

# Biosimilar insulins: guidance for data interpretation by clinicians and users

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Biosimilar insulins are approved copies of insulins outside patent protection. Advantages may include greater market competition and potential cost reduction, but clinicians and users lack a clear perspective on 'biosimilarity' for insulins. The manufacturing processes for biosimilar insulins are manufacturer-specific and, although these are reviewed by regulators there are few public data available to allow independent assessment or review of issues such as intrinsic quality or batch-to-batch variation. Preclinical measures used to assess biosimilarity, such as tissue and cellular studies of metabolic activity, physico-chemical stability and animal studies of pharmacodynamics, pharmacokinetics and immunogenicity may be insufficiently sensitive to differences, and are often not formally published. Pharmacokinetic and pharmacodynamic studies (glucose clamps) with humans, although core assessments, have problems of precision which are relevant for accurate insulin dosing. Studies that assess clinical efficacy and safety and device compatibility are limited by current outcome measures, such as glycated haemoglobin levels and hypoglycaemia, which are insensitive to differences between insulins. To address these issues, we suggest that all comparative data are put in the public domain, and that systematic clinical studies are performed to address batch-to-batch variability, delivery devices, interchangeability in practice and long-term efficacy and safety. Despite these challenges biosimilar insulins are a welcome addition to diabetes therapy and, with a transparent approach, should provide useful benefit to insulin users.

**Keywords:** biosimilar insulins, insulin therapy, safety

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## Introduction and Background

The first 'biosimilar' insulin [Eli Lilly and Boehringer Ingelheim's insulin glargine with the trade name Abasaglar in the European Union (EU) and Basaglar in the USA] has recently received market approval by the regulatory authorities in Europe [1]. In the USA it has received tentative approval but not as a biosimilar, as that regulatory pathway does not yet exist for insulins. Patents for insulin glargine are soon to expire (in mid-2015), and copies of insulin glargine made by other pharmaceutical companies are already marketed in India, China, Mexico and other countries. Merck, Biocon (Mylan) and Sanofi are known to be developing biosimilar insulins (glargine and lispro) for highly regulated markets, so it seems likely that several biosimilar insulins will come to market in the next 5 years. The documents issued by the European Medicines Agency (EMA) for Abasaglar, however, highlight the stringency with which the regulatory authorities will evaluate a market approval dossier for a prospective biosimilar insulin, and detail some of the issues that can arise [2].

Clinicians considering the use of biosimilar insulins as efficacious and safe options for people with diabetes require an

understanding of these products from regulatory, manufacturing and clinical points of view. Even if clinicians are forced into use of such products by payers and funders, there will be a need for them (and others involved in the selection of insulins for clinical use) to understand the clinical issues biosimilar insulins might present. This is particularly pertinent where choice of insulin formulation used might be determined by a pharmacist.

The aim of the present review was to assist clinician decision-making by discussing aspects of these products that may be relevant to clinical practice. To illustrate this (Table 1), the information available in the public domain is summarized in the context of current approval pathways in more highly regulated markets. A more detailed summary of global regulatory requirements is published elsewhere [3].

## Reasons for the Development of Biosimilar Insulins

Biosimilars are approved copies of already marketed biological medicines. Accordingly, they provide an alternative to existing biological medicines that have lost patent protection [4]. Biosimilars in other areas of medicine are usually offered for a lower price than the original molecules, and speculation is that price reductions of up to 50% might eventually be expected [5,6]. Enhanced competition is welcome, and keener market pricing may improve access to such medicines. For payers, reimbursing biosimilar medicines has the potential to drive down costs through substitution and/or constraints on

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**Table 1.** What does the clinician and the user need to know about a biosimilar insulin?

Domain	Required knowledge and information	Comment
Manufacturing process quality	Appropriate processes to define quality and their limitations; appropriate components, consumables and ability	No information in public domain – regarded as commercial secrets; regulators act as the consumer watchdog but are not monitored themselves; company reputation often used as default
Batch-to batch variability	Monitoring processes in place; results of such processes	No information in public domain; regulatory monitoring probably inadequate; independent studies possible on marketed materials
Toxicological considerations	Regulators performed due diligence and satisfied for both biosimilar and original insulin	Studies difficult with insulin, and need specific expert oversight; detailed information rarely in public domain
Preclinical comparability	Have cellular tests demonstrated comparable receptor and cellular metabolic activity and dynamics?	Some information in public domain (e.g. in EU EPAR for Lilly insulin glargine); such details suggest poor sensitivity for similarity
Metabolism and stability	Physicochemical stability data in more extreme conditions (warm climates, pumps); post-injection metabolism	Data assessed by regulators and not in public domain; no data on metabolism of Lilly insulin glargine after subcutaneous injection; independent studies possible on marketed products
Pharmacokinetic comparability	Similarity of metrics such as time of onset, peak and duration of profile, area under concentration curve	Insulin assays not a simple area; confounding by endogenous insulin secretion in studies with healthy subjects/patients with type 2 diabetes; antibody interference and overlap with therapeutic insulin in patients with type 1 diabetes; subcutaneous absorption erratic and reduces power for similarity
Pharmacodynamic comparability	Similarity of glucose clamp metrics such as time of onset, peak, shape and duration of profile, area under concentration curve	Similarity of glucose clamp metrics such as time of onset, peak, shape and duration of profile, area under glucose infusion curve; different metrics (e.g. peak or 24-h) important for different insulin types; poor power for demonstrating clinical similarity; interpretation of long glucose clamps problematic
Clinical efficacy	Key metrics (e.g. peak postprandial or fasting glucose) comparable; HbA1c and hypoglycaemia comparable.	HbA1c poor discriminator; hypoglycaemia not very sensitive; SMPG measures required careful quality control.
Clinical safety	Similar adverse and serious adverse event profiles	Numbers studied far too small and short to detect uncommon novel side effects; doubts about the ability to detect such events with conventional pharmacovigilance approaches/Risk Management Plans
Immunogenicity	Insulin antibody profiles including cross reacting and neutralizing	Mainly a surrogate for purity of insulin derivatives; insulin antibody assays methods not well standardized; non-specific activity confounds interpretation
Devices	Precision and ease of use data; interchangeability of cartridges/devices	Limited information available; accessible to independent studies

EPAR, European Product Assessment Report; EU, European Union; HbA1c, glycated haemoglobin; SMPG, self-monitored plasma glucose.

physician prescribing. In the EU, price discounts of up to 35% have been realized from such substitutions outside of diabetes care [7]. In the USA, savings of ~\$25 billion in expenditures for biologicals are anticipated from the introduction of biosimilar medicines between 2009 and 2018 [8]; however, it is not yet clear whether the potential for lower prices will be realized with biosimilar insulins. High manufacturing and development costs mean that price reductions will be much less than those experienced for generic drugs.

### Regulatory Issues

The production techniques used by manufacturers of biosimilar insulins may be very different from those used for the original products; for example, in using yeast rather than bacteria. To be considered the same product, a biosimilar insulin must have the same primary structure (amino acid sequence) as the original version, but it may differ in other molecular characteristics, such as protein folding and glycosylation [4]. While there is no scientific definition of two

such products being identical through evaluation of their chemical/analytical properties, their metabolic effects, their pharmacokinetic/pharmacodynamic properties and their clinical characteristics in randomized controlled trials, a decision can be made that they are clinically similar. For regulatory approval, manufacturers must provide data for their insulin copy in the areas mentioned and commit to post-marketing surveillance; however, the regulatory approach is not uniform [3], and at present there is no consensus on what constitutes ‘no meaningful clinical difference’. Below we review the domains of evidence that contribute to such an assessment.

### Manufacturing and Batch-to-batch Variability

Little information is available to the clinician about the manufacturing process of insulins (and biosimilar insulins), and essentially none about its quality. This is relevant because the required expertise for quality insulin manufacture is such that until recently it has been restricted to a small number of companies in the market for 80 years or more. The process

of manufacture does differ markedly between companies in some cases, with Novo Nordisk and Biocon using a different yeast as the primary fermentation organism, while Sanofi and Eli Lilly use *Escherichia coli*-based systems [9]. Yeasts but not bacteria may lead to glycosylated proteins [10]. Fermentation is followed by different chemical processing of the fermentation product, attributable in part to different promoters and A/B chain linkers and then different purification steps.

The information on how manufacturers have to demonstrate to the regulators that they will maintain adequate batch-to-batch quality, and how they monitor it, is not in the public domain in any useful detail, and thus not available for independent assessment. There has been an anecdotal report from India about poor-quality insulin batches (subsequently withdrawn) being marketed by a local manufacturer [11]. This highlights the fact that biosimilar medicines are not manufactured in a continuous process but in batches, determined by fermentation tank size. As the subsequent separation and purification techniques are complex, all biologicals are subject to inherent variability in quality. In addition, therapeutic proteins are unstable, a particular problem with insulin. As a result there are major challenges to maintaining the necessary batch-to-batch quality standards.

The issue then is that while results of continued internal monitoring of manufacturing processes are not made public, the guarantee of continuing biosimilarity is dependent on this monitoring. Problems in this area may be the basis of the clinical observations from Mexico and India that some copies of insulin glargine appear to have a dissimilar glycaemic effect [10,11]. As information on batch quality is not in the public domain, clinicians and users are forced to rely on any company maintaining a reputation for only bringing to market batches that meet stringent quality requirements. This requires that companies have in turn implemented a quality assurance system that can act truly independently from economic considerations. Even so, some aspects, such as immunological responses, could vary from batch-to-batch dependent on purity and stability. For insulin, to our knowledge, this is not monitored by anyone.

It is evident then, that as more biosimilar insulins come to market, independent studies of batch-to-batch variability, and if possible clinical correlates, are desirable [10,12].

## Preclinical Studies

Insulin, or for insulin glargine one of its metabolites, exerts its actions through the insulin receptors and, following activation of these, through intracellular biochemical pathways. A biosimilar insulin should then bind to, and dissociate from, the two main types of insulin receptor, and the insulin-like growth factor-1 (IGF-1) receptor, to the same measurable extent as the original insulin. The dissociation rate is thought to be important because the post-receptor signalling pathways of insulin include metabolic and growth promotional pathways, and a historical rapid-acting insulin analogue (B10-Asp-human-insulin) is believed to have manifested its tumorigenic activity as a result of slow dissociation from its receptor [13]. Assessment of both receptor binding and

post-receptor activity is further complicated because a range of tissues and cell lines have been used for preclinical studies with different insulins, often with limited clarity as to their pathophysiological relevance. As well as the type of assay, the quality with which these are performed is relevant.

Nevertheless, similar binding and activity ought to be measurable in whatever cellular models are used. It is interesting to note therefore, that this was not the case for the Lilly insulin glargine studies, where the EMA Assessment Report (public domain version) discusses increased binding to both insulin receptor types compared with original glargine, increased lipogenic activity in adipocytes, and increased mitogenic activity in transformed osteosarcoma cells (perhaps mediated by the IGF-1 receptor), and these increases were of the nominally important orders of 20–60% [2]. The assays appear to be poor discriminators, however, and as these findings were below a company-defined ‘minimum significant ratio’, they did not establish difference despite statistical significance in some cases, nor it seems did they establish biosimilarity. A conclusion might be that these methods are inherently unsuitable for these purposes. Indeed, the models failed by a large margin ( $\pm 70\%$ ) to confirm similarity of two of the company’s own formulations of insulin glargine from different manufacturing sources for mitogenic effects on hepatoma cells.

Rat pharmacokinetic data are also briefly reported in the Abasaglar European Product Assessment Report (EPAR) [2]; however, the insulin assay was noted to be ‘extremely variable’, and without correction for rat endogenous insulin secretion, and seems unlikely to have any power to contribute evidence of biosimilarity [2]. As is usual with insulin, repeated dose toxicology studies were associated with a high death rate in the animals (attributed to hypoglycaemia), and again can be regarded as non-contributory [2].

It appears then that these tissue and small animal studies were non-contributory to establishing biosimilarity. If this is the case, then it seems clinicians and consumer champions (advocates) will be able to largely ignore such studies for future biosimilar insulins, even if, as in this case, they are specified by the regulators [3].

## Human Pharmacokinetic and Pharmacodynamic Studies

Similar pharmacokinetic and pharmacodynamic profiles are suggested by the EMA as the mainstay of proof of similar efficacy of an insulin copy and the original insulin [14]. It is also a core component of most other biosimilar guidelines, whether general or specific for insulin [3]. This makes sense, in particular for insulins, where the shape of the time–concentration profile and time–action profile after subcutaneous injection is a critical part of the clinical specification of any one preparation, unlike most biopharmaceuticals. Accordingly, the EMA goes into some detail on the conduct of the cross-over, double-blind euglycaemic glucose clamp studies using suitable single subcutaneous doses [14]. Clinicians will want to know that such studies have been performed to these standards, implying full publication in peer-reviewed journals.

What constitutes a clinically significant difference in glucose-lowering efficacy between two insulins? Most clinicians

would probably respond with a figure of  $\pm 10\%$  or less, based on the clinical responses of people with diabetes to changes in insulin dose. Some guidance is available in the standard which has been set for pen-injectors, of  $\pm 5\%$  (for a  $\geq 20$  unit dose) [15]. While pharmacopoeias would allow similar ranges for differences between batches of insulin vials, most quality insulin manufacturers aim for closer to  $\pm 1\%$  based on confirmatory protein content assays and high-performance liquid chromatography; thus, the EU requirement of a confidence interval (CI) of  $-20$  to  $+25\%$  of the ratio of certain major pharmacokinetic parameters seems to be rather wide for allowing a conclusion to be drawn on clinical biosimilarity. Although such limits are not specifically set for pharmacodynamic measures, it would not be expected that clamp glucose requirements for such parameters would be tighter than for insulin assay measurements.

Again, data are now available from the Lilly insulin glargine clamp studies [16–18]. These appear to be of good quality, and the mean pharmacokinetic and pharmacodynamic curves are essentially superimposable. It is clear, however, that the precision of clamp studies in people without diabetes (even with a reasonable sample size of 46–48 people) only gives CIs of around  $\pm 15$ – $20\%$  difference from unity, and then only for grosser measures such as 24-h area under the curve and maximum concentration/glucose-lowering activity, but consistent with the EU recommendations. It will probably be unreasonable to expect future clamp studies with other biosimilar insulins to do any better than this, but clearly no one of these measurements by itself establishes biosimilarity in terms of the required clinical accuracy. The Lilly glargine studies are available in people without diabetes, where the confounder can be endogenous insulin secretion, and in people with type 1 diabetes, where the confounders are more erratic effects and the difficulties associated with the transfer from previously administered insulins without causing metabolic decompensation [19]. It might be thought that the performance of glucose clamps in different populations and with different measures within each study could provide additional reassurance, as the probability of similarity will clearly increase with each further study that shows no difference. To some extent this is true, and as a result, the Lilly data taken together give a high probability of biosimilarity.

However, some other clamp measures are also pertinent. Clearly what matters for a long-acting insulin is duration of effect (ideally exceeding 24 h) at normal insulin doses, and the peak to 24-h insulin ratio (concentration and action). The insulin concentrations (including those of the metabolites of insulin glargine, i.e. M1 and M2) can be surprisingly difficult to assess, as concentrations will be low at 24 h after a single injection. Furthermore glucose-lowering action at 24 h is affected by the prolonged fast, and thus is spuriously elevated. One logical approach from a clinical point of view would be to start the clamp 16 h after a morning injection and a normal day's eating, but this seems never to be performed. Equally, one might expect the biosimilarity of meal-time insulins to be characterized by lag time of onset after subcutaneous injection, rate of rise of insulin concentration (and effect), and rate of fall back to baseline, but such criteria are difficult

to specify, and in practice clinicians will need to use visual inspection of profiles to assure themselves of similar pharmacokinetic/pharmacodynamic profiles.

Lastly, plasma insulin measurements in people with type 1 diabetes can be problematic because of insulin antibodies (and hence antibody-bound insulin) confounding radioimmunoassays. This may account for the erratic pharmacokinetic profiles seen in the Lilly study in people with type 1 diabetes – so erratic that they do not contribute to any assessment of biosimilarity [18].

## Clinical Efficacy Studies

Clinicians will judge clinical efficacy by overall blood glucose control [glycated haemoglobin (HbA1c)] measures taken from self-monitored plasma glucose (SMPG) profiles (including prebreakfast for long-acting insulins and postprandial for meal-time insulins), and hypoglycaemia. In contrast, regulators seemingly believe that HbA1c is the only validated measure, are suspicious of SMPG measurements (particularly in open-label studies), and consider hypoglycaemia a safety issue rather than an efficacy measurement. Indeed, some regulators [including the US Food and Drug Administration (FDA)] still regard clinical laboratory-measured fasting glucose as useful, despite its irrelevance to clinical practice and major underlying difficulties. It was the insensitivity of HbA1c in showing statistically significant and clinically relevant difference between insulin types, as demonstrated by a plethora of studies of new insulins in the last 15 years, that led the EMA to choose to place little reliance on clinical studies with HbA1c measurements for assessment of biosimilarity [14].

Clinicians will want to look at blood glucose profiles, in particular, prebreakfast levels in ambulatory care for long-acting insulins, and postprandial and meal study results for meal-time insulins, before concluding that biosimilarity is established. Additionally they will want to consider hypoglycaemia, and particularly night-time hypoglycaemia for long-acting insulins, and the risk of late postprandial hypoglycaemia for meal-time insulins. None of these measures, however, is without its problem. Glucose control, for example, is highly erratic, fasting glucose levels within individuals having a coefficient of variation of  $\sim 35\%$  [20]. This is partly mitigated by clinical studies being generally large, generating statistical power to show differences. In the Lilly ELEMENT-1 clinical study in people with type 1 diabetes ( $n = 545$ ) comparing insulin glargine and Lantus, mean differences in fasting SMPG at 26 and 52 weeks were  $< 0.25$  mmol/l between the two glargine insulins, with standard errors (also  $< 0.25$  mmol/l) suggesting CIs for a difference of less than  $\pm 0.5$  mmol/l [21].

A similar issue pertains to hypoglycaemia; CIs for both the proportion of people affected and rates of hypoglycaemia (events per person-year) are wide for differences between insulins [22,23]. In ELEMENT-1 the European EPAR recorded 2301 events in 222 people with the Lilly insulin glargine, compared with 2347 events in 216 patients on Lantus. This is impressive concordance but, given the usual variance of hypoglycaemia in randomized controlled trials, is unlikely to be reproduced in future biosimilar studies for reasons of chance.

Accordingly, as with the glucose clamp data, clinicians will need to consider glucose measurements and hypoglycaemia in the totality of clinical data when assessing biosimilarity.

## Immunological Aspects

Subcutaneous administration of insulin can induce formation of antibodies, as is the case with other peptides. Immunogenicity of a protein is driven by a number of factors, such as the structural properties of the molecule (primary, secondary and tertiary structure), glycosylation, contaminants and impurities from initial production or downstream processing, formulation, dosage, length of treatment and route of application [24]. The formation of neutralizing insulin antibodies giving rise to higher insulin doses was a clinically relevant topic some decades ago, but has not been a problem since highly purified insulin formulations were introduced, even in the era of animal insulins. Historically, antibodies generated after administration of exogenous insulin were speculatively considered as detrimental to patients in other ways, including effects on remaining islet  $\beta$ -cell function and on vascular complications, but this has not been generally accepted for some while [25].

Interest in insulin antibodies in the context of biosimilars is relevant in two ways to diabetes care. Firstly, clinically relevant issues have been observed with other therapeutic peptides, notably with epoetins, where it is believed that antibody formation resulting from a change in manufacturing process led to pure red cell aplasia and the resulting deaths [26]. For insulin, the long experience with impure insulins from the 1920s might seem to make such an experience unlikely, but bioengineering does give rise to the possibility of novel insulin derivatives. While it is likely that these would be removed by the purification processes used, and if they were not removed the most likely adverse reaction would be antibody-mediated insulin resistance, this remains a background concern. Insulin antibodies may possibly be involved in the pathogenesis of diabetes, through priming of the islet  $\beta$ -cell as a target, and it is not known if novel antibodies formed in response to exogenous insulin could contribute to acceleration of islet  $\beta$ -cell decline in the early time period after diagnosis of type 1 diabetes [27].

Secondly, low levels of insulin antibodies can be used as a surrogate marker of impurities arising through inadequate production processes. There may be as many as 30 steps in the manufacture of a modern insulin analogue. Some of these steps are associated with by-products, and others are designed to remove them [9]. Conventional techniques cannot always pick up faults in the production process, a well-documented example being the thio-ester problem with biosimilar growth hormone [28]; therefore, in all guidelines for approval of biosimilar insulins, at least some evaluation of the formation of antibodies is included [3]. These evaluations differ, however, in duration, number of people exposed and assay methods, and it is unclear what pre-approval studies are optimal in a situation where only a few individuals may be particularly at risk. Another issue is that such studies are only performed pre-approval, and are not used for continued monitoring of manufacturing quality, which may be the real issue [26].

Even in countries with a well-established pharmacovigilance system (see below), it is questionable if an increase in insulin requirements or insufficient metabolic control induced by an immunological reaction will be detected. In practice most physicians will simply switch to another insulin formulation if there is suspicion of such an issue, without any systematic follow-up.

Interpreting the results of evaluation of immunological aspects of insulins is not straightforward, as the many methodological aspects and approaches need to be understood. In practice, most clinicians will be forced to follow the decisions of the regulators and perhaps published opinions from experts, but the public domain material is likely to be limited to a short summary in reports of clinical studies. Data on mean insulin antibody responses are often given in these, but care needs to be taken with the type of results given, as it is the few individuals adversely affected who are of importance from a clinical point of view. Even then a problem arises that the original insulin is often the insulin used by the study participants before randomization. Their immune systems will have adapted to it and, in the rare event of a more extreme problem, they would not be eligible for the study. Somewhat more useful can be comparative antigenicity. In many instances these are simple chance phenomena, but they might show differences compared with the original insulin. More usefully, clinicians should ask to see comparative numbers of participants reaching clinically higher levels (in many assays percent binding above 30%), bearing in mind that neutralizing effects of antibodies to other therapeutic peptides in diabetes (exenatide) may affect only 1% of the population [29]. In the Lilly ELEMENT-1 study only 1 participant appears to have exceeded 20% binding, and that was on the original glargine, with no effect on HbA1c [21], but it may well be that little such information will be put into the public domain.

## Safety

As noted above, preclinical toxicological requirements are limited for a biosimilar, and animal testing is particularly difficult to perform for insulin. It might therefore be expected that clinical studies are important in this regard; however, a 500+ person 1-year study, such as that performed for the Lilly glargine, has no power to detect a serious adverse event occurring as often as three times per 1000 people per year. Accordingly, potential novel safety issues will generally be untested for insulin copies. Most of the safety data collected in these studies are valueless background adverse events [30]. This does not mean that we should expect safety issues to show up with these insulin copies, as insulin is a well-known medication; however, we should be aware of our limited ability to detect such issues during the approval process, especially in the abbreviated process used for documenting biosimilarity of insulin copies. It is worth noting that we would have even fewer data about the safety of the Lilly glargine if this had not undergone an approval process as a new insulin in the USA.

In theory then, clinicians should be looking for good pharmacovigilance postmarketing studies to unmask potential safety issues. In the current data environment, however, such

studies too must be regarded as largely unfit for purpose, and this may become a particular problem if biosimilars are prescribed and dispensed by approved name, and people with diabetes switch (of or against their own will) between versions from different manufacturers. In the EU, legislation does require that each biosimilar has a distinct brand name [31]. In some countries, further safety distinctions between biosimilars and original products may be created. In the UK, for instance, the Medicines and Healthcare Products Regulatory Agency requires biosimilars to have a black triangle symbol (safety reporting alert) on the package, but many countries have no such measures in place.

### Insulin Devices: Pens and Pumps

Manufacturers of biosimilar insulins may develop their own disposable or reusable insulin pen-injectors, or provide cartridges that could be marketed for use in reusable pen-injectors manufactured by either the original insulin manufacturer or a third party. Any new pen-injector will have to meet normal quality standards; for example, 5% precision down to a 20-units injection, and  $\pm 1$  units below this [15]. Some current pen-injectors are likely to perform better than this, and it may be that manufacturers will now be motivated to publish that information in an attempt to persuade clinicians of advantages in clinical performance, particularly at lower doses [32,33]. Compatibility of cartridges with existing and third party pen-injectors is likely to be a requirement of regulatory approval.

Other quality issues are design issues such as prevention of injection of a last dose for which the cartridge does not have remaining capacity, readability of dial-up, and pressure of injection button. Clinicians should ask for such data for novel pen-injectors.

For insulin pumps, data on insulin stability in use will need to be provided to regulators, including reassurance that infusion set occlusion will not become any more of a problem than with the original insulin. Such issues are also affected by the excipients used in formulations [34]. Normally these issues will be covered by a comment in the label/summary of product characteristics to the effect that pump use is appropriate. Without such comment, clinicians might judge that such use is undesirable.

### Interchangeability and Substitution

There is a clear distinction between biosimilarity and interchangeability; confirmation of biosimilarity does not imply interchangeability. A perfectly interchangeable product may be substituted by a pharmacist, without intervention or even necessarily notification of the prescribing clinician [3]. A biosimilar product may yield a similar efficacy, tolerability and safety to the original, but a switch between these products may require input from a clinician. Substitution is a process, whereas interchangeability is a regulated property of a biosimilar in a particular clinical scenario.

Clinicians prescribing insulin typically avoid switching patients from one insulin formulation to another without good reason. This is based on their practical experience that, for a given individual coverage of prandial or basal insulin,

requirements might work well with a given formulation, but not with a nominally very similar insulin (e.g. another NPH insulin, or another rapid-acting analogue). Often, after taking time to optimize an insulin regimen, a person with type 1 diabetes has around two confirmed hypoglycaemic excursions a week, and a serious event yearly. People often develop a love-hate psychological relationship with their insulin, knowingly dependent on it but with a fear of instability. A proportion of people whose regimens are changed become convinced (perhaps correctly), therefore, that this has caused marked deterioration of glucose control, resulting in deterioration in quality of life and increased medical input, sometimes long term. Any decision to change is therefore not taken lightly, and neither the treating physician nor the user is usually willing to switch to a different insulin formulation without good reason. A designation of interchangeability (guarantee that insulin action is more or less identical, not just similar, to the original insulin) may however make clinicians' views on such changes more positive.

In the EU, decisions on interchangeability and substitution of biosimilars with original products are not within the remit of the EMA, and interchangeability studies are not part of the regulatory requirements [14,31]. Decisions on interchangeability and/or substitution rely on national authorities that have access to the scientific evaluation performed by the EMA and all submitted data, and use other expert opinion. European countries thus vary over substitution guidance. In the USA, the FDA has recently published a list of licensed biological products and interchangeable biosimilars [35]. The agency has designated a four-part standard for biosimilar interchangeability: not similar; similar; highly similar; and highly similar with a fingerprint-like similarity [35]. Interchangeability of biosimilar insulins is, however, not currently considered under this standard in the USA, and each state in the USA can decide for itself about how substitution will be handled.

### Summary and Conclusions

With the availability of first published data on the properties of a biosimilar long-acting insulin, and with some data on copies of insulin in other countries, it is now possible to assess what will be meant by 'similarity', and what the issues surrounding such an assessment are. Furthermore, the issues around immunogenicity for biosimilar insulins are becoming clearer. The release of data on the Lilly insulin glargine approval in the EU shows the complexity of biosimilar approval, and is for the more general understanding of such assessments for the future. It appears as if the experts at the EMA have done a thorough job in evaluating the Lilly insulin glargine [2]. For clinicians and insulin users (and their champions), however, the situation is not easy. In some areas, such as manufacturing process and quality, reliance must be placed on the regulators, but there is no opportunity to monitor their performance as nothing in this area appears in the public domain. So there may be differences in the quality of the evaluation process (if any is in place) between regulatory authorities around the globe. For batch-to-batch variability (even in already marketed insulins!) the concern is that all such monitoring is performed and retained by manufacturers.

From the published and presented data on the Lilly insulin glargine it is clear that no one domain of information, including pharmacokinetic and pharmacodynamic studies in humans, is able to provide an assurance of biosimilarity. Indeed, the contribution of preclinical studies as conducted by/for Lilly and reported in the European EPAR appears limited [2]. The glucose clamp studies are clearly contributory but only if all the evidence from pharmacokinetic and pharmacodynamic studies is taken together, including studies from people without diabetes and people with type 1 diabetes, and uses measures above and beyond those prioritized by the EMA, and visual inspection of the profiles. Some knowledge of the limitations of glucose clamps, particularly clamps of  $\geq 24$  h, is needed if findings are not to be misinterpreted. Because of this, clinical studies are clearly needed, notably to address specific questions such as comparability of attained prebreakfast glucose concentrations and of nocturnal hypoglycaemia; however, here the precision is not good enough to give assurance within a clinically meaningful  $\pm 5\%$ , unless all the evidence is assessed together.

Safety may not seem a big issue given the long history of insulin usage from diverse sources, but we are concerned that the same was believed to be true for epoetin and growth hormone; safety issues are often a case of 'hands up anyone who is not here'. Presently none of the preclinical, clinical or immunological assessments seems capable of dealing with that potential risk. Pharmacovigilance postmarketing is the traditional but rather flawed way of dealing with such risks and can only work here if prescribing is based on proprietary not approved names. Widespread substitution may destroy the chances of detecting such safety risks; in some countries in South America, patients/physicians are required to use whatever insulin was purchased by the Ministry of Health in a bidding process. Switches might be necessary as often as every 6 months.

Accordingly, we see the need for longer-term clinical studies (or at least formal registries), studies addressing batch-to-batch variability for both original and biosimilar insulins, studies of delivery devices, and interchangeability in practice, as well as comprehensive pharmacovigilance and postmarketing surveillance. Of course more extensive clinical evaluations of the efficacy and safety of new biosimilar insulins raise the risk of negating the price advantage of a slimmer development programme, and it is not our intention to protect the established insulin manufacturer and keep potential new manufacturers from entering the market.

It is also not our aim to raise mistrust against such products, but to establish a sound and rational approach with biosimilar insulins. We believe that the issue is sufficiently important to people with diabetes to be adopted and kept under review by the major diabetes associations, nationally and internationally. The database is also now mature enough for organizations such as the World Health Organization to extend advice on biosimilar products to address regulation of biosimilar insulins specifically, rather than just generally as at present [3].

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## Conflict of Interest

L. H. is a consultant for companies developing new diagnostic and therapeutic options for diabetes treatment including Biodel, InsuLine and Halozyme, a member of a Sanofi advisory board for biosimilar insulins, and a partner of Profil Institute for Clinical Research, US and Profil Institut für Stoffwechselkrankheiten, Germany. P. D. H. or institutions with which he is associated receive funding from most insulin manufacturers including the actual or prospective developers of insulin biosimilars or original products Biocon, Eli Lilly, Merck (MSD), Mylan, Novo Nordisk and Sanofi. M. H. is chief executive and partner of Profil Institute for Clinical Research, USA; Profil has worked with many of the potential or actual manufacturers of biosimilar or original insulins.

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