

# Interview with The European Generic Medicines Association

The European Generic Medicines Association (EGA) is the official representative body of the European generic and biosimilar pharmaceutical industry, which is at the forefront of providing high-quality affordable medicines to Europeans and stimulating competitiveness and innovation in the pharmaceutical sector.

*Pharmaceutical Technology Europe* spoke with Suzette Kox, Senior Director Scientific Affairs at the EGA to find out more about the environment for biosimilars.

## What is the EGA's involvement in improving access to and the quality of biosimilars?

In the context of biosimilar medicines, the EGA has been and continues to be a key stakeholder for the EU institutions, including the European Medicines Agency, as well as a key discussion partner for the World Health Organisation (WHO).

The EGA, together with its members involved in developing biosimilar medicines, has contributed very actively to the key milestones achieved to date:

- a robust legal and regulatory framework, guided by science
- clarification regarding the same International Non-proprietary Name (INN) as for the reference product
- WHO guidelines on the evaluation of similar biotherapeutic products, based on the same scientific principles as in the EU
- clear identification of all biopharmaceuticals by the approved name and the batch number for the purpose of suspected adverse reaction reports.

It is also important to point out that the term 'biosimilar' is derived from EU legislation, which refers to similar biological medicinal products.

Consequently, the term 'biosimilar' should only be applied to biopharmaceuticals that have been approved in accordance with the EU legal basis and data requirements, or following a rigorous and extensive comparability exercise at quality, non-clinical and clinical level with an ICH standard reference product, as required in the EU.

Non-originator 'copy' biopharmaceuticals worldwide are often labelled as 'biosimilars' despite the lack of thorough comparability at all levels with an ICH standard reference product. This has led to confusion, misinterpretation of the EU biosimilar concept and to unsubstantiated fears about safety. Given the high data requirements in the EU, these products would consequently not receive approval from the European Commission (EC).

The EU regulatory framework has already inspired — and is continuing to inspire — many countries and we will continue to promote these high quality and safety standards worldwide. The EU legal framework also offers the key advantage of separating patent litigation from the regulatory approval processes. By doing so, it allows timely access to competitively-priced biosimilar medicines.

## Do you believe pharmacovigilance legislation should be enforced to monitor safety?

Pharmacovigilance rules are necessary for the protection of public health to detect, assess and prevent adverse effects of all medicinal products placed on the EU market. New improved pharmacovigilance rules have now been signed off during the Spanish Presidency between the three EU institutions (the European Parliament, the Council and the EC) and are expected to be formally adopted during Autumn 2010. These rules shall apply 18 months after publication in the *Official Journal of the European Union*.<sup>1,2</sup>

There are no specific provisions regarding biosimilar medicines because such products are approved by the EC based on the same benefit/risk criteria as any other biopharmaceutical. It is important to highlight that immunogenicity is not a specific concern for biosimilar medicines because all biopharmaceuticals, in contrast to conventional pharmaceuticals, are polypeptides or proteins and demonstrate a greater capacity to elicit an immune reaction. Immunogenicity may be influenced by factors relating to the medicine itself, such as the manufacturing process and formulation, and also by factors related to the individual susceptibility of a patient, the disease and the treatment method, including the immune status of cancer patients, and the route of administration.<sup>3</sup> Because of these concerns, any biological medicinal product, approved after the enforcement of the new pharmacovigilance legislation will be subject to additional monitoring activities.

The European Medicines Agency, with the member states, will set up a list of products subject to additional monitoring. This list will include the names and active substances of future products that contain a new active substance as well as any future biological product, but other products may also be added to the list. There will also be an electronic link to the product information and the summary of the risk management plan (RMP). These products will have a black symbol in their product information and a standard sentence that invites the reporting of all adverse events. Any product specific additional monitoring activity will be listed in the RMP.

The new pharmacovigilance legislation also contains a provision which stipulates that "Member States shall make sure, through the methods of collecting information and where necessary through follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction; with due regard to the name of the medicinal product [as approved] and the batch number".

Once the new pharmacovigilance legislation is adopted, the EGA will work closely together with all stakeholders to achieve a harmonised approach regarding the appropriate measures for the identification of biological medicines, in the interest of the patients.

## Do you believe that concerns relating to the reproduction of biotechnology products are justified?

Yes, the immunogenicity concerns in relation to biopharmaceuticals are justified for the reasons outlined above; however, the concerns should not be overstated, used or misused to undermine biotechnology products in general, or biosimilar medicines in particular. For more than 20 years, patients in the EU have benefited from the availability of biopharmaceuticals, and these medicines have revolutionised the management of some of the most difficult to treat diseases and have helped to prolong and improve the lives of many patients.

The basic principle underlying the development of a biosimilar product is comparability with the reference product. This is not a new scientific concept that applies only to biosimilar medicines; comparability, as assessed through a process known as a "comparability exercise", is a critical concept that has evolved in order to perform comparisons between different versions of any new biological products under development. Data

provided by such comparisons must show that no significant differences in quality, safety and efficacy exist between the different versions of the product under development.

After a product has been approved by regulatory authorities, it is not unusual for further changes to be made during the manufacturing process. Such changes are introduced during the lifecycle of the product after the initial approval. When changes are made, the manufacturers of the product are required to demonstrate that the efficacy and safety are comparable to before the changes were implemented. As a general scientific principle, comparability does not necessarily mean that the products manufactured before and after the change are identical; instead, similarity needs to be demonstrated. This, together with the existing knowledge, needs to be sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon the safety or efficacy of the product.

The same scientific principle of comparability applies to the development of a biosimilar product, which must be similar to the reference product in terms of quality, safety and efficacy to be allowed on the EU market. The 'comparability exercise' required for the potential biosimilar and the reference product is regarded as a complicated and difficult task. However, highly sophisticated analytical and validation tools are available that enable detailed characterisation of these products and, whenever needed, scientifically sound, non-clinical and clinical programmes can be conducted to confirm comparative clinical safety and efficacy. Overall, regulators have long-standing and extensive experience with the assessment of comparability data and this should provide confidence in the EU regulatory system.

To counter remaining misinterpretations and misconceptions, more information and explanations regarding the 'comparability exercise' are needed from the regulators and from industry. It is a joint responsibility to make sure that these high quality biosimilar medicines reach patients, and that national governments seize this major opportunity to control their healthcare budgets and increase the availability of biopharmaceutical medicines.

### **How does the framework for biosimilars access in Europe compare with the rest of the world?**

In the interest of public health and better availability of high-quality medicines, there is a need to reach a global agreement on criteria and guidelines for biosimilars. As mentioned already, the EU regulatory framework is an excellent model for other parts of the world. The following countries have made progress in this area:

- Australia adopted the EU regulatory framework for biosimilar medicines in 2006.
- In March 2009, Japan issued a set of biosimilar guidelines similar to those in the EU giving clear instructions on the requirements for the development and registration of this group of biopharmaceuticals.
- In March 2010, biosimilar guidance was finalised and issued in Canada, with the country's first biosimilar medicine being approved in 2009, using the earlier draft guidelines.
- A legal framework for biosimilar medicines was finally adopted in the US on 23 March 2010 as part of the Patient Protection and Affordable Care Act.
- South Africa, Taiwan, Singapore and Malaysia are also following the EU scientific guidelines and more countries will do so.

Another important step towards a harmonised regulatory approach is the publication of the WHO's final guidelines on the evaluation of similar biotherapeutic products (SBPs) in April 2010.<sup>4</sup> The basic scientific principles underlying the WHO guidelines are the same as those in the EU. The intention of this document is to provide a globally acceptable set of principles for abbreviated licensing pathways for similar biotherapeutic products with assured quality, efficacy and safety. These guidelines will be available for adoption, either as a whole or partially, by national medicines regulators around the world, or can be used as a basis for establishing national regulatory frameworks. WHO in conjunction with the Korean Food and Drug Administration will run its first workshop on implementing the guidelines in Seoul, Republic of Korea on 24–26 August 2010.

A lot more needs to be done to achieve a harmonised approach, but we are clearly moving in the right direction. [PTE](#)

### **References**

1. 2008/0257 (COD) Proposal for a Regulation of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) N° 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (2008). [www.europarl.europa.eu](http://www.europarl.europa.eu)
2. 2008/0260 (COD) Proposal for a Directive of the European Parliament and of the Council amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. (2008). [www.europarl.europa.eu](http://www.europarl.europa.eu)
3. European Medicines Agency, Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins (CHMP/BMWP/14327/06, April 2008).
4. *Guidelines on evaluation of similar biotherapeutic products (SBPs)* (WHO, June 2010). [www.who.int](http://www.who.int)

### **Biosimilar medicines symposium**

The EGA will be holding its 8th annual international symposium on biosimilar medicines in London(UK) on 2–3 September 2010. For more information: [www.pharmtech.com/EGAsymposium](http://www.pharmtech.com/EGAsymposium)