Health Canada Santé Canada

Guidance Document

Comparative Pharmacokinetic Studies for Orally Inhaled Products

Date adopted: 2020/12/21
Effective date: 2020/12/21

Canada

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

Également disponible en français sous le titre :
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Publication date: December 2020

Cat: H164-302/2020E-PDF
ISBN: 978-0-660-36480-3
Pub: 200255

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.

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1.Introduction

1.1 Policy objectives

To provide necessary information to sponsors of:

- new drug submissions
- abbreviated new drug submissions
- supplements to such submissions

This information will help sponsors comply with the *Food and Drug Regulations* (Regulations), with respect to comparative studies, with emphasis on *in vivo* comparative pharmacokinetic studies, used in support of the safety and efficacy of subsequent-entry orally inhaled drug products (OIPs).

The relevant sections of the *Food and Drug Regulations* are:

- C.08.002(2)(h)
- C.08.002.1(1)
- C.08.002.1(2)(c)(ii)
- C.08.003(3)

1.2 Policy statement

Comparative pharmacokinetic studies should be conducted in accordance with generally accepted clinical practices. These practices are designed to ensure the protection of the rights, safety and well-being of subjects. Good Clinical Practices are referred to in Division 5 of the Regulations, and described in the International Council for Harmonisation (ICH) Guidance (Topic E6) on Good Clinical Practice.

To ensure compliance with the Regulations, follow the recommendations included in this guidance respecting study design and the conduct of comparative pharmacokinetic studies involving subsequent-entry OIPs. The principles of Good Manufacturing Practice should be adhered to wherever applicable, as indicated in Part C, Division 2 of the Regulations.

1.3 Scope and application

This guidance applies to all comparative pharmacokinetic studies that provide pivotal evidence of the safety and efficacy of a subsequent-entry OIP, including:

- orally inhaled pressurized metered dose inhalers
- dry powder inhalers
- nebulization products

These products may contain, for example, any of the following:

- inhaled corticosteroids (ICS)
- long-acting beta2-adrenergic agonists (LABA)
- long-acting muscarinic antagonists (LAMA)
- combinations of these drugs

This guidance also applies when a significant change is made to an approved product, if a comparative clinical trial would previously have been required in support of the change. The same requirements will apply in both cases.

Examples of cases where this guidance applies are:

- comparative pharmacokinetic studies in support of the equivalence of subsequent-entry products to the Canadian reference product
- bridging studies where the formulation or device to be marketed is different from the formulation or device used in the pivotal clinical trials
- studies in support of significant post-approval changes and line extensions
- safety studies for drugs that are intended to act locally, where systemic drug concentrations may be measured for safety assessment

This guidance does not address requirements for demonstration of *in vitro* similarity of subsequent-entry and reference devices.

1.4 Background

OIPs are designed to act locally in the lungs. They are commonly used in the treatment of respiratory diseases such as asthma and chronic obstructive pulmonary disease.

Subsequent-entry OIPs should be demonstrated to be pharmaceutically equivalent to the corresponding reference product. They should have the same safety and efficacy profile after administration of the same dose. The safety and efficacy of subsequent-entry OIPs, and their equivalence to a reference product, have generally been assessed based on a combination of *in vitro* and *in vivo* studies, both pharmacodynamic and pharmacokinetic.

Health Canada recognises that it may be possible to establish the safety and efficacy of some products based on *in vivo* comparative pharmacokinetic studies, combined with *in vitro* studies, without studies using clinical endpoints. For those products where *in vivo* comparative pharmacokinetic studies are not appropriate, comparative *in vivo* pharmacodynamic studies may be necessary to establish the safety and efficacy of the proposed product. In this case, consult the Health Canada guidance document Data Requirements for Safety and Effectiveness of Subsequent Entry Inhaled Corticosteroid Products Used for the Treatment of Asthma (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/inhaled-corticosteroid-profile/inhaled-corticosteroid-guidance.html) with regard to study design considerations for studies using pharmacodynamic measures or clinical endpoints.

Health Canada's currently has 2 guidance documents on comparative bioavailability studies:

- Conduct and Analysis of Comparative Bioavailability Studies (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/bioavailability-bioequivalence/conduct-analysis-comparative.html)

- Comparative Bioavailability Standards: Formulations Used for Systemic Effects (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/bioavailability-bioequivalence/comparative-bioavailability-standards-formulations-used-systemic-effects.html)

These documents do not include specific guidance on pharmacokinetic comparison of subsequent-entry OIPs with the corresponding Canadian reference products.

The present document provides guidance aligned with the November 2018 recommendations from Health Canada's Scientific Advisory Committee on Respiratory and Allergy Therapies.

2. Guidance for implementation

This guidance should be read in conjunction with other applicable guidance documents such as:

- Conduct and Analysis of Comparative Bioavailability Studies (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/bioavailability-bioequivalence/conduct-analysis-comparative.html)
- Comparative Bioavailability Standards: Formulations Used for Systemic Effects (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/bioavailability-bioequivalence/comparative-bioavailability-standards-formulations-used-systemic-effects.html)
- Use of a Foreign-sourced Reference Product as a Canadian Reference Product (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/canadian-reference-product-guidance.html)

The following sections provide guidance specific to OIPs. In addition to reviewing this guidance document, we encourage you to consult with Health Canada before filing a drug submission about the data required to establish the safety and efficacy of a particular subsequent-entry OIP.

2.1 Device and *in vitro* equivalence

Refer to Appendix I of Health Canada's guidance document Pharmaceutical Quality of Inhalation and Nasal Products (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/chemical-entity-products-quality/guidance-industry-pharmaceutical-quality-inhalation-nasal-products.html**)**. It outlines quality-related information including device and *in vitro* studies specific to subsequent-entry inhalation products. In addition to conducting the development tests as described in Section 3 of that guidance document, subsequent-entry inhalation products should be shown to be equivalent to the reference product in a number of aspects, including:

- formulation
- physicochemical properties of the drug substance and drug product
- delivery device
- *in vitro* performance

To ensure equivalence of the delivery devices, the subsequent-entry OIP device should be sufficiently similar to the reference product in physical attributes and operating characteristics. This will minimize the risk for errors made by the intended end user, particularly if the user switches from the reference device to the proposed device. All differences between the subsequent-entry device and the reference device should be reported. Significant differences should be supported by data (e.g., in-use studies in both device-naïve and -trained subjects) to demonstrate that they do not pose an unacceptable risk of error by the end user. A use-related risk analysis to address differences between the subsequent-entry and reference products should include such factors as:

- how to assemble and prime the device to deliver the correct dose
- proper technique to use the device
- how to disassemble, maintain, store and clean re-usable device components

2.2 Pharmacokinetic study design

In general, current Health Canada guidance about the study design of comparative bioavailability studies applies to comparative pharmacokinetic studies involving OIPs.

A single-dose two-way cross-over design, under fasting conditions, may usually be used if bioavailability from lung absorption is such that the drug concentrations in blood can be reliably measured using a validated assay method.

For further guidance refer to Conduct and Analysis of Comparative Bioavailability Studies (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/bioavailability-bioequivalence/conduct-analysis-comparative.html).

2.2.1 Choice of subjects

Comparative pharmacokinetic studies on subsequent-entry OIPs may be carried out in healthy subjects. It is not necessary to conduct these studies in patients.

2.2.2 Dose and administration

The highest strength in the proposed product range should be tested *in vivo* if the formulation is proportional across the range of strengths. All pharmaceutically non-proportional strengths should be tested. Refer to the section on biowaivers for additional strengths in a proposed product series. The number of actuations should be minimized, while assuring suitable assay sensitivity.

It is not necessary to use charcoal block to reduce the contribution of gastrointestinal absorption if:

- no significant gastrointestinal absorption is expected, based on published literature, or
- it is possible to differentiate lung absorption from gastrointestinal absorption, using the pharmacokinetic profile

If significant gastrointestinal absorption is expected based on published literature or pilot studies, and this absorption cannot be distinguished from lung absorption using pharmacokinetic data, studies both with and without charcoal block may be required. For the purpose of this guidance, gastrointestinal absorption that accounts for 5% or more of the total observed AUC, is considered significant. Sponsors claiming that gastrointestinal absorption of the study drug is not significant should provide supporting evidence from appropriate peer-reviewed published literature or pilot studies conducted with and without charcoal block.

Subjects enrolled in *in vivo* studies should be trained in the use of the inhalation device in a standard fashion, prior to each treatment session, for a relatively consistent inspiratory flow rate and inspiratory duration. They should be advised to rinse their mouths with water and spit the water out after each dose. They should not swallow the water.

A spacer (aerosol holding chamber, add-on device or spacing device) should not be used when dosing study subjects, unless the approved Canadian labelling of the reference product indicates that the product is to be used only with a spacer.

2.2.3 Sampling times

Sampling times should cover lung absorption, as well as gastrointestinal absorption (where it is expected). It may be necessary to include samples within 5 minutes after drug administration. The selected sampling times should be justified and specified in the study protocol.

2.2.4 Bioequivalence standards

The bioequivalence standards to be met in comparative pharmacokinetic studies involving OIPs will be based on C_{max} and AUC as for solid oral dosage forms that are intended to deliver drug to the systemic circulation. Refer to the guidance document Comparative Bioavailability Standards: Formulations Used for Systemic Effects (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/bioavailability-bioequivalence/comparative-bioavailability-standards-formulations-used-systemic-effects.html).

Bioequivalence standards may be applied to early partial AUCs (pAUC) where the parameter has been shown to be appropriate to characterise lung absorption based on the pharmacokinetics of the active ingredient and formulation.

2.3 Biowaivers for additional strengths

In general, pharmacokinetic studies are required for all strengths in a proposed product series. However, sponsors may provide a scientific rationale for waiver of comparative *in vivo* studies for lower strengths only. This would be based, in part, on formulation and proportionality of *in vitro* performance test parameters, such as delivered dose and aerodynamic particle size distribution including fine particle mass and other size ranges where applicable. The excipients

should be qualitatively the same between strengths. Differences in proportions, if any, should be scientifically justified. The potential impact on the safety and efficacy of the proposed drug product (e.g., lung deposition and absorption characteristics) should be discussed.

Glossary of terms

AUC (area under the curve) The area under the concentration versus time curve. The AUC symbol may be qualified by a specific time (e.g., 4 hours, or $AUC_{0\text{-}4h}$), time of last quantifiable concentration (AUC_T), infinity (AUC_I), or partial AUC (pAUC).

Bioavailability The rate and extent of absorption of a drug into the systemic circulation.

Bioequivalence A high degree of similarity in the bioavailabilities of two pharmaceutical products (of the same galenic form) from the same molar dose, that are unlikely to produce clinically relevant differences in therapeutic effects, or adverse effects, or both.

Bioequivalent Test and reference products are bioequivalent when they contain an identical drug or drugs and, after comparison in an appropriate bioavailability study, are found to meet the standards for rate and extent of absorption specified in the Guidance Document Comparative Bioavailability Standards: Formulations Used for Systemic Effects.

C_{max} (maximum observed concentration) The observed maximum or peak concentration.

Excipient Any ingredient, excluding the drug substances, incorporated in a formulation for the purpose of enhancing stability, usefulness or elegance, or facilitating preparation; for example, base, carrier, coating, colour, flavour, preservative, stabilizer, and vehicle.

Formulation An ingredient or mixture of specific ingredients; that is, drug substances and excipients in specific amounts, defining a given product.

ICS Inhaled corticosteroid

LABA Long-acting beta2-adrenergic agonists

LAMA Long-acting muscarinic antagonists

Label Includes any legend, word, or mark attached to, included in, belonging to, or accompanying any drug or package. (Section 2 of the *Food and Drugs Act*.)

OIP Orally inhaled product

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