Health Canada Santé Canada

May 30, 2014

Notice

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Release of Guidance Document: Biopharmaceutics Classification System Based Biowaiver

Health Canada is pleased to announce the release of a guidance document, entitled *Biopharmaceutics Classification System Based Biowaiver.*

The purpose of this document is to provide guidance to sponsors of new drugs with the information necessary to apply for a waiver from submitting comparative bioavailability studies as part of the safety and effectiveness requirements under Division 8 of the *Food and Drug Regulations*. The information required applies to only Biopharmaceutics Classification System (BCS) Class I and III drugs.

The scope of this document is limited to immediate-release, solid oral pharmaceutical drug products regulated under the *Food and Drugs Act* that are intended to deliver medication to the systemic circulation. It is not applicable to disinfectants or drugs for veterinary use.

A draft version of this guidance document was released for consultation in August 2012. Comments from stakeholders have been considered in the development of this final version.

Comments received during the most recent consultation process, together with responses from the Therapeutic Products Directorate (TPD) have been collated in a separate document, which is available upon request. Requests for this document should be directed to the e-mail address below.

This guidance comes into effect as of the date of publication.

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GUIDANCE DOCUMENT
Biopharmaceutics Classification System Based Biowaiver

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Canada

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

Également disponible en français sous le titre : *Ligne directrice sur la dispense de la démonstration de bioéquivalence fondée sur le système de classification des produits biopharmaceutiques*

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 program 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 product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

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

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1. INTRODUCTION

1.1 Objectives

To provide sponsors of new drug submissions with the information necessary to comply with Division 8 of the *Food and Drug Regulations* (*Regulations*) with respect to Biopharmaceutics Classification System (BCS) based biowaivers for comparative bioavailability studies to be used in support of the safety and efficacy of a drug. This information is applicable to all submission types where comparative bioavailability studies would normally provide pivotal evidence in support of the safety and efficacy of a product.

1.2 Policy Statements

When an application for a BCS-based biowaiver of comparative bioavailability studies versus a reference product is submitted in support of the safety and efficacy of a drug, the relevant drug substance and drug product characteristics should meet the standards described in this guidance in order to ensure compliance with the *Regulations*.

In vivo human data collected for the purpose of submission to Health Canada should be collected in accordance with generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of subjects. They should be collected in compliance with the good clinical practices referred to in Division 5 of the *Regulations* and described in the *International Conference on Harmonisation (ICH) Guidance (Topic E6) on Good Clinical Practice*. The principles of Good Manufacturing Practice as indicated in Part C, Division 2 of the *Regulations* should be adhered to wherever applicable.

1.3 Scope and Application

The data requirements and acceptance criteria outlined in this guidance are intended to be applied to all applications for a BCS-based biowaiver of comparative bioavailability studies which provide pivotal evidence of the safety and efficacy of a product. These requirements and criteria apply to both first-entry and subsequent-entry products. Examples of cases where this guidance applies are:

a. biowaivers for comparative bioavailability studies in support of the bioequivalence of subsequent-entry products to the Canadian Reference Product;
b. biowaivers for bridging studies where the formulation to be marketed is different from the formulation used in the pivotal clinical trials;
c. biowaivers for studies in support of significant post-approval changes and product line extensions (for example, if a new strength is added to the range of a subsequent-entry product by comparing with the same strength in the reference range, a biowaiver would be considered.); and

d. biowaivers for comparative bioavailability studies in support of Drug Identification Number (DIN) Applications.

The scope of this document is limited to immediate-release, solid oral pharmaceutical drug products regulated under the *Food and Drugs Act* that are intended to deliver medication to the systemic circulation and does not apply to products subject to buccal or sublingual absorption. This guidance document should be read in conjunction with other relevant Health Canada guidance documents.

1.4 Definitions

Absorption - the uptake of substance from a solution into or across tissues. Absorption can include passive diffusion, facilitated passive diffusion (with a carrier molecule), and active transport.

Critical dose drug - drugs where comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions which may be persistent, irreversible, slowly reversible, or life threatening, which could result in hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or death. Adverse reactions that require significant medical intervention to prevent one of these outcomes are also considered to be serious. See Health Canada guidance document *Comparative Bioavailability Standards: Formulations Used for Systemic Effects* (22 May 2012)

Dose solubility volume (DSV) - the highest therapeutic dose (milligrams) divided by the solubility of the substance [milligrams/millilitres (mg/mL)] at a given pH and temperature. For example, if a drug substance has a solubility of 31 mg/mL at pH 4.5 (37°C) and the highest dose is 500 mg, then DSV = 500 mg / 31 mg/mL = 16 mL at pH 4.5 (37°C).

Highest dose - the highest approved therapeutic dose for the drug substance in Canada. If not currently approved in Canada, the highest proposed dose is applicable.

Rapidly dissolving product - a product in which not less than 85% of the labelled amount is released within 30 minutes or less during a product dissolution test under the conditions specified in this guidance.

Very rapidly dissolving product - not less than 85% of the labelled amount is released within 15 minutes or less during a product dissolution test under the conditions specified in this guidance.

2. GUIDANCE FOR IMPLEMENTATION

2.1 Background

BCS-based biowaivers are meant to reduce the need for establishing *in vivo* bioequivalence in situations where *in vitro* data may be considered to provide a reasonable comparison of the performance of two products.

The Biopharmaceutics Classification System (BCS) is a scientific approach designed to predict drug absorption based on the aqueous solubility and intestinal absorptive characteristics of the drug substance. The BCS categorizes drug substances into one of four BCS classes based on these characteristics. For the purposes of this guidance, drug substances are classified as follows:

Class I: high solubility, high extent of absorption
Class II: low solubility, high extent of absorption
Class III: high solubility, low extent of absorption
Class IV: low solubility, low extent of absorption

BCS-based biowaiver applications will only be considered for immediate-release solid oral dosage forms containing eligible drug substances if the required data, as described in this guidance, ensures the similarity between the proposed drug product and the appropriate reference product.

2.2 Biopharmaceutics Classification System (BCS) Classification and Eligibility of a Drug Substance

The drug substance in an immediate-release product is eligible for a BCS-based biowaiver providing:

1. It is classified as BCS Class I or III;
2. The substance conforms to the TPD policy on *Interpretation of "Identical Medicinal Ingredient"* (2003) in comparison to the reference product; and
3. The drug substance is not considered to be a critical dose drug.

Criteria for a BCS-based biowaiver are summarised in Appendix 1.

The conditions to be employed for classification purposes are described below.

2.2.1 Solubility

Test Conditions

The stability of the drug substance at the relevant pH range of 1.2 to 6.8 should be demonstrated. A profile of the solubility of the drug substance should be developed for the physiologically relevant pH range of 1.2 – 6.8 employing the following conditions:

Conditions

Solvent: At a minimum, aqueous buffer solutions of pH 1.2, 4.5, 6.8
Temperature: 37 plus or minus (±) 1°C
Replicates: Not less than three (3) at each pH tested
Methodology: Shake-flask technique or similar method with justification

Additional information

The pH for each test solution should be confirmed before and after the addition of the drug substance in order to ensure pH stability of the buffered medium. The pH should be adjusted if necessary.

Classification

High solubility: A drug substance is classified as highly soluble if the highest therapeutic dose of the drug substance is completely soluble in 250 mL or less of aqueous media over the pH range of 1.2-6.8 at 37 ± 1°C, that is (*i.e.*)., DSV less than or equal to (≤) 250 mL over the pH range.
Low solubility: A drug substance is classified as a low solubility compound if the highest therapeutic dose of the drug substance is not completely soluble in 250 mL of aqueous media at any pH within the pH range of 1.2-6.8 at 37 ± 1°C, *i.e.*, DSV greater than (>) 250 mL at any pH within the range.

2.2.2 Absorption

A drug substance is considered to be highly absorbed when 85 percent, or more, of the highest therapeutic dose is absorbed when administered orally. If linearity within the therapeutic dosage range is established, then information obtained using a lower dose may be extrapolated to the highest therapeutic dose.

2.2.2.1 Pivotal *in vivo* evidence

Data arising from the following human studies, that are appropriately designed and conducted, will be considered as evidence of the extent of absorption:

A. Absolute bioavailability studies:
Studies comparing the bioavailability of at least the highest dose of the drug substance from an orally administered aqueous solution, or an immediate-release tablet or capsule without excipients that are known to affect absorption, with an intravenous dose.

The extent of absorption should be measured through serial blood sampling using a sampling protocol designed to characterize at least 80% of the area under the time-plasma concentration curve to infinity (AUC_I). The study population should be properly characterized and a sufficient number of volunteers should be included in order to obtain a reliable estimate of absolute bioavailability.

B. Mass balance studies:
Mass balance studies are conducted to determine the disposition of a drug substance following oral administration.

For the purposes of assessing absorption, quantification of the parent compound excreted in the urine, as well as Phase 1 oxidative and Phase 2 conjugative metabolites excreted in the urine or feces can be used. The parent compound excreted in faeces, or metabolites produced through reduction or hydrolysis should not be included due to uncertainty of their origin unless the sponsor can demonstrate that those metabolites did not result from degradation or metabolism in the gut prior to absorption. Mass balance data will support the classification of a highly absorbed drug substance if the sum of the urinary recovery of the parent compound and the urinary and fecal recovery of Phase 1 oxidative and Phase 2 conjugative metabolites of the parent compound account for greater than or equal to (≥) 85% of the administered dose.

Mass balance studies used to establish extent of absorption should be designed to thoroughly characterize the *in vivo* disposition of the drug substance in a sufficient number of volunteers to obtain meaningful estimates.

Absolute bioavailability or mass balance study data obtained from published literature may be accepted as evidence if it can be clearly established that it was derived from appropriately designed studies.

Classification

High absorption: ≥ 85% of the administered dose absorbed.
Low absorption: < 85% of the administered dose absorbed.

2.2.2.2 Supportive evidence

In vitro models may be used to provide supportive evidence in a BCS-based biowaiver application, if adequately justified. The *in vitro* model should be validated and shown to be representative of intestinal absorption. For the purpose of validation, consideration should be given to relevant guidance documents published by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

2.3 Biopharmaceutics Classification System (BCS) Classification and Eligibility of a Drug Product

A drug product is eligible for a BCS-based biowaiver providing:

1. The drug substance(s) satisfy the criteria (for example, for high solubility) outlined above;
2. The drug product is a conventional, immediate-release solid oral dosage form; and
3. The drug product is a dosage form that is the same as the reference product [for example (*e.g.*), an immediate-release tablet versus an immediate-release tablet].

Other additional dosage forms
Fixed-dose combination products may be eligible for a biowaiver when all drug substances contained in the product meet the criteria defined in Section 2.2 and the product itself meets the criteria defined above. A biowaiver for an individual drug component in a fixed-dose combination product may be justified if these criteria are met and there is no interaction between the drugs in the combination product.

Drug products subject to buccal or sublingual absorption are not eligible for a biowaiver application. As such, an orodispersable product is eligible for a biowaiver application only if there is no buccal or sublingual absorption and the product is labelled to be consumed with water.

Batch requirements
The batches of drug product used for all biowaiver testing should, at a minimum, conform to the requirements for the 'biobatch' employed in *in vivo* comparative bioavailability trials designed to demonstrate the bioequivalence of a drug product to a reference product. Where batches used for comparative testing are not of commercial scale, they should be at least 1/10 the size of the proposed commercial scale but not less than 100,000 units.

The measured drug substance content of the batches employed in comparative testing should meet requirements with respect to label claim.

For higher risk drug products meeting either of the following conditions, biowaiver testing should be conducted with at least one batch of production (commercial) scale:

1) The product is a low dose form, when the tablet/capsule strength is 5 mg or lower and/or the drug substance forms 2% weight per weight (w/w) or less of the total mass of the tablet/capsule content; or

2) When the chosen manufacturing process is prone to variability and/or scale-up difficulties (*e.g*. direct compression process for manufacturing a low dose product); complex (*e.g*. use of coating technology to add the drug substance to inert granules, lyophilisation, microencapsulation); and/or uses new technologies (*e.g*. nanotechnology).

Requirements
In order for a drug product to qualify for a biowaiver, criteria with respect to the composition and *in vitro* dissolution performance of the drug product should be satisfied. The drug product acceptance requirements are described below.

2.3.1 Excipients

Well-established excipients in usual amounts should be employed in the proposed drug product. A description of the function and a justification for the relative amount of each excipient is required. Excipients that might affect the bioavailability of the drug substance *e.g.,* mannitol, sorbitol, or surfactants, should be identified. These critical excipients should not differ qualitatively or quantitatively between the test product and reference product and should be within 10% of the amount measured in the reference product batch(es) used in comparative testing.

As a part of a biowaiver application, the following conditions should be satisfied:

BCS Class I drug substances
Although the assessment of the potential impact of excipients on absorption would be simplified if the excipients employed in the proposed product core (provided the coating is non-functional) are qualitatively the same and quantitatively similar to those in the reference product, some differences in formulation are permitted except in excipients affecting bioavailability as discussed above.

BCS Class III drug substances
Excipients in the proposed product core (provided the coating is non-functional) should be qualitatively the same and quantitatively very similar to that of the reference product

as described in the TPD policy *Bioequivalence of Proportional Formulations - Solid Oral Dosage Forms* (1996).

2.3.2 *In vitro* dissolution

Comparative *in vitro* dissolution tests should be conducted using a minimum of two batches of the proposed product and one of the reference product. Appendix 5 of Health Canada's *Post-Notice of Compliance (NOC) Changes: Quality Document* provides recommendations for conducting and assessing comparative dissolution profiles.

The following conditions should be employed in the comparative dissolution studies to characterise the dissolution profile of the product:

Conditions

Amount: One unit of the strength for which a biowaiver is requested
Methodology: Basket apparatus (USP I) or paddle apparatus (USP II)
Agitation: Basket apparatus at 100 revolutions per minute (rpm) or paddle apparatus at 50 rpm (if coning is observed for both Test and Reference products, speed may be increased, for example, to 75 rpm. However results with the lower speed should also be reported).
Dissolution media: Aqueous buffers at pH 1.0 - 1.2, 4.5, and 6.8
Volume of media: ≤ 900 mL
Sampling times: For example, 5, 10, 15, 20 and 30 minutes
Temperature of media: 37 ± 1°C
Replicates: Not less than 12 units per batch per pH medium

Additional information

Dissolution tests should be conducted using fully validated dissolution methods and analytical techniques. Care should be taken to ensure the pH of the medium is maintained throughout each trial. To prevent continued dissolution, collected samples should be filtered immediately. Additional testing may be required under the pH conditions within the range of 1.0 - 6.8 at which the drug substance displays minimum solubility.

Simulated gastric fluid without enzymes may be employed *in lieu* of the pH 1.2 buffer (or 0.1 N HCl) medium, and in the same fashion, simulated intestinal fluid without enzymes may be employed *in lieu* of the pH 6.8 buffer medium. Surfactants should not be employed in dissolution testing for a BCS-based biowaiver. The use of enzymes may be justified when gelatin capsules or tablets with a gelatin coating are being compared.

At least 12 units should be used for each profile determination. Mean dissolution values can be used to estimate the similarity factor, f2. To use mean data, the percent coefficient of variation at the earlier point should be not more than 20% and at other time points should be not more than 10%. Because f2 values are sensitive to the number of dissolution time points, only one measurement should be included after 85% dissolution of the test and reference products. Compilation of historical data is not acceptable.

Acceptance criteria

BCS Class I drug substances: The test product and reference product should display either very rapid or similarly rapid *in vitro* dissolution characteristics (>85% dissolved in ≤30 minutes) under the defined conditions in order to be eligible for a biowaiver. The similarity of dissolution profiles are demonstrated when the f_2 value is ≥50. Profile comparison (f_2 testing) is not necessary for very rapidly dissolving products (>85% dissolved in ≤15 minutes).

BCS Class III drug substances: The test product and reference product should display very rapid *in vitro* dissolution (>85% dissolved in ≤15 minutes) characteristics under the defined conditions in order to be eligible for a biowaiver.

2.4 Additional Strengths of a Drug Product

When equivalence to a reference product for one strength in a series of strengths is established on the basis of a BCS-based biowaiver, a waiver from the requirement for conducting studies with other strengths cannot then be granted based on the proportionality principles as described in the TPD policy *Bioequivalence of Proportional Formulations - Solid Oral Dosage Forms* (1996). Other strengths in the product line should conform to the requirements for a BCS-based biowaiver in comparison to the pharmaceutically equivalent reference product of the same strength.

3. REPORTING

The sponsor shall provide complete information on the critical quality attributes of the drug substance and finished product for both the test and reference product including, but not limited to: polymorphic form and enantiomeric purity; and any information on bioavailability or bioequivalence problems with the substance or drug product, including literature surveys and sponsor derived studies. All study protocols including standards, quality assurance and testing methods should be appropriately detailed and validated according to current regulatory guidance's and policies.

The reporting format should include tabular and graphical presentations showing individual and mean results and summary statistics. The tabular presentation should include standard deviation and coefficient of variation.

The report should include an identification of all excipients, and qualitative and quantitative differences between the test and reference products.

A full description of the analytical methods employed, including validation, should be provided. A detailed description of all test methods and solutions, including test and reference batch information [unit dose (mg and %), batch number, manufacturing date and batch size where known, expiry date, and any comments] examined is required. The dissolution report should also include information on the dissolution conditions such as apparatus, de-aeration, filtration process during sampling, volume, etcetera.

If an application is submitted to Health Canada subsequent to that of either the EMA or FDA, the reporting format can be identical to that of those agencies; however, the information provided should be consistent with the requirements of this guidance.

4. ADDITIONAL INFORMATION

The BCS remains an evolving field. Health Canada may update its guidance in response to new scientific knowledge, best practices, and/or on experience gained by the Department.

Questions concerning the submission of information for a biowaiver to Health Canada should be directed to:

Health Canada
Therapeutic Products Directorate
Regulatory Project Management Division
Office of Planning, Performance and Review Services
101 Tunney's Pasture Driveway
Address Locator: 0202D2
Ottawa, Ontario K1A 0K9

Phone: 613-954-6481
Fax: 613-952-9310
E-mail: RPM_Division-GPR_Division@hc-sc.gc.ca

Appendix 1: Summary of criteria for Biopharmaceutics Classification System (BCS)-based biowaiver:

Drug substance:

1. The drug substance is identical to that in reference product
2. The drug substance is not a critical dose drug
3. The drug substance should be BCS class I or III
    a. Highest therapeutic single dose is soluble in 250 mL aqueous media between pH 1.2 and 6.8.
    b. For class I requirements:
    At least 85% of highest therapeutic oral dose absorbed, based on absolute bioavailability determination in humans or mass balance data. Data from *in vitro* models considered supportive in estimating extent of absorption.
    c. For class III requirements:
    Less than 85% of highest therapeutic oral dose absorbed, based on absolute bioavailability determination in humans or mass balance data. Data from *in vitro* models considered supportive in estimating extent of absorption.

Drug product:

1. Product contains BCS Class I or III drug substance, which is identical to that in the reference product.
2. Immediate-release, solid oral pharmaceutical drug product, with no buccal or sublingual absorption, intended to deliver drug to the systemic circulation.
3. Dosage form is the same as the reference dosage form.
4. Fixed-dose combination products may be eligible for a biowaiver when all drug substances contained in the product and the product itself meet the defined criteria. A biowaiver for an individual drug component in a fixed-dose combination product may be justified if these criteria are met and there is no interaction between the drugs in the combination product.
5. Batches tested for biowaiver should meet the same requirements that a biobatch is expected to meet (that is, as in *in vivo* studies). For higher risk products, at least one commercial scale batch should be tested and meet the biowaiver requirements. Higher risk drug products include those made with potent drugs (drug substance is ≤ 2% w/w of total mass of dosage form) and those with known difficulties in scale-up or which use complex or new technologies in their manufacture.

6. Excipients:
    a. For products with BCS class I drug substances, excipients affecting bioavailability should be same as in reference product.
    b. For products with BCS class III drug substances, excipients should be qualitatively the same and quantitatively very similar to the reference product.
7. In aqueous media at pH 1.2, 4.5 and 6.8, the test and reference products should be very rapidly dissolving for products containing BCS Class III drug substances, and either very rapidly or similarly rapidly dissolving for products containing BCS Class I drug substances.