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Access to safe and effective biopharmaceuticals

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Comment on the *Letter to the Editor* by Professor Abdol Majid Cheraghali: Access to alternative biopharmaceuticals in low- and middle-income countries, published in *GaBI Journal*, 2014;4(3):164-5.

In the above *Letter to the Editor* of *GaBI Journal*, it is concluded that although biosimilars offer potentially increased global patient access to biopharmaceuticals due to lowering of prices, this may be problematic in low- and middle-income countries primarily due to local resource limitations and lack of experience.

The author questions the relevance of the World Health Organization (WHO) and European Medicines Agency (EMA) guidance and the applicability of the similarity/comparability concept for development of biosimilars in low- and middle-income countries. He considers that these processes are 'not feasible' in such countries and elaborates possibilities for regulatory procedures which could be adopted by them for approval of follow-on biological products, thus, obviating the extensive comparability studies as required by WHO, EMA and many other guidelines. We think that this proposal needs much care and consideration before it is seriously considered. The reasons for this are outlined below.

As the letter states, several follow-on biological products are marketed worldwide. As has been discussed previously, biosimilars approved in the European Union are safe and efficacious. However, some products marketed elsewhere are not. These latter products are not biosimilars as there is no evidence that they have been approved using the biosimilarity approach described in the WHO guideline. Furthermore, evaluation of product characteristics pertaining to their quality has clearly demonstrated that these products differ from the reference product [1, 2]. The letter also states that 'Most of the guidelines published for regulation of alternative biopharmaceuticals, including

WHO guidelines, rely on head-to-head comparative clinical studies for proven similarity between innovator products and alternative biopharmaceuticals.' Indeed, use of this approach, i.e. showing that the biosimilar and the reference product have very similar safety and efficacy, guarantees the safety and efficacy of true biosimilars as substantiated by the proven excellent clinical record of biosimilars approved using this regulatory process [3, 4]. Additionally, this approach allows extrapolation of the product for various therapeutic indications without the need for clinical trials in each indication providing that the therapeutic acts via the same receptor and the mechanism of action remains the same in different indications [5]. The author should also note that despite 10 years of experience with biosimilars, comparative clinical data is still required by EMA in the revised guideline on non-clinical and clinical issues to ensure that the 'claimed' biosimilar has a similar efficacy and safety profile to the reference product [6].

The letter describes the process for marketing authorization approval used in low- and middle-income countries as relying on 'a loosely designed and practised clinical study'. It is acknowledged that it is now well established that ignoring the need for appropriate assessment of quality, preclinical and clinical performance of biotherapeutics (including biosimilars) can lead to serious clinical problems: a good example of this is the high incidence of PRCA (pure red cell aplasia) development following treatment with the many EPO (erythropoietin) products which are approved in Thailand [7, 8]. In any case, quality assessment, which is the foundation of the biosimilarity exercise, is normally cheaper than conducting clinical trials and so the reason for relying solely on clinical assessment seems

illogical. The letter acknowledges that 'The manufacturing of biopharmaceuticals is somewhat different to that for small molecule chemical medicines, and the procedure is much more sensitive to change in the production process and even environmental factors'. Nevertheless, this again questions the wisdom of not conducting a quality assessment of non-innovator products of any type.

The letter considers that historical experience gained with innovator products can be used to assess possible problems with follow-on products. Although such information (when reliable) can provide a general guide for expected problems, it cannot ensure appropriate clinical safety and efficacy for a new product. This has to be assessed directly, using a proven pathway.

In addition, shortened regulatory processes are proposed involving no head to head clinical trial, no trial at all and reliance on approval followed by phase IV assessment by regulatory agencies. How this latter approach could excuse the pharmaceutical company developing the product from its obligation to guarantee safety and efficacy of their product is not explained nor is how the previously mentioned lack of resources and expertise in low- and middle-income countries would allow it. Although the author is in favour of promoting access to biotherapeutic products (which is laudable), the approaches outlined are not akin to the biosimilar philosophy and also not aligned with the WHA resolution (WHA67.21) 'Access to biotherapeutic products including similar biotherapeutic products and ensuring their quality, safety and efficacy'.

A request is made in the letter for a 'more pragmatic' guideline (perhaps from WHO or regulatory authorities), presumably describing some form of abbreviated procedure for regulatory approval of follow-on products. But, considering the above, how is this possible if safety and/or efficacy are not to be compromised? WHO already has current guidelines for Similar Biotherapeutic Products (SBPs) [9] and Biotherapeutic Products (BTPs) [10] which should be applicable to all biotherapeutic products. In a recent WHO Informal Consultation on the amendment for similar biotherapeutic products of monoclonal antibodies (April 2015) in Geneva, Switzerland, the WHO SBP

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guideline was reviewed and the consensus opinion was that it did not require revision and should be implemented globally. In addition, WHO is in the process of providing guidance on re-evaluation of products that are currently marketed, but have not been tested thoroughly or do not fulfil current international regulatory standards. This again suggests that existence of low regulatory standards is considered a global problem; reducing such standards has been identified as a threat to public health.

It is clearly the prerogative of regulatory agencies in low- and middle-income countries to adopt appropriate procedures for approval of biotherapeutic products. These need to take account of all relevant factors including clinical safety and efficacy. But if they decide to approve follow-on products by procedures which do not comply with the WHO SBP guideline, then these should not be called biosimilars or SBPs. They should be named in accordance with the process used for their approval.

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