Guidance on information and submission requirements for biosimilar biologic drugs

Health Canada Santé Canada

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Lignes directrices sur les exigences en matière de renseignements et de présentation relatives aux médicaments biologiques biosimilaires

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Foreword

Guidance documents provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. They also provide guidance to Health Canada staff on how mandates and objectives should be met fairly, consistently and effectively.

Guidance documents are administrative, not legal instruments. This means that flexibility can be applied. However, to be acceptable, alternate approaches to the principles and practices described in this document must be supported by adequate justification. They should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As always, Health Canada reserves the right to request information or material or define conditions not specifically described in this document, to help us adequately assess the safety, effectiveness and or quality of a therapeutic product. We are committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read along with the regulations and other applicable guidance documents.

In this guidance document, “must” is used to express a requirement that the user is obliged to satisfy to comply with the regulatory requirements. “Should” is used to express a recommendation that is advised but not required, and “may” is used to express an option that is permissible within the limits of the guidance document.

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1. Overview

1.1 Introduction

Health Canada, the federal regulatory authority that evaluates the safety, efficacy and quality of drugs for approval in Canada, recognizes that manufacturers may be interested in pursuing subsequent-entry versions of biologic drugs. The term ‘biosimilar biologic drug’, hereafter referred to as ‘biosimilar’, is used by Health Canada to describe a subsequent-entry version of a Canadian authorized originator biologic. It is demonstrated to be highly similar to the latter, referred to as the Canadian reference biologic drug (CRBD).

The Biologic and Radiopharmaceutical Drugs Directorate (BRDD) within the Health Products and Food Branch of Health Canada is the regulator of biologic drugs for human use. It provides regulatory oversight for biologics with its comprehensive reviews of biologic drug submissions covering quality, safety and efficacy.

Sponsors are encouraged to consult with BRDD for further guidance, if necessary (section 9. Contact us).

1.2 Scope and application

This guidance document applies to all biologic drug submissions for which the sponsor seeks authorization for sale based on a demonstrated high degree of similarity to a previously authorized biologic drug. These submissions rely on prior information regarding that biologic drug to support, in part, a reduced clinical package as part of the submission.

The following criteria determine the scope of drugs that are eligible to be authorized as biosimilars:

- a suitable CRBD exists that:
    a) was originally authorized for sale based on a comprehensive quality, non-clinical and clinical data package
    b) has a substantial body of evidence regarding quality, safety, efficacy and effectiveness of the CRBD, which has accumulated since market authorization
- the biosimilar and CRBD can be extensively characterized by a set of modern analytical methods

- the biosimilar, through extensive characterization and analysis, can be judged to be highly similar to the CRBD by meeting an appropriate set of pre-determined criteria

The demonstration of a high degree of similarity depends upon detailed and comprehensive drug characterization. This guidance applies to biologic drugs that contain, as their medicinal ingredient(s), well characterized proteins derived through modern biotechnological methods such as recombinant DNA and/or cell culture.

Short polypeptide drugs are classified as either a biologic or a pharmaceutical depending on the method of manufacture. When manufactured by recombinant DNA procedures, subsequent entry versions of short polypeptides are considered biologic drugs and are eligible for authorization as a biosimilar. When chemically synthesized, they are considered pharmaceutical drugs irrespective of the manufacturing process of the CRBD and could be eligible for authorization as a generic drug via the abbreviated new drug submission (ANDS) pathway on a case-by-case basis.

In Canada, low molecular weight heparins (LMWH) are regulated as biologic drugs because of their biologic origin, despite not being listed on Schedule D of the *Food and Drugs Act.* Sponsors of subsequent versions of LMWH products should use this guidance document together with the Policy Statement: Clarifying the appropriate regulatory pathway for subsequent entry low molecular weight heparins for additional guidance.

Biosimilars manufactured using methods different than those used to produce the CRBD are eligible for authorization. Careful consideration should be given to expression system differences that may present challenges to demonstrating a high degree of similarity of the biosimilar candidate to the CRBD.

Policy Statement: Clarifying the appropriate regulatory pathway for subsequent entry low molecular weight heparins

1.3 Policy objective

Health Canada has developed this guidance with the purpose of helping sponsors to meet the requirements of the *Food and Drugs Act (FDA)* and the *Food and Drug Regulations (FDR)* when seeking a notice of compliance (NOC) for a biosimilar.

1.4 Principles of the regulatory approach for biosimilars

Biosimilars are regulated under the *FDA* and Part C of the *FDR*. 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 approach for biosimilars.

While biosimilars are conceptually similar to generic drugs, they are not eligible for authorization through the ANDS pathway under C.08.002.1, due to their inherent heterogeneity and complexity. Rather, biosimilar drug submissions are filed using the new drug submission (NDS) pathway in accordance with C.08.002. Health Canada's issuance of a NOC for a biosimilar is a confirmation of a high degree of similarity to the CRBD but is not a declaration of equivalence. A biosimilar sponsor is eligible to apply for the indication(s) and condition(s) of use that are held by the CRBD authorized in Canada.

A biosimilar drug submission leverages the safety and efficacy information of the CRBD. Paragraphs C.08.002(2)(g) and (h) can be satisfied by establishing a high degree of similarity to the CRBD through quality, clinical and non-clinical analyses described in this document. As such, the non-clinical package included in the biosimilar drug submission does not require certain information that is typically expected in a conventional submission for a biologic drug. The clinical package is also expected to be reduced relative to the content of a conventional submission for a biologic drug. A biosimilar candidate relies on establishing a high degree of similarity to the CRBD through comprehensive physicochemical and functional characterization data. This permits the submission for a biosimilar candidate to leverage clinical data that supported the authorization of the CRBD.

1.5 Background

Biologic drugs have contributed to the health of Canadians as diagnostic, treatment and preventative tools for various diseases and medical conditions. Unlike pharmaceutical drugs, biologic drugs are derived through the metabolic activity of living organisms and are heterogeneous and structurally complex. Biologics can be labile and sensitive to changes in manufacturing processes. Biological source materials, production cells or their fermentation media can present risks to patients, such as the presence of pathogens or the growth of adventitious agents (for example, viruses). Due to these risks, stringent processes are applied to raw materials and virus inactivation and/or clearance during product purification and product testing. Changes to source materials, manufacturing processes, equipment or facilities can result in important and unexpected changes to the intermediate and/or final product.

The term biosimilar is used by Health Canada to describe a biologic drug that receives market authorization subsequent to an originator biologic that has been authorized in Canada (referred to as the CRBD). It is demonstrated to be highly similar to the CRBD.

Demonstration of a high degree of similarity enables the biosimilar sponsor to rely on relevant information about the CRBD.

1.6 Scientific considerations and principles of demonstrating similarity in the authorization of biosimilars

The purpose of a biosimilar development program is to establish a high degree of similarity between the biosimilar candidate and its CRBD based on a comprehensive comparability exercise. A biosimilar is highly similar to its CRBD in terms of physicochemical properties, functional properties and clinical pharmacology.

A biosimilar candidate requires extensive comparative analytical studies to demonstrate a high degree of similarity. It is recommended to use orthogonal analytical methods to increase confidence in the assessment of a given quality attribute. The chosen techniques should reflect current best practices and be state-of-the-art, where feasible. These studies compare the attributes of the biosimilar candidate and its CRBD, including:

- physicochemical characteristics (structure, post-translational modifications, heterogeneity, purity, impurities)
- functional properties (biological activity, immunochemical binding properties, etc.)
- stability profile (stress, accelerated, forced degradation profiles)

The demonstration of a high degree of similarity does not signify that the quality attributes of the two drugs being compared are identical, but that they are highly similar with two consequences:

1) that non-clinical and clinical data previously generated with the CRBD are applicable to the biosimilar candidate
2) the demonstration of safety and efficacy via non-clinical and clinical data previously generated for the CRBD can be inferred to be relevant to the biosimilar candidate

Given the heterogeneous nature of biologic drugs, a biosimilar can exhibit differences compared to its CRBD. The information required to address such differences is considered on a case-by-case basis and will depend on the specific difference(s) observed. These differences between the biosimilar candidate and its CRBD may be acceptable if the sponsor can provide sufficient evidence and/or scientific justification that the differences have no impact on both safety and efficacy.

The clinical studies required to support the authorization of a biosimilar are generally limited to a comparative pharmacokinetic trial conducted to demonstrate pharmacokinetic equivalence between the biosimilar and the CRBD. The study is also expected to collect data on safety and immunogenicity. Pharmacodynamic endpoints may be included, if feasible. Comparative clinical efficacy studies are not typically required for a biosimilar candidate to a CRBD when the biosimilar can be compared and extensively characterized by appropriate analytical studies. If comparative clinical efficacy studies are included, the sponsor should explain the role of the studies and the value of results in the context of the submission.

Differences between a biosimilar candidate and its CRBD should be evaluated in terms of a potential effect on function and stability. If major differences are identified between a biosimilar candidate and its CRBD, it is unlikely that the drug would be considered a biosimilar. Clinical efficacy and safety studies cannot address major differences in quality attributes between a biosimilar candidate and its CRBD.

2. General considerations

2.1 Applicable regulations

Biosimilars are subject to Part C of the *FDR* 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 *FDR*:

> 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.

2.2 Intellectual property

Biosimilars can enter the market subsequent to the CRBD previously authorized in Canada to which it has been demonstrated to be highly similar. In a new drug submission

(NDS), the biosimilar sponsor should clearly identify the biologic drug authorized in Canada (at the level of the drug identification number (DIN)) to which it is subsequent. The sponsor should also identify the biologic drug to which it is making a direct or indirect comparison or reference according to the *Patented Medicines (Notice of Compliance) Regulations* (*PM(NOC) Regulations*) and section C.08.004.1 of the *FDR*. In addition, where the sponsor makes a direct or indirect comparison to a non-Canadian sourced reference biologic drug (RBD) (refer to section 2.3), the sponsor must address the relationship between the non-Canadian sourced RBD and the drug authorized in Canada, that is, the CRBD.

For information on the data protection provisions of the *FDR* or on the *PM(NOC) Regulations*, manufacturers are encouraged to consult these guidance documents:

- Data Protection under C.08.004.1 of the *Food and Drug Regulations*"
- *Patented Medicines (Notice of Compliance) Regulations*

Alternatively, manufacturers can contact the Office of Patented Medicines and Liaison at opml-bmbl@hc-sc.gc.ca.

2.3 Canadian reference biologic drug

A thorough assessment of the physicochemical characteristics, functional properties and stability profile of the reference biologic drug should provide the foundation of knowledge that informs the development of the biosimilar candidate. For the demonstration of a high degree of similarity, side-by-side analyses of the biosimilar candidate with an appropriate CRBD must be conducted. The following should be considered when selecting a CRBD:

- The CRBD is an authorized biologic for the Canadian market that is supported by a complete quality, non-clinical and clinical data package.
- The CRBD should have a well-established safety and efficacy profile, supported by substantial pre- and post-market data.
- The dose, dosage form, frequency of dosage, strength(s) and route(s) of administration of the biosimilar candidate should be the same as that of the CRBD.
- The CRBD should be used throughout the studies supporting the comparative assessments of quality, clinical pharmacology and immunogenicity of the drug (that is, in the development program for the biosimilar candidate).

- Where more than one RBD (for example, RBDs sourced from more than one jurisdiction) are used, the sponsor should demonstrate that the RBDs are representative of each other. The required bridging data includes structural and functional data from analytical studies that directly compare all the drugs (for example, the biosimilar candidate, the U.S.-authorized drug and the E.U.-authorized drug) and may also include comparative clinical pharmacology data.

- The medicinal ingredient(s) of the biosimilar candidate and the CRBD must be shown to be highly similar.

- An authorized biosimilar should not be used as a CRBD for another biosimilar submission.

Publicly available reference standards are not to be used as the CRBD to support the demonstration of similarity.

2.3.1 Considerations for the use of a non-Canadian sourced RBD

Sponsors may use a non-Canadian sourced RBD as a proxy for the CRBD in the comparative studies. The onus is on the sponsor to demonstrate that the chosen RBD is suitable to support the submission. The sponsor is encouraged to consult with BRDD early in the drug development process to ensure the suitability of the non-Canadian sourced RBD.

In addition to the above considerations for a CRBD, the following should be considered when sourcing a non-Canadian RBD used for the purposes of demonstrating a high degree of similarity:

- The non-Canadian sourced RBD should have the same medicinal ingredient(s), dose, dosage form, frequency of dosage and route(s) of administration as the CRBD authorized in Canada. Information on the CRBD can be found in the Drug Product Database.

- The non-Canadian sourced RBD should be marketed in a jurisdiction that has regulatory standards and principles for evaluation of medicines, post-market surveillance activities and approaches to comparability that are similar to Canada.

Drug Product Database

2.4 Performance standard for a submission of a biosimilar candidate

A biosimilar candidate submission is filed and reviewed as an NDS. The performance standard for an NDS is outlined in the Guidance on management of drug submissions and applications.

Guidance on management of drug submissions and applications

3. Information requirements for new drug submissions

Part C, Division 8 of the *FDR* 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 *FDR* outlines the requirements for an NDS.

3.1 Organization of data

Electronic documents should be provided in electronic common technical document (eCTD) format.

The Filing submissions electronically webpage includes links to documents that provide detailed information on these formats and other information relating to filing submissions electronically.

The assessment of similarity should be organized as a distinct collection of data in section 3.2 R.5 Assessment of Similarity.

Learn more:

- Filing submissions electronically
- Guidance for industry on the preparation of the quality information for drug submissions in the CTD format: Biotherapeutic and blood products

4. Quality information requirements

4.1 Quality information

In addition to a chemistry and manufacturing data package that is expected for a standard new biologic drug, the biosimilar submission should include extensive and robust data demonstrating a high degree of similarity with the CRBD. A comprehensive characterization of the CRBD should be undertaken to establish the quality target product profile of the biosimilar candidate. For consideration as a biosimilar, similarity should be deduced primarily from comprehensive and appropriately designed comparative analytical studies. Comparative physicochemical, functional and stability studies to evaluate whether the proposed biosimilar candidate and the CRBD are highly similar should be included.

Analytical procedures used to demonstrate a high degree of similarity are a critical part of the comparative analytical data package and should be appropriately qualified for the intended purpose. For some analytical procedures direct or side-by-side analysis of the CRBD and the proposed biosimilar candidate may not be feasible due to matrix interference. In such cases, if samples are prepared from the finished drug product (for example, de-formulation or extraction) the impact of the technique(s) used should be appropriately documented, discussed and justified.

4.2 Considerations for demonstrating similarity

Although the comparison of two independent drug products is outside of the scope of International Council of Harmonisation (*ICH) Q5E: Comparability of Biotechnology/Biological Products Subject to Changes in their Manufacturing Process*, many of the principles and approaches are applicable in demonstrating similarity between the biosimilar candidate and the CRDB.

The sponsor should demonstrate that the biosimilar candidate and the CRBD can be judged highly similar in terms of physicochemical characteristics, functional properties and stability profiles; thus, support a conclusion of a high degree of similarity for safety and efficacy. The studies necessary to demonstrate a high degree of similarity will depend on the following:

- the nature and composition of the drug product, including inactive ingredients and excipients and their impact on safety and immunogenicity
- the availability of suitable analytical procedures to detect potential differences

- the relationship between quality attributes and safety and efficacy
- any differences between the expression systems used to manufacture the biosimilar and the CRBD

When evaluating the high degree of similarity between the biosimilar candidate and its CRBD, the biosimilar sponsor should consider:

- relevant physicochemical characteristics and functional properties, including the assessment of product heterogeneity
- results from analyses of relevant samples of the biosimilar candidate from the appropriate stages of the manufacturing process (that is, drug substance or drug product)
- stability data generated from accelerated, stress and/or forced degradation conditions, to assess any differences in degradation pathways and in profiles of product-related substances and product-related impurities between the CRBD and the biosimilar candidate

4.2.1 Lots of reference biologic drugs and biosimilars for comparative analytical assessment

The data package should describe the approach to setting the similarity criteria and specify the number of CRBD and biosimilar candidate lots used to assess a high degree of similarity for each quality attribute taking into account the complexity and knowledge of the biologic drug. This is typically acquired through characterization of multiple lots of the biosimilar candidate and the CRBD at different ages to understand the lot-to-lot variability of both drug products and processes. The number of lots of each drug product (CRBD and biosimilar candidate) to be included in the similarity assessment should be informed by the drug product and process variability and should consider the analytical procedure variability and assumptions of the statistical methodologies employed.

Note that for the comparative analytical studies, meaningful conclusions require that data points are independent. It is expected that all drug product lots of the biosimilar candidate included in the similarity assessment are manufactured from independent drug substance lots and are representative of the proposed shelf-life of the drug product.

4.2.2 Reference standards

A reference standard is distinct from a CRBD as they serve different functions. In accordance with ICH Q6B, an appropriately characterized in-house primary reference standard should be established. It should be prepared from lot(s) representative of the clinical and commercial process, should be established and used for control of the manufacturing process and product (biosimilar candidate). Neither an international reference standard, nor the CRBD, should be used as a primary reference standard. For the development of the biosimilar candidate, a CRBD or non-Canadian RBD lot(s) may be qualified as an initial reference standard.

It is expected that the lot used as the in-house reference standard for product control is representative of the clinical and commercial process via appropriate qualification studies. As necessary, comparative analytical data could be used to bridge the lots used in clinical studies to the reference standard. A two-tiered program consisting of in-house primary and secondary (or working) reference standards should be established at the time of the market application. A protocol may be included in the NDS submission to support the implementation of any future working reference standard.

4.3 Quality considerations

4.3.1 Analytical procedures

Analytical procedures should be carefully selected and optimised to maximise the potential for detecting differences in the quality attributes of the biosimilar candidate and its CRBD. To address the full range of physicochemical characteristics or functional properties, 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 principles to collect data for the same attribute to maximise the possibility that differences between the biosimilar candidate and its CRBD may be detected. The sponsor should also consider the limitations of each analytical procedure (for example, limit of detection or resolution) when evaluating a high degree of similarity of a biosimilar candidate to its CRBD. Where appropriate, methods that provide quantifiable results should be considered.

Measurement of quality attributes in characterization studies does not necessarily require use of validated assays, but assays used should be scientifically sound and appropriately qualified for the intended use. Methods used to measure quality attributes for batch release should be validated in accordance with ICH guidelines. This includes ICH Q2(R2): 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.

4.3.2 Characterization

Comprehensive and robust comparative characterization studies should be performed to evaluate the proposed biosimilar candidate and its CRBD. Characterization of a biologic drug by appropriate techniques, as described in ICH Q6B, includes the determination of physicochemical characteristics, biological activity, immunological properties (if any), purity, impurities and quantity.

The type, nature and extent of any differences between the proposed biosimilar candidate and the CRBD should be described and discussed. The discussion should explore identification and comparison of relevant quality attributes. The potential clinical effects of observed differences between the biosimilar candidate and the CRBD should also be assessed and justified.

The following criteria should be considered as key points when demonstrating a high degree of similarity:

4.3.2.1 Physicochemical characteristics

The manufacturer should consider the concept of the desired biosimilar candidate (and its variants) as defined in ICH Q6B when designing and conducting studies to demonstrate a high degree of similarity. The complexity of the molecular entity with respect to the degree of molecular heterogeneity should also be considered. Heterogeneity in therapeutic proteins may arise in a number of ways and may affect the expected clinical performance of a protein biologic product. When differences in the heterogeneity profile are observed between the biosimilar candidate and the CRBD at the physicochemical level, orthogonal approaches should be used to assess the potential impact. These approaches may include functional methods. They help determine whether the differences could affect the clinical effects of the drug.

Although an identical primary sequence between the biosimilar candidate and its CRBD is expected, low-level sequence variants may occur due to transcription and translation errors. These variants, especially those arising through amino acid misincorporation during high-level expression and should be identified if present. The presence of such variants may be acceptable when they are well controlled, characterized and shown not to impact critical quality attributes, including purity, potency or immunogenicity risk. A risk-based

assessment of the potential clinical relevance of any identified variants should be conducted using available analytical, functional and literature data to support the biosimilarity evaluation.

4.3.2.2 Purity and impurities

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

Differences observed in the purity and product-related impurity profiles of the biosimilar candidate relative to its CRBD should be evaluated to assess their potential impact on safety and efficacy. Where the biosimilar candidate exhibits different impurities, those impurities should be identified, characterized and quantified, when possible. The potential impact of differences in the impurity profile upon safety should be addressed and supported by the appropriate data and/or scientific justification.

The process-related impurities in the biosimilar candidate are not expected to match those observed in its CRBD and are not expected to be included in the similarity assessment. Clearance of process-related impurities should be assessed as per ICH guidelines and demonstrated to be safe.

4.3.2.3 Immunogenicity

The intrinsic immunogenicity of a therapeutic protein is determined by its critical quality attributes. For a biosimilar candidate, these attributes must be compared directly with those of the CRBD in order to establish that the risk of an immune response is not greater than that associated with the CRBD. A thorough analytical and functional comparison is the primary foundation of the immunogenicity risk assessment.

This comparison should include all structural and product related characteristics that are known to influence immune response. These characteristics include primary amino acid sequence, higher order structure and post translational modifications (such as glycosylation patterns and the presence of non-human glycans). They also include the presence of aggregates and subvisible particles, host cell proteins and other process or product related impurities and excipients.

The immunogenicity profile of the CRBD should be well understood based on its clinical use and post market experience. As a result, a sensitive analytical and functional comparison of the biosimilar with the CRBD provides the most reliable basis for identifying attributes that may be relevant to immune response. Any observed differences should be

examined within a structured risk-based framework to determine whether they might influence the likelihood, severity or clinical consequences of an immune reaction.

The sponsor is expected to provide evidence that any identified differences do not adversely impact safety or efficacy. When the analytical assessment demonstrates a high degree of similarity in quality attributes relevant to immunogenicity, the potential for the biosimilar candidate to present an increased immunogenicity risk relative to the CRBD is considered low.

4.2.3.4 Functional properties

Biological assay results can serve multiple purposes in the confirmation of quality attributes. The manufacturer should consider the limitations of biological assays, such as high variability, that may prevent detection of differences between a biosimilar candidate and its CRBD.

When the biosimilar candidate and its CRBD have multiple biological or functional properties, a comprehensive set of functional assays designed to evaluate the range of properties should be utilized.

The physicochemical analyses should confirm the similarity of the higher order structures. The integrity of such structures should be confirmed using comparative functional assays. Multiple functional assays should be performed as part of the similarity assessment. The functional assays should reflect the mechanism(s) of action to the extent possible. These may include, but not limited to, binding assays to determine specificity, affinity and avidity to the target and/or Fc-effector function, viral neutralization, anti-proliferation, cytotoxicity, specific activity or cell-free translation.

4.3.2.5 Stability

Comparative stability studies (for example, accelerated, stressed and forced degradation studies) should be conducted to compare degradation profiles of the biosimilar candidate to those of the CRBD. 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 differences between the biosimilar candidate and the CRBD that are not readily detectable by the characterization studies, which may warrant additional evaluation.

ICH Q5C and ICH Q1, *Stability Testing of Drug Substances and Drug Products* should be consulted to determine the conditions for stability studies that provide relevant data for a product-to-product comparison.

It should be noted that while sponsors are expected to provide long-term stability data in Module 3 to support authorization, such data does not need to be part of the comparability assessment.

4.4 Manufacturing process considerations

Therapeutic proteins can be produced in a variety of biological systems. It is expected that the expression construct for the proposed biosimilar candidate codes for the same primary amino acid sequence as the CRBD. The starting expression sequence should therefore be exactly the same as the CRBD. However, minor transcription variants that are not expected to change the functional properties of the molecule may be justified. Differences in the expression system or construct design may be acceptable, provided they do not result in differences in the primary structure of the expressed protein. Minor variants arising from the manufacturing process that are not expected to affect the functional properties of the molecule product may be scientifically justified. Any known differences in the manufacturing approach between the biosimilar candidate and the CRBD should be carefully evaluated for their potential impact on process- and product-related substances, impurities and contaminants.

4.4.1 Control strategy

The manufacturer should define a control strategy for the biosimilar candidate that is specific and appropriate to assure product quality. Although justification of the control strategy, including the specification, may be supported by data derived from the similarity assessment, it is considered stand-alone and not dependent of the CRBD.

4.5 Determination of similarity

A final determination of a high degree of similarity is based on all relevant data from comparative analytical and non-clinical and clinical studies. To be considered a biosimilar, the weight of evidence should be provided by the comparative analytical studies. Health Canada recommends that sponsors develop a risk assessment tool to evaluate and rank the CRBD quality attributes in terms of potential impact on activity, PK/PD, efficacy, safety and immunogenicity. These attributes should be evaluated using quantitative analysis, considering the risk ranking of the quality attributes, as well as other factors. It should be

noted, however, that some attributes may be highly critical (for example, primary sequence) but not amenable to quantitative analysis.

Consideration as a biosimilar is not appropriate if a high degree of similarity cannot be established by comparative analytical studies. If major differences are detected in the comparative analytical studies, they should be addressed in the development phase. Non-clinical and clinical studies cannot address major differences detected in the comparative analytical studies.

4.6 Manufacturing changes following issuance of market authorization

Any changes to the manufacturing process of the biosimilar that warrant a demonstration of comparability between the pre-change and post-change versions of the biosimilar should be conducted in accordance with ICH Q5E. Additional comparisons with the original CRBD are not required.

5. Non-clinical and clinical information requirements

5.1 General

Non-clinical and clinical requirements outlined in this guidance document apply to biosimilar candidates that have been demonstrated to be highly similar to the CRBD. This determination is based on the results of the comparative analytical studies included in the chemistry and manufacturing data package. If a high degree of similarity has not been established, then the drug cannot be deemed to be biosimilar.

This section provides general guidance on expectations related to the non-clinical and clinical information for a biosimilar candidate. Specific requirements may differ depending on the characteristics of the drug.

If clinical studies are performed, participants should receive the drug 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. Refer to ICH Q5E and, if necessary, consult with BRDD for additional guidance.

5.2 Non-clinical studies

Where a high degree of similarity is established by comparative analytical studies and where extensive *in vitro* mechanistic studies are indicative of a high degree of similarity, *in vivo* general toxicology studies are generally not needed. This includes safety pharmacology, reproductive/developmental toxicity, genotoxicity and carcinogenicity studies. In exceptional circumstances where an *in vivo* evaluation is deemed necessary, the focus of the studies (PK and/or PD and/or safety) will depend upon the type of additional information needed.

5.3 Clinical studies

The purpose of the clinical program of a biosimilar candidate is to support a demonstration of a high degree of similarity derived from the comparative analytical studies. These studies assess the physicochemical characteristics, functional properties and stability profiles between the biosimilar candidate and the CRBD.

The clinical program should primarily include a comparative pharmacokinetic study and if feasible, may include a comparative evaluation of pharmacodynamics. These studies may be followed by an additional clinical trial(s) in exceptional circumstances. Differences observed between the biosimilar candidate and the CRBD should be addressed. If differences cannot be sufficiently addressed, the candidate may not be suitable for authorization as a biosimilar.

5.3.1 Comparative clinical pharmacology studies

Comparative pharmacokinetic (PK) studies should be conducted to rule out PK differences between the biosimilar candidate and the CRBD.

PK studies should be conducted in healthy subjects when appropriate as they are generally considered to be a homogeneous and sensitive population. A sub-therapeutic dose residing on the linear part of the dose-response curve should be considered if studies are performed in healthy subjects. When the biosimilar candidate cannot be safely administered to healthy subjects, PK studies should be conducted in a suitably sensitive patient population. In these studies, the dose(s) should be within the therapeutic dosing range as recommended in the product monograph of the CRBD.

The following factors should be taken into consideration when designing a comparative PK study (for example, when choosing between cross-over versus parallel-group study):

- risk of immunogenicity
- route(s) of administration
- linearity of PK parameters
- half-life of the biologic drugs
- conditions and diseases to be treated
- the endogenous levels and diurnal variations of the protein under study, where applicable

The PK comparison should not be limited to parameters reflecting absorption only. Parameters representing distribution and elimination (for example, volume of distribution, 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 BRDD.

Acceptable criteria for the determination of similarity in comparative PK should be defined and justified prior to the initiation of the PK studies. Typically, these criteria are as follows:

- The 90% confidence interval of the relative mean area under the concentration versus time curve to the time of the last quantifiable concentration (AUC_T) of the biosimilar candidate to CRBD should be within 80.0% - 125.0%, inclusive.
- The 90% confidence interval of the relative mean maximum concentration (C_{max}) of the test to CRBD should be within 80.0% - 125.0%, inclusive.

In exceptional circumstances, when such criteria cannot be employed, the use of alternative criteria should be justified.

If available, relevant pharmacodynamic (PD) endpoints may be added to the PK study as supportive information. In most cases, the measurement of the PD marker can be incorporated into a combined comparative PK/PD study. Relevant PD markers should:

- reflect the primary mechanism of action(s) of the drug
- have dynamic range and sensitivity to detect differences between the biosimilar candidate and the CRBD

- have a temporal profile amendable to capturing a sufficient proportion of the PD profile for comparison
- have a demonstrated dose-response relationship with the drug

In cases where drug concentrations cannot be measured reliably, a PD endpoint may be used as a surrogate for PK. The primary endpoint for comparative PD studies should be the area under the effect-time curve to the last quantifiable measurement ($AUEC_T$). Maximum effect (Emax) should also be evaluated. In general:

- the 95% confidence interval of the relative geometric mean ratio (that is, the ratio of the geometric mean of the biosimilar candidate to the geometric mean of the CRBD) for $AUEC_T$ should be entirely contained within an interval of 80.0% - 125.0%
- the relative geometric mean ratio (biosimilar candidate to CRBD) for Emax should be contained within an interval of 80.0% - 125.0%

If different criteria are to be applied, a discussion with Health Canada prior to the submission is recommended; the justification for these different criteria should be provided in the submission.

For more information on the principles of comparative PK studies, refer to:

- Guidance document: Conduct and analysis of comparative bioavailability studies

5.3.1.1 Immunogenicity

As noted in 4.1, the foundation of immunogenicity risk assessment is the comprehensive analytical and functional comparison of the biosimilar with the CRBD in combination with the assessment of the quality of the biosimilar candidate itself. Descriptive comparisons of immunogenicity are expected to be incorporated into the clinical PK studies, conducted in either healthy volunteers or patients, as appropriate based on the known risk profile of the CRBD.

The measurement of anti-drug antibodies (ADAs) in PK studies is considered good scientific practice and is recommended to:

- support the interpretation of PK data
- provide a descriptive comparison of ADA incidence between products

- identify major differences in immune response that could affect the safety and/or efficacy of the biosimilar candidate in comparison with the CRBD

The following elements are expected to be included in the PK study:

- Pre-dose (baseline) and at least one post-dose ADA sample at or near the expected time of trough concentration
- Validated, drug-tolerant assays that detect binding and neutralizing antibodies
- Evaluation of the relationship between ADA status and PK parameters

If analytical comparisons demonstrate that the biosimilar candidate is highly similar to the CRBD with no added risk of immunogenicity, additional clinical immunogenicity studies are generally not warranted. This applies when the comparative PK study also demonstrates statistical equivalence in PK parameters. It also requires that and no major differences in immunogenicity are observed, including ADA incidence and impact on PK.

Where a single-dose comparative PK study is insufficient to provide meaningful data on immunogenicity, a clinical evaluation of immunogenicity may warrant a different approach, such as investigation in a multi-dose study.

It is important to re-emphasize that clinical efficacy studies are not sufficiently sensitive to resolve differences identified through comparative analytical or functional characterization. This limitation also applies to the assessment of immunogenicity risk. Where differences in quality attributes are identified between a biosimilar candidate and its CRBD, such differences cannot be mitigated through clinical studies. In such circumstances, the totality of the evidence would not support a conclusion of high similarity and the product would be unlikely to meet the criteria for authorization as a biosimilar.

5.3.2 Comparative clinical efficacy studies

Comparative clinical efficacy studies are not typically required for a biosimilar candidate to a CRBD when the biosimilar has been compared and extensively characterized by analytical and clinical pharmacology studies. Safety and comparative immunogenicity data are required and should be collected within the comparative clinical pharmacology studies. This could be supplemented with data collected using other study designs (for example, studies designed to specifically focus on safety and/or immunogenicity).
If comparative clinical efficacy studies are included, the sponsor should explain the role of the studies and the value of results in the context of the submission.

6. Indications, labelling and risk-management plan

6.1 Authorization of indications

The decision to authorize the requested indications is dependent on the demonstration of a high degree of similarity between the biosimilar candidate and CRBD based on data derived from comparative analytical and pharmacology studies.

All the indications granted to the CRBD can be applied to the biosimilar candidate without further justification if the biosimilar candidate has been shown to be highly similar:

- to the CRBD in terms of analytical characteristics **and**
- in functional properties related to the mechanism of action of the CRBD

The biosimilar candidate must be able to deliver the same posology as the CRBD for respective indications. For example, a pediatric indication would not be granted to a biosimilar if the biosimilar was not available in a presentation that could deliver the appropriate dose.

A biosimilar candidate may only be authorized for indications that are authorized for the CRBD. A submission seeking an indication that is not held by the CRBD would fall outside the scope of this guidance. In such cases, the product would not be considered a biosimilar and would not be eligible for authorization based on a comparative similarity assessment reserved for biosimilar candidates. In such circumstances, the sponsor must file the product with a different brand name, under a separate NDS and dossier identifier. The submission must include sufficient evidence to independently establish the safety, efficacy and quality of the product for the proposed indication, along with all required labelling documentation (such as a product monograph).

6.2 Labelling requirements – Product monograph

The product monograph for a biosimilar candidate should be developed in a manner consistent with the principles, practices and processes outlined in the most recent product monograph guidance document. Sponsors should use the most current Product Monograph Master Template when preparing a product monograph for a biosimilar candidate. Briefly, the contents of the product monograph for biosimilars should include the following information:

- a statement indicating that the drug is a biosimilar to the CRBD

- relevant safety and efficacy information from the product monograph of the CRBD, including contraindications, warnings and precautions, adverse drug reactions, clinical trials and non-clinical information for all indications that are authorized for the biosimilar

The product monograph of the biosimilar must be updated on an ongoing basis, as new information about the biosimilar and the CRBD becomes available or when labelling requirements change.

The naming of all biosimilars should comply with the requirements set out in the Policy Statement on the Naming of Biologic Drugs.

Consult:

- Guidance document: Product monograph
- Product monograph master template
- Policy statement on the naming of biologic drugs

6.3 Risk management plan

For details on the submission of risk management plans for biosimilars, refer to:

- *Submitting risk management plans guidance document*

7. Post-market information requirements

7.1 Adverse drug reaction reporting and periodic reports

Biosimilar sponsors are required to comply with sections C.01.016 to C.01.019 of the *FDR*, which includes ADR reporting.

The unique brand name and non-proprietary name of the biosimilar, as well as other product-specific identifiers, such as the drug identification number (DIN) and the lot number, should be included in ADR reports to facilitate the traceability of an adverse reaction to a specific suspect drug product.

The periodicity for the submission of periodic safety update reports (PSURs) or periodic benefit risk evaluation reports (PBRERs) should be consistent with appropriate ICH guidelines for marketed drugs or as determined by the Minister, when the drug is authorized for market.

Guidance Document - Periodic Benefit-Risk Evaluation Report (PBRER) International Conference on Harmonisation (ICH) Topic E2C(R2)

7.2 Post-notice of compliance (NOC) changes

A biosimilar is classified as a new drug and is subject to all of the associated regulatory requirements, including specific requirements related to changes made to a new drug that has received an NOC pursuant to section C.08.004 of the *FDR* (post-NOC changes). This guidance should be read in conjunction with the following documents for specific guidance and submission documentation requirements for applicable post-NOC changes:

- Post-notice of compliance (NOC) changes: Framework document
- Post-notice of compliance (NOC) changes: Safety and efficacy document
- Post-notice of compliance (NOC) changes: Quality guidance
- Questions and answers: Plain language labelling regulations for prescription drugs - document

Information regarding general submission requirements, current processes and performance standards for post NOC changes is outlined in the Guidance on management of drug submissions and applications.

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

There may be situations post-NOC where sponsors seek authorization of indications held by the CRBD authorized in Canada. A supplement to a 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. If accepted for review, these submissions would generally be considered a labelling-only SNDS.

Biosimilar sponsors should submit the following form in Module 1.2.3 Certification and attestations forms at the time of filing:

- Sponsor attestation: SNDS for biosimilar products – Addition of indication to product monograph to be in line with the Canadian reference biologic drug

Guidance on management of drug submissions and applications

8. Acronyms and definitions

8.1 Acronyms

ADA = anti-drug antibody

ADR = adverse drug reaction

AUC = area under the curve

BRDD = Biologic and Radiopharmaceutical Drugs Directorate

CRBD = Canadian reference biologic drug

C_{max} = maximum concentration

CTD = common technical document

ICH = International Council for Harmonisation

Emax – maximum effect

MHPD = Marketed Health Products Directorate

NDS = new drug submission

NOC = notice of compliance

PK/PD = pharmacokinetic/pharmacodynamic

PBRER = periodic benefit-risk evaluation report

PSUR = periodic safety update report

RBD = reference biologic drug

SNDS = supplement to a new drug submission

8.2 Definitions

Biologic drug

A drug listed in Schedule D to the FDA. 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

A biologic drug that obtains market authorization subsequent to an originator biologic previously authorized in Canada, referred to as the Canadian reference biologic drug (CRBD). In its biosimilar submission, a sponsor relies on prior information regarding safety, efficacy and effectiveness that is deemed relevant due to the demonstration of a high degree of similarity to the CRBD and which influences the amount and type of original data required. Biosimilar biologic drugs were previously referred to as subsequent entry biologics.

Drug product

The dosage form in the final immediate packaging intended for marketing.

Drug substance

The defined process intermediate containing the medicinal ingredient, which is subsequently formulated with excipients to produce the drug product.

Control strategy

A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications and the associated methods and frequency of monitoring and control.

Highly similar

A determination, based on robust and appropriately designed comparative analytical studies, that the proposed biosimilar and the reference biologic drug demonstrate analytical concordance in structural and functional characteristics, with critical quality attributes falling within prospectively justified, pre-defined ranges informed by reference product variability and that any observed differences have been assessed and determined not to have a meaningful impact on safety or efficacy.

Quality target product profile

A prospective summary of the characteristics of a drug product that will be achieved to ensure the desired quality, safety and efficacy, serving as a framework to guide development and define the critical quality attributes.

Reference biologic drug

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 a high degree of similarity.

Specification

A specification is defined as a list of tests, references to analytical procedures and appropriate acceptance criteria which are numerical limits, ranges or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other

stages of its manufacture should conform to be considered acceptable for its intended use.

Conformance to specification means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of authorization.

9. Contact us

9.1 Consultation and pre-submission meetings

Sponsors of biosimilar candidates are encouraged to consult with BRDD 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 candidate.

A biosimilar sponsor may request a pre-submission meeting early in the development process in order to receive advice from BRDD on their data package. Refer to the Guidance Document: The Management of Drug Submissions and Applications for instructions on filing a pre-meeting request and package with BRDD.

Sponsors should ensure their drug meets the eligibility criteria for a biosimilar candidate as outlined in this guidance. Sponsors may submit a request for a pre-submission meeting to the Office of Regulatory Affairs.

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, as well as any future legislative and regulatory changes relevant to biosimilars.

Guidance on management of drug submissions and applications

Questions about biosimilar submissions

Office of Regulatory Affairs

Biologic and Radiopharmaceutical Drugs Directorate

Health Products and Food Branch

Health Canada

Email: brdd.ora@hc-sc.gc.ca

Questions or comments about this guidance

Centre for Policy, Pediatrics and International Collaboration

Biologic and Radiopharmaceutical Drugs Directorate

Health Products and Food Branch

Health Canada

Email: brdd-cppic_brdd-cppci@hc-sc.gc.ca