Biosimilars in the EU – what have we learned so far?

With the EU set to approve its first two bioisimilar monoclonal antibodies, it is time to look back over the seven years since the first biosimilars were approved. ***Steffen Thirstrup*** considers the lessons learnt and examines the outlook in the EU for this new group of biological medicines.

The introduction of small molecule generics over the past 20 years or so has resulted in substantial savings for the mainly publicly-financed healthcare budgets in the EU. Many countries have implemented special measures to increase the use of generic medicines thereby increasing competition. Generic prescribing, automated switching/substitution to the cheapest generic at pharmacies and reference pricing are among the methods frequently used.

When generics were first introduced, they were met with much scepticism, and although most doctors and patients today have accepted and understood the concept of generics there is still sometimes doubt: "How can the same medicine be as good, safe and effective when it only costs a fraction of the originator?". This is intuitively difficult to understand because in many other areas of our lives cheaper versions of a branded product are often falsified copies. Much effort has therefore been put into explaining the high and very detailed regulatory requirements for obtaining a marketing authorization for generic drugs.

Despite generic competition, most countries have seen an increase in their overall spending on pharmaceuticals. This is partly driven by the introduction of many new and often expensive therapies for major diseases within areas of malignancies, inflammatory and other chronic conditions[1]. An increasing number of such pharmaceuticals has over the past decade been biological products made by recombinant technology. A little less than 20% of pharmaceutical sales in the EU are attributed to recombinant biological medicines. When the European pharmaceutical legislation was amended in 2004 introducing the legal requirements for approval of biosimilar medicinal products (biosimilars), many healthcare providers and payers expected to see generic competition in the area of biotech products as well.

First-wave biosimilars

In 2006, just a year after the revised EU pharmaceutical legislation came into force, the first biosimilars obtained positive opinions from the European Medicines Agency's key scientific committee, the CHMP, followed by the issue of marketing authorizations by the European Commission.

In the following four years, a total of 18 applications were evaluated by the CHMP, resulting in the approval of 14 products, the refusal of one product and the withdrawal of the application during the evaluation procedure by the applicants for three products.

Of the 14 approved products, two marketing authorizations were subsequently voluntarily withdrawn by the company before the products were marketed. This leaves 12 biosimilars with a marketing authorization valid in every EU member state. Two things are worth noting here. All these products fall within only three categories of products – growth hormone (somatropin), EPO (epoetin alfa or zeta) and filgrastim (G-CSF). Secondly, no biosimilar was approved nor applied for between July 2010 and May 2013; then, in June, the two first, long awaited biosimilar monoclonal antibodies (both infliximab) obtained positive CHMP opinions[2]. Most recently, in July, yet another filgrastim obtained a positive opinion from the CHMP.

History repeating itself

The introduction of biosimilars has been met with the same scepticism as small molecule generics were met with many years ago. Could these cheaper alternatives really be as safe and effective as the originator? And could patients be switched to biosimilars without concern? Such mistrust gained further support with publications describing the lack of comparability between originators and a number of "non-innovator" biologicals – some of them incorrectly termed biosimilars – from outside the EU[3].

Furthermore, the lack of Phase III studies and publications of trials supporting the efficacy and safety of these products as seen when new originator drugs are introduced has been a concern for many physicians. There have been efforts to explain the concept of biosimilarity and the high level of regulatory requirements that such products face in order to obtain marketing authorization, and also to reinforce the correct use of the term "biosimilar"[4]. Despite these efforts, editorials, publications and learned societies have expressed concern about the use of biosimilars, either in general terms or when used in specific indications, eg filgrastim for mobilization of stem cells for bone marrow transplantation.

EU Consensus Information Document

In September 2010, the commission launched the Process on Corporate Responsibility in the Field of Pharmaceuticals – also known as the "Tajani initiative", named after EU commissioner Antonio Tajani.

This process had many aims, among them a so-called platform on "Market Access to Medicines in EU" bringing EU member states, the pharmaceutical industry and many other relevant stakeholders such as doctors and patients together in order to collaborate on finding non-regulatory approaches to ensure adequate and balanced access to medicines post-approval.

One subgroup under this platform dealt with market access for biosimilars in the EU. This subgroup was populated with representatives from the European Patients Forum, the Standing Committee of European Doctors (CPME), the European Social Insurance Platform, the Association Internationale de la Mutualité, the European Generic medicines Association (EGA), the European Federation of Pharmaceutical Industries and Associations, the European Association for Bio-industries (EuropaBio), the European Association of Full-line Wholesalers (GIRP) and the European Hospital and Healthcare Federation (HOPE) as well as the following EU member states: Austria, Belgium, the Czech Republic, Spain, France, Hungary, Ireland, Italy, Lithuania, the Netherlands, Norway and Sweden. I myself had the privilege of representing Denmark, acting as co-chair of this group together with representatives from the commission.

The ultimate goal of this group was to create a publication – finally agreed to be termed "A Consensus Information Document"[5] – giving a detailed and unbiased description of biosimilars, their manufacturing process and further development as well as the regulatory requirement for approval followed by a snapshot of the economic consequences and current market uptake. The document also includes three Q&A sections targeting "the three P's": patients, physicians and payers.

The diversity in the background and political views of members of the working group on access to biosimilars was a challenge. However, as co-chair, I must acknowledge that, despite fierce discussions on single topics from time to time, all members contributed to the process in a fruitful manner and all strived to reach a final consensus. This article is not intended to give all the key messages from the document, but I

think the following should be highlighted in this context. The document stresses that biosimilars are not classical generics due to the complex manufacturing process, but despite this they are expected to have the same efficacy and safety as the originator products – no more, no less.

This is, among other things, secured by the complex EU regulation and guidelines issued by the CHMP's working party on biosimilars medicinal products.

Moreover, the document stresses that the same standards for good manufacturing practice apply to the manufacturer of biosimilars as to those who manufacture originator products. Additionally, it states that biosimilars may offer a less-costly alternative to existing biological products, which may enhance competition and thereby improve patient access to treatment with biologicals.

Finally – and importantly – the document stresses that any decision to substitute or interchange biological products, including biosimilars, is outside the scope of the opinion expressed by the CHMP and is a matter for each national competent authority within the EU. All the scientific data evaluated by the CHMP is publicly available through the European public assessment report (EPAR) and can be used for such decisions, which can be made either at a national level or on a case-by-case basis by a treating physician.

Market access for biosimilars

As part of the above described project, a study on market access of biosimilars covering the period from Q2 2007 until Q2 2011 was commissioned. The full presentation as given to the working group can be found on the commission's website[6].

It is interesting to note that, despite the fact that only one member state (Germany) at that point in time had allowed substitution of biologicals on certain strict criteria, uptake of biosimilars was actually taking place. The market accessible to biosimilars was small, though. This is mainly because there are only a limited number of products which are all used for fairly narrow indications and which are required to be administered to patients for long periods.

Moreover, for some products follow-on biologicals have become available (eg long-acting G-CSF), making the accessible market even smaller. The biosimilars accessible market was judged to have an overall growth rate of only 1%, but the actual growth of biosimilars themselves within this market was judged to be as high as 55% during the period studied.

Short-acting EPOs had the largest market accessible to biosimilar competition both when measured in volume (defined daily doses=DDD) and sales (€) followed by growth hormone and filgrastim. The actual uptake of biosimilars, however, did not follow this distribution completely, with biosimilar filgrastim having 18% of the share of the accessible market in 2011 (measure in DDD) followed by EPO (12%) and growth hormone (7%). It is interesting to note that the size of the markets accessible to biosimilars varies considerably among EU member states even when corrected for numbers of inhabitants, with France and Italy having the largest accessible markets. But when it comes to the actual uptake of the three available groups of biosimilars in the period studied, countries such as Greece, Austria, Sweden and Germany had the highest consumption per capita.

It is therefore fair to conclude that even though the biosimilars market is in its infancy, Europeans are using these products. The market uptake is influenced by many factors and the size of the markets actually accessible to biosimilars competition is highly variable among EU member states. Differences across European national healthcare systems, structures and processes affect the uptake of biosimilars. These differences may include one or more of the following: physician or patient perception and acceptance of biosimilars, national pricing and reimbursement systems and other policies and national requirements.

Challenges ahead

Based on the European experience with three different classes of biological products, it is clear that biosimilars most likely will continue to be an alternative that is as safe and efficacious as off-patent biologicals. Although savings have not been as dramatic as those experienced following the introduction of small-molecule generics where price cuts as high as 70-90% of the originator price have been seen, biosimilars seem to fulfil a promise for increased competition.

Moreover, this competition is not just affecting healthcare costs; it may also act as an important driver for innovation. Manufacturers of highly complex biological products are no longer protected from "generic" competition when data protection expires. This stimulates the search for new therapeutic targets as well as improvements to already approved products, resulting in what sometimes are termed follow-on or second-generation biologicals (ie new products) and among them so called biobetters (ie second-generation biologicals claimed to be better than the originator product). These products may not save money, but could contribute to improved patient outcome to the benefit of patient and society.

Over the next few years, a number of frequently used monoclonal antibodies will face loss of data protection.

Infliximab is one example, with two products having already received a positive opinion from the CHMP. Other products under threat are rituximab, cetuximab, trastuzumab, etanercept, adalimumab and others. It will be interesting to see if and when biosimilar competition will occur for each of these products, and especially to follow the consequences for patient access to these therapies and the effects on innovation in the respective therapeutic areas[7].

However matters develop, there is still a need for acceptance and understanding of the biosimilar concept among physicians, patients and patient organizations. Myths and misconceptions must be addressed with reliable and trustworthy facts and, where knowledge is lacking, we must make every effort to generate it. There is a need to clarify the non-resolved issue of interchangeability and substitution between the reference originator biological product and its biosimilar brothers and sisters. This issue is still being debated, but the increasing numbers of reports on experiences gained will hopefully enable national competent authorities to make a firmer recommendation in the near future.

I have no doubts – biosimilars are here to stay.

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Steffen Thirstrup is a medical advisor and advisory board member at pharmaceutical consultants NDA Group. He is also a professor at the University of Copenhagen, Faculty of Health Sciences in Denmark. Professor Thirstrup was closely involved in the discussions on biosimilars during his time at the European Medicines Agency's key scientific committee, the CHMP, and as head of drug licensing at the Danish Health and Medicines Authority. Email: steffen.thirstrup@ndareg.com.