Re: SM Devlin, B Bressler, CN Bernstein, RN Fedorak, A Bitton, H Singh, BG Feagan. Overview of subsequent entry biologics for the management of inflammatory bowel disease and Canadian Association of Gastroenterology position statement on subsequent entry biologics. Can J Gastroenterol 2013;27(7):567-571.

Position of Canadian Association of Gastroenterology on subsequent entry biologics is challenged by biosimilar industry representatives

To the Editor:

In the October 2013 issue of the *Journal*, Devlin et al (1) issued an overview of subsequent entry biologics (SEBs) position and position statement from the Canadian Association of Gastroenterology on SEBs. A similar position statement has been issued by ECCO (2) and subsequently challenged by European drug regulators (3).

First, Devlin et al (1) stated that subtle differences in structure and difference in manufacturing quality controls can result in drifts and potential changes in clinical efficacy and safety profile of SEB products. However, what the authors clearly failed to mention was that these subtle changes are very much what the originator drug products have been exposed to throughout their entire life cycle. The framework around product comparability has been laid in an International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline with specific reference "that the scientific principles underlying the comparability exercise for biosimilars are the same as those for changes in the manufacturing process of a given biological, for which guidance and experience already exist" (4). SEBs are not unique in terms of potential changes in quality attributes; however, the controls around these products are significantly tighter and the release specifications are significantly more narrow than with reference products that mimic the profile of originator products. The nascent biosimilar industry is developing high-quality products with a very similar target product profile. The scope of the target profile and comparability exercise required to overcome the development are carefully scrutinized and pre-agreed with numerous regulatory authorities. Schneider (5) reported that >30 manufacturing changes occurred throughout the life cycle of infliximab (Remicade, Janssen, USA). Therefore, one can argue that in the past decade of originator products being on the market, we could have expected profound changes in clinical efficacy, immunogenicity and safety profiles. However, this is clearly not the case. In contrast, a favourable benefit-risk profile and consistent product performance have been documented throughout the decade. In the case of SEBs and biosimilar products approved within developed jurisdictions such as the European Union (EU), Canada and United States, a similar control and prudent monitoring of quality changes are imposed. Therefore, in case of any quality changes, SEB sponsor in exactly the same manner as the originator company should demonstrate that these changes are of no consequential effect on pharmacological or clinical (efficacy, safety and immunogenicity) features of the product. Some minor changes in quality, in fact, are often normal part of the life cycle of any biological product and these minor variations are anticipated (6).

Second, the authors questioned an extrapolation approach that is the very foundation of SEB and biosimilar product development. SEB development is aimed at clinical comparability in most homogenous and clinically sensitive approved indications. Inflammatory bowel disease (IBD) does not represent the most homogenous and sensitive setting and, therefore, in case of anti-tumour necrosis factor (TNF) agents, other indications have been selected for the primary comparison and this has been endorsed by regulators and other stakeholders. Clearly, not all experts are willing to accept the extrapolation approach; however, a new generation of specialists across different regions is open to embrace new concepts of SEB development to streamline access of patients to biologics. These very specialists and experts are involved in recruiting patients and conducting global SEB clinical studies. Devlin et al (1) misquoted an example of 'extrapolation' with etanercept, which has no bearing on SEBs because etanercept represents an originator product and it has never been authorized or extrapolated for IBD indications because it has no efficacy in ulcerative colitis and Crohn disease.

Third, in the statement regarding impact of immunogenicity with SEBs, the authors were making references to cases of pure red-cell aplasia, which were mainly reported with the originator product Eprex (Janssen, USA) and with some copy versions of erythropoietin products available primarily in Asia and developed not in accordance with state-of-art biosimilar comparability principles. Unfortunately, inconsistency in nomenclature used for biosimilars has led to confusion in referring to some of these products. The term of 'SEB' or 'biosimilars' have been incorrectly applied in some cases to refer to products that 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. Cases of pure red-cell aplasia were reported with erythropoietin products that should not be regarded as true SEB or biosmilar products (7). Therefore, this example used by Devlin et al (1) is both scientifically inappropriate and clinically misleading.

What the authors did not mention is that a favourable safety and effectiveness profile of 16 approved biosimilar products in the European Community has been successfully documented over the period since somatropin (Omnitrope, Sandoz, Austria) was approved in the EU in 2007. A EudraVigilance study (8) has shown both reliable and consistent capture of reported safety data flows between originator and biosimilar products and, most importantly, did not identify any adverse consequences on safety or effectiveness with all currently approved in the EU biosimilar products. During development, nascent biosimilar developers are striving to establish the most sensitive and elaborate immunogenicity assays to support the comparability exercise and ensure that no clinically meaningful differences in unwanted immunogenicity were shown during clinical studies and that biosimilar candidates are both safe and well characterized in terms of immunogenicity. The example of approval of CT-P13 in the EU, Canada and in numerous other countries showed that development of biosimilar candidate requires an extensive clinical efficacy, safety and immunogenicity characterization, and that it is a feasible approach (9).

Fourth, the authors entirely misconstrued the design of the CT-P13 equivalence study in rheumatoid arthritis patients, which was an equivalence and not a noninferiority study as the authors mentioned. The study has been fully described in EMA EPAR and it is important to recognize a significant distinction between these study designs. Therapeutic equivalence studies are not only larger in size than noninferiority studies, but are also being designed with predefined and agreed on with regulatory authorities; two-sided margins are intended to exclude clinically relevant superiority as well as inferiority of a biosimilar candidate versus the reference product (9,10).

Despite numerous misconceptions about the SEB requirements in Canada and around the world, Devlin et al (1) have acknowledged that SEBs represent a potentially effective and cost-saving option for the management of IBD patients and may serve to enhance access to biologic therapy. In fact, the biological drug acquisition costs in Canada are near $0.5 billion (11). In accordance with United States administrative claims databases, IBD is responsible for 2.3 million physician visits (12), 180,000 hospital admissions (12) and costs $6.3 billion (13) annually. Approximately 33% of the cost of IBD is

due to medical therapy (13), and there are considerable and unaccounted opportunity costs associated with delayed access of IBD patients to biological treatments and impaired access due to lacking insurance and funding provisions.

There are still some provinces in Canada where the lack of reimbursement and insurance preclude IBD patients to obtain timely and affordable access to biological products. Not much has been done in Canada to address these medical needs and reduce colossal opportunity costs because only the second SEB has been approved by Health Canada throughout the entire history of SEB legislation enacted by authorities in 2010 (14).

Given the substantial clinical burden and economic cost of IBD and the proven cost effectiveness of approved anti-TNF agents, the access to SEBs, such as CT-P13, represents an opportunity to add even more cost-effective treatment into the armamentarium of treatments. In addition, the access to treatment can be expanded to more patients for whom anti-TNF agents were cost prohibitive. Furthermore, health care resources required for funding of SEBs can potentially be saved and implemented for funding of novel treatments.

In conclusion, it is reassuring that more SEB candidates are entering the clinical development pipeline and recent approvals in the EU and enactment of biosimilar legislation in the world clearly suggest that SEBs represent a long-term and positive phenomenon for global health care. It is hoped that the Canadian gastroenterology community will play an increasingly important role in assisting SEB development and improving the access of Canadian IBD patients to affordable biological therapies.

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Response from the Authors:

We thank the authors of this letter because their detailed critique of our position statement allows a further opportunity to understand and appreciate the important issues surrounding subsequent entry biologics (SEBs). There are particular points we believe warrant a response.

The authors were concerned about our statement "that subtle differences in structure and difference in manufacturing quality controls can result in drifts and potential changes in clinical efficacy and safety profile of SEB products". Our original sentence "…a different biological system that is used to produce a biosimilar agent will likely translate into subtle differences that could be difficult to characterize and that translate into relevant differences in efficacy, safety and immunogenicity." has been misquoted by the authors. This original sentence pertains to the accepted rationale supporting the need to assess clinical comparability of biosimilars with their reference product (in contrast to generic products). This rationale is indicated in all biosimilar regulatory guidelines around the world. Most importantly, the European Medicines Agency (EMA) acknowledges in its guideline related to mAbs that "it may be difficult at the current stage of knowledge to interpret the relevance of minor quality differences in the physicochemical and biological characterization when comparing a biosimilar mAb to a reference mAb" (1). The direct consequence of this concept is that minor quality differences, which may not affect the MOA of a mAb characterizing one indication, may be relevant to a different MOA important in a different indication.

Another issue raised is our apprehension regarding "an extrapolation approach that is the very foundation of SEB and biosimilar product development. SEB development is aimed at clinical comparability in most homogenous and clinically sensitive approved indications".

We agree that conducting development in the most homogenous and sensitive patient population is of paramount importance. However, it should be openly recognized that the most sensitive patient population has not been scientifically identified for any mAb including TNF blockers and, importantly, scientific frameworks for extrapolation approaches to support medicine authorization for this complex class of biological products are still to be

developed. Such scientific frameworks are especially warranted when modes of action differ across indications, as is the case for the numerous indications for infliximab including rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). In an effort to address this gap for infliximab, Lee (2) recently reviewed all pivotal trials conducted with infliximab in the approved indication with the aim of detecting the most sensitive population for this agent in terms of effectiveness. His starting principle was that if the difference in efficacy between a treatment and placebo is small, it is difficult (ie, less sensitive) to show a difference between the treatment and another treatment similar to that even if one exists. Based on this analysis, the author concluded that of the six indications for infliximab, the greatest placebo-adjusted response was found in plaque psoriasis followed by psoriatic arthritis and Crohn disease. In contrast, RA was associated with the smallest placebo-adjusted response to infliximab. He also observed that the dosing of RA may be less optimal to be sufficiently sensitive. In RA, the labelled recommended dose is 40% lower than the dose in the other indications. The practical implication is that if a biosimilar of infliximab is developed in RA and no clinical difference is identified between the biosimilar and the originator, it cannot be assumed there will be no clinical difference in other indications, particularly IBD, in which more complex mechanisms of action exist.

An issue raised was that we misquoted an example of 'extrapolation' with etanercept, which has no bearing on SEBs because etanercept represents an originator product and it has never been authorized or extrapolated for IBD indications because it has no efficacy in ulcerative colitis and Crohn disease. The reference to etanercept illustrates clinically the substantial mechanistic differences among the anti-TNF drugs and the important issue pertaining especially to extrapolation to IBD based on RA and ankylosing spondylitis studies, as explained in a recent article (2). The authors describe the important role the binding of mAbs to transmembrane TNF-a receptors play in IBD. This particular interaction leads to multiple consequences whose relative importance in mediating the clinical benefits of these medications is not completely understood. Many of these actions are Fc mediated. That Fc-mediated functions do not appear to play a role in RA and ankylosing spondylitis means that extrapolating from these particular studies to IBD is challenging according to the Health Canada authors.

An additional point raised was the statement regarding impact of immunogenicity with SEBs, the authors were making references to cases of pure red-cell aplasia (PRCA) which were mainly reported with the originator product Eprex (Janssen, USA) and with some copy versions of erythropoietin products available primarily in Asia and developed not in accordance with state-of-art biosimilar comparability principles. Immunogenicity is recognized as a key concern for biologics and can arise from any change introduced in the manufacturing process of any biological product. The PRCA cases that were clearly linked to Eprex represent the most documented example of the clinical impact of immunogenicity and also demonstrate how immunogenic outcomes could arise with any biologic. Health Canada expects that when developing a biosimilar, the study population and treatment regimen used are the most sensitive for detecting a difference in immune responses and that the most immunocompetent patient population would be preferred over immunosuppressed patients (2). As recently stated by Health Canada," immunogenicity is observed more frequently in patients that receive mAbs as monotherapy. For example, infliximab administrated RA patients have been shown to induce higher levels of ADA [anti-drug antibodies] when administrated without methotrexate. Therefore, it is considered that the most sensitive population to detect differences in immunogenic response to mAbs is one in which immunogenicity is not suppressed by concomitant therapies" (2). The use of methotrexate with CT-P13 in the RA trial does not appear to satisfy Health Canada's expectation to properly understand immunogenicity for this molecule. This is important clinically because the anti-TNF agents continue to be used as monotherapy, especially for some populations, such as elderly patients with IBD.

Finally, the authors of this letter corrected our point stating that the design of the CT-P13 study in RA patients, which was equivalence and not a no inferiority study, as it was labelled in our document.

We want to firmly state that we support the continued development of SEBs and are encouraged by the attention Health Canada has devoted to this important issue. If SEBs retain their efficacy compared with the principle comparator, then we greatly look forward to clinical trials proving this. Once proven, we hope that SEB companies will heed the pleas of the two writers of this letter and introduce SEB at substantially reduced costs: not by one-third, but rather by much less, so the products can truly be accessible to all persons with IBD including in the developing world where IBD is emerging.

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