European biosimilars conference highlights extrapolation as key issue

This paper discusses topics covered by the EGA's April 2015 biosimilars conference, where extrapolation of indications was highlighted as a key issue.

Keywords: Biosimilar, extrapolation, similarity

The European Generic medicines Association (EGA) held its 13th EGA–European Biosimilars Group Conference in London on 23–24 April 2015.

The conference was attended by more than 280 delegates from 36 different countries, and included delegates from national and international regulatory agencies, pricing and reimbursement authorities, academia, patient organizations, medical societies and healthcare professionals.

The key topic was 'the science of extrapolation of indications' but many related subjects were also covered by the conference including the basic principles of biologicals, the European Medicines Agency (EMA) overarching guideline, harmonization efforts on biosimilar clinical trials, naming/labelling of biosimilars, the World Health Organization BQ (biological qualifier) proposal, strategic approaches for the uptake of biosimilars in France, Germany, Italy, Spain, Sweden and the UK; Norway's biosimilar infliximab experience [1], and the global view of biosimilars regulatory approval with a focus on Brazil, Canada [2] and the US.

Mr Didier Laloye from Hospira France gave a presentation on behalf of the French generics association GEMME. His presentation, which covered biosimilars uptake in France, highlighted the complexity of the situation in the country regarding reimbursement, pricing, substitution and incentives for biosimilars.

France is the first European country to consider legislation on biosimilars substitution. French legislation allowing substitution of biosimilars was introduced as part of a new law concerning the social security budget (Article 47 of the Law of 23 December 2013) [3]. However, the implementing decree has not yet been published. The French healthcare authority, ANSM (*Agence nationale de sécurité du médicament et des produits de santé*), recommends that after the first administration of biological product, not to change the product given to the patient, in order to limit the risk of immunogenicity and ensure traceability for pharmacovigilance follow-up. This is also reflected in the law, which states that substitution of biosimilars is allowed only when initiating a course of treatment, if the biosimilar belongs to the same group as the prescribed product (known as a 'similar biologic group') and if the prescribing physician has not explicitly prohibited substitution of the prescribed biological by indicating *'non substituable'* (non-substitutable) in handwritten characters on the prescription.

A presentation concerning the trends from marketing authorization applications, scientific advice procedures and policies by Dr Peter Richardson, Head of Quality Office, Specialised Scientific Disciplines Department, at EMA, explored the use of statistical methodology for comparative assessment of quality attributes, global development and the increasing use of non-EU comparators, and the variety of clinical approaches proposed to demonstrate biosimilarity. A global development approach was proposed in 75% of the scientific advice requests for biosimilars in 2014.

In a presentation by Dr Jian Wang from Health Canada entitled 'Biosimilars in Canada: learning from the approval of the first mAb and future outlook', the reasons for the agency's refusal to extrapolate inflammatory bowel disease (IBD) indications to the infliximab biosimilar (Remsima/Inflectra) [4] were outlined. Dr Wang explained that extrapolation to indications and uses pertaining to IBD (Crohn's disease and ulcerative colitis) was not recommended because the comparability between the reference and biosimilar infliximab indicated insufficient similarity between the two products. This arose from the observed differences in the level of afucosylation, FcγRIIIa receptor binding and *in vitro* antibody-dependent cell-mediated cytotoxicity (ADCC) activity. Furthermore, uncertainty arose since differences were observed in the quality assessment – a lower ADCC activity, interpretation of *in vitro* test results from all assays was challenging, ADCC mediated effects in certain disease(s) cannot be ruled out, the clinical significance of a lower ADCC activity is still unclear and clinical studies were conducted only in populations where ADCC is unlikely to be involved.

Dr Wang pointed out that 'based on the same data set, regulatory agencies may render different regulatory decisions. This can happen for both innovator and biosimilar products. He added that 'further dialogue and harmonization among regulatory agencies on their decision-making could be considered as experience with the scientific and regulatory issues related to biosimilars increases.'

According to Dr Wang, the uncertainties in extrapolation of indications are due to the fact that the 'scientific and regulatory knowledge and experience are limited in dealing with these types of issues', and that the 'presubmission package was not sufficiently informative in terms of the issue of concern'.

Despite uncertainties on extrapolation of indications in certain circumstances, Health Canada does support extrapolation of indications, and emphasizes that the science of extrapolation is based on the following principles:

- Similarity is demonstrated through a detailed and comprehensive comparative product characterization.
- There is a thorough understanding of the mechanism(s) of action of the biological product, and the similarities and differences in the mechanism(s) of action that play a role in each of the indicated conditions for which a sponsor applies.
- There is an understanding of the pathophysiological process(es) of the indicated diseases, and the differences and similarities between them.
- The safety profiles in the respective conditions and/or populations are comparable.
- There is adequate clinical experience with the reference drug.

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In the session chaired by Dr Sumant Ramachandra on 'The evolving biosimilar paradigm: from a science-driven conceptual approach to a science-driven knowledge-based approach' the science of extrapolation was also discussed and highlighted as a critical issue for biosimilars makers.

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Michelle Derbyshire, PhD, *GaBI Online* Editor

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