

Bioequivalence of Follow-on Biologics or Biosimilars

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The patents for a large number of the first generation biopharmaceutical drugs or biologics are getting expired, and thus opening the doors for generic competition. It is a fact that these biopharmaceutical drugs have become an important part of pharmacotherapy in treating the so-called incurable or orphan diseases such as cancers and genetic diseases. However, these miracle drugs are highly expensive adding a lot to the health-care costs. At the same time, the blockbuster status of these biologics driving several generic drug manufacturers and large pharmaceutical industries to produce follow-on biologics or biosimilars. The term “follow-on biologics (FoB)” is used in United States while the term “biosimilars” is used in the European Union. Over a dozen biosimilars are approved across the world, mainly in Europe.

Biosimilars are copies of existing innovator biopharmaceutical drug products. However, they are made with a different cell line and a different manufacturing and purification process, and not identical with the originator products. Since they are not exact copies of originator products, their safety, activity and efficacy need to be fully validated before their release on the market. The unpredictable immunogenicity of biologics requires appropriate testing of biosimilars based on a scientific rationale and rigorous experimental evidence. Though some of the biosimilars may prove to be safe as their originator products, they are not extensively used in patients, and thus require careful handling. This warrants the manufacturers of these biosimilars and physicians to provide information to pharmacists, patients and other healthcare personnel on the possible risks associated with switching from originator product.

The launching of a normal generic drug product is easy and costs \$ 2 million only. The nature of biopharmaceutical drugs poses a challenge on testing the bioequivalence of biosimilars. A lot of clinical trials are needed to establish the equivalency and safety that would cost about \$ 40 million. Still this is far less than the cost of launching a new drug that may exceed \$ 1 billion. The regulatory agencies realize that testing the bioequivalence of biosimilars or FoB differs from that of the standard generics. The manufacturers of biosimilars must fulfill the quality, efficacy and safety requirements. The bioequivalence testing procedures for biosimilars are to be performed against the originator product as a control and include preclinical and clinical testing.

The only regulatory agency that has issued guidelines up to now has been the European Medicine Evaluation Agency (EMA) based on the EU legislation. The guidelines address requirements regarding manufacturing processes, quality, and analytical methods to assess comparability, factors to consider when choosing a reference product and physicochemical and biological characterization of biosimilars. They also address the non-clinical and clinical issues of biosimilars that include the pharmacotoxicological assessment, the requirements for pharmacokinetic, pharmacodynamic, efficacy and safety studies, with emphasis on evaluation of immunogenicity. Due to varying nature of the biopharmaceutical drugs, many of the concepts discussed in these guidelines may have to be adapted on a case-by-case basis. In addition to the general guidelines, four product class-specific guidelines were issued for the development of biosimilars containing recombinant epoetin, somatotropin, human insulin and hu-

man granulocyte colony-stimulating factor. These documents outline preclinical and clinical data requirements for marketing approval, describing the size/ design of the trials required and the best indication for demonstrating equivalence for each product, in comparison with a reference product.

To see more biosimilars in the market, the prospective manufacturers of biosimilars should come up with scientific evidence on the bioequivalence of biosimilars with an

emphasis on quality, safety and efficacy. There is a strong need as well as a great scope to conduct extensive research studies on establishing the scientifically valid guidelines on the bioequivalence of biosimilars. Certainly, this will be highly helpful to millions of patients who are now deprived the benefits of the wonderful, but expensive biopharmaceutical drugs. The scientific community is encouraged to extensively publish all the relevant data on “bioequivalence of biosimilars” in this journal.

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