Health Canada Santé Canada

Guidance Document

Data Requirements for Safety and Effectiveness of Subsequent Entry Inhaled Corticosteroid Products Used for the Treatment of Asthma

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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.

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Ligne directrice - Exigences relatives à l'innocuité et l'efficacité pour des corticostéroïdes inhalés de commercialisation subséquente utilisés dans le traitement de l'asthme

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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

This guidance is intended to assist sponsors in the collection and analysis of comparative clinical data for Inhaled Corticosteroid (ICS) products used for the treatment of asthma that contain the same medicinal ingredient and have the same conditions of use as the Canadian Reference Product (CRP) in order to meet the safety and effectiveness requirements under C.08 of the Food and Drug Regulations [Sections C.08.002(2)(h), C.08.002.1(2)(c)(ii) and C.08.003(3)]. The data and standards outlined in this guidance are intended to be applied to a new ICS product being compared to a product for which clinical safety and effectiveness data exist. For clarity, these types of products will be referred to as "subsequent entry ICS products" in this document.

1.2 Policy statements

Therapeutic equivalence studies should be conducted in accordance with generally recognized clinical practices that are designed to ensure the protection of the rights, safety and well-being of subjects. Sponsors should comply with the Good Clinical Practices referred to in Part C, Division 5, of the Food and Drug Regulations, and described in the International Council for Harmonisation (ICH) Guidance (Topic E6) on Good Clinical Practice.

The recommendations included in this guidance on study design and conduct, and statistical analysis of data should be followed in order to ensure compliance with the Regulations.

A therapeutic equivalence study should be carried out to examine the efficacy of a subsequent entry ICS product in comparison with the Canadian Reference Product (CRP) using a clinically meaningful endpoint.

A pharmacokinetic (PK) study (comparative bioavailability study) should be carried out to examine the safety of a subsequent entry ICS product in comparison with the CRP.

In addition, the conditions of use of the subsequent entry ICS product and the CRP should be the same.

1.3 Scope and application

This guidance is intended to be applied to all submissions involving the demonstration of therapeutic equivalence in order to provide pivotal evidence of the efficacy and safety of a subsequent entry ICS product in comparison with a CRP for use in the treatment of asthma. This guidance applies to subsequent entry ICS metered dose inhalers (MDI's) and dry powder inhalers (DPI's).

Examples of cases where this guidance applies are:

a) therapeutic equivalence studies in support of the equivalence of subsequent-entry products to the Canadian reference product [Abbreviated New Drug Submission (ANDS)]
b) bridging studies where the formulation to be marketed is different from the formulation used in the pivotal clinical trials [Supplemental New Drug Submission (SNDS)]

c) studies in support of significant post-marketing changes and line extensions [Supplemental Abbreviated New Drug Submission (SANDS), SNDS)]

This guidance applies to ICS products that include only one active ingredient. It does not apply to combination products.

1.4 Background

The Therapeutic Products Directorate (TPD) has been actively striving to prepare guidance documents to assist drug sponsors in filing submissions for subsequent entry ICS products. The main issues relate to the fact that bioequivalence of locally acting ICS products may not be reliably established based on in vitro and systemic exposure studies only.

The Bureau of Cardiology, Allergy and Neurological Sciences (BCANS) has prepared the present guidance document in collaboration with the Office of Science (OoS), TPD, Health Products and Food Branch (HPFB) of Health Canada. Organized consultation sessions and teleconferences have been held with the Scientific Advisory Committee on Respiratory and Allergy Therapies (SAC-RAT) to obtain their advice for the development of the guidance document. Also, drug sponsors have previously been given the opportunity to submit podium and/or written presentations before the Scientific Advisory Committee on Respiratory and Allergy Therapies (SAC-RAT).

2. Guidance for implementation

2.1 General filing requirements for subsequent entry inhaled corticosteroid products

This Guidance should be read in conjunction with the following Health Canada guidance documents for other regulatory requirements for ANDSs for subsequent entry ICS:

- “Guidance for Industry: Pharmaceutical Quality of Inhalation and Nasal Products” (Health Canada, 2006). This guidance provides information on the data requirements related to pharmaceutical quality.
- “Guidance for Industry: Conduct and Analysis of Comparative Bioavailability Studies” (Health Canada, 2018)
- “Guidance for Industry: Comparative Bioavailability Standards: Formulations Used for Systemic Effects” (Health Canada, 2018)
- “Draft Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in CTD Format” (Health Canada, 2004).
- “Guidance Document: Preparation of Drug Regulatory Activities in the Electronic Common Technical Document (eCTD) Format” (Health Canada, 2015)

2.2 Therapeutic equivalence study requirements for subsequent entry inhaled corticosteroid products

2.2.1 General considerations

A clinical endpoint therapeutic equivalence study with one of the following two designs is recommended to be conducted with the lowest dose of the marketed CRP:

1. clinical endpoint study with Forced Expiratory Volume in 1 second (FEV1) as the primary endpoint, or
2. clinical endpoint study with sputum eosinophils as the primary endpoint

An alternative approach may be used if it satisfies the requirements of the applicable regulations. It is recommended that an alternative approach be discussed with Health Canada prior to filing for market approval.

2.2.2 Clinical endpoint study with FEV1 as the primary endpoint

Study design:
An adequately designed, randomized, repeat-dose, placebo-controlled, double-blind, parallel group study.

The study should have three parallel arms: Subsequent Entry Product (Test; T), Canadian Reference Product (Reference; R), and Placebo (Formulation Placebo; P).

Cross-over design is not recommended. The study should be multicentered to increase robustness. Study blinding is a critical consideration, and it is recommended that a description of how the T, R, and P products are to be masked be carefully provided in the study protocol.

Study duration:
The study duration should, at minimum, consist of a 2-week placebo run-in period, followed by a 4-week treatment period of the placebo, T or R products.

Dose:
One dose, the lowest dose marketed by the sponsor of the CRP, should be used to determine efficacy. One dose is acceptable if the pharmaceutical equivalence criteria (Health Canada Guidance, 2006) have been met between T and R, and the excipients are proportional among the different strengths of the test product and equivalent or dose proportional in-vitro performance (e.g., delivered dose and aerodynamic particle size distribution/fine particle dose or mass, etc.) has been demonstrated. Any deviations from these assumptions will require adequate justification with respect to potential impact to safety and efficacy.

Sample size:
The sample size of the study should be calculated based on the primary efficacy endpoint to ensure there is a reasonably powered sample size in order to demonstrate therapeutic equivalence. It is the sponsor's responsibility to enroll a sufficient number of subjects for the study to demonstrate therapeutic equivalence of the T to the R product.

Study population:
The study population should include patients with mild asthma.

Inclusion criteria should at minimum include:

- adult (18 and over) male or female subjects of non-childbearing potential, or of childbearing potential committing to consistent and correct use of an acceptable method of birth control
- diagnosis of mild asthma as defined according to the Canadian Thoracic Society 2012 guideline update: "Diagnosis and management of asthma in preschoolers, children and adults"
- ≥ 12% and 0.20 L reversibility of FEV1 within 30 minutes following 400 mcg (4 puffs) of salbutamol inhalation (pMDI)
- well-controlled asthma as measured by an ACQ score of ≤ 0.75
- current asthma medications may include short acting beta-agonists (fewer than 4 doses/week) and low dose ICS (≤ 200 µg beclomethasone dipropionate (HFA) equivalent)
- patients should be stable on their chronic asthma treatment regimen for at least 4 weeks prior to screening
- ability to discontinue current asthma medication for the duration of the study, including the run-in period, except for as-needed salbutamol
- currently non-smoking; having not used tobacco products (i.e., cigarettes, cigars, pipe tobacco) within the past year, and having had ≤ 10 pack-years of historical use
- currently not using any other inhaled, smoked or vaporized products

Exclusion criteria should, at minimum, include:

- poorly controlled mild asthma, moderate, severe or life-threatening asthma
- significant pulmonary disease other than asthma (e.g., COPD, interstitial lung disease, chronic bronchitis, emphysema, etc.)
- evidence or history of clinically significant disease or abnormality such as congestive heart failure, myocardial infarction, etc.
- patients receiving β_2-blockers, anti-arrhythmics, anti-depressants, ritonavir- and cobicistat-containing products, and/or monoamine oxidase inhibitors within 4 weeks prior to the screening
- viral or bacterial, upper or lower respiratory tract infection, or sinus, or middle ear infection within 6 weeks prior to the screening visit, during the run-in period, or on the first day of treatment
- patients who received systemic or oral corticosteroids (for any reason) within the past 6 months prior to screening
- patients who have ever been intubated or had an emergency visit for asthma exacerbation within the 6 months prior to screening
- hypersensitivity to the active pharmaceutical ingredient or excipients or salbutamol

Primary efficacy endpoint:
FEV1 measured in the morning prior to the dosing of inhaled medications on the last day of treatment. Spirometry should be conducted according to ATS/ERS standards.

The primary endpoint should be baseline adjusted (i.e., change from baseline). A baseline FEV1 is defined as the average of pre-dose FEV1 values of at least two time points measured in the

morning of the first day of a 4-week treatment period. Spirometry should be performed at the same time of day at baseline and at end of treatment.

Subjects should not have taken rescue medication (salbutamol) within 6 hours prior to spirometry.

Clinical efficacy criteria:
To ensure study sensitivity, the primary endpoint for both the T and R products should be statistically superior to that of the placebo ($p<0.05$). A clinical superiority of 12% from baseline for both T and R is also expected (Lougheed, 2012).

Therapeutic equivalence criteria: To demonstrate the bioequivalence of the T compared with the R, the 90% Confidence Interval (CI) of the T/R ratio of the mean change from baseline for the primary efficacy endpoint should be within 80 - 125% for log transformed data or ± 20% for untransformed data.

Adverse Events:
All adverse events should be reported with relevant information: date of onset, description, severity, relation to study medication, outcome, etc.

2.2.3 Clinical Endpoint Study with Sputum Eosinophils as the Primary Endpoint

Study design:
An adequately designed, randomized, repeat-dose, placebo-controlled, double-blind, parallel group study.

The Study should have three parallel arms: Subsequent Entry Product (Test; T), Canadian Reference Product (Reference; R), and Placebo (Formulation Placebo; P).

Crossover design is not recommended. The study should be multicentered to avoid potential investigator bias. Study blinding is a critical consideration, and it is recommended that a description of how the T, R, and P products are to be masked be carefully provided in the study protocol.

Study duration:
The study duration should consist of a 2-week placebo run-in period followed by a minimum 3-week treatment period of the placebo, T or R products. This should allow sufficient time to see a clinically significant inflammatory improvement in the patients, and a plateau of efficacy to be achieved.

Dose:
One dose, the lowest dose marketed by the sponsor of the CRP, should be used to determine efficacy. One dose is acceptable if the pharmaceutical equivalence criteria (Health Canada, 2006) have been met between T and R, and the excipients are proportional among different strengths of the test product and equivalent or dose proportional in-vitro performance (e.g., delivered dose and aerodynamic particle size distribution/fine particle dose or mass, etc.) has been demonstrated. Any deviations from these assumptions will require adequate justification with respect to potential impact to safety and efficacy.

Sample size:
Sample size of the study should be calculated based on the primary efficacy endpoint to ensure there is a reasonably powered sample size in order to demonstrate therapeutic equivalence. It is the sponsor's responsibility to enroll a sufficient number of subjects for the study to demonstrate therapeutic equivalence of the T to the R product.

Study population:
The study population should include steroid-naïve patients (never used ICS or minimum 6 weeks free of ICS) with mild asthma.

Inclusion criteria should at minimum include:

- adult (18 and over) male or female subjects of non-childbearing potential, or of childbearing potential committing to consistent and correct use of an acceptable method of birth control
- diagnosis of mild asthma as defined according to the Canadian Thoracic Society 2012 guideline update: "Diagnosis and management of asthma in preschoolers, children and adults"
- subjects should be steroid naïve (never used ICS or no ICS treatment for at least 6 weeks prior to screening)
- evidence of active inflammation based on sputum eosinophil count (≥3%)
- well-controlled asthma as measured by an ACQ score of ≤ 0.75
- current asthma medications may include short acting beta-agonists (fewer than 4 doses/week). Patients on low dose ICS (≤ 200 µg beclomethasone dipropionate (HFA) equivalent) may be considered with justification
- ability to discontinue current asthma medication for the duration of the study including the run-in period except for as-needed salbutamol
- currently non-smoking; having not used tobacco products (i.e., cigarettes, cigars, pipe tobacco) within the past year, and having had ≤ 10 pack-years of historical use
- currently not using any other inhaled, smoked or vaporized products

Exclusion criteria should, at minimum, include:

- poorly controlled mild asthma or moderate, severe or life-threatening asthma
- significant pulmonary disease other than asthma (COPD, interstitial lung disease, chronic bronchitis, emphysema, etc.)
- evidence or history of clinically significant disease or abnormality such as congestive heart failure, myocardial infarction, etc.
- patients receiving β2-blockers, anti-arrhythmics, anti-depressants, ritonavir- and cobicistat-containing products, and/or monoamine oxidase inhibitors within 4 weeks prior to the screening
- viral or bacterial, upper or lower respiratory tract infection, or sinus, or middle ear infection within 6 weeks prior to the screening visit, during the run-in period, or on the first day of treatment
- patients who received systemic or oral corticosteroids (for any reason) within the 6 months prior to screening

- patients who have ever been intubated or had an emergency visit for asthma exacerbation within the 6 months prior to screening
- hypersensitivity to the active pharmaceutical ingredient or excipients or salbutamol

Primary efficacy endpoint:
Sputum eosinophil count measured on the last day of treatment. Sputum eosinophil count should also be measured at baseline prior to the first dose of treatment.

A standardized method of sputum induction and selection should be used to obtain sputum eosinophil count.

Clinical efficacy criteria:
A difference in the mean sputum eosinophil count (expressed as a percentage of the baseline count) of at least 50% between the active treatments and the placebo treatment will be considered clinically significant. For each treatment, the change from baseline should be calculated according to the following formulas:

$$\textbf{\% Δ Eosinophil count} = \frac{\text{\% Baseline eosinophil count - \% Post-treatment eosinophil count X 100}}{\text{\% Baseline eosinophil count}}$$

Therapeutic equivalence criteria:
To demonstrate the bioequivalence of the T compared with the R, the 90% CI of the T/R ratio of mean change from baseline of the primary efficacy endpoint should be within 80 - 125% for log transformed data or ± 20% for untransformed data.

The choice between using log-transformed or untransformed analysis is to be made based on model check of the data. Assessing normality within the SAS statistical package plus a thorough visual inspection of various plots of the data are usually sufficient. The scale that renders the data closer to normality is the scale to be used. After transformation, normality should be checked again. If the log-transformed data is closer to normality, then the log-transformed data can be used to demonstrate therapeutic equivalence. Otherwise, the original scale should be used.

If the change score is negative, a log transformation cannot be done. This can be corrected by taking the standard approach of log(x+k), where k is a constant that is chosen such that the sum of (x+k) is at least one.

Adverse events:
All adverse events should be reported with relevant information: date of onset, description, severity, relation to study medication, outcome, etc.

2.3 Clinical study requirements for systemic exposure to subsequent entry inhaled corticosteroid products

Systemic exposure should be shown to be comparable between the T and R products. Data should be obtained from a pharmacokinetic (PK) study evaluating the systemic exposure following administration of the subsequent entry ICS product relative to the CRP as a surrogate for possible long-term systemic effects.

The PK study should be a single dose study at the upper limit of the dosing range (the maximum labelled adult dose) in which the following PK parameters should be determined: Area under the curve to the last quantifiable concentration (AUCT), Area under the curve to infinity (AUCI), AUCT/AUCI, Maximum observed concentration (Cmax), Observed time at which Cmax occurred (tmax), Half-life (t1/2) and Terminal elimination rate constant (Kel). The study should be conducted with reference to Health Canada's Guidance Document: Conduct and Analysis of Comparative Bioavailability Studies, 2018 which indicates that adult healthy volunteers are preferred.

The following standards will be applied to the PK study, based on log-transformed data:

- The 90% CI of the relative mean AUCT of the test to reference product should be within 80.0 - 125.0%
- The relative mean measured Cmax of the test to reference product should be within 80.0 - 125.0%

3. Enquiries

For questions, clarification and further assistance concerning the preparation and filing of submissions for subsequent entry ICS products, contact the Bureau of Cardiology, Allergy and Neurological Sciences at the following e-mail address: hc.bcansenquiries.sc@canada.ca.

For questions, clarification and further assistance pertaining to the design and conduct of clinical pharmacokinetic studies assessing the systemic exposure of the subsequent entry products, contact the Bureau of Pharmaceutical Sciences (BPS), Division of Biopharmaceutics Evaluation at the following e-mail address: hc.bps.enquiries.sc@canada.ca.

For questions, clarification and further assistance regarding this guidance, contact the Bureau of Policy, Science and International Programs (BPSIP) at the following email address: hc.policy.bureau.enquiries.sc@canada.ca.

4. Glossary of abbreviations

ACQ	Asthma Control Questionnaire
ANDS	Abbreviated New Drug Submission
ATS	American Thoracic Society
BCANS	Bureau of Cardiology, Allergy and Neurological Sciences
BPS	Bureau of Pharmaceutical Sciences
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease

CRP	Canadian Reference Product
CTD	Common Technical Document
DPI	Dry Powder Inhaler
ERS	European Respiratory Society
FEV1	Forced Expiratory Volume in 1 second
HFA	Hydrofluoroalkane
ICS	Inhaled Corticosteroids
MDI	Metered Dose Inhaler
PK	Pharmacokinetic
SAC-RAT	Scientific Advisory Committee on Respiratory and Allergy Therapies
T/R	Test-to-reference Ratio
TPD	Therapeutic Products Directorate

5. References

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