The Indian biosimilars guidelines – a great step forward?

Cecil Nick and Ruchi Singh suggest that India’s new guidelines may represent a step towards universal acceptance of a scientifically sound global biosimilars development programme.

After two years of intense engagement with stakeholders, the Indian government has launched formal guidelines for marketing similar biologics (i.e. biosimilars)\(^2\). The new guidelines have clearly been heavily influenced by EU, World Health Organization and other major guidelines but they also reflect some local considerations.

Nevertheless, because of their general nature, it remains challenging to predict how they might be applied in actual practice, as there is much scope for review-based leeway on final decisions.

From a CMC perspective, the requirements are unlikely to be controversial and would be expected to align with those applied by the European Medicines Agency’s scientific committee, the CHMP, and other major regulatory agencies. However, it is noted that there exists a requirement for the dosage form, strength and route of administration to be the same as that of the reference biologic, which aligns exactly with the US Biologics Price Competition and Innovation Act of 2009. This limitation is currently not specified in the EU guidance, although a recently published concept paper for revision of the overarching CHMP guideline on biosimilars (CHMP/437/04)\(^3\) suggests that the current EU position on this could be revised.

Focus on non-clinical requirements

What is striking is the focus in the Indian biosimilars guidelines on non-clinical requirements. This appears to contrast with current thinking in the EU, which recognises the often potentially limited value of toxicology studies as part of a biosimilar programme apart from the need for extensive and comprehensive in vitro and in vivo pharmacodynamics studies. The Indian guideline specifies as a routine requirement the need to test three dose groups, for studies of not less than 28 days, for a 14-day recovery period and, where a representative species does not exist, for the potential to require studies in two rather than one species, which go beyond the current standard EU requirements. In fact, the CHMP queries the need for any studies in non-relevant species. It remains to be seen whether non-clinical study programmes acceptable to the CHMP will also be agreed to in India or whether more extensive studies will be required.

In line with the global recognition, including a shift within the EU\(^4\), that it is not practical to undertake studies against reference biologics sourced from multiple regions, the Indian guideline allows for comparison against a reference product not marketed in India, provided this has been licensed and widely marketed for four years post approval in the originator jurisdiction and in a country with a well-established regulatory framework. This period of four years may be waived if there is a healthcare need in India for early approval.

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From 1996 until now, biosimilars in India shared the same regulatory pathway as new drugs requiring a confirmatory Phase III clinical trial to be performed in at least 100 patients in India. The new biosimilars guidelines require information to establish comparative safety and efficacy in a relevant patient population but whether a minimum of 100 patients treated in India is a requirement is not entirely clear. However, the guidelines do make reference under the discussion on “Post-Market Surveillance” to the fact that similar biologics are not new drug products.

Furthermore, nowhere do the guidelines specify the need for trials to be conducted in India, so the optimist could assume that Indian regulators are embracing a more global outlook and acknowledging that at least in the case of biosimilars, ethnic differences are not a major concern since comparability needs to be demonstrated in a suitably sensitive population, the ethnic origin of which is immaterial.

This is a reasonable position since lack of relevant ethnic differences will in all likelihood have already been established through many years of use of the reference product, but whether this is the view that prevails in India remains to be seen.

Comparative clinical trials are now considered critical to demonstrate the similarity in safety and efficacy profiles between the similar and reference biologic with few exceptions. As is the case in the EU and US, equivalence trials are preferred but non-inferiority trials may be accepted if clearly justified. In these circumstances, applicants are advised to consult with the Central Drugs Standard Control Organisation prior to study initiation, suggesting that a much needed formal scientific advice process may evolve.

It is also stated that the confirmatory clinical safety and efficacy studies can be waived under certain conditions in which physico-chemical and biological and preclinical comparability can be confirmed to a high degree of confidence and adequate clinical PK/PD evidence for comparability are available. However, recombinant human soluble insulin products, which one might expect could meet the aforementioned conditions, are cited as an example for which only a comparative clinical safety study is required. Therefore, it is not clear in reality whether there will be any situation where comparative safety data will not be required prior to marketing approval.

As in the EU, extrapolation of the safety and efficacy data of a particular clinical indication to other clinical indications may be possible. Thus for future biosimilar approvals a more extensive clinical programme for Indian approval is likely to be required, possibly similar to current EU requirements.

It is hoped that the Indian biosimilar guidelines represent a step towards universal acceptance of a scientifically sound global programme without the need for unnecessary local clinical data. If this is achieved in practice, then the guidelines would represent a great step forward in bringing high quality biological products to the market at more affordable prices.

References


2. India demands greater non-clinical, clinical testing of biosimilars than EU, US, Scrip Regulatory Affairs, 9 July 2012


For our online news report on the guidelines, see http://bit.ly/P0Qyr7

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