Chronicle Specials

Guidelines on Similar Biologics- a milestone for India

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Thursday, October 04, 2012, 08:00 Hrs [IST]

The "Guidelines on Similar Biologics" prepared by Central Drugs Standard Control Organization (CDSCO) and the Department of Biotechnology (DBT) was released in June 2012, describing how biopharmaceutical companies should address the quality aspects of similar biologic medicines and developing such products in India. It explains the requirements for the manufacture and comparability testing for biological medicines claiming to be similar to another medicine already on the market.

The guidelines have laid down the requirements regarding manufacturing processes, the comparability exercise for quality, considering the choice of reference medicinal product, analytical methods, physicochemical characterization, biological activity, purity and quality attributes for relevant specifications of the similar biological product containing recombinant proteins and derivatives to support a Marketing Authorization Application.

The guidelines have to be read in conjunction with other applicable regulations, guidelines and handbook outlined in the draft guidelines.

The guidelines adopted the basic principles of EMA and WHO guidelines on biosimilar medicinal products and apply to products "developed in India" as well as those imported into the country.

Before the release of the guidelines the biological products whether new or similar to the original innovator product (similar biologics) are approved as 'New Drug' under Schedule-Y of Drug and Cosmetics Act'1940. The schedule 'Y' has a provision of submission of phase-I data for the products discovered in countries other than India along with the application. Phase-III trials are required to be conducted in India before permission to market the drug in India. The provisions of schedule Y were not sufficient to maintain the quality, safety and efficacy of generic biotech products as such.

An overview
The guidelines apply to similar biologics that contain well-characterized proteins as their active substance, derived through modern biotechnological methods such as use of recombinant DNA technology. The guidelines have established several scientific and technical parameters such as manufacturing, packaging, labelling, distribution and shelf-life of a product, which may directly involve in the head to head comparability exercise.

These guidelines provided analytical factors to consider when assessing similar biologics between a proposed similar biologic and a reference biologic for the purpose of marketing authorization.

This includes the importance of extensive analytical, physico-chemical and biological characterization in demonstrating, elaborate functionality and immunogenicity that the proposed similar biologics is highly similar to the reference biologics notwithstanding minor differences in clinically inactive components. Most importantly, the guidelines provide that the manufacturing process of a similar biologics should be highly consistent and robust as the reference product.

As outlined in the draft guidance, DCGI/DBT recommends a step-wise approach (sequential process) with extensive characterization revealing the molecular and quality attributes with regard to the reference biologic in the development of similar biologics. It is also important to identify critical quality attributes that may impact the safety and efficacy of the product.

Detailed regulatory pathways for indigenously developed and imported products should follow the five protocols outlined in the Report of the Task Force on Recombinant Pharma, 2005.

The guidelines permit the use of a reference biologic not authorized and marketed in India, however, provided that the biologic was licensed and "widely marketed" for four years post-approval in a country "with a well-established regulatory framework." The period of four years may be reduced or waived in a "national healthcare emergency" or where "no medicine or only palliative therapy" is available."

The comparability exercise should be a robust, head-to-head comparison between the similar biologics and the reference biologics at the levels of quality, safety, and efficacy in all preclinical and clinical exercises and the same reference biologic should be used throughout the development program for the similar biologic. The dosage form, strength, and route of administration of the similar biologics and the reference products should be the same, and the active substances should be shown to be "similar. However, it is not expected that all quality attributes will be identical and minor differences may be acceptable, if appropriately justified

Extensive state of the art analytical methods should be applied to detect even "slight differences" in all relevant quality attributes.

Pharmacopoeia monograph (if available) & ICH guidelines should be followed to validate quality attributes and stability studies that have not been identified in the reference biologics.

In case any significant differences are found in preclinical studies, these should be scientifically justified and critically examined in clinical trials.

Comparability studies such as detail biological activity study, immunological properties, purity and impurity profiles & Stability test are required to be conducted according to international guidelines

There are certain pre requisites before conducting pre-clinical studies as the applicant has to comply with the Review Committee on Genetic Manipulation (RCGM) requirements such as consistency in the product characterization, product specifications to obtain permission from RCGM to initiate toxicology studies.

Pre-clinical studies should be carried out only with the final formulation of similar biologics and wherever quantitative differences are detected, such differences should be justified.

Toxicity study should be performed in extensive manner and protocols and study reports must have complete information. The PK/PD study should be generally not less than 28 days with 14 days recovery period. However the duration may vary depending on the dosage and other parameters on case by case basis. In case of different animal models the scientific justification should be provided as per the requirements of Schedule Y with due permission from RCGM.

There would be three levels (1X, 2X and 5 X of human equivalent dose) of doses used in the animal toxicology studies corresponding to or higher test dose for repeat dose toxicity studies. Any difference in the levels of doses should be justified and approved prior to the studies.

Demonstration of consistency of the process, product characterization, specifications & similarity to reference biologics is required to be submitted to RCGM along with approval from IBSC to obtain clearance for conducting clinical trials. It is also mandatory to establish comparability of similar biologics manufactured at clinical scale against reference biologics.

Further, mandatory confirmatory safety and efficacy study is essential to establish comparative safety and efficacy in relevant patient for all similar biologics, however, can be waived if all the conditions set out in the guidelines are met with.

In case similar biologics has not demonstrated comparability to reference biologics in all preclinical evaluations and/or the PK/PD studies then the SB will be treated as a “stand-alone product”

With regard to extrapolation of the safety and efficacy data of a particular clinical indication of a similar biologic to other clinical indications may be possible if certain conditions are met, however any new indication that has not covered by innovator will be covered by a separate application to RCGM.

Post-market data for similar biologics consist of pharmaco vigilance plan; Adverse Drug Reaction reporting and post market studies along with submission of periodic safety reports have to be submitted every six months for first two years and annually for subsequent two years for evaluation of clinical safety as per Schedule Y of The Drugs & Cosmetics Act, 1940.

With regard to post-marketing safety and immunogenicity study at least one non-comparative post-marketing clinical study with focus on safety and immunogenicity on case by case basis should be performed.

All materials up to clinical evaluation for a period of five years after MA need to be archived for inspection or retrieval if required.

Conclusions

Indian biotech companies always wanted regulators to follow harmonized global standards in order to increase the competition for the product globally. Indian companies want to be global competitors and therefore they want the government to be an active participant in the understanding of the science of regulations, and to move away from procedural to science based regulation with a case by case approach. At the same time DBT/DCGI also wants to facilitate in creating an environment where international companies will be interested in using India as a place to manufacture biologic drugs. Therefore, a honest effort has been made to have the guidelines in sync with international best practices and to harmonize with international requirements for approval of similar biologics in India.

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