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## **SUBSEQUENT ENTRY BIOLOGICS (SEBs) – Biosimilars in Canada:**

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### **Background.**

Biological response modifiers or 'biologics' are a class of very complex molecules manufactured by living cells with the use of genetic material.<sup>1</sup> They are complex proteins that have a variety of functions, including targeting specific aspects of the immune system. These medications can prevent inflammation, thereby reducing disease activity and preventing structural damage.

Biologics have had a tremendous impact, particularly in rheumatology with the treatment of immune-mediated inflammatory diseases, such as rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis. However, the affordability of these medications has been a growing concern for consumers and insurance companies, especially as potentially cost-saving alternatives become available.

### **What are Subsequent Entry Biologics?**

*Subsequent entry biologic* (SEB) is the term used by Health Canada to describe 'a biologic medication that enters the market subsequent to a version previously authorized in Canada', and which has 'demonstrated similarity to a reference biologic drug'.<sup>2</sup> SEBs are also known in the European Union as *biosimilars* and in the United States as *follow-on biologics*. According to the World Health Organization, they are similar in quality and function to 'an already licensed

reference biotherapeutic product' in the absence of any clinically important differences.<sup>3</sup> SEBs are similar, but not identical, to the reference biologic drug – it is anticipated that they will achieve the same clinical result in any given patient.<sup>4</sup>

### **Why are SEBs becoming available now?**

Patents and exclusivity rights for the first reference biologic agents used in rheumatology are expected to expire in the next few years.<sup>5</sup> This has created the opportunity for the development of alternatives that are intended to replicate as closely as possible the original biological product.<sup>6</sup> Their introduction may help reduce health care costs associated with effective biologic therapies, although projected estimates suggest relatively modest cost savings, of approximately 15-30% in acquisition price.<sup>7</sup> Despite the fact that an SEB will likely be less expensive than its reference biologic, the uncertainty surrounding long-term safety and function will require ongoing analysis to determine overall cost-effectiveness.<sup>7</sup> The manufacturing expenses and subsequent implementation of monitoring programs after the drug is approved may result in lower cost savings than with traditional generic drugs.

### **Why SEBs are not generic biologics:**

Biologic medications are proteins derived from living organisms which have unique structural features intrinsic to their function. As a result, they are structurally more complex than traditional small-molecule drugs. Replicating small chemical compounds to create generic drugs is a relatively simple process compared with producing a biosimilar, which is a complicated process that is sensitive to subtle changes in manufacturing.<sup>1</sup> The final product is determined by a variety of factors, which include the cells that are used to make the protein, purification techniques, and storage conditions.<sup>1</sup> Small variations between an SEB and its reference biologic may significantly alter its biological function, and hence its effectiveness and safety profile.

According to Health Canada, 'biosimilars are not generic biologics' and 'cannot be considered interchangeable or substitutable with the reference product in the clinical or pharmacy setting'.<sup>4</sup> This is not the case for most generic, small molecule drugs. The distinction is important because it prevents pharmacists from substituting an SEB for a reference biologic without first consulting a qualified health professional who can make a well-informed decision regarding changing therapies.<sup>4</sup>

### **Are clinical trials required to obtain marketing authorization for SEBs?**

Traditional generic medications are considered identical in structure and function to the original product and do not need to undergo clinical trials. This is not the case for SEBs. Subtle changes inevitably occur during the manufacturing process of biologic drugs – even batch-to-batch variation takes place with reproduction of the original drug.<sup>8</sup> This variability can result in unpredictable changes in safety and function. As with the reference biologic, rigorous testing and ongoing surveillance of the SEB are required.<sup>9</sup>

Health Canada, the European Medicines Agency, and the Food & Drug Administration require more extensive comparative studies of biosimilars than those used for generics with traditional pharmaceuticals.<sup>2,10</sup> In order to establish the ‘biosimilarity’ of an SEB to the original reference biologic, in-vitro analytical studies and in-vivo animal studies must first be performed to show that the two proteins are highly similar.<sup>9</sup> These investigations should be followed by extensive clinical studies which must show there are no clinically meaningful differences between the SEB and reference biologic.<sup>11</sup> The studies should be of sufficient size and duration and that take place in a real-world setting in order to label an SEB as highly similar.<sup>5</sup>

### **Extrapolation – Approval of an SEB in Disease States That Have not Been Studied:**

Whether an SEB should be approved for similar but not identical diseases without further study is controversial.<sup>4</sup> This is called “extrapolation of clinical data” and allows the use of a biosimilar for ‘a therapeutic indication in which it has not been clinically evaluated, but for which the reference agent is approved.’<sup>10</sup> The American College of Rheumatology (ACR) argues against this principle, stating ‘a biosimilar proven effective for one indication may not necessarily be effective for a second indication for which the reference compound has been shown to be effective.’<sup>12</sup> This opinion is based on subtle differences that can arise in the manufacturing of biosimilars that could dramatically affect biological function ‘in ways that are not readily predictable’.<sup>12</sup>

In contrast, the position of Health Canada is that ‘extrapolation’ will be decided on a case-by-case basis. While this debate continues, it is important that this information is clearly indicated on the product label to allow the prescriber to know whether there is direct evidence to support its use.<sup>10</sup>

### **Post-marketing Surveillance and Nomenclature:**

After approval of an SEB for a given disease, ongoing monitoring is required to determine the long-term safety profile in the post-marketing phase. Because SEBs are new medications, there are currently no existing patient registries from which to draw. Health Canada guidelines for the use of SEBs require an extensive post-license marketing period in order to assess the safety and long-term outcomes, equivalent to that of the reference biologic.<sup>2</sup> While the relative risks and benefits of using biologic medications have been determined over time, obviously there is no corresponding data available for biosimilar drugs.

Given the fact that SEBs are not identical to their reference products and could have significantly different clinical outcomes, it is important that prescribers and pharmacists are able to readily distinguish SEBs on the basis of their names.<sup>4,12</sup> Appropriate strategies must be used to ensure adequate vigilance for subsequent entry biologics.<sup>13</sup> A unique product name will assist in the accurate prescribing and dispensing of SEBs and will help with attributing rare and serious side effects to a specific product or manufacturer.<sup>4,13</sup>

### **What is the process for approving SEBs in Canada?**

The complexity with which a biotherapeutic product is manufactured results in unpredictable long-term outcomes and, consequently, the 'same regulatory process that controls the use of generic medications should not be applied for biosimilars'.<sup>5</sup> Health Canada states that 'marketing approval of an SEB is not a declaration of pharmaceutical or therapeutic equivalence to the reference biologic drug'.<sup>2</sup> Therefore, each authorized SEB must be considered a new product and undergo all of the regulatory requirements of any new biologic medication.<sup>4,14</sup>

Globally, governments and industry are still developing practices concerning the use of biosimilar agents after obtaining marketing authorization.<sup>5</sup> Earlier this year, Health Canada approved the use of two new SEBs (Remsima<sup>TM</sup> and Inflectra<sup>TM</sup>) for the Canadian marketplace, with one of the approved indications being ankylosing spondylitis. The approval of both products was based on their comparison to the reference product Remicade<sup>®</sup> (infliximab). The specific details on when these products will be introduced into the market remain to be determined.

After approval of an SEB by Health Canada, patient access is determined by the provincial formulary listing or private drug plans. Health Canada does not support interchangeability of an SEB for the reference biologic medication, however, it will remain the authority of each province to determine whether substitution in both provincial reimbursement plans and private plan

coverage is allowed. Few provinces have yet to announce how SEBs will be reviewed and reimbursed.<sup>4</sup> Private drug plans often support substitution of generic medications for synthetic drugs. This should not be routinely recommended for biologic medications until more is known regarding long-term safety and clinical results.

A recent article published by Canadian rheumatologists (discussing concerns of SEBs) stated provincial formularies should not preferentially list SEBs 'if it is at the expense of patient safety, proven product-efficacy, or physician-patient choice'.<sup>4</sup> The Arthritis Society of Canada endorses a policy of 'no therapeutic substitution' based on the prevailing scientific view, believing this "policy should be explicitly incorporated into Health Canada regulation, federal, provincial and territorial drug reimbursement policies, as well as private insurance industry drug reimbursement policies."<sup>14</sup>

### **What are some of the concerns with SEBs?**

While SEBs may lead to increased availability of expensive and effective therapeutic agents, many concerns have been raised regarding their use clinically. For example: will SEBs behave in exactly the same way as the reference biologic; what are the long-term side effect profiles; and what are the possible consequences of switching from a clinically effective biologic medication to a biosimilar drug?<sup>4</sup> These concerns are not unsubstantiated, as subtle variations in the manufacturing process may significantly alter biological function.<sup>15</sup> SEBs do not have the longevity of brand name biologics, and the only way to answer these questions will be through experience gained once these products become available for use.

The development of 'immunogenicity' (i.e., an immune response associated with decreased effectiveness of a biologic medication) is another major concern. Starting and stopping a biologic medication has been shown to result in loss of biologic function. It is unclear whether switching to an SEB could result in loss of effectiveness to the original biologic medication (were it to be re-introduced). Clearly, this could be deleterious to the patient's long-term outcome, and so monitoring for this complication is required.

Reduced pricing is also a concern as it may influence the prescription and dispensing of biologic and biosimilar drugs. It is generally accepted that cost must not take priority over safety and efficacy'.<sup>4</sup> While the cost of SEBs may be lower than that of the brand name biologic, uncertainty continues to exist due to a lack of long-term data on biosimilar medications.

Physicians and prescribers should also be aware of 'intended copies' which have not undergone rigorous comparative trials and should not even be considered biosimilar agents. These products exist and are currently in use in some parts of Asia and Central and South America.<sup>10</sup>

**Conclusion:**

The advent of subsequent entry biologics may reduce the high cost of effective biologic therapies for patient and insurer, however, this should not be at the expense of patient safety. Long-term outcome data are required to determine the possible side effects that may result from subtle changes to the reference biologic drug.

As SEBs become available in the Canadian marketplace, it is important that provincial regulatory committees, insurance companies, and physicians recognize that they are not generic medications and that certain aspects of their use remain unknown at this point. It will be important for patients and physicians to have meaningful conversations in order to understand the differences between available treatment options.

Until key safety and efficacy concerns have been resolved, rheumatologists cannot confidently substitute an original biologic therapy with a biosimilar product.<sup>16</sup> It is essential to focus primarily on patient safety, with validated clinical experience.

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