The Committee for Medicinal Products for Human Use (CHMP) expressed a number of concerns that included paucity of information about the manufacturing process and its validation and phase I studies that did not show similarity

Table 2 European Medicines Agency requirements for biosimilar insulin [15]

Comparative study type	Study type	Additional considerations
Preclinical*	*In vitro* receptor binding • both human insulin receptors (IR-A and IR-B) • on/off cellular kinetics	• IGF-1 receptor binding and functional activity are optional.

	In vitro biological activity
	• receptor autophosphorylation
	• metabolic activity (at least three different assays):
	  • glycogen formation
	  • lipogenesis
	  • inhibition of stimulated lipolysis
	  • glucose transport
		• Selection of an assay should be justified.
		• Comparative IGF-1 receptor binding and an assay for functional activity can be included.

	Repeated-dose toxicity studies • not required in general	• Need for these studies should be considered following a risk-based approach.
Clinical	Phase 1 PK/PD studies • the mainstay of proof of similar efficacy • hyperinsulinaemic, euglycaemic, cross-over, preferably double-blind clamp studies • studies in homogeneous, insulin-sensitive population: healthy people or people with Type 1 diabetes	• The primary PK endpoints typically include AUC (sufficient for long-acting insulins) and C_{max}. • Similarity is demonstrated if the 90% CI of the ratio of test : reference primary PK endpoints is contained within the predefined equivalence margins, e.g. 80% to 125%. • The primary PD endpoints are the GIR, AUC and GIR_{max}. • Similarity is demonstrated if the 95% CI of the test : reference ratio of PD primary endpoints is contained within the predefined equivalence margins.
	Phase 3 studies • safety studies with specific focus on immunogenicity • include reasonable number of people with Type 1 diabetes	• Studies do not have to be powered to demonstrate noninferiority regarding immunogenicity. • There is no need for specific efficacy studies; they are typically not sensitive enough to detect potentially clinically relevant differences. • Treatment duration of at least 6 months is recommended to compare incidence and titres of antibodies to the biosimilar and reference products.

AUC, area under the plasma-concentration curve; CI, confidence interval; C_{max}, maximum insulin concentration; GIR, glucose-infusion rate; GIR_{max}, maximum GIR; IGF-1, insulin-like growth factor 1; IR-A, insulin receptor isoform A; IR-B, insulin receptor isoform B; PD, pharmacodynamic; PK, pharmacokinetic.
**In vivo* pharmacodynamic studies, safety pharmacology, reproductive toxicology, cancerogenicity and local tolerance studies are not required.

in lowering blood-sugar levels [21–24]. A second submission resulted in concerns related to manufacturing and study data, and the identification of critical and major good clinical practice findings [25–27].

A third submission dossier for the soluble human insulin was reviewed by the CHMP in 2015, and the committee recommended the refusal of the marketing authorization [28]. The CHMP's main concern was that sufficient details of the manufacturing process were not included. The concerns prevented the conclusions that the insulin is similar to the reference product [28]. This example reflects the importance of quality and manufacturing aspects of biological drugs development, which are subject to regulatory scrutiny before and after the marketing authorization is granted.

Biosimilars of insulin glargine products approved in Europe

The successful development of biosimilar insulin is illustrated by the clinical development programmes of two insulin glargine products: LY IGlar (Eli Lilly and Company and Boehringer Ingelheim) [1] and MK IGlar (Merck) [29] biosimilars of Lantus® (Sanofi) insulin glargine (SA IGlar). LY IGlar gained European marketing authorization in September 2014 [1]. Even though the submission was made before the EMA issued the

revised 'Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues' [15], the programme was generally consistent with the EMA requirements outlined in the draft versions of the guidelines. In the USA, LY IGlar received marketing authorization on the basis of the scientific principles of demonstrating similarity to the previously approved insulin glargine; however, LY IGlar is not considered a biosimilar in the USA because it was filed through the 505(b)(2) regulatory pathway [30], which has been designated for use when the reference product has been previously approved under section 505(b)(1) of the Food, Drug and Cosmetic Act.

MK IGlar gained European marketing authorization in January 2017 [29]. In August 2016, a new drug application was accepted for review by the US Food and Drug Administration (US FDA) [31]. Similar to LY IGlar, the application was filed through the 505(b)(2) regulatory pathway, therefore, if approved, this insulin will not be considered a biosimilar in the USA.

Manufacturing and quality aspects

The LY IGlar manufacturing process consists of the production of a pre-pro-protein in transformed *E. coli*, recovery of the pre-pro-protein from the fermentation broth, removal of cell debris/granule concentration by differential centrifugation, solubilization, refolding to form a proinsulin-like intermediate with correct disulfide bonds, enzymatic removal of the leader sequence and the connecting peptide, purification, crystallization, drying and filling into final containers [32]. Limited specific information is available about the manufacturing process of MK IGlar, however, the process also involves *E. coli* expression of proglargine [33].

Comprehensive comparability exercises for LY IGlar and MK IGlar with the reference EU- and US-approved SA IGlar product were conducted. The comparability exercises included structural and biological activity characterization and batch consistency and stability assessments. LY IGlar and MK IGlar were determined to meet biosimilarity criteria by the CHMP [1,32,33].

Preclinical studies

Preclinical *in vitro* studies of both LY IGlar and MK IGlar compared the binding affinity and functional activity at the insulin receptor, insulin receptor isoforms A and B and insulin-like growth factor 1 receptor (IGF-1R) with SA IGlar. The studies included assessment of metabolic activities and mitogenicity in cell culture models. The two programmes of preclinical studies differed in methodology and the choice of assays [32,33]. Some potency differences between LY IGlar and SA IGlar were noted in individual assays, and an inherent variability of assays resulted in a small magnitude of differences between the reference molecules [4,32]. This prompted Eli Lilly and Company to conduct additional *in vitro* studies with improved methodology and additional reference molecules [32]. The results were less variable and were consistent with the accepted drug discovery assay variability standards [32,34]. Thus, the additional statistical analyses supported the conclusion that overall, LY IGlar has a similar *in vitro* pharmacological profile to that of SA IGlar [32].

Although animal studies are not currently required for demonstrating biosimilarity per the revised 2015 biosimilar insulin guidance from the EMA's Committee for Medicinal Products for Human Use [15], a 4-week repeat-dose toxicity study in rats including pharmacokinetic (PK) and pharmacodynamic (PD) assessments was conducted for LY IGlar and SA IGlar [32]. The preclinical MK IGlar programme included studies in two animal models of diabetes (rats treated with streptozotocin and dogs treated with somatostatin), the assessment of PK and metabolic parameters in rodents and dogs and repeated-dose toxicity studies in rats [33]. Collectively, both sets of *in vitro* and *in vivo* studies did not identify biologically important differences between LY IGlar and SA IGlar and between MK IGlar and SA IGlar, meeting the objectives of a preclinical development programme outlined in the EMA guidelines.

Pharmacokinetic/pharmacodynamic studies

The phase I clinical trial programme for LY IGlar included six randomized, crossover, euglycaemic clamp PK/PD studies. The most important evidence for similarity of LY IGlar and SA IGlar comes from three core comparative 24-h clamp studies that were conducted in 211 healthy people and adopted bioequivalence criteria for PK and PD [35]. The meeting of bioequivalence criteria was to be concluded if 90% confidence intervals for the ratios of geometric means of the key PK and PD parameters were completely contained within the prespecified acceptance limits of 0.80 to 1.25. Two studies used EU- and US-approved SA IGlar as comparators, respectively, to meet the requirements of the two regulatory agencies. The third study compared EU- and US-approved SA IGlar reference products to meet bioequivalence criteria so that both products could be used in phase III studies and EU- and US-approved SA IGlar could be presented as a single treatment arm.

The primary PK parameters assessed were area under the concentration-versus-time curve from zero to 24 h (AUC_{0-24h}) and maximum drug concentration (C_{max}). At the time of the studies, no assays for insulin glargine metabolites M1 or M2 or for parent insulin glargine were commercially available. For this reason, concentrations of the study drugs were estimated as the difference between serum immunoreactive insulin glargine and endogenous insulin, which corresponds to the concentration of C-peptide [36]. The primary PD parameters were maximum glucose infusion rate (GIR) and total glucose infusion over the clamp duration.

Bioequivalence criteria were met in all three studies for both PK and PD [35].

Durations of action for LY IGlar and SA IGlar, defined as the times required for blood glucose levels to rise above a predefined cut-off of 8.3 mmol/L (150 mg/dl) from euglycaemia, were compared in a randomized, double-blind, single-dose, two-period, crossover study involving 20 participants with Type 1 diabetes mellitus treated with 0.3 U/kg doses of LY IGlar or SA IGlar before a 42-h euglycaemic clamp [37]. End of action was observed in 13 LY IGlar and 13 SA IGlar clamps (overall, 26 of 40). The median durations of action were 37.1 and 40.0 h for LY IGlar and SA IGlar; the mean durations of action, calculated only for participants who reached end of action, were 23.8 and 25.5 h. These time-to-event analyses demonstrated similarity of duration of action for the two study drugs [37].

Similar relative bioavailability for LY IGlar and SA IGlar at two different doses (0.3 and 0.6 U/kg) in a study that included 24 healthy individuals provided complementary evidence for meeting bioequivalence criteria [38]. The phase I programme also included a pilot study to inform subsequent clinical studies [32].

The phase I clinical trial programme for MK IGlar included two pivotal PK/PD studies [33,39,40]. In both studies, metabolites M1 and M2 and the parent MK IGlar were assessed individually. The primary PK parameters were metabolite M1 $AUC_{0–24h}$ and C_{max}. The primary PD parameters were the area under the GIR-versus-time curves from 0 to 24 h, 0 to 12 h and 12 to 24 h (GIR-$AUC_{0–24h}$, GIR-$AUC_{0–12h}$, and GIR-$AUC_{12–24h}$) and the maximum GIR.

The first study was a single-dose, double-blind, three-period, three-treatment, crossover euglycaemic 24-h clamp study that compared the PK and PD of MK IGlar, US-approved SA IGlar and EU-approved SA IGlar in 109 healthy participants [33,39]. The second study was conducted in 76 people with Type 1 diabetes. As a secondary objective, treatment with 0.4 U/kg of either MK IGlar or SA IGlar was followed by a 30-h euglycaemic clamp to allow comparison of duration of action [33,40]. Although PK and PD bioequivalence criteria were met in both studies [33,39,40], durations of action could not be compared because of the high percentage of participants who did not achieve end-of-PD action at 30 h; therefore, post hoc survival analysis provided evidence for similarity of duration of action [33]. An additional pilot study and formulation bridging study comparing the PK of vial and cartridge formulations was also conducted [33].

Phase 3 studies

Two phase III LY IGlar and two phase III MK IGlar randomized, controlled clinical trials were conducted in people with Type 1 and Type 2 diabetes to confirm the efficacy findings from the PK/PD studies and to evaluate safety and immunogenicity. According to the EMA biosimilar guidelines [15], there is no anticipated need for specific efficacy studies; since, endpoints used in such studies, usually HbA_{1c}, are not considered sufficiently sensitive to detect potentially clinically relevant differences between two insulins (Table 2). However, in these programmes, all four studies were powered to demonstrate noninferiority to SA IGlar in HbA_{1c} level change from baseline to 24 weeks. Their durations, enrolled populations and sample sizes were considered sufficient to provide evidence for biosimilarity of safety of the new glargine products to SA IGlar.

In people with Type 1 diabetes in open-label, 52-week trials (primary endpoints at week 24), 535 participants were assessed to compare the efficacy and safety of LY IGlar with those of SA IGlar in combination with premeal insulin lispro (ELEMENT 1 [41]), and 506 participants were assessed to compare the efficacy and safety of MK IGlar with those of SA IGlar in combination with prandial insulin [42]. Some 756 participants with Type 2 diabetes previously treated with SA IGlar or who were insulin naive and were taking at least two oral anti-hyperglycaemic medications were assessed in a 24-week double-blind trial to compare the efficacy and safety of LY IGlar with those of SA IGlar (ELEMENT 2 [43]); 531 participants eligible for or taking basal insulin were assessed in an open-label trial to compare the efficacy and safety of MK IGlar with those of SA IGlar [44].

The primary efficacy objective to demonstrate noninferiority to SA IGlar in HbA_{1c} level change from baseline to 24 weeks (margins of 4 mmol/mol, 0.4%, and then 3 mmol/mol, 0.3%, for LY IGlar; 4 mmol/mol, 0.4%, for MK IGlar) was met in all four trials [41–44]. The secondary objectives of demonstrating noninferiority of SA IGlar to LY IGlar and MK IGlar also were met, fulfilling the predefined criteria for equivalent efficacy.

The LY IGlar and MK IGlar programmes assessment of hypoglycaemia was comprehensive, followed both US and EU guidelines [32,33], and included total asymptomatic, relative, nocturnal and severe hypoglycaemic events. The MK IGlar programme included total, symptomatic, asymptomatic, severe, requiring nonmedical assistance and requiring medical assistance episodes of hypoglycaemia [33]. Blood glucose levels of ≤ 3.9 mmol/L (≤ 70 mg/dl) were considered confirmatory in both development programmes [32,33].

The incidences of total hypoglycaemia reported in the LY IGlar trials in participants with Type 1 diabetes at 52 weeks were 96% for LY IGlar and 97% for SA IGlar (severe hypoglycaemia: 4% for LY IGlar and 4% for SA IGlar), and the incidences of total hypoglycaemia reported in participants with Type 2 diabetes at 24 weeks were 79% for LY IGlar and 78% for SA IGlar (severe hypoglycaemia: < 1% for LY IGlar and < 1% for SA IGlar) [41,43]. The incidences of total hypoglycaemia reported in the MK IGlar trials in participants with Type 1 diabetes at 52 weeks were 77% for MK IGlar and 80% for SA IGlar (severe hypoglycaemia: 22% for MK IGlar and 24% for

SA IGlar), and the incidences of total hypoglycaemia reported in participants with Type 2 diabetes at 24 weeks were 54% for MK IGlar and 54% for SA IGlar (severe hypoglycaemia: 9% for MK IGlar and 8% for SA IGlar). [33]. There were no meaningful differences between hypoglycaemic incidences, events or rates between the study arms in any of the four trials, which led to the conclusions that LY IGlar and SA IGlar, and MK IGlar and SA IGlar confer similar risks of hypoglycaemia in people with Type 1 and Type 2 diabetes [33,41,43].

Immunogenicity was assessed in all trials and included antibody development. Similarity of LY IGlar and MK IGlar to SA IGlar for other efficacy and safety outcomes such as allergic reactions and insulin antibodies also was demonstrated. A conclusion of similar immunogenicity was reached for LY IGlar on the basis of the percentages of participants in ELEMENT 1 and ELEMENT 2 with detectable antibodies throughout the treatment periods [41,43,45] (Table 3). Measures included the presence of cross-reactive antibodies, incidences of treatment-emergent antibody response, insulin antibody levels, incidences of allergic events and incidences of injection-site reactions. Insulin antibody levels were low in both treatment groups, and there was no association between developing treatment-emergent antibody response or insulin antibody levels and clinical outcomes [45]. There were no significant differences in maximum post-baseline antibody levels, and participants with the highest levels of antibody binding demonstrated no significant differences in clinical efficacy outcomes or adverse events from those in participants with low antibody binding.

Similar immunogenicity of MK IGlar and SA IGlar was concluded on the basis of similar insulin antibody responses, including incidence and titres, similar neutralizing antibody responses, association between efficacy outcomes and

Table 3 Summary of ELEMENT 1 and ELEMENT 2 results

	ELEMENT 1 (N = 535) [41]				ELEMENT 2 (N = 756) [43]			
	24 weeks		52 weeks		Insulin naive		Previous SA IGlar	
Parameter	LY IGlar n = 268	SA IGlar n = 267	LY IGlar n = 268	SA IGlar n = 267	LY IGlar n = 220	SA IGlar n = 235	LY IGlar n = 155	SA IGlar n = 144
HbA_{1c}, mmol/mol								
Endpoint	58 (1)	56 (1)	59 (1)	58 (1)	51 (1)	51 (1)	56 (1)	56 (1)
Change	–4 (1)	–5 (1)	–3 (1)	–3 (1)	–16 (1)	–17 (1)	–11 (1)	–11 (1)
HbA_{1c}, %								
Endpoint	7.42 (0.05)	7.31 (0.05)	7.52 (0.06)	7.50 (0.06)	6.86 (0.07)	6.79 (0.07)	7.31 (0.08)	7.32 (0.08)
Change	–0.35 (0.05)	–0.46 (0.05)	–0.26 (0.06)	–0.28 (0.06)	–1.48 (0.07)	–1.54 (0.07)	–1.02 (0.08)	–1.01 (0.08)
≤ 48 mmol/mol (6.5%), n (%)	54 (20)	49 (18)	42 (16)	36 (14)	65 (30)	86 (37)	34 (22)	28 (20)
Insulin dosage, U/kg/day	–	–	–	–	0.42 (0.03)	0.44 (0.03)	0.60 (0.03)	0.53 (0.03)
Basal	0.37 (0.01)	0.36 (0.01)	0.38 (0.01)	0.36 (0.01)	–	–	–	–
Prandial	0.35 (0.02)	0.35 (0.02)	0.37 (0.02)	0.37 (0.02)	NA	NA	NA	NA
Body weight, kg	74 (1)	73 (1)	74 (1)	73 (1)	NR	NR	NR	NR
Body weight change, kg	NR	NR	NR	NR	2.0 (0.3)	2.2 (0.3)	1.4 (0.3)	1.7 (0.3)
Hypoglycaemia rate overall, mean (SD) (events/person/year)*								
Total	86.5 (77.3)	89.2 (80.1)	77.0 (68.7)	79.8 (74.5)	21.6 (25.6)	22.9 (27.4)	20.8 (22.7)	21.5 (29.6)
Nocturnal	18.3 (23.6)	18.4 (21.5)	16.1 (20.2)	17.3 (19.5)	6.7 (10.7)	7.6 (12.5)	8.5 (13.1)	8.8 (17.5)
Hypoglycaemia incidence, %†								
Total	94	95	96	97	NR	NR	NR	NR
Nocturnal	82	80	86	88	NR	NR	NR	NR
Severe	2	3	4	4	NR	NR	NR	NR
Participants with detectable antibodies overall (median), n (%)‡	80 (30)	90 (34)	107 (40)	105 (39)	NR	NR	NR	NR
Insulin antibody binding (median), %	1.17	1.10	0.92	0.89	NR	NR	NR	NR

Data are given as least squares means (SD) unless otherwise indicated. For all comparisons, $P > 0.05$.
SA IGlar, Lantus® (Sanofi) insulin glargine; LY IGlar, LY2963016 insulin glargine; NA, not applicable; NR, not reported.
*The hypoglycaemia rate overall includes all events reported during the 24-week treatment (ELEMENT 1 and ELEMENT 2) or 52-week study (ELEMENT 1) periods. Hypoglycaemia was defined as blood glucose levels of ≤ 3.9 mmol/L (≤ 70 mg/dl) or a sign or symptom associated with hypoglycaemia. Nocturnal hypoglycaemia was defined as any hypoglycaemic event that occurred between bedtime and waking.
†In participants with Type 2 diabetes at 24 weeks (ELEMENT 2), the incidence of total hypoglycaemia was 79% (LY IGlar) and 78% (SA IGlar), nocturnal hypoglycaemia was 57% and 54%, and severe hypoglycaemia was < 1% for both [43].
‡Participants with detectable antibodies overall include the overall 24-week treatment period and the overall 52-week study period and not at LOCF.

antibody levels and similar risk of potential hypersensitivity reactions [33,42,44] (Table 4).

LY IGlar and SA IGlar showed similar efficacy and safety profiles in a subgroup of people with Type 1 or Type 2 diabetes treated with SA IGlar before randomization [45]. These phase III trials support the medically supervised use of LY IGlar after use of the reference product SA IGlar, however, no switching trials to support interchangeability or substitution (see the section on 'Interchangeability and substitution') have been conducted with LY IGlar.

Other biosimilar insulins in development

Sanofi is currently developing a biosimilar insulin lispro (SAR342434). SAR342434 has been studied in two phase I trials (NCT02273258 [46] and NCT02603510 [47]) and two phase III trials (SORELLA 1: EudraCT 2013-002945-12 [48], NCT02273180 [49], and SORELLA 2: EudraCT 2014-002844-42 [48], NCT02294474 [50]). The primary objectives of the phase III trials were to demonstrate the noninferiority of SAR342434 to insulin lispro in HbA_{1c} level change in people with Type 1 diabetes (NCT02273180) and Type 2 diabetes (NCT02294474) also treated with SA IGlar [49,50]. In September 2016, a marketing authorization application of SAR342434 was accepted for review in the EU [51].

Mylan and Biocon are co-developing a biosimilar insulin glargine (Basalog®), an insulin lispro and an insulin aspart. The biosimilar insulin glargine has been studied in phase III clinical trials in people with Type 1 and Type 2 diabetes (INSTRIDE 1: EudraCT: 2014-000747-32 [52], NCT02227862 [53], and INSTRIDE 2: EudraCT: 2014-000881-23 [52], NCT02227875 [54]) and an extension trial in people with Type 1 diabetes (EudraCT 2015-004353-40 [52], NCT02666430 [55]). The primary objectives of INSTRIDE 1 and INSTRIDE 2 were to demonstrate noninferiority to SA IGlar in HbA_{1c} level change from baseline to 24 weeks [53,54], and the primary objective of the extension study was to assess the safety and efficacy of biosimilar insulin glargine and SA IGlar [55]. In November 2016, the EMA accepted Mylan's marketing authorization application for review [56]. Biocon-manufactured insulin glargine has been approved in India and Japan (in collaboration with Fujifilm), but limited information is available regarding clinical trials supporting submissions in Europe and other regulated markets. To date, there is little publicly available information on the insulin lispro and insulin aspart development programmes.

Biosimilar medicines: practical considerations for clinical care

Treatment options

LY IGlar, MK IGlar and the emergence of biosimilar insulins in general will add to the choice of insulins available in clinical care, offering products at reduced costs [2]. According to a recent analysis of the European biosimilar medicines market, the prices of biosimilars typically are 10–35% lower than those of their reference products [9,57]. For example, in the United Kingdom, the price difference between the originator product and the biosimilar product of epoetin was 10% to 25% [57]. Among 24 European countries, the average price differences for epoetin, somatropin and filgrastim were 17%, 14% and 35%, respectively.

Biosimilar insulins may broaden treatment choices in other ways. A negative history with a given insulin product could promote the decision to prescribe a similar insulin product that might not trigger an allergic reaction. A person's preference also could be incorporated in the choice of biosimilar insulins through individual features such as pen injectors for delivery.

Interchangeability and substitution

The introduction of biosimilars may also result in concerns over interchangeability (the ability of prescribers to switch between the reference product and a biosimilar) or substitution (the automatic substitution of the reference product without prescribers' consent) [58]. The possibility of medically unsupervised substitution of insulin products including, but not limited to, biosimilars has important clinical implications, because it might prevent proper attribution of adverse events to specific insulin products, especially if people switch between insulin products repeatedly. Establishing the comparative safety profile of the newer biosimilar product to support switching requires not only evaluation of safety in the clinical development programme before regulatory approval, but also careful reporting and tracking of post-marketing rare adverse events, which might become evident with a high number of people treated for diabetes.

Current requirements for approval of biosimilars in Europe do not include robust evidence supporting substitution. By contrast, the general standard of evidence for the substitution of biosimilar products has been established by law under the US biosimilar pathway and may include repeated-switching and post-marketing safety data, which are reflected in the recently issued FDA draft guidelines [59,60].

Substitution supersedes the physician's decision and therefore may not take into account reasons for prescribing a particular biological medicine such as the history of an allergic reaction. Substitution also may overlook the well-accepted need for additional training on a new injection device that is compatible with the new insulin product or additional monitoring of the well-being and glycaemic control of people with diabetes. In Europe, there are no centrally adopted criteria for interchangeability or substitution; criteria are decided by the local authorities and therefore could differ from one country to another [2,7].

Table 4 Summary of MK IGlar results

Parameter	Home et al. (*N* = 506) (24 weeks) [42]			Hollander et al. (*N* = 531) (24 weeks) [44]		
	MK IGlar	SA IGlar	Difference*	MK IGlar	SA IGlar	Difference*
HbA_{1c} change from baseline, mmol/mol†	–7 (–9, –5)	–7 (–9, –6)	0 (–1, 2)	–14 (–15, –13)	–14 (–16, –13)	0 (–1, 2)
HbA_{1c} change from baseline, %†	–0.65 (–0.82, –0.48)	–0.68 (–0.85, –0.52)	0.03 (–0.12, 0.18)	–1.28 (–1.41, –1.15)	–1.30 (–1.43, –1.18)	0.03 (–0.12, 0.18)
Total insulin dosage, U/day‡	49.4 (44.4, 54.4)	50.4 (45.5, 55.2)	–1.0 (–4.5, 2.6)	NR	NR	NR
Basal insulin dosage, U/day‡	36.3 (33.1, 39.4)	37.0 (33.9, 40.1)	–0.8 (–2.6, 1.1)	48.3 (45.0, 51.6)	46.8 (43.5, 50.1)	1.5 (–2.1, 5.1)
Prandial insulin dosage, U/day‡	22.2 (18.6, 25.8)	24.5 (20.9, 28.1)	–2.3 (–5.2, 0.5)	NR	NR	NR
FPG change from baseline, mg/dl‡	–16.4 (–33.3, 0.4)	–25.9 (–42.1, -9.7)	9.5 (–3.2, 22.2)	–35.0 (–41.3, –28.6)	–38.5 (–44.8, –32.1)	3.5 (–3.7, 10.7)
Anti-insulin antibodies, *n*/*N* (%) participants						
Positive at or before week 24 irrespective of Ab status at baseline	168/240 (70.0)	190/257 (73.9)	–3.9 (–11.8, 4.0)	91/262 (34.7)	76/261 (29.1)	5.6 (–2.4, 13.6)
Negative at baseline	33/101 (32.7)	35/98 (35.7)	–3.0 (–16.1, 10.1)	37/192 (19.3)	29/196 (14.8)	4.5 (–3.0, 12.1)
Safety endpoints of interest, *n*/*N* (%) participants						
Symptomatic hypoglycaemia	170/240 (70.8)	196/257 (76.3)	–5.4 (–13.2, 2.3)	140/263 (53.2)	137/263 (52.1)	1.1 (-7.4, 9.6)
Injection-site reaction	2/240 (0.8)	1/257 (0.4)	–	5/263 (1.9)	1/263 (0.4)	1.5 (–0.4, 4.0)
Systemic allergic reaction§	1/240 (0.4)	0	–	1/263 (0.4)	0	–
Anaphylactic response	0	0	–	1/263 (0.4)	0	–

	Study P003 (52 weeks) ¶ [33]			Study P006 (24 weeks) ¶ [33]		
	MK IGlar, *n* (%) 241	SA IGlar, *n* (%) 258	Difference**	MK IGlar, *n* (%) 263	SA IGlar, *n* (%) 263	Difference**
Participants with adverse events of hypoglycaemia						
≥1 event	185 (76.8)	205 (79.5)	–2.7 (–10.0, 4.6)	142 (54.0)	142 (54.0)	0.0 (-8.5, 8.5)
Symptomatic††	184 (76.3)	204 (79.1)	–2.7 (–10.1, 4.6)	140 (53.2)	137 (52.1)	1.1 (-7.4, 9.6)
Severe‡‡	54 (22.4)	63 (24.4)	–2.0 (-9.3, 5.5)	24 (9.1)	22 (8.4)	0.8 (–4.2, 5.7)
Requiring nonmedical assistance	39 (16.2)	41 (15.9)	0.3 (-6.2, 6.8)	22 (8.4)	20 (7.6)	0.8 (–4.0, 5.6)
Requiring medical assistance	25 (10.4)	31 (12.0)	–1.6 (-7.3, 4.0)	2 (0.8)	3 (1.1)	NR
Asymptomatic§§	41 (17.0)	47 (18.2)	–1.2 (-7.9, 5.6)	18 (6.8)	18 (6.8)	0.0 (–4.5, 4.5)
Unknown symptoms¶¶	8 (3.3)	5 (1.9)	1.4 (–1.6, 4.7)	4 (1.5)	1 (0.4)	1.1 (–0.7, 3.5)

SA IGlar, Lantus® (Sanofi) insulin glargine; MK IGlar, MK-1293 insulin glargine; NR, not reported.
*MK IGlar minus SA IGlar (least squares means for efficacy endpoints; % people for safety endpoints).
†Least squares mean in change from baseline (95% CI).
‡Least squares mean (95% CI).
§Systemic allergic reaction was allergic rhinitis (non-serious and not attributed to study medication).
¶Participants were counted a single time for each applicable category.
**Difference in % MK IGlar and % SA IGlar (95% CI). 95% CI was calculated for only those endpoints with ≥ 4 participants with events in ≥ 1 treatment group.
††Symptomatic event: event with clinical symptoms attributed to hypoglycaemia without regard to biochemical documentation.
‡‡Severe event: event that required medical or nonmedical assistance. Events with a markedly depressed level of consciousness, a loss of consciousness or a seizure were considered to require medical assistance, whether or not medical assistance was obtained.
§§Asymptomatic event: event without symptoms attributed to hypoglycaemia but with a glucose level ≤ 3.9 mmol/L or ≤ 70 mg/dl.
¶¶Unknown symptom event: event that could not be classified as symptomatic or asymptomatic because of incomplete information.

Conclusions

Biosimilar insulins, unlike generic medicines, are not exactly the same as marketed reference insulins, and minor differences in their structures have the potential to affect their clinical properties. To ensure that clinical efficacy and safety of biosimilar insulins are similar to those of their reference products, stringent criteria have been adopted by the EMA and US FDA. The criteria include assessment of quality; the demonstration of similarity in physicochemical and biological characterization, including receptor binding; metabolic potency and mitogenicity; PK/PD profiles in phase I studies and assessment of safety endpoints in phase III clinical trials, with special focus on immunogenicity. The practical application of EMA guidelines is illustrated by the clinical development programmes and successful submissions and approvals of LY IGlar, the first biosimilar insulin in Europe, and newly approved MK IGlar.

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Competing interests

MD has acted as consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Eli Lilly and Company, Merck Sharp & Dohme Ltd, Boehringer Ingelheim, AstraZeneca and Janssen, as a speaker for Mitsubishi Tanabe Pharma Corporation and has received grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi-Aventis and Eli Lilly and Company. DD declares no competing interests. TH is a member of advisory panels for Novo Nordisk, received speaker honoraria and travel grants from Eli Lilly and Company, Mylan and Novo Nordisk, is shareholder of Profil, Neuss, which received research funds from Adocia, Astra Zeneca, Becton Dickinson, Biocon, Boehringer Ingelheim, Dance Pharmaceuticals, Eli Lilly and Company, Grünenthal, Gulf Pharmaceuticals, Johnson & Johnson, Marvel, Medimmune, Medtronic, Novartis, Novo Nordisk, Roche Diagnostics, Sanofi, Senseonics and Zealand Pharma. JK is an employee of and owns stock in Eli Lilly and Company. CM has served on the advisory panel for Novo Nordisk, Sanofi, Merck Sharp and Dohme Ltd, Eli Lilly and Company, Novartis, Bristol-Myers Squibb, AstraZeneca, Pfizer, Janssen Pharmaceuticals, Boehringer Ingelheim, Hanmi Pharmaceuticals, Roche Diagnostics, Medtronic and Mannkind and on the speakers bureau for Novo Nordisk, Sanofi, Merck Sharp and Dohme Ltd, Eli Lilly and Company, Boehringer Ingelheim, Astra Zeneca and Novartis. KU Leuven has received research support for CM from Novo Nordisk, Sanofi, Merck Sharp and Dohme Ltd, Eli Lilly and Company, Roche Diagnostics, Abbott and Novartis.

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