Publication : BioSpectrum
Date : September 2012
Page : 22, 24
Title : Bioanalysis

The brighter side: These guidelines have been able to dispel the ambiguity as seen in the draft guidelines over a range of issues

Aspects	Before guidelines	Present scenario as per guidelines
Cell Banking	No clear ground rules for establishment of cell banking, establishment and characterization	Section 6.3: Direct reference to the ICH guidelines having clear specifications for this aspect.
Fermentation process development	As per Form C3, five batches of reproducible fermentation data is required for seeking pre-clinical approval from RCGM.	Section 6.2.2 reduces the requirement to "at least three batches of reproducible fermentation data."
Preclinical studies	Lack of clarity on whether the drug substance, the drug product, or both of need to be tested pre-clinically.	Guideline clearly recommends that the preclinical studies should be conducted with the final formulation of the similar biologic.
Toxicological studies	Schedule Y did not have any clear specifications for the pre-clinical studies of biosimilars	Section 7.2.2 gives an explicit blueprint for design of toxicological studies in case of biosimilars.

**with inputs from Dr Ashok Kumar, president, R&D, Ipca Laboratories*

The nebulous part: These guidelines still seem to have left some questions unanswered

Aspects	Specifications as per guidelines	Limitations
Analytical methods	Section 6.3.1: "Extensive State of the art analytical methods should be applied so as to detect even slight differences in all relevant quality attributes."	Difficult to execute unless the scope of the term "slight differences" is defined.
Product characterization	Section 6.3.2: "In case where post-translational modifications are taking place, these modifications need to be identified and quantified."	Exact nature of post-translational modifications not defined. Absolute quantification of these modifications is not a practically viable approach.
Confirmatory clinical studies	Section 8.3: "...the confirmatory clinical studies can be waived off if, structural and functional comparability of similar biologic and reference biologic can be characterized to a high degree of confidence by physicochemical and invitro techniques, among other pre-requisites."	Difficult to execute unless the scope of the term "high degree of confidence" is defined.

**with inputs from Dr Ashok Kumar, president, R&D, Ipca Laboratories.*

Welcoming the government's initiative, KV Subramaniam, president and CEO, Reliance Life Sciences, who was a member of the drafting committee said, "The Indian biosimilars guidelines are comprehensive in nature and address the pre-market and post-market regulatory requirements for biosimilars. The document clearly delineates the roles and responsibilities of authorities like DBT (RCGM) and DCGI in the approval process of a biosimilar. Accordingly, the RCGM oversees product quality, characterization, approval of protocols and review of preclinical toxicology studies while DCGI focuses on the approval and review of clinical trials and marketing authorization."

He further said, "The guidelines state that all biosimilars should be compared to the reference or innovator product through all phases of development. There is clarity on the quality and quantity of data expected, for example, number of batches, bioassays, and analysis of products for post translational modifications. Animal studies have also been rationalized by allowing short term studies in relevant animal species. When such models are not available, it is recommended to follow Schedule Y of drugs and cosmetics act. Some redundant studies have been eliminated reflecting the current scientific understanding."

Dr Krishna Ella, chairman and managing director, Bharat Biotech International, hailed the government step by remarking that, "Guidelines will streamline the approval process and bring clarity to all biosimilar manufacturers. The new guidelines clarify several issues relating to product development and licensure. It is a highly welcome step in the right direction. Such guidance which documents several aspects of the regulatory process in India would be welcomed by industry. Guidelines laid out for clinical evaluation, pre-clinical evaluation, manufacturing process validations, and product characterization are widely accepted by the industry and these guidelines should be enforced strictly across the industry. We are happy that with introduction of this policy, there is going to be an

adherence of International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines (Q5A,Q5B, Q5D)."

This comes as a welcome step in the wake of rapid growth of the Indian biosimilars market, which has grown by a whopping 200 percent in a relatively short span of time since 2008. "These guidelines have come a long way from the abridged regulatory guidelines followed till now," commented Dr Ashok Kumar, president, R&D, Ipca Laboratories.

Issues faced by the industry

"The guidelines have taken into consideration the exceptions in the generally outlined product development pathway. For example the innovator product may have been developed in a particular host, but if the current expression systems are better in terms of quality of the product and yield, the guidelines have provisions for approval of products developed in a different host on a case-to-case basis. Similarly approval of new formulation of existing drug can be sought based on sound scientific data," pointed out KV Subramaniam. However, some areas such as critical indications, or where very long-term end points are measured, it could have been further clarified leading to faster approval of the drugs.

Dr Krishna Ella, however, raised concerns about some points in the draft by saying more has to be done to streamline the existing regulatory framework for biologics, vaccines and biosimilars. It is too complex due to the involvement of multiple departments from different ministries. The Indian biotech industry requires a single window regulatory authority that is strict and transparent. The current system has companies applying to multiple regulatory authorities under different ministries to obtain permissions for biologic material import, product development, preclinical testing, clinical trials, and marketing authorizations. A single window or single agency system is the norm in several countries with organizations such as the USFDA (USA), EMA (EU), ENVISA (Brazil), and SFDA (China), which operates as the central nodal agency.

Dr Krishna's suggestion was to streamline the regulatory processes for CROs working for international clients on international products. Increased timelines for receipt of biologic test articles from foreign locations would reduce the competitiveness of the CRO industry. Dr Ella further recommended that Central Drugs Laboratory (CDL), Kolkata has to take responsibility for the availability of authorized reference standards and their identities, which currently is under ambiguity. CDL, Kolkata also could be developed along the lines of CDL, Kasauli, which receives batch samples for vaccines for testing and product release.

Commenting on the challenges that the industry will face with the new regulations levied, William Lee of Quintiles Asia said, "The Indian guidelines are not too dissimilar from the EU and WHO guidelines and the draft US guidelines. As these international guidelines are widely available and have been used for several years, most Indian biopharmaceutical companies are likely to be familiar with them. A major difference between the Indian guidelines and that of the international guidelines referred above is that there is no data exclusivity for first-approved products. This could lead to a situation where companies might get into patent related battles as there is lack of clarity in terms of data exclusivity."

"The balance between the requirement of supporting data and time allotted for obtaining marketing authorization encapsulated in the guidelines enables to provide an environment conducive to companies to manufacture drugs at an affordable cost benefiting the larger patient population," opined Subramaniam.

"Overall, inspite of their limitations, these set of guidelines have come as a relief to the industry. The fact that the regulatory requirements are more or less at par with that of the international regulatory agencies (including ICH and USFDA), would make it much easier for the biopharmaceutical manufacturers of India to meet the international quality standards," said Dr Ashok Kumar. "We believe that the presence of a lucid framework would surely expedite the development of biosimilars in India that had been dawdling for want of a clear blueprint," he added.

Indian biosimilar players will now be able to compete on par with global biosimilar players. With this development, we may well see India leading the way in the development of biosimilars for the global market in the coming years. Also, more importantly, in providing a boost to biosimilar development, the government of India is creating a clear pathway for the development of cost effective and safe biologics for the people of India which fits in with the government's agenda of more affordable healthcare. "I do believe that the Indian guidelines are a step in the right direction and will evolve with more clarity in the next couple of years," concludes Lee. BS

NARAYAN KULKARNI