Health Canada Santé Canada

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Draft Guidance Document

Generic Drug Equivalence: Medicinal Ingredients

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Draft Date: 2019/04/08

Canada

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Également disponible en français sous le titre :
Ébauche de ligne directrice Équivalence des médicaments génériques : Ingrédients médicinaux

Publication date: April 2019

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

Health Canada is the federal regulatory authority that evaluates the safety, efficacy and quality of drugs for market authorization in Canada. The department is providing a general outline of information and recommendations on submission content for a subsequent market entry drug product (e.g., a generic drug product) for demonstrating equivalence to the Canadian Reference Product (CRP)in relation to the term “pharmaceutical equivalent” as proposed in amendments to the Food and Drug Regulations (the Regulations) for section C.08.001.1 (http://gazette.gc.ca/rp-pr/p1/2019/2019-03-30/html/reg2-eng.html).

This draft guidance document sets out considerations for the general information and submission content for Abbreviated New Drug Submissions (ANDSs) for a generic drug product containing a different medicinal ingredient with the identical therapeutically active component in comparison to the CRP.

The draft guidance document Identifying and Labelling Medicinal Ingredients in New Drug Products (https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/drug-products/drug-products/consultation-profile-draft-generic-drug-equivalence/document-2.html) outlines the general principles and considerations for identifying the medicinal ingredient of a drug product evaluated under Division 8 of the Regulations.

1.2 Policy objectives

The objective of this guidance document is to outline the general principles and considerations for demonstrating the safety, efficacy and quality of generic drug products submitted to Health Canada pursuant to subsection C.08.002.1(1) of the Regulations where a generic drug product contains a different medicinal ingredient with the identical therapeutically active component in comparison to the CRP.

The current regulations (including the definition for pharmaceutical equivalent), guidance documents and polices will apply until the proposed regulatory amendments are finalized and come into force. The current regulations, guidance documents and polices will continue to apply to submissions that were filed prior to the proposed regulatory amendments coming into force.

Once finalized, this guidance document will replace past policy interpretations of identical medicinal ingredient and should be read in conjunction with the Regulations.

1.2 Policy statements

As proposed in the amendments to the Regulations for section C.08.001.1:

- “**therapeutically active component**” means a medicinal ingredient, excluding those appended portions, if any, that cause the medicinal ingredient to be a salt, hydrate or solvate.

As proposed in the amendments to the Regulations for section C.08.001.1, for a new drug not referred to in Schedule C or Schedule D of the Food and Drugs Act (the Act):

- "**pharmaceutical equivalent**" means a new drug that, in comparison with another drug, contains identical amounts of the identical therapeutically active components, in comparable dosage forms, but that does not necessarily contain the same non-medicinal ingredients.

The submission sponsor is responsible for providing the necessary evidence to demonstrate the safety, efficacy and quality for a generic drug product.

Depending on the proposed generic drug product containing a different medicinal ingredient with the identical therapeutically active component in comparison to the CRP, the submission sponsor is encouraged to submit information and materials that demonstrate that the difference, if any, is inconsequential with respect to the safety or effectiveness of the generic drug product.

Generic drug products with the following differences in the medicinal ingredient with the identical therapeutically active component in comparison to the CRP are eligible to be filed via the ANDS regulatory pathway:

- different hydrated or solvated forms
- different polymorphic forms and
- different salt forms

Generic drug products with the following differences in the medicinal ingredient are not eligible to be filed via the ANDS regulatory pathway:

- different esters
- different complexes
- different clathrates and
- different isomers or mixtures with different proportions of isomers

In these circumstances, submissions must be filed via the New Drug Submission (NDS) pathway.

As proposed in the amendments to the Regulations, the Notice of Compliance (NOC) for generic drug products approved by way of an ANDS will state the difference, if any, between the medicinal ingredient of the generic drug product and the CRP to improve transparency of information (e.g., for provincial and territorial formularies, healthcare professionals and patients).

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.

1.3 Scope and application

This guidance document will apply to ANDSs that are filed pursuant to Part C, Division 8 of the Regulations with the Therapeutic Products Directorate (TPD), the Veterinary Drugs Directorate (VDD), and the Natural and Non-prescription Health Products Directorate (NNHPD) of Health Canada once the proposed amendments to the Regulations come into force. The current

regulations, guidance documents and polices will continue to apply to submissions that were filed prior to the proposed regulatory amendments coming into force.

The information provided in this guidance document regarding the acceptability of a different medicinal ingredient with the identical therapeutically active component in comparison to the CRP is applicable to the following dosage forms:

- immediate-release solid oral tablets and capsules used for systemic effects
- oral aqueous solutions
- ophthalmic aqueous solutions and
- intravenous (IV) aqueous solutions

This guidance document does not apply to drugs referred to in Schedule D (biologicals) or Schedule C (radiopharmaceuticals) of the Act, to drug products containing more than one medicinal ingredient, to drug products with medicinal ingredients which do not possess a unique chemical structure (e.g., polymers with varying molecular weights), to critical dose drugs[1], or drugs requiring patient monitoring (to avoid the consequences of under- or over-treatment).

For changes to the drug substance or drug product after receipt of a NOC, Health Canada's Post-Notice of Compliance (NOC) Changes: Framework (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/post-notice-compliance-changes/framework-document.html) and Post-Notice of Compliance (NOC) Changes: Quality (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/post-notice-compliance-changes/quality-document.html) documents should be consulted.

1.4 Definitions

Active ingredient means a drug that, when used as the raw material in the fabrication of a drug in dosage form, provides its intended effect.

Active pharmaceutical ingredient (API) (or **drug substance)** means an active ingredient that is used in the fabrication of a pharmaceutical. For the purpose of this guidance document, the terms "drug substance" and "active pharmaceutical ingredient" are considered interchangeable.

Clathrate means a solid mixture in which small molecules of one compound or element are trapped in the holes of the crystal lattice of another substance. Molecules are not held by chemical bonding interactions, but rather by physical entrapment.

Dosage form means the physical manifestation of a product that contains the active ingredient(s) and inactive ingredients that are intended to be delivered to the patient. Note, 'dosage form' can refer to the administrable dosage form or the manufactured dosage form, depending on the product that it is describing. However, for the purpose of this guidance document, dosage form means the manufactured dosage form.

Dose solubility volume (DSV) means the highest therapeutic dose (milligrams) divided by the solubility of the substance [milligram/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 the DSV = 500 mg / 31 mg/mL = 16 mL at pH 4.5 (37°C).

Drug product means any substance or combination of substances that may be administered to human beings (or animals) for treating or preventing disease, with the view to making a medical diagnosis or to restore, correct or modify physiological functions.

Hydrate means a compound that contains water within its crystal structure.

Isomers mean compounds that have identical molecular formulae, but differ in the nature or sequence of bonding of their atoms in space.

Non-medicinal ingredient means a substance – other than the pharmacologically active drug – that is added during the manufacturing process and that is present in the finished drug product.

Pharmaceutical equivalent as proposed in the amendments to the Regulations for section C.08.001.1, in respect of a new drug not referred to in Schedule C or Schedule D of the Act, means a new drug that, in comparison with another drug, contains identical amounts of the identical therapeutically active components, in comparable dosage forms, but that does not necessarily contain the same non-medicinal ingredients.

Polymorph means different crystalline or amorphous forms of the same medicinal ingredient and may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms.

Salt means a compound formed by the ionic interaction of the ionized form of an acid or a base with a counter ion.

Solvate means a compound which during the crystallization process traps a fixed molar ratio of solvent molecules in the crystal structure. The solvent may be highly bound in the crystal or it may be more loosely bound in channels within the crystal. Hydrates are a class of solvates where the solvent is water.

Therapeutically active component as proposed in the amendments to the Regulations for section C.08.001.1, means a medicinal ingredient, excluding those appended portions, if any, that cause the medicinal ingredient to be a salt, hydrate or solvate.

1.5 Background

An updated Notice and an Interim Policy (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/policies/notice-interim-policy-health-canada-interpretation-identical-medicinal-ingredient.html)were published in October 2017 (replacing the 2015 Interim Policy) to reflect Health Canada's current interpretation of medicinal ingredient and regulatory decision-making. The 2017 Interim Policy clarified various scenarios that may be approvable as an ANDS. The scenario in which the generic drug product contains a medicinal ingredient that differs in form (e.g., salt form) compared to the CRP, is contingent on the therapeutic moieties being the same and the safety and effectiveness between the two products being demonstrated to be equivalent.

From June to October 2017, Health Canada consulted on a Notice to Interested Parties (NOI) - Possible Changes to the Food and Drug Regulations: Generic Drug Equivalence and Related Terminology (https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/drug-products/generic-drug-equivalence-notice.html). The NOI solicited comments on possible changes to the Regulations with respect to the establishment of equivalence between a proposed generic drug product and the CRP. The feedback received on the NOI was taken into consideration during the development of the proposed amendments to the Regulations published for comment in Canada Gazette, Part I and this draft guidance document.

2. Guidance for implementation

The proposed amendments to the Regulations would permit drug submissions to be filed via the ANDS pathway with certain different medicinal ingredients with the identical therapeutically active component in comparison to the CRP. Sponsors should conduct the appropriate in vivo and/or in vitro studies to demonstrate that a difference, if any, in the medicinal ingredient with the identical therapeutically active component between the generic drug product and the CRP is inconsequential with respect to the safety and/or efficacy of the generic drug product. The results of these studies should be included in the submission.

In addition to reviewing the information provided in this guidance document, submission sponsors are advised to consult with Health Canada, in advance of filing a drug submission, when there is doubt regarding whether the generic drug product could be considered the pharmaceutical equivalent of the CRP or what supporting information is required to establish pharmaceutical equivalence.

2.1 The medicinal ingredient

As proposed in the amendments to the Regulations for section C.08.001.01 (1), a reference to the medicinal ingredient of a new drug is a reference to the form of the medicinal ingredient in the dosage form of the new drug.

The guidance document entitled Identifying and Labelling Medicinal Ingredients in New Drug Products (https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/drug-products/drug-products/consultation-profile-draft-generic-drug-equivalence/document-2.html) outlines the general principles and considerations in this area.

2.2 Quality (Chemistry and Manufacturing)

Complete chemistry and manufacturing information on the API and drug product should be provided in the drug submission as described in the Health Canada guidance document Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) for human drug products (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/chemical-entity-products-quality/guidance-document-quality-chemistry-manufacturing-guidance-new-drug-submissions-ndss-abbreviated-new-drug-submissions.html).

For veterinary drug products, submission sponsors should refer to the document Guidance for Industry: Preparation of Abbreviated Veterinary New Drug Submissions – Generic Drugs (https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/pdf/vet/legislation/guide-ld/vdd-guide-ands-padn-eng.pdf).

Unsolvated and the various solvated forms of the identical therapeutically active component are generally considered identical. Levels of the solvate within the limits recommended in the International Council for Harmonisation of Technical Requirements for Pharmaceutical for Human Use (ICH) Q3C "Impurities: Guideline for Residual Solvents" (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3C/Q3C__R6___Step_4.pdf) are considered qualified without further justification. Solvate levels exceeding the ICH Q3C limits should be justified and supporting data provided in the drug submission. Supporting data may be based on concepts of qualification outlined in the ICH impurity guidelines Q3A (http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html), Q3B (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3B_R2/Step4/Q3B_R2__Guideline.pdf), and Q3C (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3C/Q3C__R6___Step_4.pdf).

Biowaivers for aqueous solutions which start with APIs that are different salts with the identical therapeutically active component are only acceptable if the dosage form is qualitatively the same and quantitatively essentially the same as the CRP in terms of ionic components and other excipients. For the purposes of this document, essentially the same would be interpreted as the amount (or concentration) of each excipient in the generic drug product to be within ±10% of the amount (or concentration) of each excipient in the CRP. Minor differences in the qualitative nature of the solution composition may be acceptable with adequate scientific justification that the differences will not affect safety and efficacy. Any difference in the qualitative nature of the ionic components and/or any excipients will generally not be acceptable without adequate scientific evidence to support that the proposed product and the CRP have the same safety and efficacy profile.

Information and data may be requested to demonstrate that any difference in a medicinal ingredient with the identical therapeutically active component in comparison to the CRP is inconsequential to the safety and efficacy of the generic drug product. In vitro data is generally not sufficient to support a different medicinal ingredient in the generic drug product and the CRP.

2.3 Bioequivalence

2.3.1 Comparative solubility

Different medicinal ingredients with the identical therapeutically active component may vary in their solubility across the physiological pH range, which could influence bioavailability. A comparative solubility assessment is an integral part of the safety and efficacy assessment when the proposed generic drug product contains a different medicinal ingredient with the identical therapeutically active component in comparison to the CRP. The dose solubility volume (DSV) of the medicinal ingredients of the proposed generic drug product and the CRP

should be determined, and the impact of any differences in the DSV on pharmacokinetic characteristics (absorption, disposition, metabolism and excretion) should be addressed in the drug submission.

2.3.2 Bioequivalence studies with pharmacokinetic endpoints for drugs submitted as an ANDS

When the proposed generic drug product contains a different medicinal ingredient with the identical therapeutically active component in comparison to the CRP, then bioequivalence could be demonstrated in vivo against the CRP. This guidance document does not apply to critical dose drugs[2] or drugs requiring patient monitoring (to avoid the consequences of under- or over-treatment).

If the proposed generic drug product is eligible to be filed as an ANDS and is administered orally, bioequivalence studies should be performed under both single-dose fasting and single-dose fed (high-fat, high-calorie) conditions.

The bioequivalence studies should be conducted on at least the highest and lowest strength in the proposed series of strengths to demonstrate that the pharmacokinetic properties (i.e., linearity of the in vivo pharmacokinetic profile) of the medicinal ingredient (in the dosage form) are the same as the CRP.

Bioequivalence standards, as defined in Health Canada guidance documents, should be met.

In accordance with Health Canada's policy, Bioequivalence of Proportional Formulations – Solid Oral Dosage Forms (1996) (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/policies/bioequivalence-proportional-formulations-solid-oral-dosage-forms.html), a waiver of in vivo bioequivalence studies may be requested for additional strengths in a series of strengths (i.e., non-biostudy strengths) if they are formulated proportionally to the lot of a test strength administered in the bioequivalence studies .

A stereospecific assay may be required for bioequivalence studies where it is not clear whether the proposed generic drug product versus the CRP (e.g., different salt form) will produce the same amount of the active enantiomer.

2.3.3 Biopharmaceutics Classification System (BCS)-based biowaivers

A test product is not eligible for a BCS-based biowaiver when the medicinal ingredient of the generic drug product is a different salt, ester, isomer, mixture of isomers, complex or clathrate compared to that of the CRP.

2.4 Non-clinical toxicology

Evidence should be provided to demonstrate that there is no change in the toxicity profile of the salt form of the medicinal ingredient in the generic drug product that would significantly change the safety of the drug product when compared with the CRP. This may include a literature review of toxicity data for the counter ion, derived acceptable daily intake values for the counter ion, or outlining the regulatory status of the new counter ion (e.g., Generally Recognized as Safe (GRAS) status).

In cases where there is insufficient toxicity data available on the counter ion in the public domain, non-clinical studies may be required to characterize the toxicity profile of the salt form of the medicinal ingredient in the generic drug product. This could include a 13-week repeat-dose toxicity bridging study in rodents comparing the toxicity profile of the CRP with the salt form of the generic drug product. On a case-by-case basis, it may be warranted to also evaluate the toxicity profile of the salt-forming agent alone.

Additional non-clinical toxicology studies (in silico and/or in vitro and/or in vivo) may be required to demonstrate the safety of drug substance-related and/or drug product-related impurities of the salt form of the medicinal ingredient in the generic drug product [refer to ICH Q3 (http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html)series of guidelines and ICH M7 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M7/M7_R1_Addendum_Step_4_2017_0331.pdf)].

If it is determined that the proposed generic drug product has a significant safety concern that differs from the CRP that would result in a change to the conditions of use, it would no longer be considered to have the “same conditions of use” as the CRP and may need to be filed as an NDS.

2.5 Labelling

A separate draft guidance document entitled Identifying and Labelling Medicinal Ingredients in New Drug Products (https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/drug-products/drug-products/consultation-profile-draft-generic-drug-equivalence/document-2.html) has been developed to outline the general principles and considerations in this area.

In most cases, information in the approved Canadian labelling for the CRP should be applied to the generic drug product, with the exception of additional information that is specific to the generic drug product.

Relevant information from all comparative data versus the CRP should be included in the Product Monograph for generic drug products which differ from the CRP with respect to the medicinal ingredient in the dosage form.

Information in the approved Canadian labelling that is specific to the CRP should not be directly transferred, to the labelling of the generic drug product (e.g., new drug containing the new salt form); however, additional text modifications may be made if supported by appropriate evidence or justification.

2.6 Intellectual property considerations

Submissions filed under the ANDS pathway are subject to the Patented Medicines (Notice of Compliance) Regulations and the data protection provisions of section C.08.004.1 of the Food and Drug Regulations. For more information, please refer to the related guidance documents entitled Guidance Document: Patented Medicines (Notice of Compliance) Regulations (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/patented-medicines/notice-

compliance-regulations.html) and Guidance Document: Data Protection under C.08.004.1 of the Food and Drug Regulations (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/guidance-document-data-protection-under-08-004-1-food-drug-regulations.html).

2.7 Notice of Compliance (NOC)

Where there is a difference between the medicinal ingredients with the identical therapeutically active component in the dosage forms of the generic drug product and the CRP, the Notice of Compliance (NOC) for the generic drug product will make note of this difference.

2.8 Post-market considerations

2.8.1 Non opioid containing products

The expectations for submission sponsors are outlined in Guidance Document – Submission of Risk Management Plans and Follow-up Commitments (https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/medeffect-canada/guidance-document-submission-risk-management-plans-follow-commitments.html). As outlined in the guidance document, with the exception of some opioid drugs, the submission of a risk management plans (RMP) or sections of a RMP are requested by Health Canada for generic drug products when it is determined that an RMP is required for the establishment of an adequate risk minimization framework.

Health Canada may request an RMP for a generic drug product with a different medicinal ingredient containing the identical therapeutically active component in comparison to the CRP, Health Canada may request an RMP. Therefore, sponsors are advised to consult within advance to determine if may be required in specific cases.

2.8.2 Opioid containing products

Following amendments to the FDR via the Regulations Amending the Food and Drug Regulations (Opioids) (http://gazette.gc.ca/rp-pr/p2/2018/2018-05-02/html/sor-dors77-eng.html), the Minister of Health has the authority to place terms and conditions on authorizations for opioids to require and enforce RMPs on prescription drugs set out in Part B of the List of Opioids (https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/medeffect-canada/list-opioids.html), including generic drug products which are opioids. The specific requirement regarding RMPs for prescription drugs set out in Part B of the List of Opioids, including generic drug products which are opioids are outlined in the document Submission of targeted risk management plans and follow-up commitments for prescription opioid-containing products - Guidance for industry (https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/medeffect-canada/submission-targeted-rm-plans-commitments-prescription-opioid-containing-products-guidance-industry.html).

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[1] "Critical Dose Drug" is defined in Health Canada's guidance document, Comparative Bioavailability Standards: Formulations used for Systemic Effects (2018) (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)

[2] "Critical Dose Drug" is defined in Health Canada's guidance document, Comparative Bioavailability Standards: Formulations used for Systemic Effects (2018) (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)