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EBE Position paper on labelling of biosimilars –Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL)- draft April 2013

Introduction

This document seeks to lay out EBE's thinking on considerations for labelling for biosimilars[1] in the EU. Specifically we would like to consider what guiding principles should apply to developing the SmPC and Patient Information Leaflet (PIL) for biosimilars taking into account the QRD (Quality Review of Documents) guidance[2] and also the labelling approaches outlined in the publication "Setting the stage for biosimilar monoclonal antibodies", C.K. Schneider et al.[3]

At present there is no labelling guidance specific to biosimilars in the EU even though a number of biosimilar products hold valid MAs with the first approval being issued in 2006 for Omnitrope.
The current QRD guidance does not distinguish between biosimilars, generics and hybrid products in terms of labelling. This guidance states:

- *"Following the same general principles, the SmPC content for a hybrid or biosimilar medicinal product has to be consistent with the reference medicinal product for the common information applicable to the hybrid or biosimilar product. In other words, the information from the reference medicinal product's SmPC that applies to the hybrid or biosimilar should be included in the SmPC of the hybrid or biosimilar.*
- *The applicant should discuss and justify any differences of the proposed SmPC vis-à-vis the SmPC of the reference medicinal product".*

We consider that the current grouping of labelling guidance for biosimilars alongside generics and hybrid products is inappropriate as this does not take into account some of the unique considerations which apply for biosimilars. There are three main reasons why it would be beneficial to consider development of specific guidance for biosimilars:

1. **Biosimilars are distinguished from generic products and other types of products in terms of the legal framework (article 10.4 2001/83).**
The reasons for this are based on sound regulatory science considerations and lead to some unique

[1] It is necessary to be clear that these principles apply only to products developed under the biosimilars legal and scientific framework under 2001/83 Article 10.4.
[2] QRD General Principles regarding the SmPC Information for generic/hybrid/biosimilar products, EMA 6267621/2011, 3 May 2012
[3] Schneider C et al. (2012), Setting the stage for biosimilar monoclonal antibodies. Nature Biotechnology volume 30(12), December 12. Although the options outlined in this paper are made within the context of monoclonal antibodies, we consider that the scope should also apply to all types of biosimilars and therefore we have considered them in this light

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distinctions from generic products which need to be accommodated in the approach to labelling.
For chemically derived products which are regulated as generics and are therefore deemed to be identical to their reference product it is standard practice to include the data/labelling statements generated on the originator reference product in the generic label as per the existing QRD guidance. Such products do not generate large scale clinical efficacy data and their licensure rests primarily on analytical and human pharmacokinetic similarity. Thus the issue never arises as to how to handle clinical data generated on a generic product in the label nor does the issue arise as to which indications may be extrapolated since all indications are automatically granted since the generic product is identical to its reference product.

In contrast to small molecule chemically derived generic products, a biosimilar product is similar but not identical to its reference product and biosimilars are regulated differently from generics in the European Union. This is because biological manufacturing processes are inherently variable and therefore biosimilar development aims to match the variability of the reference product. The occurrence of differences from the reference product is inevitable due to the biological production system itself but so long as these differences can be categorised as "microheterogeneity" and can be demonstrated as not being clinically meaningful, this does not preclude a product being approved as a biosimilar. For instance, in recognition of these considerations , in addition to the distinct legal basis for approval, the new EU pharmacovigilance frameworks groups biosimilars alongside novel biologics in needing to be clearly identified for the purpose of adverse event reporting and subjects them to enhanced safety monitoring. Such stipulations clearly do not apply to generic products.

A tailored clinical development program is conducted for biosimilar products and the program will be different from biosimilar to biosimilar (in contrast to generics). Therefore it is important to mention which studies were conducted and to specify which indications on the label were approved based on extrapolation of data and which indications were supported by clinical studies. Global development of biosimilars will tend to have the net effect of increasing the amount of clinical data generated and thus products developed for the EU market alone may have less clinical data generated than those intended for the US and EU for example. Thus the amount of clinical data generated reflects the geographic scope of the development plan not necessarily the quality of the biosimilar product. The most important consideration should be to ensure that the SmPC contains the information most relevant to the prescriber.

2. There is a need for a consistent approach to the labelling of biosimilars to facilitate physician and patient's understanding and acceptance of these products.

The over-riding intention in the current QRD guidance is that the labelling for a biosimilar should be identical to that of the reference product unless otherwise justified. Whilst this position is the accepted norm for generics and hybrids we contend that this is inadequate for biosimilars as explained above. Consequently, biosimilars have more uniquely generated preclinical and clinical information than generics or hybrids. Under the current QRD guidance this information then has to undergo a case by case assessment on how this should appear in the label. This will inevitably continue to lead to an inconsistent approach between biosimilar product labels.

The biosimilar concept which was pioneered in the EU is one of the most novel regulatory concepts to have emerged in recent years. As the concept is novel it has proved challenging for physicians and patients to understand. This has been compounded by the fact that there are products which have been developed outside the EU and which are referred to as "biosimilars" in publications when in fact these products have not been developed in accordance with the standards applicable in the EU. With all this in mind, it is of paramount importance that biosimilars are labelled in a consistent manner as

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this will help these products to be properly accepted and understood.

3. There is a need to address the disconnect between preclinical and clinical data that have been generated on the biosimilar and the data that are reflected in the label.
In the EU also it is expected that the SmPC fully reflects the data generated to support the Marketing Authorisation and that no data are excluded from the label. The SmPC structure has sections for both preclinical and clinical data. It would therefore be wholly inappropriate to selectively only include the information generated either on the reference product alone or the biosimilar alone or vice versa.

Description of An Appropriate Labelling Standard

Having established the need for specific labelling guidance for biosimilars and why the case-by-case approach in the existing QRD guidance is inadequate to achieve a consistent approach, we now need to consider what type of approach could be applied and what considerations are important.

The publication by C.K Schneider et al [4] considers general regulatory issues under consideration for the licensure of biosimilar monoclonal antibodies. It also mentions the label as a key source of information on the biosimilar and points out that this is the only document which is regularly updated. This paper also outlines the pros and cons for 3 possible approaches to be considered for labelling of biosimilars as outlined below.

Table 3 Pros and cons regarding the product label of a biosimilar mAb

Option	Pros	Cons
Product label is an identical copy of the reference mAb label	Consistent with the generic approach (chemical generics usually have identical product labels).	Prone to misunderstanding regarding information specifically generated with the reference mAb, particularly results from pivotal clinical studies; the reader would assume that the studies were made with the biosimilar. Results obtained from the biosimilarity exercise are not included.
Product label only gives information obtained with the biosimilar mAb	Transparent regarding which studies were performed with the biosimilar Could allow inclusion of more specific messages, such as the need to monitor switching of products in a class (likely to be part of the label of all products of that class, including the originator).	Prone to misperception by prescribers who could falsely conclude that the level of evidence created is not according to 'usually expected' standards for a novel mAb if the concept of biosimilars is not understood (or not explained in the label). Misses important information generated from the long-term use of the reference mAb, such as safety information. Not consistent with the generic approach; implicitly suggests a difference between the biosimilar and the reference mAb, although such differences were excluded when licensing the biosimilar.
Product label is a combination of information (for example, studies performed with the biosimilar mAb) and relevant safety and/or efficacy data from the reference mAb	Could be seen as a balanced approach. Gives relevant information to prescriber. Could allow inclusion of more specific messages, such as the need to monitor switching of products in a class (likely to be part of the label of all products of that class, including the originator).	Not consistent with the generic approach; implicitly suggests a difference between the biosimilar and the reference mAb, although such differences were excluded when licensing the biosimilar. Prone to misperception by prescribers who could falsely conclude that the level of evidence created is not according to usually expected standards for a novel mAb if the concept of biosimilars is not understood (or not explained in the label).

We have considered these three approaches. These have been designated A, B and C respectively for convenience and ease of reference:

A. Label to be an identical copy of the Reference Product
B. Label to only include information on the biosimilar MAb
C. Label to be a combination of information on both the biosimilar MAb and the Reference Product.
We consider that approaches A and B are inappropriate for the following reasons:

Approach A
This approach is consistent with the "generic approach" to labelling but we would contend that it is

[4] Schneider CK, Vleminckx C, Gravanis I, Ehmann F, Trouvin JH, Weise M, Thirstrup S. Setting the stage for biosimilar monoclonal antibodies. Nat Biotechnol. 2012 Dec;30(12):1179-85.

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clearly inappropriate for the labelling of biosimilars to follow this approach as biosimilars are not regulated as generics. Most importantly, unlike generics, biosimilars may not necessarily have the same range of indications as the reference product .Therefore in the interests of ensuring the correct use of the product in accordance with the Marketing Authorisation their labelling must make it clear to patients and prescribers which indications are approved and which are not. Furthermore, if only the information generated on the reference product were to be included this would result in exclusion of specific data generated on the biosimilar, particularly on preclinical and clinical aspects for which there are existing specific sections in the SmPC. It is a generally accepted principle that all clinical and preclinical data submitted within a MA and of relevance to the prescriber should be reflected in the label. It is inappropriate to exclude such data when there are specific sections in the SmPC on preclinical and clinical data. Comparative clinical data in particular between the reference product and the biosimilar are highly relevant to the prescriber as this will include comparative immunogenicity which can only be assessed by clinical means. Any nonclinical data generated should also be reflected in the appropriate section of the label.

Approach B

This approach is inappropriate as only including data on the biosimilar does not take into account that proof of biosimilarity means that the long term safety profile for the reference product should be applied to the biosimilar including any class warnings etc. Further, some information on the safety and/or efficacy expected for the biosimilar product in various settings (based on data on the Reference Product) is necessary to provide perspective to prescribers. From a user point of view it would not be practical for the physician to revert to the originator label to be able to see these data. As mentioned in table 3 prescribers may have the misconception that the authorisation of biosimilars is based on a lower level of evidence.

Approach C

Approach C represents the best way forward as this allows full and transparent disclosure of all the clinical and nonclinical data generated on the biosimilar and the reference product while maintaining useful information found in the Reference Product's labelling. We further suggest that the data should be clearly identified to indicate whether it was generated on the reference product alone by the originator or by the biosimilar developer. The label should clearly indicate which indications are approved (as for any product) and further which indications are granted by extrapolation or not granted at all (unique to biosimilars).

Improve appropriate safety reporting through labelling

We also suggest that this approach be developed to take into account the fact that enhanced safety reporting requires biological products (including biosimilars) to be clearly identified.

All biological products (including biosimilars) are subject to additional monitoring according to the revised pharmacovigilance legislation, (Directive 2010/84/EU, Art 102e). In addition, the cross-border prescription template requires that prescription of biologics always contain the brand name.[5] This means in our view that there is a clear need for identification of the product via the name, always including the invented/brand name, and batch number so that ADRs may be correctly assigned. A clear statement must be made in the labelling to this effect. This is especially relevant when similar, but not identical, biological products bear the same INNs.

[5] Official Journal (22/12/2012), L356/68, Commission implementing Directive 2012/52/EU of 20 December 2012 laying down measures to facilitate the recognition of medical prescriptions issued in another Member State

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The practice consisting of using the INN and the Company name as a proxy for the invented/brand name, instead of using a new and distinct invented/brand name as a unique identifier, is far from ideal from a pharmacovigilance point of view and should normally only be treated as a temporary solution. Indeed, since the company name is only hyphenated to the INN, there is a risk that it will be omitted from patient records and just the INN alone used, with consequential potential confusion as to which product was administered. Again, this risk of confusion increases when the biosimilar and the reference product share the same INN. EBE welcomes the initiative by the WHO to consider applying a prefix/suffix system to biosimilar INNs to allow unique identification of these products. However, the fact that the INN system is largely optional means that this measure alone is likely to be insufficient.

Thus, consideration should be given -to adding into the section 4.4 of the SmPC - Special warnings and precautions for use, for all patients the following requirement:

- "*In order to improve the traceability of [*[biologic or biosimilar Y or Z]*, the batch number, invented/brand trade name of the administered product should be clearly recorded in the patient file*."

The question also arises as to how to handle comparative quality data in particular as there is no place in the current SmPC structure for inclusion of such data. The best way to handle this in our view would be to include some brief standard text explaining the step-wise approach to assessment of biosimilarity and the pivotal importance of such data. It seems inappropriate and impractical to include such data in the SmPC as this would not be widely understood and would make the biosimilar label extremely long. Furthermore, information on a biosimilar product should fit within the existing framework of headings for SmPCs as diverging from this format would incorrectly imply that such products are more different to other types of products than they actually are thus potentially exacerbating pre-existing misconceptions.

Conclusion

We recommend that the label should be a combination of information on both the biosimilar and the reference product (Approach C). We also recommend that specific guidance for the labelling of biosimilars is developed on this basis taking into account the above suggestions and that the QRD template and guidance are similarly amended. In addition, prescribing requirements should be included in order to improve traceability and enhance pharmacovigilance. Details should be further developed in consultation with the relevant stakeholders. We recommend against following approach A, namely the "generic approach", for the labelling of biosimilars, which are not generics. We believe that the generation of specific guidance on the labelling of Biosimilars is of crucial importance in developing the understanding and acceptance of these products with all stakeholders.

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