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Professor Philip D Walson, MD

The informed, appropriate use of follow-on pharmacological agents can provide significant cost savings for patients and payers. These savings can then be used by governments and patients to increase access to health care. However, the actual savings realized depend on a complex series of factors including how 'similar' the products actually are to the innovator products they compete with, at what per cent of the innovator products' costs they can be purchased, and whether they are prescribed by physicians, accepted by patients, and their costs reimbursed by payers. This issue of *GaBI Journal* contains a number of manuscripts that illustrate the huge differences in uptake, acceptance and use of follow-on products, both generics and biosimilars, as well as the many methods used to increase their use taken in both different countries and in different regions of the same countries.

The Letter to the Editor by de Vlieger et al. concerns a paper previously published in *GaBI Journal* 2016 [1] on the European Medicines Agency's regulatory approach to non-biological complex drugs. This is an important, still evolving, but very important class of agents for which (as is very well explained in the letter) there are still many unclear or unresolved, yet clinically important, regulatory and scientific issues remaining to be clarified.

In Commentary, Mestre-Ferrandiz et al. from the Office of Health Economics in London, UK discuss barriers to the uptake of biosimilars and propose concrete steps that could be taken to overcome these barriers. Based on research published elsewhere by this group they 'recommend a policy which provides: (1) incentives for budget holders to use safe and effective lower-cost products; (2) market support to collect real world outcomes evidence to increase prescribers' confidence in biosimilars'.

In the Review Article that follows, Siu and Wyatt present in a not so brief 'overview of … regulatory, reimbursement, clinician, and patient perspectives' concerning the still very limited use of subsequent entry biologics (SEBs) in Canada. They conclude that, 'More support is needed in order to allow stakeholders to fully comprehend the concept of SEBs so that these therapies can be properly evaluated and utilized'.

The lack of such 'support' is perhaps responsible for the understandable, relatively slow uptake of high quality, well-studied follow-on biologicals, i.e. true biosimilars, given that the development, testing, regulatory approval of biosimilars are all still relatively new to physicians, payers, regulators and patients. It is less clear however why the use of well-defined, relatively easily characterized, non-biological, generic medicines are not better understood or more widely used. The Review Article by Fontolan et al. documents the rather low and highly variable use of generic medicines in various regions of Italy. The authors claim, based on a summary of questionnaire data they collected, that the low uptake of generics is the result of a series of barriers that result 'mainly because general practitioners are uncomfortable with generic medicines companies, in particular those whose chain of production is unclear to them'. The authors propose, based on an analysis of the potential economic effects of various changes, that to overcome this problem there needs to be, 'a clear and definitive commitment of companies to increase production in Italy; a system with equal opportunities for all pharmaceutical companies, with the removal of the obstacles to growth; and an initiative … to promote … reindustrialization processes'. While the economic effects of such changes were well described, it is less clear how much effect they would have on physician, patient or pharmacist's acceptance or behaviours.

A Perspective paper by Dr Benedicte Lunddahl, discusses a Danish perspective on biological and biosimilar pharmacovigilance programmes that provide the 'support' for the uptake of follow-on products. There are many differences between Denmark and Italy other than just size, but the uptake of both generics and follow-on biologicals has been much greater in Denmark than in Italy and many other European Union countries. The differences may be related to the fact that the Danish Medicines Agency has focused on, and continues to evaluate the effectiveness of 'the pharmacovigilance of biologicals and is implementing an action plan jointly with a working group comprising representatives from the Danish Medical Association, the pharmaceutical industry and the five Danish Regions'. These programmes include attempts to simplify and encourage adverse event reporting, initial and continuous dialogue with all 'stakeholders' including patients, and attempts to raise 'awareness on biosimilarity through targeted information'.

The next Perspective paper by Dr Mathias Flume 'describes prescription standards and approaches to manage the uptake of biosimilars in Westphalia-Lippe', Germany. Dr Flume describes how successful Germany in general and this region in particular have been in increasing biosimilar TNF-alpha uptake and argues that this success has been the result of, 'intensified reporting and increased information supplied to physicians'. This claim is similar to that of Dr Lunddahl in Denmark.

The need to provide the 'support' mentioned by Siu and Wyatt, including the targeted, unbiased information distributed in Denmark, is illustrated by the slow uptake of oncology biosimilars in Canada. Two quotes from the Perspective paper by Ms Cherie C Severson from Canada are especially revealing, 'it is time to re-examine the use of biosimilars in our province and understand if the potential

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risks outweigh the benefit of cost savings' and 'the general consensus regarding the use of biosimilars is to take baby steps'. The author cites problems with interchangeability to answer the question, 'If biosimilars are more cost-effective and are proven to be safe and equally efficacious while ensuring positive outcomes for patients, the question remains why they are not being utilized more often?' However, biosimilar interchangeability is a complex, and very separate issue from the use of these products, especially in treatment naïve subjects as discussed in the paper. More widespread use of biosimilars, both in oncology and other patient populations will clearly require greater dissemination of unbiased information to all healthcare practitioners, including the causes of variability in efficacy, immunogenicity and toxicity in both innovator and follow-on products, if the reluctance to use these products is ever to be overcome. The smaller the 'baby steps' are, the more limited opportunities to save money and expand access will be and there is growing evidence and real-life experience suggesting that the reluctance to change is seldom justified.

Practitioners' reluctance to use biosimilars is also evident in the next Perspective paper by Annese et al. who discuss Italian gastroenterologists' concerns about extrapolation of indications for anti-TNF products. Such concerns should at least be partially lessened by the fact that a growing number of studies have failed to find evidence of any danger posed by the extrapolation of indications when it is based on scientifically valid considerations and common mechanism of action. However, despite recently reported study results that support such extrapolation, the authors express concerns about switching inflammatory bowel disease patients from an innovator product to a biosimilar. They point out that, 'according to Hypocrates' oath, doctors are committed to *primum non nocere*; this means they must know and reiterate information surrounding the safety, efficacy and reliability of any new treatment option to their patients'. However, doctors also have a duty to consider health care availability.

The next paper by my co-editor Dr Robin Thorpe and myself, is a Meeting Report of another *GaBI Journal* educational conference, this one in Ankara, Turkey that brought together academics, practitioners and regulators to discuss best practices for the evaluation, approval, use and monitoring of biosimilars. These educational conferences are attempts by GaBI to meet its goal of providing unbiased educational information on these topics.

The next Meeting Report summarizes a presentation given by Dr Steven Kozlowski of the US Food and Drug Administration (FDA) at the 2016 Generic Pharmaceutical Association Biosimilars Council Conference held on 6–7 September 2016 in North Bethesda, Maryland, USA. Dr Kozlowski outlined the FDA's approach to biosimilarity and interchangeability and included the FDA's 'definition of biosimilarity, its stepwise approach to the approval process and factors/issues that should be considered when providing scientific justification for extrapolation'.

A Special Report summarizes in detail Dr Leah Christl's important presentation on FDA's draft proposal for the naming and labelling of biologicals that is available for public comments.

The final paper is another Special Report summarizing a study by Mr Edward Kong from the Yale University's Department of Economics in which a 'discreet game model' identified, perhaps not surprisingly, the size of the firm, the total available market revenue and the amount of competition as the main factors influencing a manufacturer's decision to enter a biosimilar market. The effects of financial subsidies, incentives and fixed taxes on competition were also examined.

The editorial staff and I welcome comments from both our readers and our authors about any of the manuscripts or opinions expressed in this and other *GaBI Journal* issues including comments on how the FDA approach either does or does not deal with their concerns.

Professor Philip D Walson, MD
Editor-in-Chief, GaBiJournal

Reference

1. Ehmann F, Pita R. The EU is ready for non-biological complex medicinal products. Generics and Biosimilars Initiative Journal (GaBI Journal). 2016;5(1):30-5. doi:10.5639/gabij.2016.0501.008

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