Draft Guidance Document

Comparative Pharmacokinetic Studies for Orally Inhaled Products

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

1.1 Policy Objectives

To provide sponsors of new drug submissions and abbreviated new drug submissions with the information necessary to comply with Sections C.08.002(2)(h), C.08.002.1(2)(c)(iii) and C.08.003(3) of the Food and Drug Regulations (Regulations) with respect to comparative pharmacokinetic studies, with emphasis on \textit{in vivo} comparative pharmacokinetic studies, used in support of the safety and efficacy of subsequent-entry orally inhaled drug products (OIPs).

1.2 Policy Statement

Comparative pharmacokinetic studies should be conducted in accordance with generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of subjects and the good clinical practices referred to in Division 5 of the Regulations and described in the International Council for Harmonisation (ICH) Guidance (Topic E6) on Good Clinical Practice. The recommendations included in this guidance respecting study design and conduct of comparative pharmacokinetic studies involving subsequent-entry orally inhaled drug products, should be followed in order to ensure compliance with the Regulations. 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 and nebulization products. These products may contain, for example, inhaled corticosteroids (ICS), long-acting beta2-adrenergic agonists (LABA), long-acting muscarinic antagonists (LAMA), or combinations of these drugs. This guidance also applies when a significant change is made to a reference product, such that a comparative clinical trial would previously have been required in support of the change. The same requirements will be applicable in both cases.

Examples of cases where this guidance applies are:

a) comparative pharmacokinetic studies in support of the equivalence of subsequent-entry products to the Canadian reference product

b) bridging studies where the formulation or device to be marketed is different from the formulation or device used in the pivotal clinical trials

c) studies in support of significant post-approval changes and line extensions

d) safety studies for drugs that are intended to act locally, where systemic drug concentrations may be measured for safety assessment.

Requirements for demonstration of \textit{in vitro} similarity of subsequent-entry and reference devices are not addressed in this guidance.

1.4 Background

Orally inhaled products are designed to act locally in the lungs and 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 and 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 such 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, the Health Canada guidance document Data Requirements for Safety and Effectiveness of Subsequent Entry Inhaled Corticosteroid Products Used for the Treatment of Asthma¹ should be consulted with regard to general study design considerations for studies using clinical endpoints.

Health Canada’s current guidance documents on comparative bioavailability studies, entitled Conduct and Analysis of Comparative Bioavailability Studies² and Comparative Bioavailability Standards: Formulations Used for Systemic Effects³, do not include specific guidance on pharmacokinetic comparison of subsequent-entry OIPs, with the corresponding Canadian reference products. The present document provides guidance in keeping 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 Studies² and Comparative Bioavailability Standards: Formulations Used for Systemic Effects³. The following sections provide guidance specific to OIPs. In addition to reviewing the information provided in this guidance document, submission sponsors are encouraged to consult with Health Canada, in advance of filing a drug submission, on what supporting information is required to establish the safety and efficacy of a particular subsequent-entry OIP.

2.1 Device and In Vitro Equivalence

Submission sponsors are referred to Appendix I of Health Canada’s current guidance document Pharmaceutical Quality of Inhalation and Nasal Products⁴, which 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,

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including formulation, physicochemical properties of the drug substance and drug product, delivery device and \textit{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, such that the risk for errors made by intended end users is minimized, 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 assessed. Significant differences should be supported by data (e.g., in-use studies in both device-naive 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, and how to disassemble, maintain, store and clean re-usable device components.

### 2.2 Study Design

In general, current Health Canada guidance with respect to study design would apply 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 reproducibly measured using a validated assay method.

For further guidance refer to the document entitled \textit{Conduct and Analysis of Comparative Bioavailability Studies}.

### 2.3 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.

### 2.4 Dose and Administration

The highest strength in the proposed product range should be tested \textit{in vivo}. The number of actuations should be minimized, while assuring suitable assay sensitivity. All pharmaceutically non-proportional strengths should be tested. Refer to Section 2.7 regarding biowaivers for additional strengths in a proposed product series.

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 if it is possible to differentiate lung absorption from gastrointestinal absorption, using the pharmacokinetic profile. If significant gastrointestinal absorption is expected based on published literature and this absorption cannot be distinguished from lung absorption using pharmacokinetic data, studies both with and without charcoal block may be required.

Subjects enrolled in \textit{in vivo} studies should be trained in the use of the inhalation device in a standard fashion, prior to each treatment session, to assure a relatively consistent inspiratory flow rate and inspiratory duration. The subjects 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.
2.5 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 five minutes after drug administration. The selected sampling times should be justified and specified \textit{a priori}.

2.6 Bioequivalence Standards

The bioequivalence standards to be met in comparative pharmacokinetic studies involving OIPs will be based on $C_{\text{max}}$ and AUC as for solid oral dosage forms that are intended to deliver drug to the systemic circulation. Refer to the guidance document \textit{Comparative Bioavailability Standards: Formulations Used for Systemic Effects}\textsuperscript{3}.

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.

2.7 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, 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, and differences in proportions, if any, should be scientifically justified and the potential impact on the safety and efficacy of the proposed drug product (e.g., lung deposition and absorption characteristics) should be discussed.

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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$_{0-4}$h), 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$_{\text{max}}$ (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