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India announces New Biosimilar Policy to tap $35 billion global market by 2020

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The Narendra Modi government has announced another major initiative to help the biotech industry by formulating the revised guidelines for biosimilars that has become effective from August 15, 2016. The new biosimilars policy, called the "Guidelines on Similar Biologics" prepared by Central Drugs Standard Control Organization (CDSCO) and the Department of Biotechnology (DBT), has been notified by DBT on August 18, 2016.

The Guidelines were prepared jointly by the members of a taskforce set up by CDSCO and sub-committee of the Review Committee on Genetic Manipulation (RCGM). The guidelines of 2012 were revised through a consultative process with various stakeholders led by members of ABLE (Association of Biotechnology Led Enterprises), other industry associations, leading scientific institutions and labs and through the public review process.

"Although case-by-case examination is important, these guidelines provide the required clarity and essentiality of data requirements for providing the similarity, physico-chemical characterization, preclinical structures and clinical trials," said Dr K VijayRaghavan, Secretary, Department of Biotechnology (DBT), Government of India.

How will the guidelines help the biotech industry?

"I expect to see a surge in Indian companies developing Biosimilars. This will lead to a large global opportunity along the lines of generic drugs where India can attain leadership," said an optimistic Dr Kiran Mazumdar Shaw, Honorary Chairperson of

ABLE and CMD, Biocon. She has been a key member of the CDSCO task force that deliberated for over a year and finalized the guidelines at a meeting in New Delhi on 6th August 2016.

According to a Special Report on Biosimilars prepared by Invest India, under the Department of Industrial Promotion and Policy (DIPP), the global market for biological drugs will touch the $290 billion mark in 2020 and account for 27 per cent of the pharma sales. In that the biosimilars will be a $25-35 billion opportunity by 2020.

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Currently, 450 biosimilars have been approved globally and another 250 are in the pipeline.

Added Dr G N Singh, the Drug Controller General of India (DCGI): "These revised guidelines will go a long way in providing guidance and documentation support to both applicants and regulators for the development, approval and post-marketing evaluation of safety and efficacy of similar biologics in the country and provide access to affordable biotherapeutics to the patients across the globe." The guidelines provide the regulatory pathway for a Similar Biologic claiming to be Similar to an already authorized Reference Biologic. These guidelines are for the guidance of all stakeholders and are not meant to substitute or rephrase the Rules made under Drugs and Cosmetics Act, 1940 or any other relevant Acts and are subject to being in conformity with the Drugs and Cosmetics Act and Rules as may be amended from time to time.

Here are some of the key changes that have been incorporated in the revised biosimilars guidelines.

Ã˜ If the reference biologic (for which the biosimilar is being developed) is not marketed in India, the reference biologic can be licensed in any ICH country (i.e. EU, Japan, US, Canada and Switzerland)

Ã˜ CDSCO is calling for specific post marketing safety data "through a predefined single arm study of generally, more than 200 evaluable patients and compared to historical data of the Reference product. The study should be completed preferably within 2 years of the marketing permission/manufacturing license unless otherwise justified."

Ã˜ CDSCO added primary endpoint should be safety (Phase IV), while secondary endpoint should be safety and immunogenicity.

Ã˜ "If immunogenicity is evaluated in clinical studies, it is not mandatory to carry out additional non comparative immunogenicity studies in post marketing studies

Ã˜ "If the firm conducts preapproval studies that included more than 100 patients on the proposed Similar Biologic drug, the number of patients in phase IV study can be reduced accordingly so that the safety data (from both Phase III and IV) is derived from a minimum of 300 patients treated with Similar Biologics." If a product is found to be similar "in preclinical, in vitro characterization having established PK [pharmacokinetic] methods and a PD [pharmacodynamics] marker that is surrogate of efficacy, the residual risk is significantly reduced in the Phase I study if equivalence is demonstrated for both PK and PD. Phase III clinical trials of such a Similar Biologics product may be waived...[and] where considered necessary, an appropriate single arm study in at least 100 evaluable subjects may be carried out in the most sensitive indication to address any residual uncertainty."

Ã˜ "In case the safety and efficacy study is waived all the indications approved for reference product may be granted based on comparable quality, non?clinical as well as convincing PK/PD data. Wherever the phase III trial is waived, the immunogenicity should have been gathered in the PK/PD study and will also need to be generated during post approval Phase IV study.

Some of the other highlights are:
Reference Biologic

§ These 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 demonstration of similarity depends upon detailed and comprehensive product characterization, preclinical and clinical studies carried out in comparison with a Reference Biologic.

§ Similar Biologics can only be developed against the Reference Biologic that has been approved using a complete data package in India. In case the Reference Biologic is not authorized in India, it should have been approved / licensed and marketed in an ICH (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) country.

§ Any product can be considered as a Similar Biologic, only if it is proven to be Similar using extensive quality characterization against the Reference Biologic. Further product development should only be considered once the similarity of the Similar Biologic is demonstrated in quality to a Reference Biologic.

§ These guidelines are applicable for Similar Biologics to be developed in India or imported into the country for marketing authorization. Detailed regulatory pathways for indigenously developed and imported products are mentioned under Annexure 1.

Manufacturing

§ The Similar Biologics manufacturer should develop the manufacturing process to yield a comparable quality product in terms of identity, purity and potency to the Reference Biologic.

§ If the host cell line used for the production of Reference Biologic is disclosed, it is desired to use the same host cell line for manufacturing Similar Biologics. Alternatively any cell line that is adequately characterized and appropriate for intended use can be used to develop a Similar Biologic, with appropriate justification in order to minimize the potential for signi?cant changes in quality attributes (QAs) of the product and to avoid introduction of certain types of process related impurities that could impact clinical outcomes and immunogenicity. For the establishment and characterization of the cell banks, the guidelines issued by the ICH should be referred for guidance.

§ The data requirements for review of manufacturing process at preclinical submission stage include a complete description of the manufacturing process from development and characterization of cell banks, stability of clone, cell culture/ fermentation, harvest, excipients, formulation, purification, primary packaging interactions (if different from Reference Biologic), etc. and the consequences on product characteristics.

Preclinical

§ The applicant has to comply with the RCGM requirements like demonstration of consistency of the process and product, product characterization and product specifications. The applicant should submit the data generated along with basic clinical information and preclinical study protocols to RCGM for obtaining permission. The toxicology studies should be initiated after the approval of RCGM.

§ The application to RCGM should be accompanied by approval of Institutional Biosafety Committee (IBSC) of the developer (copy of the minutes should be submitted), and approval of Institutional Animal Ethics Committee (IAEC), if available. The applicant should also provide details of the proposed site for conduct of toxicity testing and personnel to be involved e.g. study director, principal investigator, pathologist, other Investigators and quality assurance officer at the site. Status of GLP certification of proposed facility should also be provided.

Clinical Trial Application

Besides the information submitted in the preclinical application, the applicant has to submit application for conduct of clinical trial as per the CDSCO guidance for industry, 2008. The quality data submitted should indicate that there are no di?erences in Critical Quality Attributes (CQAs), and that all Key Quality Attributes (KQAs) are well controlled in order to allow the initiation of clinical evaluation.

Post-Market Data for Similar Biologics

It is important to establish a formal Risk Management Plan to monitor and detect both known inherent safety concerns and potential unknown safety signals that may arise from the Similar Biologic since authorization is based on a reduced preclinical and clinical data package. The risk management plan should consist of Pharmacovigilance Plan, Adverse Drug Reaction (ADR) Reporting, and Post Marketing Studies (Phase IV Study).

Source: ABLE