Health Canada Santé Canada

# Guidance Document

## Information and Submission Requirements for Biosimilar Biologic Drugs

Published by authority of the
Minister of Health

| | |
|---|---|
| Date Adopted | 2010-03-05 |
| Revised Date | 2016-11-14 |
| Administrative Changes Date | 2017-04-20 |

**Health Products and Food Branch**

Canada

| | |
|---|---|
| Our mission is to help the people of Canada maintain and improve their health.<br>*Health Canada* | Our mandate is to take an integrated approach to managing the health-related risks and benefits of health products and food by:<br>• minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,<br>• promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.<br>*Health Products and Food Branch* |



Available in Canada through

Health Canada – Publications
Address Locator 0900C2
Ottawa, Ontario
K1A 0K9

E-mail: publications@hc-sc.gc.ca
Telephone: 613-957-2991, 1-866-225-0709
Web address: www.hc-sc.gc.ca/index-eng.php

***Également disponible en français sous le titre : Ligne directrice - Exigences en matière de renseignements et de présentation relatives aux médicaments biologiques biosimilaire***

## 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 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.

## Document Change Log

| Version | Change made | Date |
|---|---|---|
| **1** | Initial issuance of document | 2010-03-05 |
| **2** | Comprehensive revision | 2016-11-14 |
| **3** | 2.3.5 Labelling requirements - Product Monograph<br>• Section revised with reference to the *Product Monograph Template - Schedule D - Biosimilar Biologic Drug* added | 2017-04-20 |

## Table of Contents

# 1. 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. The term biosimilar biologic drug, hereafter referred to as biosimilar, is used by Health Canada to describe subsequent entry versions of a Canadian approved innovator biologic with demonstrated similarity to a reference biologic drug. Biosimilars were previously referred to as Subsequent Entry Biologics (SEBs) in Canada.

## 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 Part C of the *Food and Drug Regulations* for the authorization of biosimilars in Canada.

## 1.2 Scope and application

This guidance document 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 criteria determine the scope of products that are eligible to be authorized as biosimilars:

- a suitable reference biologic drug exists that: a) was originally authorized for sale based on a full quality, non-clinical and clinical data package; and b) has been used in the post market setting such that the demonstration of similarity will bring into relevance a substantial body of reliable data on safety, efficacy and effectiveness;
- the biosimilar and reference biologic drug can be well characterized by a set of modern analytical methods;
- the biosimilar, through extensive characterization and analysis, can be judged similar to the reference biologic drug by meeting an appropriate set of pre-determined criteria.

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

Biosimilars employing clearly different approaches to manufacture than the reference biologic drug may be eligible; however, careful consideration should be given to expression system

differences that may present challenges to demonstrating similarity to the reference biologic drug.

In this guidance document, "must" is used to express a requirement 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 used to express an option or that which is permissible within the limits of the guidance document.

### 1.3 Policy statements

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

1.3.1 The sponsor is responsible for providing the necessary evidence to support all aspects of a biosimilar submission.

1.3.2 A biosimilar sponsor is eligible to apply for the indication(s) and condition(s) of use that are held by the reference biologic drug authorized in Canada.

1.3.3 Biosimilars are new drugs subject to the *Food and Drugs Act* and Part C of the *Food and Drug Regulations*. The concepts and the 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 biosimilars.

1.3.4 The basis for accepting a reduced non-clinical and clinical data package for a biosimilar hinges on demonstrated similarity between the biosimilar and the suitable reference biologic drug. A final determination of similarity will be based on the entire submission, including data derived from comparative structural, functional, non-clinical and clinical studies.

1.3.5 Biosimilars are not "generic biologics" and many characteristics associated with the authorization process and marketed use for generic pharmaceutical drugs do not apply. Authorization of a biosimilar is not a declaration of pharmaceutical equivalence, bioequivalence or clinical equivalence to the reference biologic drug.

1.3.6 A biosimilar submission involves a comparison to another product. Hence all biosimilars 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*.

1.3.7 As a biosimilar is authorized using a reduced non-clincial and clinical package, it should not be used as a reference biologic drug for another biosimilar 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.

***Biosimilar biologic drug (Médicament biologique biosimilaire)***
A biologic drug that obtains market authorization subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug. A biosimilar relies in part on prior information regarding safety, efficacy and effectiveness 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. Biosimilar biologic drugs were previously referred to as Subsequent Entry Biologics.

***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 a biosimilar is compared to demonstrate similarity.

***Specification (Spécification)***
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.

**Abbreviations and acronyms**
ADA = Anti-Drug Antibody
ADR = Adverse Drug Reaction
BGTD = Biologics and Genetic Therapies Directorate
CTA = Clinical Trial Application
CTD = Common Technical Document
ICH = International Council for Harmonisation
NDS = New Drug Submission
NOC = Notice of Compliance

PK/PD = Pharmacokinetic/Pharmacodynamic
PBRER = Periodic Benefit-Risk Evaluation Reports
PSUR = Periodic Safety Update Reports
RMP = Risk Management Plan
SAM = Scientific Advice Meeting
SNDS = Supplemental New Drug Submission

## 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. Unlike pharmaceutical drugs, biologic drugs are derived through the metabolic activity of living organisms and are variable and structurally complex. 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 presence of pathogens or the growth of adventitious agents such as viruses. Due to these risks, 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 expiration of patents and/or data protection for some biologic drugs is creating opportunities for subsequent entry versions. The term biosimilar is used by Health Canada to describe a biologic drug that receives market authorization subsequent to a version previously authorized in Canada and with demonstrated similarity to a reference biologic drug. Demonstration of similarity enables the sponsor to rely partially on relevant information about the reference biologic drug and to seek authorization based on a reduced non-clinical and clinical data package tailored to a particular class of products or to a specific case. In order to clearly distinguish between the regulatory process and product characteristics for biosimilars and those for generic pharmaceutical drugs, the terms “biogeneric” or “generic biologic” are not used.

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.

# 2. GUIDANCE FOR IMPLEMENTATION

## 2.1 General

### 2.1.1 Applicable regulations

Biosimilars, like all new biologic drugs, are subject to Part C of 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, Division 8 of the *Food and Drug Regulations*:

> C.08.002 (1)(*a)*: No person shall sell or advertise a new drug unless the manufacturer of the new drug has filed with the Minister a new drug submission 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 effectiveness of the new drug.

### 2.1.2 Patents, intellectual property, and data protection

All biosimilars enter the market subsequent to a biologic drug product previously authorized in Canada and to which the biosimilar is considered similar. As such, biosimilars 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* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/data_donnees_protection-eng.php) and *Guidance Document: Patented Medicines (Notice of Compliance) Regulations* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/patmedbrev/pmreg3_mbreg3-eng.php).

In the New Drug Submission (NDS), the biosimilar sponsor must clearly identify the biologic drug authorized in Canada 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*. In addition, where there is a non-Canadian reference biologic drug (refer to section 2.1.3), the sponsor must address the relationship between the non-Canadian reference biologic drug and the Canadian version.

### 2.1.3 Reference biologic drug

A biosimilar must be subsequent to a biologic drug that is authorized in Canada and to which a reference is made. Sponsors may use a non-Canadian sourced version as a proxy for the Canadian drug in the comparative studies. The onus is on the sponsor to demonstrate that the chosen reference biologic drug is suitable to support the submission. The sponsor should consult with BGTD early in the drug development process to ensure the suitability of the reference biologic drug.

The following should be considered when selecting a reference biologic drug:

- The dosage form(s), strength(s), and route(s) of administration of the biosimilar should be the same as that of the reference biologic drug.
- The same reference biologic drug should be used throughout the studies supporting the quality, safety and efficacy of the product (i.e. in the developmental programme for the biosimilar).
- In certain circumstances, it may be possible to use more than one reference biologic drug (e.g. versions of the reference biologic drug sourced from more than one jurisdiction) in clinical studies. As a scientific matter, the type of bridging data needed will always include structural and functional data from analytical studies that directly compares all the products (e.g. the proposed biosimilar product, the U.S.-authorized product, and the EU-authorized product) and may also include clinical pharmacokinetic (PK) and, if appropriate, clinical pharmacodynamic (PD) study data for all the products.
- The active substances (medicinal ingredients) of the biosimilar and the reference biologic drug must be shown to be similar.
- The reference biologic drug should have accumulated adequate safety, efficacy, and effectiveness data in the post market setting such that the demonstration of similarity will bring into relevance a substantial body of reliable data.

A biosimilar should not be used as a reference biologic drug, as it was authorized using a reduced non-clinical and clinical data package.

#### *2.1.3.1 Considerations for the use of a non-Canadian reference biologic drug*

In addition to section 2.1.3, the following should be considered when selecting a non-Canadian reference biologic drug used for the purposes of demonstrating similarity:

- The non-Canadian reference biologic drug should have the same medicinal ingredient(s), dosage form and route of administration as the version authorized in Canada. Information on the Canadian version can be found in Health Canada’s Drug Product Database.

- The non-Canadian reference biologic drug should be marketed in a jurisdiction that formally adopts International Council for Harmonization (ICH) guidelines and that has regulatory standards and principles for evaluation of medicines, post-market surveillance activities, and approaches to comparability that are similar to Canada.
- If the non-Canadian reference biologic drug is used in clinical studies in Canada, data must be provided to satisfy chemistry and manufacturing (quality) information as per C.05.005 of the *Food and Drug Regulations*. Refer to section 2.2. for more information.

### 2.1.4 Review time

The target time for review of a biosimilar is the same as that for an NDS. Refer to the Health Canada *Guidance for Industry: Management of Drug Submissions* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/mgmt-gest/mands_gespd-eng.php) for details on review timelines.

## 2.2 Information requirements for clinical trial applications (CTA)

Clinical trials conducted in Canada involving biosimilars 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* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec-eng.php) and the *Clinical Trials Manual* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_intro-eng.php).

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 (quality) information. At a minimum, this should include confirmation that the non-Canadian reference biologic drug is sourced from an ICH country and that there is evidence of a history of safe use in the country of origin.

If the comparative structural, functional and non-clinical *in vitro* studies are considered satisfactory and no issues are identified that would preclude administration into humans, *in vivo* animal studies may not be necessary.

Sponsors are encouraged to request scientific advice meetings and pre-CTA consultation meetings for biosimilars. Refer to Section 3 for information on biosimilar scientific advice meetings and Health Canada's *Guidance for Clinical Trial Sponsors: Clinical Trial Applications* for instructions on how to request a pre-CTA meeting.

## 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, which include biosimilars, 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 Organization of data

Electronic documents should be provided in electronic common technical document (eCTD) format. The regulatory activities provided in eCTD format should be prepared using applicable sections of the *Guidance Document: Preparation of Drug Regulatory Activities in the Electronic Common Technical Document Format* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ectd/prep_ectd_format-eng.php).

Alternatively, Health Canada will also accept electronic documents in "non-eCTD electronic-only" format in accordance with the applicable sections of the *Guidance Document: Preparation of Drug Regulatory Activities in the "Non-eCTD Electronic-Only" Format* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ctd/gd_prep_non_ectd_ld-eng.php).

The assessment of similarity should be organized 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 regulatory activity already prepared for another regulatory jurisdiction should not be necessary. Sponsors should provide a note to reviewers indicating the location and organization of the similarity assessment. The biosimilar sponsor is encouraged to consult with BGTD for further guidance.

### 2.3.2 Quality information

In addition to a typical chemistry and manufacturing data package that is expected for a standard new biologic drug, the biosimilar submission should include extensive data demonstrating similarity with the reference biologic drug. This should include characterization studies conducted in a side-by-side format. For consideration as a biosimilar, similarity should be deduced primarily from comprehensive and well rationalized quality studies.

If excipients do not limit the sensitivity of assays used for characterization, it may be feasible to undertake studies to demonstrate similarity using the formulated drug products. Frequently, studies comparing the 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 biosimilar drug product and compare the isolated (de-formulated) biosimilar drug substance to the biosimilar drug substance obtained prior to formulation. The approach used should be justified.

*2.3.2.1 Quality considerations for demonstrating similarity*

Although the comparison of two independent products is outside of the scope of *ICH Q5E: Comparability of Biotechnology/Biological Products Subject to Changes in their Manufacturing Process*, many of the principles and approaches are applicable.

The sponsor should demonstrate whether the biosimilar and the reference biologic drug can be judged highly similar in terms of quality attributes and thus support a possible conclusion of similarity for safety and efficacy. The product should be evaluated at the process steps most appropriate to detect a difference in the quality attributes. However, in most situations this evaluation will be limited to the drug substance, the drug product, or both. The extent of the studies necessary to demonstrate similarity will depend on the following:

- The nature of the product.
- The availability of suitable analytical techniques to detect potential product differences.
- The relationship between quality attributes and safety and efficacy based on overall non-clinical and clinical experience.
- Differences between the expression systems used to manufacture the biosimilar and the reference biologic drug.

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 biosimilar and the reference biologic drug to help generate an understanding of ranges in variability. This evaluation may not

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 consider if the results provide insights regarding the following:

- 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 biosimilar should be confirmed, modified, or created, as appropriate, to maintain the quality of the product.

The comparative structural and functional studies will determine the type and extent of data to be derived from non-clinical and clinical studies on the drug product.

*2.3.2.2 Quality considerations*

*Analytical Techniques*

Analytical tests should be carefully selected and optimised to maximise the potential for detecting relevant differences in the quality attributes of the biosimilar and the reference biologic drug. It may be appropriate to modify existing tests used in biosimilar product development or to 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 between the biosimilar and the reference biologic drug may be detected.

Measurement of quality attributes in characterization studies does not necessarily entail use of validated assays, but assays used should be scientifically sound and provide results that are reliable. Methods used to measure quality attributes for batch release should be validated in accordance with ICH guidelines, *ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology*, *ICH Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*, and *ICH Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products* 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.

A complete side-by-side characterization should be performed to directly compare the biosimilar and the reference biologic drug. The significance of any differences should be evaluated.

The following criteria should be considered as a key point when demonstrating similarity:

*Physicochemical Properties*

The manufacturer should consider the concept of the desired product (and its variants) as defined in ICH Q6B when designing and conducting studies to demonstrate similarity. 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 the higher order structure (secondary, tertiary, and, where applicable, quaternary) is comparable. If 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 (e.g. 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 a biosimilar is not appropriate.

When the products being compared have multiple biological or functional activities, a set of relevant functional assays designed to evaluate the range of activities should be utilized.

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 biosimilar 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 specific properties of the biosimilar are comparable to those of the reference biologic drug.

*Purity and Impurity*

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 biosimilar relative to the reference biologic drug should be evaluated to assess their potential impact on safety and efficacy. Where the biosimilar exhibits different impurities, those impurities should be identified and characterized 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 biosimilar. The potential impact of differences in the impurity profile upon safety should be addressed and supported by appropriate data.

*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 characterize it. The manufacturer should confirm that the specifications chosen for the biosimilar are appropriate to demonstrate product quality.

*Stability*

For certain manufacturing processes, even slight differences in the production procedures used for the biosimilar 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 biosimilar 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 biosimilar and the 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, forced degradation, and photostability studies are often useful tools to establish degradation profiles and can therefore contribute to a direct comparison of a biosimilar 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 biosimilar to eliminate these unexpected differences. Appropriate studies should be considered to confirm that suitable storage conditions and controls are selected.

ICH Q5C and *ICH Q1A (R2): Stability Testing of New Drug Substances and Products* should be consulted to determine the conditions for stability studies that provide relevant data for a product-to-product comparison.

*2.3.2.3 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 the development data generated.

Where details of the manufacturing process for the reference biologic drug are available to the biosimilar sponsor, a comparison with those for the biosimilar may help to identify which tests should be performed.

*2.3.2.4 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 biosimilar; and 2) that non-clinical and clinical data previously generated with the reference biologic drug are relevant to the biosimilar.

A final determination of similarity will be based on all relevant data from structural, functional, non-clinical and clinical studies. To be considered a biosimilar, the weight of evidence should be provided by the structural and functional studies. The degree of similarity at the quality level will determine the scope and the breadth of the required non-clinical and clinical data. The non-clinical and clinical programs should be designed to complement the structural and functional studies and address potential areas of residual uncertainty.

Consideration as a biosimilar may not be appropriate in situations where extensive reliance on the contribution of non-clinical and clinical studies would be expected, such as:

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 biosimilar and the reference biologic drug are likely to be observed.

*2.3.2.5 Manufacturing changes following issuance of market authorization*

A biosimilar is a new drug 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 biosimilar. Studies should be conducted in accordance with ICH Q5E. Comparisons with the original reference biologic drug are not required.

### 2.3.3 Non-clinical and clinical information

*2.3.3.1 General*

Non-clinical and clinical requirements outlined in this guidance document are applicable to biosimilars that have been demonstrated to be similar to the reference biologic drug based on the results of the comparative structural and functional studies included in the chemistry and manufacturing data package. If similarity has not been established, reduced non-clinical and clinical data cannot be justified and the product cannot be considered a biosimilar.

This section provides general guidance on non-clinical and clinical information required for biosimilars. Specific requirements for drug classes (e.g. insulin and 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 elements such as therapeutic index and the type and number of indications for which biosimilar sponsors apply.

A biosimilar 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 biosimilar sponsor must be supported by suitable scientific data. Proposals for indications and uses that are not supported by clinical data specific to the biosimilar can be considered for authorization; refer to Section 2.3.4 for additional information.

Clinical data should be generated based on the product for which market authorization is sought. Chemistry and manufacturing changes introduced during the clinical development phase or at the end of the clinical development program may result in the need for additional bridging data. Sponsors should refer to ICH Q5E and consult with BGTD for additional guidance.

*2.3.3.2 Non-clinical studies*

Where similarity is well established by structural and functional studies, and where extensive *in vitro* mechanistic studies are indicative of similarity, *in vivo* non-clinical studies may not be necessary. Refer to the Biological Activity section within 2.3.2.2. for more information on *in vitro* studies. Sponsors should provide a scientific justification for their approach and should consult with BGTD at the scientific advice and/or pre-submission stage.

If filed in more than one module, sponsors should provide a note to reviewers that communicates where in the e-CTD non-clinical studies are located.

Specialized toxicological studies, including safety pharmacology, reproductive toxicology, mutagenicity and carcinogenicity studies, are not generally required for a biosimilar submission.

*2.3.3.3 Clinical studies*

The purpose of the clinical program is to show that there are no clinically meaningful differences between the biosimilar and the reference biologic drug.

The clinical program should begin with a PK/PD study(ies) which may be followed by an additional clinical trial(s). Differences observed between the biosimilar and reference

biologic drug, such as differences in immunogenicity, should be addressed. If differences cannot be addressed, the sponsor should consider whether the biosimilar submission route is still appropriate or whether the traditional new drug submission route would be more suitable.

*Pharmacokinetic (PK) studies*

Comparative PK studies should be conducted to rule out differences in PK characteristics between the biosimilar and the reference biologic drug.

PK studies should be carried out in healthy subjects when appropriate as they are usually considered to be a homogeneous and sensitive population. A low or sub-therapeutic dose residing on the linear part of the dose response curve should be considered if studies are performed in healthy subjects.

Studies should be conducted in the patient population when the PK or PK/PD in the patient population is known to be substantially altered by the disease states for which authorisation is requested. The dose(s) used in the PK studies in a relevant patient population should be within the therapeutic dosing range specified in the product monograph of the reference biologic drug.

The following factors should be taken into consideration during comparative PK study design (e.g. when choosing between cross-over versus parallel-group study):

- 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 biosimilar sponsor is applying.

General principles of study design and statistical methods for comparative bioavailability studies should be considered when assessing the similarity of the PK parameters between the biosimilar and the reference biologic drug. The PK comparison should not be limited to parameters reflecting absorption only. Parameters representing elimination (e.g. clearance and terminal half-life) should also be compared. Data should not be excluded from the analysis unless the exclusion can be justified and is considered acceptable by BGTD.

Acceptable criteria for the determination of similarity in comparative pharmacokinetics should be defined and justified prior to the initiation of PK study(ies). The acceptance

criteria should be defined taking into consideration the PK parameters being evaluated and their variations, assay methodologies, and available safety and efficacy information regarding the reference biologic drug and the biosimilar. The criteria for comparative bioavailability studies as outlined in Health Canada's *Guidance Document: Conduct and Analysis of Comparative Bioavailability Studies* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/gd_cbs_ebc_ld-eng.php) and *Comparative Bioavailability Standards: Formulations used for Systemic Effects* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/gd_standards_ld_normes-eng.php) should be considered. When such criteria are not employed or not met in the comparative PK studies, a discussion should be provided regarding the implication of the findings in conjunction with data obtained from other clinical studies.

*Pharmacodynamic (PD) studies*

As for all other studies in the biosimilar developmental program, PD studies should be comparative in nature.

Parameters investigated in PD studies should be clinically relevant. Use of a particular PD marker should be scientifically justified. PD markers should be relevant to the mechanism of action of the drug but may not need to be established surrogates for efficacy.

In general, the principles regarding study design, conduct, analysis and interpretation that are relevant to equivalence trials with a clinical outcome as the primary endpoint are applicable to equivalence trials with a PD marker as the primary outcome.

PD studies should be combined with PK studies, in which case the PK/PD relationship should be characterized.

*Clinical efficacy trial(s)*

In most cases, a comparative clinical trial(s) is important to rule out clinically meaningful differences in efficacy and safety between the biosimilar and the reference biologic drug. A clinical efficacy trial may not always be necessary, e.g. where there is a clinically relevant PD endpoint. In such cases, a scientific justification is needed and safety as well as comparative immunogenicity data are still required.

The comparative clinical trial should be adequately sensitive to rule out clinically meaningful differences within predefined comparability margins. Sponsors should consider the following factors when designing an adequately sensitive clinical trial:

- The characteristics of the studied population(s) (e.g. underlying disease, immune

competence).
- The characteristics of the clinical trials, such as study duration, route of administration, dosage regimen, clinical endpoint(s) and time of assessment.
- The risk and impact of immunogenicity.
- The impact of concomitant therapies (e.g. monotherapy vs. combination therapy).
- The use of appropriate comparability margins.

In some instances, evaluation of more than one sensitive population may be necessary.

Careful consideration should be given to the design of the study(ies) including the choice of primary efficacy endpoint(s) and clinical comparability margin. Each of these aspects are important and should be justified on clinical grounds. The study should be conducted using a clinically relevant and sensitive endpoint to show that there are no clinically meaningful differences between the biosimilar and reference biologic drug. The chosen endpoint could be different from the original study endpoint for the reference biologic drug (e.g. a well-established surrogate or a more sensitive endpoint). In all cases, an acceptable comparability margin should be defined taking into account the smallest effect size that the reference biologic drug would reliably be expected to have based on publicly available historical data. If multiple endpoints are used, then the principles described above should apply.

In line with the principle of similarity, equivalence trials are generally preferred. If non-inferiority trials are considered, they should be clearly justified and sponsors are advised to consult with BGTD prior to study initiation. Sponsors should be aware that the results from such trials could suggest statistical superiority of the biosimilar relative to the reference biologic drug. In such instances, the superiority observed should 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 a biosimilar. In addition, demonstration of non-inferiority of the biosimilar to the reference biologic drug might not provide strong support for the authorization of other indications, particularly if the other indications include different dosages than those tested in the clinical trial.

*Safety*

The nature, severity and frequency of adverse events should be compared between the biosimilar and the reference biologic drug. 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 rule out clinically meaningful differences in safety between the biosimilar and the reference biologic drug.

*Immunogenicity*

The purpose of the comparative immunogenicity study(ies) is to rule out clinically meaningful differences in immunogenicity between the biosimilar and the reference biologic drug. Of most concern are those antibodies that have the potential to impact safety and/or efficacy; for example, by altering PK, inducing anaphylaxis, or by neutralising the product and/or its endogenous protein counterpart. For each treatment arm, the comparative study(s) should characterise the incidence and magnitude of the anti-drug antibody (ADA) response, the time-course of ADA development, ADA persistence, and the impact of ADA on safety, efficacy and PK.

A suitable population should be selected in which to compare immunogenicity. In selecting an appropriate population, factors such as immunocompetence, prior or concomitant use of immunosuppressant therapies, and historical data with respect to the immunogenicity of the reference biologic drug should be considered. Because the investigation of immunogenicity is usually undertaken as part of the pivotal comparative safety and efficacy study(ies), it is important that the aforementioned factors are considered during the design of the clinical portion of the program to demonstrate biosimilarity.

Comparative immunogenicity testing should be conducted using a tiered approach that involves screening assays, confirmatory assays and assays to determine whether binding ADA are neutralising. Independent binding ADA assays incorporating the biosimilar or the reference biologic drug as the capture ligand should be developed in parallel. Each assay should be validated and have demonstrated ability to sensitively detect ADA in the presence of drug. Samples from both treatment arms should be tested for ADA using both assays to demonstrate ADA cross-reactivity against the biosimilar and the reference biologic drug. Deviation from this approach should be scientifically justified.

Patient samples that test positive for binding ADA in confirmatory binding assays should be tested for their ability to neutralise the drug unless there exists a strong rationale for not doing so. The selection of an appropriate format for neutralising antibody testing is important and should take into account the mechanism of action of the drug. Depending on the mechanism of action, competitive ligand binding assays or cell based assays may be appropriate.

### 2.3.4 Authorization of indications

A biosimilar sponsor may request authorization for all indications held by the biologic drug authorized in Canada to which a reference is made.

The decision to authorize the requested indications is dependent on the demonstration of similarity between the biosimilar and reference biologic drug based on data derived from comparative structural, functional, non-clinical and clinical studies. Where similarity has been established, indications may be granted even if clinical studies are not conducted in each indication. A detailed rationale that scientifically justifies authorization of the biosimilar in each indication should be provided taking into consideration mechanism(s) of action, pathophysiological mechanism(s) of the disease(s) or conditions involved, safety profile, dosage regimen, clinical experience with the reference biologic drug, and any case-by-case considerations. Certain situations may warrant additional clinical data for a particular indication.

Situations where a clinical indication being sought is not authorized in Canada for the reference biologic drug fall outside the scope of this guidance document.

### 2.3.5 Labelling requirements - Product Monograph

The product monograph for a biosimilar should be developed in a manner consistent with the principles, practices and processes outlined in the *Guidance Document: Product Monograph* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/monograph/pm_mp_2013-eng.php). Sponsors should use the *Product Monograph Template - Schedule D - Biosimilar Biologic Drug* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/monograph/pmappj_mpannj-eng.php) when preparing a product monograph for a biosimilar.

The contents of the product monograph for biosimilars should include the following information:

- A statement indicating that the product is a biosimilar to the reference biologic drug.
- A statement that indications have been granted on the basis of similarity between the biosimilar and the reference biologic drug.
- Comparative data generated by the biosimilar sponsor on which the decision for market authorization was made summarized in a tabular format.
- Relevant safety and efficacy information from the product monograph of the biologic drug authorized in Canada to which a reference is made, including warnings and precautions, Adverse Drug Reactions/Adverse Drug Effects and key post-market safety information for all indications that are authorized for the biosimilar.

There should be no claims for bioequivalence or clinical equivalence between the biosimilar and the reference biologic drug.

### 2.3.6 Risk Management Plan

A risk management plan (RMP) should be submitted as part of the drug submission. 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 biosimilar. The biosimilar sponsor should continue the assessment of unwanted immunogenicity and its clinical significance following market authorization.

The RMP should consider all identified and potential risks associated with the use of the reference biologic drug and should provide details on how these risks will be addressed in a post-market setting.

Health Canada will work with sponsors to ensure a suitable RMP is developed prior to authorization of the product. The minimum surveillance criteria for the biosimilar should be described in accordance with requirements for a new biologic drug. The RMP should include detailed information on systematic evaluation of the immunogenicity potential of the biosimilar.

The RMP should include specific (routine or additional) pharmacovigilance and risk minimisation activities similar to those in place for the reference biologic drug or justify that these activities are not relevant for the biosimilar.

A discussion about methods to distinguish adverse event reports for the biosimilar from those for other licensed products, including the reference product should be included. The RMP should be maintained and implemented throughout the life-cycle of the product.

For more information on RMPs, please refer to the *Guidance Document - Submission of Risk Management Plans and Follow-up Commitments*(http://www.hc-sc.gc.ca/dhp-mps/pubs/medeff/_guide/2015-risk-risques_management-gestion_plans/index-eng.php).

## 2.4 Post-market requirements

### 2.4.1 Adverse drug reaction (ADR) reporting and periodic reports

Sponsors are required to comply with sections C.01.016 to C.01.019 of the *Food and Drug Regulations*, which includes ADR reporting.

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.

Periodic safety update reports (PSURs) or periodic benefit-risk evaluation reports (PBRERs) should be prepared and/or submitted as discussed in the risk management plan. The periodicity for the submission of PSURs or PBRERs should be consistent with appropriate ICH guidelines for marketed products, or as determined by the Minister, when the product is authorized for market. For more information on PBRERs, please refer to the Health Canada *Guidance Document - Periodic Benefit-Risk Evaluation Report (PBRER) International Conference on Harmonisation (ICH) Topic E2C(R2)* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e2c(r2)_step4_etape4-eng.php).

### 2.4.2 Post-notice of compliance (NOC) changes

A biosimilar is a new drug with all of the associated regulatory requirements. For guidance on post- NOC changes, refer to the applicable Health Canada guidance documents *Post-Notice of Compliance (NOC) Changes: Framework Document* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/postnoc_change_apresac/noc_pn_framework_ac_sa_cadre-eng.php), *Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/postnoc_change_apresac/noc_pn_saf_ac_sa_inn-eng.php) and *Post-Notice of Compliance (NOC) Changes: Quality Document* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/postnoc_change_apresac/noc_pn_quality_ac_sa_qualite-eng.php).

Biosimilar sponsors should follow labelling requirements set out in the post-NOC guidance documents referenced above. This includes monitoring any product class type-specific safety information that may indicate the need for a change in labelling.

There may be situations post-NOC where biosimilar sponsors seek authorization of indications held by the reference biologic drug authorized in Canada. A Supplemental New Drug Submission (SNDS) for a biosimilar that relies on the previously demonstrated similarity provided in the original biosimilar NDS may be considered by Health Canada on a case-by-case basis. Biosimilar sponsors should consult with BGTD for regulatory guidance for their specific SNDS.

## 3. CONSULTATION WITH THE BIOLOGICS AND GENETIC THERAPIES DIRECTORATE (BGTD)

Biosimilar sponsors are encouraged to consult with BGTD for regulatory guidance as early as possible in the development of their biosimilar submission package. Consultation can occur at any stage of the development of a biosimilar.

BGTD is undergoing a 3 year pilot to explore a stepwise review approach that would be complementary to the biosimilar development process. During the pilot, a biosimilar sponsor may request a Scientific Advice Meeting (SAM) in order to receive advice from BGTD on their quality package early in the development process. Sponsors should ensure their drug meets the eligibility criteria for a biosimilar as outlined in this guidance. Sponsors wishing to participate in the pilot should contact the Office of Regulatory Affairs.

For more information, please refer to the *Notice - Subsequent Entry Biologics Scientific Advice Meeting Pilot* (http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/subsequent-entry-biologics-produits-bio-ulterieurs-eng.php).

## 4. ADDITIONAL INFORMATION

Health Canada will review this guidance document on an ongoing basis in response to new scientific knowledge, best practices and/or experience gained by the Department.

Contact Information:

Questions concerning biosimilar submissions should be directed to:

**Office of Regulatory Affairs**
Biologics and Genetic Therapies Directorate
Health Products and Food Branch
Health Canada
E-mail: BGTD.ORA@hc-sc.gc.ca

Questions or comments on this guidance document should be directed to:

**Office of Policy and International Collaboration**
Biologics and Genetic Therapies Directorate
Health Products and Food Branch
Health Canada
Email: BGTD.OPIC@hc-sc.gc.ca