Health Canada Santé Canada

Draft Guidance Document

Identifying and Labelling Medicinal Ingredients in New Drug Products

This guidance document is being distributed for comment purposes only.

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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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Ébauche de ligne directrice L'étiquetage des ingrédients médicinaux dans les drogues nouvelles

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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 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

Health Canada is the federal regulatory authority that evaluates the safety, efficacy and quality of drugs for market authorization in Canada.

This draft guidance document sets out considerations for identifying and labelling the medicinal ingredient for a new drug product submitted as a New Drug Submission (NDS) or an Abbreviated New Drug Submission (ANDS) as proposed in the amendments to the Food and Drug Regulations (the Regulations) (http://gazette.gc.ca/rp-pr/p1/2019/2019-03-30/html/reg2-eng.html).

The guidance document Generic Drug Equivalence: Medicinal Ingredients (https://www.canada.ca/en/health-canada/services/drugs-health-products/public-involvement-consultations/drug-products/consultation-profile-draft-generic-drug-equivalence/document-1.html) outlines 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.

1.1 Policy objectives

The objective of this guidance document is to outline the general principles and considerations for identifying the medicinal ingredient of a drug product evaluated under Division 8 of the Regulations.

In an effort to clarify prescribing information and product labelling, this guidance document also outlines recommendations for the labelling of the medicinal ingredient in new drug products.

The current regulations, 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.

1.2 Policy statements

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

As proposed in 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. If there is uncertainty as to what constitutes the medicinal ingredient in the dosage form, the submission sponsor may be asked to provide additional information to assist in this determination.

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.

The medicinal ingredient in the dosage form must appear on the label of a new drug. As proposed in the amendments to the Regulations for sections C.01.004(1)(c), C.01.004.02(1) and C.01.004.03 if the therapeutically active component and the medicinal ingredient are not the same, the name of the medicinal ingredient and a quantitative list of the therapeutically active components of the drug should appear on the label.

The strength of the dosage form should be expressed in terms of the therapeutically active component. If there is no difference between the medicinal ingredient and the therapeutically active component, the strength of the dosage form should be expressed in terms of the medicinal ingredient.

The acceptability of a 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 will apply to new drugs evaluated under Division 8 of the Regulations not referred to in Schedule C or Schedule D of the Food and Drugs Act. This includes NDSs and ANDSs that are filed with the Therapeutic Products Directorate (TPD), the Veterinary Drugs Directorate (VDD), and the Natural and Non-prescription Health Products Directorate (NNHPD).

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

1.4 Background

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) from June to October 2017. 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 and a proposal to define the meaning of “medicinal ingredient” and other key terms.

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.

1.5 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.

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.

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.

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.

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.

2. Guidance for implementation

2.1 Identifying medicinal ingredients

2.1.1 Medicinal ingredient

Where an active pharmaceutical ingredient undergoes a chemical change during the manufacture of the drug product and may be present in the drug product in a different form with the identical therapeutically active component, the converted form present in the drug product is considered the medicinal ingredient. In many cases (e.g., when there is no in situ conversion), the API and the medicinal ingredient in the drug product are the same.

In paragraph C.08.002(2)(c) of the Regulations a reference to the ingredient means the ingredients used in the manufacture of the new drug.

2.2 Information on the Active Pharmaceutical Ingredient

Submission sponsors should provide the information on the complete characterization of the API (also referred to as the drug substance) as described in the Health Canada guidance document Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) (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).

2.3 In situ changes during the manufacturing process of the drug product

If submission sponsors are aware of the potential for an in situ conversion, submission sponsors are encouraged to include information in the drug submission as described in the guidance document Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and

Abbreviated New Drug Submissions (ANDSs) (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 human drug products. For veterinary drug products, submission sponsors should refer to the document Guidance for Industry Preparation of Veterinary New Drug submissions (https://www.canada.ca/en/health-canada/services/drugs-health-products/veterinary-drugs/legislation-guidelines/guidance-documents/guidance-industry-preparation-veterinary-new-drug-submissions-health-canada-2007.html) or Guidance for Industry: Preparation of Veterinary Abbreviated 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).

In cases where there is potential for in situ conversion to a different salt form of the medicinal ingredient, results from studies should be provided to determine whether in situ salt conversion is taking place. These studies could include:

- equilibrium calculation of the extent of ionization (free acid or base/ionized forms) based on the pKa of the reacting components to determine the extent of salt formation
- x-ray diffraction (XRD)
- solid-state nuclear magnetic resonance (SS NMR)
- differential scanning calorimetry (DSC)
- thermal gravimetric analysis (TGA)
- single crystal x-ray studies
- dissolution studies comparing the API vs. theoretical/suspected salt form in the dosage form and
- other studies as considered appropriate for the situation

The salt form that is likely present in the dosage form following in situ conversion during the manufacturing process of the drug product should be synthesized and data on the API and this modified form should be compared to the results in the dosage form. Characteristic peaks should be identified and used for determination of the extent of in situ conversion. The intermediate should also be studied, if intermediates are isolated during the manufacturing process of the dosage form (e.g., spray dried materials after wet granulation).

For dosage forms in solution, the in situ ionic components should be characterized by equilibrium calculations based on the pH of the drug product.

Whether the potential for in situ conversion of an API is such that a different salt is considered the compound in the dosage form (i.e., the API and medicinal ingredient are different), the determination will be made on a case-by-case basis based on the available information.

The medicinal ingredient will generally be considered the API for solution dosage forms unless the data suggest a more appropriate medicinal ingredient be declared based on the in situ ions present.

Direct comparison between the different salt and the medicinal ingredient in the CRP is the preferred way to demonstrate that there are no differences in the safety and/or efficacy of the

generic drug product and the CRP. Such direct comparison would include comparative results of the relevant physicochemical properties (e.g., solubility over the physiological pH range) should be provided of the salt form in the generic drug product compared to that in the CRP.

Indirect, non-comparative evidence may be acceptable, if scientifically justified. However it is noted that indirect, non-comparative evidence may be less compelling.

2.4 Labelling medicinal ingredients

For general labelling recommendations for NDSs and ANDSs, submission sponsors should refer to the guidance documents Product Monograph (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/product-monograph.html) and Labelling of Pharmaceutical Drugs for Human Use (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/labelling-pharmaceutical-drugs-human-use-2014-guidance-document.html). For general and specific labelling recommendations for veterinary NDSs and ANDSs, please contact the Veterinary Drugs Directorate by telephone (613-954-5687) or by e-mail (vetdrugs-medsvet@hc-sc.gc.ca).

The labelling should reflect the therapeutically active component and medicinal ingredient most likely present in the dosage form (if different from the therapeutically active component). As proposed in the amendments to the Regulations for sections C.01.004(1)(c), C.01.004.02(1) and C.01.004.03.

If an in situ change is theoretically likely and evidence on the conversion is equivocal, the decision on how to express the strength and the medicinal ingredient on the label should be discussed and the totality of evidence will determine the most appropriate labelling of the strength and the medicinal ingredient.

For ANDSs, 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.

2.5 Product monograph

The Product Monograph is a factual, scientific document on a drug product that, devoid of promotional material, describes the properties, claims, indications, and conditions of use for the drug, and that contains any other information that may be required for optimal, safe, and effective use of the drug. Health Canada's Product Monograph (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/product-monograph.html) guidance provides details on the information that should be included about the drug product.

Of particular note for ANDSs, 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.

The API should be listed in Part II of the Product Monograph. If an in situ conversion occurs, the Composition section should include a description of the conversion. If evidence to confirm that the in situ conversion is partial or if the evidence is equivocal, then the description of the conversion should address this in appropriate plain language.

For veterinary drugs a Product Monograph is not required.

2.6 Package labels and package inserts

The labelling for new drugs should express the strength of the dosage form in terms of the therapeutically active component.

If the medicinal ingredient in the dosage form is not the therapeutically active component, the labels should also include the name of the medicinal ingredient (e.g., “Each tablet contains 10 mg of new drug (as new drug sodium)”).

For generic drug products, 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.

Labelling materials should be submitted per the Health Canada Guidance documents Labelling of Pharmaceutical Drugs for Human Use and the Questions and Answers: Plain Language Labelling Regulations (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/questions-answers-plain-language-labelling-regulations.html). For all veterinary drugs a specific format (order of headings) is recommended for the package insert. Please contact the Veterinary Drugs Directorate (http://www.hc-sc.gc.ca/contact/dhp-mps/hpfb-dgpsa/vdd-dmv-eng.php) for further information.

2.6.1 Co-marketing of products with different forms of the medicinal ingredient

In line with the documents Guidance for Industry – Review of Brand Name Drugs (https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/medeffect-canada/guidance-document-industry-review-drug-brand-names.html) and Assignment of Drug Identification Number (DINs) According to Product Name (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/policies/assignment-drug-identification-numbers-dins-according-product-name.html), when a company chooses to co-market products with different medicinal ingredients with the identical therapeutically active component (e.g., different salt forms) and all other fields in the form are identical, each product must be identified with a separate brand name.

2.7 Post-Notice of Compliance (NOC) changes

A change in the form of the medicinal ingredient after receipt of a Notice of Compliance should be filed as an NDS or an ANDS (as appropriate) and not as a Supplement.

For changes to the drug substance or drug product after receipt of a Notice of Compliance, 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.

3. Contact information

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