Editorial

Biosimilar insulins: Informed choice for South Asia

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Diabetes Care

As diabetes has become endemic in South Asia, we, as health care professionals, have to reassess our strategy to tackle the condition. One way in which this is done is by encouraging development, and rational usage, of modern pharmaceuticals. Such drugs are expected to be effective, safe and well-tolerated. In a chronic condition such as diabetes, it is imperative to be aware not only of short-term side effects, but of the potential for long-term adverse consequences as well.

Evolution of Insulin

The glucose-lowering drug in existence for the longest period of time is insulin. For almost a century now, insulin has helped save the lives of millions of people with diabetes. Over the decades, however, the type and quality of insulin has changed significantly. Newer methods of manufacturing have allowed production of larger amounts of effective, pure drug forms. This has been achieved by using recombinant deoxyribonucleic acid technology, with either bacteria (*Escherichia coli*) or yeast (*Saccharomyces cerevisiae*, *Pichia pastoris*) as host.[1] The use of these living organisms, as vectors for insulin synthesis, classifies insulin, along with other hormones, like a biological product [Table 1]. Enhanced awareness about the "therapeutic triad" (efficacy, safety, and tolerability) has prompted stringent regulatory processes, which ensure that no innovator biological molecule reaches the customer without going through a robust preclinical and clinical development program.

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Biosimilars

At the same time, however, copies of such innovator biological products are being produced. These copies, termed as biosimilars, are marketed in regulated countries after expiry of patent production, but have been made available in less regulated markets (e.g. China) even prior to this. Biosimilars may be similar to, but are not exactly the same as, generics, or originator/innovator biological products [Tables 2 and 3].[2,3]

Analogies to biosimilars can be drawn from the scientific world. To explain the concept, biosimilar products may be compared with water vapor, water, and ice: All have the same chemical formula (H_2O) but have totally different structures. Similarly, diamond, coal, and graphite are the same carbon atom, but totally dissimilar in appearance. To take a typically South Asian analogy, various varieties of mango, rice, or fish, may be biosimilar to each other, but are in no way the same. The average South Asian can easily distinguish between farm-grown and wild catch fish; various types of mango; or different types of rice. In a similar fashion, the diabetes care professional understands the subtle defining characteristics of an original biologic and its follow-ons on copies.

South Asian Scenario

South Asia is known as the drug factory of the world. Large pharmaceutical manufacturers, in Bangladesh, India, and Pakistan, meet both domestic and international demand. While no biosimilar insulin is approved in USA as of date August 2015, the European Medicines Agency and Japanese drug regulatory authorities have given approval to only one insulin-a biosimilar insulin glargine produced by Eli Lilly (Abasria).[4,5] The number of biosimilar insulin approvals in some South Asian countries is more, however [Table 4].

Table 1: Definitions

Generic drug, =Generic medicine: One that is similar to a medicine which has already been authorized (the "reference medicine")
Biopharmaceutical, =Biological medicinal product, =Biological medicine: A medical product whose active substance is made by or derived from a living organism
Biosimilar, =Similar biological medicinal product, =Follow-on biologic, =Bio generic. A medicine that is similar to a biological medicine that has already been authorized (the biological reference medicine). Their active substances are similar yet not identical

Table 2: Comparison of biosimilar and generic drugs

	Generic	Biosimilar
Structure		
Molecular weight	Low	Large
Molecular structure	Small, well-defined	Complex, tertiary and quaternary structures
Production	Synthetic	Synthetic
Use of living organism hosts	No	Yes
Posttranslational modification	No	Yes (sialylation, glycosylation)
Inherent variability	Low	High
Inter manufacturer heterogeneity	Low	High
Effect		
Immunogenic potential	No	Yes
Pharmaceutical equivalence	Yes	-
Biopharmaceutical equivalence	-	No
Bioequivalence (kinetics)	Yes	Yes

Table 3: Comparison of biosimilars and innovator molecules

	Innovator biological	Biosimilar
Nonclinical studies		
Pharmacokinetics	Required	Required
Safety pharmacology	Required	Limited
Reproduction toxicology	Required	Not required
Mutagenicity	Required	Not required
Carcinogenicity	Required	Not required
Pharmacodynamics	Required	Required
Repeat dose toxicity	Required	Required
Local tolerance testing	Required	Required
Clinical studies		
Clinical pharmacokinetics	Required	Required
Clinical pharmacodynamics	Required	Required
Short-term efficacy/tolerability	Required	Required
Long-term efficacy/tolerability	Required	Not required
Clinical indications to be studied	All indications to be assessed separately for approval	Only one indication needs to be studied approval is granted for all*
Pharmacovigilance	Required	Required

*India gives indication-specific approval

Most South Asian countries have well laid out regulatory pathways for biosimilar approval. India, for example, expects a biosimilar to prove efficacy for each indication that it is approved in.[6] Sri Lanka is one nation which has applied strict World Health Organization (WHO) good manufacturing practice rules.[7] Sri Lanka now requires all biosimilars applying for approval to demonstrate safety and efficacy through a locally conducted randomized controlled trial. This has resulted in many poorly studied biosimilars losing their license. The Organization of Pharmaceutical Producers of India, in its position paper on biosimilars, has also called for national regulatory guidelines to conform to those of the WHO.[8]

Patient's Perspective

Studies have been carried out in the West to assess public opinion regarding biosimilars. In an American study of 3214 patients with diabetes, 27% replied that they would "definitely use" biosimilar while 13% and 4% stated they would be "unlikely to use" and "definitely not use" biosimilars, respectively. Participants mentioned that they would consider the delivery device, brand quality, and trust as significant factors in their decision not to take biosimilars. While many respondents appeared to favor biosimilars because of low cost, there were a few who were hesitant to switch for precisely the same reason: They equated low cost with low quality.[9]

In another survey of 629 Americans, only 9% persons with Type 2 diabetes and 27% of Type 1 diabetes were familiar with the term "biosimilar." Though 30% prescribers and 12% pharmacists said, they used biosimilars, almost all of them identified biosimilars wrongly. Awareness about regulatory pathways for approval of biosimilars was poor.[10] The studies mentioned above reflect the need for aggressive public and health provider education before biosimilars can be used safely.

Challenges with Biosimilars

The approval and use of biosimilars is associated with novel challenges, which must be met by sustained awareness and education campaigns.[10] All stakeholders in diabetes care, including regulatory authorities, prescribers, counselors, pharmacists, and patients, should be aware of the distinction between biosimilars and innovator products [Table 5].[11,12]

Efficacy and safety

Health cost payers, whether governmental authorities or insurance companies, are faced with the challenge of achieving "health for all" within a limited budget. Therefore, they tend to prefer economical drugs.[11]

Insulin, however, is different from other pharmaceutical compounds. Insulin potency can be affected by variations in the raw material source, production process, and factory equipment. The presence of host-related, process-related, and product-related impurities may cause differences in

Table 4: Biosimilar insulins and insulin analogs marketed in South Asia

Country	Biosimilar insulins	Biosimilar insulin analogs		
		Glargine	Aspart	Lispro
Sri Lanka	None	None		
Pakistan	Insuget R, 70/30, N Innogen R, 70/30, N Zansulin R, 70/30, N	Basagine		
Nepal	Wosulin R, 30/70, N	Glaritus		
India	Insugen R, 30/70,50/50, N Humstard 30/70 Humarap Lupisulin-R, M30, M50, N Recosulin-R, 30/70, 50/50, N Human Fastact, Mixact 30/70 Wosulin R, 30/70,50/50, N	Basalog Basugine Glaritus		
Bangladesh	Insul R, 30/70, 50/50, N Maxulin R, 30/70, 50/50, N Ansulin R, 30/70,50/50, N Diasulin R, 30/70,50/50, N Insulet R, 30/70,50/50, N	Glargin Glargin C Vibrenta Insulet glargine Glarine	Glyset R, Glyset Mix Acilog, Acilog R Insulet Asp, Insulet Asp 30/70	Insul Lispro, Insul Lispro C

Table 5: Clinical issues with biosimilar use

Labeling and naming
Substitution
Extrapolation of clinical data
Health economics
Informed choice
Shared decision-making
Pharmacovigilance

pharmacokinetic and pharmacodynamic properties. There is a theoretical risk of formation of insulin-neutralizing antibodies, and "iatrogenic" insulin resistance, if frequent switching of insulin preparations is done.[11]

Labeling

Labeling of marketed products must clearly mention the name of the biological molecule, its method of production, and whether it is an originator or biosimilar drug. As all preparations of aspart insulin or glargine insulin, for example, cannot be equated with each other, the trade name, or unique identifying name must be used. Biological product usage is different from generic prescription in this regard. The product insert should clarify which indications the molecule has been studied in, as opposed to which indications it is approved for.[13]

Substitution

Substitution of biological products carries potential for harm. No insulin preparation should be substituted unless clinically indicated. The substitution must be informed to the patient, and frequency of clinical as well as glycemic monitoring stepped up in such cases. The need to avoid insulin substitution is an integral part of insulin technique guidelines.[14]

Pharmacovigilance

Pharmacovigilance data must reflect the actual product being described, whether biosimilar or innovator. A recent report of hypersensitivity to biosimilar glargine is an exemplar of this concern.[15] Just as the safety of biosimilars is of paramount importance, so is efficacy. There is evidence that higher doses of biosimilar insulin are needed to achieve glycemic control.[16]

Patient-Centred Approach

Modern diabetes care prides itself upon a patient-centered approach, which respects the patient's attitudes, wishes, and needs. Such an attitude is evident in Ayurveda teachings from India and is exemplified by the behavior and work of great pioneers such as National Professor Mohammed Ibrahim of Bangladesh.[17,18] To achieve optimal therapeutic outcomes, we practice informed, shared decision making with the patients in every sphere of diabetes management.

Such combined decision making should extend to choice of insulin preparations. Patients should be able to make an informed choice regarding the choice of originator or biosimilar molecules, based upon available evidence, and socioeconomic reality. All factors which may influence this decision, including robustness of clinical data, quality of cold chain maintenance, and availability of postmarketing pharmacovigilance activities, should be made public.[19,20]

Our call for shared decision-making, based upon informed choices, is not in contradiction to earlier recommendations for prescriber-based choice (as suggested by the American College of Rheumatology).[21] The prescriber, too, is an integral part of shared decision making. In a chronic disease such as diabetes, the choice of therapy cannot be dictated by a single shareholder, whether physician, pharmacist or payer. The patient has the right to participate in management-related decisions and choose the best available (or optimal product for himself or herself).

Conclusion

As the diabetes pharmacotherapeutic arena expands, more debate and discussion will be needed to decide appropriate, patient-friendly means of using newer insulins. Regulatory authorities will need to apply stringent mechanisms to ensure that only scientifically rational molecules, with robust preclinical and clinical development programs, are approved for use. Once and biosimilar are required to conform to stringent rule as applied to innovators, quality will be assured.

Postapproval pharmacovigilance must be maintained, in order to ensure safety and tolerability. The patient, along with prescriber, (and payer, if relevant) should be allowed to take shared, informed decisions regarding the insulin they wish to use. This will be "patient-centeredness" in its true spirit.

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Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.164033

Cite this article as: Kalra S, Azad Khan AK, Raza SA, Somasundaram N, Shrestha D, Latif ZA, *et al*. Biosimilar insulins: Informed choice for South Asia. Indian J Endocr Metab 2016;20:5-8.