



Canadian Roundtable on
Clinical Considerations for
Subsequent Entry Biologics

Key Learning Points
for Physicians,
Pharmacists
and Patients

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Table of Contents

The Global Experience with Subsequent Entry Biologics	3
Immunogenicity and the European Guidelines	4
Subsequent Entry Biologics in Canada	6
Risk Management	8
Population Safety	9
Pharmacovigilance	10
Legal Liability Issues	11
Roundtable Consensus	14

The Global Experience with Subsequent Entry Biologics

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This area is very topical and should also be recognized as a dynamic subject. Of course it is relatively easy to manufacture a new SEB but it is critically important to further understand the new product. Recognition of the incredible differences among biologics is found in Europe's first grouping of approved products. Everyone felt initially comfortable with the sensible and collaborative approach taken and then we were suddenly confronted with monoclonal antibodies. The process of approving an SEB is not going to be a "stop-start" phenomenon. There is a regulatory process to be designed and, when that has been dealt with, we will need to look at issues of reimbursement and market access.

As we consider different frameworks and pathways for SEBs it is common to go back to Europe and conclude that that is the most advanced process. Nonetheless, frameworks are being developed in other jurisdictions and my company has so far been involved in discussions in Thailand, Taiwan, Japan, and the US as well as in Europe.

We cannot take a "one size fits all" approach to SEBs. The most attractive thing about the European model is that it adopts flexibility by product class. A commitment was made through the Biomedicines Working Party and the Committee for Medicinal Products for Human Use (CHMP) to look on an individual basis at additional product classes coming up for consideration.

Another important question is the choice of appropriate reference product. When we look at monoclonal antibodies or antitumour necrosis factors (antiTNF) we note that the antiTNFs are vastly different in safety and efficacy profile. With erythropoietin, the challenge appears relatively simple and the same is true for growth hormones. An initial question is whether or not there is already data on file that would permit a comprehensive assessment. It is important to consider whether or not it is possible to accept reference products that are not already registered. In such cases there is unlikely to be a full data file available for comparison.

The question of interchangeability will come up early in discussion and represents a key question. It is important to tease away the competitive and reimbursement aspects of the discussion from the scientific aspects. Eventually when SEBs are approved there will be issues of post-marketing surveillance that must be addressed. Although the complexity in approval of SEBs is challenging, we need to retain flexibility in our thinking.

I believe, and most people believe, that the process defines the product. That doesn't mean that a new product is better, worse, or the same but it does indicate the need to be aware that these products are manufactured genetically in living cells. The new product is

not just the output of the process. It is also affected by cellular byproducts and a number of other related factors with potential biological effect.

The European Medicines Evaluation Agency (EMA) has taken a simple view of interchangeability; that it is not possible to guarantee that two biological products are the same and so this should not be done. At a national level there are many member countries in the EU forbidding substitution. It is important to note that part of the issue with substitution and interchangeability goes beyond concerns about whether these products are the same. It goes back to the basic issue in pharmacovigilance which is “how do you know who received what product?” Traceability is a major issue. At Johnson & Johnson we receive reports of over 200,000 adverse events a year and trying to understand which adverse event is related to your own products is highly problematic. In China, 40% of adverse events result from products that are apparently counterfeit. It has been recommended that marketed erythropoietins be prescribed by brand name in order to support traceability.

The most recent guidelines produced by CHMP invite public consultation regarding monoclonal antibodies, in particular, antibodies directly against TNF-alpha. When these products are used, between 30 and 60% of recipients develop antibodies. If methotrexate is administered with the antiTNF-alpha, antibody development drops below 20%. We do not yet understand these phenomena, although there are now three competing products on the market based on monoclonal antibodies to TNF.

In the United States, the fight has been over data exclusivity and identification of appropriate rewards for innovation. However, if you go beyond the rhetoric and examine the difficulties experienced by divisional reviewers, the FDA is quite clear that there is no basis on which to conclude that the science exists to permit a conclusion that two compounds of a similar biologic nature can be considered identical. In Europe to date, eleven biosimilars have been submitted to the approval process: six have been approved, two have been rejected, and three have been withdrawn.

Immunogenicity and the European Guidelines

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In Europe SEBs have been established for a number of years and the Committee for Medicinal Products for Human Use of the EMA has a specific working party addressing SEBs, particularly from a clinical perspective. That group has produced a number of guidance documents, not legally applicable but intended to serve as guidelines. These documents are used by regulators when assessing SEBs.

There is a general guideline on “similar biological medicinal products”, the official EU term for SEBs. There are general guidances that deal with clinical, non-clinical, and quality issues and these are complemented by specific guidances for particular products, including erythropoietin, granulocyte colony stimulating factor, human insulin, and growth hormone. Two new guidances have been recently been drafted, one on low molecular weight heparin and one on alpha interferons. The latter is a more concept paper than a guideline.

The major issue which has been confronted by the EMEA is immunogenicity. When considering SEBs regulators are faced with a product, usually a protein or glycoprotein that will be given to patients for beneficial effect. The benefit does not involve induction of immunological response; however, antibodies and other immune responses are likely to be induced with considerable variability.

There are many possibilities from a clinical perspective of what these antibodies, if induced, may or may not do. The most widely known example of unwanted immunogenicity is the development of antibodies against erythropoietin. Investigators in France noted a cluster of 13 cases that, during treatment for chronic renal failure with erythropoietin, failed to respond to the treatment product or any similar product. These patients also failed to respond to natural erythropoietin because they had made antibodies against the product which cross reacted and neutralized the biological effect of any erythropoietin. As a result they developed pure red cell aplasia.

The underlying problem with unwanted immunogenicity is multifactorial. It cannot be related to a single cause; there are products and patient related factors. The molecular structure of the product may be important but there are also other considerations. There are product impurities, formulation differences, aggregates, and it is further necessary to consider the protein’s biological properties, for example, if it is an immunostimulant. Other factors influencing response are the mode of use, the physiological importance of the protein, the dose, route, frequency and duration of administration. Of course, outcome will also be affected by the immune status, age, and previous exposure of the patient being treated.

Any subtle change introduced into the manufacturing process for a given product may have enormous implications for immunogenicity. This will have impact on the introduction of SEBs. It is impossible to predict everything that needs to be known, including the incidence of unwanted immunogenicity, the characteristics of the immune response, and the clinical significance of such immunogenicity. In the end the only way of understanding immunogenicity is to carry out appropriate prospective immunogenicity studies.

The EU has a specific guideline on immunogenicity that applies to all biotechnology derived therapeutic proteins. In fact, it applies to all biological products. The guideline development process included a six month consultation in the latter half of 2007 which attracted widespread comment. The EU guideline was eventually published in April 2008.

In conclusion, we should keep in mind the much quoted observation: “unwanted immunogenicity is the biggest challenge for the approval of biosimilars” made by both recent Chairmen of the Biosimilars Working Party of the EMEA.

Subsequent Entry Biologics in Canada

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Health Canada has been interested in the subject of SEBs since at least 1999, although progress has been constrained because of limited demand for regulatory decisions. Health Canada is now aligned in its thinking with the EU which has made great strides and is currently the world leader with respect to the SEB approach.

Three issues will be reviewed:

- demonstration of comparability, which is the origin of the concept of demonstrating similarity among products. This includes the challenges of characterizing any new product.
- the Canadian perspective on questions related to SEBs and some of the challenges inherent in the current regulatory approach, and
- those arising from the draft guidelines released by Health Canada.

When we address comparability, the question for any manufacturer when revising a production process is, “Is the product of the revised process Y truly comparable to the product of process X”? This is very important because if one can’t demonstrate comparability, the preclinical and clinical data generated with the original version of the product may no longer be relevant to consideration of a revised product. A decision on such comparability is critical because it will determine whether or not there is a need for new clinical trials. If there is a desire to show comparability, the scope of studies required will depend on a number of things, including the stage and extent of process changes undertaken, the impact on the product, the analytical capability available to evaluate the outcomes, and the link previously demonstrated between quality criteria, safety and efficacy. The principal concern not be efficacy but rather safety, and we have heard extensive discussions already about immunogenicity which remains a prime concern.

Even though Canada is making progress towards a framework for approval of SEBs, we are fully aware of the challenges and the difficulties that the sponsor must go through in order to convince the regulator that their product is safe and efficacious when considering SEBs. These relate to the size and complexity of the desired product, heterogeneity issues, and the potential presence of adventitious agents which are not usually a factor in evaluation of small molecule drugs. There are also limitations to current methods for

product characterization and, beyond that, there is the added challenge of immunogenicity.

The current Canadian perspective holds that there are no “generic” biological products. These products should be examined on a case-by-case basis and full chemistry and manufacturing data will be required. Beyond that, the sponsor of an SEB must go further than the type of chemistry and manufacturing data that an innovator would normally provide for a new product since the sponsor of a new SEB must also provide an extensive comparability study with respect to a reference product.

It is Canada’s position that prospective clinical data is required. The extent of the clinical data required may be negotiable and proof of one indication will not necessarily support all indications. However, if a second indication is dependent on the same mechanism of action, and an adequate rationale is provided, then it may be possible to acquire the additional indication without additional clinical studies.

Over time, there is the possibility that there will be some kind of drift between the SEB, at the time it was approved based on its comparison to the reference product, and the same product five years later. When a SEB gets on the market, if the sponsor of the SEB makes a major manufacturing change they will have to provide comparability data to Health Canada to show that the product of the revised manufacturing process is comparable to the product of the previous manufacturing process, the same way that the innovator does. They will not have to go and redo any similarity studies with the named reference product. Even if the reference product was still available (which it may not), such studies would be impractical, expensive and discourage worthwhile manufacturing changes. This element of manufacturing drift over time is one argument why SEBs should not be automatically substituted for their reference product.

From the Health Canada perspective SEBs will be viewed as stand-alone products once they are on the market. The demonstration of similarity to the reference product brings additional clinical data into relevance but does not imply automatic substitutability. We hold that opinion because SEBs will not be viewed as generics. Scientific and pharmacovigilance issues must be addressed in relation to individual products.

One controversial issue arising from Health Canada’s draft guidance is the suggestion that “we will, in appropriate and special circumstances, permit the use of a reference biologic drug that is not authorized for sale in Canada.” A main consideration is that the reference biologic drug should have significant safety and efficacy data accumulated such that the demonstration of similarity will bring into relevance a substantial body of reliable data. To offset concerns relating to patent market exclusivity issues, a recent addition to the guidance states that a link must be explained between a reference product and a product that is authorized for sale in Canada.

Risk Management

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It is important to understand the potential and identified risks associated with SEBs and to have a plan to evaluate and manage them throughout not only the development cycle, but after marketing. Pre-approval evaluations provide limited data even in the best of circumstances. It is the common or very common events, not the rare ones, that are going to be identified premarketing. Post approval monitoring and surveillance, therefore, is essential for SEBs. Post marketing surveillance for SEBs should be conducted to ensure that there is a similar clinical safety and efficacy profile relevant to the innovator product and to look at the concerns about eventual outcomes related to interchangeability and substitutability.

The risk management challenge is that immune responses in pre-clinical studies are generally not predictive of clinical immunogenicity. Pre-clinical evaluations can provide some insight into the potential clinical consequences of immunogenicity if animal exposure can be maintained but these insights are often limited due to species-specificity, immune system differences, and lack of predictive power. The risks related to clinical immunogenicity must be fully evaluated in patients as the impact can vary from no effect to reduction in efficacy or life-threatening anaphylaxis. The potential for cross-reactivity with endogenous proteins could lead to antibodies forming that completely neutralize the endogenous and require long-term replacement. The formation of immune complexes and complement activation may result in mild to severe hypersensitivity reactions. Delayed consequences of immunogenicity can manifest as injection site or infusion related reactions or alterations in drug clearance. Differences from the innovator molecule in areas such as source material or master cell bank, or variations in the manufacturing process, formulation or container closure system, can all affect the potential for immunogenicity. Development of neutralizing antibodies could alter the intended pharmacokinetics of the biologic or pharmacodynamics by altering drug clearance, causing drug accumulation or interfering with PK assays and/ or target engagement.

Beyond the patient safety concerns, reductions in efficacy can result through the effect of neutralizing or clearing antibodies. The potential for deficiency arising from neutralization of an endogenous protein or other alterations to pharmacokinetics and pharmacodynamics need to be considered. The focus from a risk management standpoint should be on examination of the clinical consequences of immunogenicity associated with the SEB.

SEBs (biosimilars) should not be considered as substitutable or interchangeable at this point in time in the absence of more extensive evaluation. Analytical methodology alone is not able to provide sufficient evidence. It will be necessary to require extensive clinical evaluation and post approval studies in order to ensure that SEBs are safe and effective.

A rigorous risk management approach is needed and, at an early stage in product development, a sponsor must be expected to have a plan in place to better understand identified and potential risks. These safety risks will need to be monitored through post marketing surveillance and possibly new prospective clinical studies, even after approval. Longer term surveillance is needed to identify further clinical safety implications once the SEB is on the market. A high prevalence of immunogenicity, allergic or anaphylactic reactions, and other specific safety concerns may drive the need for additional studies. Manufacturers should plan ahead; consider what the risks might be; and then implement a plan to manage them.

Population Safety

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Risk, or the predictable consequence of an untoward outcome, is often inadequately discussed. Although drugs on the market in Canada are the product of a very well-developed, well thought out drug evaluation process which looks at the safety of drugs in populations, individual health practitioners don't treat populations. Physicians and pharmacists are concerned with the effect of therapeutic products on their individual patients.

Although "our drug" may be safe in a population, the responsiveness of a patient is not actually a percentile response. Patients have a binary response; the therapy either works or it doesn't, it is either safe or it isn't. Within populations there are some people for whom a particular therapy will not work. For others the product will be efficacious, and for some the result will be an adverse event. All of these outcomes have consequences. In particular, we must consider the over-riding impact of therapeutic failure.

There are many sources of variability in therapeutic response: genetics, a patient's underlying health, concurrent disease, concurrent therapy, or ontogeny. All can factor into a situation in which a therapy is ineffective or causes an adverse outcome. Of course, there is a popular perception that the FDA, other drug regulators, and industry are sitting on enormous data sets that are never considered and this accounts for serious misadventures after marketing. Recent high profile cases include concerns about Cisapride and nonsteroidal anti-inflammatory drugs. In general, this is a misperception on the part of the public and the media. What is required is more active drug safety studies both pre and post marketing. Such studies should be both epidemiologic and biological.

In spite of extensive premarketing studies it must be recognized that most new therapies are tested on either northern European or African American populations, although most of the world isn't northern European or African American.

If small molecule variability is problematic, biologicals and SEBs add a new dimension of complexity compounded by both age and indication creep. As has been noted, immunogenicity is a prime concern and we always think in the first instance about antibodies; however, for serious adverse events it is likely that T-cell function is more germane. People receiving small molecules or more complex biological products may form antibodies that cause hypersensitivity and that may or may not be relevant to other serious adverse events. T-cell activation is most certainly an equally important consequence. There are currently three competing theories concerning the pathophysiology of hypersensitivity to therapeutic products. We must consider how drugs are processed by the immune system, how T-cells react, and further knowledge is required about the body's mechanism for remembering previous exposures to biological molecules.

Because of all of these issues questions about SEBs are going to remain complex. Given the complexity of serious adverse events in response to small molecules, it is important to recognize the need to treat SEBs as new products. Permission for substitution of SEBs would be a bad idea in most cases.

Pharmacovigilance

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My previous experience in a contract research organization led me to carefully consider the advantages and disadvantages of generic products. To me, the only advantage that justifies the study of generic products and, I think, the only advantage to be seen for SEBs is cost relative to innovator products. If that is the case, then we must be very cautious in decisions about introduction of new products to replace existing validated therapies.

When an SEB is prescribed or dispensed we must ask who assumes liability. Is it going to be Health Canada accepting responsibility if something untoward happens? Is it going to be the people sitting on the formulary committee within a hospital? Is it the prescribing physician? Is it the dispensing pharmacist?

We have heard numerous comments about SEBs possibly being worse or more dangerous than or not as efficacious as the innovator product. Is it, however, possible that they are going to represent an improvement? I have seen many products introduced over recent decades that are much better, possess a better pharmacokinetic dissolution profile, or produce a more consistent therapeutic profile than the innovator compound. Why? Because new products, as well as old products made using new processes or equipment, are likely to demonstrate better pharmacokinetics and less variability in clinical effect.

If we consider substitution with SEBs, it is unrealistic to assume that by having some quick, efficient in vitro test or other form of testing of a very limited population, that we can pick up all aspects of toxicity or be able to manage the risks of substitution. I am very apprehensive about the degree of power or discretionary ability a test will need in order to really identify phenotypic subsets of responders to a new therapeutic agent. Dr. Rieder discussed genotypes, but what we are really attempting is to find the phenotype among patients that will identify those at an increased risk. What we would really like to achieve is identification a priori of patients who will be at risk on exposure to a product. Otherwise the risk benefit may be too high to permit widespread use of SEBs..

In dealing with small molecules we have faced difficult challenges in patient safety. For biological products, including SEBs, we cannot even be sure that we are giving exactly the same thing in the same way. We will need large pharmacovigilance programs and good risk management programs if we want to employ these products with the view that they are equivalent or even highly “similar” to the innovator products.

Legal Liability Issues

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Back in 2000 the Auditor General of Canada observed that “there was a wide range of safety risks associated with biologics.” She focused on contamination with adventitious agents, but this soon put the issues of biologics and SEBs as deserving of special attention on the radar screen.

The expression “the process is the product” is very true. There are at least three factors that contribute to product differences in the case of SEBs:

- the cell lines in which metabolic activities necessary to produce compounds that will become the biologic therapeutic product take place;
- the growth media in which the cell lines or micro-organisms used to produce the end products are grown; and
- the fermentation methods used in the production process and the harvesting, purification, and inactivation techniques employed.

Each of these factors can affect the end product in different and potentially significant ways.

For all of the reasons already discussed, there are unique potential liability concerns posed by SEBs, indeed by biologic therapeutic products in general. These issues should be of particular concern to:

- the doctors who prescribe the products;
- the pharmacists who dispense them;

- the various provincial insuring or publicly-funded reimbursement programs that list products on their public formularies; and,
- the regulators who approve these products as safe and effective for use in Canada.

On the latter point, the position of Health Canada as the Canadian regulator of therapeutic products has been clarified by a recent decision in Ontario. In the United States, the Food and Drug Administration is statutorily immunized against civil action for regulatory negligence. That has never been the case in Canada and it is still not the case in Canada. It is possible to name Health Canada as a defendant in an action if the agency fails to exercise “reasonable care” in approving a product for market. A litigant in a recent Ontario case involving a medical device named the regulator as a defendant in the action. The Court of Appeal for Ontario for various reasons found that, even though the statute didn’t specifically immunize the regulator, nevertheless, as a matter of public policy, the particular action would not be permitted to proceed against the regulator. I believe that a recent appeal to the Supreme Court of Canada has been refused.

It is probably safe to say that it would be found as fact that the average physician who prescribes biological drugs (innovator or follow-on products) ought to know that the SEB is less well-characterized, less well-defined, and less well-understood than the innovative product. If he or she prescribes that product, in my view, that fact might be used against the prescriber. There is recent case law in Canada to support the fact that simple approval by Health Canada of a product under the *Food and Drugs Act* may allow the product to be deemed safe and efficacious, but that fact alone is insufficient to insulate a prescriber from liability.

Are pharmacists liable if they substitute or interchange an SEB for a brand name or innovative product when the innovator has demonstrated efficacy, and has a lengthier safety profile and track record? The general rule in Canadian provinces is that pharmacists may interchange, or “must” interchange in some provinces, although in general, the pharmacist does not have the power to substitute. However, in Alberta and in British Columbia there is a move toward empowering the dispenser to make therapeutic substitutions. This is a matter of provincial law rather than federal.

Ontario legislation permits the designation of a product as interchangeable but a condition of such designation is that a drug must be deemed “bioequivalent”. At the moment it is unclear whether or not a SEB could be declared interchangeable under Ontario’s legislative definition. From today’s discussion, it seems that there is a very high barrier to the demonstration of unequivocal bioequivalence.

The irony is that under my interpretation of the legislation, the Ontario physician who actually prescribes an SEB would not be able to shelter under the protection of the (Ontario) *Drug Interchangeability and Dispensing Fee Act* because there was no interchange. The pharmacist is protected and this leaves us obligated to advise physicians that, for their own legal protection, they should never prescribe anything other than the innovator product. The decision to perform a substitution should be left to others who have been extended legal protection.

In British Columbia, pharmacists are permitted to adapt a prescription as of March 15th 2009. A pharmacist may dispense a drug contrary to the terms of a prescription if the action is intended to optimize the therapeutic outcome of treatment with the prescribed drug and meets all of the elements of a protocol for prescription adaptation. This, in effect, permits therapeutic substitution in British Columbia, although it would still be difficult to justify the action of substituting an SEB for an innovative biologic.

The situation concerning legal liability is highly dependent on specific legislation in place in each province as it relates to both physician and prescriber. There are remaining questions about the liability of the provincial government for either designating something as interchangeable or indeed requiring mandatory dispensing of the lower cost alternative in the absence of fully acceptable evidence on safety and efficacy.

It is early days for consideration of these challenging issues, many of which will need to be tested in the courts. It is certain that there will be litigation if there are any untoward incidents based on a clinical situation with some unique aspects with respect to prescribing or substitution of a SEBs.

Roundtable Consensus

- 1) Subsequent entry biologics, or biosimilars or follow-on biologics, are not generic replacements. They should be viewed as stand alone products; the model for regulatory approval of small molecule generic products should not apply to them. Agreement should be reached on a single name to describe these products and the preferred nomenclature from this roundtable would be subsequent entry biologics (SEBs).
- 2) SEBs should not be considered pharmaceutically or therapeutically equivalent to preceding products and mandatory substitution should not be recommended.
- 3) SEBs should not normally be deemed interchangeable; however, if a physician and an informed, consenting patient agree to interchange products, they should do so with full understanding of potential health risks and legal liabilities.
- 4) SEBs cannot be safely or effectively managed by non-physicians through automatic substitution.
- 5) Canada should follow the EMEA process with respect to SEBs. With suitable adaptation following expert review, the EMEA policies and practices could become the standard for Canadian regulatory practice.
- 6) Systems should be developed for proactive risk management, post market surveillance, and pharmacovigilance studies relevant to SEBs.
- 7) Science, industry, and regulatory approaches are evolving with respect to SEBs. The academic community needs to evolve a recognized subspecialization in product and patient safety relevant to these issues.
- 8) Given that specialized human resources in these fields are scarce, a more targeted approach to patient safety is needed. With respect to SEBs, immunogenicity would be an appropriate primary target.
- 9) There is a need for at least one international centre of expertise to be established independent from government and industry, and capable of developing and using appropriate criteria and statistical methods to support the conduct of long term comparability studies among SEBs.
- 10) From a Canadian perspective it should be recognized that there are numerous remaining issues to be addressed with respect to SEBs, including pharmacoeconomics and outcomes research, reimbursement policies, intellectual property protection, patent life, data protection, and market exclusivity policies. There are an equal number of unresolved medicolegal questions.