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Biosimilars collaboration at Amgen and Actavis

Representatives from Amgen and Actavis have spoken to GaBi (Generics and Biosimilars Initiative) about biosimilars. Topics covered included the clinical development of biosimilars, the need for further education, how the partnership model between the companies was working, the commercialization of biosimilars and their views on non-proprietary names for biosimilars.

Keywords: Biosimilar, clinical development, commercialization, International Nonproprietary Name (INN)

Biotech giant Amgen and generics and speciality drugmaker Actavis entered into collaboration for the development and commercialization of several cancer antibody biosimilars back in December [1]. In an interview on 3 April 2014, Dr Richard Markus, Executive Medical Director at Amgen, Dr Philip Ball, Director of Biologicals Alliance Management and Government Affairs at Actavis, and Dr Virginia Acha, Director of Regulatory Affairs at Amgen, spoke to GaBi (Generics and Biosimilars Initiative) about their views on biosimilars and the biosimilars plans for the two companies.

Clinical development programme for biosimilars

In order to develop biosimilars, understanding and reverse engineering of the reference product is necessary and this fundamentally includes development of a new and specific cell line. This also includes a thorough understanding of the molecule function, which requires specific assays to be developed. High quality sensitive assays are very important to correctly understand the molecule. Amgen uses the quality-by-design concept, and because of the originator company's history and experience in biopharmaceutical development and manufacturing, they already have a good understanding of the structure/function of antibodies.

The company knows where to look for differences between biosimilar molecules and their originator molecules, have sensitive assays, and can re-engineer the molecule. This is a difficult process.

When considering clinical development of biosimilars, the view of Dr Richard Markus is that it is necessary to create the foundation of a clinical development programme before establishing the 'appropriate extent of trials needed'. The basic assumption that needs to be proven is that the biosimilar molecule is highly similar; therefore, it needs to first demonstrate the same functions as the originator molecule across sensitive assays before proceeding. This is the foundation for the clinical development plan.

For the pharmacokinetic trial, this should be carried out in a sensitive population, using a tight margin to provide confidence in equivalent kinetics and hence dosing. Both companies believe that there is no reason for biosimilars to have a lower confidence level than generics and therefore support the use of the 80–125% as a general rule. This rule states that two versions of a drug are generally said to be bioequivalent if the 90% confidence intervals for the ratios of the geometric means (brand-name versus generic) of the area under the curve (AUC) and maximum concentration (C_{max}) fall within 80% and 125%.

Amgen and Actavis are prioritizing three aspects of the clinical development of their biosimilars:

Efficacy – use of sensitive efficacy endpoints and appropriate equivalent margins to prove the same or equivalent efficacy

Safety – use of a sensitive population to see if a difference can be found or not in a controlled setting, to show that any adverse

events observed with the biosimilar are no worse than with the originator

Immunogenicity – use of sensitive immune competent patients, preferably who are not on methotrexate or chemotherapy

Following these three key concepts to design the clinical development of biosimilars, the clinical results should ideally be achieved in a single trial.

Information from this trial, if efficacy, safety, and immunogenicity are the same and the structure/function and kinetics were already shown to be equivalent, may possibly then be extrapolated to other approved indications.

Biosimilars education

Both companies agree there is a need for further education on the subject of biosimilars in order to establish confidence for those using biosimilars, i.e. physicians and patients.

In particular, it is important to build confidence in prescribers, as it is prescribers who make the choice to use a biosimilar and it is prescribers who are talking to patients. Physicians may review scientific information in a publication or disseminated during a conference and it is important that this information is in context to help them incorporate biosimilars into treatment planning.

One way suggested to improve confidence in prescribers is to make sure that key data in the label on the risk and benefits such as head to head study information and safety and immunogenicity data, is transparent. Inclusion of further information such as trials carried out in the appropriate or most sensitive population can also help build confidence in physicians.

According to Dr Philip Ball, 'confidence in biosimilars' is the key to increasing uptake, not necessarily only via cost savings. Offering a high quality biosimilar with independent trust-worthy scientific information is a practical measure to help build confidence in biosimilars.

Partnership model

The collaboration between Amgen and Actavis for biosimilars is not unusual, said Dr Ball, but it does represent a unique combination of capabilities.

Amgen is developing six biosimilar monoclonal antibodies, four of which are in collaboration with Actavis. Amgen has extensive manufacturing capabilities with stringent quality control systems for manufacturing both biosimilars and originator biologicals, and plans to begin launching its biosimilars portfolio in 2017.

Actavis is experienced in developing complex generics as well as novel pharmaceuticals and is also developing a biosimilar outside of the Amgen collaboration. Actavis also has the experience and capabilities to launch in non-patent environments.

Commercialization

Commercialization of biosimilars is a very different process to that for generics. The European Commission's platform on 'Access and uptake of biosimilars' and the consensus document on 'What you need to know about biosimilars', makes it clear that a much more proactive approach is needed to bring information on biosimilars to stakeholders. It is critical that companies work with patients, physicians and nurses to offer them education on biosimilars and to provide relevant scientific data.

Biosimilars is a new science/drug category, with the first biosimilars being approved in Europe only eight years ago [2]. Therefore, according to Dr Virginia Acha, even though the public understand the concept of biosimilars 'they still have to believe in it and appropriate data has to be provided, engaging with them and helping them to understand biosimilars as therapeutic alternatives'.

According to Dr Philip Ball, the industry has a responsibility to continue to educate stakeholders. There will always be new entrants, new groups, with new or slightly different questions, and the industry needs to understand their needs – what is useful is public discussion. 'As an industry we need to work together on providing proper educational information, and talking to the right groups in addition to regulators as there are questions beyond the authorization of a biosimilar', adds Dr Ball.

Naming of biosimilars

Whether biosimilars should have a common or distinct International Nonproprietary Name (INN) is a hot topic amongst academia, regulators, originator biologicals companies and biosimilars companies [3, 4]. Amgen is supporting the World Health Organization's (WHO) proposal for a unique global 'biological qualifier (BQ)' which Amgen would like to see applied for all biologicals, as being non-discriminatory. The company believes that the principal of adding a BQ to be used together with the INN could help further enable identification of the product, supporting product-level traceability and global pharmacovigilance to effectively trace biologicals (including biosimilars). According to Amgen, if the WHO BQ system is applied by national regulatory bodies, it could be a very effective system for a world that has multi-source biological products. This simple identifier may be useable anywhere in the world, and could serve as an effective means of additional identification information.

The majority of EU (European Union) Member States, however, have said that they strongly support that the names of biosimilars should be closely aligned with their reference product and that it is not problematic to identify which biological products are associated with adverse reaction reports [6]. In the EU, the policy is for both the brand name and INN as well as batch number to be used to identify the specific biological product, for all biological medicines.

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Reported by Michelle Derbyshire, PhD, *GaBi Online* Editor

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