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This issue of the journal contains a number of manuscripts that discuss proposals to simplify the evaluation of, and therefore decrease the cost of developing, follow-on biological products. These controversial proposals include extrapolation of indications, abbreviated approval processes in resource-poor countries, biological/biosimilar nomenclature, and patent litigation strategies.

Dr Frits Lekkerkerker, reviews the paper by Gerrard et al. in light of the history of biosimilars in the European Union (EU). He comes to the thought-provoking, controversial conclusion (in agreement with Gerrard et al.) that biological products could be approved for all registered indications for the originator product based only on preregistration studies that demonstrate clinical equivalence using modern preclinical analytical data and pharmacokinetics/pharmacodynamics data plus immunogenicity results in both volunteers and during post-marketing surveillance. Comments from *GaBI Journal* readers are both expected and welcomed concerning both his conclusions and his claim that modern analytical techniques 'will provide more discriminatory clinical evidence than large pre-approval therapeutic equivalence studies.'

Drs Robin Thorpe and Meenu Wadhwa provide an editorial response to a Letter to the Editor from Professor Cheraghali published in a previous *GaBI Journal* issue [1] that proposed implementing alternative approval processes to improve patient access to biological products in resource-poor countries. Drs Thorpe and Wadhwa raise many concerns about the 'more pragmatic' method based on 'a loosely designed and practiced clinical study' that was proposed in Professor Cheraghali's letter. They conclude that while alternate proposal methods may be necessary, if countries 'decide to approve follow-on biological products by procedures that do not comply with the World Health Organization's (WHO) similar biotherapeutic products (SBP) guidelines [2], then these should not be called biosimilars or SBPs.'

The naming of biologicals/biosimilars is an important, controversial issue. Dr James S Robertson, a member of the WHO's International Nonproprietary Names (INN) Expert Group, discusses the background and rationale behind the pending WHO proposal to include 'a novel global and company specific biological qualifier, distinct from the … INN' as part of the official name of biologicals. This would be an important 'entirely new, global nomenclature scheme for naming biological active substances' that deserves careful review by our readers who are encouraged to send their responses to the proposal to both the WHO and *GaBI Journal*. The WHO proposal is very similar to the US Food and drug Administration's recently (27 August 2015) released draft guidance [3] on the unique naming of biologicals, which is generating considerable debate. The Editors would welcome comments from our readers about these proposals.

In the first of a planned two part series of Review Article, Mr Brian J Malkin presents a 'strategic overview' that compares relevant EU and US biosimilar patent laws and litigation cases. He discusses how these affect the development and approval of follow-on biological products. The paper should be of interest to readers both with and without training or experience in dealing with these legal issues.

A Review Article by Gerrard et al. present data and experience in support of their opinion that for therapeutic proteins and monoclonal antibodies 'analytical and clinical sciences justify the approval of biosimilars for all the clinical indications of the reference products' based on demonstrated similarity for a single indication. They argue that advances in the preclinical evaluation of such products justify this approach and claim that 'failure to extrapolate to all clinical indications would cause confusion and undermine the concept of biosimilars.' The authors make an important proposal, but their proposal does not discuss some important questions. What would happen if post-marketing data did indicate that safety or efficacy was found to differ for an approved product compared to the innovator when used to treat only one of multiple indications? What should be done with those follow-on products for which the most modern processes were not used for approval? What should be done if an already approved product (either the innovator or its biosimilar) is found to have meaningful differences using a new preclinical test? The paper does not discuss drugs for which even the most modern preclinical testing is inadequate to assure similarity as has been found to be true for some non-biological complex drugs (NBCDs) [4]. Please note that *GaBI Journal* will soon introduce a section devoted to NBCDs. Readers' opinions about these questions as well as authors' proposal are welcomed.

A Review Article by Godman et al. discusses the regulatory and patent issues concerning extrapolation of pregabalin indications. This generic drug product has both an off-patent indication as well as a second, more common, on-patent indication. The manuscript describes the many widely different approaches taken by the many co-authors, working at literally dozens of regulatory groups in a number of European countries, in dealing with these issues. The manuscript demonstrates the important impact of extrapolation of indications has on the use and costs of small-molecule generics. Such extrapolation clearly also has major implications for biosimilars.

Much of the drive to develop follow-on products is related to their potential to decrease healthcare costs. This potential is not always realized as exemplified by the very slow uptake of generic drugs in many countries. An example of this problem is given in the first Perspective paper by Drs Jacques Rottembourg and Jessica Nasica-Labouze. This paper describes the 20-year history of the still limited use of generic drugs in France, 'a country

reluctant to switch to generics' despite the described efforts of legislators and insurers to encourage this switch. The authors present data on generic drug use and question whether efforts to encourage biosimilar use will meet similar resistance.

A second Perspective paper by Dr Christoph Baumgärtel describes the use of generics in Austria, a country that has had more rapid generics uptake than seen in France but where not all possible savings are being realized. Dr Baumgärtel lists initiatives that could be used to improve generics uptake including education and training, financial incentives, prohibiting originator rebates and free samples in hospitals, and improving counselling and guidance. Dr Baumgärtel suggests that the uptake of biosimilars will also be limited based on the experience with generics.

The delayed uptake of quality follow-on therapeutics is important not only for France and Austria but for all countries. Delayed uptake decreases cost savings that could be used by governments to provide other needed services. It also decreases the incentives needed to encourage pharmaceutical companies to develop less costly, quality products. This is even more important for biosimilars than for generic drug products because of the greater economic, scientific, educational, regulatory and clinical barriers they face.

GaBI conducts educational workshops as one way to meet its objective of providing unbiased education because, as suggested by Dr Baumgärtel, lack of understanding may be one of the barriers to the uptake of adequately tested, high quality follow-on pharmaceuticals. A Meeting Report by myself and *GaBI Journal*'s Deputy Editor-in-Chief, Dr Robin Thorpe, describes a recent workshop held in Mexico City at which many participants suggested that there is a need for both professional education and consensus guidelines for the best practice regulation, use and monitoring of follow-on biologicals. Providing descriptions of the different regulatory approaches being used by various countries to handle follow-on biological products is a useful step towards the development of such consensus guidelines.

The final paper by Leng et al. in this issue describes the approach being used in South Africa, which 'follows the same principles as those proposed by the European Medicines Agency, Health Canada and the WHO.' The authors explain that as of July 2015 not one of a number of follow-on biological products submitted for registration contained data adequate to allow registration as a biosimilar using these guidelines despite the fact that they were registered for use in their countries of origin. This is only one of the problems created by poor quality, but already marketed follow-on biologicals that are not true biosimilars, see the Letter to the Editor by Drs Thorpe and Wadhwa in this issue.

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References

1. Cheraghali AM. Access to alternative biopharmaceuticals in low- and middle-income countries. Generics and Biosimilars Initiative Journal (GaBI Journal). 2014;4:164-5. doi.10.5639/gabij.2014.0304.038
2. World Health Organization. Guidelines on evaluation of similar biotherapeutic products (SBPS). Annex 2, WHO Technical Report Series No 977 [homepage on the Internet]. [cited 2015 Sep 9]. Available from: http://www.who.int/entity/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf?ua=1; 2009
3. GaBI Online – Generics and Biosimilars Initiative. FDA issues draft guidance on naming biosimilars [www.gabionline.net]. Mol, Belgium: Pro Pharma Communications International; [cited 2015 Sep 9]. Available from: www.gabionline.net/Guidelines/FDA-issues-draft-guidance-on-naming-biosimilars
4. Walson PD, Mühlebach S, Flühmann B. First Asia-Pacific educational workshop on non-biological complex drugs (NBCDs), Kuala Lumpur, Malaysia, 8 October 2013. Generics and Biosimilars Initiative Journal (GaBI Journal). 2014;3(1):30-3. doi:10.5639/gabij.2014.0301.010

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