

## Subsequent Entry Biologics

Remarkable advances in the treatment of a virulent form of breast cancer and of lymphomas followed the introduction of Herceptin and Rituxan. These and other innovative treatments like Neupogen, Avastin, Erbitux, and Vectibix comprise a new class of anticancer treatment called biologics. Only living organisms are able to produce such very large, complex molecules.

Biotherapeutic products also known as biologic drugs have a successful record in treating many life-threatening and chronic diseases. The recent expiration of patents and/or data protection for the first major group of originator biologics and the anticipation of additional expirations has led to the development of products that are designed to be “similar” to a licensed originator product.<sup>1</sup> In Canada, they are referred to as Subsequent Entry Biologics (SEBs), copies of previously approved biological products.

In order for a product to be considered an SEB it should have the same therapeutic effects as the originally approved biologic, a similar safety profile and the same guarantees to be free of contaminating viruses or other infectious agents. The expectation is that the introduction of SEBs will provide competition for the original products and that price competition will lower cost, as has been the case with generic forms of name brand chemical pharmaceuticals. Cost is a major concern for payers; safety and efficacy are of greater concern to health care providers and patients.

The term “generic” medicine is used to describe chemical, small molecule medicinal products that are structurally and therapeutically equivalent to an originator product whose patent and/or data protection period has expired. The demonstration of bioequivalence of the generic medicine with a reference product is usually appropriate and sufficient to infer therapeutic equivalence between the generic medicine and the reference product. However, this approach is not suitable for development, evaluation and licensing of SEBs since biologics consist of relatively large and complex proteins that are difficult to characterize. The clinical performance of biologics can also be significantly influenced by the manufacturing process and therefore some clinical studies will also be required to support the safety and efficacy of an SEB.<sup>1</sup>

### **PART 1** by ROSEMARY COLUCCI **Regulatory Framework in Canada**

Health Canada is currently developing a regulatory process for the approval of Subsequent Entry Biologics (SEBs). According to Health Canada, regulatory decision-making regarding SEBs will be based on science and regulatory principles existing within the *Food and Drug Act* regulations. Therefore, Health Canada intends to regulate the approval of SEBs through guidance documentation without amendments to regulations of the *Food and Drug Act* or the *Patented Medicines (Notice of Compliance) Regulations*.

The Biologics and Genetics Therapies Directorate (BGTD) within the Health Products and Food Branch (HPFB) of Health Canada is the regulator of biologic drugs and therefore will be the regulator of SEBs.

#### **Guidance documents**

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada’s mandates and objectives should be implemented in a manner that is fair, consistent and effective. Guidance documents are administrative instruments not having force of law and as such allow for flexibility in approach.<sup>2</sup>

#### **The trend toward SEB regulations in foreign countries**

Canada’s use of guidance documents and existing legislation varies from the approach taken in Europe, Australia and other countries where SEB approvals have generally followed legislative and/or regulatory amendments.<sup>3,4</sup> In the United States specific SEB regulation is under review.

#### **Consultation process**

Health Canada released a revised version of the Draft Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) on March 27, 2009 for public comment. Comments were accepted until May 26, 2009. The revised version reflects written comments following its original release in January 2008, as well as comments received during a public consultation held in June 2008. The document was released in conjunction with the Proposed Revisions to Guidance Document: Data Protection under C.08.004.1 of the Food and Drug Regulations and Proposed Additions to Guidance Document: Patented Medicines (Notice of Compliance) Regulations (“PM(NOC) Regulations”).

The revised version of the Guidance Documents will be released in the early part of 2010. There will be no further public consultation on these documents, although the Guidance Documents may undergo subsequent changes as the need arises.

#### **Submission process**

According to Health Canada, a manufacturer of an SEB will be required to submit a New Drug Submission. The basis for a product being authorized as an SEB, hinges on the ability of the manufacturer to demonstrate similarity to a suitable reference biologic product. SEBs are not “generic biologics” and many characteristics associated with the authorization process and marketed use for generic pharmaceutical drugs do not apply.<sup>5</sup>

Full quality data (chemistry and manufacturing), in addition to data that demonstrates comparability between SEB and the reference biologic product, is required for authoriza-

tion of an SEB. The reference biologic product should be a biologic product authorized for use and marketed in Canada. The use of a reference biologic product that is not approved in Canada may be considered on request to the Minister.<sup>5</sup>

## Reference products

According to Health Canada, an SEB applies to all biologic drug submissions where the sponsor seeks authorization based on demonstrated similarity to a biologic drug that was previously authorized for sale in Canada. The sponsor therefore relies, in part, on prior information regarding the authorized innovative biologic drug in order to present a reduced clinical and non-clinical package as part of the submission. An SEB will only be authorized if a submission demonstrates similarity based on a direct or indirect comparison to such an authorized innovative biologic drug.<sup>1</sup>

To provide flexibility to sponsors, Health Canada will, in appropriate and special circumstances, permit the use of a reference biologic drug that is not authorized for sale in Canada, as part of the demonstration of similarity between the SEB and the reference product. However, in all instances where a non-Canadian reference product is used, the submission must explicitly and clearly explain the link between the reference product and the SEB seeking authorization for sale in Canada.<sup>1</sup>

Once again, Health Canada's approach to reference products varies from that of European countries, where the reference product for the SEB must be authorized in the European Union.<sup>3,4</sup>

## SEB approved in Canada

On April 20, 2009, Health Canada issued a Notice of Compliance (approval) to Sandoz Canada for the drug product Omnitrope.<sup>6</sup> This is the first biologic product to be approved under the regulatory term Subsequent Entry Biologic. It is a recombinant human growth hormone used for the treatment of children with growth failure due to growth hormone deficiency (GHD) and for the treatment of adults with either adult onset or childhood onset (GHD). The product received market authorization in both the European Union and United States in 2006.<sup>7</sup>

## PART 2 by PIERRE MAJOR

### Quality Control of Subsequent Entry Biologics

A major difference between medicines produced in the controlled environment of an industrial chemistry plant and those produced in living organisms is the ability to control purity and identify contaminants.<sup>8</sup>

Recently, the biologic heparin sourced from China led to the death of patients in the US and Europe because the clinical effectiveness of this adulterated heparin was not detected by laboratory tests.<sup>9,10</sup> A change of manufacturing facility for a biologic Epoetin, a stimulant of red blood cell production, led to an unforeseen complication with patients developing an inability to produce red blood cells. Detailed investigation of this adverse outcome identified a minute change in the Eprex molecule that was the result of the production in a different plant under what appeared to be identical conditions to the original production site. This illustrates the

complexity of manufacturing biologics and the disastrous outcome that can result from minute differences in production.<sup>11</sup>

The production of chemical drugs can be carefully controlled and the end product, a relatively small molecule, can be verified by chemical analysis. In contrast, biologics require close monitoring of the production process to ensure their purity. In addition to such monitoring, extensive testing of the end products for the presence of contaminants such as viruses that could enter the organism producing the biologics is necessary.

The fact that a biologic can be 200 times larger than an average chemical anti-cancer drug provides only a glimpse into the much greater complexity of biologics. The therapeutic activity of all currently available anticancer biologics cannot be judged only by the activity in laboratory tests that are currently available. Ongoing monitoring of clinical effectiveness is required as part of post-marketing surveillance.

Health Canada is in the process of developing a regulatory framework to approve SEBs. In order for a product to qualify as an SEB the manufacturer must demonstrate that the SEB has the same efficacy as the original product. Because of the complexities involved in manufacturing biologics and in particular SEBs concerns have arisen about the ability of regulatory agencies to monitor production facilities located outside North America or Europe on a regular basis.

The number of pharmaceutical producers located outside our borders will continue to increase rapidly. Data available from the US FDA shows that this very large agency is overextended and cannot adequately monitor overseas production facilities with its current resources.<sup>12</sup>

In Europe the Medicines Evaluation Agency has been able to coordinate the efforts of its member countries. Any assessment of Canadian capabilities in this regard is hindered by the difficulty in accessing Health Canada reports of production facility audits.

## Generic drugs versus Subsequent Entry Biologics

Most chemicals used to produce the generic medicines sold in Canada are produced in Asia; this information is very difficult to access because it is considered proprietary information. These chemical production methods are well established and the end product purity and quality can be easily monitored. Biologics are far more complicated to produce and companies who first introduced biologics to market have themselves had production difficulties. The stringent reporting rules that govern production in North America have ensured that no biologics manufactured here and used for treating cancer have been tainted.

## PART 3

### Conclusions

Canada is using guidance documents and existing regulations for the approval process for SEBs as opposed to amendments to regulations under the *Food and Drug Act*.

Canada will allow for foreign reference products, unlike most other developed nations that will only allow domestic reference products.

It is not apparent how Health Canada will be able to meet

### A Comparison<sup>13</sup>

- Aspirin (chemical drug) contains 21 atoms and is produced synthetically in a lab using simple ingredients
- IgG antibody (biologic) contains 25,000 atoms and is produced using unique organisms (cell lines), unique manufacturing process conditions and unique in process controls
- This level of uniqueness means that even very minor changes to the environment or process conditions can yield dramatic differences in the final biologic structure (and therefore differences in efficacy and safety)

### Examples of Biologics<sup>13</sup>

abatacept (Orencia) – rheumatoid arthritis  
alefacept (Amevive) – chronic plaque psoriasis  
etanercept(Enbrel) – rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis  
infliximab (Remicade) – rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease  
trastuzumab (Herceptin) – breast cancer  
ustekinumab (Stelara) – chronic plaque psoriasis  
filgrastim (Neupogen) – neutropenia  
interferon alfa2a (Roferon) – hepatitis C  
erythropoietin alfa (Eprex) – anemia  
insulin (Humulin) – diabetes mellitus

the expectations of Canadians for effective and safe biologics. At a minimum, it will be necessary to conduct inspections of production facilities in emerging biopharmaceutical producer nations to guarantee that SEB products used in Canada are as effective and safe as those initially introduced.

As the Epoetin experience illustrates, careful adverse event surveillance was key in understanding the cause of the serious toxicity that developed following the use of a slightly modified biologic. This emphasizes the need to establish effective post marketing drug surveillance of adverse drug reactions in Canada and develop a close working relationship with health authorities worldwide to monitor product safety. Our current drug surveillance system relies on health care professionals reporting adverse effects of drugs and biologics. This passive system is insufficient to protect Canadian consumers.

### Recommendations

1. Health Canada must formulate policies and allocate budgets that are adequate to the complex task of ensuring any SEBs brought to the Canadian market are safe and effective.
2. Canada will need to cooperate with other nations to monitor production of overseas biologics and collaborate in the development of innovative quality control methods.
3. A comprehensive surveillance system is urgently needed to establish active drug surveillance of pharmaceutical products in Canada.
4. Greater transparency of our health agencies is required so that their effectiveness in protecting Canadians can be monitored.

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