

28 March 2007

EBE-EFPIA POSITION PAPER

LABELLING OF BIOSIMILAR MEDICINAL PRODUCTS

1. Introduction

The introduction of similar biological medicinal products (biosimilars) into clinical practice presents new challenges that are not ordinarily presented by small-molecule generic medicines. This is because a biosimilar can only be proven to be similar and not identical to its reference product. This fundamental difference has been acknowledged throughout the development of the pharmaceutical legislation for biosimilars, which takes the approach that biosimilars are not generics and must therefore be treated differently.

The summary of product characteristics (SmPC) and package leaflet, collectively “the labelling” are important documents for all medicinal products. The SmPC sets out the agreed regulatory position on the medicinal product as determined during the course of the regulatory assessment process and forms the basis of information for healthcare professionals and patients on how to use the medicinal product safely and effectively ¹.

With regard to fulfilling these criteria for biosimilar medicinal products (biosimilars), EBE and EFPIA believe that there are two principles that should be observed in the labelling:

1. As for any medicinal product the labelling should provide transparent information to healthcare professionals and patients on issues that are relevant to the safe and effective use of the medicinal product
2. In addition, the labelling for biosimilar medicinal products should provide clear guidance to healthcare professionals and patients on the interchangeability/substitution of the biosimilar with its reference product or other medicinal products of the same class

The purpose of medicinal product labelling is to ensure the clear unambiguous identification of the medicine and to define the conditions for its safe and effective use. As biosimilars are a new category of medicinal product, EBE and EFPIA believe that the European Medicines Agency (EMA) should define standards for the labelling of biosimilars in order that healthcare

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professionals and patients are able to identify them as such, and that they are provided with appropriate and transparent information to ensure the safe and effective use of this new category of medicinal product.

This document further describes this position and provides supportive background.

Finally, this paper should be read in conjunction with the EBE-EFPIA paper on Inapplicability of Automatic Substitution Rules to Biotechnology Products (dated 31 July 2006), as the issue of substitution and labelling of biotechnology medicines are closely linked.

2. Importance of Labelling in Clinical Practice

The labelling of medicinal products is the basis for providing healthcare professionals and patients with information on how to use a medicinal product safely and effectively. Biosimilars are a new category of medicinal product that are similar, but not identical to their reference product. It is important to note that the EMEA has stated in their guideline on biosimilars ²:

“It should be recognised that, by definition, similar biological medicinal products are not generic medicinal products, since it could be expected that there may be subtle differences between similar biological medicinal products from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use has been established.”

Therefore, adopting the standard approach for labelling of generic small-molecule drugs (ie. labelling that is, to all intents and purposes, identical to that of the reference product) is not appropriate for biosimilars as there may be clinically important information that needs to be communicated to healthcare professionals and patients. Clearly the exact nature of this information will need to be defined on a case-by-case basis for each product; however, EBE and EFPIA believe that a standard and consistently applied set of criteria for the labelling of biosimilars should be developed by the EMEA.

2.1 Transparent and Accurate Information to Healthcare Professionals and Patients

Consistent with Notice to Applicants “Guideline on Summary of Product Characteristics” (October 2005) and in the interests of providing transparent information to healthcare professionals and patients, EBE and EFPIA recommend that the SmPC should contain the following information in sections 4.8 (Undesirable effects) and section 5. (Pharmacological properties):

Section 4.8 (Undesirable effects)

Notice to Applicants states “This section should provide comprehensive information based on all adverse reactions (ADRs) from clinical trials, post-marketing studies or spontaneous reports

attributed to the medicinal product .”. EBE / EFPIA’s interpretation of this requirement would be to ensure that section 4.8 of the SmPC for a biosimilar contains the following information:

- Safety data observed for the biosimilar “based on all ADRs from clinical trials, post-marketing studies or spontaneous reports attributed to the medicinal product”
- A summary table (or equivalent) describing the safety profile of the biosimilar and comparing it, qualitatively and quantitatively with that of the reference product

Section 5. (Pharmacological properties)

Notice to Applicants states “Sections 5.1 – 5.3 should normally mention information, which is relevant to the prescriber *and to other health-care professionals*, taking into account the approved therapeutic indication(s) and the potential adverse drug reactions. Statements should be brief and precise.” EBE/EFPIA ’s interpretation of this requirement would be to ensure that section 5 of the SmPC for a biosimilar contains the following information:

- For most categories of biotechnology medicinal products, there will be multiple innovator products which could serve as a reference product (eg. erythropoietin, G-CSF, somatropin, insulin). The labelling should contain a clear indication that the medicine is a biosimilar and the exact identity of the reference product ie. the invented name, common or scientific name and the manufacturers name eg.

“*{Product X}* is a biosimilar medicinal product. The marketing authorisation for *{Product X}* has been approved following demonstration of similarity to its reference product *{Product Y}*”.
- Unique clinical data for the biosimilar “Such information on clinical trials should be concise, clear, relevant and balanced and summarise evidence from relevant studies supporting the indication” ¹.
- An overview describing the clinical similarity (ie. safety and efficacy) to the reference product and in which indication(s)
- In case the reference product has more than one indication, a statement defining in which indications safety and efficacy have been demonstrated independently in controlled clinical studies using the biosimilar medicinal product and for which indications such clinical studies have not been conducted ie. extrapolated without independent demonstration of safety and efficacy

In all circumstances and consistent with SmPCs for innovative medicinal products, these sections should be updated as relevant data becomes available from on-going clinical studies, post-marketing commitments and spontaneous reports.

Such information described above will allow healthcare professionals and patients to make informed decisions, without prejudice, about their choice of medicinal product.

2.2 Guidance to Healthcare Professionals and Patients on Interchangeability/Substitution

Clearly, an approved biosimilar may be considered by prescribing physicians, without prejudice, as a therapeutic option alongside the reference product. However, we firmly believe that a pharmacist should not be able to change (substitute) a biotechnology medicinal product without the physician's knowledge and explicit prior consent. This topic was discussed in detail in the EBE-EFPIA position paper adopted in July 2006.

EBE and EFPIA understand that the EMEA will not guarantee that biosimilars are interchangeable with their reference products³ as a scientific assessment required to make such a decision will not be undertaken during the review by the EMEA. Accordingly, EBE believes that, when scientific data establishing interchangeability do not exist, it is important that healthcare professionals and patients are aware that biological medicinal products with similar molecular composition may not be interchangeable.

EBE and EFPIA believe that it would be appropriate for the EMEA to provide guidance on this topic and make it clear at the Member State level, to healthcare professionals and to patients that it should not be assumed that at approval, biosimilars are interchangeable with their reference product.

EBE and EFPIA recommend that the EMEA achieve this in the labelling for a biosimilar, the reference product and products of the same class (eg. epoetin, somatropin). The labelling should contain advice to healthcare professionals and patients on substitution. Consistent with the position discussed above, such advice is intended to ensure that the treating physician is involved in the management of patients and any decision to change a biotechnology medicine. For example, section 4.4 (Special warnings and precautions for use) of the SmPC could contain the following advice:

“Changes from {Product X} to other {common name} preparations should be done under strict medical supervision.”

EBE and EFPIA believe that providing such advice in the SmPC would be consistent with the requirements for section 4.4 of the SmPC as defined in Notice to Applicants “Guideline on Summary of Product Characteristics” (October 2005) ie. providing information on “The conditions under which use of the medicinal product could be acceptable, provided that special conditions for use are fulfilled” and is similar to advice already provided in other cases, for example, modified release theophylline or calcium-channel blockers and insulin.

Similarly, corresponding advice could be included in the package leaflet.

3. Labelling of Approved Biosimilar Medicinal Products

Two biosimilar medicinal products are approved in the European Union (Omnitrope[®] and Valtropin[®]) and it is instructive to review their labelling in the context of the recommendations being made by EBE. The labelling for Omnitrope[®] is effectively indistinguishable to that of its reference product (Genotropin[®]). It is therefore not clear that Omnitrope[®] is a biosimilar or which data quoted in the labelling were generated with Omnitrope[®] or with Genotropin[®].

Conversely, the labelling for Valtropin[®] goes some way to providing the transparent information to healthcare professionals and patients discussed in this position paper. For example, sections 4.8 and 5 of the SmPC reference the unique safety and efficacy data for Valtropin[®] from clinical studies. However, the exact name of the reference product, which could be one of five or more approved somatotropins, and advice on interchangeability/substitution are not included.

EBE and EFPIA believe that a consistent approach to the labelling of future biosimilars is essential.

4. Summary and Recommendations

Biosimilars are a new category of medicinal product. In order to enable their safe and effective use, it is important that healthcare professionals and patients are provided with clear and unambiguous information about the biosimilar medicinal product.

EBE and EFPIA recommend that the EMEA adopt a consistent approach to the labelling of biosimilar medicinal products that provides transparent information to healthcare professionals and patients on issues that are relevant to the safe and effective use of the medicinal product; and clear guidance on interchangeability/substitution of the biosimilar with its reference product or other medicinal products of the same class.

Such a consistent approach would help ensure that this new category of medicinal product is safely and effectively introduced into clinical practice and prevent risks to public health due to medication errors associated to problems with medicinal product labelling.

References

1. European Commission; Notice to Applicants; Guideline on Summary of Product Characteristics (October 2005).
2. Committee for Medicinal Products for Human Use (CHMP) Guideline on Similar Biological Medicinal Products (CHMP/437/04)
3. APM Health Europe (Nick Smith) interview with Thomas Lönngren. Posted Friday, 21 July 2006 04:00 GMT at: <http://www.apmhealthurope.com/story.php?depsPage=3&numero=3250>

PAPEL DE LA POSICIÓN DE EBE-EFPIA

ETIQUETADO DE LOS PRODUCTOS MEDICINALES DE BIOSIMILAR

5. 1. Introducción

La introducción de los productos medicinales biológicos similares (biosimilars) en práctica clínica presenta los nuevos desafíos que no son presentados ordinariamente por las medicinas genéricas de la pequeño-molécula. Esto es porque una poder biosimilar solamente se demuestre ser similar y no idéntica a su producto de la referencia. Esta diferencia fundamental se ha reconocido a través del desarrollo de la legislación farmacéutica para los biosimilars, que toma el acercamiento que los biosimilars no son generics y se deben por lo tanto tratar diferentemente.

El resumen del prospecto de las características (SmPC) y del paquete del producto, “ el etiquetado” es colectivamente documentos importantes para todos los productos medicinales. El SmPC precisó la posición reguladora convenida respecto al producto medicinal según lo determinado durante el curso del proceso regulador del gravamen y forma la base de la información para los profesionales y los pacientes del healthcare en cómo utilizar el producto medicinal con seguridad y con eficacia ¹.

Con respeto a satisfacer estos criterios para los productos medicinales biosimilar (biosimilars), EBE y EFPIA creen que hay dos principios que se deben observar en el etiquetado:

1. En cuanto a cualquier producto medicinal el etiquetado debe proporcionar la información transparente a los profesionales y a los pacientes del healthcare en las ediciones que son relevantes al uso seguro y eficaz del producto medicinal
2. Además, el etiquetado para los productos medicinales biosimilar debe proporcionar la dirección clara a los profesionales y a los pacientes del healthcare en la capacidad de intercambio/la sustitución del biosimilar de su producto de la referencia u otros productos medicinales de la misma clase

El propósito del etiquetado del producto medicinal es asegurar la identificación inequívoca clara de la medicina y definir las condiciones para su uso seguro y eficaz. Pues los biosimilars son una nueva categoría del producto medicinal, EBE y EFPIA creen que la agencia europea de las medicinas (EMA) debe definir los estándares para el etiquetado de biosimilars para que los profesionales y los pacientes del healthcare puedan identificarlos como tal, y que les proporcionan la información apropiada y transparente para asegurar el uso seguro y eficaz de esta nueva categoría del producto medicinal.

Este documento más futuro describe esta posición y proporciona el fondo de apoyo.

Finalmente, este papel se debe leer conjuntamente con el papel de EBE-EFPIA en la no aplicabilidad de las reglas automáticas de la sustitución a los productos de la biotecnología (con

fecha del 31 de julio de 2006), como la aplicación la sustitución y el etiquetado de las medicinas de la biotecnología se liga de cerca.

6. 2. Importancia del etiquetado en práctica clínica

El etiquetado de productos medicinales es la base para proveer de profesionales y de pacientes del healthcare la información en cómo utilizar un producto medicinal con seguridad y con eficacia. Biosimilars es una nueva categoría del producto medicinal que es similar, pero no idéntico a su producto de la referencia. Es importante observar que el EMEA ha indicado en su pauta en biosimilars ²:

“ Debe ser reconocido que, por la definición, los productos medicinales biológicos similares no son productos medicinales genéricos, puesto que podría esperar que puede haber diferencias sutiles entre los productos medicinales biológicos similares de diversos fabricantes o comparados con los productos de la referencia, que pueden no ser completamente evidentes hasta que la mayor experiencia en su uso se ha establecido.”

Por lo tanto, adoptando el acercamiento estándar para etiquetar de las drogas genéricas de la pequeño-molécula (IE. etiquetando es decir, para fines prácticos, idéntico a el del producto de la referencia) es no apropiado para los biosimilars como puede haber clínico la información importante que necesita ser comunicada a los profesionales y a los pacientes del healthcare. La naturaleza exacta de esta información necesitará claramente ser definida sobre una base del caso-por-caso para cada producto; sin embargo, EBE y EFPIA creen que un estándar y un sistema constantemente aplicado de los criterios para el etiquetado de biosimilars se deben desarrollar por el EMEA.

6.1 2.1 Información transparente y exacta a los profesionales y a los pacientes de Healthcare

Constante con el aviso a los aspirantes “pauta en el resumen de las características del producto” (octubre de 2005) y en interés de proporcionar la información transparente a los profesionales y los pacientes del healthcare, EBE y EFPIA recomiende que el SmPC debe contener la información siguiente en las secciones 4.8 (efectos indeseables) y la sección 5. (Características farmacológicas):

Sección 4.8 (efectos indeseables)