Tighter EU rules on pharmacovigilance for biologicals

The new EU pharmacovigilance legislation which comes into force in July 2012 will include a tightening of requirements relating to product information and identification, as well as the regulations surrounding biosimilars and automatic substitution by pharmacists.

The new regulations will provide a legal framework for patients to report adverse events to their national medicines authority, and a legal obligation for the systematic tracking of medicines from manufacturer to patient. The legislation recognises that biosimilars, and other biological medicinal products, present distinctive safety challenges and aims to guarantee their traceability after they have been dispensed, through the provision of product information and identification. According to a briefing by Professor Burkhard Sträter, Bonn, Germany, the new requirements will have a significant impact on Member States, physicians, pharmacists and pharmaceutical companies [1].

Biosimilars are relatively large biological molecules whose manufacturing process is more complex than that for small molecule generics. As a result, biosimilars cannot be assumed to have an identical safety profile to the originator. So far, EMA has centrally approved 14 biosimilars for marketing in Europe. These include the first approved biosimilar Omnitrope (somatropin), for the treatment of growth hormone deficiency, and Tevagrastim (filgrastim) and other similar products for the treatment of cancer. Monoclonal antibodies are the next major class of biosimilars that will begin appearing on the market once their patents expire.

In many European countries pharmacists are permitted to do automatic substitution of small-molecule generic medicinal products. Automatic substitution is a practice whereby pharmacists can substitute the brand-name product specified by the prescribing physician with an alternative product. However, this is not the case for biosimilars. In January 2011, for example, the European biopharmaceuticals enterprises called for European and national prescribing/dispensing guidelines to advise physicians and pharmacists that automatic substitution should not apply to biological medicines including biosimilars [2].

Underscoring the importance of the new regulations is the case of a transient increase, between the years 1998 and 2003, in the number of patients developing the condition of pure red cell aplasia (PRCA) while receiving the Eprex brand of epoetin alfa (recombinant human erythropoietin) as a subcutaneous injection, following a formulation change [3]. One of the first biosimilars of epoetin alfa, HX 575 (marketed as Binocrit, EPO Hexal and Abseamed), authorised in 2007, has also been found in clinical trials to be associated with PRCA (in one case in Germany), and the production of neutralising antibodies against erythropoetin (in one case in Russia), following subcutaneous injection [4]. This is possibly due to subcutaneous route of delivery the drug appeared to have become more immunogenic, causing some patients to develop antibodies against both the drug and their own native erythropoietin, with a depletion of red cell precursors in their bone marrow [5, 6]. Reformulation and some other changes then helped to reduce the incidence of PRCA. Guidelines have subsequently recommended IV use only for biosimilar erythropoetin.

The new EU legislation will result in closer post-market surveillance of medicinal products. The new Regulation (EC) 1235/2010 tightens provisions for centrally authorised medicinal products, which include biosimilars [7]. Directive 2010/84/EU revises reporting and general requirements on adverse events for products authorised both nationally and centrally [8].

With regard to Regulation (EU) No. 1235/2010, Recital 17, in particular, deals with biosimilars. It recognises the risks associated with biosimilars and puts these products in the same class as new substances. This means that manufacturers must include a 'black symbol' (a black triangle in the UK) in the product information. Furthermore, Article 23 of Regulation (EU) No. 1235/2010 calls for the establishment and maintenance of a public list of medicinal products that are subject to additional monitoring. This covers biosimilars as 'any biological medicinal product' authorised after 1 January 2011.

Reporting adverse events

With regard to the reporting of adverse events, Directive 2010/84/EU now amends Article 102 of the medicinal products Directive 2001/83/EU, by requiring that Member States record the name and batch number of any dispensed medicinal product. This is to ensure 'that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of an adverse reaction report.'

In this way, it should be possible to determine which product a patient has taken before suffering an adverse event, and not only which active substance the medicine contained.

Physicians, pharmacists and other healthcare professionals will be subject to 'specific obligations' in order to comply with Article 102 of Directive 2010/84/EU. Doctors are required, therefore, to maintain accurate records of prescribing and dispensing, so that if a pharmacist does make a substitution, and the patient has an adverse event, it will be possible to trace the product responsible.

Article 102 of Directive 2010/84/EU has consequences too for pharmaceutical companies, who must now include warnings that their product information only applies to a specifically named biological medicinal product. The warning should include that 'changing to any other biological medicinal product should be authorised by the prescribing physician who should document the name of the product prescribed for pharmacovigilance reasons.'

On 20 February 2012, EMA published the drafts of the first seven modules of its guidelines on good pharmacovigilance practices, including Module 6 on 'management and reporting of adverse reactions to medicinal products' [9]. A further nine modules are expected. These are intended to support marketing authorisation holders, EMA and medicines regulatory authorities in EU Member States, in implementing the new pharmacovigilance legislation.

So far, the manufacturers of the approved biosimilars Retacrit (epoetin zeta), Nivestim (filgrastim) and Silapo (epoetin zeta) have added wording relating to biosimilars in their summary of product characteristics section 5.1.

In the meantime, pharmaceutical companies are working to improve patient safety. For example, generics company Hospira is applying bar codes to all injectable drugs and intravenous solutions, and incorporating bar code-reading technology into several infusion devices, in order to help ensure that patients receive the right dose of the right medicine. In 2010, Hospira was licensed to produce Retacrit (epoetin zeta) as the first biosimilar for both subcutaneous and intravenous delivery for the treatment of renal anaemia [10].

Editor's comment

GaBI Journal proposes that the call for all additional data should include also any data on original biologicals when any aspect of their manufacturing process is changed since this could also cause problems.

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READERS' COMMENTS

A patient-centred paradigm for the biosimilars market

This article provides important insights into the use and application of complex biologicals, particularly biosimilars, in health delivery systems. One aspect of care that has been traditionally ignored by providers as well as the private sector is the patient experience. Although much has been said about 'patient-centeredness', what this means generally is lip service to minor changes and form, rather than a substantive focus on what, how, and when patients receive 'treatment', not just a drug.

Importantly, patient safety principles have more recently indicated the essential nature of including the patient in systems of care to both improve communications and reduce harm associated with potential medical errors. For biosimilars, these principles have heightened importance, as biosimilar molecules and forms have not been cooperatively designed and hence may be associated with higher level of potential adverse reactions, particularly unwanted immunogenicity. Hence, developing a pathway of care that addresses the needs of patients–from the outset of care when these drugs are considered, through education on use, through feedback on (potentially adverse) reactions, through feedback on systems that allow for patient needs to be communicated to the delivery structure–must be the new normal. Biosimilars have tremendous potential to improve quality and quality of life as well as access to cutting edge therapeutics, but their increased risks associated with immunogenicity heighten the need to focus on the pathways of care relevant to the patient, rather than simply creating a drug, or dispensing a drug, or injecting a drug.

Hopefully, this work is disseminated widely to the public sector, the private sector, and providers as well as patients so that a coordinated 'system' of care employing these molecules becomes standard. Patients must be empowered to be part of the system, not merely a 'market', or a 'constituency', or a passive participant in treatment. Only in this way can the maximum benefits from these molecular entities be inured to all patients, wherever they are, whichever culture they are in, and however they receive their therapies. As the world becomes a smaller place, these global health concerns will only grow, and the need to focus on true partnerships between all stakeholders engaged in delivery will be needed to address the needs of patients now and for generations to come.

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South Korean guidelines for biosimilars

It is crucial for the drug price control authority to take more responsibility to protect interests of patients. At least to fix prices in case of an adverse situation where a pharma and generics collaborate to create a monopoly.

http://gabi-journal.net/news/south-korean-guidelines-for-biosimilars

Indian Government issues first compulsory licence

The practices of the two biggest Delhi patent law firms are absolutely no indicator of the right position on the law.

Section 79 of the Patents Act, 1970, lays down only the procedural requirements, not the substantive law requirements which will still be guided by the Evidence Act, 1872. One can use a particular patent document as evidence through an affidavit but then the admissibility or that particular patent document can be objected to by both the opposite side and the patent office on the grounds that it has not been authenticated as per Section 65B of the Evidence Act.

http://gabi-journal.net/news/indian-government-issues-first-compulsory-licence