

GUIDANCE DOCUMENT

Drug Submissions Relying on Third-Party Data (Literature and Market Experience)

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Health Products and Food Branch

<p>Our mission is to help the people of Canada maintain and improve their health.</p> <p style="text-align: right;"><i>Health Canada</i></p>	<p>The Health Products and Food Branch's (HPFB) mandate is to take an integrated approach to managing the health-related risks and benefits of health products and food by:</p> <ul style="list-style-type: none"> -minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health 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. <p style="text-align: right;"><i>Health Products and Food Branch</i></p>
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Également disponible en français sous le titre : LIGNE DIRECTRICE Présentations de drogue fondées sur les données de tierces parties (source documentaire et expérience de commercialisation)

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's 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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1.0 INTRODUCTION

Health Canada is the federal regulatory authority that evaluates the safety, efficacy and quality of drugs for market authorization in Canada. To promote predictability of evidence expectations and consistency in Health Canada's regulatory decision making, the Health Products and Food Branch (HPFB) is publishing criteria for assembling a Submission Relying on Third-Party Data (SRTD) and clarifying the evidence requirements for the proposed commercial products. For the purpose of this document, SRTDs are defined as New Drug Submissions (NDSs) and Supplements to New Drug Submissions (SNDSs) that substantially rely on literature and market experience.

The guidance sets out the Regulator's expectations for sponsors of NDSs and SNDSs in the absence of clinical study reports of safety and efficacy. Sponsors are encouraged to carefully review the established conditions and requirements and discuss the details of their submission with the appropriate HPFB review areas prior to filing such a submission.

1.1 Policy Objective

The objective of this document is to ensure that sponsors of SRTDs have the necessary information to satisfy the regulatory requirements under the *Food and Drug Regulations* (http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.%2C_c._870/) with respect to safety, efficacy and quality which provides the basis of Health Canada's drug review and approval process.

In an effort to improve the quality of submissions that rely on third-party data, Health Canada has developed applicable criteria for cases where sponsors seek to satisfy the evidence requirements [namely, C.08.002(2)(g) and (h)] by way of a reference product (as reported in the literature) and its domestic and/or foreign market experience. To satisfy evidentiary standards, sponsors are expected to demonstrate (in a coherent and consistent manner) the comparative safety and efficacy profile of the proposed commercial product to the reference product.

1.2 Policy Statements

A SRTD should only be submitted to Health Canada with appropriate justification. The acceptability of the submission will be considered on a case by case basis, and regulatory decisions will be based on the details and circumstances of each submission and category of drug product.

1.3 Scope and Application

This guidance applies to New Drug Submissions (NDSs) and Supplements to New Drug Submissions (SNDSs) involving pharmaceuticals, certain biologics, and radiopharmaceuticals submitted under Division 8 of the *Food and Drug Regulations*. It provides guidance on the conditions and requirements of SRTDs to assist sponsors in the preparation and filing of their drug submission.

This guidance does not apply to natural health products regulated under the *Natural Health Product Regulations*, applications for Drug Identification Numbers (DINAs) [including DINs for biological products (DINBs)] under Division 1 of the *Food and Drug Regulations*, clinical trial applications as per Division 5 of the *Food and Drug Regulations*, or Veterinary New Drug Submissions, Extraordinary Use New Drug Submissions (EUNDS), new drug submissions for certain biologics such as vaccines and Subsequent Entry Biologics (SEBs), and Abbreviated New Drug Submissions (ANDSs) as per Division 8 of the same *Regulations*.

1.4 Definitions

Biologic – for the purpose of this guidance, a drug listed in Schedule D of the *Food and Drugs Act* that is in dosage form.

Clinical Trial - an investigation of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug.

Conventional Drug Submission – a new drug submission (or supplement) that contains complete study reports of clinical safety and efficacy [that is (i.e.) clinical data] generated by the drug sponsor or for the drug sponsor.

Literature – articles published in peer-reviewed journals, study reports of trials not conducted or sponsored by the applicant, books and guidelines from professional bodies, containing information and data on the safety and efficacy of the proposed product or medicinal ingredient.

Market Experience - post-marketing data or information on the proposed product or medicinal ingredient in relation to its therapeutic use and effects. This can include, but is not limited to, information pertaining to the relevant domestic reference product (if one is available; see definition below), evidence of the extent of population exposure, information concerning the product's safety profile from domestic and/or foreign

markets, details of adverse reactions from foreign authorities, and copies of all post-market safety information [including periodic safety update reports (PSURs) and Periodic Benefit-Risk Evaluation Reports (PBRERs)].

Pharmaceutical - a new drug other than a drug listed in Schedule C or D of the *Food and Drugs Act*.

Radiopharmaceutical - for the purpose of this guidance, a drug listed in Schedule C of the *Food and Drugs Act* that is in dosage form.

Reference product - a drug product administered in clinical trials for which complete study reports or published reports are submitted as evidence to establish the safety and efficacy of the proposed commercial product.

Submission Relying on Third-Party Data (SRTD) – a new drug submission (or supplement) substantially relying on literature and market experience. In the absence of clinical study reports to support the safety and efficacy of a proposed product or medicinal ingredient, sponsors seek to satisfy the evidence requirements of the *Food and Drug Regulations* [namely, C.08.002(2)(g) and (h)] by way of a reference product (as reported in the literature) and its domestic and/or foreign market experience. It is understood that the safety and efficacy evidence of a SRTD may not necessarily be derived from studies using the same formulation or manufacturer of the drug for which a Notice of Compliance (NOC) is being sought.

1.5 Background

Although conventional drug submissions include substantial original non-clinical, clinical, chemistry and manufacturing data, increasingly, drug sponsors are seeking market authorization for drug products based largely on literature and market experience.

As required by the *Food and Drug Regulations*, before a new drug is authorized for sale in Canada, the sponsor is responsible for providing the necessary scientific evidence to allow drug regulatory decision making. The contents of a New Drug Submission (NDS) and Supplement to a New Drug Submission (SNDS) are specified in section C.08.002(2) and C.08.003(3) of the *Food and Drug Regulations*, and apply equally to SRTDs. Of particular relevance to these submissions are C.08.002(2)(g) and (h), which require that an NDS includes:

- (g) detailed reports of the tests made to establish the safety of the new drug for the recommended purpose and conditions of use;
- (h) substantial evidence of the clinical effectiveness of the new drug for the purpose and the conditions of use recommended;

Thus, in circumstances where an NDS or SNDS substantially relies on literature and market experience to support clinical safety and efficacy, sponsors are required to provide evidence demonstrating the extent to which the data forming this part of the submission mirrors the proposed indication for use in terms of dosing, population, intervention, and outcome measures.

2.0 GUIDANCE FOR IMPLEMENTATION

Although SRTDs may differ in the source of information used to support safety and effectiveness, it is of primary importance that it meets the same standards for approval as a conventional submission, i.e., substantial evidence of safety and efficacy, as stipulated in C.08.002(2)(g) and (h) for NDSs and C.08.003(3) for SNDSs. **In addition, these submissions should only be submitted when all of the following conditions and requirements are adequately addressed by the sponsor:**

1. A rationale supporting SRTD filing to explain why a conventional drug submission was not assembled;
2. A complete chemistry and manufacturing data package for the proposed commercial drug product;
3. In accordance with requirement C.08.002(2)(m) of the *Regulations*, evidence, based on comparative pharmaceutical and/or comparative bioavailability data, to establish that the product used in studies reported in the literature (i.e. reference product) is representative of the proposed commercial product (see details further below);
4. Evidence of extensive current foreign market experience with the same medicinal ingredient (for a minimum of 10 years under the same conditions of use), or evidence that the same medicinal ingredient is currently or has previously been marketed in Canada (under the same conditions of use);
5. For the published literature-based evidence, sponsors are expected to provide a systematic review using the methodology outlined in the Cochrane Handbook for Systematic Reviews of Interventions (www.cochrane.org/handbook) and presented in the form as outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (<http://www.prisma-statement.org>)¹;
6. Copies of all documents, as detailed in Health Canada's Guidance Document: *Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ctd/ctd_prep_nds-eng.php);
7. The most complete and current evidence-based information for the development of a Canadian Product Monograph (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/monograph/pm_mp_2013-eng.php);

¹ Sponsors may find it useful to consult an information retrieval expert when planning and conducting systematic literature searches.

8. A Canadian Risk Management Plan as described in the Health Canada Notice Regarding Implementation of Risk Management Planning including the adoption of International Conference on Harmonisation (ICH) Guidance Pharmacovigilance Planning - ICH Topic E2E (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/vigilance/notice_avis_rmp_pgr_e2e-eng.php); and
9. A pre-submission meeting with Health Canada to discuss the safety and efficacy evidence required to support market authorization and the data requirements to bridge the proposed product to the reference product.

The sponsor should provide the available information [for example (e.g.) source, formulation and, where details are provided in the literature, method of preparation] about the drug product administered in studies identified as pivotal in the systematic review and provide appropriate data to establish that the reference product used in those pivotal studies is representative of the proposed commercial product, based on comparative pharmaceutical and/or bioavailability characteristics.

Clinical studies reported in the literature and included in the submission will not be considered sufficient to establish the clinical safety and efficacy required by the *Regulations* unless it is demonstrated that the proposed commercial product will have the same *in vivo* performance as the reference product used in the studies reported in the literature. For some drug products, such as simple aqueous solutions, comparative physico-chemical data between the reference product and the proposed drug product may be considered sufficient [See Health Canada's Guidance Document *Pharmaceutical Quality of Aqueous Solutions* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/chem/aqueous_aqueuses-eng.php) for details]. For other drug products (e.g., solid oral dosage forms), demonstration of comparative bioavailability between the proposed and the reference products would be required. Of note, unless otherwise justified, demonstration of comparative bioavailability between the proposed product and the reference product should be conducted after administration of the same dose, in comparable dosage form, and using the same route of administration (consistent with the proposed recommended dosing instructions).

Additional Sources of Supportive Information

The following evidence may be included in the submission but will not be deemed sufficient on its own to support the safety and efficacy of the proposed commercial product.

Foreign Review Reports

Although foreign approvals and/or review reports may be used to inform Health Canada's regulatory decision on a health product, they cannot be used as exclusive evidence to support the safety and efficacy profile of the proposed product.

Post-Marketing Reports

While data from clinical trials are required to establish a drug's safety profile, Periodic Safety Update Reports (PSURs) or Periodic Benefit-Risk Evaluation Reports (PBRERs) are valuable to supplement clinical trial data with additional post-market data (e.g., worldwide exposure estimates and uncommon or long-latency drug related safety concerns not detected in clinical trials).

Intellectual Property Considerations

If the proposed drug product relies on a drug product already authorized by Health Canada and still marketed in Canada, there are Intellectual Property considerations pursuant to the Guidance Document: *Patented Medicines (Notice of Compliance) Regulations (PM(NOC) Regulations)* (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/patmedbrev/pmreg3_mbreg3-eng.php) and data protection provisions of the *Food and Drug Regulations*. These regimes govern an innovator's patent rights and market exclusivity rights.

If the submission contains direct or indirect comparisons with, or references to a Canadian product that is still marketed in Canada, the *PM(NOC) Regulations* and/or data protection provisions will be triggered. It is important to note, that reliance on foreign products cannot be used to circumvent Intellectual Property considerations.

3.0 CONTACT INFORMATION

Questions related to this guidance document should be directed to:

Bureau of Policy, Science and International Programs

Therapeutic Products Directorate

Health Products and Food Branch

Health Canada

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Holland Cross, Tower B, 2nd Floor,

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Ottawa, Ontario

K1A 0K9

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Telephone: 613-948-4623

Facsimile: 613-941-1812

4.0 REFERENCES

Guidance Document - *Comparative Bioavailability Standards: Formulations Used for Systemic Effects* (Effective 2012-05-02) (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demandede/guide-ld/bio/gd_standards_ld_normes-eng.php)

Guidance Document - *Conduct and Analysis of Comparative Bioavailability Studies* (Effective 2012-06-06) (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demandede/guide-ld/bio/gd_cbs_ebc_ld-eng.php)

Guidance Document - *Data Protection under C.08.004.1 of the Food and Drug Regulations* (Effective October 11, 2011) (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demandede/guide-ld/data_donnees_protection-eng.php)

Guidance Document - *Patented Medicines (Notice of Compliance) Regulations* (Revised 2012), (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demandede/guide-ld/patmedbrev/pmreg3_mbreg3-eng.php)

Guidance Document - *Pharmaceutical Quality of Aqueous Solutions* (Effective 2005-02-15) (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demandede/guide-ld/chem/aqueous_aqueuses-eng.php)

Guidance Document - *Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format* (June 22, 2012) (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demandede/guide-ld/ctd/ctd_prep_nds-eng.php)

Guidance Document - *Product Monograph* (2014/06/01) (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demandede/guide-ld/monograph/pm_mp_2013-eng.php)

Guidance for Industry: *Management of Drug Submissions* (December 20, 2013) (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demandede/guide-ld/mgmt-gest/mands_gespd-eng.php)

Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, (www.cochrane.org/handbook)) Higgins JPT, Green S (editors). (Updated March 2011). The Cochrane Collaboration, 2011 (www.cochrane.org/handbook)

Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement (2009) (<http://www.prisma-statement.org/>) Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. (<http://www.prisma-statement.org/>)

Notice Regarding Implementation of Risk Management Planning including the adoption of International Conference on Harmonisation (ICH) Guidance Pharmacovigilance Planning - ICH Topic E2E (February 12, 2009) (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/vigilance/notice_avis_rmp_pgr_e2e-eng.php)

Patented Medicines (Notice of Compliance) Regulations, S.O.R./93-133 (as amended) and data protection provisions of section C.08.004.1 of the *Food and Drug Regulations*. (<http://laws-lois.justice.gc.ca/eng/regulations/sor-93-133/FullText.html>); (http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.%2C_c._870/).