





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



Published by authority of the
Minister of Health



Draft Date	2010/03/05
------------	------------

Health Products and Food Branch

<p>Our mission is to help the people of Canada maintain and improve their health.</p> <p><i>Health Canada</i></p>	<p>The Health Products and Food Branch's (HPFB) mandate is to take an integrated approach to managing the health-related risks and benefits of health products and food by:</p> <ul style="list-style-type: none"> • minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. <p><i>Health Products and Food Branch</i></p>
-------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

© Minister of Public Works and Government Services Canada 2008

Available in Canada through
 Health Canada - Publications
 Brooke Claxton Building, A.L. #0913A
 Tunney's Pasture
 Ottawa, Ontario
 K1A 0K9

Tel: (613) 954-5995
 Fax: (613) 941-5366

Également disponible en français sous le titre : LIGNES DIRECTRICES À L'INTENTION DES PROMOTEURS: Exigences en matière de renseignements et de présentation relatives aux produits biologiques ultérieurs (PBU)

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.

TABLE OF CONTENTS

1.0	INTRODUCTION	- 1 -
1.1	Objective.....	- 1 -
1.2	Scope and application.....	- 1 -
1.3	Policy statements.....	- 2 -
1.4	Definitions.....	- 2 -
1.5	Background.....	- 3 -
2.0	GUIDANCE FOR IMPLEMENTATION	- 4 -
2.1	General.....	- 4 -
2.1.1	<i>Applicable Regulations</i>	- 4 -
2.1.2	<i>Patents, Intellectual Property, and Data Protection</i>	- 5 -
2.1.3	<i>Reference biologic drug</i>	- 5 -
2.1.4	<i>Review time</i>	- 6 -
2.1.5	<i>Consultation with Health Canada</i>	- 6 -
2.2	Information requirements for Clinical Trial Applications (CTA).....	- 6 -
2.3	Information requirements for New Drug Submissions (NDS).....	- 7 -
2.3.1	<i>Quality information</i>	- 7 -
2.3.2	<i>Non-clinical and Clinical Information</i>	- 12 -
2.3.3	<i>Risk Management Plan (RMP)</i>	- 16 -
2.4	Post-Market Requirements.....	- 16 -
2.4.1	<i>Adverse Drug Reaction (ADR) Reporting</i>	- 16 -
2.4.2	<i>Periodic Safety Update Reports (PSURs)</i>	- 16 -
2.4.3	<i>Suspension or revocation of NOC</i>	- 16 -
2.5	Labelling requirements (Product Monograph).....	- 17 -
2.6	Harmonization with other international regulators.....	- 17 -

1.0 INTRODUCTION

Health Canada, the federal regulatory authority that evaluates the safety, efficacy, and quality of drugs available in Canada, recognises that with the expiration of patents for biologic drugs, manufacturers may be interested in pursuing subsequent entry versions of these biologic drugs.

1.1 Objective

The objective of this document is to provide guidance to sponsors to enable them to satisfy the information and regulatory requirements under the *Food and Drugs Act* and *Regulations* for the authorization of subsequent entry biologics (SEBs) in Canada.

1.2 Scope and application

The concept of an SEB applies to all biologic drug submissions where the sponsor seeks authorization for sale based on demonstrated similarity to a previously approved biologic drug and relies, in part, on prior information regarding that biologic drug in order to present a reduced clinical and non-clinical package as part of the submission.

The following are additional criteria to determine the scope of products that will be eligible to be authorized as SEBs:

- a suitable reference biologic drug exists that: a) was originally authorized for sale based on a complete data package; and b) has significant safety and efficacy data accumulated such that the demonstration of similarity will bring into relevance a substantial body of reliable data;
- the product (i.e., SEB) can be well characterized by a set of modern analytical methods; and
- the SEB, through extensive characterization and analysis, can be judged similar to the reference biologic drug by meeting an appropriate set of pre-determined criteria.

Products employing clearly different approaches to manufacture than the reference biologic drug may not be suitable for authorization as SEBs.

The demonstration of similarity depends upon detailed and comprehensive product characterization. The guidance applies 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.

1.3 Policy statements

The following statements outline the fundamental concepts and principles of the regulatory framework for SEBs:

- 1.3.1 The sponsor is responsible for providing the necessary evidence to support all aspects of an application for authorization.
- 1.3.2 Regulatory decisions regarding SEBs will be based on the *Food and Drugs Act* and *Regulations*. The concepts and scientific and regulatory principles within the existing regulatory frameworks for biologic, pharmaceutical, and generic pharmaceutical drugs are used as the basis for the regulatory framework for SEBs.
- 1.3.3 The basis for accepting a reduced non-clinical and clinical data package for an SEB hinges on demonstrated similarity between the SEB and the suitable reference biologic drug.
- 1.3.4 SEBs are not “generic biologics” and many characteristics associated with the authorization process and marketed use for generic pharmaceutical drugs do not apply. Authorization of an SEB is not a declaration of pharmaceutical or therapeutic equivalence to the reference biologic drug.
- 1.3.5 An SEB submission involves a comparison to another product. Hence all SEBs are subject to the laws, and patent and intellectual property principles outlined within the *Food and Drug Regulations (Data Protection)*, *Patented Medicines (Notice of Compliance) Regulations*, and the *Patent Act*.
- 1.3.6 Once a Notice of Compliance (NOC) is issued, the SEB is a new biologic drug and regulated accordingly. However, an SEB should not be used as a reference biologic drug for another SEB submission.

1.4 Definitions

Biologic drug (Médicament biologique)

A drug listed in 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 drugs are derived through the metabolic activity of living organisms and tend to be significantly more variable and structurally complex than chemically synthesized drugs.

Subsequent Entry Biologic (SEB) (Produit biologique ultérieur (PBU))

A biologic drug that enters the market subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug. An SEB relies in part on prior information regarding safety and efficacy that is deemed relevant due to the demonstration of

similarity to the reference biologic drug and which influences the amount and type of original data required.

Note: A product of this type is referred to as similar biological medicinal product (biosimilar) in the European Union and follow-on protein product in the United States of America.

Specification (Spécification)

A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. A specification establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform in order 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 authorized by regulatory authorities as conditions of approval for sale.

Reference biologic drug (Médicament biologique de référence)

A biologic drug authorized on the basis of a complete quality, non-clinical, and clinical data package, to which an SEB is compared in studies to demonstrate similarity.

Note: In appropriate circumstances, a biologic drug that is not authorized for sale in Canada may be used as a reference biologic drug (see section 2.1.3.1)

Abbreviations and Acronyms

ADR = Adverse Drug Reaction
AUC = Area Under the Curve
BGTD = Biologics and Genetic Therapies Directorate
C&M = Chemistry and Manufacturing
CTA = Clinical Trial Application
CTD = Common Technical Document
ICH = International Conference on Harmonisation
NDS = New Drug Submission
NOC = Notice of Compliance
PK/PD = pharmacokinetic/pharmacodynamic
PM = Product Monograph
PSUR = Periodic Safety Update Reports
PvP = Pharmacovigilance Plan
RMP = Risk Management Plan
SEB = Subsequent Entry Biologic

1.5 Background

Biologic drugs have contributed to the health of Canadians through their use as treatments in the management of various complex diseases and medical conditions. The expiration of patents and/or data protection for some biologic drugs is creating opportunities for subsequent entry versions of these biologic drugs. Sponsors may seek market authorization by relying partially on available information about a biologic drug authorized for sale in Canada.

Biologic drugs, unlike pharmaceutical drugs which are synthesized, are derived through the metabolic activity of living organisms and are variable and structurally complex. They are typically manufactured from animals, microorganisms, or through the use of animals or microorganisms. Biologics tend to be 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.

The term “subsequent entry biologic” (SEB) is used by Health Canada to describe a biologic drug that enters the market subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug. Accordingly, an SEB will in all instances be a subsequent entrant onto the Canadian market. In consideration of supporting information generated using the reference biologic drug, an SEB approval could be granted based on a reduced amount of original non-clinical and clinical information tailored to a particular class of products or a specific case. The term, subsequent entry biologic, was chosen as an alternative to “biogeneric” or “generic biologic” in order to clearly distinguish between the regulatory process (and product characteristics) for SEBs and that which is currently used for generic pharmaceutical drugs.

The Biologics and Genetic Therapies Directorate (BGTD) within the Health Products and Food Branch of Health Canada is the regulator of biologic drugs for human use and provides regulatory oversight for biologics with its comprehensive reviews of biologic drug submissions covering quality, safety, and efficacy, Lot Release and On-site Evaluation.

2.0 GUIDANCE FOR IMPLEMENTATION

2.1 General

2.1.1 Applicable Regulations

SEBs, like all new biologic drugs, are subject to the *Food and Drug Regulations* for authorization and oversight. Conforming to the guidance provided in this document, along with other guidance for biologics, should enable a sponsor to satisfy the following notable requirements in Part C of the *Food and Drug Regulations*:

C.08.002 (1)(a): No person shall sell or advertise a new drug unless the manufacturer has filed with the Minister a New Drug Submission (NDS) relating to the new drug that is satisfactory to the Minister.

C.08.002 (2): A New Drug Submission shall contain sufficient information and material to enable the Minister to assess the safety and efficacy of a new drug.

2.1.2 Patents, Intellectual Property, and Data Protection

All SEBs enter the market subsequent to a biologic drug product previously approved in Canada and to which the SEB is considered similar. As such, SEBs are subject to existing laws and regulations outlined in the *Patented Medicines (Notice of Compliance) Regulations* and C.08.004.1 of the *Food and Drug Regulations*, and related guidance documents entitled, “*Guidance Document: Data Protection under C.08.004.1 of the Food and Drug Regulations*” and “*Guidance Document: Patented Medicines (Notice of Compliance) Regulations*”. In the NDS, the SEB sponsor must clearly identify the product to which it is subsequent and to which it is considered to be making a direct or indirect comparison according to the *Patented Medicines (Notice of Compliance) Regulations* and C.08.004.1 of the *Food and Drug Regulations*.

2.1.3 Reference biologic drug

A sponsor must name the reference biologic drug authorized in Canada to which the SEB will be subsequent. The following provides general guidance on factors affecting the choice of reference biologic drug:

- The onus is on the sponsor to demonstrate that the chosen reference biologic drug is suitable to support the submission;
- The reference biologic drug should be authorized for sale and should be marketed in Canada;
- The same reference biologic drug should be used throughout the studies supporting the safety, quality, and efficacy of the product (i.e. in the developmental programme for the SEB);
- The dosage form, strength, and route of administration of the SEB should be the same as that of the reference biologic drug;
- The active substance (medicinal ingredient) of the reference biologic drug and that of the SEB must be shown to be similar;
- An SEB should not be used as a reference biologic drug; and
- The reference biologic drug should have adequate safety, efficacy, and effectiveness data accumulated such that the demonstration of similarity will bring into relevance a substantial body of reliable data.-

2.1.3.1 Considerations for the use of a Non-Canadian reference biologic drug

A sponsor must name the biologic drug authorized in Canada to which the SEB will be subsequent; and while it is preferable that this product be used in the comparative studies, in instances where a non-Canadian reference biologic drug is used, the following should be considered:

- a. The sponsor is responsible for showing that the non-Canadian reference biologic drug used for the purposes of demonstrating similarity is a suitable proxy for the version of the product approved in Canada. The submission should explicitly explain the link between the two products and confirm that both are marketed by the same innovator company or corporate entity that is approved to market the medicinal ingredient in the same dosage form in Canada;

- b. The sponsor has the responsibility of ensuring that the chosen non-Canadian reference biologic drug has associated with it sufficient information and data to support the submission;
- c. The non-Canadian reference biologic drug is from a jurisdiction that has an established relationship with Health Canada;
- d. The non-Canadian reference biologic drug is widely marketed in a jurisdiction that formally adopts International Conference on Harmonization (ICH) guidelines and has regulatory standards and principles for evaluation of medicines, post-market surveillance activities, and approach to comparability that are similar to Canada; and
- e. If the non-Canadian reference biologic drug is used in clinical studies in Canada, data must be provided to satisfy chemistry and manufacturing information as per C.05.005 of the *Food and Drug Regulations* (Refer to section 2.2. for more information).
- f. The sponsor should contact Health Canada early in the drug development process to ensure the reference biologic drug is appropriate;

2.1.4 Review time

The target time for review of an SEB will be the same as that for an NDS. Please refer to the *Management of Drug Submission Guidance* for further details on review timelines.

2.1.5 Consultation with Health Canada

Sponsors of SEBs are encouraged to consult with BGTD for regulatory guidance at any stage of the development of an SEB.

Contact Information:

Biologics and Genetic Therapies Directorate
Director Generals Office
Office of Regulatory Affairs
200 Tunney's Pasture Driveway
Ottawa, Ontario K1A 0K9
Address Locator: 0701A
Phone: 613-957-1722
Fax: 613-941-0364
Email: BGTD_RAD_Enquiries@hc-sc.gc.ca

2.2 Information requirements for Clinical Trial Applications (CTA)

Clinical trials conducted in Canada 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*.

Sponsors need to include all information identified in C.05.005 of the *Food and Drug Regulations* in their application for authorization. If a non-Canadian reference biologic drug is used in clinical studies in Canada, data must be provided to support its safety and to satisfy the intent of the regulatory requirements for chemistry and manufacturing information.

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, including SEBs, and prohibits the sale of new drugs unless the manufacturer has filed a submission that is satisfactory to the Minister. Section C.08.002 of the *Food and Drug Regulations* outlines the requirements for an NDS.

2.3.1 Quality information

In addition to a full chemistry and manufacturing (C&M) data package that is expected for a standard new biologic drug, the SEB package should provide extensive data on the demonstration of similarity with the reference biologic drug, including characterization studies conducted in a side-by-side format. For consideration as an SEB, similarity should be primarily deduced from these quality studies which should be comprehensive and well rationalized.

In some cases, if excipients do not limit the sensitivity of assays used for characterization, it may be feasible to undertake comparability studies using the formulated drug products; but frequently, studies comparing drug substance will be beneficial or may be the only scientific option. If the reference drug substance used for characterization is isolated from a formulated reference drug product, additional studies should demonstrate that the drug substance is not changed by the isolation process. One approach to potentially qualifying the isolation process is to use the process on the formulated SEB drug product and compare the isolated (de-formulated) SEB drug substance to the SEB drug substance obtained prior to formulation. Any approach used should be justified.

2.3.1.1 Considerations for the comparability exercise

Although the comparison of two independent products is outside of the scope of ICH Q5E, many of the principles and approaches are applicable.

The goal of the comparability exercise is to ascertain whether the SEB and the chosen reference biologic drug can be judged highly similar in terms of quality attributes, and thus provide support for a possible conclusion of similarity for safety and efficacy. Ideally, to meet this goal, the product should be evaluated at the process steps most appropriate to detect a difference in the quality attributes but in most situations this will be limited to the drug substance and the drug product and may entail evaluating both. The extent of the studies necessary to demonstrate comparability will depend on:

- The nature of the product;
- The availability of suitable analytical techniques to detect potential product differences;

and,

- The relationship between quality attributes and safety and efficacy, based on overall non-clinical and clinical experience.

When considering the similarity of products, the manufacturer should evaluate, for example:

- Relevant physicochemical and biological characterization 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 drug product and, hence, potential differences in product-related substances and product-related impurities;
- Data obtained from multiple batches of the SEB and of the reference biologic drug to help generate an understanding of ranges in variability. This need not necessarily entail performing all tests on all batches; a matrix approach may be possible but should be rationalized.

In addition to evaluating the data, the manufacturer 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;
- The type and extent of data to be derived from non-clinical and clinical studies on 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 drug. It may be appropriate to modify existing tests used in the SEB product development or add new tests. 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. 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 drug may be detected.

An early decision on the choice of reference biologic drug 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 characterization 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 Q2(R1), Q5C, Q6B), as appropriate.

Characterization

Characterization 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 characterization is generally warranted to directly compare the SEB and the reference biologic drug. However, additional characterization may be indicated in some cases. For example, when the product characterization 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. The manufacturer should attempt to determine that higher order structure (secondary, tertiary, and, where applicable, quaternary) 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 characterization 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 highly 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 consideration as an SEB is not appropriate.

When the products being compared have multiple biological activities, a set of relevant functional assays designed to evaluate the range of activities should be utilized. These activities may result from multiple functional domains. In such situations, all functional activities should be evaluated as part of the comparability study.

Where any of the multiple activities is not sufficiently correlated with clinical safety or efficacy,

or if the mechanism of action is not understood, justification should be provided that non-clinical or clinical activity of the SEB associated with the clinical indication being sought is not compromised.

Immunochemical Properties

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

Purity and Impurities

The combination of analytical procedures selected should provide data to allow evaluation of relevant differences in the purity and impurity profiles.

Differences observed in the purity and impurity profiles of the SEB relative to the reference biologic drug 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.

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 drug 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 stability studies should be conducted on the SEB and reference biologic drug to compare the stability behaviour of both using the same storage conditions and analytical methods. In some cases, it may be possible and beneficial to conduct side-by-side stability studies on samples 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 drug that are not readily detectable by the characterization 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 an SEB and the reference biologic drug. The results may show product differences that warrant additional evaluation. The results may 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 for a product-to-product comparison.

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 drug are available to the SEB sponsor 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 similarity

The demonstration of similarity does not signify 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 drug are relevant to the SEB.

A final determination of similarity can be based on a combination of analytical testing, biological assays, and non-clinical and clinical data. However, to be considered an SEB, the weight of evidence should be provided by the analytical and biological characterization.

Consideration as an SEB may not be appropriate in the following situations where extensive reliance on the contribution of non-clinical and clinical studies would be expected:

- 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 drug are likely to be observed.

2.3.1.5 Organization of data

The assessment of 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 containing appropriate cross-references. However, the reorganization of modules 2 and 3 of a CTD submission already prepared for another regulatory jurisdiction should not be necessary; consult Health Canada for guidance.

2.3.1.6 Changes following issuance of the market authorization

Once granted an NOC, an SEB is considered to be a new (“stand-alone”) product with all of the 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 drug are not required.

2.3.2 Non-clinical and Clinical Information

2.3.2.1 General

Non-clinical and clinical requirements outlined in this guidance document are applicable to SEBs that have been demonstrated to be similar to the reference biologic drug, based on the results of the comparability exercises included in the C&M data package. If the similarity of an SEB to the reference biologic drug cannot be established based on the C&M data package, reduced clinical data cannot be justified and the product cannot be considered as an SEB.

This section provides only general guidance on non-clinical and clinical information required for SEBs. Specific requirements for drug classes (for example, insulin, growth hormone) may differ, depending on the class; requirements may also differ depending on various clinical parameters related to each specific drug product or class, including such elements as therapeutic index, and the type and number of indications for which SEB sponsors apply.

An SEB product sponsor is eligible to apply for one or more clinical indications granted to the reference biologic drug in Canada. Any claims made by the SEB sponsor should be supported by suitable scientific data, which should typically include safety and efficacy data generated with the SEB. However, in some situations, proposals for additional indications held by the reference biologic drug may be granted to the SEB in the absence of such clinical data. In some cases, comparative pharmacokinetic/pharmacodynamic (PK/PD) data to bridge two or more indications may be sufficient. It may also be possible to extrapolate clinical data to other indications where rationales are sufficiently persuasive. The extrapolation should be justified based on: mechanism(s) of action; pathophysiological mechanism(s) of the disease(s) or conditions involved; safety profile in the respective conditions and/or populations; and clinical experience with the reference biologic drug. A detailed scientific rationale that addresses appropriately the benefits and risks of such a proposal should be provided to adequately support the data extrapolation.

Where a clinical indication being sought is not held by the reference biologic drug, full clinical trial data shall be provided in support of that indication.

The reference biologic drug should be the same for the clinical and non-clinical studies as the one used for comparison in the C&M studies. Additionally, the SEB product used in the non-clinical and clinical studies should be the same as that for which market authorization is sought. In some instances, C&M changes introduced during the clinical development phase or at the end of the clinical development programme should be bridged by additional PK/PD data and/or clinical data. In such instances, sponsors are advised to consult with BGTD for additional guidance.

2.3.2.2 Non-clinical studies

Appropriate non-clinical studies should be conducted prior to the initiation of any clinical studies following principles recommended by ICH S6. These studies should be comparative and designed to detect significant differences between the SEB and the reference biologic drug.

In vitro studies

Receptor binding studies or cell-based assays should be conducted when appropriate.

In vivo studies

These should include:

- Animal pharmacodynamic studies relevant to the clinical application(s);
- At least one repeat-dose toxicity study, including characterization of toxicokinetic parameters, 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 drug can be detected; and
- Other relevant safety observations (e.g., local tolerance), which 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 an SEB submission unless warranted by the results from the repeat-dose toxicological studies.

2.3.2.3 Clinical studies

Pharmacokinetic studies

Comparative pharmacokinetic studies should be conducted to demonstrate the similarities in PK characteristics between the SEB and the reference biologic drug.

The design of comparative pharmacokinetic studies (e.g. cross-over study versus parallel study) should take the following factors into considerations:

- half-life of the biologics;
- linearity of PK parameters;

- where applicable, the endogenous levels and diurnal variations of the protein under study;
- conditions and diseases to be treated;
- route(s) of administration; 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. However, where it is justifiable and where there is no undue risk, PK studies may be conducted in healthy subjects. Dose(s) used in the PK studies should be within the therapeutic dosing range specified in the Product Monograph (PM) of the reference biologic drug.

General principles of study design and statistical methods for comparative bioavailability studies should be considered for comparing and analyzing similarities of the PK parameters between the SEB and the reference biologic drug. PK parameters should not be limited to parameters reflecting absorption only. Differences in elimination (clearance and terminal half-life) should also be compared. Data should not be excluded from the analysis unless they can be justified and considered to be acceptable to BGTD.

In all instances, acceptable criteria for the determination of similarity in comparative pharmacokinetics between the SEB and the reference biologic drug should be defined and justified prior to the initiation of PK studies, taking into consideration known PK parameters and their variations, assay methodologies, and all available safety and efficacy of the reference biologic drug and SEB. The criteria for the comparative bioavailability studies of generic pharmaceuticals in Canada¹ should be considered and it is expected that the criteria generally can be met in comparative pharmacokinetic studies of SEBs. When such criteria are not employed or not met in the comparative pharmacokinetic studies, a discussion should be provided regarding the implication of the findings in conjunction with the efficacy data obtained from the comparative clinical efficacy and safety trials.

Pharmacodynamic studies

The parameters investigated in PD studies should be clinically relevant and surrogate markers should be clinically validated. PD studies may be combined with PK studies, in which case the PK/PD relationship should be characterized. As for all other studies in the SEB developmental programme, the PD studies should be comparative in nature.

¹ The following standards are currently used in Canada to demonstrate bioequivalence or comparative bioavailability of the test product to the reference product.

- The 90% confidence interval of the relative mean AUC_T of the test to reference product should be within 80 percent to 125 percent, and
 - The relative mean measured C_{max} of the test to reference product should be between 80 percent and 125 percent.
- These standards must be met on log transformed parameters calculated from
- the measured data; and
 - data corrected for measured drug content (percent potency of label claim).

These bioequivalence standards may not be applicable to all biologics.

Clinical efficacy and safety trials

Comparative clinical trials are critically important to demonstrate the similarity in efficacy and safety profiles between the SEB and the reference biologic drug with few exceptions (e.g. recombinant human soluble insulin products for which only a comparative clinical safety study is required). The design of the studies and the clinical comparability margins of the primary efficacy endpoints are important and should be given careful consideration and justified on clinical grounds. In line with the principle of similarity, equivalence trials are generally preferred. If non-inferiority trials are considered, they must be clearly justified and sponsors are advised to consult with BGTD prior to study initiation. Sponsors should be aware of the possibility that the results from such trials could suggest superiority of the SEB relative to the reference biologic drug. In such instances, the superiority observed must be assessed for clinical relevance including its impact on safety. In the event that the superiority observed is considered clinically meaningful and/or is associated with increased adverse drug reactions over those seen with the reference biologic drug, the product would no longer be considered as an SEB. Demonstration of non-inferiority of an SEB to the reference biologic drug might not provide strong support for the extrapolation to other indications, particularly if the other indications include different dosages than those tested in the clinical trial.

The nature, severity, and frequency of adverse events should be compared between the SEB and the reference biologic drug and be based on safety data from a sufficient number of patients treated for an acceptable period of time. Efforts should be made to ensure that comparative clinical studies have a sufficient number of patients treated for an acceptable period of time in order to allow the detection of significant differences in safety between the SEB and the reference biologic drug.

The immunogenicity of the SEB should be evaluated using appropriately designed clinical studies with state-of-the-art methods, taking into consideration the potential impact on both the efficacy and the safety.

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), as well as the type of antibodies formed. Of most concern are those antibodies that have a potential serious impact on safety and efficacy, such as neutralizing antibodies and antibodies with cross-reactivity.

When neutralizing antibodies are detected in patients in clinical trials, the impact of the antibodies on the PK/PD parameters of the SEB should be analyzed, where the data are available. Furthermore, an assessment of the impact of the neutralizing antibodies and cross-reacting antibodies (if applicable) on the overall efficacy and safety of the SEB should be conducted. Should there be cause for concern; the duration of the clinical trials should be extended, in order to obtain longer-term safety and efficacy data prior to authorization. In some cases, a detailed Pharmacovigilance Plan and Risk Management Plan may need to be implemented in the post-marketing phase.

2.3.3 Risk Management Plan (RMP)

An SEB is not the first in its class to be brought to market; however, it will be authorized based on a reduced non-clinical and clinical data package due to reliance on information from a reference biologic drug. It is therefore important that an RMP be presented prior to issuance of marketing authorization. The RMP should be designed to monitor and detect both known inherent safety concerns and potentially unknown safety signals that may result from the impurity profile and other characteristics of the SEB.

Health Canada will work with sponsors to ensure a suitable RMP is developed prior to authorization of the product for marketing. The minimum criteria for surveillance for each SEB product should be described in accordance with the requirements for a new biologic drug. The RMP should include detailed information of a systematic evaluation of the immunogenicity potential of the SEB. A discussion about methods to distinguish adverse event reports from those for other licensed products, including the reference product, should be included in the RMP. The RMP may be maintained and implemented throughout the life-cycle of the product.

2.3.3.1 Pharmacovigilance Plan (PvP)

A PvP should be provided and should include the submission of periodic safety update reports (PSURs). The PSURs for an SEB should include a discussion of the benefit-risk balance of the SEB post-market.

2.4 Post-Market Requirements

2.4.1 Adverse Drug Reaction (ADR) Reporting

ADR reporting is required post-market under section C.01.016 of the *Food and Drug Regulations*: any serious 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.

2.4.2 Periodic Safety Update Reports (PSURs)

PSURs should be submitted as discussed in the PvP. The periodicity for submission of PSURs should be consistent with ICH guidelines (ICH E2E) for new products or as determined by the Minister on approval.

2.4.3 Suspension or revocation of NOC

At any time after an NOC is issued, the authority to suspend such an authorization is set out in C.08.006 of the *Food and Drug Regulations*. The Minister may, by notice to a manufacturer, suspend for a definite or indefinite period, a NOC issued to that manufacturer in respect of an

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 pharmaceutical drugs, the sponsor of an SEB will not be able to utilize the PM of the reference biologic drug in its entirety as that of its own product. The PM for an SEB should be developed in a manner consistent with the principles, practices, and processes outlined in the “*Guidance for Industry: Product Monograph (2004)*”. The contents of the PM for SEBs will include following information:

- A statement indicating that the product is an SEB²
- Key data on which the decision for market authorization was made
- Tables showing the results of the comparisons between the SEB and reference biologic drug
- Information on the indications approved for use
- There should be no claims for bioequivalence between the SEB and reference biologic drug
- There should be no claims for clinical equivalence between the SEB and the reference biologic drug

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. Hence, Health Canada may be adapting suitable definitions, terminology, and applicable guidance documents.

Health Canada recommends that sponsors refer to the product class specific guidance documents developed by the Similar Biological (Biosimilar) Medicinal Products Working Party, European Medicines Agency as the scientific principles are consistent with those of Health Canada.

² Under Part I: HEALTH PROFESSIONAL INFORMATION, DESCRIPTION, a statement will follow the description of the SEB to indicate that similarity between the SEB and the reference product was established in accordance with the *Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)*.

References

1. ICH Q1A (R2): Stability Testing of New Drug Substances and Products (Second Revision)
2. ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology
3. ICH Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
4. ICH Q5E: Comparability of Biotechnology/Biological Products Subject to Changes in their Manufacturing Process.
5. ICH Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
6. ICH S6: Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals