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# Terminology for biosimilars— a confusing minefield

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Biosimilars are firmly established in the EU as copy biologicals with a clear and effective regulatory route for approval. Unfortunately, inconsistency in nomenclature for biosimilars has caused confusion. This problem of terminology has been the subject of a recent publication. The confusion is not just a potential concern for patient safety and efficacy, but also can lead to misconceptions in published reports. Several examples of this have occurred, some of which are discussed below. The definitions provided should be adopted for clarity in the future.

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**B**iosimilars are now firmly established in the EU as copy biologicals with a clear and effective regulatory route for approval, which allows marketing of safe and efficacious biological products.

The comparability studies required for comparing the innovator (reference) product and the potential biosimilar product are crucial for the regulatory process and guarantee the quality and clinical performance of the biosimilar. Clear guidelines have been produced by the Committee for Medicinal Products for Human Use and its working parties, describing the desired criteria including quality, non-clinical and clinical studies needed for biosimilars and requirements for their regulatory approval in the EU [1-5, 20]. The comparability of quality aspects required is significant and some data from such studies have been partially published [6, 7]. To date, 14 marketing authorisations have been approved for biosimilars in the EU and many more are in the pipeline.

Outside the EU, several countries have adopted an identical or similar regulatory

approach to the EU for approval of biosimilars, e.g. Australia, Canada, Japan. In addition, the World Health Organization (WHO), with the aim of achieving harmony in regulations and increasing access to safe medicines globally has produced a guideline [8] for evaluation of 'similar biotherapeutic products' (effectively biosimilars) which proposes a very similar approach to that described in the EU guidelines [1-3].

Unfortunately, inconsistency in nomenclature used for biosimilars has led to confusion in referring to some products. Thus the terms 'follow-on biologic', 'subsequent entry biologic', 'similar biotherapeutic product', 'similar biological medicinal product', 'biogeneric', 'me-too biologic', 'non-innovator biologic' have all been used to describe biosimilars. An even greater problem is that all of these terms have in some cases been used to refer to products which are not biosimilars according to the EU/WHO definitions and have not been evaluated using the comparability approach which is essential if the guidelines are followed. This problem of terminology and its implications has been the subject of a recent publication by Weise et al. [9], and this

paper also recommends the use of more precise terminology for biosimilars (and non-biosimilars) to attempt to clarify the confusing situation.

The confusion over terminology is not just a potential concern for patient safety and efficacy, but also can lead to misconceptions which arise from misleading published reports on apparent problems with 'biosimilars'. Several examples of this have already occurred, some of which are discussed below.

A case of pure red cell aplasia (PRCA) in an end-stage renal disease patient associated with induction of antibodies to administered erythropoietin (EPO) was described in India [10]. The patient had received the EPO product Wepox (Wockhardt Limited, India) which is referred to as a 'follow-on' product. In the paper the authors state that 'in Europe, follow-on EPOs are also referred to as biosimilar EPOs'. However, there is no evidence that this product has been approved using the comparability approach required in the EU for biosimilarity and described in the WHO and other guidelines. This is in fact unlikely as the Indian regulatory process at that time did not include biosimilars (or follow-on products) and approved non-innovator products based on a stand-alone system [11]. Thus the product Wepox which is not a biosimilar and should not be described as such as this clearly misleads the reader by using incorrect terminology.

In some cases, the type of product referred to in studies is unclear. An example of this is a report [12], describing two cases of antibody mediated PRCA in South Korea which developed following treatment with a locally produced EPO (Epokine, CJ Corp, Korea) or a mixture of three such products and an innovator product. The procedure adopted for approval of the locally produced EPOs is not reported, but is unlikely to be via the biosimilar route as the Korean biosimilar guideline was produced only recently. The Korean regulatory process however includes both comparative (biosimilar) and non-comparative procedures, and use of correct terminology in publications would avoid ambiguity and misunderstanding.

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Another serious example of misuse of terminology in a publication appeared with the alarming title 'Biosimilar recombinant human erythropoietin induces the production of neutralizing antibodies' [13]. This paper describes loss of response to EPO in a number of patients being treated with what are called biosimilar EPOs in Thailand. These products were produced in Argentina, China, India and South Korea, and 14 different such products were approved for use in Thailand. Laboratory evaluation showed 23 of these patients to be EPO antibody positive, all of whom progressed to PRCA. However, none of these products were really biosimilars as all were approved using the process employed for chemical generics, i.e. no comparison with originator product was conducted. The editor of the journal in which this report appeared seems to have noted a potential problem with terminology for biosimilars as an editor's note appears in the paper providing an explanation of the term. Unfortunately, this simply states that the term 'biosimilar' is applied to subsequent versions of products that have been approved in a given country, and not that the approval process should involve a comparative assessment of the 'biosimilar' with the innovator product. This report is particularly misleading as the implication is that biosimilar EPOs are more likely to cause antibody induction and PRCA than innovator products which is not shown in the study as none of the products used were biosimilars in the sense of correct terminology.

It is particularly important that correct terminology for biosimilars is used in reviews highlighting their potential importance. However this is often not done. For example, in a recent review of the current development of 'biosimilars' in India [14], a number of products produced and sometimes approved in India, including filgrastim, epoetins, interferons and a monoclonal antibody are listed as biosimilars even though the limitations described for the above mentioned Indian Wepox/PRCA case also apply to these products. Again, this is a clear misuse of terminology.

Granulocyte colony-stimulating factor (G-CSF) has been widely used clinically and several biosimilar G-CSF products have been approved for marketing. There has been considerable discussion of the pros and cons of biosimilar G-CSFs in the literature. However, in many cases,

it is not clear whether products referred to as biosimilars are really biosimilars. For example, in a review of the use of G-CSF for mobilization of stem cells [15], an Argentinean product (Neutromax) is described as a biosimilar although it has not been approved using the biosimilar procedure [16]. This is particularly confusing as the review also discusses 'real' biosimilars approved in the EU using the correct regulatory system. This confusion could be easily avoided by only using the term 'biosimilar' for products approved using the correct procedure and referring to other subsequent entry products as 'non-innovator products'.

A glaring example of misleading terminology is evident in a recent publication [17], from Iran describing a comparative study in multiple sclerosis patients receiving Avonex (an innovator beta interferon (IFN) product) and Cinnovex (a locally produced non-innovator beta IFN product). Both products are referred to as 'biosimilar forms' of beta IFN and the title refers to 'biogeneric/biosimilar IFN beta-1a'. Cinnovex is clearly designated a biosimilar in the report, but no reference is made in the text to what the term 'biogeneric' as used in the title means. No mention of any comparative quality evaluation between Cinnovex and an originator product is provided and so it is unlikely that it is a true biosimilar.

The above are only a few of many similar examples in the literature. The current situation is very misleading and alarming for healthcare professionals who could be easily misinformed concerning the safety (including the important issue of unwanted immunogenicity [5]) of biosimilars. They may be dissuaded from prescribing biosimilars because of a false concern for patient safety.

It has been shown that the quality of different non-innovator/copy products can vary significantly and even different batches of what appears to be the same product can differ, with implications for both efficacy and safety [10, 18, 19, 20]. It is therefore imperative that clear terminology is used to accurately describe the nature and particularly the regulatory procedure used for particular biologicals.

In order to avoid future problems with terminology for biosimilars and non-biosimilars, it is emphatically proposed that the recommendations expressed in the Weise

et al. publication [9], are followed. The definitions provided in the publication for the terms 'biosimilar' and 'non-innovator biologic' should be adopted in future for accurately referring to the nature of relevant products.

These measures should hopefully lead us out of the confusing and often misleading minefield with terminology for biological products which we are in at present.

### For patients

Patient access to biosimilars is an important factor in economic health care. But this requires assurance that biosimilars are safe and efficacious. This is dependent on a clear definition of what is, and is not, a biosimilar. Unfortunately, inconsistency in nomenclature for biosimilars has caused confusion and this problem of terminology has been the subject of a recent publication. The confusion is not just a potential concern for patient safety and efficacy, but also can lead to misconceptions in published reports. The definitions provided here should be adopted for clarity in the future, so that healthcare professionals and patients are clearly aware of the regulatory processes used to approve the products they are using.

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