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EDITORIAL

Biosimilars for Healthcare Professionals

Advances in analytical characterization of biosimilars

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The substantial improvement in the power of analytical methods to compare different versions of a given protein molecule should be taken into account when considering the value of clinical studies for designation of biosimilarity. Arguably, demonstration of comparative pharmacokinetic, allied to post-registration monitoring, will provide more discriminatory clinical evidence than large pre-approval therapeutic equivalence studies.

Keywords: Analytical, biosimilar, comparability, quality, registration, similarity

In this issue of *GaBI Journal*, Gerard et al. conclude that extrapolation to other indications of biosimilars on the basis of throughout analytical characterization of biosimilars can be done [1]. Their message is that the analytical methods available today have evolved enormously compared to the time the first biosimilars came to the market. On analytical grounds it is possible to predict efficacy and safety. Will this have consequences for the registration requirements in the near future?

In 2003, the Committee for Medicinal Products for Human Use (CHMP) came to a positive opinion for the first biosimilar product Omnitrope (genotropin). Legal issues prohibited an approval by the European Commission but the company resubmitted two years later and in 2006 Omnitrope was approved as the first biosimilar biological. This procedure initiated and stimulated the publication of biosimilar European Union (EU) guidelines. The principle behind these guidelines is that similarity demonstration is crucial. Full demonstration of efficacy and safety is no longer required, but a biosimilar application should be supported by an extensive comparability exercise at quality, preclinical as well as at clinical level. The idea behind this approach is that for biologicals comparability is impossible to demonstrate on analytical grounds alone.

Since 2006 several biosimilars have been approved in the EU. Clinical data were limited; studies were often restricted to one indication. This indication is chosen because of being the most sensitive indication to show a potential difference if such a difference really exists. In a few cases clinical data were even more limited to pharmacodynamic data alone.

Since 2006, major advances have been made in analytical techniques, exquisite methods exist nowadays to characterize the primary amino acid sequence, the tertiary conformational structure, post-translational modifications, e.g. glycosylation, and to assess any impurities and degradation products both after release and during shelf life. Biological activity is further compared by *in vitro* and *in vivo* activity assays.

These advances in technology have already influenced regulators. Updates of existing guidelines show that regulators keep an eye on new possibilities to show comparability and especially to extrapolate to other indications. The recent clinical EU guideline mentioned that extrapolation should be considered in the light of the totality of data, i.e. quality, non-clinical and clinical data [2]. Gerard et al. highlight the possibilities available today to fully establish analytical comparability with quality tools and receptor assays alone and that these possibilities are able to fully justify extrapolation to other indications. The authors point out that these analytical possibilities are already in place for approved biologicals in case of manufacturing changes. Analytical comparability of the product before and after the manufacturing change is common practice. Only in an exceptional case is a clinical efficacy study performed and seldom is an immunogenicity study initiated.

Extrapolation to all the indications of the reference product is essential to the concept of biosimilarity. It is regrettable that clinicians sometimes have difficulty understanding this extrapolation. It requires a full understanding of all the required analytical, preclinical and clinical study data available. It is the task of regulators to explain and convince the medical community about the background of the approval of biosimilar products, a few have already done so [3].

The present abilities to demonstrate on the analytical level similarity/comparability to the reference product raise the question of whether there is still a need for all the clinical data currently required. How much efficacy and safety will really be needed for the approval of biosimilar products in the future? Would it not be possible to restrict the comparability exercise to analytical and just pharmacokinetic (PK)/pharmacodynamic (PD) data alone? The clinical data currently required are costly and burdensome. Is this compatible with the correct use of our medical resources? Institutional review boards sometimes hesitate to approve these extensive studies with their major burden on patients.

One reason to ask for long-term clinical studies is the risk of unexpected immunogenicity. However, the experience gained during the last 10 years has failed to identify any immunogenicity-related issues for approved biosimilars. In a few cases, quality-related issues were already identified in the preauthorization phase as being potentially relevant for an increased immunogenicity risk. It is possible to identify and control these immunogenicity-related risks for biosimilar candidate product [4]. With the advances in analytical technologies, the

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risk of incremental immunogenicity can, to a large extent, be avoided by analytical characterization, batch release testing and stability testing. PK/PD studies in volunteers could give valuable information on immunogenicity. Preregistration, short-term immunogenicity testing will also give valuable information. The need for preregistration clinical data should be decided on a case-by-case basis depending on what is known about the reference biological and on available analytical and preclinical data. Accumulation of additional information on longer-term safety, including immunogenicity, is already a standard element of the EU Risk Management Plan in the post-registration phase. Immunogenicity would be much better studied by less costly post-authorization monitoring. These studies will provide a better and more sensitive approach for detecting real world differences in efficacy, safety and immunogenicity and are less costly. Yes, analytical advances are a challenge for regulators. They make it possible to consider requiring much less expensive, preregistration clinical study data.

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