





DRAFT GUIDANCE FOR SPONSORS: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)

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Published by authority of the
Minister of Health



Draft Date	2008/01/30
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Health Products and Food Branch

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Available in Canada through
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Également disponible en français sous le titre :

Catalogue No. E
ISBN

FOREWORD

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. Alternate approaches to the principles and practices described in this document **may be** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant programme area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

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1.0 INTRODUCTION

1.1 Objective

Health Canada, the federal regulatory authority that evaluates the safety, efficacy, and quality of health products available in Canada, recognises that with the expiration of patents for biologic drugs, there will be the introduction of subsequent entry versions of biologic drugs. This document provides guidance to sponsors on information and regulatory requirements for subsequent entry biologic (SEB) products¹ in Canada.

1.2 Scope and application

The concept of a SEB applies to all biologic drug submissions in which the sponsor would, based on demonstrated similarity to a reference biologic product, rely in part on publicly available information from a previously approved biologic drug in order to present a reduced clinical package as part of the submission.

The demonstration of similarity depends upon detailed and comprehensive product characterization, therefore information requirements outlined within this document apply to biologic drugs that contain, as their active substances, well characterized proteins derived through modern biotechnological methods such as use of recombinant DNA and/or cell culture.

The following is additional criteria to determine the scope of eligible products:

- there exists a suitable reference biologic product that: a) was originally approved based on a complete data package; and b) has a suitable duration and volume of marketed use such that the demonstration of similarity will bring into relevance a substantial body of acceptable data dealing with safety and efficacy;
- the product can be well characterized by a set of modern analytical methods; and
- through extensive characterization and analysis, the biologic product can be judged similar to the reference biologic product by meeting an appropriate set of pre-determined criteria.

In this guidance document, “shall” is used to express a requirement, i.e., a provision that the user is obliged to satisfy in order to comply with the regulatory requirements; “should” is used to express a recommendation or that which is advised but not required; and “may” is

¹ A biologic product that would enter the market subsequent to, and ‘similar’ to, an approved innovator biologic, which would rely in part, on prior information regarding safety and efficacy that is deemed relevant due to the demonstration of similarity to a reference biologic product.

used to express an option or that which is permissible within the limits of the guidance document.

1.3 Policy statements

The following policy statements outline the fundamental concepts and principles constituting the basis of the regulatory framework for SEBs.

- 1.3.1 The principles within the existing regulatory frameworks for biologic, pharmaceutical, and generic pharmaceutical drugs shall be the basis for the regulatory framework for SEBs.
- 1.3.2 Where appropriate, the regulatory principles and practices for the regulation of generic pharmaceuticals shall be applicable to SEBs:
- SEBs should be eligible to apply for indication(s) within those granted to the reference biologic product and any claims made by the SEB shall be supported by suitable scientific data. However, each indication claimed by the SEB must be supported by scientific data.
 - The pharmaceutical form, strength, route of administration of the SEB shall be the same as that of the reference biologic product.
 - The chosen reference biologic product should be a product approved and marketed in Canada. Use of a reference biologic product with market experience in other jurisdictions may be considered on request of the Minister or on recommendation by the Minister.
 - All the laws, patent and intellectual property principles outlined within the *Patent Act*, *Food and Drug Regulations (Data Protection)*, and *Patented Medicines Notice of Compliance Regulations* are applicable to SEBs.
- 1.3.3 Eligibility for the SEB pathway hinges on the ability to demonstrate similarity to a suitable reference biologic product. Products employing clearly different approaches to manufacture than the reference biologic product (for example, use of transgenic organisms versus cell culture, or use of eukaryotic versus prokaryotic host cell) will not be eligible for the regulatory pathway for SEBs. Any use of a non-analogous host cell line or change to the culture conditions (cell monolayer versus suspension) would require a strong rationale in order to be considered eligible.
- 1.3.4 The *Food and Drug Regulations* will be amended to provide a comprehensive legal basis for the regulatory framework for SEBs. In the interim, the regulatory pathway for new biologic drugs affords the appropriate flexibility for SEBs.
- 1.3.5 SEBs are not “generic biologics”. Thus many characteristics associated with the approval process and marketed use for generic drugs do not apply.
- 1.3.6 Approval of a product through the SEB pathway is not an indication that the SEB may be automatically substituted with its reference biologic product. Substitutability with the reference biologic product may be granted separate from and/or subsequent to market

authorization of a SEB. The decision for substitutability with the reference biologic product shall be based on science.

- 1.3.7 Regulatory decision making regarding SEBs shall be based on science and regulatory principles existing within the *Food and Drugs Act* and *Regulations*.
- 1.3.8 Guidance documents are planned that will further elaborate information and data requirements for specific classes of SEBs.
- 1.3.9 Once a Notice of Compliance (NOC) is granted, the SEB is a new biologic product and regulated like any other new biologic product.
- 1.3.10 A SEB cannot be used as a reference biologic product because a reference biologic product is a biologic product already authorized on the basis of a complete quality and clinical data package.
- 1.3.11 The regulatory framework for SEBs is not intended to be a disincentive to innovation nor to become unduly burdensome for SEB sponsors.

1.4 **Definitions**

Biologic drug

- Biologics are drugs listed on Schedule D to the *Food and Drugs Act*. Schedule D lists individual products (such as “insulin”), product classes (such as “immunizing agents”), references to particular sources (such as “drugs, other than antibiotics, prepared from microorganisms”), and methodology (such as “drugs obtained by recombinant DNA procedures”).
- Biologic products are derived through the metabolic activity of living organisms and tend to be more variable and structurally complex than chemically synthesized drugs. Biologics are manufactured from animals, microorganisms, or through the use of animals or microorganisms.

Biosimilar or similar biological medicinal product

- The term “biosimilar” is used as a short designation for “similar biological medicinal products”. A new biological medicinal product is one claimed to be “similar” to an approved reference medicinal product, marketed by an independent applicant and is subject to all applicable data protection periods and/or intellectual property rights for the originator product. The requirements for the Marketing Authorization Applications for biosimilars are based on the demonstration of the similar nature of the two biological medicinal products (biosimilar versus reference biologic product) and require comparative quality, non-clinical, and clinical studies to demonstrate safety and efficacy. For details, see <http://www.emea.eu.int/pdfs/human/biosimilar/043704en.pdf>.

Follow-on biologic

- The term “follow-on biologic” is used to describe similar biological medicinal products. The term “follow-on protein products” generally refers to protein and peptide products that are intended to be sufficiently similar to a product already approved or licensed, permitting the

applicant to rely for approval on certain existing scientific knowledge about the safety and effectiveness of the approved protein product. (Taken from: <http://www.fda.gov/cder/drug/infopage/somatropin/qa.htm>).

Interchangeability

- A product is interchangeable with another if both products are approved for the same indication, and can be used for the said indication. For interchangeable products, one or the other can be used (prescribed) but these products can not be substituted with one another during a treatment period. Hence Interchangeability does not imply substitutability.

Subsequent Entry Biologic (SEB)

- A biologic product that would enter the market subsequent to, and ‘similar’ to an approved innovator biologic, and would rely in part on prior information regarding safety and efficacy that is deemed relevant due to the demonstration of similarity to a reference biologic product.

Similarity

- If a company chooses to develop a new biological medicinal product claimed to be “similar” to a reference medicinal product, comparative studies are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product (see <http://www.emea.eu.int/pdfs/human/biosimilar/043704en.pdf>)

Specification

- A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. “Conformance to specification” means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval. (see ICH Q6B, <http://www.ich.org/LOB/media/MEDIA432.pdf>)

Substitutability

- Two products are substitutable with each other if they can both be used in lieu of the other during within the same treatment period. Substitutable products are interchangeable with each other. Cross-over studies are required to demonstrate substitutability.

Reference Biologic Product

- A biologic product already authorized on the basis of a complete quality and clinical data package chosen as a reference product by the manufacturer of the SEB.

Abbreviations and Acronyms

ADR = Adverse Drug Reaction
BGTD = Biologics and Genetic Therapies Directorate
C&M = Chemistry and Manufacturing
CTA = Clinical Trial Application
CTD = Common Technical Document
HPFB = Health Products and Food Branch
MOU = Memorandum of Understanding
NDS = New Drug Submission
NOC = Notice of Compliance
PK/PD = pharmacokinetic/pharmacodynamic
PM = Product Monograph
PSUR = Periodic Safety Update Reports
QOS = Quality Overall Summary
SEB = Subsequent Entry Biologic

1.5 Background

The availability of generic versions of pharmaceutical drugs tends to contribute significantly to reduction in prices for those drugs and also increase access to alternative products for patients. Biologic drugs have contributed greatly to the health of Canadians through their use as treatments and in the management of a various complex diseases and medical conditions. The expiration of patents and/or data protection for some biologic drugs is ushering in an era of a new group of biologic drugs, which would be subsequent entry versions of authorized biologic products. These products would be seeking market authorization by relying on publicly available data and information from innovator biologic drugs whose patents and data protection periods have ended.

Biologic drugs, unlike pharmaceutical drugs, are derived through the metabolic activity of living organisms and are more variable and structurally complex. They are manufactured from animals, microorganisms, or through the use of animals or microorganisms. Biologics are typically labile and sensitive to changes in manufacturing processes. Biological source materials, production cells, or their fermentation media can present risks, such as the initial presence of pathogens or the growth of adventitious agents such as viruses. Because of this, careful attention is paid to raw material controls, viral/bacterial inactivation, or clearance during product purification and product testing. Changes to source materials, manufacturing processes, equipment, or facilities can result in significant unexpected changes to the intermediate and/or final product. Thus the phrase “the process is the product” is often used in reference to biologics, and much effort is focussed on manufacturing control and quality assurance.

The term “subsequent entry biologic” (SEB) is used by Health Canada to describe a biologic

product that would be similar to and would enter the market subsequent to an approved innovator biologic. By definition, an SEB relies on publicly available information from the reference drug and an approval could be granted based on reduced amount of clinical information tailored to each class of products and/or case. The term, SEB, was chosen as an alternative to “biogeneric” to clearly indicate a distinction between the regulatory process for SEBs and that which is currently used for generic pharmaceutical drugs.

It is generally accepted that the principles and procedures for a standard generic approach to the approval of generic pharmaceutical drugs (for example, demonstration of bioequivalence to a reference biologic product using bioequivalence studies) are unacceptable for biologics. Hence a full complement of quality information will be provided to support an SEB application. The concept of granting approval to a new biologic drug based on reduced clinical information would be based on demonstrated similarity between the SEB and the chosen reference biologic. The level and extent of clinical data required to support an application will depend on the level of demonstrated similarity between the SEB and the reference biologic product.

The Biologics and Genetic Therapies Directorate (BGTD) within the Health Products and Food Branch (HPFB) of Health Canada is the regulator of biologic drugs. BGTD provides regulatory oversight for biologics with its Lot Release Program, On-site Evaluation Program, comprehensive safety and quality reviews of biologic submissions, extensive scientific capacity, and expertise appropriate for regulating biologic drugs.

2.0 GUIDANCE FOR IMPLEMENTATION

2.1 General

2.1.1 Regulatory pathways

The New Drug Submission (NDS) pathway will be amended to provide clear regulatory pathways for SEBs enabling authorizations based on demonstrated similarity to the chosen reference biologic product.

2.1.2 Indications

The indications granted to a SEB shall be based on data provided by the sponsor. Hence an SEB shall not be automatically be granted all the indications of the reference biologic product. Where the mechanism of action strongly supports an indication, a SEB sponsor would be granted additional indications for which data has not been provided. Factors to be considered in granting indications for an SEB application, while on a case-by-case basis, would depend on the product, the level of reliance on the reference biologic product in the development programme for the product, the demonstrated level of similarity between the SEB and the reference biologic product, and the availability of post-market information.

2.1.3 Reference biologic product

The following provides general guidance on choice of reference biologic product in a development programme for an SEB:

- The reference biologic product should be a biologic product approved 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 or on recommendation by the Minister. Biologic products approved by regulatory agencies which have Memoranda of Understanding (MOUs) and information sharing agreements with HPFB have a better chance of being approved as suitable reference biologic products. Consultation with BGTD is required for use of a non-Canadian approved reference biologic product.
- The chosen reference biologic product shall be used throughout the studies supporting the safety, quality, and efficacy of the product (i.e. in the developmental programme for the SEB).
- The active substance of the reference biologic product and the SEB must be similar.
- A SEB should not be used as a reference biologic product.
- The chosen reference biologic product should have a suitable duration and volume of marketed use such that the demonstration of similarity will bring into relevance a substantial body of acceptable data dealing with safety and efficacy.

2.1.4 Review time

The target time for review of an SEB shall be the same as that for a NDS.

2.1.5 Consultation with Health Canada

Sponsors of SEB products are encouraged to consult with BGTD at any stage of the developmental process for an SEB.

2.2 Information requirements for Clinical Trial Applications (CTA)

Clinical trials involving SEBs are subject to Part C, Division 5 of the *Food and Drug Regulations*, which outlines the requirements applicable to the sale and importation of drugs for use in human clinical trials in Canada. Clinical Trial Applications (CTAs) should be submitted in accordance with Health Canada's *Guidance for Clinical Trial Sponsors: Clinical Trial Applications* and the *Clinical Trials Manual*.

Clinical trials may be conducted on authorized and unauthorized products. Sponsors need to include all information identified in C.05.005 of the *Food and Drug Regulations* in their application for authorization.

Studies are required to demonstrate that the SEB is similar with respect to safety, quality, and

efficacy to the reference biologic product.

Studies to demonstrate similarity with respect to quality are additional to what is normally required for a new biologic.

2.3 Information requirements for New Drug Submissions (NDS)

Part C, Division 8 of the *Food and Drug Regulations* sets out the requirements for the sale of new drugs in Canada, and prohibits the sale of new drugs unless the manufacturer has filed a submission that is satisfactory to the Minister. Sections C.08.002 and C.08.002.1 of the *Food and Drug Regulations* outline the requirements for a New Drug Submission (NDS). Supplemental New Drug Submissions (SNDS), found in C.08.003 of the *Food and Drug Regulations* are not considered differently in the case of SEBs when compared to other biologic products.

2.3.1 Quality requirements

In addition to a full chemistry and manufacturing (C&M) data package that would be required for a standard new biologic drug, the SEB package must provide extensive data focussed on the demonstration of comparability/similarity, including extensive side-by-side characterization of the SEB and the chosen reference biologic product.

If the reference drug substance used for characterization is isolated from a formulated reference drug product, additional studies must demonstrate that the drug substance is not changed by the isolation process. One approach to qualifying the isolation process would be to use the process on the formulated SEB drug product and compare the isolated SEB drug substance to the SEB drug substance obtained prior to any further manufacturing.

2.3.1.1 Considerations for the comparability exercise

- The goal of the comparability exercise is to ascertain if the SEB and the chosen reference biologic product are comparable in terms of quality, safety, and efficacy. To meet this goal, the product should be evaluated at the process steps most appropriate to detect a change in the quality attributes. This may entail evaluating both the drug substance and the drug product. For a SEB, comparability should be primarily deduced from comprehensive quality studies, but may sometimes need to be supported by comparability bridging studies. The extent of the studies necessary to demonstrate comparability will depend on:
 - ▶ The availability of suitable analytical techniques to detect potential product modifications and the results of these studies; and
 - ▶ The relationship between quality attributes and safety and efficacy, based on overall non-clinical and clinical experience.
- When considering the comparability of products, the manufacturer should

evaluate, for example:

- ▶ Relevant physicochemical and biological characterisation data regarding quality attributes;
 - ▶ Results from analysis of relevant samples from the appropriate stages of the manufacturing process (i.e. drug substance, and drug product);
 - ▶ Stability data, including those generated from accelerated or stress conditions, to provide insight into potential product differences in the degradation pathways of the product and, hence, potential differences in product-related substances and product-related impurities;
 - ▶ Batches used for demonstration of manufacturing consistency.
- In addition to evaluating the data, manufacturers should also consider if the results provide insights regarding:
 - ▶ Critical control points in the manufacturing process that affect product characteristics;
 - ▶ Adequacy of the in-process controls including critical control points and in-process testing: in-process controls for the SEB should be confirmed, modified, or created, as appropriate, to maintain the quality of the product;
 - ▶ Need for supplement data derived from non-clinical or clinical characteristics of the drug product.

2.3.1.2 Quality considerations

Analytical Techniques

- The battery of tests for the comparability exercise should be carefully selected and optimised to maximise the potential for detecting relevant differences in the quality attributes of the SEB and the reference biologic product. To address the full range of physicochemical properties or biological activities, it may be appropriate to apply more than one analytical procedure to evaluate the same quality attribute (i.e. molecular weight, impurities, secondary/tertiary structures). In such cases, each method should employ different physicochemical or biological principles to collect data for the same parameter to maximise the possibility that differences in the SEB relative to the reference biologic product may be detected.
- It can be difficult to ensure that the set of analytical procedures originally chosen for the SEB will be able to detect differences from the reference biologic product due to the limitations of the assays (i.e. precision, specificity, and detection limit) and the complexity of some products due to molecular heterogeneity. Consequently, the manufacturer should determine:
 - ▶ Whether or not existing tests remain appropriate for their intended use or should be modified. For example, when there is a different impurity profile in the host cell proteins, manufacturers should confirm that the test

used to quantitate these impurities is still suitable for its intended purpose. It may be appropriate to modify the existing test to detect the new impurities;

- ▶ The need to add new tests as a result of differences in quality attributes that the existing methods are not capable of measuring. That is, when specific changes in quality attributes are expected as a result of a process difference (i.e. different raw material or different chromatographic purification step), it may be appropriate to develop new analytical procedures, i.e., to employ additional analytical techniques above and beyond those used previously for characterisation or routine testing.
- ▶ Whether the results from the comparability studies should cause reflection regarding the current tests used for the SEB and perhaps influence changes.
- Ideally, an early decision on the choice of reference biologic product may allow selection of the most appropriate set of analytical procedures for development of the SEB and the eventual comparability exercise.
- The measurement of quality attributes in characterisation studies does not necessarily entail the use of validated assays, but the assays should be scientifically sound and provide results that are reliable. Those methods used to measure quality attributes for batch release should be validated in accordance with ICH guidelines (ICH Q2A, Q2B, Q5C, Q6B), as appropriate.

Characterisation

- Characterisation of a biotechnological/biological product by appropriate techniques, as described in ICH Q6B, includes the determination of physicochemical properties, biological activity, immunochemical properties (if any), purity, impurities, contaminants, and quantity.
- When conducting a comparability study, a complete side-by-side characterisation is generally warranted to directly compare the SEB and the reference biologic product. However, additional characterisation may be indicated in some cases. For example, when the product characterisation profiles differ, the significance of these differences should be evaluated.

Each of the following criteria should be considered as a key point in the conduct of the comparability exercise:

Physicochemical Properties

- The manufacturer should consider the concept of the desired product (and its variants) as defined in ICH Q6B when designing and conducting a comparability exercise. The complexity of the molecular entity with respect to the degree of molecular heterogeneity should also be considered. Manufacturers should attempt to determine that higher order structure (secondary, tertiary, and quaternary

structure) is comparable. If the appropriate higher order structural information cannot be obtained, a relevant biological activity assay (see biological activity below) could indicate a correct conformational structure.

Biological Activity

- Biological assay results can serve multiple purposes in the confirmation of product quality attributes that are useful for characterisation and batch analysis, and in some cases, could serve as a link to clinical activity. The manufacturer should consider the limitations of biological assays, such as high variability, that may prevent detection of differences between two similar products.
- In cases where the biological assay also serves as a complement to physicochemical analysis, for example, as a surrogate assay for higher order structure, the use of a relevant biological assay with appropriate precision and accuracy may provide a suitable approach to confirm that a change in specific higher order structure has not occurred. Where physicochemical or biological assays are not considered adequate to confirm that the higher order structure is maintained, data from non-clinical or clinical studies may be supportive. However, too much reliance on such studies may indicate that the regulatory pathway for SEBs is not appropriate.
- When the products being compared have multiple biological activities, manufacturers should perform a set of relevant functional assays designed to evaluate the range of activities. For example, certain proteins possess multiple functional domains that express enzymatic and receptor mediated activities. In such situations, manufacturers should evaluate all relevant functional activities.
- Where one or more of the multiple activities are not sufficiently correlated with clinical safety or efficacy or if the mechanism of action is not understood, the manufacturer should justify that non-clinical or clinical activity of the SEB is not compromised.

Immunochemical Properties

- When immunochemical properties are part of the characterisation (for example, for antibodies or antibody-based products), the manufacturer should confirm that the SEB is comparable to the reference biologic product in terms of the specific properties.

Purity, Impurities, and Contaminants

- The combination of analytical procedures selected should provide data to evaluate whether there is a difference in purity profile in terms of the SEB.
- If differences are observed in the purity and impurity profiles of the SEB relative to the reference biologic product, the differences should be evaluated to assess their potential impact on safety and efficacy. Where the SEB exhibits different impurities, those impurities should be identified and characterised when possible.

Depending on the impurity type and amount, the conduct of non-clinical and clinical studies will help to confirm that there is no adverse impact on safety or efficacy of the SEB.

- Contaminants should be strictly avoided and/or suitably controlled with appropriate in-process acceptance criteria or action limits for drug substance or drug product. New contaminants should be evaluated to assess their potential impact on the quality, safety, and efficacy of the product.

Specifications

- The tests and analytical procedures chosen to define drug substance or drug product specifications alone are not considered adequate to assess product differences since they are chosen to confirm the routine quality of the product rather than to fully characterise it. The manufacturer should confirm that the specifications chosen for the SEB are appropriate to ensure product quality.

Stability

- For certain manufacturing processes, even slight differences in the production procedures used for the SEB and reference biologic product may cause differences in the stability of the products.
- Proteins are frequently sensitive to changes, such as those made to buffer composition, processing and holding conditions, and the use of organic solvents. Therefore, real-time/real temperature, side-by-side stability studies should be conducted on SEB and reference biologic product products that have been matched, as far as possible, with respect to date of manufacture.
- Such stability studies may be able to detect subtle differences between the SEB and reference biologic product that are not readily detectable by the characterisation studies. For example, the presence of trace amounts of a protease may only be detected by product degradation that occurs over an extended time period. Or in some cases, divalent ions leached from the container closure system may change the stability profile because of the activation of trace proteases.
- Accelerated and stress stability studies are often useful tools to establish degradation profiles and can therefore contribute to a direct comparison of SEB and reference biologic product. The results thus obtained may show product differences that warrant additional evaluation, and also identify conditions indicating that additional controls should be employed in the manufacturing process and during storage of the SEB to eliminate these unexpected differences. Appropriate studies should be considered to confirm that suitable storage conditions and controls are selected.
- ICH Q5C and Q1A(R) should be consulted to determine the conditions for stability studies that provide relevant data to be compared before and after a change.

2.3.1.3 Manufacturing process considerations

A well-defined manufacturing process with its associated process controls assures that an acceptable product is produced on a consistent basis.

- Approaches to determining the impact of any process differences will vary with respect to the specific process, the product, the extent of the manufacturer's knowledge of and experience with the process, and development data generated.
- Where details of the manufacturing process for the reference biologic product are known and can be compared with those for the SEB, such an analysis may help identify which tests should be performed during the comparability exercise.

2.3.1.4 Determination of comparability/similarity

- The demonstration of comparability/similarity does not necessarily mean that the quality attributes of the two products being compared are identical, but that they are highly similar with two consequences: 1) that the existing knowledge of both products is sufficient to predict that any differences in quality attributes should have no adverse impact upon safety or efficacy of the SEB; and 2) that non-clinical and clinical data previously generated with the reference biologic product is relevant to the SEB.
- A final determination of comparability/similarity can be based on a combination of analytical testing, biological assays, and non-clinical and clinical data. However, to be considered a SEB, the weight of evidence should be provided by the analytical and biological characterization.

In situations where:

- ▶ i) the analytical procedures used are not sufficient to discern relevant differences that can impact the safety and efficacy of the product; or
- ▶ ii) the relationship between specific quality attributes and safety and efficacy has not been established, and differences between quality attributes of the SEB and the reference biologic product are likely to be observed;

therefore, non-clinical and clinical studies are expected to contribute significantly to a potential determination of comparability/similarity, the regulatory pathway for SEBs may not be appropriate.

2.3.1.5 Organization of data

- The assessment of comparability/similarity should be organized in the Common Technical Document (CTD) as a distinct collection of data in module 3 with an associated section in the Quality Overall Summary (QOS) and appropriate cross-references.

2.3.1.6 Changes post-approval

- Once granted a NOC, a SEB is considered to be a stand-alone product with associated regulatory requirements. For any changes to the manufacturing process that warrant a demonstration of comparability, the products to be compared will be the pre-change and post-change versions of the SEB. Comparisons with the original reference biologic product are not required.

2.3.2 Clinical requirements

2.3.2.1 General

- Non-clinical and clinical requirements outlined for SEB submissions in this guidance document are applicable to SEBs that have been demonstrated to be similar to the chosen reference biologic product, based on results of the biocomparability exercises from C&M perspective. When comparability of an SEB to the reference biologic product cannot be adequately established, the submission for such a product should be filed as a full NDS with complete non-clinical and clinical data.
- The information in this section provides only general guidance on non-clinical and clinical data requirements for SEBs containing well characterized proteins derived through modern biotechnological methods.
- The requirements for the drug classes (for example, insulin, growth hormone) may vary. The requirements may also vary depending on various clinical parameters such as therapeutic index, the type and number of indications for which SEB sponsors apply.
- Proposed indications for SEBs must be identical or within the scope of the indications granted to the reference biologic product. Clinical studies should be provided for each indication being sought. In some cases, comparative pharmacokinetic/pharmacodynamic (PK/PD) data to bridge two or more indications may be sufficient. If extrapolation of results from clinical studies for one indication to one or more different indications can be justified based on mechanism of action, pathophysiological mechanism of the diseases or conditions involved and clinical experiences of the reference biologic product, a rationale based on scientific arguments, not only regulatory, must be provided to adequately address the data extrapolation.
- The reference biologic product should be the same for the C&M studies and the pre-clinical/clinical studies.
- The final SEB product should be used in pre-clinical and clinical studies. In some instances, C&M changes introduced in the clinical development phase could be bridged by additional PK/PD data and/or clinical data. Consult BGTD for additional guidance.

2.3.2.2 Non-clinical studies

- Non-clinical studies should be conducted prior to the initiation of any clinical

studies. These studies should be comparative and aim to detect differences between the SEB and the reference biologic product.

In vitro studies:

- ▶ Receptor binding study or cell-based assay should be conducted.

In vivo studies:

- ▶ Animal pharmacodynamic studies relevant to the clinical applications;
 - ▶ At least one repeat dose toxicity study, including characterization of toxicokinetic parameters, should be conducted in a relevant species. The duration should be sufficiently long so that differences in toxicity or immune response between the SEB and the reference biologic product can be detected;
 - ▶ Relevant safety observations (for example, local tolerance) can be made during the same toxicity study.
- Other toxicological studies, including safety pharmacology, reproductive toxicology, mutagenicity and carcinogenicity studies are not generally required for a SEB submission unless warranted by the results from the repeated toxicological studies.

2.3.2.3 Clinical studies

Pharmacokinetic studies

- Comparative pharmacokinetic studies should be conducted to demonstrate the similarities in pharmacokinetic (PK) characteristics between SEB and the reference biologic product.
- The designs of comparative bioavailability studies (single dose study versus multiple dose study, cross-over versus parallel study) should take the following factors into considerations: half-life, linearity of PK parameters, where applicable the endogenous level and diurnal variations of the protein under study, production of neutralizing antibody, conditions and diseases to be treated, and indications for which the SEB sponsor is applying. Results from healthy subjects may not adequately reflect the PK parameters in the patient population where the product is indicated. Therefore, it is best to conduct the studies in the relevant patient population. Dose(s) used in the PK studies should be within the therapeutic dosing range specified in the Product Monograph (PM) of the reference biologic product.
- The principles of study design and statistical methods outlined in the TPD's "*Conduct and Analysis of Bioavailability and Bioequivalence Studies – Part A*" should be used as a general guidance for comparing and analysing similarity of the pharmacokinetics between the SEB and the reference biologic product. PK parameters should not be limited to parameters reflecting absorption only. Differences in elimination (clearance and terminal half-life) should be compared as well. No data or patients should be excluded from the analysis unless it is for to compliance or safety (clinical) reasons.

- Acceptable criteria for the similarity in comparative pharmacokinetics between the SEB and the reference biologic product should be defined prior to the initiation of study, taking into consideration known PK parameters and their variations, assay methodologies, safety and efficacy of the reference biologic product and SEB products. Criteria for the comparative bioavailability studies for generic pharmaceuticals, outlined in *Guideline A* are desirable and are achievable in comparative PK studies of SEBs. When such a criteria is not met, a discussion should be provided on its implication on the clinical efficacy, in conjunction with efficacy data obtained from the comparative clinical trials.

Pharmacodynamic studies

- Parameters should be clinically relevant or a surrogate marker which is clinically validated. The pharmacodynamic (PD) study may be combined with a PK study and the PK/PD relationship can be characterized. PD studies should be comparative in nature.

Clinical efficacy and safety trials

- Comparative clinical trials are required to demonstrate the similarity in efficacy and safety profiles between the SEB and the reference biologic product. The design of the studies and the clinical comparability margins are important and should be given careful consideration and justified on clinical grounds.
- Safety data from sufficient number of patients and sufficient study duration should be provided to compare the nature, severity, and frequency of adverse reactions between the SEB and the reference biologic product. Efforts should be made to ensure that comparative clinical studies have the statistical power to detect major safety differences..
- The immunogenicity of the SEB shall be tested using state of the art methods from both efficacy and safety perspectives.
- A written rationale on the strategy for testing immunogenicity should be provided. Assay methods should be validated and be able to characterize antibody content (concentration or titre), neutralizing antibody and cross-reactivity.
- When the neutralizing antibody is detected from subjects in PK/PD studies, the impact of the antibody on PK/PD parameters should be analyzed. When the neutralizing antibody is detected in patients enrolled in the comparative clinical trials, further assessment of efficacy and safety of the SEB from these patients should be conducted.
- Any post-market risk management plan should include detailed information of a systematic testing plan for monitoring immunogenicity of the SEBs post-market.

2.3.2.4 Post market requirements

- A post-market safety surveillance plan should be presented prior to issuance of marketing authorization and it should be implemented post-market. The

surveillance plan should be designed to monitor and detect both known inherent safety concerns and potentially unknown safety problems that may have resulted from the impurity profile of an SEB.

- Periodic safety update reports (PSURs) of SEBs should be submitted and evaluation of benefit/risk of the SEB post-market should be discussed.

2.4 Information required for Supplementary New Drug Submissions (SNDS)

2.4.1 Information required for continuous product monitoring and post-market surveillance activities

- Adverse Drug Reaction (ADR) Reporting is required in the post-market under section C.01.016 of the *Food and Drug Regulations*: any ADR that is reported requires the manufacturer of that drug to submit all information with respect to that report within 15 days after receiving the information. Furthermore, on an annual basis or as requested by the Director, the manufacturer will conduct a concise, critical analysis of the adverse drug reactions and serious adverse drug reactions after such an occurrence. After an analysis, the Director may request written summary reports where safety is questionable.
- At any time after a NOC is issued, the authority to suspend such an authorization is set out in C.08.006. The Minister may, by notice to a manufacturer, suspend, for a definite or indefinite period, a NOC issued to that manufacturer in respect of a NDS if the Minister considers that the drug is not safe for the use represented in the submission, as shown by evidence obtained from clinical or other experience or tests by new methods.

2.5 Labelling requirements (Product Monograph)

Unlike generic pharmaceuticals, the sponsor of a SEB will not be able to utilize the PM of the reference biologic product. A PM for the SEB will have to be developed as outlined in the guidance document for PM.

2.6 Harmonization with other international regulators

It is Health Canada's intention to harmonize as much as possible with other competent regulators and international organizations such as the World Health Organization (WHO) and the International Conference of Harmonization (ICH). Hence Health Canada will be adapting suitable definitions, terminology, and applicable guidance documents.

3.0 APPENDICES