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Regulations in Development of Biosimilars

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With the recent advances in biotechnology, a number of biological products including vaccines, growth hormones, monoclonal antibodies, recombinant DNA products, cytokines, therapeutic genes etc., are being manufactured. These products are evolving as promising therapeutic agents for protection of mankind against various fatal and life threatening diseases. However, several original biologics used principally in the field of oncology, diabetes and autoimmune disorders approach patent expiry, and have emerged as frontrunners for biosimilar development.

The US-FDA in its guidance defined biosimilar as, "a product that is approved based on demonstrating similarity to 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. As manufacturing of biologics are based on culture of living cells, these molecules are difficult to reproduce. Hence, biosimilars are not identical copies of their originators. Therefore, the regulators require extensive investigations to demonstrate that they are sufficiently similar. For this, the product characterization, non-clinical and clinical testing versus the originator is much needed to obtain approval.

In most markets, regulatory agencies have set up their own regulatory pathways for biosimilars approval. The EMA has set the guide in 2005 while the WHO and a number of developed countries and other developing nations have followed the EMA's lead by adopting similar principles in their guidelines. For eg., in 2010, various guidelines were enacted on similar biotherapeutic product (SBP) by WHO, biocomparable product by Mexico and subsequent entry biologic by Canada. USA published first guidance on biosimilars in 2012. In 2009, South Africa and Japan adapted guidance on similar biological medicinal product (SBMP) & biotechnology follow-on product respectively. Likewise, New Zealand developed biological medicinal product (SBMP) guidance in 2011 and guidelines on similar biologics were designed by India, in 2012. Russia and China have neither specific regulations nor guidelines; these countries regulate biosimilars in the same way as they do new biological products, requiring that they comply with similar requirements to earn market approval. Several other countries like Philippines, Taiwan, Indonesia, Thailand etc. are evolving their regulatory framework for control of biosimilars. The definition and naming of biosimilar products is also different in different regulations.

Despite the progress in this field because of differences in legal framework in each country with local regulatory requirements, will inevitably slow the process and definitely lack the harmonization. Manufacturers are unable to meet all the regional regulatory requirements for global development of biologics. It is also a time consuming and costly process. None of the guidance documents are descriptive. There is no consensus across regions on what is an acceptable pathway and parameters, if the reference product is sourced outside own region. In addition, internationally, the approved formulation and/or presentations of the reference product may be different. For testing biosimilars, the application of most sensitive disease model is suggested by various countries. However, possibly an indication not licensed globally could be the most sensitive model. Would this approach be acceptable by different regulatory bodies? Most of the guiding principles apart from EMA guidelines are not very comprehensive on this issue.

For assessment of similarity through acceptable endpoints and equivalence margins, is an important task and different regulators have different opinions. This may result in inflation of patient numbers and/or duplication of studies. Extrapolation across indications in different therapeutic areas is not readily accepted by all regulatory agencies globally. In cases, where mechanism of action is poorly understood; the views of one agency may differ significantly from another. Patient to patient variability, unidentified risk associated with biosimilar and uncertainty about phase-III trials are few of the major challenges for the clinical studies. Also with changing and evolving guidelines, the pharmaceutical companies may be cautious with clinical studies.

As the global biosimilar market continues to grow, there is a need for harmonization of the guidelines. Companies should address country by country differences in regulations and develop plans accordingly. Industry experts must read and understand the guidance, and accordingly should prepare and execute the development plan for biosimilars. Emerging regions play an increasingly important role and can provide potential opportunity for biopharmaceutical companies for low-cost manufacturing. Many emerging nations are establishing biosimilars regulatory pathways, giving sponsors opportunities to select research sites strategically to optimize overall development timelines and achieve registration goals. In order to implement studies across countries with varying regulations involves layers of complexity, an in-depth knowledge of local environment, regulatory systems and an early strategic planning is utmost important.

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