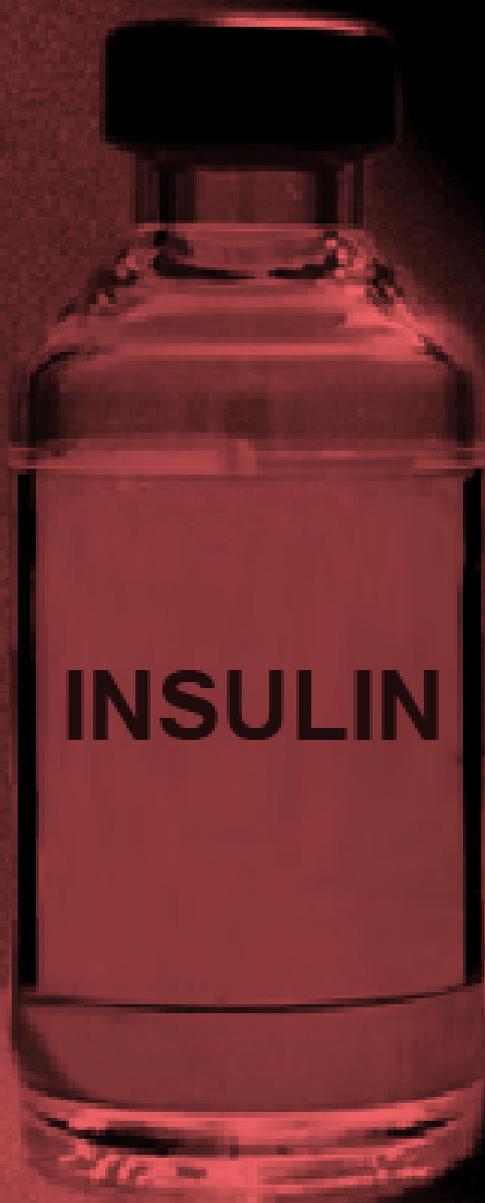


BIOSIMILAR INSULIN REGULATORY PROFILE

April 2017



acciss 
Addressing the Challenge and Constraints
of Insulin Sources and Supply



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Profile Summary & Annex 1

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Acronyms

CHMP	Committee for Medicinal Products for Human Use
Eli Lilly	Eli Lilly and Company
EMA	European Medicines Agency
EU	European Union
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LMICs	Low- and middle-income countries
Marvel Life Science	Marvel Life Science Ltd.
MHLW	Japan's Ministry of Health, Labour and Welfare
PD	Pharmacodynamics
PK	Pharmacokinetic
RMP	Reference Medicinal Product
TGA	Australia's Therapeutic Goods Administration
US	United States
USFDA	US Federal Drug Administration
WHO	World Health Organization

1. Introduction

The ACCISS Study

Today, approximately 100 million people around the world need insulin, including all people living with type 1 diabetes and between 10-25 percent of people with type 2 diabetes. Although insulin has been used in the treatment of diabetes for over 90 years, globally more than half of those who need insulin today still cannot afford and/or access it. Without insulin, people living with type 1 diabetes will die. Many more will suffer from diabetes-related complications, like blindness, amputation and kidney failure, and, ultimately, premature death.

There are many complex issues that affect access to this life-saving medicine, creating inequity and inefficiency in the global insulin market. These issues include the global insulin market domination by three multinational manufacturers, import duties affecting the price of insulin entering different countries, and mark-ups, taxes and other charges in the public and private sector supply chains that affect the final patient price.

The innovative global study, Addressing the Challenge and Constraints of Insulin Sources and Supply (ACCISS), sets out to identify the causes of poor availability and high insulin prices and develop policies and interventions to improve access to this essential medicine, particularly in the world's most under-served regions. The three-year study involves a unique group of leading international experts as members of the study's advisory and technical groups. ACCISS is co-led by Margaret Ewen at Health Action International, David Beran from Geneva University Hospitals and the University of Geneva, and Richard Laing from Boston University School of Public Health.

The study is being carried out in three phases. The first phase was mapping the global insulin market from various angles. In phase 2, a greater understanding on insulin manufacturers and the distribution chain was sought. This profile on the biosimilar insulin regulatory process is part of this work. All profiles can be accessed on the ACCISS Study section of HAI's website: <http://haiweb.org/what-we-do/acciss/>.

2. Profile Summary

Over 422 million people are living with type 1 or type 2 diabetes. Type 2 diabetes accounts for an estimated 85-95 percent of all diabetes cases. Given that insulin analogues are now also prescribed for type 2 diabetes and that the incidence of diabetes has been rapidly increasing in low-income countries (e.g. 3.1 to 7.1 percent in Africa), access to insulin represents an urgent unmet medical need in many regions (1,2). As recently reported by the ACCISS Study, of approximately 100 million people worldwide requiring insulin, one in two cannot reliably access this life-saving medication because it is unavailable, unaffordable or both.

The global insulin market is currently dominated by three multi-national companies: Eli Lilly and Company (Eli Lilly), Novo Nordisk, and Sanofi. Biosimilars (similar versions of biological medicinal products - principally recombinant proteins – e.g. insulins) have a key role to play in improving availability and affordability of medicines when data and market exclusivity of the originator's reference medicinal product expire. The originator's research, development and marketing experience contribute to the reduced developmental costs (and time) of biosimilars, which in turn render them more affordable. Although cost reductions at market launch for biosimilars (20-30 percent) are more modest compared to those offered by small molecule generics (up to 80 percent), the increased cost of biologicals compared to more

traditional pharmaceuticals and the increasing contribution of biologicals to healthcare expenditure means that these cost savings can nevertheless have a substantial impact on affordability. In addition to these direct cost savings, the introduction of lower priced biosimilars is expected to provide much needed market competition resulting in both improved availability and affordability for patients and health care systems.

Although a number of "similar" insulins are now available in less regulated markets such as China, India, and Mexico, commercialisation of biosimilar insulins in more highly regulated regions such as the European Union (EU) and the United States (US) have lagged behind that of other biosimilar recombinant proteins such as erythropoietin, somatropin or granulocyte-colony stimulating factor. The first biosimilar –'glargine' (Eli Lilly) – received marketing authorisation in US, Europe, Japan, and Australia only last year (2015). However, it will not be introduced before 15th December 2016 in the US. Recently, Biocon Ltd. (India) received approval from Japan's Ministry of Health, Labour and Welfare (MHLW) to market its biosimilar glargine, providing the first example of another company other than the traditional pharma giants being able to produce high quality biosimilar insulins for more regulated markets (3) .

The objective of this report is to gain an understanding of the regulatory pathways and the challenges faced by companies seeking marketing authorisation for insulin biosimilars, particularly in regulated markets such as the EU and US. Regulatory agencies serve to ensure the quality, efficacy, and safety of medicines. The EU's established legal and regulatory framework for biosimilars frequently serves as a benchmark for biosimilar licensing pathways in countries around the world.

It is clear that the development of an exact copy of a complex biologic is extremely difficult without knowledge of the innovator's recipe for the reference product. Unlike chemically-synthesised molecules which can be replicated exactly, the composition, conformation and biological activity of the recombinant proteins are sensitive to changes in the expression system, culture conditions, purification, and processing conditions as well as formulation and storage parameters. Therefore, the approval process of a biosimilar – although abridged compared to the dossier requirements for new pharmaceuticals of the same class – is more onerous compared to that of a small molecule generic product. Consequently, the evidence to prove biosimilarity can include early stage non-clinical data as well as results from clinical Phase 3 studies in addition to mandatory physicochemical characterisation and comparison to the reference medicinal product (RMP).

It is important to note that regulatory pathways for the authorisation of biosimilars are not present in all countries. The European Medicines Agency's (EMA) pathway for licensing biosimilars, including biosimilar insulins, is the most long-standing. The EMA was also the first regulatory authority to develop insulin specific guidelines and many countries have adopted the EMA's guidelines for insulin biosimilars. The approval requirements through the biosimilar pathway for insulins appear to be simpler than those for a number of other recombinant proteins: if the quality attributes of the biosimilar insulin are highly comparable to the reference product, the non-clinical and clinical data can be limited to pharmacokinetic (PK), pharmacodynamics (PD), and immunogenicity studies(4) .This is because insulin is easier to characterise and to control from a quality perspective than many other recombinant proteins such as those that have a high degree of post-translational heterogeneity (e.g. glycosylated proteins). For both EMA and the US Food and Drugs Administration (USFDA), the use of a foreign comparator is accepted in order to facilitate the development of biosimilars (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] adherent countries are preferred). In the European legal framework, a head-to-head comparison of quality, safety, and efficacy that demonstrates that the biosimilar and the RMP do not present any differences to potentially impact safety

and efficacy underpin the dossier. The extent of the non-clinical and clinical testing may be reduced depending on the similarity of the quality profile. In contrast, differences in quality profile necessitate further testing with respect to the safety and efficacy of the product.

Similarly, the FDA recommends the use of a “stepwise approach” to develop the evidence needed to demonstrate biosimilarity, i.e. comparison of the proposed product and the RMP with respect to structure, function, animal toxicity, human PK, PD, clinical immunogenicity, and clinical safety and effectiveness. In each investigation step “residual uncertainties” should be identified and tested in further development steps. In the US, access to biosimilars has recently been facilitated by the advent of the Biologics Price Competition and Innovation (BPCI) Act, creating an abbreviated approval pathway [section 351(k)] under the Public Health Service (PHS) Act for biosimilars. However, as insulins are not regulated as biologicals in the US (for historical reasons), “biosimilar” insulins (referred to as “follow-on” biological products or insulins in the US) cannot use the 351(k) pathway, but instead are regulated through the 505(b)(2) pathway under the FD&C Act. The first “similar” or “follow-on insulin” (Basaglar[®], Eli Lilly) of the RMP, insulin glargine (Lantus[®], Sanofi), was approved in 2015 via the 505(b)(2) pathway under the FD&C Act. Nevertheless, this situation is expected to evolve by 2020 when all biologicals licensed under section 505 of the FD&C Act will be considered as biologics licensed under section 351 of the PHS Act (5, 6). A comparison on regulatory guidelines on biosimilars of insulin in FDA, EMA, MHLW and Australia’s Therapeutic Goods Administration (TGA) is detailed in Annex I.

The fact that a biosimilar is—true to its name—very similar to the reference biological product does not ensure that it will be considered as legally substitutable and interchangeable with the reference product even though during cross-over clinical studies patients are switched from reference product to the biosimilar to demonstrate similar PK and PD. Substitutability and interchangeability are key issues in the present debate on insulin products. These characteristics are essential from an economic point of view, as they condition the level of potential competition that the entry of the biosimilar will produce on the market. If the biosimilar is not legally defined as substitutable or interchangeable, it can hinder prescribing and patient acceptability, even if it has a lower price. Unlike the FDA, the EMA does not take a position on the interchangeability of the biosimilars it authorises and leaves it to the national authorities; however, the FDA also lets the individual states take the final decision (7,8). The use of brand names and the marketing activities of originators often lead to a consumer loyalty to an existing brand, which is not always justified in terms of quality and price.

Thus far, European regulatory experience with biosimilar insulins has not been as extensive as for other proteins for which several biosimilars have been authorised (e.g. filgrastim or erythropoetin). Fewer biosimilar insulin scientific advice procedures (EMA and also nationally at member state level) have taken place in comparison to other potential biosimilar proteins (e.g. filgrastim or etanercept) and biosimilar monoclonal antibodies (e.g. infliximab, trastuzumab, or rituximab). Such advice procedures are used to discuss and agree product development programmes with prospective reviewers. This is possibly because fewer developers were pursuing EU registration of biosimilar insulin products as compared to other recombinant products. It may also reflect the possibility that some developers were underestimating the complexity of the development and registration of insulin products and therefore not seeking timely scientific advice from EU regulators. (Note: As of October 2016, two insulin biosimilars are currently under evaluation by the EMA – one for glargine and the other for lispro).

The comparative case study of Marvel Life Sciences Ltd (Marvel Life Sciences) and Eli Lilly applications sheds further light on the EMA’s requirements(9,10). Marvel Life Sciences failed with two attempts to gain approval for its biosimilar insulin products and later officially

withdrew its applications. The Marvel Life Sciences applications were not sufficiently comprehensive in terms of the technical aspects relating to requirements for both general and biosimilar products. They also lacked the requisite level of detail and communication that supports EU regulatory assessment. The Marvel Life Sciences application was mainly confined to pharmacopoeial methods for the development of insulin biosimilars and did very little to demonstrate comparability to the RMP. Critically, the biosimilarity quality exercise should use a wide panel of sensitive and discriminatory analytical methods to assess content, purity/impurities, activity, and safety. Being different in composition to the RMP, the safety and quality of the biosimilar product were not demonstrated. Efforts to prove biosimilarity can begin from early stage, pre-clinical data all the way through to clinical Phase 3 results. If any of the criteria used to assess the quality of the biosimilar product change during development, without demonstration of comparability, then the data from earlier pre-clinical or clinical studies become devalued in the final assessment of the biosimilarity exercise – and might be required to be rerun with more “relevant” product. It is recognised that some assays will only be developed/validated in later stages of the development programme – however, it might be required that these assays be retrospectively applied to appropriately stored samples to substantiate the comparability claim. The suitability of the administration device for delivering the required dose should also be substantiated. Detailed description on the differences in the application of Marvel Life Sciences versus Eli Lilly biosimilar insulin is presented in Annex II.

For insulin, *in vitro* receptor binding data can be used to support primary pharmacology, however, preclinical PK data might be very variable and evidence from the clinical PK study is more relevant for substantiating biosimilarity. Clinical Phase 3 efficacy studies are not expected for insulin and the focus should be on robust quality biosimilarity evidence, compelling evidence from the *in vitro* pre-clinical programme, and confirmatory comparative Phase 1 PK/PD studies (4, 11, 12). Even so, the Eli Lilly application did include two Phase 3 studies, using a non-inferiority statistical design and the data were accepted as supportive.

Sufficient evaluation of the unwanted immunogenic potential in clinical studies was required in both the Marvel Life Sciences and Eli Lilly applications. However, the relevant Committee for Medicinal Products for Human Use (CHMP) guideline for non-clinical and clinical development of insulin products does allow for the waiver of pre-licensing clinical immunogenicity studies, if appropriately justified (13). The stronger the evidence about structural, biological and formulation similarity between the biosimilar and the RMP, the less non-clinical and clinical data will be needed for approval; therefore, the efforts of the manufacturer should be focused on demonstrating the quality of the biosimilar product and its comparison with the RMP.

Finally, CHMP guidance documents are available to guide non-clinical and clinical development for biosimilar insulins (14). When the developer foresees that they will deviate from these guidelines, ideally this would be agreed upfront with the regulator, with a robust justification for the deviation. This emphasises the importance of prior consultation with regulators prior to deviating from the defined expectations.

Importantly, obtaining EU regulatory advice on the development programme is important for success, especially for products where regulatory experience is still growing, such as these biosimilar insulin applications. In the case of Marvel Life Sciences and Eli Lilly, both of these companies did obtain EU regulatory/scientific advice. However, one company achieved regulatory success whilst the other, with a much weaker dossier, did not. Therefore, it might follow that asking the right questions at the right time, is important, as well as following through on the advice received or providing sufficiently robust explanations for any deviations or alternative strategies.

An insulin manufacturer intending to submit a biosimilar application will have to provide evidence of the quality, clinical efficacy, and safety of the proposed product. The main difficulty remains the manufacturing of a biological that can satisfy the requirements of similarity to the reference product with respect to its chemical structure, post-translational modifications, presence of variants, impurity profile, physicochemical properties, stability and many other parameters without necessarily having access to the proprietary know-how of the reference product manufacturer.

Access to insulin biosimilars depends on many factors including the general socio-economic characteristics of a country and its health system and more specifically to whether, and how far, the latter covers the medicine needs of the population (proportion of the population covered, inclusion of insulin products in the positive list, existence and level of co-payments for insulin products, etc.). To cover a larger percentage of the patient population it is important to access insulin at a lower cost than for the originator product.

Since the discovery of insulin, traditional pharma giants like Eli Lilly, Novo Nordisk, and Sanofi have been introducing new “improved” insulin products to the market – new formulations or new analogues – and the concomitant patent protection (and extension thereof) has prevented generic competition in highly regulated regions. Indeed, it might be argued that companies whose main business is the development and sale of new medicines are more likely to advocate stringent regulatory requirements and standards for authorising and manufacturing biosimilars beyond what might be required from a purely clinical/public health perspective, because this means higher entry barriers and higher prices of follow-on competitors, which allows innovators to maintain higher prices and larger market shares during longer periods for its originator products. In contrast, countries with no (or few) innovative companies might benefit if they avoid unnecessarily high standards in order to promote access to support the local (generic) industry. Now that the patents of the insulin analogues are expiring and fewer insulin products are on the horizon, there is a greater interest in developing biosimilar insulin analogues, as evidenced by the recently approved glargine biosimilars. The first biosimilar ‘glargine’ received marketing authorisation in the US, Europe, Japan, and Australia in 2015. In less stringent regulatory environments, e.g. India, China, and Mexico, several biosimilar insulins already exist at lower prices (15). In India, a glargine biosimilar was first introduced by Biocon in 2011 at a price that was 40 percent lower than Lantus®; more recently, Lupin Ltd. in agreement with LG Life Sciences launched its biosimilar ‘Basugine’ in 2014 (16-18) . Comprehensive information on the global insulin market, including the type, extent and impact of barriers to global insulin access is discussed in Annex III (dated 15.08.2015).

The EMA, in cooperation with the World Health Organization (WHO), also evaluates and offers a scientific opinion on certain medicinal products for human use intended exclusively for markets outside the Community under Article 58 of the EC Regulation N° 726/2004 [19]. The aim of this pathway is to *“help address public health challenges existing in low- and middle- income countries (LMICs) by providing a mechanism through which scientific and manufacturing expertise could be provided to manufacturers, the WHO, National Regulatory Authorities from LMICs, and the broader global health community regarding development and assessment of products intended to be marketed outside the EU and in LMICs.”*[20] Hence, seeking scientific advice from the EMA in respect of the Article 58 pathway may certainly be worth considering if the focus of biosimilar insulin development is for the marketing of insulins outside Europe in LMICs.

In conclusion, the approval and commercialisation of biosimilar/follow-on insulins in many countries worldwide, including those in highly regulated territories, indicates that this is certainly a scientifically feasible exercise. Whether or not the development of biosimilar insulins to meet the more exacting standards of the EMA or FDA for commercialisation in

LMICs is necessary or indeed can be translated into economic and healthcare benefits to patients and health systems in LMICs remains to be ascertained.

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Annex I

Comparison of Regulatory Guidelines for Insulins/Biosimilars

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Executive Summary

The increased prevalence of diabetes worldwide has rendered the access to insulins an urgent unmet medical need. The marketing authorisations to manufacture and to provide insulin are mostly shared between a few “big pharma” companies – Novo Nordisk, Eli Lilly and Sanofi. However, due to the expiration of patents, the introduction of cheaper biosimilar insulins should be possible and has already begun to occur.

At a global level, biosimilar products are often introduced under local standards, which may differ from standards in more highly regulated regions. Recently, Biocon Ltd (India) has received approval from the Ministry of Health, Labour and Welfare (MHLW) of Japan to market its biosimilar insulin glargine suggesting that smaller companies are able to produce biosimilar insulins of sufficient quality to enter the more regulated International Conference of Harmonization (ICH) member markets.

The aim of this report is to identify and to discuss the regulatory issues that a biosimilar / similar insulin manufacturer would face when filing an approval dossier with the European Medicines Agency (EMA), United States Food and Drug Administration (FDA), Saudi Food and Drug Authority (SFDA), Ministry of Health, Labour and Welfare of Japan (MHLW), and Australia Therapeutic Goods Administration (TGA).

First and foremost, guidelines for the authorization of biosimilars – and more specifically, biosimilar insulins – are not present in all countries. Second, there is considerable heterogeneity in the definition of a biosimilar among the different countries. EMA guidelines for biosimilars seem to be the most complete and are accompanied by a specific guideline on biosimilar insulins. The approval requirements through the biosimilar pathway for insulins appear to be simpler than those for a number of other recombinant proteins: if the quality attributes of the biosimilar insulin are highly comparable to the reference product, the amount of non-clinical and clinical data can be limited to pharmacokinetic, pharmacodynamic and immunogenicity studies.

The situation is similar for the SFDA, MHLW, and TGA since their guidelines are based on EMA and ICH recommendations.

In contrast, the regulatory landscape is more complex in the US. While the access to biosimilars has recently been facilitated by the advent of the Biologics Price Competition and Innovation (BPCI) Act, creating an abbreviated approval pathway under the Public Health Service (PHS) Act for biosimilars, insulins are not yet regulated as a biological and thus “biosimilar” insulins cannot use this pathway. The first “biosimilar” insulin was approved in 2015 via the 505(b)(2) pathway under the FD&C Act. Nevertheless, this situation is expected to evolve by 2020 since all biologicals licensed under section 505 of the FD&C Act will be considered as biologics licensed under section 351 of the PHS Act.

The WHO has no licensing activity but edits general guidelines for the approval of similar biotherapeutic products. In addition, the WHO collaborates with EMA for the Article 58 pathway to

facilitate the approval of medicines to address public health challenges existing in low and middle income countries (LMICs).

An insulin manufacturer intending to apply to any of the above mentioned authorities will have to provide evidence of the quality, clinical efficacy and safety of the proposed product. The main difficulty remains the manufacturing of a biological that can satisfy the requirements of similarity to the reference product with respect to its chemical structure, post-translational modifications, presence of variants, impurity profile, physicochemical properties, stability and many other parameters without necessarily having access to the proprietary know-how of the reference product manufacturer.

For now, it would seem easier to apply for EMA/SFDA/MHLW/TGA approval since the guidelines are clearer, but in the context of a harmonization policy it is probable that the US FDA will implement similar insulin-specific guidelines to the EMA. Until 2020, the approval of similar insulins by the US FDA is possible via the 505(b)(2) pathway. The utility of the Article 58 pathway (EMA-WHO) for the marketing of insulins outside Europe in LMICs is unclear due to the lack of precedents, but may be worth considering.

Acronyms

ANDA	Abbreviated New Drug Application
ARGB	Australian Regulatory Guidelines for Biologicals
AUC	Area under the plasma concentration curve
BLA	Biologics License Application
BPCI act	Biologics Price Competition and Innovation Act
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
C _{max}	Maximum plasma concentration;
CMC	Chemistry, Manufacturing and Controls
C _{min}	minimum plasma concentration;
CTD	Common Technical Document
C _{trough ss}	concentration prior to the next dose during multiple dosing
DNA	Deoxyribonucleic acid
EC	European Union
eCTD	electronic Common Technical Document
EEA	European Economic Area
EGA	European Generic Medicines Association
EMA	European Medicines Agency
EU	European Union
FD&C act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
HWMP	High molecular weight protein
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonization

IND	Investigational New Drug
INN	International Nonproprietary Name
JGA	Japanese Generic Medicines Association
LMICs	Low and Middle Income Countries
LMWHs	low molecular weight heparins
MHLW	Ministry of Health, Labour and Welfare
NDA	New Drug Application
NRAs	National Regulatory Authorities
PBS	Pharmaceutical Benefits Scheme
PD	Pharmacodynamics
PHS act	Public Health Service Act
PK	Pharmacokinetics
PMDA	Pharmaceutical and Medical Devices Agency
PQ	Prequalification programme
rDNA	Recombinant DNA
RMP	Reference medicinal product (EMA) (RP in the report)
RP	Reference Product (FDA)
SBMP	Similar Biological Medicinal Product
SBP	Similar Biotherapeutic Product
SFDA	Saudi Food and Drug Authority
SmPC	Summary of Product Characteristics
TGA	Therapeutic Goods Administration
US	United States
WHO	World Health Organization

1. Aim

To identify the regulations for marketing authorisation of biosimilar insulins.

To prepare a report:

- Comparing and contrasting the regulatory guidelines, for gaining market authorisations for insulin/biologicals, of the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), the Saudi Arabian Food and Drug Authority (SFDA), the Ministry of Health, Labour and Welfare (MHLW) of Japan, and Therapeutic Goods Administration (TGA) of Australia and the World Health Organization (WHO).

Note: only the EMA has insulin-specific guidelines and several annexes for other biologics. The SFDA, MHLW and TGA have adapted guidelines from EMA. Insulin is covered in the FDA and WHO guidelines for biologicals.

- Discussing key regulatory issues that biosimilar insulin manufacturers would need to overcome to gain marketing authorisations from the EMA and FDA.

2. Background

Insulin is an endogenously secreted protein hormone playing a major role in glucose metabolism. It was first extracted from animal tissue in 1921 by Frederick Grant Banting and Charles Best. It has been marketed in several forms: first from animal sources, then came the first recombinant human insulin (Humulin[®], Eli Lilly and Company [Eli Lilly]) and this was then followed by insulin analogues, meaning that these insulins have altered amino acid sequences that modify their clinical properties (i.e. short-acting [e.g. insulin lispro, insulin glulisine and insulin aspart] or long-acting [e.g. insulin glargine, insulin detemir and insulin degludec] and combinations thereof).

Given that the prevalence of diabetes worldwide has been increasing over the last few decades, especially in low income countries (e.g. 3.1 to 7.1 percent in Africa), there is a dire need for accessible treatments (1).

Original product patent expiry would allow the marketing of “biosimilar” products. However, only glargine (original product: Lantus[®], Sanofi) has recently been approved in its “biosimilar” form as Abasaglar[®] (09.09.14, EMA, Eli Lilly) and Basaglar[®] (16.12.15, FDA, Eli Lilly).

At a global level, biosimilar products are often introduced under local standards, which may differ from standards in more highly regulated regions. Due to the risks and cost associated with the development of a biosimilar, generic manufacturers usually do not try to compete. Recently, Biocon Ltd. (India) received approval from the MHLW to market its biosimilar glargine, suggesting that companies other than the big three (Eli Lilly, Novo Nordisk, and Sanofi) are able to produce high quality biosimilar insulins for more regulated markets (2).

The aim of this report is to compare the regulatory pathways in Europe, US, Saudi Arabia, Japan, and Australia in order to understand the key hurdles to the approval of biosimilar products.

2.1 Biosimilars: Definitions

First, it is interesting to note that the term “biosimilar” is not defined in the same way by the different competent authorities.

2.1.1 EMA

Biological

“A biological medicine is a medicine that contains one or more active substances made by or derived from a biological source.” (3)

Biosimilar

“A biosimilar medicine is a biological medicine that is developed to be similar to an existing biological medicine (the ‘reference medicine’). Biosimilars are not the same as generics, which have simpler chemical structures and are considered to be identical to their reference medicines. The active substance of a biosimilar and its reference medicine is essentially the same biological substance, though there may be minor differences due to their complex nature and production methods. Like the reference medicine, the biosimilar has a degree of natural variability. When approved, its variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness.” (3)

Insulins are considered as biologicals by EMA, so a similar product is considered a biosimilar.

2.1.2 FDA

Biological

“The term “biological product” means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.” (4)

Biosimilar

The term “biosimilar” or “biosimilarity”, in reference to a biological product that is the subject of an application under subsection (k), means

(A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and

(B) there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.

The term “interchangeable” or “interchangeability”, in reference to a biological product that is shown to meet the standards described in subsection (k)(4), means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

The term “reference product” means the single biological product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k). [4]

For the FDA, insulins are NOT considered as biologicals, so similar products are currently licensed under the 505(b)(2) pathway for medicines. This pathway means that there are significant differences from the reference product for which additional non-clinical and clinical data are submitted to demonstrate the proposed product’s safety and efficacy (5)

2.1.3 SFDA

Biological

Not defined

Biosimilar

“Biosimilars are therapeutic biologicals that follow previously-approved innovative biological medicinal products. They are not copies (generics), but are similar. In this Guideline on Biosimilars, we are using the term “biosimilar(s)” to denote proteins produced by means of recombinant DNA technologies following the footsteps of an innovator product after the expiration of the innovator’s patent.” (6)

2.1.4 MHLW

Biological:

“Drugs, quasi-drugs, cosmetics, or medical devices using materials manufactured from humans or other organisms (excluding plants) as raw materials or packaging materials, which are designated as requiring special precautions in terms of public health and hygiene.” (7)

The biological products that are not included in the Japanese guideline are allergen extracts, antibiotics, cells or whole blood/cellular blood components (blood cell components), conventional vaccines based on antigens such as attenuated or inactivated pathogenic microorganisms and extracts, metabolic products of cells, nucleic acid products, polysaccharides, synthetic peptides/polypeptides and vitamins. However, manufacturers can also consult with the appropriate regulatory authority about the applicability of the guideline to their products.

Follow-on biologic (biosimilar)

Biosimilars are known as follow-on biologics in Japan. By definition, *“a “follow-on” biologic is a biotechnological drug product developed to be comparable in regard to quality, safety and efficacy to an already approved biotechnology-derived product of a different company.” (7)*

2.1.5 TGA

Biological:

As per Australian Regulatory Guidelines for Biologicals (ARGB), *“a biological is an item made from, or containing, human cells (T cell therapies, human stem cells, etc.) or human tissues (skin, bone, ocular, cardiovascular, etc.) for therapeutic use.”*

In contrast to EU, FDA, Japan – and many other countries – many biological products such as products of genetically modified organisms (e.g. insulin), vaccines (that do not contain human cells), peptides (e.g. insulin, cytokines), monoclonal antibodies and blood plasma products are not regulated as biologicals but as biological medicines under therapeutic goods(8). However, abbreviated versions of biological medicines are evaluated as biosimilars.

Similar biological medicinal product (biosimilar)

“A biosimilar or similar biological medicinal product (SBMP) is a version of an already registered biological medicinal product that has demonstrable similarity in physicochemical, biological and immunological characteristics, efficacy and safety, based on a comprehensive comparability analysis and has been evaluated by the TGA according to its guideline ‘Evaluation of Biosimilars’ and other relevant EU guidelines adopted by the TGA.” (9)

There is still a lack of harmonisation among the countries regarding the definition of a biosimilar, so sponsors should make sure that the proposed product fits the definition in a given regulatory region. In fact, the EMA has identified the inconsistent use of terminology as

a major concern in the approval of these medicines. An effort towards a harmonised terminology would be highly valuable(10).

2.1.6 WHO

Biotherapeutic / Biological

“This guideline applies to well-established and well-characterized biotherapeutic products such as recombinant DNA-derived therapeutic proteins. Vaccines, plasma derived products, and their recombinant analogues are excluded from the scope of this document. WHO recommendations and regulatory guidance for these products are available elsewhere (<http://www.who.int/biologicals/areas/en/>).”

Similar biotherapeutic product (biosimilar)

“A SBP (similar biotherapeutic product) is intended to be similar to a licensed biotherapeutic product for which there is a substantial evidence of safety and efficacy. The ability for the SBP to be authorized based on reduced non-clinical and clinical data depends on proof of its similarity to an appropriate RBP through the comparability exercise.” (11)

2.2 Biosimilars vs Generics

Biosimilars may wrongly be considered as generic medicinal products; however, due to complexity and variability of manufacturing, biosimilars do not meet all of the conditions to be considered as generics:

“Biological medicinal products similar to a reference medicinal product do not usually meet all the conditions to be considered as a generic medicinal product mainly due to manufacturing process characteristics, raw materials used, molecular characteristics and therapeutic modes of action.” (12)

Thus, the clinical development is not limited only to a Bioequivalence study. Table 1 compares the main steps in generic and biosimilar product development.

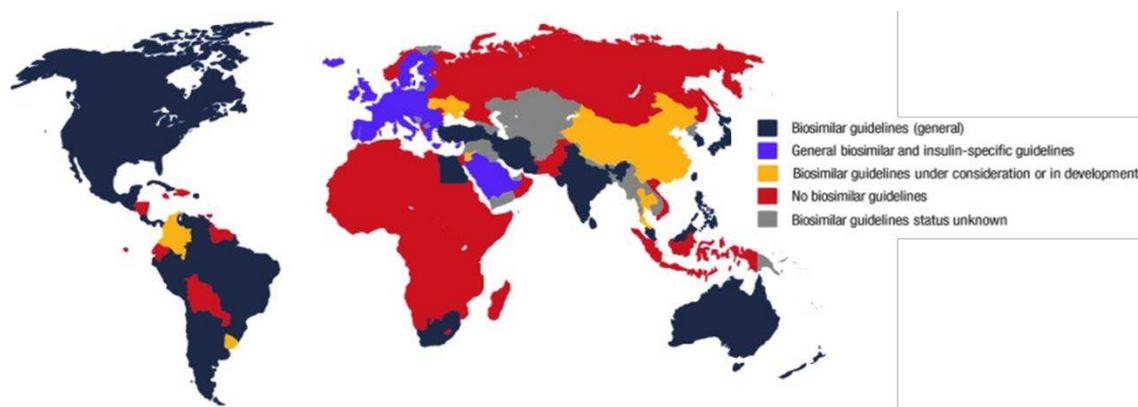
Table 1. Development of a generic vs biosimilar product.

	Generic medicinal product	Biosimilar
Quality	<ul style="list-style-type: none"> • CMC (Chemistry, Manufacturing, and Controls) development GMP manufacturing, stability... 	<ul style="list-style-type: none"> • CMC development Full process and product development fulfilling same quality standards as the reference medicinal product (RP) (cell line, expression, purification, characterization, stability...
	<ul style="list-style-type: none"> • Formulation development 	<ul style="list-style-type: none"> • Formulation development Formulation/administration device development
	<ul style="list-style-type: none"> • No preclinical development 	<ul style="list-style-type: none"> • Preclinical development (vs RP) <i>In vitro/in vivo</i> bioassays Pharmacology studies Toxicity studies Local tolerance
Safety / Efficacy	<ul style="list-style-type: none"> • Clinical development Bioequivalence study (pharmacokinetics - C_{max}, T_{max}, AUC in approx.. 50 patients) in comparison with the RP. 	<ul style="list-style-type: none"> • Clinical development (vs RP) Phase I PK-PD comparison with RP. Phase III studies (limited number of patients), comparison with RP. Pharmacovigilance and risk management plan

2.3 Approval of Biosimilars: General Considerations

2.3.1 Biosimilar Guidelines Availability

Figure 1. Availability of general and insulin-specific biosimilar guidelines. Adapted from (13).



There is significant heterogeneity in the availability of general biosimilar guidelines and specific insulin guidelines – as is clearly observed in Figure 1. However, a harmonisation process is on-going, especially in the developed countries.

2.3.2 Regulatory Pathways for Biosimilars

Table 2 summarises the regulatory pathways via which biosimilars can be approved by the different regulatory bodies.

Table 2. Regulatory pathways for biosimilars.

EMA	<p>Application via the centralised procedure is mandatory for a biosimilar product.</p> <p>Review: CHMP Working parties: Safety, Quality, Biologicals, Biosimilar medicinal products</p>
FDA	<p>Biologics Price Competition and Innovation Act (BPCI act) (2009) creates an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with a licensed RP.</p> <p>This licensure pathway allows a biosimilar biological product to be licensed under 351(k) of the Public Health Service Act (PHS Act) based on less extensive preclinical and clinical.</p> <p>Insulin, glucagon, somatropin, and low molecular weight heparins (LMWHs) are currently licensed under the Federal Food, Drug, and Cosmetic (FD&C) Act.</p>
WHO	<p>The WHO has no licensing activity.</p> <p>The intention of the WHO SBPs guidelines [11] is to provide globally acceptable principles for licensing biotherapeutic products that are claimed to be similar to biotherapeutic products of assured quality, safety, and efficacy that have been licensed.</p> <p>This guideline can be adopted entirely or partially by National Regulatory Authorities.</p>
SFDA	<p>A consensus group meeting in 2008 recommends following the EMA guidelines for the registration of biosimilars.</p> <p>SFDA guidelines on biosimilars (6) are based on EMA and ICH recommendations and also cover insulins.</p>
MHLW	<p>Biosimilar applications are examined by the MHLW through its Pharmaceutical and</p>

	Medical Devices Agency (PMDA).
	The guideline on biosimilars was first published in 2009 by MHLW based on EMA guidelines on biosimilars.
TGA	The evaluation process is done as per the legislation applicable for prescription medicines by the TGA. Applications to register biosimilars are managed through the prescription medicines registration process that is submitted in Common Technical Document (CTD) format.
	TGA adopts EU guidelines on biologicals and biosimilars and where possible it follows ICH guidelines to assess comparability.

However, it is important to note that while in the EU insulins are considered as biologicals, in the US, certain biologicals (often old molecules including insulin, glucagon, somatropin, and low molecular weight heparins (LMWHs)) are not considered as “biologicals” and are thus approved under the Federal Food, Drug, and Cosmetic (FD&C) Act.

Following an agreement between the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) in 2003 (Federal Register, vol. 68, no. 123, June 26, 2003, pp. 38067-38068), biological products such as monoclonal antibodies, proteins intended for therapeutic use (interferons, thrombolytic enzymes), immunomodulators (other than vaccines and allergenic products), and, growth factors, cytokines, and monoclonal antibodies intended to alter production of blood cells fall under section 351 of the PHS Act of CDER and thus their copies are called biosimilars. In contrast, some hormones (insulin, glucagon, etc.) and certain enzymes (hyaluronidase and urokinase) are regulated as medicines under the FD&C Act and not as biologicals, regardless of the method of manufacture(14), unlike in the EU where, as mentioned above, insulin is considered as a biologic(15).

Since insulin falls into the medicines category, two abbreviated pathways under the FD&C Act—505(j) and 505(b)(2) are available. Section 505(j) means that the generic version has the same active ingredient as the reference product and section 505(b)(2) means there is significant difference from the reference product for which additional non-clinical and clinical data are submitted to show the proposed product’s safety and efficacy. Given that most biologics and their methods of manufacture are complex, it is extremely difficult to develop a biologic that is identical to the reference product. This makes the 505(j) pathway unavailable. However, if a biological product is sufficiently similar to the innovator product, the 505(b)(2) pathway may be used by an applicant for the approval of its biologic by justifying the difference between the two and by proving the quality, safety and efficacy(5).

A recent example of such a 505(b)(2) application is Basaglar® (Eli Lilly) that received approval in December 2015. Basaglar® is the first “similar” product of glargine (Lantus® developed by Sanofi). Eli Lilly scientifically justified the similarity of Basaglar® to Lantus® by providing data on the quality, safety and efficacy for its approved uses after conducting two clinical trials with 534 and 744 patients with type 1 and 2 diabetes mellitus, respectively. Indeed, *Basaglar® is not approved as a biosimilar. In fact no insulin products are currently licensed under the PHS Act, so there is no “reference product” for a proposed biosimilar product.* Therefore, from a regulatory point of view, the FDA does not refer to a product approved via this abbreviated pathway as a “biosimilar”(16).

3. Comparison of Guidelines

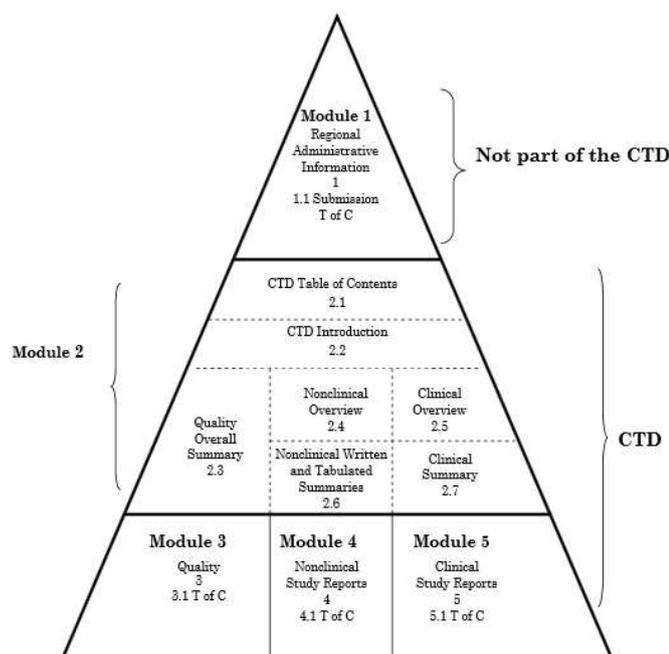
3.1 CTD (Common technical document)

To obtain a marketing authorisation, the applicant must submit to the competent authority an application dossier proving the quality, safety and efficacy of the product together with all the administrative documents (application forms, labelling, package leaflets, summary of product characteristics (SmPC)).

Following the International Conference on Harmonization (ICH), the EMA, FDA, MHLW, and TGA have agreed to a common format for the application dossier – the common technical document (CTD) – that can also be submitted in an electronic format – (eCTD).

The CTD is organised into five modules (Figure 2).

Figure 2. CTD structure.



Module 1 contains the administrative information that is specific to each country/region, in the appropriate language.

Module 2 content is based on the details presented in Modules 3, 4 and 5. It should begin with a general introduction and provide the overall summary of the quality, the non-clinical and clinical overview (discussion), as well as the non-clinical and clinical summaries.

Module 3 contains detailed information on quality topics.

Modules 4 and 5 contain detailed nonclinical and clinical study reports, respectively (17). If reduced Module 4 and 5 datasets are submitted evaluation will commence on the assumption that the Module 3 data will demonstrate sufficient comparability of the proposed biosimilar to the reference product(18).

The regulatory guidelines will now be reviewed below, following the structure of a CTD.

3.2 Comparison of EMA and FDA Guidelines for Biosimilars

Since SFDA, MHLW and TGA adopted the EMA guidelines for biosimilars, we can simply make a direct comparison between the EMA and FDA. In the European legal framework, the biosimilar product quality has to be demonstrated and additionally the CTD modules 3, 4 and 5 should be the result of the so-called “Comparability exercise”. It consists of a head-to-head comparison of quality, safety and efficacy to demonstrate that the biosimilar and the RP do not present any differences that could impact the safety and efficacy. The extent of the non-clinical and clinical testing may be reduced depending on the similarity of the quality profile. In contrast, differences in quality profile will necessitate further testing with respect to the safety and efficacy of the product.

Similarly, FDA recommends the use of a “stepwise approach” to develop the evidence needed to demonstrate biosimilarity, i.e. comparison of the proposed product and the RP with respect to structure, function, animal toxicity, human pharmacokinetics (PK), pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness. In each investigation step “residual uncertainties” should be identified and tested in further development steps.

For both EMA and FDA, the use of a foreign comparator is accepted in order to facilitate the development of biosimilars (ICH adherent countries are preferred). However, the applicant must provide the proof of the similarity between the EU or FDA-authorized comparator and the foreign one.

A list of the relevant guidelines is available in Appendix I: List of available guidelines.

3.2.1 Quality (Module 3)

For both the EMA and FDA, a standalone manufacturing process should be developed according to ICH guidelines(19 – 21). The quality of the manufactured product should be demonstrated and the comparability exercise (EMA) and the stepwise approach (FDA) should compare biosimilar and the RP using a series of sensitive orthogonal methods to determine similarities AND differences in quality attributes. *“Any differences detected in the quality attributes will have to be appropriately justified with regard to their potential impact on safety and efficacy”.*(19)

The stronger the evidence about structural, biological and formulation similarity between the biosimilar and the RP, the less non-clinical and clinical data will be needed for approval; therefore, the efforts of the manufacturer should be focused on demonstrating the quality of the biosimilar product and its comparison with the RP.

Nevertheless, the manufacturing process for a biosimilar is far more complex than for generic medicines. Indeed, like the reference biological products, biosimilars:

- are mainly protein in nature and produced in living organisms (bacteria, yeasts, mammalian cells ...) by recombinant DNA (rDNA) technology. This can lead to quality issues such as contamination (viruses, transmissible spongiform encephalopathy...), lack of post-translational modifications, poor reproducibility. An adequate documentation and traceability of the expression cells are mandatory (master and working cell banks; MCB/WCB)
- need a complex purification process to remove the host cell proteins, genetic material and product related impurities.
- need formulation stabilisation (to avoid aggregation, oxidation, adsorption to surfaces...)
- are often injectable and as such need a heat-avoiding sterilisation process(22).

One may argue that the manufacturing process has already been optimised and validated by the RP manufacturer; however, the latter has no interest or obligation to share this proprietary know-how. Consequently, the manufacturer of the biosimilar can only use powerful analytical tools to characterise the RP available on the market and so develop a biosimilar product to match all its quality attributes. It is also the reason why a biosimilar is not required to be identical but only similar to the RP, provided that the observed differences do not impact on safety and efficacy. In that sense, Module 3 of a biosimilar application dossier should contain even more information than that of the RP since it has not only to prove the quality of the product but also the similarity to the RP(23).

In comparison to an EU guideline that has separate guidelines or annexes for almost every biological medicinal product, Japan has a common guideline for all biological products focusing on proving the similarity of the biosimilar to the RP in all respects for a given dosage form – with the notable exception of the formulation composition.

EMA and MHLW closely follow the ICH guidelines. For biologics and follow-on biologics, ICH quality guidelines Q5A-E, Q6B and Q11 and ICH safety guideline S6 are very important. ICH guideline Q5C is followed to perform stability testing of biological products and a minimum 6 months of stability data should be submitted at the time of submission. However, before approval, results of long-term, real-time, real-condition stability studies should be produced and the effect and safety of any impurity falling out of specification limits should be generated by standard procedures and if necessary should be clinically confirmed. For biosimilar and RP, the storage conditions and storage period need not be identical. Whereas stress and accelerated stability studies are part of the biosimilar application in EU, they are optional in Japan.

Consequently, the main barrier to the development of biosimilars seems to be the difficulty in manufacturing high quality products that share enough quality attributes with the RP without having complete knowledge about the manufacturing of the RP.

3.2.2 Non-Clinical and Clinical Safety and Efficacy (Modules 4 and 5)

Once the biosimilar has been proven similar to the RP from a physicochemical point of view, it can undergo non-clinical and clinical comparison.

A. Non-clinical studies

***In vitro* studies**

In the EMA guidelines, *in vitro* biological activity assays should assess any difference between the biosimilar and the RP. They should cover the entirety of relevant pharmacological and toxicological aspects and be predictive of the *in vivo* situation. *In vitro* biological activity assays are covered by *FDA Quality and Scientific considerations Guidelines(20)*; the content is similar to EMA recommendations.

***In vivo* studies**

For both EMA and FDA the relevance of *in vivo* animal toxicity and pharmacology studies depends on the extent of known similarities or differences between the biosimilar and RP. *In vivo* studies are needed if:

- Differences in the quality attributes have been detected between the biosimilar and the RP, especially if these differences are thought to affect the toxicity profile of the biosimilar (i.e. impurities, immunogenicity...)
- Additional *in vivo* data are required

Animals should be handled humanely and non-relevant species should not be used. Animal immunogenicity assessments may help the interpretation of the animal study results but generally are not predictive of potential immune responses in humans. There is no need to

provide reproductive and developmental toxicity as well as carcinogenicity studies if the biosimilar and the RP have been demonstrated to be highly similar after structural and functional characterisation(20 – 24).

B. Clinical studies

In both EMA and FDA guidelines, clinical testing is dependent on the previously obtained data and the extent of demonstrated similarity. It consists of assessments of the PK and PD similarity, clinical efficacy and clinical safety (mainly immunogenicity). If convincing PK and PD results are provided, the extent of subsequent clinical trials can be reduced. However, if “residual uncertainties” remain, additional studies may be demanded.

PK and PD studies

The test population may be composed of healthy volunteers or patients. Importantly, the selected population should enable the detection and evaluation of differences in PK and PD profiles between the proposed biosimilar product and the RP, so this choice can be dependent on the previously detected “residual uncertainties”.

The selected dose should also be the most sensitive to enable the detection and evaluation of differences in the PK and PD profiles. Moreover, human PK and PD studies should be conducted using the same route of administration for the proposed biological product as the RP. If more than one route of administration is approved for the RP, the route selected for the assessment of PK and PD similarity should be the one that is most sensitive for detecting clinically meaningful differences.

The primary and secondary PK parameters that need to be measured are similar in both guidelines.

PD studies are useful when a clear dose-response relationship has been demonstrated and the selected PD marker/biomarker is an accepted surrogate. A combination of markers may provide sufficient evidence to conclude on clinical comparability.

Efficacy trials (also called “Comparative Clinical studies” in FDA regulation)

The EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues states that:

“Usually, it is necessary to demonstrate comparable clinical efficacy of the biosimilar and the reference”(24)

Whereas the FDA guideline mentions that in cases where the structural analysis, the *in vitro* and *in vivo* data point to a biosimilarity and *“there is a meaningful correlation between PK and PD results and clinical effectiveness, convincing PK and PD results may make a comparative efficacy study unnecessary”*(20).

In the case where an efficacy trial is indicated, comparable clinical efficacy should be demonstrated by an adequately powered, randomised, parallel group comparative clinical trial (equivalence design), preferably double-blind. The study population should be representative of the approved therapeutic indication(s) of the RP. The statistical treatment of data should be able to detect differences between the RP and the biosimilar.

Safety trials (also called “Clinical immunogenicity assessment” in FDA regulation)

In both regulations, it is recommended (if possible) to collect the safety data alongside the efficacy data in the same clinical trial; therefore, the size of the study population should be sufficient to detect possible safety concerns.

Both FDA and EMA state the importance of the assessment of clinical immunogenicity given the chemical nature of biosimilars:

“Immune responses may affect both the safety and effectiveness of the product by, for example, altering PK, inducing anaphylaxis, or promoting

development of neutralizing antibodies that neutralize the product as well as its endogenous protein counterpart. Thus, establishing that there are no clinically meaningful differences in immune response between a proposed product and the RP is a key element in the demonstration of biosimilarity”(20).

The EMA provides a specific guideline: *Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins*(25). Overall recommendations state that

- The selection of clinical immunogenicity endpoints or PD measures associated with immune responses to therapeutic protein products should take into consideration the immunogenicity issues that have emerged during the use of the RP.
- The duration of follow-up evaluation should be determined based on the time course for the generation of immune responses; the time course of disappearance of the immune response; the length of administration of the product. (i.e. 1 year for chronically administered agents)

However, the extrapolation of immunogenicity data to other indications is different for both authorities: EMA clearly states that immunogenicity should be assessed for each indication separately.

Pharmacovigilance (also called “Postmarketing safety monitoring considerations” in FDA regulation)

In both guidelines it is acknowledged that clinical trial populations are too small to detect rare adverse reactions. Therefore, EMA requires the implementation of a “Risk management plan” (Guideline on good pharmacovigilance practices(26); Guideline on good pharmacovigilance practices, Module V –Risk management systems (27)). In the FDA guideline such a plan is mentioned as the “Postmarketing safety monitoring”.

3.3 Comparison of EMA and FDA guidelines for Insulins

Insulin was first discovered in 1921 and the details and methods of preparation were disclosed to allow it to be made available to the public as rapidly as possible. Therefore, there was no incentive for a pharma company since it could not secure a very lucrative monopoly by controlling access to insulin. Initially, animal source insulins were available but they presented numerous problems. Over the years, pharma companies like Novo Nordisk, Eli Lilly, Sanofi and Pfizer launched several improved and safer versions of insulins. Analogues were prepared that had different pharmacokinetic properties; examples of long-acting insulins include, glargine (Lantus® from Sanofi) and detemir (Levemir® from Novo Nordisk). Glargine’s patent expired in 2014 and Eli Lilly has already received the approval for its biosimilar version in several highly regulated markets – EU (09.09.14), USA (16.12.15), Japan (21.01.2015), and Australia (10.11.2014).

3.3.1 EMA

Insulins are considered as biologicals in the EU. Module 3 has to follow general biosimilar quality guidelines whereas for Modules 4 and 5 there is a specific guideline: *Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues*(28). The key points can be found in *Appendix II: EMA Recombinant insulins Reference Guideline*.

In order to illustrate the difficulty of a CMC (Module 3) development for a biosimilar, the following table compares the quality assessment of following two biosimilar insulin applications to EMA:

- Solumarv® - biosimilar insulin; (negative assessment from EMA)
- Abasaglar® (previously Abasria®) - biosimilar insulin; (positive assessment from EMA)

Table 3. Quality assessment of two biosimilar insulin applications from Marvel Lifesciences for Solumarv® and Eli Lilly for Abasaglar® to EMA.

Solumarv (29) (RP: Humulin S®)	Abasaglar (30) (RP: Lantus®)
<p>The quality of the product was not sufficiently demonstrated and the analytical comparability between Solumarv and Humulin S from Eli Lilly could not be established :</p> <ul style="list-style-type: none"> ▪ Lack of manufacturing process documentation. ▪ Process validation data was not provided. ▪ The traceability, reproducibility and robustness were not sufficiently documented. ▪ Uncertainty remains on the quantity of two Solumarv-specific insulin variants in commercial active substance batches. There are three major process-related stable impurities, which derive from the insulin molecule. Two of these impurities are a unique feature Solumarv which can be explained by a different production process. The possibility exists that these impurities might lead to increased immunogenicity. ▪ Analytical comparability between Solumarv and Humulin S from Eli Lilly, however, cannot be drawn on the basis of the data provided. While overall the number of batches of the test and the reference product introduced into the comparability exercises is deemed sufficient, the representativeness of the test product batches for the commercial process and product has been questioned. ▪ Since the quality of the product cannot be demonstrated, the benefit/risk balance cannot be established. 	<p>Overall, comparability between Abasaglar (LY2963016) and the reference product Lantus®, has been satisfactorily demonstrated from the quality perspective.</p> <ul style="list-style-type: none"> ▪ Physico-chemical characterization has demonstrated biosimilar comparability between LY2963016 and the reference medicinal product (EU-approved Lantus®) for the primary, secondary, tertiary and quaternary structure. ▪ LY2963016 and Lantus® were comparable in the average relative potency assay when batches of LY2963016 from Lilly (France) and a contract manufacturer (USA) were compared directly with EU-approved Lantus® or US-approved Lantus®. Biological identity test data from LY2963016 finished product and Lantus® were also demonstrated to be comparable in batches tested concurrently. ▪ LY2963016 has the same quantitative formulation as Lantus®, with comparable levels of metacresol and zinc, also similar pH. ▪ Levels of total impurities and HMWP were comparable in LY2963016 and Lantus®. ▪ Comparable chromatographic profiles were demonstrated for LY2963016 and Lantus®, except for low levels of an impurity in LY2963016. This product-related impurity was shown to be active in the reporter gene assay and was qualified in toxicology studies. This impurity is controlled in the purification process. ▪ LY2963016 finished product and Lantus® have similar in vitro precipitation characteristics under physiological conditions. ▪ Low levels of citrate were detected in the Lantus® samples (both EU and US Lantus®) by NMR, which is not present in LY2963016. ▪ Differences were observed in the degradation pathways under accelerated conditions, although no differences were observed under long term storage conditions.

Conclusion: Solumarv received a negative assessment from EMA because the quality of the product itself was not satisfactory *and* there was a lack of comparability to the RP. Abasaglar® received a positive quality assessment despite minor differences in citrate levels and degradation pathways. See Annex II for a more information.

The non-clinical testing of biosimilar insulins should include the *in vitro* investigation of insulin binding to both human insulin receptors and to the IGF-1 receptor if applicable. Comparative *in vitro* PD studies are not required.

If no novel excipients are introduced, separate repeated dose toxicity, reproduction toxicology, carcinogenicity and local tolerance studies are not required.

A clinical PK/PD study (comparison of PK and PD profiles) is considered the mainstay of proof of similar efficacy of the biosimilar and the RP insulin thus allowing the avoidance of efficacy trials.

For this purpose, cross-over, double-blind hyperinsulinaemic euglycaemic clamp studies using single subcutaneous doses of the biosimilar and RP are needed. Different PK and PD endpoints are chosen depending on the insulin (*See Appendix II for details*).

Clinical safety focuses on immunogenicity by quantification of anti-drug antibodies during 6 months. This pre-licensing safety study including immunogenicity assessment may be waived when similarity in physicochemical (quality) and functional characteristics (non-clinical data) can clearly be shown for the biosimilar and the RP insulin, similarity of PK and PD profiles and if impurity profile and excipients are not a source of concern.

A risk management plan should be proposed.

It is interesting to note that the Abasaglar® (previously Abasria®) EMA dossier contained two additional efficacy trials despite the guideline recommendation, probably because of a simultaneous application to the FDA.

3.3.2 FDA

In contrast, in the USA, certain biologicals like insulin, glucagon, somatropin, and low molecular weight heparins (LMWHs) are regulated under the Federal Food, Drug, and Cosmetic (FD&C) Act and are therefore open to the 505(b)(2) abbreviated pathway [15, 16]. For instance Basaglar® (Eli Lilly) was approved under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C) in December 2015(31).

Figure 3 presents the evolution of regulatory pathways concerning the approval of biological and biosimilar drugs by FDA.

Until 2010 there was no abbreviated pathway to facilitate the approval of biosimilars, it was introduced by the BPCI act. However, this abbreviated pathway can apply only if the RP is a biological (approved via the section 351 of PHS Act). Therefore, medicine such as insulins do not fulfil this requirement and the approval of a similar insulin must go via the 505(b)(2) abbreviated pathway.

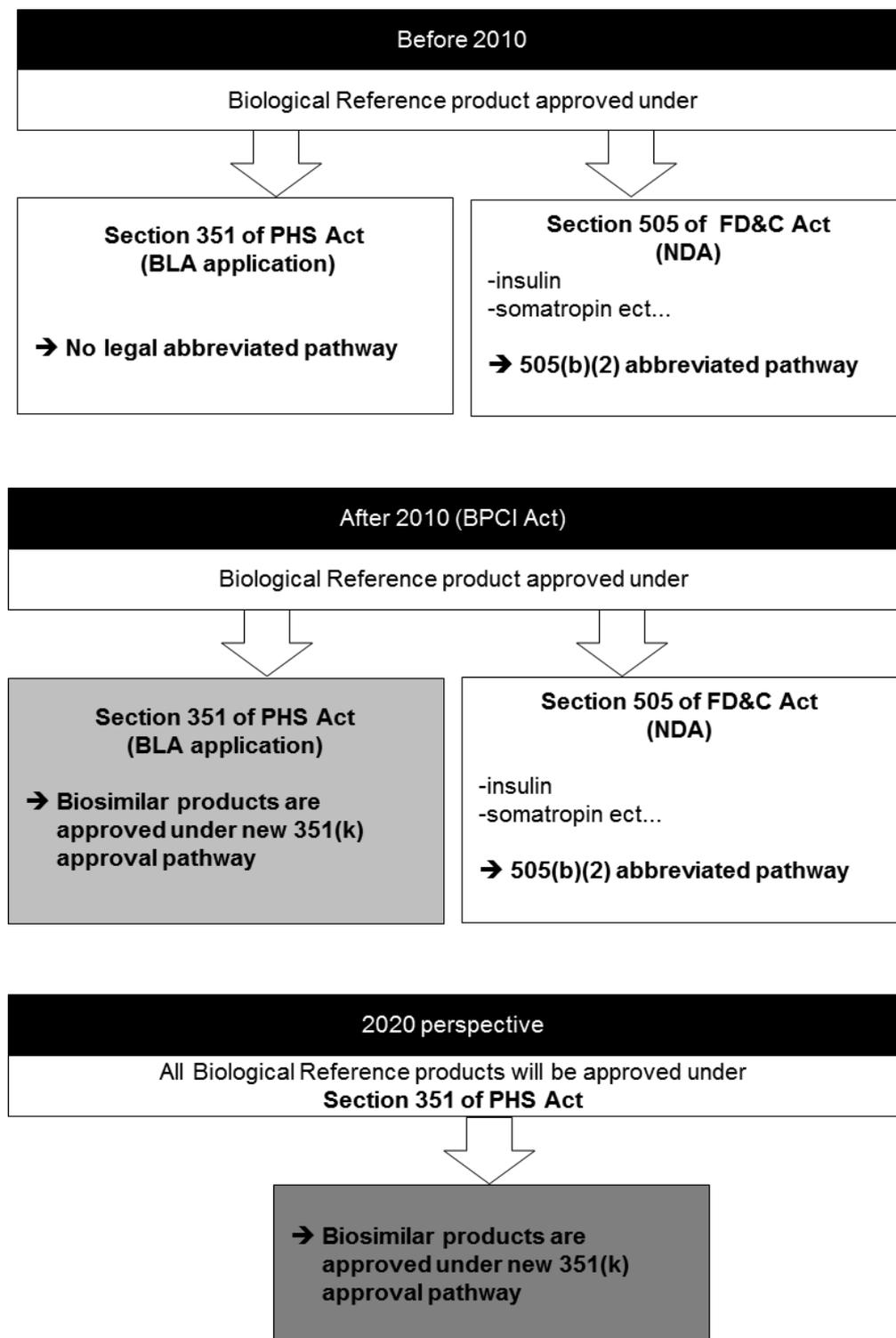
The Guidance for Industry: Applications Covered by Section 505(b)(2) states that:

“an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference (section 505(b)(2))” (5).

Consequently a 505(b)(2) application should provide more data than an ANDA, but less than an NDA. More generally the exact amount and nature of data to be provided has to be sufficient to demonstrate the effectiveness and safety of the proposed medicine and usually requires a case-by case evaluation and discussion with the FDA(32).

However, *“As of March 23, 2020, an application for a biological product approved under section 505 of the FD&C Act will be deemed a biologics license application (“BLA”) licensed under section 351 of the PHS Act”*. (33)

Figure 3. Evolution of biosimilar approval pathways by FDA. Adapted from (13,34,35).



In order to understand whether the 505(b)(2) pathway is more interesting for the approval of similar insulins than a section 351 pathway, Table 4 compares the applications of two products to FDA:

- Basaglar® - similar insulin - 505(b)(2) pathway
- Zarxio® – similar Filgrastim - 351(k) pathway

Table 4. Comparison of CMC, non-clinical and clinical data in the application dossier of two insulins submitted to FDA via 505(b)(2) pathway and 351(k) pathway.

Basaglar® - similar insulin - 505(b)(2) pathway	Zarxio® – similar Filgrastim - 351(k) pathway (37) RP - Neupogen®
RP –Lantus® (36)	
Chemistry review	Chemistry / Quality review
<ul style="list-style-type: none"> Assessment of 11 quality attributes (identity, potency assay, impurities, sterility, endotoxins...) by simple techniques such as HPLC, AA spectroscopy...) 	<ul style="list-style-type: none"> Assessment of 19 quality attributes (primary and higher order structures, Bioactivity, variants...) by one to six independent analytical methods.
Medical review and Clinical pharmacology review	Medical review and Clinical pharmacology review
<ul style="list-style-type: none"> Pharmacology/toxicology studies in rats Clinical pharmacology studies 	<ul style="list-style-type: none"> Pharmacology/toxicology studies in rats Clinical pharmacology studies
<p>ABEO Single-center, randomized, double-blind, single-dose (0.5 U/kg), 2-treatment, 4-period crossover, replicate, euglycemic clamp study to compare the PK and PD of BASAGLAR® to US-approved LANTUS®</p> <p>91 Healthy volunteers</p>	<ul style="list-style-type: none"> two studies in which the PK and PD of Zarxio® was compared in normal human subjects to US-licensed Neupogen® (n=26) Four studies in which the PK and PD of Zarxio® was compared to EU-approved Neupogen® at doses ranging from 1, 2.5, 5 and 10 mcg/kg in normal human subjects (n ranging from 23 to 32)
<p>ABEA Single-center, randomized, double-blind, single-dose (0.5 U/kg), 2-treatment, 4-period crossover, replicate, euglycemic clamp study to compare the PK and PD of BASAGLAR® to EU-approved LANTUS®</p> <p>80 Healthy volunteers</p>	
<p>ABEI Single-center, randomized, open-label, single-dose (0.5 U/kg), 2-treatment, 2-period crossover euglycemic clamp study to evaluate the relative bioavailability and PD response of BASAGLAR® to EU-approved LANTUS®</p> <p>40 Healthy volunteers</p>	
<p>ABE M Single-center, randomized, subject-and investigator-blind, 4-treatment, 4-period, crossover euglycemic clamp study to compare the PK and PD of BASAGLAR® to EU-approved LANTUS® following single-dose administration at 2 different dose levels (0.3 U/kg and 0.6 U/kg)</p> <p>16 Healthy volunteers</p>	
<p>ABEE Single-center, randomized, subject-and investigator-blind, single-dose (0.3 U/kg), 2-period crossover, 42-hour postdose euglycemic clamp study to compare the PK and PD of BASAGLAR® to EU-approved LANTUS®</p> <p>20 Type 1 diabetes patients</p>	
<p>ABEN Single-center, randomized, subject-and investigator-blind, single-dose (0.5 U/kg), 2-treatment, 4-period crossover, replicate, euglycemic clamp study to compare the PK and PD of EU-approved LANTUS® to US-approved LANTUS®</p> <p>24 Healthy volunteers</p>	
<p>ABEB Phase 3, randomized, multinational, multicenter, 2-arm, active-control, open-label, parallel, 24-week treatment study with a 28-week active-controlled extension and 4-week post-treatment follow-up to compare BASAGLAR and LANTUS® when each was used in combination with mealtime insulin lispro</p> <p>535 Adults with type 1 diabetes</p>	
<p>ABEC Phase 3, randomized, multinational, multicenter, 2-arm, active-control, double-blind, parallel, 24-week treatment study with a 4-week post-treatment follow-up to compare BASAGLAR and LANTUS® when used in combination with at least 2 OAMs, in adult patients with T2DM</p> <p>756 Adults with type 1 diabetes</p>	
<ul style="list-style-type: none"> Safety: The primary safety data comes from the Phase 3 studies ABEB and ABEC. Immunogenicity was assessed as a 	<ul style="list-style-type: none"> Efficacy: randomized, double-blind, parallel-group, multi-center study of Zarxio® and US-licensed Neupogen® in histologically proven patients with breast cancer (192 patients) Safety / Immunogenicity: The patient population included 53 subjects randomized to treatment with EP2006, 52 subjects to treatment with US-licensed Neupogen®, and 109 subjects to treatment with both study agents in an alternating fashion.

Conclusion: According to the Basaglar® approval reviews, in the 505(b)(2) pathway the similar insulin is considered to be a small chemical substance; therefore, a thorough characterisation of “biosimilar” quality attributes such as structures, variants, product related impurities was not demanded; however, the Basaglar® approval dossier contained extensive PK/PD, efficacy and safety trials (up to 735 subjects).

According to the Zarxio® approval reviews in the section 351 pathway, the biosimilar is extensively compared to the RP by complex analytical tools in order to detect potential differences in quality attributes; however PK/PD, efficacy and safety trials seem to involve a lesser number of subjects.

Note that under the proposed biosimilar pathway, it is plausible that an efficacy study may not be required by the FDA if there is adequate demonstration of PK/PD similarity.

Therefore, the choice of the most convenient pathway relies on the ability of the applicant to manufacture the biosimilar insulin and the relative costs of CMC, non-clinical and clinical development.

3.3.3 MHLW

As in the European Union (EU), insulin is considered as a biologic in Japan. The first biosimilar of glargine (Lantus®) was introduced in Japan in January 2015 jointly by partners Eli Lilly and Boehringer Ingelheim. Biocon Ltd. is Asia’s largest insulin producer and has marketing approvals for rh-insulin in over 60 countries (Insugen® in India) and for glargine in over 20 countries (Basalog® in India). In order to enter a more regulated market, Biocon applied for its follow-on biologic (i.e. term used for biosimilar in Japan) with its partner Fujifilm Pharma Co. Ltd. and received approval in Q1 of 2016. The reimbursement price of Lantus® in Japan (set by NHI) was originally \$19.50. When Basalog® was marketed, the prices of Lantus® was set at \$15 and Basalog® at \$14.50.

Since the Japanese regulatory authorities have already inspected and approved Biocon’s manufacturing facilities for glargine and its state-of-the-art disposable pen assembly facility, Biocon is now developing glargine biosimilar for the other developed markets in collaboration with Mylan.

The Japanese Generic Medicines Association (JGA), the Nippon Keidanren (Japanese Industry Association), the European Generics Medicines Association (EGA) and the EU delegation to Japan met in March/April 2014 to promote regulatory cooperation on generics and biosimilars as part of the EU–Japan free trade negotiations. According to EGA, Japan and the EU share similar objectives to promote generics and biosimilars as key components of sustainable healthcare models. The association is therefore supporting efforts to improve regulatory cooperation in this field. In particular, they are focused on the single development for the approval of biosimilars and complex specialty generics to avoid the unethical duplication of clinical studies. While another area of importance is the mutual recognition of good manufacturing practice (GMP) inspections to reduce unnecessary duplication of inspections (38).

3.3.4 TGA

As per ARGB, insulin is not regulated as a biological but as a biological medicine regulated as therapeutic goods(8). However, abbreviated versions of biological medicines are evaluated as biosimilars.

For the evaluation of the glargine biosimilar, TGA used the following guidelines:

- a) Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (19). Draft guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues(39).
- b) Guideline on evaluation of biosimilars(9).
- c) Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues(28).
- d) Revised guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues (24).
- e) Guideline on the Investigation of bioequivalence(40).
- f) Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (25).

Abasria® (name later changed to Basaglar® in Australia) was approved by TGA on November 10, 2014. Eli Lilly demonstrated the similarity of Basaglar® to EU and US-approved Lantus®. Comparative PK and PD studies demonstrated high similarity within predefined bioequivalence acceptance limits. During the evaluation period of the Basaglar® application by TGA, Eli Lilly received approval for the same product in the EU from the EMA – since TGA follows EMA guidelines this may have influenced the assessment (NB: at the same time, it was under consideration by the US FDA). Since, most of the guidelines to evaluate Basaglar® similarity to Lantus® were adopted from EMA, most of the data generated using EU-approved Lantus® was produced to compare similarity with Basaglar®. In certain cases, US-approved Lantus® was also used as a RP. However, a bridge study between Australian and EU and/or US sourced Lantus® was performed to show their comparability and identicalness.

When a medicine is approved for supply in Australia it is not automatically included in the Government subsidy scheme known as the Pharmaceutical Benefits Scheme (PBS). In order for a medicine to be listed on the PBS a sponsor (usually a pharmaceutical company) must apply to the Pharmaceutical Benefits Advisory Committee (PBAC). PBAC has listed Lantus® in the country's Pharmaceutical Benefits Scheme (PBS) that allows patients to obtain Lantus® at a subsidised cost; thus, the launch of a biosimilar will help to lower the burden on the Australian government. At its March 2015 meeting, PBAC recommended the listing of Basaglar® on the PBS [41]. To-date, Lilly has chosen not to proceed with this listing. Basaglar® remains available to Australians but only via private (non-PBS) prescription where the cost is set by the supplier (i.e. Lilly). PBAC wants to give 'a' flagging to Basaglar® and so permit substitution between Lantus® and Basaglar® at pharmacy level because in two clinical trials approximately 81 percent and 41 percent of patients receiving Lantus® were switched to Basaglar® [41, 42]. However, Lilly's view is that interchangeability was not demonstrated in the clinical studies and as a result there is uncertainty associated with patients being switched back and forth between products. Furthermore, Lilly found a difference in maximum doses delivered between disposable pens and the potential for mismatch between cartridge and reusable pen, thus they maintained that substitution was not possible (43,44) . Hence, it is a "wait and see" situation over the listing of Basaglar® with respect to the PBS. So far, 'a' flagging has been given to a biosimilar of infliximab, 'Inflixtra®(45).

For comparison, in the US the decision on substitution is taken by the individual states but for that to occur a biosimilar should be already approved as interchangeable by the Biologics Price Competition and Innovation Act (BPCIA) (46). In the EU it is regulated at the national level(47).

3.3.5 SFDA

In 2008, a consensus group meeting recommended to follow the EMA guidelines for the registration of biosimilars (48). The eCTD is mandatory as of January 3, 2015 for human

medicine applications (49). SFDA [guidelines on biosimilars](#) are based on EMA and ICH recommendations and also cover insulins (6).

3.3.6 Discussion

Overall guidelines concerning the authorisation of biosimilars in the EU and USA are similar: both EMA and FDA agree that the marketing of these at reduced cost would benefit patients and healthcare-systems; however, due to the physicochemical complexity of these medicines and their biological origin, a thorough comparison with the RP is needed.

With respect to the approval of insulins there is currently a major divergence of FDA and EMA regulatory pathways.

Indeed, whereas EMA provides extensive guidelines for the approval of insulins as biosimilars, currently in the USA, insulins do not need to be approved via the biosimilar pathway (licensed under 351(k) of the PHS Act). A submission under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) is demanded. The reason for this is that insulins are not yet licensed as biologicals, meaning that there is no biological RP licensed under the PHS Act. (16)

However, in the constantly evolving world of regulatory pathways there is a trend towards the harmonisation of guidelines (ICH guidelines, EMA/FDA collaborations (i.e. EMA/FDA efforts towards regulatory harmonisation in the Transatlantic Trade and Investment Partnership).[50] Therefore, “As of March 23, 2020, an application for a biological product approved under section 505 of the FD&C Act will be deemed a biologics license application (“BLA”) licensed under section 351 of the PHS Act.” (33,35).

Sponsors applying before 2020 will benefit from the 505(b)(2) pathway where less physicochemical data is needed; however, clinical efficacy and safety need to be thoroughly demonstrated.

Sponsors applying after 2020 will need to collect all necessary data to be able to demonstrate the physicochemical similarity of the insulin and the RP as FDA biosimilar guidelines will apply and any additional studies will depend on the remaining “residual uncertainties”.

3.4 WHO Guidelines

The WHO has no licensing activity. The intention of the WHO SBPs guidelines (11) is to provide:

“Globally acceptable principles for licensing biotherapeutic products that are claimed to be similar to biotherapeutic products of assured quality, safety, and efficacy that have been licensed based on a full licensing dossier. This 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 of these products.”

However, the WHO has a Prequalification (PQ) programme that aims to ensure that diagnostics, medicines, vaccines and immunisation-related equipment and devices for high burden diseases meet global standards of quality, safety and efficacy, in order to optimise use of health resources and improve health outcomes (51) . However, at present these high burden diseases do not include non-communicable diseases such as diabetes.

3.5 EMA-WHO: Article 58 Application - An Alternative Pathway?

Since insulin access is a major problem in markets outside developed countries, the Article 58 pathway could also be of interest.

Article 58 of the EC Regulation N° 726/2004 states that:

“The Agency may give a scientific opinion, in the context of cooperation with the World Health Organization, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community.”(52)

Thus, the aim of this pathway is to:

“help address public health challenges existing in low and middle income countries (LMICs) by providing a mechanism through which scientific and manufacturing expertise could be provided to manufacturers, the WHO, NRAs from LMICs, and the broader global health community regarding development and assessment of products intended to be marketed outside the EU and in LMICs.”(53)

Ten years after the introduction of the Article 58 pathway EMA, the European Commission and the Bill & Melinda Gates Foundation studied the awareness, experience and views of different stakeholders on the procedure.(54)

It appears that this pathway is not as widely used as expected and only 8 products have received a positive opinion so far:

- Antiretrovirals - lopinavir + ritonavir (Aluvia; AbbVie)
 - lamivudine and lamivudine/zidovudine (EpiVir/3TC and Combivir, ViiV)
- Hexavalent vaccine against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and Haemophilus influenzae type b (Hexaxim, Sanofi)
- Quadrivalent vaccine against diphtheria, tetanus, pertussis and hepatitis B (Tritanrix, GSK)
- Misoprostol for postpartum hemorrhage; (Hemoproston, Linepharma)
- Pyronaridine / artesunate anti-malarial (Pyramax, Shin Poong)
- Recombinant malaria/Hep B vaccine (Mosquirix, GSK)

Example of the regulatory history of Hexaxim, Sanofi (Figure 4).

Figure 4. Regulatory history of Hexaxim, Sanofi. Adapted from (54).



The main reasons for this limited success are thought to be due to:

- Lack of successful precedents
- Prohibitive fees
- Unawareness of the NRAs of the Article 58 pathway or consideration as a lower grade review since it does not give access to the EU market

- Slow pace of approval by NRA's
- Poor coordination between EMA and WHO (54)

EMA is currently working on strategies to promote the use of the Article 58 pathway.

Despite the absence of precedent cases, the Article 58 pathway is probably applicable to the approval of biosimilar insulins to be marketed outside EU. Nevertheless, the quality, safety and efficacy of the product have still to be proven. For instance, the recombinant vaccine (Mosquirix, GSK) dossier contained extensive data proving the quality; non-clinical and clinical safety and efficacy,(55) leading to the conclusion that a similar insulin manufacturer would still need to provide a full dossier to the EMA. Furthermore, no other biosimilar has been approved under this pathway so it is not known if the comparability exercise needs to be implemented.

If the applicant has no interest in marketing their biosimilar insulin in the EU, then the Article 58 pathway may provide an interesting mechanism for gaining approval. A scientific discussion with the EMA may be useful.

4. What this Means

Proving the similarity of a biosimilar to the RP is scientifically challenging and several different studies are potentially required in order to obtain approval of the biosimilar in a highly regulated market.

With respect to insulin, the introduction of new “improved” insulin products to the market – be they new formulations or new analogues – and the concomitant patent protection (and extension thereof) have prevented generic competition in highly regulated regions. As mentioned above, the first glargine biosimilar was only introduced in Japan and Australia last year. In less stringent regulatory environments, e.g. India, China, and Mexico, several biosimilar insulins have already been introduced at lower prices (56,57).

There are several issues that biosimilar pharma companies might consider:

- a) Upon the launch of a new insulin product, the parent company lowers the price of its existing product. This means that a biosimilar company has to compete in price with the existing reference form and also with the new “improved” product which may have improved efficacy or be more patient friendly. An example is the launch of Toujeo® after the expiry of Lantus® patent and launch of Lilly’s Basaglar®.
- b) Today, in high-income countries, animal sourced insulin has disappeared and there is a decline in the use of human insulin (virtually the only insulin formulation available in 1999). Over the past decade, we have seen a dramatic growth in the use of insulin analogues in high-income countries(58). Older insulin products have not been able to compete (i.e. generate sufficient sales) with the new analogue products. Therefore, it was not commercially worthwhile for biosimilar companies to invest in the good manufacturing practice facilities required to produce these “patent unprotected” but effectively “obsolete” insulins that had been superseded by new insulin products in these high income countries. Now that the patents of the insulin analogues are expiring and fewer insulin products are on the horizon, there is more serious interest to develop biosimilar insulin analogues as evidenced by the recently approved glargine biosimilars.
- c) Unlike generics, the biosimilars are launched at a price that is, at most, only 20-40 percent lower than the RP. Development of a biosimilar requires a lot of investment and furthermore, sometimes the patients have to remain under the company’s pharmacovigilance program to monitor any chance of immunogenic reaction even after the product’s launch – an additional cost burden(59,60).

- d) Insulin is a parenteral formulation that has to be stored in heavy glass containers under refrigeration and the cold-chain respected during transit. This makes an expensive shipping and distribution process, perhaps more than the manufacturing cost. Such prohibitive costs could certainly be effective barriers to entry and discourage traditional biosimilar companies(61).

It is important to note that the demand for insulin is increasing; in the past it was mostly type 1 diabetics that received insulin, now it is also being prescribed to type 2 patients(62). With the development of clearer guidelines for biosimilars and guidelines specific to insulin, it should be easier to apply for a biosimilar in EU and other EMA-following countries. These guidelines can also be used, to some extent, for the US market and in the future FDA may implement similar guidelines specific to insulin. As of now, at least one biosimilar of insulin is already available in each of the highly regulated markets. Therefore, a proper case study can be carried out on how to develop a biosimilar in a cost effective manner.

An advantage for insulin is that it is an “old” molecule and much is known about its production, structure and characterisation. Therefore, it might be easier to demonstrate the quality, safety and efficacy by *in vitro* methods and compare PK/PD parameters with RP using a smaller number of patients, which could reduce the cost and time.

5. Conclusions

The overall process of biosimilar product approval remains demanding: it requires substantially more data to demonstrate quality, efficacy and safety than would be required for a simple generic medicine.

An insulin manufacturer applying via a biosimilar pathway to any of the above-mentioned authorities will have to provide evidence of the quality, clinical efficacy and safety of the proposed product.

The main difficulty remains in the manufacturing of a biological molecule that is similar to the RP with respect to its chemical structure, post-translational modifications, presence of variants, impurity profile, physicochemical properties, stability and other parameters. A full process and product development, fulfilling high quality standards is required. State-of-the-art orthogonal analytical methods have to be used to detect similarity and differences, not to mention that the use of living organisms for the production of the medicine *per se* brings a high level of variability. All of this has to be done without access to the proprietary know-how of the RP manufacturer. Consequently, the manufacturer of the biosimilar can only use powerful analytical tools to characterise the RP available on the market and so develop a biosimilar product that has to match all of the quality attributes of the RP.

Nevertheless, the effort and money invested in a thorough CMC development and the demonstration of similarity at the physicochemical level can be recovered by the avoidance of additional non-clinical and clinical studies.

For now, it would seem easier to apply for approval from EMA and EMA-following countries since the guidelines are clearer, but in a context of policy harmonization it is probable that the FDA will implement similar specific insulin guidelines to the EMA. Until 2020, the approval of a similar insulins by the FDA is possible via the 505(b)(2) pathway. Given the lack of precedents, the suitability of the Article 58 pathway for the approval of insulins which are to be marketed outside Europe / in LMICs is unclear but may be worth pursuing.

Another detail concerning insulin administration that is frequently overlooked is the patenting/approval of the injection device; however, this subject is outside the scope of the present report, moreover insulin can still be provided in vials and injected with a syringe(63).

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Annex II

Case Study: Applications to the European Medicines Agency of Marvel Life Sciences' Biosimilar Insulin Versus Eli Lilly and Company Biosimilar Insulin

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Abstract

In EU countries, applications for marketing approval of insulin are reviewed by the European Medicines Agency (EMA). To better understand the process for biosimilar insulin, applications for six biosimilar human insulins manufactured by Marvel Life Sciences Ltd (Marvel Life Sciences) (which were unsuccessful despite three submissions) were compared with the application for biosimilar glargine manufactured by Eli Lilly and Company (Eli Lilly) (successful on the first submission). The purpose of comparing these applications was to identify what was appreciated by the EMA and what was problematic, to inform future applications for companies seeking marketing authorisation for biosimilar insulin in Europe.

Acronyms

AHO	Animal or human origin
CHMP	Committee for Medicinal Products for Human Use
Eli Lilly	Eli Lilly and Company
EMA	European Medicines Agency
EPAR	European Public Assessment Reports
EU	European Union
Marvel Life Sciences	Marvel Life Sciences Ltd
PD	Pharmacodynamics
PK	Pharmacokinetic
RMP	Referential medicinal product

Term Glossary

Major Objections - *“Major objections”, preclude a recommendation for marketing authorisation.*

Other Concerns *“Other concerns”, may affect the proposed conditions for marketing authorisation and product information.*

1. Regulatory Considerations

Insulin is relatively easier to characterise and control from a quality perspective compared to many other recombinant proteins such as those that have a high degree of post-translational heterogeneity (e.g. glycosylated proteins). Recombinant insulin can be produced by bacterial or yeast fermentation thus reducing risks around potential transmission of adventitious agents. Therefore, in general, an insulin manufacturing process does not have to be developed in order to demonstrate clearance of such agents. If materials of animal or human origin (AHO) are used upstream, then the implications are relatively reduced compared to the situation where mammalian cell substrates are used. All this would point towards insulin, on the basis of technology and complexity, being a relatively good candidate for a biosimilar company to develop.

However, European regulatory experience with biosimilar insulins is not as extensive as has been the case for other biosimilar biotech proteins for which several biosimilars have been authorised (e.g. filgrastim, epoetin).

Fewer biosimilar insulin agency scientific advice procedures (EMA and also nationally at member state level) have taken place compared to that for other potential biosimilar proteins (e.g. filgrastim, etanercept) and especially the biosimilar monoclonal antibodies (e.g. infliximab, trastuzumab, rituximab). Such advice procedures are used to discuss and agree on product development programmes with prospective reviewers. This likely reflects that fewer developers are pursuing European Union (EU) registration of biosimilar insulin products compared to other recombinant products. It may also reflect that some developers are underestimating the complexity of the development and registration of insulin products and therefore not seeking timely scientific advice from EU regulators. The knock-on effect of this is also that EU regulators have not been exposed to a wide panel of biosimilar insulin programmes and so are less able to provide ‘mature’ or ‘precedent-based’ advice and feedback to Industry. It is more ‘case-by-case’ until regulatory experience grows. Another major complication for biosimilar insulins is that apart from ensuring similarity at the level of the active moiety, there is an additional hurdle in that insulin formulations in many cases are more complex than many other regular biotech proteins; many have modified release characteristics which are critical for patient safety and also efficacy. On the flip side, a developer for an insulin product benefits from a very well accepted pharmacodynamic surrogate for efficacy, which aids the clinical development programme.

Notably, in terms of actual EU insulin biosimilar dossier submissions, there are two main programmes to be highlighted (see Table 1). Marvel Life Sciences has pursued EU registration, without success, for almost a decade in Europe with their proposed suite of

biosimilars to Eli Lilly's Humulin® S, Humulin® I and Humulin®M3. A number of separate fully developed applications for registration to the EMA were submitted in 2007, again in 2012, and then again in 2014. On the other hand, in 2013, Eli Lilly Regional Operations GmbH was able to successfully register their version of Insulin Glargine (Lantus® Sanofi) on their very first submission. Lantus was originally developed by Sanofi and has gained substantial market share in the insulin analogue market. Eli Lilly is one of the “big three” insulin manufacturers. The production of a biosimilar form of insulin glargine by Eli Lilly was subject to substantial litigation and a final agreement between the two companies. The Eli Lilly insulin glargine product was originally named Abasria and is now approved for marketing as Abasaglar®.

2. Methodology and Results

European Public Assessment reports (EPARs) are available for all these insulin submissions, published by the EMA, from which confidential information and detail is removed, but still provides some transparency into the review of the dossiers. These are available for both the Marvel Life Sciences' insulins and Eli Lilly's insulin (reference 8 EPARs)

We have performed an analysis of these EPARs to establish the main strengths and weaknesses for these dossiers:

- Table 1 for a high level overview of differences/similarities in EU biosimilar market authorisation applications
 - Table 2 and 3 for analysis of quality dossier deficiencies
 - Table 4 and Table 5 for the quality biosimilarity analysis
 - Table 6 and 7 for biosimilarity analysis of non-clinical and clinical reviews for these dossiers.
 - Table 8: Details on clinical studies conducted in the Abasria® programme.
- Composition and other information

When considering the composition of the Marvel Life Sciences' insulins versus the Eli Lilly Insulin (Table 1), the first observation could be that the Marvel insulins were actually identical to the reference medicinal product (RMP) from a composition perspective. For the Eli Lilly insulin, the Committee for Medicinal Products for Human Use (CHMP) noted that a minor difference in the excipients existed but was this was not considered a barrier for the ultimate approval for this application. With respect to the cell substrate used for production these were the same as for the respective RMP for both Marvel Life Sciences and Eli Lilly applications.

It should also be noted that both programmes (Eli Lilly and Marvel Life Sciences) sought CHMP scientific advice – but that it is difficult to ascertain from the EPAR the exact topics/questions for the consultation, whether the advices were conducted early enough in the development programme to make relevant changes, and whether the CHMP advice was followed (for the Eli Lilly application, CHMP did state that the advice was broadly followed).

Table 1. Overview of EU biosimilar insulin marketing authorisation applications.

Product	Insulin Human Rapid Marvel 100iU/mL	Insulin Human Long Marvel 100iU/mL	Insulin Human 30/70 Mix Marvel 100iU/mL	Solumarv 100iU/mL	Isomarv medium 100iu/mL	Combimarv 100iu/mL	Solumarv 100iU/mL	Abasria (LY2963016) (now Abasaglar)
Date of Submission to EMA	2007	2007	2007	2012	2012	2012	2014	2013
Applicant	Marvel Life Sciences Ltd			Marvel Life Sciences Ltd			Marvel Life Sciences Ltd	Eli Lilly Regional Operations GmbH
Legal basis	Art 10 (4) of Directive 2001/83/EC							
Active substance	Insulin human			Insulin human			Insulin human	Insulin Glargine
Excipients	Identical to RMP	Identical to RMP	Identical to RMP	Identical to RMP	Identical to RMP	Identical to RMP	Identical to RMP	Similar to RMP. Zinc oxide (biosimilar) is used instead of zinc chloride (RMP). [However, this is chemically converted to zinc chloride by dissolving it in excess 10% hydrochloric acid before its addition to the formulation solution]. 100% glycerol (biosimilar) is used instead of 85% glycerol (RMP). Finally levels of glycerol in both products are the same. CHMP accepted that these were 'minor differences'
Cell substrate	Same as RMP (E.coli)			Same as RMP (E.coli)			Same as RMP (E.coli)	Same as RMP (E.coli)
Primary amino acid sequence versus RMP	Identical			Identical			Identical	Identical

Pharmaceutical form and strength (versus RMP)	Identical			Identical			Identical	Identical
Selection of RMP	Humulin S 100iu/mL (Eli Lilly and Co Ltd)	Humulin I 100iu/mL (Eli Lilly and Co Ltd)	Humulin M3 (Eli Lilly and Co Ltd)	Humulin S 100iu/mL (Eli Lilly and Co Ltd)	Humulin I 100iu/mL (Eli Lilly and Co Ltd)	Humulin M3 (Eli Lilly and Co Ltd)	Humulin S 100iu/mL (Eli Lilly and Co Ltd)	Lantus (Sanofi)
Indication	“the treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis and for the initial control of diabetes mellitus and diabetes mellitus in pregnancy”			“treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis”.			“treatment of patients with diabetes mellitus who require insulin for the maintenance of glucose homeostasis”.	“Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.”
CHMP or National Agency Scientific Advice	Yes (National advices from Finland, The Netherlands and Sweden)			Yes (CHMP advice in 2008 and 2010)– after withdrawal of 2007 submission.			Yes (CHMP advice in July 2008, December 2008, February 2011 and April 2013). It is stated that the Scientific Advice pertained to non-clinical and clinical aspects of the dossier.	Yes – (CHMP advice in 2011 (quality, non-clinical and clinical)) CHMP comment was that advice was broadly followed.
Information pertaining to manufacturers	Active substance stated to be manufactured by a third party – further information not given. For one of the submitted PK studies, the test product (drug product) ‘manufacturer and Supplier [is] BIOTON Sp. Z o.o., Poland’. This is deduced from the EPAR of the 2014 Marvel submissions wherein this manufacturer is stated for the same pharmacokinetic study as included in this 2007 application.			For one of the submitted PK studies, the test product (drug product) ‘manufacturer and Supplier [is] BIOTON Sp. Z o.o., Poland’. This is deduced from the EPAR of the 2014 Marvel submissions wherein this manufacturer is stated for the same pharmacokinetic study as included in this 2012 application.			One active substance manufacturer is in France. The EPAR states that ‘the active substance...is manufactured at two EU contract manufacturers by means of an upstream and a downstream process’. For one of the submitted PK studies, it is also stated that the test product ‘manufacturer and Supplier [is] BIOTON Sp. Z o.o.,	Active substance: - Lilly del Caribe, Inc. 12.3 km 65th Infantry Road Carolina, PR 00985 Puerto Rico - Eli Lilly and Company Indianapolis Indiana 46285 USA Finished product: Cartridges: Lilly France

			Poland’.	Vials: Lilly Indianapolis The use of a Contract manufacturer for finished product, in USA, is also noted in the Epar.
Product licenced in any other country	Not stated	Applicant states it is marketed in 20 countries – no further information is provided in the EPAR so it is not possible to identify the countries from the EPAR.	No. [This statement contradicts the same statement made in the EPAR for the 2012 Solumarv application but no further explanation is given].	No.

➤ Drug substance quality

The comparison of the CHMP evaluation for the drug substance, as discussed in the EPARs, has been made by the author and is reported in Table 2. The main findings are summarised below:

1. For both the 2012 and 2014 Marvel Life Sciences applications, and also the 2013 Eli Lilly application, the CHMP was satisfied with the production, control and quality of the cell banks established for the ongoing production of the insulin. The EPAR for the 2007 Marvel Life Sciences application did not mention the adequacy of the cell banks so this could not be concluded unambiguously by the author but the aspect was potentially acceptable as there was no other comment made in the EPAR.
2. As for conventional biological products, particular focus should be given to the description of the manufacturing process and controls. Major Objections were raised for the 2007 Marvel Life Sciences applications but not for the 2012 Marvel Life Sciences applications (except for one objection on the proposal for reprocessing). However, for the 2014 Marvel Life Sciences application for Solumarv, the CHMP raised a Major Objection on all aspects again; the EPAR did not explain what exactly differed from the 2012 application for Solumarv.
3. The comparability of the manufacturing process over non-clinical and clinical batches through to proposed commercial batches should be well documented and demonstrated. The Eli Lilly application met this requirement, whereas the Marvel Life Sciences application failed to do so in their 2014 application – resulting in a major objection on their application.
4. Insufficient attention to the characterisation of insulin impurities can lead to a major objection – as was the case for the Marvel Life Sciences applications, unlike the Eli Lilly application. Other characterisation results for both the Marvel Life Sciences and Eli Lilly insulin applications seemed to meet regulatory requirements.
5. Solely meeting Ph.Eur monograph requirements regarding controls is insufficient – it needs to be assessed by a company which additional controls might be required due to the quality of the specific product and process. The 2012 Marvel Life Sciences applications were challenged with a major objection because of inadequacy in control of product related impurities. By 2014, Marvel Life Sciences had improved their testing strategy and it was overall considered acceptable with a few ‘other concerns’ (no major objections) for Solumarv.
6. The CHMP accepted the process validation studies for the Eli Lilly application whereas none of the Marvel Life Sciences application’s met the relevant EU regulatory expectations and this was raised as major objection for each of these applications (2007, 2012, and 2014).
7. No major objections were raised on the stability sections (for drug substance) for either the Marvel Life Sciences or Eli Lilly applications.

Table 2. Adequacy of drug substance quality dossier sections for EU biosimilar insulin applications.

				Drug Substance				
	Insulin Human Rapid Marvel 100iU/mL	Insulin Human Long Marvel 100iU/mL	Insulin Human 30/70 Mix Marvel 100iU/mL	Solumarv 100iU/mL (2012)	Isomarv medium 100iu/mL	Combimar v 100iu/mL	Solumarv 100iU/mL (2014)	Abasria (LY2963016) (now Abasaglar)
Production of cell banks, quality and control	Adequacy of sections not mentioned.			Adequate information is provided for the generation of the producer cell, the master cell bank (MCB) and subsequently the working cell bank (WCB). For testing of MCB and WCB satisfactory results were achieved. The stability of cells is further verified by analysis of end of production-cells. The Company has adequately described the preparation of a future WCB.			The description of the construction of the insulin expression plasmid is considered satisfactory. Adequate information is provided for the generation of the producer cell, the master cell bank (MCB) and subsequently the working cell bank (WCB). For testing of MCB and WCB satisfactory results were achieved. Stability of the cell substrate was not considered adequately analysed in accordance with ICH Q5D. This remains an outstanding issue at the time of the negative opinion of the application.	The development of the transformed host strain and construction and control of the working and master cell banks is considered adequate.
Description of manufacturing process and controls for the drug substance	The provided description of the fermentation and recovery/purification process is not detailed and contains incomplete information about the process. Fermentation controls, the limits set and their justification are not or barely addressed. All critical process parameters and action limits			Manufacturing process controls and the respective acceptance criteria and acceptance ranges have been provided (CHMP did not raise any major objection on this aspect). A major objection has been raised with respect to reprocessing of the			A major objection was raised on this section: “the description of the manufacturing process, which contains contradictory information on the fermentation process, pooling procedure, reprocessing of non-complying RP-HPLC side-fractions and blending of batches. Reprocessing of undefined, not-complying RP-	The manufacturing process is well described, and in general the process controls are appropriate.

	<p>should be added to each step. For the purification process details are lacking for in-process controls and action limits (tolerance limits), pH adjustments, titres, chromatographic media and processes, splitting/pooling steps, holding times/storage times, all potential intermediates and their justification. Since the process is by no means 'fixed' in the dossier, major objections have been raised on the descriptions of the DS manufacturing.</p>	<p>manufacturing process.</p>	<p>HPLC side-fractions and blending and homogenisation of batches are not acceptable and need to be removed from the process and the dossier”.</p>	
<p>Comparability over the development of the manufacturing process for the drug substance</p>	<p>No batch traceability is given in the dossier.</p>	<p>Not mentioned.</p>	<p>A major objection was raised on this section: relating to “the comparability of Solumarv product used for nonclinical and clinical studies with the commercial product that has not been established. The applicant has failed to identify and document process history. The manufacturing processes differ with regards to fermentation scale, origin of enzymes, pooling and blending procedures, for example. Information on the distinct differences between the manufacturing processes used to generate material for nonclinical and clinical studies and the proposed commercial active substance manufacturing process have not been provided and the applicant has not evaluate process changes in line with ICH Q5E requirements. A science based risk assessment on the changes</p>	<p>Several active substance manufacturing processes have been utilised throughout LY2963016 development.</p> <p>On the whole, comparability between clinically qualified material and proposed commercial material was demonstrated using extensive characterisation of active substance and finished product batches. Additional structural characterization data have been provided, with tests performed directly on active substance batches and some tests performed on finished product batches manufactured using active substance from the two processes and representing both finished product sites (contract manufacturer, USA and Lilly, France).</p> <p>Comparability was demonstrated for primary structure, secondary structure, tertiary structure and quaternary structure. Stability data under both long term and accelerated conditions was</p>

			implemented during the manufacturing process history has not been presented. In addition, the impact of the process changes on the impurity pattern including the Solumarv specific insulin variants has not been demonstrated. Representativeness of materials used for characterisation, justification of specification and stability for the commercial material is also questioned. Hence the commercial active substance material cannot be confirmed to be representative for the active substance material used in nonclinical and clinical studies”.	also provided to support the comparability.
Characterisation	Some characterisation data was presented in the dossier. A single batch was compared to recombinant human insulin isolated from a reference product (Humulin Regular Lilly 100, batch Z33319 EU sourcing unconfirmed) and three reference human insulins (USP Insulin human RS, Ph Eur human insulin. It has not been demonstrated that this batch is fully representative for the current commercial production process. Characterisation studies included amino acid analysis, amino acid sequence, circular dichroism, X-ray crystallography, Iso Electric Focusing (IEF), SDS-PAGE, 1H-NMR (1D) spectra, Fourier Transform Infrared Spectroscopy (FT-IR) and no significant differences were found	<p>Characterisation studies were performed with one drug substance batch. The primary, secondary and tertiary structure of insulin was studied in comparison to the Ph.Eur. CRS, the USP reference material and an in-house standard. By using a variety of adequate methods the correct amino acid composition and sequence, a similar distribution of the secondary structures, an accurate molecular mass for the intact protein as well as for the two chains A and B and an accurate secondary and tertiary structure was confirmed for the recombinant insulin human. The isoelectric point was determined.</p> <p>No impurities of different size (e.g. aggregates) could be detected in the insulin samples when tested by SDS-PAGE under reducing conditions.</p>	<p>A first characterisation study was executed with one active substance batch in comparison to the Ph.Eur. insulin reference standard (CRS), the USP reference material and an in-house standard.</p> <p>An additional comparability study on structural characteristics of insulin was conducted using retained samples of different manufacturing process development stages. The results confirm similarity of the primary, secondary and tertiary structure of the insulin.</p> <p>In addition to the known insulin product related species and degradation products there are</p>	<p>The structure of LY2963016 has been elucidated through detailed structural characterization of the primary reference standard and a commercial-scale finished product demonstration batch. Consistency with the expected LY2963016 amino acid sequence has been demonstrated. Higher order structural characterization has been demonstrated. Additional structural characterization data and biological potency data have been provided, with tests performed directly on active substance batches and some tests performed on finished product batches manufactured using active substance from the two processes and representing both finished product sites (contract manufacturer, USA and Lilly, France).</p> <p>The biological activity has been</p>

	<p>between the tested recombinant human insulins.</p> <p>The comparative investigation of related impurities/compounds is not sufficient to draw the conclusion that the purity of insulin Drug Substance is comparable to Lilly insulin.</p>	<p>Analysing the same samples by use of SEC combined with DLS detection resulted in a distinct peak of aggregates.</p> <p>No forced degradation studies were performed in order to examine the impact of degradation on the impurity profile of insulin human. However, by using a modified RP-HPLC method a detailed impurity profile of insulin human could be obtained including product related substances.</p> <p>It is considered essential to control the product related impurities specific for insulin human through individual specification limits and using an adequate analytical method. This is reflected in a Major Objection.</p>	<p>two insulin variants present only in Solumarv. The exact amount of these variants in a commercial batch is uncertain. This was due to inadequate bridging between analytical methods used over development for these two impurities and the issue was raised as a major objection.</p>	<p>characterised utilising several physiologically relevant assays. LY2963016 related impurities that are seen in the final active substance were isolated and characterised.</p>
<p>Specification for the drug substance</p>	<p>Adequacy not mentioned.</p>	<p>The specification is based on the Ph Eur requirements and lacks justification of the acceptance criteria in terms of manufacturing experience and levels used in the clinical trials and the comparability exercise which is a requirement of ICH Q6B and "Guideline on similar biological medicinal products containing Biotechnology-derived proteins as active substance: quality issues (EMA/CHMP/BWP/49348/2005). However, control of drug substance in compliance with the Ph Eur Monograph is not considered sufficient in itself.</p> <p>Product-related impurities specific for the manufacturing process should be specified with a reasonable acceptance</p>	<p>For the active substance a set of specifications has been provided which includes testing of identity by RP-HPLC and peptide map, solubility characteristics, purity by determination of high molecular mass proteins (SE-HPLC) and related substances (A21-desamido, others total by RP-HPLC), single chain precursor content, determination of sulphated ash, loss on drying, Zinc, host cell proteins and endotoxins. This set of specifications is in compliance with the Ph. Eur. monograph.</p> <p>Additionally, appearance and colour, visible impurities, assay RP-HPLC (as such) and assay RP-</p>	<p>The control tests proposed for the active substance are considered appropriate to ensure sufficient quality with respect to identity, purity/impurities, potency and safety (microbial).</p> <p>The potency assay is an HPLC method. The method has demonstrated specificity for LY2963016. The specification limit is consistent with the specification for total impurities and allows for assay variability. The assay quantifies mg of LY2963016 per mg of total solid and is corrected for any volatiles that may be present via the LOD method. The proposed limit is aligned with the human insulin active substance compendial and registered</p>

		<p>limit and using an appropriate analytical method. This constitutes a Major Objection.</p>	<p>HPLC (on dried substance), related substance including, microbial quality (TAMC) and content of residual solvent are specified. The test methods comply with the methods described in the Ph. Eur. monograph for insulin human, except for determination of certain impurities and related substances.</p> <p>Determination of a particular process-related impurity is not included in the active substance specification. This has been sufficiently justified by data. The active substance specifications still need some amendment in particular with regards to the implementation of acceptance criteria for purity determination performed by SE-HPLC and all applied HPLCs.</p>	<p>limits.</p> <p>The bioidentity method for LY2963016 is a cell-based reporter gene assay.</p> <p>The analytical procedures used to characterise and control LY2963016 quality are generally appropriate and validated.</p>
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<p>Validation of the manufacturing process for the drug substance</p>	<p>The information provided on the process validation for the fermentation and the purification processes, including the removal of process related impurities, is too limited and insufficient for assessment of the performance, robustness and consistency of the process. Relevant details are lacking, including filter and column materials used during downstream processing. Full validation data in accordance with the guideline ICH M4Q should be supplied.</p> <p>No batch traceability is given in the dossier.</p>	<p>Validation data for the fermentation process has been presented using three validation batches and presenting data of additional batches manufactured according to the proposed manufacturing process. Validation data for the purification process focus on the presentation of performance of few distinct manufacturing steps only. Only a few acceptance criteria have been reported and due to the lack of acceptance criteria for the process parameters presented, the discussion of the results is of limited value. The average release data leads to the conclusion that the drug substance complies with the proposed release specification. However, validation of the manufacturing process cannot rely on compliance with the release specification alone. Consequently reproducibility and robustness of the proposed manufacturing process is not considered demonstrated. This was raised as a major objection.</p>	<p>A major objection was raised on this section: Process validation data have been provided from a manufacturing process, which has not been clearly identified and documented. Prospective process validation data only cover the upstream process but do not include operational parameters for fermentation, harvest and recovery. Retrospective process validation data for the processes are considered insufficient to reflect splitting, pooling and blending of the maximum defined batches and batch traceability as proposed for the commercial process. Thus, adequate process validation data covering the intended commercial manufacturing process remain to be generated to demonstrate reproducibility and robustness of the intended commercial active substance manufacturing process.</p> <p>Issues relating to virus validation for a number of raw materials were also raised during the assessment.</p>	<p>Batch data has been presented for multiple validation batches. Data from the validation batches, clinical batches and primary stability batches are all comparable.</p>
<p>Stability and shelf-life of the Drug Substance</p>	<p>DS: Slight trends of degradation (increase of RP-HPLC impurities) were visible at all tested temperature, but all values remained clearly within the specifications.</p>	<p>A number of 'other concerns' were sought by the CHMP. No major objection raised.</p>	<p>A number of 'other concerns' were sought by the CHMP. No major objection raised.</p>	<p>The stability data presented support the proposed shelf-life of 30 months at -10°C.</p>

➤ Drug product quality

The comparison of the CHMP evaluation for the drug product sections of the Marvel Life Sciences and Eli Lilly insulin applications, as discussed in the EPARs, is reported in Table 3. The main findings are summarised below:

1. Regarding the description of the manufacturing process and controls at the level of the drug product, Major Objections were not raised for the 2012 and 2014 Marvel Life Sciences applications, nor the Eli Lilly application. However, for the 2012 Marvel Life Sciences application for Combimarv and Isomarv, the CHMP raised some ‘other concerns’ relating to the control and characterisation of protamine crystals to ensure consistency between batches. This reflects the complexity of the drug product formulation for the modified release products for which the regulators are seeking a greater degree of control and characterisation over this part of the process.
2. Adequacy for the comparability of the manufacturing process for drug product over non-clinical and clinical batches through to proposed commercial batches is not specifically mentioned for either the Eli Lilly or 2014 Marvel Life Sciences application. In absence of any specific comment in the EPAR, the author assumes that the information provided in the applications were satisfactory. It appears that the CHMP also found the 2012 Marvel Life Sciences applications also acceptable in this regard.
3. Insufficient attention to the characterisation of insulin impurities can lead to a major objection – as was the case for the Marvel Life Sciences applications (leading to a major objection) unlike the Eli Lilly application. Other characterisation results for both the Marvel and Eli Lilly insulin applications seemed to meet regulatory requirements.
4. Regarding regulatory specifications for the drug product, the proposal in both the Marvel Life Sciences application for Solumarv in 2014 and the Eli Lilly application were considered acceptable overall. For Marvel Life Sciences, this was an improvement over the major objection raised in their 2012 applications on this aspect.
5. The CHMP accepted the process validation studies for both the Eli Lilly and 2014 Marvel Life Sciences application.
6. No major objections were raised on the stability sections (for drug product) for either the Marvel Life Sciences or Eli Lilly applications.
7. Details of the administration devices and their validation for use with the product have been given for both Marvel Life Sciences and Eli Lilly applications, with no major objections raised.

Table 3. Adequacy of drug product quality dossier sections for EU biosimilar insulin applications.

	Drug Product							
	Insulin Human Rapid Marvel 100iU/mL	Insulin Human Long Marvel 100iU/mL	Insulin Human 30/70 Mix Marvel 100iU/mL	Solumarv 100iU/mL (2012)	Isomarv medium 100iu/mL	Combimarv 100iu/mL	Solumarv 100iU/mL (2014)	Abasria (LY2963016) (now Abasaglar)
Description of manufacturing process and controls for the finished product	<p>The Drug Product manufacturing site is in EU (actual site not stated). Data from another Insulin product (which is also made at this site but from a different insulin Drug Substance) has been used throughout the dossier. This data cannot be considered as directly supporting the Marvel products and such background data should be presented in an appendix. None of the manufacturing process steps have been properly validated and the in-process controls have consequently not been verified as satisfactory.</p>			<p>No major objections were raised in this section.</p> <p>The manufacturing process consists of dissolving of the ingredients, mixing, pH adjustment, filtration and filling (including cartridge assembly, sealing and labeling) of the drug product. The procedures are conventional for this type of formulations.</p> <p>The manufacturing process has been adequately described.</p> <p>For Isomarv/Combimarv, the control of the formation of the insulin-protamine crystals is currently missing and should be included. Furthermore, although the isophane coefficient for each batch of protamine sulphate is routinely determined by use of a tritrimetric method the respective IPC is missing.</p> <p>For Isomarv/Combimarv, Due to the heterogeneous nature of protamine sulphate a consistent quality should be ensured for future batches and results from a number of batches showing that</p>	<p>No major objections were raised in this section.</p>	<p>The process is well described and a detailed risk assessment was carried out to assign critical, non-critical and operational parameters. The process is well controlled.</p>		

			ingredients consistently meet the requirements should be provided. In addition the applicant is requested to perform an extended physicochemical characterisation and based on the outcome of this, update the control of protamine sulphate as appropriate.		
Comparability over the development of the manufacturing process for the drug product	Adequacy not mentioned.	The source, quality and suitability of the protamine used to form the isophane crystals have not been demonstrated and the protamine reference material is not adequately described and qualified. Virtually no data, including how the isophane coefficient is determined and detailed characterisation of the crystal properties, are described in the pharmaceutical development. Neither is there any evidence that they are satisfactorily controlled during manufacture or in the specifications. This is required for determining the quality and consistency of the product even before biosimilarity is considered.	The production scale batches have been used in clinical studies, stability studies, validation studies, toxicity studies and comparability studies	Adequacy not mentioned.	Adequacy not mentioned.
Validation of the manufacturing process	The validation	The validation data provided for Marvel	Process validation has been provided based on data of three validation batches.	Process validation has been confirmed based on data of	The batch data presented are consistent on the whole for each

for the finished product	data provided for Marvel Rapid is significantly deficient. All key manufacturing steps require to be validated and in-process controls justified.	<p>Long is significantly deficient. All key manufacturing steps require to be validated and in-process controls justified. Key aspects of the isophane insulin production processes have not been addressed including solution preparation and mixing and aseptic preparation. There is no assurance that insulin-protamine crystal formation, (for Marvel mix, the production of the 30/70 mixture) processing, and filling of suspensions and inclusion of glass bead to the cartridge are adequately controlled.</p> <p>Details of formulation studies to determine the correct quantities of excipient to product an adequately stabilised 30/70 mix are absent.</p>	The three consecutive validation batches comply with the predefined in-process control acceptance criteria and the proposed release specification.	three commercial validation batches. The three consecutive validation batches comply with the predefined in-process control acceptance criteria and the proposed release specification.	manufacturing site, with data provided from process validation batches from both sites. Validation for components, equipment and aseptic processing is in place.
Device	The cartridge is intended for administration by a reusable device. The dose delivery properties from the cartridge when using a recommended device have not been addressed in the dossier.		The vendor and the brand name of a potential device are mentioned in the SPC. However, further information on this medical device is not presented. Issues remain in relation to the suitability of the pen device for the three Marvel drug products. A copy of the certification (CE), the indication of suitable needles for the pen system and considerations on	The finished product is administered after incorporating the cartridge into a re-usable pen. The brand name of the device is AdvaPen; the use of Solumarv cartridge with AdvaPen is	Details for the cartridge and pen-injector (KwikPen) have been provided. The pen assembly process validation strategy has been described and successful process validation gives assurance that these meet the required quality standards.

			how to prevent mix-up of different insulin preparations are missing.	indicated in SmPC section 6.5. The pen-injector, CE-marked Advapen, is intended for use with 3 mL insulin cartridges along with CE-marked Type A pen needles. The pen is designed to administer insulin doses in the range of 1 to 60 units, in increments of one unit. Dose accuracy test results are in compliance with the dose accuracy acceptance criteria according to ISO 11608-1:2012.	
Specification for the drug product	Minimal information has been supplied regarding the analytical procedures and the Human Insulin Reference Standards, for which the source, specifications and qualification procedures have not been provided. Some data from a different insulin product has been used to support batch release and stability data.	Specifications for the finished product do not take sufficient account of the physicochemical properties of the suspension formulations.	The drug product release and shelf-life specifications are mainly based on the Ph Eur monograph which is not considered to be in line with the requirements of ICH Q6B and the "Guideline on similar biological medicinal products containing Biotechnology-derived proteins as active substance: quality issues" (EMA/CHMP/BWP/49348/2005). The proposed acceptance criteria for the drug product specification should be established and justified based on analytical data obtained from batches used in non-clinical and/or clinical studies and data obtained from the biosimilar comparability exercise (quality, safety and efficacy). Taken this into account and given the results of batch data, results from stability and comparability studies, the proposed specification raises concerns. Tightening the limits, in particular of the insulin impurities is considered essential and	The finished product specification include tests for appearance, identity of the active substance and preservative (meta-cresol), High Molecular Weight Proteins (HMWP), related proteins, pH, extractable volume, total zinc, assay, meta-cresol content, sterility, bacterial endotoxins, and sub-visible particles. The proposed release and shelf life specifications are mainly based on the Ph. Eur. monograph (0854) but have tightened limits with respect to determination of HMWP, related proteins (desamido insulin, total proteins (without desamido insulin)), human insulin content and content of zinc. In addition, Ph. Eur.	The control tests proposed for the finished product are considered appropriate to ensure sufficient quality with respect to identity, purity/impurities, potency and safety (microbial).

			<p>this is being raised as a Major Objection.</p>	<p>procedures and specifications are included for fill volume, sub-visible particles, sterility and bacterial endotoxins.</p> <p>Furthermore, it was confirmed to establish an upper limit for the Extractable volume.</p>	
<p>Stability and shelf-life for the drug product</p>	<p>Stability data is inadequate and the material appropriateness of the material used unclear. The in- use stability studies for the Drug Product are also inadequate.</p>	<p>Final assessment not given - pending clarifications</p>	<p>Seven commercial scale batches and three validation batches were tested for storage at 5 °C for 36 months packaged in 3 mL cartridges proposed for marketing. Stability data from six batches stored at accelerated conditions (25°C) for 6 months is also available. All stability results obtained during 36 months of storage under long term conditions comply with the proposed finished product shelf life specification. The conditions used in the stability studies were in line with ICH requirements.</p>	<p>The proposed shelf life of 24 months at 5°C is supported by data. Stability studies are being conducted for 3 primary batches from each site according to ICH Q5C</p>	

➤ Quality biosimilarity exercise

The comparison of the CHMP evaluation for the quality biosimilarity exercise for the Marvel Life Sciences and Eli Lilly insulin applications, as discussed in the EPARs, is reported in Table 4 at the level of the drug substance and Table 5 at the level of drug product. The main findings are summarised below:

Drug substance

1. From the perspective of a quality biosimilarity exercise, the data comparing the biosimilar candidate versus the quality/impurity of the PhEur and USP standards were not meaningful or valid. It is the direct comparison to the RMP that is the valid test.
2. Information on purification/pretreatment of the insulin drug substance in order to prepare it for quality analysis is required in the submission, especially the demonstration of the validity of the purification/pre-treatment.

Drug Product

1. The biosimilarity exercise should pay particular focus to the time-action characteristics of the modified release preparations. Biosimilarity should be demonstrated in terms of the formulation, specifications, stability and delivery (for the cartridges). Comparability data of critical excipients such as protamine should be included.
2. Even if the total amount of impurities may be below the pharmacopoeial acceptance limit (NMT 2 percent) when applying the RP-HPLC method as described by the monograph, this is not sufficient to demonstrate biosimilarity. Importantly, the compendial method is stated to be not suitable to separate all relevant impurities specific to a particular product/process for the purposes of the biosimilarity exercise, and the CHMP recommends that a modified RP-HPLC method should be used.
3. Even if an additional impurity is detected in the biosimilar product but not in the RMP, justifications based on potential clinical implications could be accepted, as was the case for the Eli Lilly application. Also, for the Eli Lilly insulin, the assay results between indicate that the RMP was formulated to a slightly higher concentration, but this did not block approval of the application as this observation did not translate into consistent PK differences.
4. Forced degradation studies are necessary (in addition to the accelerated stability studies) in order to demonstrate comparative degradation profiles.
5. Detailed impurity analysis as part of the biosimilarity exercise and also for demonstration of equivalence through manufacturing process evolution, has been shown to be a critical assessment point. Therefore, adequately sensitive methods should be used as early as possible during development.
6. Sufficient number of batches sourced from the market of the proposed regulatory region should be enrolled in the biosimilarity exercise.

Table 4. Quality biosimilarity exercise: drug substance.

Product	Insulin Human Rapid Marvel 100iU/mL	Insulin Human Long Marvel 100iU/mL	Insulin Human 30/70 Mix Marvel 100iU/mL	Solumarv 100iU/mL (2012)	Isomarv medium 100iu/mL	Combimarv 100iu/mL	Solumarv 100iU/mL (2014)	Abasria (LY2963016) (now Abasaglar)
Quality biosimilarity exercise: drug substance	<p>The comparability exercise on the level of the drug substance consists of a comparison of impurity profile by HPLC of insulins from several sources. The Applicant submitted data derived from the following batches: Marvel's drug substance batch; Lilly human insulin; USP insulin human RS; EP Insulin (human). From the viewpoint of a comparability exercise, the data from EP, USP are not meaningful. Consequently this data cannot be considered valid. Furthermore, information on purification/pre-treatment of the insulin drug substance is lacking. A more detailed description of the data, especially demonstrating the validity of the purification/pre-treatment, is asked for and should be submitted.</p> <p>The Applicant should submit a satisfactory side-by-side comparison exercise for both drug substance and finished products in line with current Guidance. Robustness of the comparability exercise, e.g. by including data from more than one batch of both Marvel's insulin and reference product, has not been addressed. Biological data,</p>			<p>Comparability exercises were performed including drug substance from batches of biosimilar material and batches of the Eli Lilly reference product material which has been extracted from products obtained on the market. The structural comparability of biosimilar insulin and the reference product was studied by applying numerous analytical state-of-the-art methods, such as NMR, Dynamic Light Scattering (DLS), IEF, SDS PAGE, Fluorescence spectroscopy, far and near UV, peptide mapping with UPLC-UV and UPLC-MS (ESI-Q). Comparable primary, secondary and tertiary structure could be demonstrated and identical molecular masses and size distributions were obtained. Identification and Assay by HPLC (as per Ph Eur), HMWP (SE-HPLC), related proteins (HPLC as per Ph Eur), total zinc and m-cresol content have been analysed. Although all results met the acceptance criteria of the monograph quantitative differences between the two products are apparent. Particularly, the content of zinc is significantly higher in the reference product when compared with the biosimilar product.</p>	<p>A historic (2008) analytical comparability study was presented comparing four Solumarv active substance batches, active substance extracted from one Solumarv finished product batch and insulin extracted from three Humulin S lots.</p> <p>All active substance samples extracted from the Solumarv batch contained insulin material produced between 2003 and 2007.</p> <p>No evidence has been provided that these batches are representative for the commercial active substance manufacturing</p>	See under drug product (table E)		

	<p>confirming the biological activity <i>in vitro</i>, were not found in the quality part of the dossier.</p>	<p>Although the comparison of the impurity profiles is based on limited data only, the biosimilar product is assumed to have a consistent higher amount of impurities. Due to the limited data available, it cannot be finally concluded whether the quantitative differences are significant. The total amount of impurities is still below the pharmacopoeial acceptance limit of total < 2% when applying the RP-HPLC method as described by the monograph. However, the compendial method is not suitable to separate all relevant impurities from the main and further comparative data covering the entire impurity profile by using a modified RP-HPLC method are not presented. However, further studies are considered necessary to characterise especially the impurity profile of the drug product and to identify the product-related substances by using appropriate analytical techniques.</p> <p>In order to demonstrate comparable degradation profiles, forced degradation studies are considered necessary in addition to the accelerated stability studies.</p> <p>As the panel of analytical methods used is more or less limited to Ph Eur methods, the comparability studies should be extended. State of the art methods not included in the Ph Eur monograph allowing in depth analysis should be used, such as DSC or Mass spectrometry investigation.</p>	<p>process taking into account the different changes implemented in the manufacturing process since that time.</p> <p>Structural comparability ... was evaluated using numerous analytical state-of-the-art methods. Similarity in terms of primary, secondary, tertiary structure, molecular mass and size distribution was shown. A similar pI was confirmed.</p> <p>One Solumarv active substance sample and three Eli Lilly insulin samples resulted in comparable peptide maps also when peptide mapping was performed under reducing conditions.</p> <p>The same insulin samples were also used to evaluate the differences in the impurity profiles. Similar levels of hydrophilic and hydrophobic</p>	
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		<p>In summary, for the drug substance substantial structural similarity between the biosimilar insulin and the reference product is suggested, but the qualitative and quantitative impurity profile of the biosimilar insulin human is not identical to the reference product. In particular it has to be considered that the compendial method is not suitable to separate all relevant impurities from the main due to the limited data available, a final conclusion on comparability cannot be drawn prior to an assessment of data/information requested by the List of Questions.</p>	<p>impurities were found in Humulin S and Solumarv batches. Likewise comparable amounts were determined for the insulin variants B3 desamido, B4and/or A5 desamido and A21 desamido insulin. However two specific variants could only be detected in Solumarv insulin.</p> <p>Stress studies by applying different stress conditions (heat, acidic pH, basic pH, oxidation, agitation and light exposure) confirmed similar degradation curves for high molecular weight proteins, desamido variants, DesThreB30 insulin and total related proteins between the test and reference product. It was further demonstrated that stress conditions do not have an effect on the amount of Solumarv specific insulin in the finished product batch.</p>	
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Table 5. Quality biosimilarity exercise: drug product.

Product	Insulin Human Rapid Marvel 100iU/mL	Insulin Human Long Marvel 100iU/mL	Insulin Human 30/70 Mix Marvel 100iU/mL	Solumarv 100iU/mL (2012)	Isomarov medium 100iu/mL	Combimav 100iu/mL	Solumarv 100iU/mL (2014)	Abasria (LY2963016) (now Abasaglar)	
<p>Quality biosimilarity exercise: drug product</p>	<p>From a quality point of view, biosimilarity has not been established for the drug products either. This is of particular importance for the Long and Mixed 30/70 product as the formulation is designed to directly determine the time-action characteristics of the modified release preparations.</p> <p>Biosimilarity should be demonstrated in terms of the formulation, specifications, stability and delivery (for the cartridges). Comparability data of the critical excipient protamine have not been submitted.</p> <p>For isophane and biphasic insulin, the critical excipient protamine has not been included in the comparability exercise.</p>			<p>A comparability study has been provided for the finished product with the reference medicinal product. This includes biosimilarity exercises in relation to formulation, presentation, specification and quality comparison side-by-side.</p> <p>The panel of analytical methods used is more or less limited to Ph Eur methods and this is not considered sufficient. With regard to the quantitative and qualitative impurity profile further studies, using state of the art technologies, are needed. Due to the limited data available, a final conclusion on comparability cannot be drawn prior to an assessment of data/information requested in the List of Questions. However, the available data indicate that the biosimilar is slightly less pure compared to the reference product, although still well within the Ph Eur limits. The possible impact of the differences seen has not been commented upon by the Company. In conclusion, there is insufficient data to evaluate biosimilarity with the reference products.</p> <p>Further comparison of the biological</p>			<p>A Major Objection is raised for this section.</p> <p>Three Solumarv batches produced with certain active substance material were tested in comparison to five Humulin S batches. Analyses were conducted based on the release specification only. The panel of test parameters chosen and the methods applied were far below the requirement ... to support a biosimilar approach. The related proteins were not tested in detail. Only results for A21 desamido insulin and total amount of impurities (without A21 desamido) have been presented. The same test program has been applied in a recent comparability study with one Solumarv finished product lot</p>		<p>The applicant initially proposed to first confirm comparability between US-approved and EU approved Lantus, and between LY2963016 injection that is manufactured at Lilly France and contract manufacturer. Once the two populations of each product were shown to be comparable, it was proposed that comparability would be demonstrated between Lantus and LY2963016 Injection. This approach to the biosimilar comparability exercise was not fully in line with the CHMP guidelines for biosimilars. For the quality biosimilarity exercise, the proposed biosimilar product should be demonstrated to be comparable to the EU reference medicinal product, using multiple batches. In addition, the recommended approach of generating the required quality, safety and efficacy data for the biosimilar comparability study with product manufactured using the final manufacturing process and therefore representing the quality profile of the batches to be commercialised was not followed.</p> <p>The applicant subsequently provided data for additional batches of EU-approved Lantus and segregated the information derived from EU-approved and US-approved Lantus. Data from LY2963016 batches manufactured by Lilly France and the contract manufacturer has also been presented separately to allow appropriate assessment. Data comparing LY2963016 and EU-approved Lantus side-by-side has been presented</p>

		<p>activity of the Marvel and Eli Lilly products is considered essential prior to the assessment of comparability. An appropriate specific cell-based assay should be used for the comparative determination of the biological activity.</p> <p>The impurity profile of the drug substance and drug product should be further investigated and comparability with the reference product discussed. In addition, it should be demonstrated that the batches used to evaluate comparability is representative of the intended commercial drug substance and product.</p>	<p>against two Humulin S batches.</p> <p>The difference in the Zn content in Solumarv finished product solution versus Humulin S has been... justified. In addition, comparable biological activity of Humulin S and Solumarv was confirmed by applying different biological assays.</p> <p>Furthermore, a structural and physiochemical comparison study between the test and the reference product was conducted in 2015 (Protagen study). Retained samples from previous active substance manufacturing processes stated to represent the commercial process were compared versus insulin from Humulin S. The results confirmed the expected primary, secondary and tertiary structure of human insulin for insulin generated from</p>	<p>and orthogonal methods have been used for the structural analysis of the primary, secondary, tertiary and quaternary structure. The biosimilar comparability exercise has compared the LY2963016 with the EU-approved Lantus, followed by comparison of the EU-approved Lantus with the US-approved Lantus, to demonstrate the validity of the supportive clinical studies carried out with US-approved Lantus. Additional data from the process validation batches has allowed comparison of the final proposed commercial process with the EU-approved Lantus.</p> <p>Physico-chemical characterisation has demonstrated biosimilar comparability between LY2963016 and the reference medicinal product, EU-approved Lantus, with the only observed difference being the presence of low levels of citrate in the Lantus samples detected by NMR. Reference has been made to data using <i>in vitro</i> biological assays with process validation batches and this has been reviewed in the non-clinical assessment. Biological potency has also been evaluated by testing LY2963016 Injection and Lantus in a comparability study. This demonstrated that the average relative potency was comparable for all these batches of LY2963016 Injection and Lantus. The applicant has also provided biological identity test data from LY2963016 Injection and</p> <p>Lantus with batches tested concurrently, which were demonstrated to be comparable, showing that the original differences observed were due to analytical variability and diverse testing times for the samples.</p> <p>Total impurities and HMWP measured by release</p>
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			<p>different stages of process development and similarity to the insulin structure of Humulin S. A comparison of the impurity profiles was not performed as it would not be meaningful considering the age of retained samples.</p> <p>A final conclusion on analytical comparability between Solumarv and RMP, however, cannot be drawn on the basis of the data provided. While overall the number of batches of the test and the RMP introduced into the comparability exercises is deemed sufficient, the representativeness of the test product batches for the commercial process and product has been questioned.</p> <p>Furthermore, different analytical methods were used to determine the two Solumarv specific variants and equivalence among</p>	<p>methods were lower in LY2963016 Injection batches compared with Lantus, which is attributed to the increased age of the reference medicinal product. One impurity, not found in measurable amounts in Lantus but present in LY2963016 Injection clinical trial batches is below the ICH threshold for toxicity. This impurity is controlled and the applicant has discussed potential clinical implications. The assay results between LY2963016 Injection and Lantus indicate that Lantus is formulated to a slightly higher concentration, which did not translate into consistent PK differences.</p> <p>The Applicant has provided data to support the claim that LY2963016 Injection and Lantus have similar precipitation characteristics under physiological conditions (in phosphate-buffered saline pH 7.4). This demonstrates that these two products have comparable <i>in vitro</i> precipitation and the finished products would be expected to behave in a similar manner <i>in vivo</i>.</p> <p>The proposed shelf-life for Abasria is 24 months at 2-8°C, including an in-use period of up to 28 days at 30°C. For Lantus it is also 24 months at 2-8°C, but including an in-use period of up to 28 days at 25°C. Stability is comparable on the whole for LY2963016 Injection and Lantus batches, in terms of rates of degradation.</p> <p>Both products showed significant degradation on exposure to iron, but the pathway of degradation appeared different. Further studies demonstrated that these differences are likely to be due to citrate, which has been detected in Lantus. Differences were not observed with lower levels of iron, particularly at the levels expected to be present in LY2963016 Injection. Therefore, this</p>
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			<p>these methods was not demonstrated. The reported amounts of the two Solumarv specific variants in Solumarv active substance development lots cannot be directly compared with those of the commercial lots.</p>	<p>discrepancy in iron-induced degradation is not expected to have any impact on the Abasria product under normal conditions.</p> <p>Overall, comparability between LY2963016 and the reference medicinal product Lantus has been satisfactorily demonstrated from the quality perspective.</p>
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➤ Non-Clinical biosimilarity exercise

The comparison of the CHMP evaluation for the non-clinical biosimilarity exercise for the Marvel Life Sciences and Eli Lilly insulin applications, as discussed in the EPARs, is reported in Table 6. The main findings are summarised below:

- In-vitro studies should have sufficient number of replicates in order to facilitate the biosimilarity conclusions – this was a short-falling noted in the 2014 Marvel application but on account of the appropriately studied insulin receptor binding assay and lipogenesis assay, the overall biosimilarity was established.
- In-vitro receptor binding studies can be useful to interpret the comparative activity of insulin impurities versus native insulin.
- In-vivo pharmacology studies are not required but could be used to interpret glucose suppressive activity of, or immune reactions to, insulin impurities.
- The Eli Lilly application justified not conducting a single-dose toxicity study.
- Similarity in a repeat dose toxicity and local tolerance study and in toxicokinetic parameters were established for both the Eli Lilly and 2014 Marvel Life Sciences application

Table 6. Adequacy of non-clinical dossier sections for EU biosimilar insulin applications.

Product	Insulin Human Rapid Marvel 100iU/mL	Insulin Human Long Marvel 100iU/mL	Insulin Human 30/70 Mix Marvel 100iU/mL	Solumarv 100iU/mL (2012)	Isomarv medium 100iu/mL	Combimarv 100iu/mL	Solumarv 100iU/mL (2014)	Abasria (LY2963016) (now Abasaglar)
Primary Pharmacology	<p>In vitro: binding to insulin receptor and cellular response to insulin-receptor binding (using CHO-T cells and 3T3-L1 adipocytes).</p> <p>Insufficient (detail of studies, suitability and sensitivity of tests and interpretation of results). CHMP concludes not enough detail and discussion to prove the claim of comparability.</p>			<p>Similarity shown in in vitro (NIH-3T3, human fibroblasts) and in vivo studies - <u>pending</u> request for raw data and statistical analysis.</p>		<p>Seven comparative primary pharmacodynamic (PD) studies were provided which are considered of limited usefulness because of the small number of replicates. These experiments included concentration-response curves for insulin receptor binding, phosphorylation of the insulin receptor, AKT, GSK3 and MAP kinase, and for insulin-stimulated glucose uptake in 3T3-L1 adipocytes. The Applicant has also provided insulin receptor binding assays and lipogenesis assays with a sufficient number of replicates to allow meaningful conclusions (for</p>		<p>In vitro similarity demonstrated (IGF-1, IR-A, IR-B receptors). Similarity also accepted for lipogenic potency in mouse adipocytes and mitogenic response in human osteosarcoma SAOS-2 cells and rat H4IIE hepatoma cells.</p> <p>Initially (D120) a Major Objection was raised as biosimilar batches were not truly representative of final commercial product – a series of in vitro studies were performed to address the issue and some of the analysis reconducted. Variability of the assays was reduced. The issue was solved within the procedure.</p>

			<p>similarity).</p> <p>Regarding analysis of the impurity, an in-vitro receptor binding study with the modified insulin impurities as compared to native insulin was performed. This study showed binding activity of the modified forms which was very similar to native insulin.</p>	
	In vivo not required	In vivo not required but one study is performed in mice.	<p>Study in rats to compare the glucose suppressive activity of the isolated impurity of with Marvel recombinant human insulin DS itself. No relevant differences between the impurity and native insulin were observed.</p> <p>The effects of the three product-related impurities on the immune system of rodents was investigated with an antigenicity study using male Balb/C mice comparing</p>	In vivo not required

			<p>Recombinant Human Insulin (Marvel soluble insulin) with the three purified impurities. In the absence of adjuvant, antibody formation was hardly detected.</p> <p>The results of day 32 indicate a comparable immunogenic potential of native insulin and the tested derivatives, although the findings of day 42 could indicate increased immunogenic potential of at least two of the product-related impurities but this might have been due to a lower than expected response for native insulin. Therefore, the obtained results cannot provide a definite answer.</p>	
Secondary PD, safety PD, PD drug interaction and PK studies	Not required	Not required.	Not required.	Not required. Data from comparative studies provided but there was a large variability – and cross-reactivity with rat insulin was likely. It was accepted that clinical PK data would be more relevant.

<p>Toxicology</p>	<p>General tox in single dose and repeat dose in rats and local tolerance in rabbits. No difference between products.</p> <p>No toxicokinetics or immunogenicity in animals – CHMP sought justification.</p>	<p>Single dose toxicology in rats and local tolerance in rabbits. No difference between products.</p> <p>Repeat dose toxicology not conducted- CHMP sought explanation</p>	<p>GLP status of the toxicity study to be confirmed.</p> <p>Single-dose, repeated-dose and local tolerance studies accepted as demonstrating similarity.</p> <p>Toxicokinetic data provided.</p> <p>Immunogenicity data requested by reviewer in order to interpret differing impurity content in Marvel versus Biosimilar batches as well as to help interpret potential hypersensitivity difference detected in clinical studies.</p> <p>Studies were conducted with soluble insulin; CHMP did not ask for studies to be done on isophane or biphasic insulin.</p>	<p>Single dose toxicology and local tolerance shown to be comparable between the biosimilar and the RMP.</p> <p>Two 28-day repeat-dose toxicity studies (one with non-EU-sourced RMP and the other with EU-sourced RMP) were performed comparing soluble Marvel insulin with Eli Lilly insulin – no relevant differences were seen.</p> <p>A 7-day TK study in rats was conducted separately comparing soluble Marvel insulins with EU-sourced RMP (in accordance CHMP scientific advice 2008). In conclusion, the kinetics of test substance and the reference substance are comparable with each other, showing nearly similar TK parameters without any biologically significant difference under conditions and</p>	<p>Lack of single dose toxicity study accepted.</p> <p>Rat repeat dose toxicity study accepted as demonstrating and local tolerance studies showed no difference to RMP.</p> <p>Toxicokinetic data accepted to be similar to RMP.</p>
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				procedures followed. The results can be considered as supportive to biosimilarity.	
Genotoxicity, carcinogenicity, reproductive toxicity	Not required.		Not required.	Not required.	Not required.

➤ Clinical biosimilarity exercise

The comparison of the CHMP evaluation for the clinical biosimilarity exercise for the Marvel Life Sciences and Eli Lilly insulin applications, as discussed in the EPARs, is reported in Table 7. Neither the 2014 Marvel Life Sciences nor the Eli Lilly applications had Major Objections raised on the clinical similarity exercise per se – the issue with the Marvel Life Sciences 2014 application was that the quality bridge between clinical trials lots to commercial lots was not established. Had the quality issues raised as part of the assessment been solved/solvable, it seems that the 2014 Marvel Life Sciences application would have been approvable from the non-clinical and clinical perspective.

Table 7. Adequacy of clinical dossier sections for EU biosimilar insulin applications.

Product	Insulin Human Rapid Marvel 100iU/mL	Insulin Human Long Marvel 100iU/mL	Insulin Human 30/70 Mix Marvel 100iU/mL	Solumarv 100iU/mL (2012)	Isomarv medium 100iu/mL	Combimarv 100iu/mL	Solumarv 100iU/mL (2014)	Abasria (LY2963016) (now Abasaglar)
Overview	One Phase I and one Phase III study			Two Phase I trials, Two Phase III trials. Concerns about the GCP status of the study			One pivotal and one supportive PK-PD study, two PhIII trials. CHMP concluded that though data showed similarity, that comparability of the clinical trial lots to the proposed commercial lots remained to be proven.	Four Phase I and two Phase III studies Additionally one Phase 1 study comparing EU versus US sourced Lantus.
Clinical pharmacology	An adequate pharmacokinetic comparison to the reference product has not been carried out. The pharmacodynamic study did not demonstrate equivalent blood glucose-lowering effect to that of the reference product.			CHMP conclude that the two PK/PD studies could support equivalence if multiple and serious issues relating to reliability/validity of the data are resolved.	CHMP conclude that the two PK/PD studies, in terms of PK, could support equivalence if multiple and serious issues relating to reliability/validity of the data are resolved. But in terms of PD, one of the studies does not support comparability whereas the	CHMP conclude that the two PK/PD studies, in terms of PK, could support equivalence if multiple and serious issues relating to reliability/validity of the data are resolved. But in terms of PD, one of the studies does not support comparability whereas the	One pivotal comparative PK-PD clamp study in healthy volunteers (2014) One supportive comparative PK-PD clamp study in healthy volunteers (2002)	CHMP concluded that PK and PD equivalence was demonstrated based on an extensive comparability exercise performed in five studies which tested several dose levels and were conducted in healthy volunteers as well as patients with type 1 diabetes.

			other does – but there are multiple and serious issues relating to reliability/validity of the data.	other does – but there are multiple and serious issues relating to reliability/validity of the data.		
Clinical efficacy	The efficacy and safety data, which cannot be used to compensate for the failure of pharmacodynamic similarity, showed consistent trends in favour of the reference products.	Clinical efficacy measured as glycaemic control was demonstrated in the phase 3 trials and was comparable to the reference product – but this data is only supportive data, since the clinical PD data are more sensitive.			A 6-month safety and efficacy study (2005) in patients with Type I or Type II diabetes with a further 6-month open-label extension (investigation of immunogenicity). Primary endpoint was HbA1c at week 24. Taken together, the data from the clinical trials, with some limitations, reasonably support similar efficacy of the test insulin used in those studies and reference insulin as demonstrated in the pivotal clamp study.	Two clinical studies conducted in patients with type 1 and 2 diabetes demonstrated that LY2963016 is non-inferior to Lantus in achieving HbA1c at week 24 and therefore provided strong supportive evidence about the comparability of the two products. Importantly, both studies provided data on patients switching from Lantus to LY2963016 at the same dose regimen; no difference in dose changes after titration to tighten glucose blood control was reported between the two treatment arms. The study in type 1 diabetes was pursued up to 52 weeks and non-inferiority of LY2963016 to Lantus was confirmed at this further time point.
Clinical safety	See above for safety. The immunogenicity of the Marvel insulin products has not been properly evaluated.	Potential hypersensitivity reactions, regarded as related and leading to discontinuation of study drug, were more frequent in the Marvel than in the Humulin group.			A 6-month immunogenicity study (2009) in both Type I and Type II diabetes	CHMP concluded that the total amount of comparative safety data up to 6 months is adequate. In addition, 499/643 patients were of Caucasian origin and there was

		<p>The immunogenic potential of Marvel insulin needs further evaluation</p>	<p>patients with a 6 months open-label extension.</p> <p>The general safety profile of Marvel insulin, with regard to the test material used in those studies, appears comparable to that of the reference product Humulin.</p>	<p>a substantial subset of patients ≥ 65 years of age with only few patients exposed in the age group of >75 years.</p> <p>CHMP concluded that anti-insulin antibodies up to 52 weeks, showed no difference between biosimilar and RMP.</p>
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Table 8. Tabular overview of clinical studies conducted to support EU registration for Abasria (now marketed as Abasglar® by Eli Lilly).

Study Alias	Objective	Study Population	Number of Subjects Randomised
Phase I Studies			
ABEA	Comparison of the PK and PD of LY2963016 and EU-approved Lantus	Healthy subjects	80
ABEE	Comparison of the PD of LY2963016 and EU-approved Lantus	Patients with T1DM	20
ABEI	Relative bioavailability of LY2963016 to EU-approved Lantus	Healthy subjects	16
ABEM	Relative bioavailability of LY2963016 to EU-approved Lantus	Healthy subjects	24
ABEN^a	Comparison of the PK and PD of EU- and US-approved Lantus	Healthy subjects	40
Phase III Studies			
ABEB	Comparison of LY2963016 with Lantus (EU- and US-approved), as measured by change in HbA1c, when each is used in combination with pre-meal insulin lispro	Patients with T1DM (open-label)	536
ABEC	Comparison of LY2963016 with Lantus (EU- and US-approved), as measured by change in HbA1c, when each is used in combination with OAMs	Patients with T2DM (double-blind)	759

^a Study ABEN was a comparison of EU- and US-approved Lantus; no LY2963016 was administered

3. Recommendations

EU regulatory experience with biosimilar insulin products is still relatively limited, especially considering other candidate biosimilar biotech proteins. Because of this, engagement from an early stage with regulators is advisable to ensure agreement with the development strategy and expectations.

It should be obvious that the general requirements for a biotech regulatory dossier should be fulfilled but in the case of the Marvel Life Sciences suite of dossiers, this was a fundamental issue leading to Major Objections (see Table 2 and 3). CHMP reviewers stated for the 2007 submissions that: “There is a general consensus amongst all assessors that the overall quality of the dossier is very poor”.

Batch transparency should be clearly communicated in dossiers for biological products, including which batches, of which scale and quality, were used in which study (quality, nonclinical, clinical). The bridging studies conducted to establish the comparability between non-clinical, clinical and commercial lots is a critical aspect which has led to Major Objections during CHMP assessment.

Fundamental experience with biosimilar products is that particular attention has to be paid to the choice/sourcing of EU reference medicinal product (RMP) and the strategy of its use in the comparative quality, non-clinical and clinical studies.

The quality biosimilarity exercise requires an extensive and thorough comparative analysis of the biosimilar candidate versus the original EU reference medicinal product (RMP) using state of the art and sensitive/discriminatory analytical methods. The panel of methods employed increases as the stage of development matures (e.g. research and development, pre-clinical, Phase 1 and Phase 3 where required) as well as the number of EU RMP batches analysed for comparison. This goes much beyond what is documented in the European Pharmacopoeia (Ph.Eur.) monographs as appropriate testing strategies for insulin. Specifically, sufficient focus should be given to the analytical method used to determine individual impurity levels – such methods should be optimized to measure and control process/product specific insulin-related impurities.

Importantly, EU regulators expect that multiple (orthogonal) analytical methods are also used, where possible, to analyse quality attributes to provide a greater degree of certainty on the data. In EU regulatory procedures, “Major Objections” are commonly raised in relation to the acceptability of the characterisation package for the biosimilar candidate and also the assessment of its quality similarity to the RMP. This is a significant area of disagreement between regulators and Industry for all biosimilars in general, and was also the case for the Marvel Life Sciences suite of insulins and also, initially, for the Eli Lilly biosimilar insulin (see Table 4 and 5).

Some biosimilar insulin products will be easier to develop than others. EU regulators are particularly sensitive to the formulation aspects for modified-release insulins as the formulation, development, validation, and control of these aspects is critical for patient safety. This was a major failing point for the Marvel Life Sciences Ltd modified release preparations.

Finally, CHMP guidance documents are available to guide non-clinical and clinical development for biosimilar insulins. When the developer foresees that they will deviate from these guidelines, ideally this would be agreed up front with the regulator, with a robust justification for the deviation. This emphasises the importance of prior consultation with regulators prior to deviating from the defined expectations.

Final conclusions and lessons learned from the case studies:

1. The Marvel Life Sciences applications were not sufficiently comprehensive in their EU filing, both in terms of technical aspects relating to requirements for both general and biosimilar products but also in terms of the requisite level of detail and communication that supports EU regulatory assessment.
2. Qualitative and quantitative differences in excipients might be acceptable between the biosimilar product and RMP as long as these are concluded to not have any impact on the biosimilarity conclusions.
3. The panel of analytical methods should not just be confined to pharmacopoeial methods for the particular product – a common mistake made by a number of developers. The Marvel Life Sciences Ltd application was deficient in this respect, leading to many other issues relating to their inability to demonstrate comparability over product development and also in their analysis of biosimilarity to the RMP. Critically, the quality biosimilarity exercise should use a wide panel of sensitive and discriminatory analytical methods to assess content, purity/impurities, activity, and safety.
4. Comparability between the early and late stage biosimilar product is even more critical in a biosimilar development programme. This is because the biosimilarity exercise considers the non-clinical, phase 1 and phase 3 data sets as part of the totality of evidence that confirms biosimilarity to the RMP. If the quality of the biosimilarity product evolves over development, without demonstration of comparability, then the data from those earlier pre-clinical or clinical studies becomes devalued in the final assessment of the biosimilarity exercise – and might be required to be rerun with more “relevant” product. It is recognised that some assays will only be developed/validated in later stages of the development programme – however, it might be required that these assays retrospectively applied to appropriately stored retained samples to substantiate the comparability claim.
5. The suitability of the administration device for delivering the required dose should be substantiated.
6. *In vivo* data to support the primary pharmacology is not required in the EU – the focus should be on reliable *in vitro* receptor binding data. Secondary/Safety PD studies are also not required.
7. It has been accepted that preclinical PK data might be very variable and that evidence from the clinical PK study is more relevant for substantiating biosimilarity.
8. Clinical Phase 3 efficacy studies are not expected for insulin and the focus should be on robust quality biosimilarity evidence, compelling evidence from the *in vitro* pre-clinical programme, and confirmatory comparative phase 1 PK/PD studies. Even so, the Eli Lilly application did conduct two Phase 3 studies, using a non-inferiority statistical design rather than an expected equivalence design, and the data were accepted as supportive.
9. Sufficient evaluation of the unwanted immunogenic potential in clinical studies was required in both Marvel Life Sciences and Eli Lilly applications. However, the relevant CHMP guideline for non-clinical and clinical development of insulin products does allow for waiver of clinical immunogenicity studies if appropriately justified based on compelling quality (including impurity profile) and PK/PD biosimilarity.

Importantly, obtaining EU regulatory advice on the development programme is important for success, especially for products where regulatory experience is still growing, such as these biosimilar insulin applications. However, in these case studies, both Marvel Life Sciences and Eli Lilly did obtain EU regulatory/scientific advice – and one Company achieved regulatory success whilst the other did not. Therefore, it might follow that asking the right questions at the right time, is important, as well as following through on the advice received or providing sufficiently robust explanations for any deviations or alternative strategies.

4. References

EPARs

Insulin Human Long Rapid (2008):

http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500067086.pdf

Insulin Human Long Marvel (2008):

http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500067170.pdf

Insulin Human 30/70 Mix Marvel (2008):

http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500067169.pdf

Solumarv:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003858/WC500201969.pdf

Isomarv medium:

http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2013/02/WC500138885.pdf

Combimarv:

http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2013/02/WC500138884.pdf

Solumarv (2014)

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003858/WC500201969.pdf

Abasria (Abasaglar)

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002835/WC500175383.pdf

Other

Current Insulin non-clinical and clinical guideline:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500184161.pdf

Previous Insulin non-clinical and clinical guideline:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003957.pdf

Annex III

Regulation of Insulin Biosimilars

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Acronyms

AI	Active ingredient
ANVISA	Agencia de Vigilancia Sanitaria, Brazil
BIO	Biotech Industry Organization
(CIM)	Centro de Inmunología Molecular
EMA	European Medicines Agency
EU	European Union
FDA	Federal Drug Agency
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International non-proprietary name
Marvel	Marvel Life Sciences Ltd
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
R&D	Research and development
RDPAC	R&D-based Pharmaceutical Association Committee
US	United States
WHO	World Health Organization

1. Introduction

The specific aim of this report is to contribute to landscaping the insulin market by drafting a profile, based on literature, on the current regulatory requirements of national and regional medicines regulatory authorities (in high-, middle- and low-income countries) for gaining market authorisation for biosimilar insulin. More concrete objectives include:

- *to identify regulatory requirements for biosimilars as they apply to insulin (human and analogue) in selected middle-income and high-income countries, including countries with local insulin manufacturers.*
- *to document the registration status of insulins in selected middle-income and high-income countries, whether they are assessed as interchangeable or not, and the regulatory rules in place for insulin vs other biosimilars.*

Medicines regulation refers, on one hand, to measures mainly aimed at ensuring the safety, efficacy and quality of medicines.

The main purpose of the technical regulation of medicines is to ensure its quality, efficacy and safety. Regulations affect the costs of developing and manufacturing a medicine and, consequently, its accessibility, i.e. availability and affordability. This is obvious in relation to the evidence required by regulators to grant a marketing authorisation: the higher the level of evidence is required, the larger the type of effects involved, the number of individuals recruited and the duration of clinical trials is, the higher the research and development (R&D) costs will be, and the proportion of projects that fail in placing a medicine on the market.

With the generalisation of public health insurance and the rising prices of new medicines, access to medicines and financial sustainability of health systems have become key concerns of public health authorities. Given the market failures that characterise medicine markets, the economic regulation of medicines – especially price and expenditure control – has been introduced in most countries.

One of the main drivers of high prices of medicines is the lack of competition. At present, the main mechanism to incentivise private biomedical research is the granting of patents and other exclusive marketing rights to innovators. One of the problems of exclusive marketing rights is that they provide right holders with a certain degree of market power, which allows them to set prices well above a competitive price, which in turn can lead to problems of affordability and financial sustainability of the health systems. Generics and biosimilars have a key role in improving availability and affordability of medicines when exclusivity marketing periods (patents, test data protection) expire. Legal market exclusivity is, however, not the only barrier that generics and biosimilars must overcome in order to gain market access; other market barriers include high development costs, often caused by market authorisation and other regulatory requirements or brand loyalty and the consequent reluctance of doctors and patients to replace originators with the respective generics and biosimilars. In the case of chemical, small molecule medicines, the entry of generics have been shown to lower the price of the medicine to about 20 percent or more of its price under

exclusivity. In the case of biologic products, the corresponding reduction is much lower, leading the competitive price to about 70 to 80 percent of the previous exclusivity price. Still, given the high prices of biologic medicines, such a reduction can have a substantial impact on the cost of the medicine to users and health insurers.

The economic regulation of medicines aims at ensuring an efficient price by removing the market failures that prevent the market forces behind competition to work according to the theoretical competitive model. The most obvious type of economic regulation is price regulation (control). But the authorities have other tools available to affect medicine prices, for instance, by promoting competition: using tender mechanisms for procurement, improving the information of prescribers and patients on medicines quality and prices, providing incentives to prescribers and patients to consider both health effects and costs when choosing among the existing therapeutic options, or providing incentives to pharmacists to dispense the less costly version of a certain medicine.

Finally, it is important to also consider financing/reimbursing mechanisms, although these are usually classified as demand side, rather than regulatory policies. Although the main purpose of public financing of medicines is to ensure equitable access, it usually also has a crucial impact on prices. Depending on the way financing is designed, the effects on the amount and efficient utilisation of medicines can vary enormously.

Quality and accessibility of medicines are both desirable objectives of medicine policies. In fact, most policies aim at ensuring equitable access to quality medicines. But quality usually comes at a cost and quality and access might conflict.

Companies which main business is the development and sale of new medicines have an obvious financial interest in countries rising regulatory requirements and standards for authorising and manufacturing follow-on products beyond what might be required from a purely clinical/public health perspective, because this means higher entry barriers and higher prices of follow on competitors, which allows innovators to maintain higher prices and larger market shares during longer periods for its originator products. Health authorities must address the potential conflict between quality and affordability and define the appropriate trade-off, taking into account the global interest and welfare of society. Countries with a strong R&D industry have an incentive to set high standards not only in order to ensure efficacy, safety and quality, but also to support their own industry; they are also lobbied by the domestic industry to do so. Countries with no - or few - innovative companies might benefit if they avoid unnecessarily high standards in order to promote access to new medicines and to support the local generic industry. Technical requirements have been often used by countries as an additional non-tariff barrier to protect local industry from foreign competition. In the pharmaceutical sector, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) standards have been often criticised by countries with an emerging industry for allegedly being unnecessarily restrictive and being used as a tool to restrict competition.

In order to take informed decisions, policy makers should have evidence on both the potential health effects of all elements of biosimilar regulation, as well as the likely impact on development and manufacturing costs, which ultimately determine availability and price/affordability.

The ultimate objective of this study is to provide evidence on how regulation can affect the access to insulin treatment. This draft report presents the findings of a literature review aimed at identifying the regulation that applies to insulin biosimilars in general and, particularly, in a selected sample of countries: Brazil, China, Colombia, Cuba, the European Union (EU), India, Iran, Mexico, South Africa, and the United States (US).

There are several key aspects of medicine regulation which affect both public health and economic objectives in the case of biologics and biosimilars.

One of the main potential barriers to the availability and affordability of biosimilars are the requirements for granting marketing authorisation, mainly, the type and characteristics of clinical trials and other studies required as part of the application and the criteria for considering a biosimilar, similar enough to the reference product. The higher the requirements, the higher will be the cost of putting a biosimilar on the market and the risk of being rejected by the regulatory authority, which is also a component of the costs of biosimilar producer. This situation was in the past a source of controversy in the case of generics of small size molecules and is becoming a hotter issue in the case of large size molecules (biologic medicines) where the nature of the manufacturing process makes it more difficult to assess the therapeutic equivalence of a biosimilar in relation to the reference product.

Once in the market at a certain price, it is important from the point of view of competitiveness that the potential users have the possibility and incentives to choose the biosimilar instead of the originator. Here is where the legal definition of substitutability and interchangeability of biosimilar plays a key role¹.

Still, the fact that a biosimilar is legally substitutable and interchangeable does not ensure that it will be effectively used instead of the reference product, i.e. prescribed by doctors and accepted by patients, even if it has a lower price. The use of brand names and the marketing activities of originators often lead to a consumer loyalty to an existing brand, which is not always justified in terms of quality and price. Hence the

¹"Substitution (sometimes referred to as automatic substitution) occurs at the point of dispensing and refers to the practice of a pharmacist dispensing a generic/biosimilar medication in place of the prescribed drug, without the prior consent of the healthcare provider". (DeVries et al. 2005)

"... automatic substitution between reference and biosimilar products is not expected. In fact, as clearly stated in the SPC of all insulin-containing medicines, every change may require an adjustment of the dosage and therefore has to be evaluated by healthcare professionals. However, it should be considered that in diabetic patients, blood glucose levels can be affected by many factors including diet, exercise, stress, and illness.

Therefore, dosage adjustment is constantly required, independently from the switch from one brand of insulin to another. In the first years of commercialisation of a biosimilar, the switching has to be carefully evaluated for patients already receiving treatment, while no problem arises for treatment-naïve patients. In the latter case, the physician may decide, or be compelled by the health insurance company, to prescribe directly the cost-saving product affecting the market share of all the other rapid-acting insulin analogues". (Franzè et al, 2015)

"Interchangeability refers to a decision made by a national or regional health authority that a biosimilar drug has met the data requirements needed for automatic substitution with the reference product". (DeVries et al. 2015)

"Over time, switching from one biosimilar insulin manufacturer to another could lead to formation of insulin-neutralizing antibodies and development of insulin resistance". (Carter et al. 2014)

relevance of biologicals and biosimilars being marketed and prescribed by either the INN (International Non-proprietary Name) or the brand name.

2. Literature Review

The review of academic/scientific literature was carried out searching in the Pubmed - Medline database using the key words "biosimilar" and "insulin" (updated 28th April 2015), giving as a result 33 references. 15 articles were achieved and revised (see list of references in Annex 3). Annex 1 provides a summary of the most relevant articles. The parts which are literally copied are written in italics.

In order to complement the previous literature search, we carried out an additional search in Google using the terms "insulin" and "biosimilar" and the names of the countries selected in our study sample. This second search provided mainly grey literature (from newspapers, professional journals, national and international organisations, etc.) and a few academic papers that did not appear in the first search.

After the previous searches were completed we identified a late publication by Heinemann et al. (2015) that aimed at our same goal – identifying and comparing insulin biosimilars regulation in a set of countries, and presented a very comprehensive analysis (up to August 2014) of the regulatory guidelines for biosimilar insulin and biosimilars regulation that is relevant for insulin biosimilars in 34 countries. Thirteen countries are found to have enacted guidelines for biosimilars: Australia, Canada, China, Colombia, Cuba, Egypt, the EU, Jordan, India, Iran, Malaysia, Mexico, New Zealand, Saudi Arabia, South Africa, South Korea and the US.

In the following sections we report the findings on certain key topics – the definition of biosimilar, mapping biosimilar regulation/guidelines, both general and insulin-specific and problems found in the development of biosimilar-insulin development - as well as the results for six countries in our study sample not included in the Heinemann et al. (2015) article (Brazil, Colombia, Cuba, China, Iran, and Ecuador). A broader transcription of results of the results and links of sources for all countries in our sample is available in Annex II.

Definition of Biosimilar

The international differences in the regulation of biosimilars begin at the stage of naming and defining them. Tsuruta et al. (2015) made a comparative analysis of some country descriptions:

Names and Definitions of Biologic Copies According to Different Regulatory Agencies

FDA (Food and Drug Administration), USA

Follow-on Biologic or Biosimilar

“A biological product that is highly similar to a U.S.-licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product”.

EMA (European Medicines Agency)

Biosimilar

“A biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product) in the EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established”.

WHO (World Health Organization)

Similar Biotherapeutic Product

“A biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product”.

PMDA (Pharmaceutical and Medical Devices Agency), Japan

Follow-on Biologic or Biosimilar

“A biotechnological drug product developed by a different company to be comparable to an approved biotechnology-derived product (hereinafter “reference product”) of an innovator”.¹⁸

Health Canada

Subsequent Entry Biologic

“A biologic product that is similar to and would enter the market subsequent to an approved innovator biologic product”.

ANVISA (Agencia de Vigilância Sanitária), Brazil

Biologic Product

A biologic medicine with known biologic activity that contains no new molecules, already licensed in Brazil and that has gone through all the production steps (including formulation, vialing, freeze drying, labelling, packaging, storage, quality control and biologic product lot release)².

Dolinar et al. (2014) state that, *“The regulatory requirements and protocols for assessing the safety and efficacy of biosimilar insulins have not yet been developed in the United States and only recently defined in Europe; however, some copies of current insulins have already been approved for commercialization in China, India, Pakistan, Thailand, Peru, and Mexico, where regulatory requirements are less stringent”* (see table 2 below).

² Source: Lilian Rumi Tsuruta, Mariana Lopes dos Santos, Ana Maria Moro. Biosimilars Advancements: Moving on to the Future. *Biotechnol. Prog.*, 2015, Vol. 00, No. 00 <http://onlinelibrary.wiley.com/doi/10.1002/btpr.2066/pdf>

This article also provides an up to date theoretical and institutional analysis of the regulation of biosimilars.

TABLE 2. MARKETED INSULIN GLARGINE COPIES (BIOSIMILARS)

<i>Status, brand name</i>	<i>Injectible form (UI100/mL)</i>	<i>Company (manufacturer)</i>	<i>Country (year)</i>	<i>Clinical studies, comments</i>
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	East West Pharmaceutical (Gan & Lee)	Pakistan (2009)	
Bonglixan [®]	10-mL vials 3-mL cartridges	Landsteiner Scientific (Gan & Lee)	Mexico (November 2008)	NA
Glaritus [®]	10-mL vials 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 Nacional de Vigilancia de Medicamentos y Alimentos; NA, no information available; NCT, U.S. National Institutes of Health (United States) clinical trials registry (www.clinicaltrials.gov/).

One clear finding from the search is that there still are multiple definitions of a medicine that aims at replicating a biologic originator. The variety and heterogeneity of definitions would become larger when additional country legislations were considered. This heterogeneity might become an obstacle to international trade and, ultimately, to improving access to insulin medicines via importations from countries able to produce them.

Mapping Biosimilars Regulation

We tried to find information on the historical evolution and present state of biosimilars and insulin biosimilars regulation worldwide. We report the various sources of information found that try to provide a global picture and made comparative analyses of biosimilar regulation in a set of countries, for instance:

1. Biologics and biosimilars. An overview Amgen, March 2014
http://wwwext.amgen.com/pdfs/misc/Biologics_and_Biosimilars_Overview.pdf

ADOPTION OF GUIDELINES

2005 EMA (EU)

2007 AUSTRALIA

2008 TURKEY, MALAYSIA, TAIWAN

2009 SOUTH KOREA, JAPAN, SINGAPORE, WHO

2010 CANADA, (ZAF), BRAZIL, SAUDI ARABIA

2011 ARGENTINA, MEXICO, CUBA, (IRI), INDIA, PERU

2012 USA (draft) COLOMBIA (draft) JORDAN (draft) THAILAND (draft) EU (Update to Quality. Issues Guideline)

2013 EU Revised Guidelines, EU Non-clinical and clinical Guidelines

The EMA was the first Regulatory Agency to create biosimilar guidelines in 2005, swiftly followed by the first approved biosimilar products in 2006. As of December 2013, 16 biosimilar products were approved by the EMA. (17) Regulation has evolved rapidly with many countries establishing national guidelines based on the WHO and EMA/EC framework. Guidelines are helping to open up the development and approval of biosimilars worldwide, but definitions and terminology for biosimilarity vary, as does guidance on the original reference product for comparability studies and the scope of data required for marketing approval. (31).

2. Infographic on the regulation of biosimilars (available in Spanish and in English)

<https://www.flickr.com/photos/ifpma/14791396799/in/photostream/>

<https://www.flickr.com/photos/ifpma/14791377379>



3. Heinemann et al (2015) present a worldwide map of insulin regulation, which is a modification and update of a previous map by Scheinbert el al (2012) that referred to general biosimilar regulation.

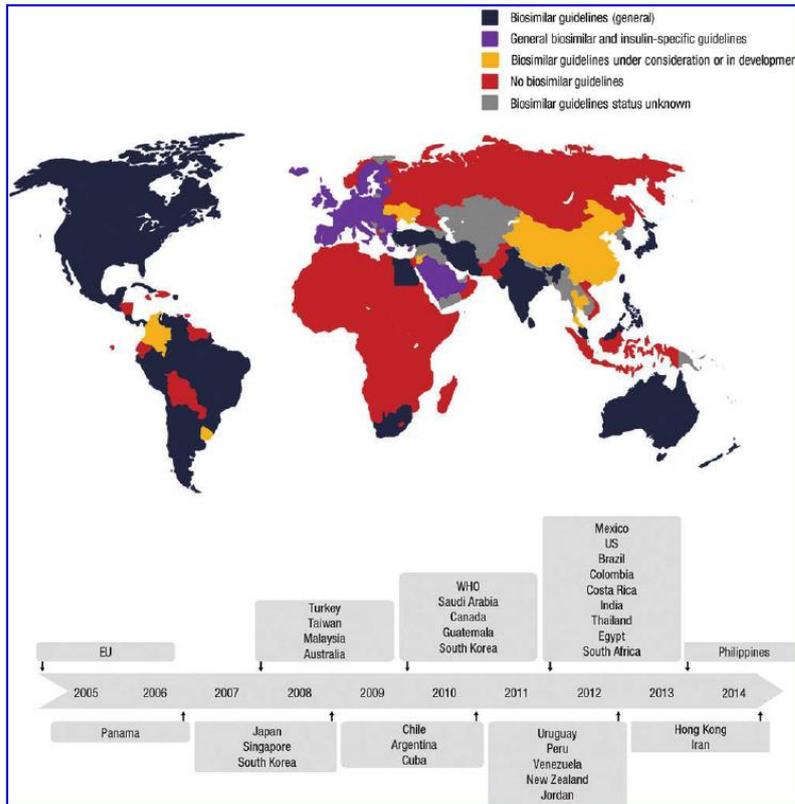


FIG. 1. Global overview of availability of general and insulin-specific biosimilar guidelines. EU, European Union; WHO, World Health Organization. After Scheinberg and Kay.⁹ © 2012 Macmillan Publishers Limited. All rights reserved.

PERSPECTIVES

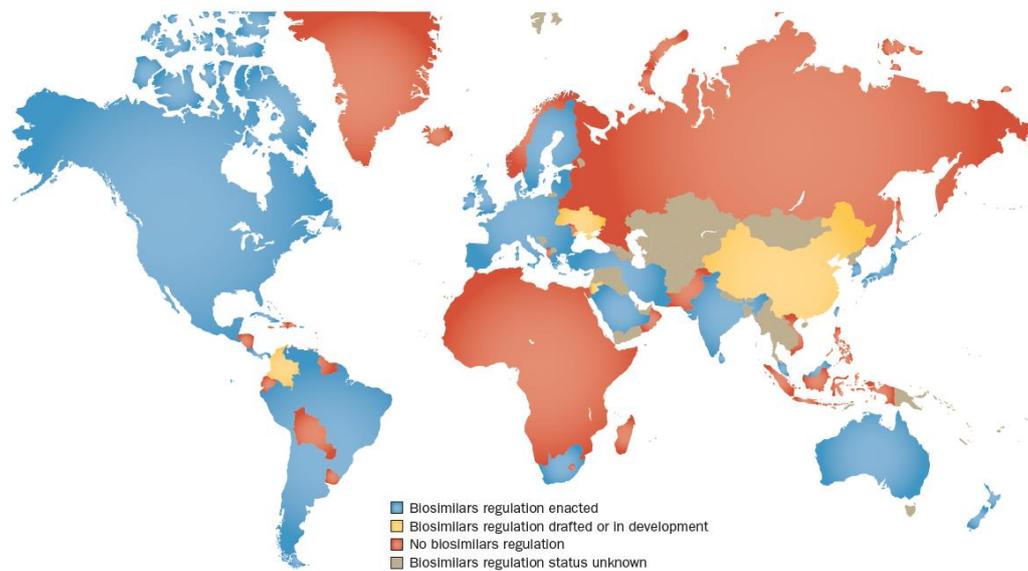


Figure 1 | Worldwide status of regulations for the approval of biosimilar agents. April 2012.

Source:

Scheinberg, M. A. & Kay, J. *Nat. Rev. Rheumatol.* 8, 430–436 (2012); The advent of biosimilar therapies in rheumatology—“O Brave New World”

Problems with the Registration of Insulin Biosimilars: the Marvel Life Sciences Case

The specific requirements of the EMA for authorising insulin biosimilars seem to be lower than for other biologics. This might lead to conclude that developing an insulin biosimilar is easier than other classes of biosimilars. However, there is some evidence against this assumption. Between 2006 – 2012, five biosimilar products were withdrawn after submission to the EMA – Somatropin by Biopartners in 2012, three insulins by Marvel Life Sciences 2008 - or rejected - Interferon alfa 2^a by Biopartners, 2006.

"One example is Marvel Pharmaceuticals, which has already failed at 2 attempts to gain approvals for its biosimilar insulin products. In both applications, several weaknesses were identified in the study reports, including statistical errors, unclear calculations (the statistical analysis plan was not provided) and inconsistent or missing information. In the second application, reviewers criticized the glucose duration of the clamp procedure used, which was considered to be too short (5 hours) to fully reflect the PD profile of these short-acting insulins. In addition, reviewers determined that the glucose infusion rate (GIR) reported in the studies showed a constant plateau over the course of the clamp test, which is unexpected for short-acting insulins and not consistent with the PK profiles of these insulins." (Dolinar)

"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 percent soluble, 70 percent 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" (Owens)

See also: <http://www.gabionline.net/Biosimilars/News/Marvel-withdraws-biosimilar-insulin-applications>

Moreover, according to a personal communication from an official of the Cuban MOH (Dr. Dulce Calvo), Cuba tried to develop an insulin biosimilar, but abandoned the project due to its technical complexity.

This would be an important point to explore further as long as local production of insulin biosimilars is considered a potential solution for improving access to insulin.

National Regulations

Introduction

The aim of this report is to map the regulatory situation of insulin biosimilars in a set of countries with different characteristics regarding population size, income and industrial capacity. Initially the following countries were selected: Brazil, China, Colombia, Cuba, the EU, India, Iran, Mexico, South Africa and the US. Information on the regulation of biosimilars is easily accessible for the EU and the USA, and also for the WHO Guidelines on that issue, for many other countries it is quite difficult to identify the relevant information. In several countries the official regulatory documents are only available in the local language (Iran/Farsi, China/Chinese). As mentioned above, the search of academic literature yielded limited results. We therefore turned to a Google search to identify grey literature and professional publications.

Brazil, Colombia, Cuba and Iran are the only countries selected in the sample of our study which were not considered in the paper by Heinemann et al (2015). We therefore focused our analysis of the grey literature on the former four countries, plus China, which enacted biosimilars regulation in 2015, after the publication of the Heinemann et al. article, and Ecuador. We included this country because we had the opportunity to have first hand information from a local expert and because Ecuador might be an interesting model for other small countries.

In our review of the grey literature we did not limit the extraction of information to purely regulatory issues and to insulin biosimilars, but included also available information on biosimilars regulation in general and on other relevant topics, such as the local productive capacity and economic information on the biosimilars market. This approach seems justified because a) only two (EU and Saudi Arabia) out of the 13 countries in the Heinemann et al. article have insulin-specific guidelines and b) because several aspects of the general biosimilars regulation are highly relevant to insulin biosimilars. We also thought that information on the capacity of the local industry, industrial pharmaceutical policies and the characteristics of the insulin and, in general, biosimilars markets might be useful to explain the regulatory approaches taken in a country.

We provide a brief summary of the situation in the six countries mentioned above (China, Brazil, Colombia, Cuba, Ecuador and Iran). Annex 2 provides more detailed information and the respective sources and links to the references found in the grey literature search.

Summary Results

Brazil

Brazil is one of the largest medicines markets and it also has a large pharmaceutical industry. The Brazilian government has been also committed to ensure the access of the population to high cost medicines (e.g. ARVs). Pharmaceutical strategies have been aimed at reducing the costs of medicines and to improve the local industry. In 2010,

the MOH defined a list of strategic medicines of high technological and economic value and proposed partnerships between public and private industries, usually a foreign API supplier and a domestic private industry that out-sourced production for the government-owned industry.

Brazil was one of the first countries in Latin America to issue guidelines for biosimilars (2010) and by 2013 187 biosimilar applications had been approved by ANVISA. There are two pathways for the approval of biosimilars, the comparative and the individual pathway. The former pathway closely follows the WHO guidelines and requires phase III trials, while in the second one, regulatory and clinical trial requirements are reduced. Only products licensed according to the comparative pathway are considered biosimilars.

Colombia

According to the MOH, 9 of the 12 medicines with the highest institutional sales are monopolistic biological medicines. Insulin glargine is one of these 9 biologicals; its sales grew by a factor of 8 between 2008 and 2014.

In 2014, Columbia approved a decree on the requisites and procedures to authorise marketing of both new biologicals and biosimilars. One of the main concerns that prompted the regulation of biosimilars was the financial sustainability of the health system.

The Colombian regulation of biological considers 3 options:

- 1. Full dossier option. The applicant is requested to submit preclinical (in-vivo and/or in-vitro) and clinical trials of the biological subject to evaluation (for new medicines)*
- 2. Comparability option (for medicines that are not new, but still not enough known and contain complex active ingredients (AI), the reason why pre-clinical and comparative clinical studies with the new medicine are required.*
- 3. “Fast track” comparability option (for medicines completely known and which has wholly characterised AI). It is therefore assumed that there is no point in duplicating the experiments with animals and humans, nor doing them as long and complex.*

The approval of the decree generated a hot debate. Criticisms from originator manufacturers and the US government mainly pointed to the fast track comparability option, claiming that it opens the entry in the Colombian market of biotechnological non-comparable products of uncertain quality.

Cuba

Cuba has a large diversified biotechnological industry, especially if one considers its size and the general industrial development. This result has been attained thanks to a strong commitment of the government, which gave a high priority to health. Production was centralised in Medicuba, created in 1972, that soon began the production of biosimilars. Several biotechnology institutes were set up and in 1993 the recombinant streptokinase was launched. Research seems aimed at diseases of high mortality.

Cuba adopted ICH quality standards, which allows it to make direct applications for market authorisation in (and export to) higher income countries, such as Argentina,

Brazil, Colombia and Mexico. The Centro de Inmunología Molecular (CIM) reports the registration of products in 50 countries. Up until October 2010, 133 biological products have been licensed, of which 67 are locally manufactured. For locally produced approved products, vaccines are the largest product type followed by alfa interferon and blood derivatives, whilst for imported products, insulins as well as pegylated compounds ranked first, followed by vaccines.

Cuba does not produce insulin apparently for two reasons. First, there is the technological difficulty of insulin manufacturing. The second one is the fact that Cuba gets a relatively low price from its single supplier, Novo Nordisk (personal communication from Dra. Dulce María Calvo Barbado, MINSAP).

The Ministerial Resolution “Requirements for Marketing Authorization, Renewal and Variation Applications of Medicinal Products for Human Use” describes the information to be submitted for marketing authorization. The volume of data to be presented depends on the category of its classification. That is, for a category A product a full dossier is required for quality, non-clinical and clinical information whereas for a category C product, a reduced data package could be accepted particularly for non-clinical and clinical information. Most of the biological products were licensed on a basis of a full dossier for quality, non-clinical and clinical data. Nevertheless some products were approved considering comparability information for non-clinical and/or clinical data... Regarding the products included on category C, there is a particular case for biological products that claim to be similar to an already approved biological product. In this case the term known biological product instead biosimilar was adopted in Cuba, as this term is defined in our regulations.

Although the rules for marketing authorization establish the legal basis for the approval of known biological products, there is not yet any biological product approved under this category.

Iran

According to Business Monitor International predictions, the pharmaceutical market in Iran was worth US\$3.26 billion in 2011, with a compound annual growth rate of 12.2 percent. Iran produces 95 percent of its medicines locally, of which 5 percent are biosimilars. Iran is the only country in the region that has the capability to produce such a high proportion of medicines domestically.

Iran started biopharmaceutical projects about 10 years ago. As it is not a member of the WTO and has not signed the TRIPS, it has not IP restrictions to produce medicines on-patent in other countries.

Biopharmaceuticals which were produced in past decade did not receive comprehensive evaluation according to those of internationally recognized guidelines for biosimilars. Registration of these biopharmaceuticals has mainly followed registration path for “biogeneric” medicines and their application for marketing authorization handled based on case by case. Since 2003 about 6 biopharmaceuticals produced as non originator copy have been registered by Iran national authority. A national guideline which was mainly adapted from WHO guideline, made since 2006 performing a double blind controlled clinical trial with small sample size for locally manufactured biopharmaceuticals obligatory. However, there are clearly differences between WHO

guideline and current Iran national guideline for registration of locally produced biopharmaceuticals.

Following close cooperation with WHO over the past decade, the Iran NRA prepared a draft guideline on the registration of biosimilars based on the WHO draft guideline of 2009. This was revised in two steps based on WHO draft guideline changes. It has been finalized and approved in September 2010 by the Iran expert committee on biologicals and as the last step approved by the Head of the Iran FDA in February 2011. After its issuance, there will be a six month time limit for manufacturers to implement the guideline. The guideline will not apply to previously registered products.

Most clinically important biopharmaceuticals, especially recombinant proteins, are manufactured locally by Iran's national industry, but not insulin. Medicines, including biopharmaceuticals in Iran, have their prices set by national authorities... The prices of locally manufactured biopharmaceuticals are between 27–72 percent lower than their corresponding imported original brands.

China

China's biopharmaceuticals industry began in the 1980s, when the Chinese government introduced a series of national programs and placed biotech and related industry as one of the "major development sectors." Today, Chinese biopharmaceutical companies have marketed 361 recombinant biogenerics (including therapeutics and vaccines) and 25 biotech medicines. More than 10 innovative biotech medicines have been launched into the market, and more than 100 biopharmaceuticals are currently at clinical trial stages.

Biopharmaceutical production value has grown from \$30 million in 1986, to \$4.2 billion in 2005. In 2005, biopharmaceuticals accounted for 7 percent of the pharmaceutical market. According to the China Biopharmaceutical Engineering Industry Outline, the country's biopharma industry production value is projected to exceed \$12.5 billion by 2015.

Domestic copy biologicals have been on the market in China for 20 years. The first recombinant human interferon beta 1 was launched in 1989. Domestic erythropoietins, granulocyte colony-stimulating factors and monoclonal antibodies are also commercialized in China. The country has approved 382 genetically, but only 21 products are innovative and the rest are copy biologicals.

Since biogenerics account for over 95 percent of China's biopharmaceuticals, the biopharmaceutical industry in China today is virtually a biogenerics industry. The approval of the Guidelines means that biosimilars approval will now include a rigorous comparability exercise with the reference product, which can fuel the development of biosimilar production in China.

CFDA, the medicines regulatory agency of China, issued technical guideline for development and evaluation of biosimilars on the 5th of March 2015, which specify relevant requirements on the application procedure, registration classification, and application documents of biosimilars.

Before the guidance was approved, biosimilars had to go through a new approval process, as is the case for all biologicals. This means that phase III trials had to be carried out.

The new guidelines have nevertheless raised some criticisms from some organisations, such as the U.S.-based Biotechnology Industry Organization (BIO) and the China-based R&D Pharmaceutical Association Committee (RDPAC), which “*want changes in the China FDA's most recent biosimilar approval guidelines, particularly a provision that allows for additional assessment of a biosimilar candidate if a comparability study showed differences between the candidate and its reference product*” and ask for clarification on some points, although they globally applaud the new regulation.

Ecuador

The main health law in Ecuador outlines the procedures for authorising new medicines. A by-law develops the medicines registry. An addendum to the by-law was finally approved specifically for biological medicines (originators and biosimilars). The Agencia Nacional de Regulación, Control y Vigilancia Sanitaria-ARCSA (the medicine regulatory agency of Ecuador) authorises new medicines on the basis of a documentary procedure or by homologation, which applies if the product has been approved by the medicine regulatory agencies of some predefined countries.

Ecuador is one of the most active countries in the region regarding compulsory licensing. Ecuador issued a CL and then authorised infliximab - a treatment for rheumatoid arthritis - using the homologation route (infliximab had been approved by the EMA). ENFARMA (a state owned company) played an active role in searching for an appropriate supplier of infliximab and obtained in 2013 the registry of the first biosimilar. Recently it started importing and marketing REMSIMA, a biosimilar version of infliximab manufactured by Clarion in South Korea.

3. Conclusions

Main Findings

The main findings of the literature review are:

Most of the articles retrieved are dealing with regulation on marketing authorization (relating to safety, efficacy and quality), but no academic articles - nor much gray literature - has been found on pricing and reimbursement issues and other types of regulation for insulin biosimilars, e.g. interchangeability and substitutability.

Several countries have introduced general biosimilar guidelines for marketing authorisation, starting by the EMA/EU in 2005. We found only two insulin-specific guidelines on biosimilars (EU and Saudi Arabia). Some references to insulin are however found in general guidelines and, of course, most of the content of general biosimilars guidelines applies to insulin.

"According to these (insulin-specific EMA) guidelines, in the MAA dossier for an insulin biosimilar the applicant has to fully characterise the manufacturing process, the active substance, including the structures, the variants and the isoforms, as well as each component included in the final formulation. The biosimilar must not be

identical to the reference product in terms of formulation or excipients but the changes made should be appropriately justified and they do not have to impact on the safety of the final product". The clinical studies required for insulin biosimilars include a pharmacokinetic (PK) study and a pharmacodynamic (PD) study to demonstrate comparability with respect to the time-effect profile of hypoglycemic effect (Franzè et al. 2015)

There is not much information on some of the countries selected as a pilot sample for our study. Data gathering will have therefore to rely in these cases on a survey and/or personal contacts with local informants.

The two main benchmarks for the regulation of biosimilars are the EU and the WHO guidelines. The EU guidelines are more specific and demanding for applicants than those of WHO. Countries usually refer to one of the two models when developing their own national guidelines. Countries which have an internationally competitive domestic industry and intend to export to foreign markets try to reach the more stringent EU and even ICH standards, whereas low-income countries that see local affordability and sustainability as their main priorities tend to rely on the less specific WHO guidelines.

The first EU marketing authorization of insulin biosimilars was approved in September 2014, but insulin biosimilars/copies have been available for several years in countries such as China, India, Pakistan, Peru, Thailand, Mexico, etc. These products were authorised before any rigorous biosimilars regulation was introduced in the respective country.

Patent protection for several insulin analogues expired on June 2014 and others will follow in the coming years. This makes the debate on insulin biosimilars regulation very relevant and timely. Insulin implies a significant expenditure for many countries. There are expectations that biosimilars can increase market competition, making insulin treatment more affordable and providing saving/cost reduction to the healthcare system/payers that are already providing it to the population in need.

There are some concerns among doctors and patients on the issues of interchangeability (by doctors) and substitutability (by pharmacist). Most countries do not address these topics explicitly.

4. Discussion

The regulation of biosimilars is a complex matter, which raises public health (access, safety and efficacy) as well as economic concerns (affordability, financial sustainability, feasibility of local production)

Although there seems to be consensus on the fact that therapeutic equivalence is more difficult to attain in biologic medicines compared to traditional molecules obtained by chemical synthesis, there is still an apparently technical debate on the precise requirements that biosimilars should fulfil in order to be properly considered similar or therapeutically equivalent. But, in fact, there seem to be strong hidden economic motives behind the technical arguments made by the various interested parties.

Regulatory standards of pharmaceuticals have both strong health and economic implications, and it is difficult to discuss and define the appropriate quality standards

taking only into account their health effects. For the originator firms, higher regulatory standards and requirements reinforce their market position at the expense of the non-originators and buyers. On the other hand, national health authorities might judge certain requirements unjustified from a public health perspective and detrimental for the financial sustainability the health systems and for the development of local pharmaceutical production.

The biosimilars debate seems to mimic, to a large extent, the previous – and in some countries still on-going - debate on the quality, equivalence, substitutability and interchangeability of (small-molecule) generics vs. the originators/reference products. Substitutability and interchangeability are also essential issues in the present debate on biosimilars. These characteristics are essential from an economic point of view, as they condition the level of potential competition that the entry of the biosimilar will produce on the market. If the biosimilar is not legally defined as substitutable or interchangeable, is very unlikely that doctors are willing to prescribe it and patients to use it. In fact, most regulations are not very clear on these issue. Unlike the FDA, the EMA does not even intend to take a position on the interchangeability of the biosimilars it authorises and leaves it up to the national authorities.

Access to biosimilars in general and to insulin biosimilars in particular seem to depend on a set of factors. Some factors are related to the general socio-economic characteristics of a country and its health system and more specifically to whether (and how far) the latter covers the medicine needs of the population (proportion of the population covered, inclusion of insulin products in the positive list, existence and level of co-payments for insulin products, etc).

A second factor is the strength of patents and other market exclusivity rights in the country concerned and whether (and how) far IP protection affects insulin products. For instance, if the former rights have a longer duration, this will mean a stronger barrier to biosimilar entry and competition.

An equally important point refers to the technical regulatory requirements for granting marketing authorisation to a biosimilar. The requirement of clinical trials of longer duration and larger population imposes higher costs to potential biosimilar manufacturers and hence becomes a strong entry barrier. The same can be said on the requirements of similarity in the effects of a biosimilar insulin in relation to the reference insulin.

The regulation of substitutability and interchangeability also affects the relative market power of originators and biosimilars. If these characteristics are not allowed and promoted, it will be more difficult for biosimilars to attain market penetration.

Related to the previous point is the issue of INN vs. brand names in labelling and prescribing. Use of brand names leads to product differentiation and brand loyalty, which work against product substitution, irrespective of legal substitutability and interchangeability rules.

Main Information Gaps and Proposed Next Steps

As indicated above, the literature review has provided an acceptable amount of information on the regulation of safety, efficacy and quality, but much less on the issues

of substitutability and interchangeability and almost nothing on the more economic types of regulation, such as intellectual property rights and price control. It might well be the case that, similar to technical regulation – where only the EU and Saudi Arabia have introduced insulin-specific rules – most countries do not apply insulin-specific economic regulations. Still, in order to get a good picture of the main barriers of access to insulin it would be necessary to know more about these types of regulation.

In order to assess the strength of technical regulations as market barriers it would be necessary not only to identify which requirements are in place, but to quantify or estimate the impact of alternative regulatory options in terms of additional cost and health risks. For instance, it would be necessary to assess the cost of clinical trials requested by a given MRA for granting marketing authorisation.

Some of these issues can be addressed by means of a survey to and personal communications from health authorities, regulators and biosimilars manufacturers. Annex 4 contains a draft questionnaire that can be used either as a written questionnaire or as an outline for personal semi-structured interviews. We advocate for a sequential mix of the two approaches, starting with the written questionnaire and trying to get more in depth information from countries which appear to apply best practices

Another important question to consider in designing the following steps of the study is:

Should the teams continue working under the present vertical approach - i.e. collecting information on their specific topics with limited or no coordination at country level? Or would it be better to take an horizontal approach – i.e. the ACCISS teams agreeing on a set of questions/information to be collected and addressing country informants as a single team?

5. References

Below are the references for this article divided by a summary of academic journal articles (Annex 1), country information (Annex 2) and references found in the literature search.

Annex 1.

Summary of the Academic Journal Articles Found in the Literature Search

1. Heinemann L, Khatami H, McKinnon R, Home P. An Overview of Current Regulatory Requirements for Approval of Biosimilar Insulins. *Diabetes Technol Ther*. 2015 Mar 19. <http://online.liebertpub.com/doi/pdfplus/10.1089/dia.2014.0362>

The authors searched the websites of a number of MRAs, as they found that a conventional search did not yield satisfactory results (they provide only information from websites written in English). The results provide the most comprehensive and updated review (up to August 2014) of the regulatory guidelines for biosimilar insulin and biosimilars regulation that is relevant for insulin biosimilars in 34 countries. Thirteen countries are found to have enacted guidelines for biosimilars: Australia, Canada, China, Colombia, Cuba, Egypt, the EU, Jordan, India, Iran, Malaysia, Mexico, New Zealand, Saudi Arabia, South Africa, South Korea and the US (Brazil, Colombia, Cuba and Iran are the only countries selected in the sample of our study which were not considered in the paper by Heinemann et al.).

Only the EU and Saudi Arabia have guidelines providing details specific to insulin biosimilars. However, there are some references (insulin-specific guidance) in the general biosimilar guidelines - see below.

TABLE 1. INSULIN-SPECIFIC GUIDANCE IN GENERAL BIOSIMILAR GUIDELINES

Country	Year	Insulin-specific guidance	Comments
Australia	2013	Crystal structure should be determined where this is necessary for action, such as for protamine zinc insulin; refer to product-specific guidelines from the EMA	Adapted from the 2005 EMA guidelines
Canada	2008	Specific nonclinical or clinical information (not specified) may be required for some products, including insulin; recombinant human soluble insulin products are an exception to the requirement for comparative clinical efficacy trials; only a comparative clinical safety study is required	Based on the WHO and EMA guidelines
Malaysia	2008	Requirements for drug classes such as insulins may vary (no specific guidance)	Reference to EU/EMA guidelines
India	2012	Recombinant human soluble insulin products are an exception to the requirement for comparative clinical efficacy trials; only a comparative clinical safety study is required	Based on the WHO and EMA guidelines
Egypt	2012	For clinical studies of insulin, the study population should consist of nonobese healthy volunteers or patients with type 1 diabetes, rather than insulin-resistant obese patients with type 2 diabetes	Based on the WHO, EMA, and ICH guidelines
South Africa	2012	Well-characterized, low-molecular-mass, medicinal biological compounds may be excluded by specific Council decision from biological medicine status	Based on the WHO and EMA guidelines
Jordan	Draft 2013	Requirements for some drug classes such as insulins may vary; EMA guidelines (EMA/134217/2012) are presented	Apply EMA guidelines

EMA, European Medicines Agency; EU, European Union; ICH, International Conference on Harmonisation; WHO, World Health Organization.

2. Greene JA, Riggs KR. Why is there no generic insulin? Historical origins of a modern problem. N Engl J Med. 2015 Mar 19;372(12):1171-5

This article describes the history of insulin (discovered in 1921), the importance of patents for controlling quality (their goal was not profit), or how the innovations in insulin in the 70s "helped to improve purity and reduce these side effects". In 1988, the first recombinant insulin came to the market from Novo Nordik. "Glargine became the first long-acting analogue insulin in 2000, followed by Detemir in 2005; the first patents on these products expired in June 2014".

"Last summer, Lilly and Boehringer Ingelheim announced that the Food and Drug Administration (FDA) had granted tentative approval to a biosimilar version of insulin glargine. Other companies have also announced plans to produce biosimilar analogue insulins in the United States. The European Medicines Agency (EMA) recently granted approval to the first biosimilar glargine on the European market, and unregulated biosimilar insulins have already popped up in countries with less-stringent regulatory bodies, including China, India, Mexico, and Peru."

"The history of insulin highlights the limits of generic competition as a public health framework. Nearly a century after its discovery, there is still no inexpensive supply of insulin for people living with diabetes in North America, and Americans are paying a steep price for the continued rejuvenation of this oldest of modern medicines".

3. Franzè S, Cilurzo F, Minghetti P. Insulin Biosimilars: The Impact on Rapid-Acting Analogue-Based Therapy. BioDrugs. 2015 Mar 14.

This article focuses on rapid-acting insulin analogues and the EU regulation framework, taking into account that the patent of some of them have expired or will expire soon.

Key Points

The first biosimilar of an insulin-based product has been recently approved in the EU.

Three rapid-acting analogues are available on the EU market; they have slightly different pharmacokinetic parameters that don't seem to influence the safety and efficacy profile.

Market availability of a rapid-acting analogue biosimilar will have an impact on the prescription of all the products in the same class and their use in clinical practice.

In this case, the problem addressed is that *"recombinant proteins are obtained by complex biotechnological processes, molecules produced by different manufacturers may present different structural features that can lead to distinct pharmacokinetic (PK) and pharmacodynamic (PD) profiles"*.

There are specific guidelines for insulin in Europe - EMA. *"According to these guidelines, in the MAA dossier for an insulin biosimilar the applicant has to fully characterise the manufacturing process, the active substance, including the structures, the variants and the isoforms, as well as each component included in the final formulation. The biosimilar must not be identical to the reference product in terms of formulation or excipients but the changes made should be appropriately justified and they do not have to impact on the safety of the final product"*. Then, the article describes the characteristics of the EMA guidelines on quality clinical and non-clinical issues for similar biological medicinal products containing biotechnology-derived proteins as the active substance.

4. DeVries JH, Gough SC, Kiljanski J, Heinemann L. Biosimilar insulins: a European perspective. Diabetes Obes Metab. 2015 May;17(5):445-51

This article focuses on the European clinical and regulatory perspective for biosimilar insulin. The article clarifies the difference between generics and biosimilar (*"for a generic drug, it is usually sufficient to demonstrate pharmaceutical equivalence (identical amounts of same active ingredient in the same dosage form) and bioequivalence to the reference drug to obtain regulatory approval. In contrast, for a biosimilar drug, the EMA requires a comprehensive analysis, that includes an extensive head-to-head comparison of the new product's characteristics (physicochemical and biological activity), pharmacology and clinical safety and possibly efficacy outcomes, with those of the reference biological product."*)

As it is indicated in the article *"The EMA considers the 'demonstration of similar pharmacokinetic and pharmacodynamic profiles' as 'the mainstay of proof of similar efficacy of the biosimilar and the reference insulin.'"*

EMA requisites

** For the primary endpoints in the pharmacokinetic studies (i.e. the area under the curve and the maximum concentration), the goal is to show that the 90 percent confidence interval of the ratio test/reference is within the range 80–125 percent, the conventional acceptance range for bioequivalence, unless otherwise justified.*

** The primary endpoint for pharmacodynamic studies is based on the area under the curve of the glucose-infusion rate (GIR) over time and the maximum GIR.*

Secondary pharmacodynamic endpoints are the time to reach maximum GIR and the time to reach half-maximum GIR.

** The EMA requires that clinical trials of at least 12 months' duration are conducted to collect safety and immunogenicity data, with a comparative phase of at least 6 months' duration to be completed before approval.*

** The primary outcome measure for immunogenicity is the incidence and titres of antibodies to the biosimilar and the reference insulin.*

5. Dolinar RO, Edelman S, Heinemann L, Home P, Goyal S, Polonsky WH, Schellekens H. Impact of Biosimilar Insulins on Clinical Practice: Meeting Report. *J Diabetes Sci Technol.* 2014 Jan 1;8(1):179-185

"The clinical studies required for insulin biosimilars include a pharmacokinetic (PK) study and a pharmacodynamic (PD) study to demonstrate comparability with respect to the time-effect profile of hypoglycaemic effect. According to the guidelines, there is no anticipated need for specific efficacy studies since endpoints used in such studies (usually HbA1c) are not considered sensitive enough for the purpose of showing biosimilarity of two insulins. The guideline states that the study population should be homogenous and insulin-sensitive to best detect potential product related differences and may consist of normal-weight healthy volunteers or patients with type 1 diabetes"

"A key concern is ensuring the long-term safety of biosimilar insulins after they have been approved. Although pharmacovigilance legislation and practice, including risk management plans (RMPs), are currently undergoing considerable change and development in the EU, it is uncertain whether diabetologists have a good understanding of how such procedures should be performed, and how to implement these guidelines in clinical practice. One obstacle to effective pharmacovigilance is that European physicians currently have no incentive to consistently report adverse effects of the medications they prescribe. Moreover, how biosimilars are identified can impact the traceability of biosimilar insulins, which is important if safety issues related to immunogenicity emerge".

6. Carter AW. FDA-approved biosimilar insulin: good enough for critical care, adulterated, or counterfeit? How can we tell? J Diabetes Sci Technol. 2014 Sep;8(5):1052-4

The author proposes to create a post-market surveillance system through a random selection of 0.001 percent of the containers produced for complete comparison assay to the FDA's original files to prevent undesired outcomes.

Abstract. "If a biosimilar insulin is discovered post-marketing to be subpotent, superpotent, or contaminated or the contents mislabelled, it is an adulterated product and must be quarantined for removal including from a patient's home. Adulterated products could be considered "counterfeit" since they do not meet the original standards established by the FDA. The FDA must establish a method of regularly assaying samples of biosimilar insulin drawn directly from the supply pipeline to help ensure patient safety and evaluate clinical performance. Independent groups without conflict of interest would perform confidential comparison assay. For less than 5 cents per vial/pen, manufacturers could easily support an independent, FDA-recognized, random sample program and create a functional post-market surveillance system that better protects the public and the manufacturer from undesired outcomes"

7. Minocha M, Gobburu J. Drug Development and Potential Regulatory Paths for Insulin Biosimilars. J Diabetes Sci Technol. 2014 Jan 1;8(1):14-19.

This articles focus on the clinical aspects of developing insulin biosimilars, comparing EMA and FDA regulation.

Abstract. "Under the Biologics Price Competition and Innovation Act (BPCI Act), a biological product may be demonstrated to be "biosimilar" if data show that, among other things, the product is "highly similar" to an already-approved biological product. Biosimilar insulins have the potential to reduce ever growing costs associated with insulin treatment by allowing competition. In this article, we describe the current drug development and regulatory paths for biosimilar insulins. Most likely basis of market approval for biosimilar insulins by the US Food and Drug Administration (FDA) and guidance for developing insulin biosimilars by European Medicines Agency (EMA) are discussed in detail. Currently, no product specific biosimilar FDA guidance for insulin biosimilarity assessment exists. We propose efficient and cost-effective drug development and potential regulatory paths based on scientific justification. In addition, novel trial designs for demonstrating interchangeability between the biosimilar and the reference insulin products are presented."

8. Heinemann L, Hompesch M. J. Biosimilar Insulins: Basic Considerations. Diabetes Sci Technol. 2014 Jan 1;8(1):6-13.

Table 1. Differences Between Generics and Biosimilar Insulins.

	Generics	Biosimilar insulins
Product characteristics	Small molecules	Large complex molecules
	Often very stable	Stability requires maintain cooling chain
	Typically taken orally	Devices are often the differentiating factor
Production	Produced by chemical synthesis	Produced in living organisms
		Highly sensitive to manufacturing changes
		Often high production costs
Development	Very limited clinical trials (only bioequivalence studies)	Significant R&D (ie, cell lines)
		Clinical trials to a limited extend
Regulation	Shorter registration procedures in Europe and the United States	Regulatory pathway defined by EMA
		“Comparability” status
	Usually enjoy “substitutability” status	In United States; not part of the BPCI Act
Marketing	No or limited detailing to physicians	Detailing to (specialist) physicians required
		Pharmacists may not substitute (depends on national law)
	Market substitution in pharmacies	Price sensitivity is product specific

Annex 2.

Detailed Country Information

United States

Biosimilars regulation

The Patient Protection and Affordable Care Act (Affordable Care Act), signed into law by President Obama on March 23, 2010, amends the Public Health Service Act (PHS Act) to create an abbreviated licensure pathway for biological products that are demonstrated to be “biosimilar” to or “interchangeable” with an FDA-licensed biological product. This pathway is provided in the part of the law known as the Biologics Price Competition and Innovation Act (BPCI Act). Under the BPCI Act, a biological product may be demonstrated to be “biosimilar” if data show that, among other things, the product is “highly similar” to an already-approved biological product.

A biosimilar product is a biological product that is approved based on a showing that it is highly similar to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products.

An interchangeable biological product is biosimilar to an FDA-approved reference product and meets additional standards for interchangeability. An interchangeable biological product may be substituted for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product.

FDA requires licensed biosimilar and interchangeable biological products to meet the Agency’s rigorous standards of safety and efficacy. That means patients and health care professionals will be able to rely upon the safety and effectiveness of the biosimilar or interchangeable product, just as they would the reference product.

<http://thehill.com/blogs/congress-blog/healthcare/207642-regs-and-costs-will-bring-a-decade-of-limited-biosimilars>

For more information about biosimilars, visit the links below and FDA’s consumer, health care professional and industry pages on biosimilars.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm>

This article explains the likely barriers to market access of biosimilars in the US. <http://gabi-journal.net/barriers-to-market-uptake-of-biosimilars-in-the-us.html>

Press release: Approval of Zarzio, 1st Biosimilar in the US

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm>

<http://www.drugs.com/news/biosimilars-2015-can-we-expect-55159.html>

European Union/Europe

Biosimilars regulation

"The precautionary approach adopted by the EMA for biosimilars is exemplified by the fact that, in Europe, the first Marketing Authorisation for a copy of a specific insulin was only issued in September 2014, whereas many applications had been submitted and various insulin biosimilars were already on the market in other countries, such as China, India, Pakistan, Peru, Thailand, and Mexico". Franzè

<http://www.slideshare.net/eipg/regulatory-perspectives-on-biosimilars-in-europe>

<http://www.mmm-online.com/sandoz-gets-ready-to-make-the-biosimilar-case-with-oncologists/article/393451/>

EMA Draft Guideline on Biosimilar Insulin Products, Posted 18 December 2012

<http://www.raps.org/focus-online/news/news-article-view/article/2655/ema-publishes-draft-guideline-on-biosimilar-insulin-products.aspx#sthash.7weNueWA.dpuf>

European Medicines Agency. Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues. EMEA/CHMP/BMWP/32775/2005_Rev.1. 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/12/WC500136392.pdf.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/12/WC500136392.pdf.

2012/12/WC500136392.pdf.

European Medicines Agency. Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues. EMEA/CHMP/BMWP/32775/2005_Rev.2. 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/04/WC500165988.pdf.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/04/WC500165988.pdf.

2014/04/WC500165988.pdf.

Authorised biosimilar products

Table 1 Insulin medicinal products authorised in the EU with a centralised procedure

Insulin class	INN	Proprietary name	Manufacturer of the biological active substance responsible for batch release	MA date
Rapid-acting insulin	Insulin aspart	NovoRapid	Novo Nordisk A/S	07/09/1999
Rapid-acting insulin analogue	Insulin glulisine	Apidra	Sanofi-Aventis Deutschland GmbH	27/09/2004
Rapid-acting insulin analogue	Insulin lispro	Humalog	Eli Lilly	30/04/1996
Rapid-acting insulin analogue	Insulin lispro	Liprolog	Eli Lilly	01/08/2001
Short-acting insulin (neutral insulin solution)	Insulin human (rDNA)	Actrapid	Novo Nordisk A/S	07/10/2002
Short-acting insulin (neutral insulin solution)	Insulin human (rDNA)	Insulin Human Winthrop Rapid	Sanofi-Aventis Deutschland GmbH	17/01/2007
Short-acting insulin (neutral insulin solution)	Insulin human (rDNA)	Insuman Rapid	Sanofi-Aventis Deutschland GmbH	21/02/1997
Intermediate-acting insulin (insulin + protamine isophane)	Insulin human (rDNA)	Insulatard	Novo Nordisk A/S	07/10/2002
Intermediate-acting insulin (isophane insulin suspension)	Insulin human (rDNA)	Insuman Basal	Sanofi-Aventis Deutschland GmbH	21/02/1997
Intermediate-acting insulin (insulin + protamine isophane)	Insulin human (rDNA)	Insulin Human Winthrop Basal	Sanofi-Aventis Deutschland GmbH	17/01/2007
Intermediate-acting insulin (insulin protamine suspension)	Insulin lispro	Liprolog Basal	Eli Lilly	01/08/2001
Intermediate-acting insulin (insulin isophane [NPH] suspension)	Insulin human (rDNA)	Protaphane	Novo Nordisk A/S	07/10/2002
Mix of short-acting (soluble) insulin and intermediate-acting insulin (isophane)	Insulin human (rDNA)	Actraphane	Novo Nordisk A/S	07/10/2002
Mix of short-acting (soluble) insulin and intermediate-acting insulin (isophane)	Insulin human (rDNA)	Insuman Comb	Sanofi-Aventis Deutschland GmbH	21/02/1997
Mix of short-acting (soluble) insulin and intermediate-acting insulin (isophane)	Insulin human (rDNA)	Insulin Human Winthrop Comb	Sanofi-Aventis Deutschland GmbH	17/01/2007
Mix of short-acting (soluble) insulin and intermediate-acting insulin (isophane)	Insulin human (rDNA)	Mixtard	Novo Nordisk A/S	07/10/2002
Mix of rapid insulin lispro and intermediate-acting insulin lispro-protamine	Insulin lispro	Liprolog Mix	Eli Lilly	01/08/2001
Mix of rapid-acting insulin aspart and intermediate-acting protamine-crystallised insulin aspart	Insulin aspart	NovoMix	Novo Nordisk A/S	01/08/2000
Long-acting insulin analogue	Insulin glargine	Lantus	Sanofi-Aventis Deutschland GmbH	09/06/2000
Long-acting insulin analogue	Insulin glargine	Optisulin	Sanofi-Aventis Deutschland GmbH	27/06/2000
Long-acting insulin analogue	Insulin detemir	Levemir	Sanofi-Aventis Deutschland GmbH	01/06/2004
Long-acting insulin	Insulin degludec	Tresiba	Novo Nordisk A/S	21/01/2013
Mix of long-acting insulin (degludec) and rapid-acting insulin aspart	Insulin degludec/insulin aspart	Ryzodeg	Novo Nordisk A/S	21/01/2013

Source: France

Brazil

The literature search (three page Google search: biosimilars in Brazil (150420) provided a comprehensive picture of the situation in Brazil.

The biopharmaceutical market

“In 2011, the Brazilian Government spent US\$ 4.9 billion on the importation of medicaments [5], and among them, 8 biopharmaceuticals imported represented 18 percent of the total costs, including: philgastim, glucagon, growth hormones, human recombinant insulin, α -interferon, β -interferon and somathrophin. For this reason, the development of biosimilar molecules in Brazil can be seen as a strategy for the improvement of Brazilian Biopharmaceutical Industries” Baso et al 2013 p.60 (<http://omicsonline.org/biopharmaceutical-and-biosimilar-products-in-brazil-from-political-to-biotechnological-overview-jbb.1000135.pdf>)

“Moreover, in Brazil, the Government elaborated the Politics for Biotechnology Development, through the Decree 6.041 (February, 8 of 2007), which incentivized Brazilian companies to produce national biosimilar molecules in order to reduce costs of medicaments and strengthen the bioindustry of the country [33]. Hence, the production of biopharmaceutical and biosimilar components by a Brazilian Biotechnology company is of extreme importance for the country, once that it will establish an alternative path, instead of the acquisition of high cost important medicaments.” Baso et al 2013 p.63

Industrial policy

The generic and biosimilar industries are of relatively recent origin in Brazil. They were created through the publication of:

Law No. 9,782 of 26 January 1999, which founded ANVISA.

Law No. 9,787 of 10 February 1999, which defined similar medicines, generic medicines, reference medicines and interchangeable pharmaceutical products.

The Executive Group of the Industrial Health Complex (GECIS) (Grupo Executivo do Complexo Industrial da Saúde) was established by Decree of 12 May 2008 to address these deficiencies in production and technology, and other imperfections in the health sector, and to contribute to reducing the vulnerability of the domestic pharmaceutical productive chain. As a result of this, the Ministry of Health has compiled a list of strategic products, and the GECIS proposed public private partnerships (see below, Public private partnerships).

Strategic products

The Ministry of Health formulated a list comprising strategic products for SUS (Sistema Único de Saúde), where domestic production should be undertaken to reduce the deficit in the sector. Strategic products are divided into pharmaceutical products (including products of high social significance, high technological and economic value, and so on), and medical devices and health support devices (Ordinance No. 1284 of 26 May 2010).

Public private partnerships

The Ministry of Health has proposed "partnerships" between public (government-owned) and private industries, with the aim of transferring technology to nationalise the production of strategic products and their active pharmaceutical ingredients (APIs).

Generally, two private companies are involved in partnerships, that is, an API source (supplier), usually foreign, responsible for transferring the technology to the public laboratory (buyer), and a domestic private pharmaceutical industry, used to outsource production for the public government-owned pharmaceutical industry.

GECIS would manage the partnerships and the public laboratories would receive government support in selecting the private partner. This model requires the selection of partners that are capable of transferring the technology not only to produce the finished product but also to ensure domestic manufacture of some parts of the API.

About 30 agreements between public and private pharmaceutical industries are pending or in progress (see table, Examples of partnerships for productive development (PDPs) with partners that are known to possess proven and reliable technology to transfer), usually established by discriminatory treatment, rendering the ability to compete for such agreements impossible, and in direct infringement of Law No. 8,666 of 1993 (concerning rules for biddings and public administration), and Law No. 9,279 of 1996 (concerning rights and obligations regarding industrial property).

In this scenario the lack of patent rights of many of the strategic medicines involved in the public private partnerships enables the government to conduct the processes with private Brazilian domestic partners, which have not developed the innovator products and have no technology to transfer, acting as "brokers" for undisclosed Chinese and Indian companies. These Brazilian companies are being called "surrogated companies", alleging that they are profiting from political connections with the Brazilian government.

Table: Examples of partnerships for productive development (PDPs) with partners that are known to possess proven and reliable technology to transfer

Governmental pharmaceutical industry	Private pharmaceutical industry	Medicine	Therapeutic category or indication
<i>Farmanguinhos (the biggest public laboratory)</i>	<i>Bristol-Myers Squibb</i>	<i>Atazanavir</i>	<i>Antiretroviral</i>
<i>Farmanguinhos</i>	<i>Roche</i>	<i>Mycophenolate mofetil</i>	<i>Immunosuppressant</i>
<i>Farmanguinhos</i>	<i>Boehringer</i>	<i>Pramipexole</i>	<i>Parkinson disease</i>

	<i>Ingelheim</i>		
<i>LAFEPE (Pharmaceutical Laboratory of Pernambuco State, the second biggest public laboratory)</i>	<i>Merck Sharp & Dohme</i>	<i>Raltegravir</i>	<i>Antiretroviral</i>

(Source: Ministry of Health and Oswaldo Cruz Foundation (FIOCRUZ) website www.fiocruz.br)

Conclusions of the paper

The Brazilian registry system for medicines does not follow worldwide standards. This lack of compliance represents the political choice made by the local government to reduce the barriers to the domestic pharmaceutical industries. A recent example of this industrial policy is the Public Consultation No. 10 of 23 January 2012, in which ANVISA proposes a resolution that states that generic or similar copies may be considered as reference products for comparison with new applications of generic and similar copies. The risk of a bio-creep phenomenon, which has been issued by the World Health Organization, was neglected by the government. In this scenario, it is possible to imagine that Brazilian legislation is lenient regarding the marketing approval of substandard medicines. This represents a huge challenge to public health in Brazil, especially because it is aligned with the absence of an effective system of pharmacovigilance.

Source: Industrial policy <http://us.practicallaw.com/3-518-3314?q=&qp=&qo=&qe=>

Biosimilars approved in Brazil

Brazil was one of the first countries in Latin America to issue guidelines for biosimilars.

Approximately 187 biosimilar applications have been approved by ANVISA by 2013. Examples of some of the biosimilars that have been approved and registered (namely, received marketing authorization by ANVISA) include:

1. Somatropin
2. Filgrastim
3. Enoxaprin
4. Etanercept, and
5. Recombinant erythropoietin (The individuals products are also provided in the document). No reference to insulin biosimilars has been found.

Source: Understanding Biologics and Biosimilars in Brazil. Posted on September 4, 2013 by lvmueller

<https://bricwallblog.wordpress.com/2013/09/04/understanding-biologics-and-biosimilars-in-brazil/>

According to Aceituno Álvarez (2014) *“In Brazil, two pathways for the approval of biosimilars have emerged: a ‘comparability’ pathway and an ‘individual development’ pathway. The comparative pathway is almost identical to the WHO guidelines on evaluation of Similar Biotherapeutic Products (SBP) [2]. In the ‘individual development’ pathway, quality issues and clinical study requirements are reduced relative to the comparative pathway, but an extrapolation of indications, one important and controversial point regarding biosimilars, is not permitted. The comparability pathway is more rigorous and requires comparative phase I and phase III trials to the reference biotherapeutic product (RBP) and will allow extrapolation into other indications [28, 29]. Copy products that are licensed using the comparability pathway are considered biosimilars. With government support and local production capabilities, the future commercial outlook of biosimilars in Brazil seems very promising. Under the new product development partnerships (PDPs) framework, local companies have made partnerships with international companies with expertise in producing both new biological products and biological products, see ‘Glossary of Terms’ below. The resulting products have a shorter timeline to approval and they also have a five-year exclusivity to sell their product to the Brazilian Government.”*

According to a post at GaBI, *“Brazil has now introduced new regulations to specifically address and establish specific pathways to license follow-on biological products. The Brazilian regulations (Resolution no. 55/2010) are based on different regulations and guidelines from around the world, including the WHO Similar Biological Product Guidelines. They follow the same scientific principles as the WHO guidelines but contain some differences due to the specific needs of Brazil. Concepts in the Brazilian guidelines that are common with the WHO guidelines include: use of a reference biological product based on a suitable period of market use and the demonstration of sufficient scientific information on quality, efficacy and safety, as well as the need for specific pharmacovigilance. ANVISA has the following guideline regarding follow-on biological products:*

1) Overarching Guideline: This guideline covers all follow-on biological products.

2) Resolução RDC nº 55 de 16 de dezembro de 2010. Dispões sobre o registro de produtos biológicos novos e produtos biológicos e da outras providências, Date: 16 December 2010, (www.sivs.org/pt/juridico/resolucoes/451-resolucao-rdc-no-55-de-16122010-dispoe-sobre-o-registro-de-produtos-biologicos-novos-e-produtos-biologicos-e-da-outras-providencias.html)

The guideline provides two regulatory pathways for follow-on biological products: a comparative pathway and an individual development pathway. In the individual development pathway, a reduced dossier can be presented. The applicant needs to present complete data regarding quality issues but it does not have to be comparative [1]. (Editor’s comment. It should be noted, however, that follow-on biological products approved in Brazil may not have been authorized following as strict a regulatory process as is required for biosimilars in the EU. EMA regulatory requirements ensure the same high standards of quality, safety and efficacy for biosimilars as for originator biologicals, and also include a rigorous comparability exercise with the reference product.)

Important terms for understanding Brazilian regulation of biologicals:

1. A “biological product” is a biological that is not new or is known and contains a molecule with known biological activity that is already registered in Brazil (namely, with ANVISA) and has undergone all stages of manufacturing (namely, formulation, bottling, lyophilisation, labelling, packaging, storage, quality control and release of the biological product batch for use). The following are considered to be “biological products”: a. Vaccines; b. Hyper-immune serums; c. Hemoderivatives; d. Biodrugs (i. Drugs obtained from biological fluids or tissues of animal origin; and ii. Drugs obtained by biotechnological procedures); e. Monoclonal antibodies; and f. Drugs containing live, attenuated or dead microorganisms.
2. A “new biological product” is a biological product containing molecules with known biological activity that are not registered in Brazil (namely, with ANVISA) and that have undergone all stages of manufacturing (namely, formulation, bottling, lyophilisation, labelling, packaging, storage, quality control and release of the new biological drug batch for use).
3. A “comparer biological product” is a biological product already registered with ANVISA based on submission of a complete dossier and that has already been sold in Brazil.

There are two routes by which a biological product registration may be filed:

1. Individual development route (used for new biological products and biological products); or
2. Comparability route (used for biological products, namely, biosimilars).

Individual Development Route

An applicant can seek regulatory approval for a new biological product or a biological product pursuant to the “individual development route.” Under the “individual development route,” not only must an applicant present all of the above information, but the applicant must provide a full report of all nonclinical studies as well and the complete protocols and reports of clinical studies (namely, phase I, II and III studies). Additionally, if available, data from phase IV clinical studies should be presented. An applicant submitting a new biological product or biological product registration application under this route must submit sufficient information and data (through nonclinical and clinical studies) to demonstrate the quality, safety and efficacy of the new biological product or biological product.

With respect to the nonclinical studies, the extent of these studies may be reduced depending on the complexity and the level of characterization of the molecule and the extent of the characterization of the biological product's impurity level, toxicity potential and therapeutic index. Regarding clinical studies, phase I, II and III studies are required with phase III studies being absolutely mandatory.

Brazil does not require that the phase I and II studies be comparative; however, phase III studies must be comparative when an application is for a new biological product (except in the case of hemoderivatives, vaccines and biological products having an oncology indication).

Comparability Route (Biosimilars)

An applicant can seek regulatory approval for a biological product pursuant to the "comparability route." The "comparability route" is a regulatory route that an applicant can use to obtain registration for a biological product by demonstrating comparability in terms of quality, efficacy and safety between a biological product and a "comparer biological product."

When an applicant files a biological product registration application under this route, not only must the applicant present all of the above information (namely, the detailed application and technical report), but must also submit the following documents:

- 1. A report with data on the biological product, including the following, mandatory information:
 - a. A description of the analytical techniques used to detect any potential differences between the biological product and the comparer biological product; and*
 - b. Data on the biological, physical and chemical characterizations related to the quality attributes of the biological product;**
- 2. A declaration providing the name of the comparer biological product;*
- 3. A declaration with evidence demonstrating that the same comparer biological product was used during the biological product's development studies;*
- 4. Information on the expression system used to manufacture the biological product and the comparer biological product;*
- 5. A comparison of the molecules comprising the biological product and the comparer biological product;*
- 6. Reports on the comparative analysis between the main active ingredients, whenever required;*
- 7. A report containing a detailed description of head-to-head comparability tests, with an indication of the capacity of the tests to detect differences in the quality attributes between the biological product and the comparer biological product;*

8. Reports of the comparative stability studies that have been generated in accelerated and under stress conditions according to the legislation in effect;
9. A report containing a description of the differences observed in the purity and impurity profile between the biological product and the comparer biological product;
10. An evaluation of the contaminants and impurities identified in the biological product and a discussion of their potential impact on the quality, safety and efficacy of the biological product;
11. An analytical characterization of the biological product and the comparer biological product;
12. Results of comparative biological tests to determine the level of comparability between the biological product and the comparer biological product; and
13. A conclusive report, including a demonstration of comparability, containing sufficient information to predict if the differences detected in the quality attributes result in an adverse impact on the safety and efficacy of a biological product.

All studies in a development program where registration is sought for a biological product through the comparability route must be of a comparative nature. Also, a biological product may not be considered to be comparable if the analytical procedures used are not sufficient to point out any relevant differences that could impact the safety and efficacy of the biological product and/or the relationship between specific quality attributes, safety and efficacy have not been established.

In addition to providing all of the above information, an applicant must also submit complete reports of nonclinical studies. The nonclinical studies must be comparative and designed to detect significant differences between the biological product and the comparer biological product. Specifically, an applicant must submit reports of the following *in vivo* nonclinical studies:

1. Relevant pharmacodynamic studies for the therapeutic indication intended; and
2. Cumulative toxicity studies (including at least one repeated dose), including a characterization of the parameters of toxicity kinetics conducted in a relevant animal species.

In addition to the nonclinical studies, an applicant must submit reports of the following clinical studies (including the protocols):

1. Pharmacokinetic studies;
2. Pharmacodynamic studies; and
3. Pivotal clinical safety and efficacy studies (namely, Phase III studies).

The pharmacodynamic and pharmacokinetic clinical studies can be combined provided that the pharmacokinetic/pharmacodynamic relationship is characterized. However, any comparative clinical studies must demonstrate the comparability in terms of the safety and efficacy profiles between the biological product and the comparer biological product. Moreover, the design and comparability margins of any

safety and efficacy studies must be statistically and clinically supported. Finally, data from a phase IV study must also be submitted if available.

Availability of regulatory/data exclusivity for biologics in Brazil

Brazilian law does not provide for specific periods (or “periods of non-reliance”) during which third parties are prohibited from obtaining registration (namely, marketing approval) for a biological product (biosimilar) from ANVISA by referring to an originator’s data for a comparer biological product. According to Law n^o 10,603, data/regulatory exclusivity periods in Brazil are only available for pharmaceutical products relating to veterinarian use, fertilizers, agrochemicals, their components and the like. Therefore, Brazilian law does not provide any regulatory/data exclusivity periods for new pharmaceuticals (small molecules) or new biological products (biologics) for human use.

Thus, in practice, ANVISA will register any generic drug (such as a branded or non-branded small molecule) or biological product (biosimilar) for human use any time after the registration of a new drug or new biological product (biologic). The only option available for an originator to try and secure regulatory/data exclusivity for its new drug or biologic would be by filing a lawsuit against ANVISA.

Source: Understanding Biologics and Biosimilars in Brazil. Posted on September 4, 2013 by lvmueller

<https://bricwallblog.wordpress.com/2013/09/04/understanding-biologics-and-biosimilars-in-brazil/>

Differences Between WHO And ANVISA Biologic And Biosimilar Guidelines

Table 1. Adapted from Castanheira, L.G. et al (2011).

1 Castanheira, L. G. et al (2011). Current development in regulation of similar biotherapeutic products in Brazil. *Biologicals*, 39, 308-311. Retrieved from <http://bit.ly/NVjsdh>

Comparison of Critical Components Between WHO and ANVISA Biosimilar Guidelines		
Critical Element	ANVISA*	WHO
Development pathway for similar biologic/biosimilar products	Comparative and individual pathway	Comparative pathway
Quality and Comparability	No reference to international guidelines	Reference to EMA guidelines and IHC documents
Pharmacovigilence	Specific pharmacovigilence plan and post-market reports	Specific pharmacovigilence plan and post-market reports
Extrapolation to additional indications	Extrapolation is possible, but additional guidelines needed	Specific guidance regarding extrapolation is provided
Pharmaceutical/therapeutic equivalence	Authorization of biosimilar does not indicate equivalence	Authorization of biosimilar does not indicate equivalence
Pre-clinical/clinical trials	Less detailed; specific guidelines to disease state/product will determine	More detailed; increased emphasis on design and statistical analysis

There are a number of similarities between the guidelines published by ANVISA and those from WHO. The Table provides highlights of the differences between the critical components of the WHO and ANVISA comparative guidance. As shown, the WHO regulations do not provide an individual pathway as outlined by the ANVISA guidelines. While both agencies provide for specific pharmacovigilence plans and post-marketing reports, WHO offers a more detailed approach surrounding the need for preclinical/clinical trials with an emphasis on design and statistical analyses.

In contrast, ANVISA intends to release subsequent guidelines specific to disease states/products that will provide additional details surrounding how much data will be required. In Brazil, only the copies licensed by the comparability pathway will be considered as a biosimilar and can therefore claim for extrapolation of indications.⁴ By considering guidelines from other global agencies, ANVISA has been able to adapt best practices into an approach that works best for Brazil.

<http://www.genengnews.com/gen-articles/biosimilars-in-brazil/4551/>

The generic and biosimilar industry is relatively new in Brazil. Despite the fact of having non-interchangeable, non-bioequivalent branded copies since the mid 1970s (similar), generic medicines were introduced into Brazil through Law No. 9,787 of 10 February 1999, as a government strategy to support the local industry and cope with the deficit in the trade balance of medicines and active pharmaceutical ingredients. Biosimilars are fairly recent developments (beginning in approximately 2002) with a new legal framework established in 2010. Major international players in the generic

business do not receive national treatment from Brazilian regulators, where 88 percent of the generic industries are local companies.

Biological products that were registered without comparative clinical studies.

Comparative clinical studies are required to obtain a marketing approval for copies of new biological products (see above, Marketing Approval). However, there are several examples of biological products where registration was approved by ANVISA without the presentation of these studies, including copies of enoxaparin and at least one copy of granulocyte colony-stimulating-factor (G-CSF).

Source: Industrial policy <http://us.practicallaw.com/3-518-3314?q=&qp=&qo=&qe=>

Beatriz Serrapio PeresI; Gabriela PadilhaII; Cristiane Quental. Relevant issues to biosimilars licensing. Rev. bras. epidemiol. vol.15 no.4 São Paulo Dec. 2012

<http://dx.doi.org/10.1590/S1415-790X2012000400007>

http://www.scielo.br/scielo.php?pid=S1415-790X2012000400007&script=sci_arttext&tlng=en

The article compares the regulation of biosimilars in the EU, US and Brazil.

09/12/2014 17h37 Orygen's plant for the production of biosimilars will be located in São Carlos.

This reference reports a “Joint venture between Biolab and Eurofarma expects to invest R\$ 500 million in the construction of the factory that will nationalize the production of drugs for diseases such as cancer and arthritis”

“Pfizer will begin the process of technology transfer for the production of up to five monoclonal antibodies to Orygen, which include the biosimilars Adalimumab, Bevacizumab, Infliximab, Rituximab and Trastuzumab used to fight diseases such as cancer and autoimmune illnesses.”

“For the construction of the plant, Orygen relies on the support from the National Bank for Economic and Social Development (BNDES) and the Financier of Studies and Projects (FINEP). The plant is expected to start operating in 2017, with the first drugs coming out in 2018.”

<http://www.en.investe.sp.gov.br/news/post/orygen-s-plant-for-the-production-of-biosimilars-will-be-located-in-sao-carlos/>

“Today, the National Sanitary Vigilance Agency (ANVISA) granted marketing authorization to Celltrion Healthcare Distribuidora de Produtos Farmaceuticos dos Brasil Ltda's (the Brazilian subsidiary of Celltrion, Inc. (a Korean company)) for the monoclonal antibody Remsima, a copy of Janssen's Remicade (infliximab). The

approved indications include rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, adult and pediatric Crohn's Disease, fistulizing Crohn's disease and adult and pediatric ulcerative colitis or retocolitis.

Today's approval is the first granted by ANVISA for a biosimilar monoclonal antibody. Celltrion's approval followed the abbreviated pathway as set forth in ANVISA's Rule #55/2010, which does not use the terms "biosimilar" or "biogeneric", but instead refers to a "new biologic product" for an innovator product and a "biologic product" for a biosimilar."

See report in Portuguese at:

<<http://portal.anvisa.gov.br/wps/content/anvisa+portal/anvisa/sala+de+imprensa/menu+-+noticias+anos/2015/primeiro+medicamento+biologico+por+comparabilidade+e+registrado+pela+anvisa>>

Posted on April 28, 2015 by lvmueller

<https://bricwallblog.wordpress.com/tag/brazil/>

Colombia

The literature search (three page Google search: biosimilars in Colombia 150422) resulted in an interesting set of grey literature.

The biological medicines market

According to the SISMED from the Ministry of Health, 9 of the 12 medicines with highest institutional sales are monopolistic biological medicines. These 9 biologicals account for 75 percent of the total sales of this group of products, 4174 billion Colombian pesos in the period 2008-2014. Insulin glargine, one of these 9 biologicals, had sales of about 300 billion. Annual sales of insuline glargine grew by a factor of 8, between 2008 and 2014³.

A journal new reports that the first private laboratory for the design and production of biotechnological medicines at clinical trial scale is already available⁴.

Regulation

In 2014, Colombia approved a highly debated Decree on the requisites and procedures to approve biological medicines, including biosimilars, which in the Colombian legislation are called *productos bioterapéuticos similares* (similar biotherapeutic products). (MINISTERIO DE SALUD Y PROTECCIÓN SOCIAL DECRETO NÚMERO 1782 DE 2014, 18 SEP 2014, por el cual se establecen los requisitos y el procedimiento

³ Fuente Observamed, http://www.med-informatica.net/BIS/BisBcm15de2015_06a12abr15.htm

⁴

http://federacionmedicacolombiana.com/OLD/index.php?option=com_content&view=article&id=2822:en-colombia-ya-se-disenan-medicamentos-biotecnologicos&catid=43:publicaciones&Itemid=145

para las Evaluaciones Farmacológica y Farmacéutica de los medicamentos biológicos en el trámite del registro sanitario.)⁵

The main features of the Decree are summarised below by Dr. Julio César García Casallas, Universidad de la Sabana⁶:

The transitory paragraphs of the “Artículo 89 de la ley 1438 del 2011” mandated the health regulation of biologicals, and so does the CONPES 155 on Pharmaceutical Policy (2012) and the CONPES 3697 (2011) on the commercial development of biotechnology. Moreover, applications for market authorisation of biologicals were on the rise. Last but not least, there were the issues related to the financial sustainability of the health system.

The purpose of the Decree is to set up the health requirements as well as the procedure of the pharmacological and pharmaceutical evaluations for registration purposes.

The Decree considers three possible options for submitting the information required for the marketing authorisation:

- 1. Full dossier option (Ruta del expediente Completo)*
- 2. Comparability option (Ruta de Comparabilidad)*
- 3. “Fast track” comparability option (Ruta abreviada de Comparabilidad)*

In all three cases the applicant will have to submit the following information.

- 1. Detailed description of the process and production site.*
- 2. Biologic identity tests*
- 3. Evaluation of strength (potencia)*
- 4. Physico-chemical properties*
- 5. Evaluation of the biologic activity*
- 6. Evaluation of purity*
- 7. Immunogenicity tests*
- 8. Risk management plan*

1. Full dossier option. The applicant is requested to submit preclinical (in-vivo and/or in-vitro) and clinical trials of the biological subject to evaluation (For new medicines)

⁵

<http://wsp.presidencia.gov.co/Normativa/Decretos/2014/Documents/SEPTIEMBRE/18/DECRETO%201782%20DEL%2018%20DE%20SEPTIEMBRE%20DE%202014.pdf>

⁶ <http://es.slideshare.net/garciaj.cesar/medicamentos-biologicos-y-biosimilares-reglamentacion>

2. *Comparability option (for medicines that are not new, but still not enough known and contain complex active ingredients (AI), the reason why pre-clinical and comparative clinical studies with the new medicine are required.*

3. *“Fast track” comparability option (for medicines completely known and which has wholly characterized AI). It is therefore assumed that there is no point in duplicating the experiments with animals and humans, nor doing them as long and complex.*

The MINSA will adapt and enforce recommendations from the a) Evaluation of Similar Biotherapeutic Products, Expert Committee of Biological Standardization of the WHO; b) From the WHO Technical Reports Series on GMP and c) Good Pharmacovigilance Practices for the Americas PARF Network and other guides on (vaccine stability, Immunogenicity and Immunogenicity evaluation, it will define the pre-clinical (in-silico/in-vitro/in-vivo) and clinical and establish the principles of pharmacovigilance required. The Decree will be enforceable within a year, as soon as the MINSA approves the two most important guides: (immunogenicity and stability).⁷

A draft of the Decree was released for public consultation and feedback could be given via the Ministry of Health and Social Protection. Written submissions and comments on the new version were accepted by the Ministry of Health and Social Protection for a period of one month, until 21 February 2013. The ministry published proposed changes to the draft on its website on 25 June 2013 and published comments received after the fourth round of discussions on the draft decree on 12 September 2013. Draft Decree 2013⁸

Three industry associations ASINFAR, AFIDRO and BIO, and other interested parties published reports or made statements supporting or opposing the Decree:

ASINFAR is the Association of Colombian Pharmaceutical Manufacturers. Although they do not make a clear set of recommendations, they clearly seem to favour a flexible approach to the authorization of biosimilars⁹: “EMEA allows a pharmaceutical company to introduce substantial changes in the process of manufacture, resulting in a biotechnological similar but not identical product to the original, and authorizes the marketing of the second molecule without subjecting it to clinical trials. Therefore, the same criteria should apply when a competitor develops a biotech product and it shows in the performance of analytical and preclinical comparability which is similar to drug reference. Likewise, it accepted in the specific case of the insulin that the physico-chemical analysis and preclinical biological studies are sufficient to demonstrate the similarity to the reference product and that additional clinical studies are not necessary. If this applies to a particular biotech product (Insulin), it opens the possibility that this approach might also be accepted in other molecules obtained by similar processes, such as monoclonal antibodies. [Woodcock 2007]”

⁷ <http://es.slideshare.net/garciaj.cesar/medicamentos-biologicos-y-biosimilares-reglamentacion>

⁸ <http://www.gabionline.net/Guidelines/Colombia-issues-draft-decree-for-registration-of-biologicals>

⁹ http://asinfar.com/Archivos/PROPUESTA_DE_REGULACION_BIOTECNOLOGICOS.pdf

AFIDRO, the association of foreign R&D pharmaceutical manufacturers in Colombia, wrote an open letter to the Colombian president showing its opposition to the third option included in the Decree, for submitting proposals for the authorisation of biosimilars (“Fast track” comparability option). They claimed that these would imply the entry in the Colombian market of biotechnological non-comparable products of uncertain quality, which are not supported by the WHO and not authorised by most countries of the region¹⁰.

Bio, an international Biotechnology Industry Organization, also opposed the abbreviated pathway (third option) on similar grounds to AFIDRO¹¹.

The FDA (USA) expressed concerns for the Abbreviated Pathway, stating that it was unclear how the safety, purity, and potency of products in this Pathway would be assured: “It is unclear if this abbreviated pathway is intended to describe the approval of a product based on comparison to a reference standard, rather than a reference product. “If that is the intent, it is unclear what the scientific standard is when compared to a reference standard, or what the scientific standard of the reference standard is.”¹²

The Ministry of Health has posted its explanation and justification of the Decree¹³. The MINSA apparently suffered some pressures from the US government aiming at modifying some aspects of the Decree which were considered contrary to US companies rights/interests¹⁴, but also encouragement and praises from the pro-access community (e.g. German Velazquez¹⁵ and Antonio Iniesta¹⁶)

The Decree required three years of intense debate and five drafts, as well as strong pressure from big pharma and from the US government. Joe Biden, the US vice-president, is said to have sent a letter to the Colombian president Juan Manuel Santos warning him of the health risks that the approval of the Decree could imply for the health of Colombians, according to WHO and US experts. Also, the Colombian ambassador in Washington sent a letter to the Colombian Ministry of Health,

¹⁰ <http://www.afidro.org/wp-content/uploads/Carta-de-AFIDRO-al-Presidente-de-Colombia.pdf>

¹¹

https://www.bio.org/sites/default/files/BIO%20WTO%20Comments_Colombia%20Proposed%20Biologics%20&%20Biosimilars%20Regulations.pdf

¹² <http://www.afidro.org/wp-content/uploads/United-States-Department-of-Health-and-Human-Services-1.pdf>

¹³ <http://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/VS/MET/abc-biotech-drugs.pdf>

¹⁴ <http://keionline.org/node/2085>

¹⁵ http://www.twn.my/title2/intellectual_property/info.service/2015/ip150201.htm

¹⁶ <http://fecoaquesta.blogspot.com.es/2014/12/biosimilares-o-biocompetidores-en.html>

expressing the concerns of the USTR, the Biotech Association and the Trade Chamber of the USA regarding the Decree¹⁷.

Cuba

The literature search (three page Google “biosimilars in Cuba”, 150420) resulted only in two academic references (Yamane, 20011; Echavarría, 2011) and some news from electronic journals and web sites. We also found some regulatory texts which include the principles and practical criteria for authorising the marketing of both biologicals and biosimilars in Cuba. We copy the relevant part of the first two documents as they provide a comprehensive picture of the Cuban biosimilar market and its regulation.

The biotechnological industry and market

Cuba has a large diversified biotechnological industry. According to Yamane (2011):

“Medicuba is the entity that handles pharmaceutical production as well as exports and imports of medical equipment and products. It was established in 1972 and began the production of biosimilars approved elsewhere. After 1980 the government set up various biotechnology institutes. The CIGB was established in 1986. By 1991, 53 scientific, manufacturing and commercial entities were organized under the Ministries of Health and Agriculture. Heber Biotech SA owns the exclusive rights for commercialization of technologies developed by biotech and seven other biotech institutions: all these are organized as a closed circle strategy.

In 1993 the recombinant streptokinase was launched and the focus was set on innovative biogenerics. In 1993 Cuba produced 1150 vaccines and medicines (vaccines against meningitis B) and other products amounting to US\$1 billion. Forty percent of API are imported from China.

Cuban companies patent products in the US, but very seldom in Cuba.

Most patented products developed in Cuba are biosimilars with some incremental innovation: haemophilus influenza type B synthetic vaccine, recombinant vaccine for Hepatitis-B, etc. They were patented and licensed internationally.

In 2004 3 cancer vaccines developed by the Cuban Center of Molecular Immunology were licensed to a US bioventure company, CancerVax. There are relationships with Indian biotech companies as well (e.g. joint venture in 2002 between Panacea and Heber Biotech) to develop a vaccine for Hepatitis-B and other examples.

They are not brand new NMC but products with a significant technological improvement (e.g. a method for enhancing healing of diabetic foot ulcers was patented in 2002, as a new use of a known substance, epidermal growth factor).

Biotechnology research in Cuba seems aimed at diseases with a high mortality. Cuba has adopted ICH standards, which allows Cuba to make direct applications for market authorization in developed countries. Cuba export markets include both high-

¹⁷ <http://www.pharmabaires.com/index.php/features/typography/390-colombia-reglamento-biotecnologicos-pese-a-las-presiones-de-estados-unidos>

*income countries in Europe, US and Japan, but also LA countries, such as Argentina, Brazil, Colombia and Mexico.*¹⁸

A new industrial organization called, BioCubaFarma, formed by more than 40 companies, 12 thousand employees (including 7000 scientists) carry on public health oriented research that started in the 1980s.

The Centro de Inmunología Molecular (CIM) reports the registration of products in 50 countries. The center continues its involvement beyond registration in the products developed.

In the last three decades the Cuban company developed 30 vaccines for infectious diseases and more than 30 oncologic products, some already registered and other under research. According to Doctor Tania Crombet, director of the CIM, Cuba has obtained more than 230 patents in the country and more that 1800 international applications of Cuban patents.

Some of the leading institutions in this area are the Centro de Inmunoensayo (CIE) and the Centro de Ingeniería Genética y Biotecnología, which developed Heberprot P – for diabetic foot – the vaccines HEBERPENTA and Heberbiovac HB, against hepatitis B. The Instituto Finlay has as its main function the development of anti-infectious vaccines, especially VA-MENGOC-BC®, (for meningococcal disease) with an estimated effectiveness of 90 percent. The Centro de Inmunología Molecular (CIM) is a key institution, focusing on cancer research. The CIM has 25 medicines in research state, including monoclonal antibodies classified as biosimilars e.g. a biosimilar of anti CD-20, for non-Hodkins lymphoma therapy. Research is also going on relating to the molecule antiher2 (Trastuzumab) for breast and stomach cancer. Other key products in the CIM portfolio are the gCSF, for the treatment of neutropenia, the monoclonal antibody Itolizumab and nimotuzumab.) The later has three registrations in the Cuban MRA and 30 outside Cuba). The CIGB has developed two therapeutic vaccines against cáncer (Cimvax-EGF) and Vaxira (racotumomab), both for lung cancer¹⁹.

“Different products have been developed and introduced into the Cuban market, and also exported to others countries. Most of them are medicinal products for human use, such as vaccines, cytokines and monoclonal antibodies but culture media, veterinary medicinal products, diagnostics and medical equipment are also included.”

“Up until October 2010, 133 biological products have been licensed, of which 67 are locally manufactured. For locally produced approved products, vaccines are the largest product type followed by alfa interferon and blood derivatives, whilst for imported products, insulins as well as pegylated compounds ranked first, followed by vaccines (Fig. 1) [3]. It should be highlighted that local products are mostly produced by a unique manufacturer. However, the same imported product is usually manufactured by more than one company.

¹⁸ Hiroko Yamane. Interpreting TRIPS: Globalisation of Intellectual Property Rights and Access to Medicines. Bloomsbury Publishing, 21 March 2011 - 582 pages

¹⁹ <http://www.cigb.edu.cu/index.php/es/2012-10-05-19-51-16/utimas-noticias/item/743-biotecnologia-cubana-tres-decadas-despues>

Monoclonal antibodies are an interesting case because there are only 4 imported products (Mabthera rituximab, Herceptin trastuzumab, Avastin bevacizumab, Simuleet basiliximab) and 1 locally manufactured (CIMAher nimotuzumab) product approved [3]”

“In 2009, for instance, only the 64 percent, 15 percent and 5 percent of Mabthera, Herceptin and Avastin respectively, of the real patient needs were imported, which is clearly insufficient to treat all patients reported in the country. For this reason, one of the main objectives of the cancer control program is to expand local production of products for oncology use (cytostatics, support products and new biotechnology products) [4] and the pipeline of the science park of the western Havana for the next decade incorporates the production of cancer therapeutic vaccines and similar monoclonal antibodies.” Echevarria et al (2011)

Other occasional news reinforce the impression that Cuba has a vibrant biotechnological industry which is able to produce and export at international standards²⁰.

Regulatory framework

From Echevarria et al (2011)

Regulatory framework in Cuba

“The legal basis for marketing authorization of medicinal products is based on the Ministerial Resolution “Rules for Marketing Authorization of Medicinal Products for Human Use” [6]. This document sets up the classification of medicinal products in different categories according to their degree of novelty. Traditionally biological and biotechnological products were included in category A, with the greatest degree of novelty. After several years of implementation of these classification criteria, CECMED identified the need to redesign it, taking into account the evidence at the level of quality, safety and efficacy, as well as the time the product has been in the market and therapeutic effect of the products. As a result, the rules for marketing authorization were updated on 2009 and new classes and classification categories were defined (Table 1). The new classification categories consider three basic concepts: the definition well delimited of two classes of medicinal products: new and known; the period of use in the international and/or national market of the medicinal product and the inclusion of biological products within the class of known medicinal products. Moreover, the information to be submitted for marketing authorization application is described in the Ministerial Resolution “Requirements for Marketing Authorization, Renewal and Variation Applications of Medicinal Products for Human Use” [7]. This document is divided as follows: Information for Drugs and Information for Biological/Biotechnological products. The volume of data to be presented depends on the category of its classification. That is, for a category A product a full dossier is required for quality, non-clinical and clinical information whereas for a category C product, a reduced data package could be accepted particularly for non-clinical and

²⁰ http://www.diariodecuba.com/cuba/1429645395_14134.html,
<http://www.cigb.edu.cu/index.php/es/2012-10-05-19-51-16/utimas-noticias/itemlist/category/54-noticias>

clinical information. Most of the biological products were licensed on a basis of a full dossier for quality, non-clinical and clinical data. Nevertheless some products were approved considering comparability information for non-clinical and/or clinical data. That is the case of a recombinant erythropoietin locally manufactured, which was approved in 2004. The application included information related to comparative studies developed for non-clinical and clinical information using EPREX, a product not licensed in Cuba as comparator, while for quality a stand-alone approach was adopted.

Other guidelines concerning the development of stability studies, validation of analytical assays and the characterization of reference materials, amongst others, are available [8] because all functions are covered by a regulatory system based on laws, regulations, decisions and procedures. Additionally, recommendations from WHO, ICH and PARF network are also considered, as well as some specific guidelines issued by FDA and EMA.

4. Similar biotherapeutic products

Regarding the products included on category C, there is a particular case for biological products that claim to be similar to an already approved biological product. In this case the term known biological product instead biosimilar was adopted in Cuba, as this term is defined in our regulations.

Although the rules for marketing authorization establish the legal basis for the approval of known biological products, there is not yet any biological product approved under this category. In March, 2009 a position paper was issued, defining the general strategy to be followed for the approval of a known biological product. A working group was also created, comprising NRA and industry staff, charged with discussing scientific and regulatory issues on known biological products. The main issues identified were related to clinical trial design (equivalence vs non-inferiority vs non-comparative); quality and non-clinical information required for known biological products, particularly Mabs, and whether the reference product must be licensed in Cuba and the strategy to be adopted when it is not licensed in our country. Specific guidelines were developed taking into account the experience accumulated by CECMED, as a result of the evaluation of applications for clinical trials and marketing authorizations of the biological products approved in Cuba, the assessment of comparability studies submitted due to manufacturing process changes and non-clinical and clinical comparability studies conducted in the country. The findings generated from the debate in the working group were also considered.

Table 1

Classification categories for medicinal products established on the Rules for Marketing Authorization.

Class 1. New Medicinal Product: Requires demonstration of quality, safety and efficacy and has been marketed for less than five years. Are divided into two categories	
Category A	New molecular entity.
Category B	New salt, ester, isomer, dosage form, administration route, drug substances association.
Class 2. Known Medicinal Product: Requires demonstration of quality, as well as elements of safety, efficacy or therapeutic equivalence, when applicable, and has been marketed for more than five years. Are grouped into one category:	
Category C	Multisource medicinal products, including biological products, which present the same drug substance, dosage form, strength or concentration and indications of other medicinal products, already licensed in Cuba or another country.

In general, the guideline took into account the following principles: - A full dossier is requested for quality, according to the requirements for marketing authorization approval in force. An additional section comprising all the information relating to comparative studies conducted for the known biological product with the biological reference product should be submitted. This section will include data on the determination of physicochemical, biological activity, immunological properties, purity and impurities and contaminants, and other tests that could be considered necessary (e.g., pH and osmolality of the final product). - The magnitude and complexity of non-clinical and clinical data will depend on the existing knowledge about the biological reference product, pharmacological classification, the claimed therapeutic indication as well as the differences detected during the quality comparative characterization. Non-clinical information should include results of comparative studies for biological activity, bioavailability and single-dose toxicity studies. Local tolerance and immunogenicity data will be also requested.

- For the clinical data, a detailed analysis of safety studies reported for the biological reference product and those conducted for the known biological product should be presented. Also, results of efficacy clinical trials should be included; the design of this can be equivalence, non-inferiority or non-comparative, but the choice should be justified. A non-comparative study is an exceptional case, for molecules like monoclonal antibodies, where a comparative trial might be not feasible due to heterogeneity in the response of the patient population would require a higher number of patients to prove similarity. This choice will be analyzed case-by-case. All clinical trials carried out for the known biological product to support the marketing authorization application should be previously authorized by CECMED.

- A specific section of information is added for similar monoclonal antibodies, given particular characteristics of these molecules. - A risk management program/active post-marketing surveillance plan should be also presented.

- The Reference Biological Product should be licensed based on full quality, safety, and efficacy data. This product should preferably be approved in Cuba. However, as Cuba is a country with a small market, it is possible that the RBP may not be licensed. In this case, the applicant has two choices: select a product licensed in countries with

experience in manufacturing, control, regulation and post-marketing surveillance activities for biological/biotechnological products or a product authorized by NRAs of the region of Americas that has passed the evaluation process carried out by PAHO (these are NRAs that has been considered “matured” in the regulation and control of biological/biotechnological products). The rationale for RBP selection should always be presented.

Some general principles established in the WHO guidelines for similar biotherapeutic products [9] were considered. However, there are some differences between the WHO and the Cuban guidelines (Table 2). The first draft of the Cuban guideline was released for regulatory consultation during October and November 2010 [10]. It is expected to have the final document approved during the first semester of 2011.

Legal documents

REPUBLICA DE CUBA MINISTERIO DE SALUD PÚBLICA. RESOLUCIÓN MINISTERIAL No. 321 (2009): REGLAMENTO PARA EL REGISTRO SANITARIO DE MEDICAMENTOS DE USO HUMANO

REPÚBLICA DE CUBA. MINISTERIO DE SALUD PÚBLICA. CENTRO PARA EL CONTROL ESTATAL DE CALIDAD DE LOS MEDICAMENTOS (CECMED) RESOLUCION 78 (2011): Aprobar la Regulación "Requisitos para el Registro Sanitario Condicional de Medicamentos de Uso Humano" (*Supposed to be attached, but not found*)

REPÚBLICA DE CUBA. MINISTERIO DE SALUD PÚBLICA. CENTRO PARA EL CONTROL ESTATAL DE CALIDAD DE LOS MEDICAMENTOS (CECMED) RESOLUCION 70 (2011): Aprobar la Regulación "Requisitos para el Registro de Productos biológicos Conocidos" que se adjunta a la presente resolución y forma parte integrante de la misma. (*Supposed to be attached, but not found*)

REPÚBLICA DE CUBA. MINISTERIO DE SALUD PÚBLICA. CENTRO PARA EL CONTROL ESTATAL DE CALIDAD DE LOS MEDICAMENTOS (CECMED) RESOLUCION 64 (2012): Aprobar la Regulación No. 61 - 2012 "Requisitos para el Registro Sanitario de Medicamentos de Uso Humano", que se adjunta a la presente resolución y forma parte integrante de la misma. (*Supposed to be attached, but not found. Substitutes Resolución Ministerial No. 68, 4 October 2000*)

Iran

Search: (three page Google search “biosimilars in Iran” accessed 150422)

There is not much information available on the biosimilars market in Iran. Draft guidelines for marketing authorisation of biosimilars have been recently produced, but they are available only in Farsi. A recent article (below) provides a summary of the guidelines:

Basic traits of Iran's Drug Market

Population: expected to reach 79 million by 2016.

Iran produces 95 percent of its medicines locally, of which five percent are biosimilars.

Generic medicines cover 65 percent of the medicines market in Iran.

According to Business Monitor International predictions, the pharmaceutical market in Iran was worth US\$3.26 billion in 2011, with a compound annual growth rate of 12.2 percent.

Iran is the only country in the region that has the capability to produce such a high proportion of medicines domestically.

Source: <http://www.mums.ac.ir/shares/6icpe/6icpe/powerpoint/day3/part1/Dr-jahed.pdf>

Short description of the Iranian pharmaceutical market made by the industry association

<http://www.behestandarou.com/IranPharmaIndustry.html>

According to Charaghali (2012) the pharmaceutical industry in Iran has a 50 year history. It consists mainly of generic based companies producing small quantities: Biopharmaceutical projects started about 10 years ago. Iran is not a member of the WTO and has not signed the TRIPS; it has therefore no IP restrictions on producing medicines on-patent in other countries.

“Despite the fact that biopharmaceuticals which were produced by local Iranian industry in past decade including INFs, GCSF and GH have received marketing authorization for local market, none of them received comprehensive evaluation according to those of internationally recognized guidelines for biosimilars. Registration of these biopharmaceuticals has mainly followed registration path for “biogeneric” medicines and their application for marketing authorization handled based on case by case. Since 2003 about 6 biopharmaceuticals produced as non originator copy have been registered by Iran national authority. These include erythropoietins, INFs, GH and GCSF. Another 16 are in pipeline and expected to reach Iran market with similar approach in coming years [17]”

“...based on a national guideline which was mainly adapted from WHO guideline, since 2006 performing a double blind controlled clinical trial with small sample size for locally manufactured biopharmaceuticals becomes obligatory. Although Iran national regulatory authority (NRA) has tried to use WHO guideline on biosimilars for granting marketing authorization, there are clearly differences between WHO

guideline and current Iran national guideline for registration of locally produced biopharmaceuticals [17].”

Source: Biosimilars; a unique opportunity for Iran national health sector and national pharmaceutical industry. Abdol Majid Cheraghali DARU Journal of Pharmaceutical Sciences, 2012, 20:3 <http://www.biomedcentral.com/content/pdf/2008-2231-20-35.pdf>

Cheraghali AM. Current status of biopharmaceuticals in Iran’s pharmaceutical market. Generics and Biosimilars Initiative Journal 2013; 2 (1).26- 9

<http://gabi-journal.net/current-status-of-biopharmaceuticals-in-iran-s-pharmaceutical-market.html>

This article expands the content of the previous article by the author. It provides some interesting new information regarding the biogenerics both in the market and in the registration process.

Table 1: Market status of locally manufactured biopharmaceuticals in Iran as of September 2012	
Locally manufactured biopharmaceuticals	Market status
Bevacizumab	Applied for registration
Erythropoetin	On the market
Etanercept	Applied for registration
rFVIIa	On the market
Filgrastim	On the market
Follitropin alpha	On the market
Chorionic gonadotropin	On the market
Infliximab	On the market
Interferon gamma	On the market
Interferon alpha-2b	On the market
Interferon beta-1a	On the market
Interferon beta-1b	Applied for registration
Interferon beta-1a	On the market
Pegylated interferon alpha 2a	On the market
Pegylated interferon alpha 2b	On the market
Parathyroid hormone (teriparatide)	Applied for registration
Rituximab	Applied for registration
Somatropin	On the market
Streptokinase	Applied for registration
Trastuzumab	Applied for registration

“Since 2003, about 20 locally manufactured biopharmaceuticals either entered the market or are awaiting marketing authorization, see Table 1; from Iran’s national regulatory authority (NRA). This table shows that the most clinically important biopharmaceuticals, especially recombinant proteins, are manufactured locally by Iran’s national industry. Some additional monoclonal antibodies have already been filed for registration and are expected to enter the market in 2013–2014. All medicines, including biopharmaceuticals in Iran, have their prices set by national authorities, and have to be sold at a fixed price all over the country. The prices of

locally manufactured biopharmaceuticals are between 27–72 percent lower than their corresponding imported original brands. Obviously, this could significantly improve affordability and accessibility of the biopharmaceuticals for both patients and the national health service.”

“In 2001, Iran became a member of the World Intellectual Property Organization and registers trademarks for medicines. However, there is no patent protection for imported medicines in Iran [5]. As of mid 2005, Iran became an observer member of WTO. However, due to the current international political situation full WTO membership is unlikely to happen in the near future. Iran’s local industry does not consider WTO membership to be an eminent concern with regard to producing copies of patented biopharmaceuticals. Therefore, the local pharmaceutical companies would be able to manufacture both patented and off-patent biopharmaceuticals provided that they gain access to their production procedures.”

“Iran established its NRA in the 1950s, and passed the first laws for the regulation of the national pharmaceutical market in 1955. The Ministry of Health and Education of Iran is responsible for regulation of the market. Although the registration of small molecule medicines is a well-developed system it is not always as transparent as it should be according to NRA’s guidelines for the marketing of locally produced copied biopharmaceuticals [5]. In 2006, the Iranian NRA announced national guidelines for the marketing of biosimilars. These guidelines, which are mainly adapted from the WHO guidelines, specify the need for a clinical trial with a small sample size comparing locally manufactured biopharmaceuticals with the original brand. However, there are clear differences between the WHO guidelines and current Iranian national guidelines for the registration of locally produced biopharmaceuticals [19–20]. Currently, the Iranian NRA does not ask for comprehensive new preclinical or clinical data for proving similarity between locally produced biopharmaceuticals and original brand medicines.

The Iranian NRA has so far relied on national post-marketing surveillance to produce data on the ‘safety’ of all marketed, copied biopharmaceuticals. Iran has a fairly well-established national adverse drug reaction (ADR) reporting system and so far no serious or unexpected ADRs related to administration of locally manufactured biopharmaceuticals have been reported to the national health authorities [20–21].”

“The Iranian pharmaceutical market is susceptible to the use of counterfeit medicines. Iran is one of the major transit routes for illicit narcotics produced in Afghanistan. It is assumed that the same transit pathways could also be used for counterfeit medicines including biopharmaceuticals. Indeed, illegal medicines and supplements now comprise up to 10 percent of the total pharmaceutical market [7]. There is a danger that the ambiguity and uncertainty in the regulatory requirements for the marketing of biopharmaceuticals in Iran will encourage manufacturers to avoid doing the clinical trials necessary for proving the comparable efficacy and safety of their products. The use of clinically not comparable biopharmaceuticals could then impose extra medical and financial burdens on patients and the national health system if this leads to treatment failure, toxicity, and the need for corrective interventions. This also raises the possibility of yet unidentified short- and long-term safety concerns. The government of Iran currently supports the local pharmaceutical industry by imposing high tariffs on imported medicines. Therefore, it is expected that

patients should benefit from the availability of copied biopharmaceuticals through improved access for effective treatment of chronic and lifelong diseases.”

Naser Hadavanda, Mahboubeh Valadkhania, Aida Zarbakhshb Current regulatory and scientific considerations for approving biosimilars in Iran, Biologicals Volume 39, Issue 5, September 2011, Pages 325–327

<http://www.sciencedirect.com/science/article/pii/S1045105611000844> :

This article provides a summary of the draft guidelines and a comparison between the Iranian and the WHO guidelines.

“4. The guideline on marketing authorization of biosimilars in Iran

Following close cooperation with WHO over the past decade, the Iran NRA prepared a draft guideline on the registration of biosimilars based on the WHO draft guideline of 2009. This was revised in two steps based on WHO draft guideline changes. It has been finalized and approved in September 2010 by the Iran expert committee on biologicals and as the last step approved by the Head of the Iran FDA in February 2011. After its issuance, there will be a six month time limit for manufacturers to implement the guideline. The guideline will not apply to previously registered products.

The framework of the guideline is very similar to the WHO guideline and consists of the following sections:

- a) Introduction and Scope: definition of biosimilars, original brand, registration process and general consideration*
- b) Quality: production process, characterization(physiochemical, biological activity, immunochemical, accelerated stability test), specifications, analytical techniques, stability*
- c) Non clinical evaluation*
- d) Clinical evaluation: pharmacokinetic studies, confirmatory pharmacokinetic/pharmacodynamic studies, efficacy studies, safety and immunogenicity*
- e) Pharmacovigilance*
- f) Prescription and labelling information*

5. Similarities and differences between biosimilars registration guideline in Iran in comparison with WHO guideline

Iran requires a full head to head comparative study of a new follow-on product vs. a Reference Biological Product in the quality, non-clinical and clinical characteristics as stated in the published 2009 WHO guideline.

5.1. Similarities

- 1. In Iran, there is a requirement for a head to head comparison of a SBP (similar biotherapeutic product) to a reference product in quality, non-clinical and clinical attributes in exactly the same way as in the final adopted version of the WHO Guidelines.*
- 2. As in the WHO guideline, the regulatory body believes that pharmacopoeial monographs provide only a minimum set of requirements for a particular product and additional test parameters are required depending on the dossier and other documents relating to the RBP available to the NRA.*
- 3. According to the Iran guideline, the drug substance and finished product of the RBP (reference biotherapeutic product) and SBP must be shown to be similar. This is exactly the same to WHO guideline in terms of quality.*
- 4. According to WHO and Iran regulatory opinion, the dosage form and route of administration should be the same of SBP as that of RBP.*

5.2. Differences

- 1. According to WHO Guidelines, the RBP should be a product licensed on a full quality, safety and efficacy data package. Usually, an SBP should not be considered as a choice for an RBP. However, in the I.R. Iran, there are instances where the original brand has not been registered and indeed may never be since the RBP producer has no intention of doing so. Nevertheless, there is a need to register products made in Iran. In such cases, the Iran guidelines allow a local producer to evaluate an SBP produced in Iran in a head to head comparison to a reference product consisting of an SBP with FDA or EMEA approval and accessible PSUR and which has already been licensed in Iran and marketed for a suitable period of time.*
- 2. After registration and the provision of sufficient data on consistency of production, one characterized batch of this similar product may be used as a reference for quality control tests for batch release. This approach does not exist in the WHO guideline.*
- 3. According to the WHO, guideline specifications for a SBP may not be the same as for the RBP, since the manufacturing processes will be different and different analytical procedures and laboratories will be used for the assays. But in Iran, specifications for a SBP should be the same as for the reference product or meet pharmacopoeial specifications.*
- 4. According to the WHO guideline, head-to-head accelerated stability studies comparing the SBP to the RBP will be of value in determining the similarity of the products by showing comparable degradation profiles. Based on Iran regulations, an accelerated stability study is required as an important element in determination of*

similarity between a SBP and a RBP but it has not been required for this study to be in a head to head style.”

<http://www.gabionline.net/Guidelines/Development-of-Iranian-guidelines-for-biogenics>

*“The guideline defines a biogeneric as a medicine that demonstrates similarity in terms of quality, safety and efficacy to a reference brand-name biological product registered either by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA). **The guideline, which is in the local language (Farsi), is available from the FDO website** (<http://fdo.behdasht.gov.ir/>).”*

Ecuador

The report on Ecuador is mainly based on personal communication with Carlos Duran, researcher at the Yachai Institute and former official of the Ministry of Public Health.

The main health law in Ecuador (Ley Orgánica de Salud²¹) outlines the procedures for authorising new medicines. A by-law²² develops the medicines registry. An addendum to the by-law²³ was finally approved specifically for biological medicines (originators and biosimilars). The Agencia Nacional de Regulación, Control y Vigilancia Sanitaria-ARCSA (the MRA of Ecuador) authorises new medicines on the basis of a documentary procedure or by homologation (if the product has been approved by the MRA of some predefined countries).

The positive list (essential medicines list) of the public health system (CNMB - Cuadro Nacional de Medicamentos Básicos, 9^a revisión, 2013²⁴) includes human insulin, rapid action and human insulin NPH, intermediate action), but not the insulin glargine. The latter product was initially included in the CNMB, but was later taken out. Patients and doctors have been lobbying for its inclusion.

It is interesting to note that Ecuador is one of the most active countries in the region regarding compulsory licensing (about 10 CL issued up to 2015). Ecuador issued a CL

²¹ LEY ORGANICA DE SALUD. Ley 67, Registro Oficial Suplemento 423 de 22 de Diciembre del 2006.
http://www.vertic.org/media/National%20Legislation/Ecuador/EC_Ley_Organica_de_Salud.pdf

²² REGLAMENTO DE REGISTRO SANITARIO PARA MEDICAMENTOS EN GENERAL (Ultima modif. 2013)
http://instituciones.msp.gob.ec/images/Documentos/vigilancia_sanitaria/reglamentos/reglamento3/REGLAMENTO_REGISTRO_SANITARIO_MEDICAMENTOS.pdf

²³ REGLAMENTO PARA LA OBTENCIÓN DEL REGISTRO SANITARIO, CONTROL Y VIGILANCIA DE MEDICAMENTOS BIOLÓGICOS PARA USO Y CONSUMO HUMANO (2013)
<http://www.controlsanitario.gob.ec/wp-content/uploads/downloads/2014/09/A-3344-Reglamento-para-la-obtenci%C3%B3n-de-registro-sanitario-de-medicamentos-biol%C3%B3gicos.pdf>

²⁴ Cuadro Nacional de Medicamentos Básicos, 9^a revision, 2013.
<http://www.conasa.gob.ec/phocadownload/cnmb9na/CNMB9na.REVversionfinal9-X-2013.pdf>

and then authorised infliximab - a treatment for rheumatoid arthritis - using the homologation route (infliximab had been approved by the EMA). ENFARMA (a state-owned company) played an active role in searching for an appropriate supplier of infliximad and obtained in 2013 the registry of the first biosimilar²⁵. Recently, it started importing and marketing REMSIMA, a biosimilar version of infliximab manufactured in South Korea. The originator/reference product is REMICADE (Jansen&Jansen, USA)

²⁵ http://www.farmacos.gob.ec/enfarma_biosimilar/

China

(Three page Google “biosimilars in China”; accessed on 15.04.20)

The biogenerics market and industry

Biologics represent a small but growing part of the total pharmaceutical market in China. According to estimates, sales of biologics amounted to two percent (\$1 billion) of the \$75 billion Chinese pharmaceutical market in 2013. China has moved into second place behind the United States in pharmaceutical sales and is expected to maintain its annual growth of 10 percent to 20 percent for the near future. Biologics are expected to be a major contributor to this growth.

Source: <http://www.innoventbio.com/en/News.aspx?key=news&Id=1144&type=%E6%96%B0%E9%97%BB%E4%B8%AD%E5%BF%83>

The concept of biogenerics in the West is seen as an IP issue. In China, it is a healthcare issue. Chinese biogenerics today include both off-patent and generic biological products developed by Chinese biopharmaceuticals before China entered the WTO. Since biogenerics account for over 95 percent of China's biopharmaceuticals, the biopharmaceutical industry in China today is virtually a biogenerics industry.

China's biopharmaceuticals industry began in the 1980s when the Chinese government introduced a series of national programs (e.g., the 863 Program, 85 and 95 Key Tech R&D Program) and placed biotech and related industry as one of the "major development sectors." Since the first Chinese-developed biotech medicine-recombinant human interferon alb (produced by Shenzhen Kexing Biotech Co.) entered the Chinese market in 1989, China's biopharmaceuticals industry has undergone rapid expansion. Today, Chinese biopharmaceutical companies have marketed 361 recombinant biogenerics (including therapeutics and vaccines) and 25 biotech medicines. More than 10 innovative biotech medicines have been launched into the market, and more than 100 biopharmaceuticals are currently at clinical trial stages.

Biopharmaceutical production value has grown from \$30 million in 1986, to \$4.2 billion in 2005. China's biopharmaceuticals sales revenue has grown 20-30 percent over the past five years. In 2005, biopharmaceuticals accounted for seven percent of the pharmaceutical market (Figure 1). According to the China Biopharmaceutical Engineering Industry Outline, the country's biopharma industry production value is projected to exceed \$12.5 billion by 2015.

There are over 2,000 biological products made by more than 200 Chinese biopharmaceutical companies, 95 percent of which could be classified as biogenerics. Chinese biogenerics include a wide range of biologics, such as genetically engineered medicines, vaccines, antibodies, and diagnostic agents. The major biogenerics and manufacturers are summarized in Table 4A and B.

Some Chinese biogenerics (e.g., rhG-CSF and EPO) have been manufactured and sold legally in China. G-CSF is manufactured by more than 30 Chinese biogenerics companies. Amgen applied for administrative protection for its Neupogen (G-CSF) and Epogen (EPO) in 1993, but did not win approval from the Chinese regulatory authorities. Other court cases are pending.

<http://interblog16.blogspot.com.es/2012/03/biogenerics-in-china-evolving-industry.html>

The most successful foreign biotech player in the Chinese market today is Novo Nordisk, which entered the Chinese market in 1993 and opened its first production facility in Tianjin in 1996. Novo Nordisk has grown rapidly in China, and the company has dominated the human insulin market there for many years, with 1.9 billion RMB (\$261 million) sales in 2006.

Source: Eliza Yibing Zhou. The Top-60 Chinese Biopharma Companies. The Evolution of Modern Biotechnology in China Is Continuing at a Rapid Pace.

http://www.bioplanassociates.com/publications/articles/GEN_ChinaTop60_biopartners_02-15-08.pdf

Insulin

Biocon and Wockhardt are producing insulin and Bhat Bio-tech India is planning to do so in the future.

The entrance of domestic manufacturers—with their cost-effective and efficient processes—has also led to price competition with foreign competitors, further improving the availability of affordable products for local consumers. For example, the cost of imported human insulin fell nearly 40 percent once multiple domestic manufacturers entered the market, including Wockhardt (Mumbai) and Biocon (Bangalore).

Source: Sarah E. Frew, Hannah E. Kettler and Peter A. Singer. The Indian And Chinese Health Biotechnology Industries: Potential Champions Of Global Health? Health Affairs, 27, no.4 (2008):1029-1041

<http://content.healthaffairs.org/content/27/4/1029.full.pdf>

<http://www.biopharmadive.com/news/best-of-bd-biosimilars-in-china-the-coming-revolution/324525/>

Recombinant insulins are in demand in China where diabetes is a major health problem. According to the International Diabetes Foundation, nine percent of the Chinese population (~100 million people) suffer from some form of diabetes or its complications. According to a 2014 report by Chinese Research Intelligence the CAGR (compound annual growth rate) of sales of insulin glargine in a Chinese sample hospital market exceeded 70 percent from 2005 to 2013. The diabetes market is expected to continue to grow to \$3 billion by 2016. Recombinant human insulin such as Lantus (insulin glargine) and Victoza (liraglutide) are blockbuster medicines in the West, generating billions of dollars in revenue. Lantus has been sold in China since 2004. Victoza was launched in 2011. A 10 to 15 day course of Victoza costs 878 yuan (\$140) and, China has become one of the top markets beyond the US, Europe and Japan with sales of \$22 million in 2013. At least two insulin glargine FOBs, Basalin (Gan and Lee Pharmaceuticals; Beijing) and Uslin (United Laboratories International; Hong Kong) have been launched since 2005 and more versions are under development by other firms. Basalin holds second place in market share behind Lantus.

Source: David Dunn Significant Changes Ahead for the Chinese Biologics and Biosimilars Industry (03 Feb 2015) See more at: <http://lsconnect.thomsonreuters.com/significant-changes-ahead-chinese-biologics-biosimilars-industry/#sthash.57zdeg2v.dpuf>

Biosimilars Guidelines

CFDA, the medicines regulatory agency of China, issued technical guideline for development and evaluation of biosimilars on the 5th of March 2015, which specify relevant requirements on the application procedure, registration classification, and application documents of biosimilars. A draft guidance for research and evaluation techniques for biosimilars was released for consultation on 29 October 2014 (until 29 November 2014).

CFDA Finalizes Biosimilars Guidance. The China Food and Drug Administration (CFDA) has released the final version of its biosimilars guidance. Authorities have made a handful of notable changes to the document since a draft version was released in November.

Law firm Ropes & Gray has published a summary of the major revisions to the guidelines. Four of the five changes picked out in the summary are tweaks to sections that were already in the draft. The final version clarifies that biosimilars will follow the new drug approval pathway and are defined as being similar to reference products approved in China or overseas. In the original draft, CFDA made no mention of where the reference product must be approved.

Other changes in the final version include an expanded definition of reference products – which states they must be approved in China before trials of the biosimilar start – and the dropping of the need to choose at least three batches for comparative tests. The final text also includes a new line stating manufacturers should source samples used in comparative tests from the same production plant.

<https://www.ropesgray.com/news-and-insights/Insights/2015/March/China-Announces-Final-Biosimilars-Guideline.aspx>

Before the guidance was approved, biosimilars had to go through a new approval process, as is the case for all biologicals. This means that phase III trials had to be carried out.

Domestic copy biologicals have been on the market in China for 20 years, according to data from the Southern Medicine Economic Research Institute (SMEI) of CFDA. The first recombinant human interferon beta 1 was launched in 1989. Domestic erythropoietins, granulocyte colony-stimulating factors and monoclonal antibodies are also commercialized in China. The country has approved 382 genetically engineered drugs and genetically engineered vaccines, but only 21 products are innovative and the rest are copy biologicals, according to SMEI data.

Source: <http://gabionline.net/Guidelines/Chinese-guidelines-for-biosimilars>

The approval of the Guidelines means that biosimilars approval will now include a rigorous comparability exercise with the reference product, which can fuel the development of biosimilar production in China. The new guidelines have nevertheless raised some criticisms from some organisations, such as the U.S.-based Biotechnology Industry Organization (BIO) and the China-based R&D Pharmaceutical Association Committee (RDPAC), which “*want changes in the China FDA's most recent biosimilar approval guidelines, particularly a provision that allows for additional assessment of a biosimilar candidate if a comparability study showed differences between the candidate and its reference product*” and ask for clarification on some points, although they globally applaud the new regulation.

<http://www.fiercepharmaasia.com/story/big-pharma-bodies-ask-china-fda-review-comparability-biosimilar-approval-gu/2015-03-04>

Other articles on biosimilars guidelines

<http://gabionline.net/Biosimilars/Research/Strategy-for-biosimilars-in-China>

<https://www.bio.org/sites/default/files/Biotechnology-Industry-Pg62-64.pdf>

<http://www.raps.org/Regulatory-Focus/News/2015/03/10/21685/Asia-Regulatory-Roundup-Chinas-New-Biosimilars-Guideline-and-Price-Controls-10-March-2015/>

<http://www.innoventbio.com/en/News.aspx?key=news&Id=1144&type=%E6%96%B0%E9%97%BB%E4%B8%AD%E5%BF%83>

India

(Three page Google search on ‘biosimilars in India’ 15.04.22)

<https://bricwallblog.wordpress.com/2014/05/21/an-overview-of-biosimilars-and-the-biosimilar-pathway-in-india/>

<http://www.gabionline.net/Biosimilars/General/Similar-biologics-approved-and-marketed-in-India>

<http://www.gabionline.net/layout/set/print/content/view/full/2259>

<http://www.biosimilarnews.com/indian-biosimilars-guidelines>

http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=13&ved=0CCkQFjACOAO&url=http%3A%2F%2Fijpsr.com%2F%3Faction%3Ddownload_pdf%26postid%3D7743&ei=j7I3VYezL8aR7Abv84HICg&usq=AFQjCNGWuecjrpr9Rca9TeF2iFmXVz3_nA

<http://www.mondaq.com/india/x/352370/Life+Sciences+Biotechnology/Developing+Biosimilars+In+India+Prescriptions+And+Problems>

http://www.nature.com/nbt/journal/v28/n9/fig_tab/nbt0910-883a_T1.html

<http://www.financialexpress.com/article/economy/biosimilars-are-the-next-big-thing-for-indian-pharma/23516/>

<http://www.slideshare.net/brandsynapse/the-newindiabiosimilarguidelines>

<http://igmoris.nic.in/files%5CCDSCO-DBTSimilarBiologicsfinal.pdf>

http://www.ijapjournal.com/File_Folder/245-258.pdf

<http://www.biosimilarnews.com/lupin-launches-insulin-glargine-in-india>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4137643/>

<http://www.biopharminternational.com/development-and-commercialization-biosimilars-india?id=&pageID=1&sk=&date=>

<http://www.slideshare.net/debashishkar7/indian-strategic-outlook-biosimilars>

<http://www.slideshare.net/debashishkar7/indian-strategic-outlook-biosimilars>

<http://www.biocon.com/>

<http://www.sciencedirect.com/science/article/pii/S1045105611000832>

Mexico

(Three page Google 'biosimilars in Mexico' 15.04.22)

In Mexico, until recently, criteria for the approval of an intended copy of biological drug was the same as for generics, meaning that preclinical and clinical data were not required. That is why in 2011 there were 23 intended copy biological drugs registered in Mexico as generics and more than 100 million doses of treatments using these drugs have been sold from 1993 to 2012. Unfortunately, due to the lack of pharmacovigilance, it has not been possible to establish the risk of using these inadequately evaluated drugs [27]. However, according to new criteria approved in Mexico in 2011, previously licensed drugs must be renewed every five years, and therefore these intended copy biological drugs will have to demonstrate true biosimilarity with physico-chemical, preclinical and clinical studies as well as pharmacovigilance, including detection of immunogenicity. At this time, Mexico has not approved a biosimilar but these intended copy biological drugs have to demonstrate true biosimilarity with physico-chemical, preclinical and clinical studies as well as pharmacovigilance, including detection of immunogenicity. However, several products are currently under evaluation at various steps of the process, and it is expected that at least one of them will be approved this year. Source: Alexis Aceituno Álvarez 2014

Additional references:

<http://www.fdanews.com/articles/170432-new-regulation-on-biosimilars-goes-into-effect-in-mexico?v=preview>

<http://www.gabionline.net/Guidelines/Mexican-guidelines-for-biocomparables>

<http://www.mondaq.com/x/375056/food+drugs+law/Mexican+Health+Ministry+Establishes+Requirements+For+Approving+Biotech+And+Biosimilars>

<https://www.bio.org/advocacy/letters/bio-comments-mexicos-proposed-biologics-and-biosimilars-regulations>

https://www.bio.org/sites/default/files/FINAL%20BIO%20Comments%20on%20Mexico%20Biologics-Biosimilars%20Regulations_o.pdf

<http://www.sciencedirect.com/science/article/pii/S0734975013000864>

<http://www.reumatologiaclinica.org/es/medicamentos-biocomparables-mexico-postura-del/articulo/90193744/>

<http://www.biosimilarnews.com/new-biologics-and-biocomparables-guidelines-are-effective-in-mexico>

http://fecoainesta.blogspot.com.es/2014/12/biosimilares-o-mejor-biocomparables-en_5.html

http://www.biocon.com/docs/PR_Biocon_Mexico_Glargine_09042015v.pdf?subLink=news&Fileid=467

<http://www.reumatologia.org.mx/index.php/widgetkit/documentos-de-postura/11-documentos-de-postura/71-medicamentos-biocomparables-en-mexico> o bien:

<http://www.elsevier.es/ficheros/eop/S1699-258X%2812%2900268-9.pdf>

http://www.anmm.org.mx/GMM/2012/n1/GMM_148_2012_1_083-090.pdf

South Africa

(Three page Google 'biosimilars in South Africa' 15.04.22)

<https://www.z2systems.com/neon/resource/kca/File/What%20are%20biosimilars.docx.pdf>

Medicines Control Council, Department of Health. BIOSIMILAR MEDICINES QUALITY, NON-CLINICAL AND CLINICAL REQUIREMENTS (Version 2: Finalised version for Implementation, March, 2012)

http://www.mccza.com/genericDocuments/2.30_Biosimilars_Mar2012_v2.pdf

GROUPS OF MEDICINES THAT ARE NOT SUBSTITUTABLE

Biosimilars are not generic products and cannot be identical to their reference products. Further, the formulations may be different and this can have a profound effect on their clinical profiles.

In addition, a biosimilar does not necessarily have the same indications or clinical use as the reference product. Therefore, given current science, they cannot be considered interchangeable with the reference product or products of the same class.

Equally, automatic substitution (i.e. the practice by which a different product to that specified on the prescription is dispensed to the patient without the prior informed consent of the treating physician) cannot apply to biosimilars.

This approach ensures that treating physicians can make informed decisions to ensure that treatment is in the interest of patients' safety.

This guideline is effective from the date of publication of this document.

Source: Medicines Control Council, Department of Health GROUPS OF MEDICINES AND INDIVIDUAL MEDICINES THAT HAVE BEEN DECLARED NOT SUBSTITUTABLE BY COUNCIL

http://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=3&ved=0CCwQFjAC&url=http%3A%2F%2Fwww.mccza.com%2FgenericDocuments%2F2.10_Substitution_of_medicines_Jan10_v2.doc&ei=aZs3VZXFJpLg7Qbq2IGoBw&usg=AFQjCNEem1kW8-qSYbvvsYrpTgKY2fmBmQ&bvm=bv.91071109,d.ZGU

2.7.5 Biological medicines: Biopharmaceuticals and Biosimilars

Biological medicine: A medicine where the active ingredient and/or key excipients have been derived from living organisms or tissues, or manufactured using a biological process. Biological medicines can be defined largely by reference to their method of manufacture (the biological process). These include inter alia medicines prepared from the following substrates:

- (i) Microbial cultures (fermentation);
- (ii) Plant or Animal Cell cultures (including those resulting from recombinant DNA or hybridoma techniques);
- (iii) Extraction from biological tissues; and
- (iv) Propagation of live agents in embryos or animals.

The living substrate may be genetically modified in a number of ways to provide the required active ingredient, including recombinant DNA technology or hybridoma techniques.

Biological Medicines include, but may not be limited to the following:

- (i) Plasma-derived products, e.g. Clotting factors, Immunosera, etc;
- (ii) Vaccines;
- (iii) Biotechnology-derived medicinal products (rDNA products) e.g. rHu-antithemophilic factors, Hormones, Cytokines, Enzymes, Monoclonal antibodies, erythropoietins;
- (iv) Human Gene therapy.

It has been the practice, in South Africa, that Council will decide that certain well-characterised low-molecular weight medicinal biological compounds, such as antibiotics, insulin etc be excluded from biological medicine status, and they are therefore not reviewed by the Biological Medicines Committee.

Biopharmaceutical: *Patented biological medicine.*

Biosimilar: *A biological medicinal product referring to an existing biological medicinal product for which registration has been applied for.*

**Source: GUIDELINES FOR THE REGISTRATION OF MEDICINES
GENERAL INFORMATION**

Regulation of biosimilars in LMICs

Publications that mainly focus on middle- and low- income countries include:

<http://www.healthtrustpg.com/biosimilars/pdf/ppd.pdf>

http://www.bioinfo.com/Biosimilars_ROW.pdf

http://www.bioinfo.com/Biosimilars_ROW.pdf

<http://www.bioprocessonline.com/doc/biosimilars-in-emerging-markets-0001>

Latin America

<http://gabi-journal.net/recommendations-for-the-regulation-of-biosimilars-and-their-implementation-in-latin-america.html>

Abstract.

In order to understand the regulatory framework in Latin America, it is necessary to know the historical background and worldwide situation. In the early 1980s, the introduction of biopharmaceuticals dramatically changed the treatment of some diseases. Soon after, three Latin American countries – Argentina, Cuba and Mexico – started the production of biopharmaceuticals. At that time, most Latin American countries did not have patent law, which prompted industry to make drugs that were copies of the reference drug. Around the year 2000, when countries belonging to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (including Europe, Japan and the US) began discussing how to approve ‘follow-on biologics’ because patents were close to expiration, Latin America had about 100 products in the market that were intended copies of reference products and registered as generics.

Under these conditions, the first regulation needed was to define the pathway for a biopharmaceutical to be approved, separate from a generic drug. Brazil and Venezuela were the first countries in Latin America to distinguish between the approval process for generics and that for biopharmaceuticals [25]. It was not until 2010 that other countries in Latin America made this distinction and even today there are countries in the region still operating under the original guidelines. For countries in the region that have regulations for the approval of biosimilars, the WHO

guidelines [2] have been adopted. Although countries have adopted these regulations in general terms, there are many countries whose regulations differ from WHO.

A significant issue in Latin America is how to re-evaluate products that were previously approved but no longer fit the current criteria for a biosimilar. As mentioned above, intended copies of biologicals have been used in Latin American countries for many years and in general there were no criteria for the establishment of similarity between these products and their reference products. In 2002, Brazil began requiring more robust clinical studies in order for a product to be renewed as a biological product. Today, no country in Latin America requires a previously approved intended copy of biological drug to meet all the requirements now in effect to be considered a biosimilar as proposed by the WHO guidelines. A Aceituno Alvarez 2014

http://www.pmlive.com/pharma_intelligence/unfolding_the_biosimilar_landscape_in_latin_america_470137

Additional articles on Latin America

<http://www.pahofoundation.org/es/2012/315-actividades-de-la-pahef-sobre-productos-biosimilares-y-las-realidades-medicas-en-america-latina.html>

<http://www.ispor.org/ValueInHealth/ShowValueInHealth.aspx?issue=B76D2B0A-C5EB-4CAE-8E47-8151AC7BA1AD>

<http://gabi-journal.net/recommendations-for-the-regulation-of-biosimilars-and-their-implementation-in-latin-america.html>

<http://www.valuehealthregionalissues.com/article/S2212-1099%2812%2900068-4/fulltext>

<http://www.dovepress.com/similar-biotherapeutic-products-in-latin-america-regulation-and-opport-peer-reviewed-article-BS>

<http://www.dovepress.com/similar-biotherapeutic-products-in-latin-america-regulation-and-opport-peer-reviewed-article-BS#>

WHO Biosimilar Guideline

The WHO biosimilar guideline, aimed at providing a consistent scientific standard, is the reference for many newly developed biosimilar pathways. Some emerging markets have developed their own regulatory pathways for biosimilars, hoping to meet a growing demand for biologic medicines. Singapore and Malaysia amended their guidelines mainly in accordance with the EMA guidelines, while Brazil and Cuba chose the WHO and Canadian guidelines as the basis for developing regulations. (31) India released official guidelines in June 2012, (33) before which around 20 biosimilars were approved for use within India under an ad hoc abbreviated process. (34) The WHO will continue to monitor progress.

On WHO guidelines see also:

WHO Biologicals <http://www.who.int/biologicals/en/>

Guidelines on evaluation of Similar Biotherapeutic Products (SBPs). World Health Organization. Available from:

http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

See also <http://www.gabionline.net/Reports/WHO-guidelines-on-biosimilars-case-studies-and-discussion-highlights>

Annex 3.

List of References Found in the Literature Search

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An Overview of Current Regulatory Requirements for Approval of Biosimilar Insulins.	/pubmed/25789689	Heinemann L, Khatami H, McKinnon R, Home P.	Diabetes Technol Ther. 2015 Mar 19. [Epub ahead of print]
Why is there no generic insulin? Historical origins of a modern problem.	/pubmed/25785977	Greene JA, Riggs KR.	N Engl J Med. 2015 Mar 19;372(12):1171-5. doi: 10.1056/NEJMms1411398. No abstract available.
Insulin Biosimilars: The Impact on Rapid-Acting Analogue-Based Therapy.	/pubmed/25773234	FranzÃ S, Cilurzo F, Minghetti P.	BioDrugs. 2015 Mar 14. [Epub ahead of print]
The biosimilar insulin landscape: current developments.	/pubmed/25414937	Lavalle-GonzÃlez FJ, Khatami H.	Postgrad Med. 2014 Oct;126(6):81-92. doi: 10.3810/pgm.2014.10.2823. Review.
Biosimilar insulins: a European perspective.	/pubmed/25376600	DeVries JH, Gough SC, Kiljanski J, Heinemann L.	Diabetes Obes Metab. 2015 May;17(5):445-51. doi: 10.1111/dom.12410. Epub 2014 Nov 27.
Hypersensitivity reaction to a biosimilar insulin glargine.	/pubmed/25350350	GarcÃ-a-Nares H, Leyva-Carmona MI, PÃ©rez-Xochipa N, Chiquete E.	J Diabetes. 2015 Mar;7(2):155-7. doi: 10.1111/1753-0407.12241. Epub 2015 Jan 7. No abstract available.
FDA-approved biosimilar insulin: good enough for critical care, adulterated, or counterfeit? How can we tell?	/pubmed/25172881	Carter AW.	J Diabetes Sci Technol. 2014 Sep;8(5):1052-4. doi: 10.1177/1932296814539275. Epub 2014 Jun 16.
Biosimilar insulins are coming: what they are, what you need to know.	/pubmed/25105307	Edelman S, Polonsky WH, Parkin CG.	Curr Med Res Opin. 2014 Nov;30(11):2217-22. doi: 10.1185/03007995.2014.952718. Epub 2014 Aug 20.

[Biosimilars in rheumatology and other fields of medicine].	/pubmed/25055035	Milchert M, FliciaÅ,,ski J, Brzosko M.	Postepy Hig Med Dosw (Online). 2014 Jul 22;68:970-5. Review. Polish.
Biosimilar insulins are coming: the top 10 things you should know.	/pubmed/24918796	Blumer I, Edelman S.	Postgrad Med. 2014 May;126(3):107-10. doi: 10.3810/pgm.2014.05.2760. Review.
Impact of Biosimilar Insulins on Clinical Practice: Meeting Report.	/pubmed/24876554	Dolinar RO, Edelman S, Heinemann L, Home P, Goyal S, Polonsky WH, Schellekens H.	J Diabetes Sci Technol. 2014 Jan 1;8(1):179-185. [Epub ahead of print]
Patient Perspectives on Biosimilar Insulin.	/pubmed/24876533	Wilkins AR, Venkat MV, Brown AS, Dong JP, Ran NA, Hirsch JS, Close KL.	J Diabetes Sci Technol. 2014 Jan 1;8(1):23-25. [Epub ahead of print]
Multiple Source Biosimilar Insulin, What's a Provider to Do?	/pubmed/24876532	Carter A.	J Diabetes Sci Technol. 2014 Jan 1;8(1):20-22. [Epub ahead of print]
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Biosimilar Insulins: Basic Considerations.	/pubmed/24876530	Heinemann L, Hompesch M.	J Diabetes Sci Technol. 2014 Jan 1;8(1):6-13. [Epub ahead of print]
The future of basal insulin.	/pubmed/23965036	Shah VN, Moser EG, Blau A, Dhingra M, Garg SK.	Diabetes Technol Ther. 2013 Sep;15(9):727-32. doi: 10.1089/dia.2013.0228. Epub 2013 Aug 21. No abstract available.
Biosimilar insulin and insulin antibodies.	/pubmed/23911600	Heinemann L, Owens D.	J Diabetes Sci Technol. 2013 Jul 1;7(4):806-7. No abstract available.
The Biosulin equivalence in standard therapy (BEST) study - a multicentre, open-label, non-randomised, interventional, observational study in subjects using Biosulin 30/70 for the treatment of insulin-dependent type 1 and type 2 diabetes mellitus.	/pubmed/23802207	Segal D, Tupy D, Distiller L.	S Afr Med J. 2013 Apr 2;103(7):458-60. doi: 10.7196/samj.6345.
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The emergence of biosimilar insulin preparations-a cause for concern?	/pubmed/23046400	Owens DR, Landgraf W, Schmidt A, Bretzel RG, Kuhlmann MK.	Diabetes Technol Ther. 2012 Nov;14(11):989-96. doi: 10.1089/dia.2012.0105. Epub 2012 Oct 9. Review.
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Biosimilar peptides: need for pharmacovigilance.	/pubmed/21818998	Joshi SR.	J Assoc Physicians India. 2011 Apr;59 Suppl:44-7.
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