Health Canada Santé Canada

Date: 2003-07-23

# NOTICE

Our file number: 03-100595-20

Health Canada is pleased to announce the finalization of the policy *Interpretation of "Identical Medicinal Ingredient"*.

A draft version of this document of the same title was released for Stakeholder consultation in January 2003. This finalized version has been to revised (where appropriate) to provide additional clarification as a result of comments that have been received. A summary of the comments received during the consultation process, together with discussions and recommendations is provided in a separate "Questions and Answers" document.

The effective date of this policy is 2003/07/09.

This and other Policies and Guidance documents are available on the **Therapeutic Products Directorate Website** (**http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/**). The availability of printed copies of guidance documents may be confirmed by consulting the *Guidelines and Publications Order Forms* (available on the TPD Website) or by contacting the Publications Coordinator[1].

Should you have any questions regarding the content of the policy, please contact:


Bureau of Pharmaceutical Sciences
Therapeutic Products Directorate
Health Canada
Finance Building (A/L 0202A2)
Ottawa, Ontario
K1A 1B9

Internet: bps_enquiries@hc-sc.gc.ca
Phone: (613) 941-3184
Fax: (613) 957-3989


[1] Tel: (613) 954-6466; E-mail: publications_coordinator@hc-sc.gc.ca

Health Canada Santé Canada

# POLICY
# Interpretation of "Identical Medicinal Ingredient"

Published by authority of the
Minister of Health

| | |
|---|---|
| Date Adopted | 2003/07/09 |
| Effective Date | 2003/07/09 |

**Health Products and Food Branch**
**Policy**

Canada

Our mission is to help the people of Canada maintain and improve their health.

*Health Canada*

HPFB's Mandate is to take an integrated approach to the management of the risks and benefits to health related to health products and food by:

- 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.

*Health Products and Food Branch*

**LET YOUR COMPUTER DO THE SEARCHING!**

... Need to know how to market a new drug in Canada?

... Want information on the drug regulatory process?

... Need to know what the newest drugs on the Canadian market are?

... Want direct access to forms and policies?

... Need to know the requirements for labelling drugs?

All this and more is available on the

**Therapeutic Products Directorate / Biologics and Genetic Therapies Directorate / Marketed Health Products Directorate Website (s)**

at

**http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/**

**http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/**

## 1. PURPOSE

The purpose of this policy is to delineate the guiding principles that will be used to determine if two medicinal ingredients with the same active moiety are considered "identical" or "non-identical". This is used in establishing the pharmaceutical equivalence of dosage forms within the meaning of the term "identical medicinal ingredient" as mentioned in Section C.08.001 of the *Food and Drug Regulations*.

## 2. BACKGROUND

As outlined in Section C.08.001.1 of the *Food and Drug Regulations* (which defines a Canadian reference product):

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

As part of a drug submission for a subsequent market-entry product (e.g., a generic), a sponsor would provide evidence to demonstrate that their drug product meets the above criteria of the *Regulations*. It has been determined that a consistent and transparent interpretation of the term identical medicinal ingredient would be useful in the comparison of two medicinal ingredients and would be of a benefit to the review process and to Stakeholders.

An assessment of the criteria used by the various Regulatory Authorities has been undertaken to determine the approaches on the subject. For example, the International Conference on Harmonization (ICH) defines a New Drug Substance as:

> *The designated therapeutic moiety that has not been previously registered in a region or member state (also referred to as a new molecular entity or new chemical entity). It can be a complex, simple ester, or salt of a previously approved drug substance.*[2]

The content of this policy is intended to be consistent with these international standards.

## 3. SCOPE

This document is intended to apply to drug submissions that are filed with the Therapeutic Products Directorate pursuant to Division C.08 of the *Food and Drug Regulations*. It is not intended to apply to biological (Schedule D) or radiopharmaceutical (Schedule C) products or medicinal ingredients which do not possess a unique chemical structure (e.g., polymers with varying molecular weights).

[2] ICH Q3A(R): Impurities in New Drug Substances, 2002.

This policy does not alter existing requirements in the policy "Changes to Marketed New Drug Products" when changes are made to the drug substance route of synthesis that may result in a different polymorphic form of the same active moiety.

## 4. GUIDING PRINCIPLES

The term identical medicinal ingredient could literally be interpreted to imply medicinal ingredients that are both physically and chemically identical. However, in the context of the *Regulations*, only the "chemical identicality" of the medicinal ingredients is taken into account while determining pharmaceutical equivalence. Pharmaceutically equivalent drug products should contain chemically identical, but not necessarily physically identical, medicinal ingredients. It is recognized that differences in physical properties (e.g., particle size, polymorphism) of the medicinal ingredients could potentially cause differences in the safety and efficacy profiles of the drug products. To address concerns arising from differences in physical properties, appropriate *in vivo* and / or *in vitro* studies should be conducted and results provided with the drug submission. The term identical is to be understood in this context.

Based on the above considerations, medicinal ingredients containing the same active moiety are classified into *identical* or *non-identical* medicinal ingredients according to the following guiding principles:

4.1 Anhydrous, anhydrate and the various hydrated forms of the same active moiety would generally be considered identical.

4.2 Unsolvated and the various solvated forms of the same active moiety would generally be considered identical, provided the solvate content is within acceptable levels. Levels within the limits recommended in the ICH Q3C "Impurities: Guideline for Residual Solvents", would be considered acceptable without further justification. Solvate levels exceeding the ICH Q3C limits should be justified, on a case by case basis, and supporting data provided. Supporting data could be based upon concepts of qualification outlined in ICH impurity guidelines Q3A, Q3B and Q3C.

4.3 Different complexes, esters, or salts of the same active moiety are considered non-identical.

4.4 Different isomers or mixtures with different proportions of isomers are considered non-identical.

Submission sponsors are advised to discuss with Health Canada, in advance, when the "identicality" of two medicinal ingredients is in doubt for the purposes of establishing pharmaceutical equivalence.

## 5. GLOSSARY

**Active moiety (or Therapeutic moiety)**
The molecule or ion, excluding those appended portions of the molecule that cause the drug substance to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

**Anhydrate form**
A crystal form that does not include water bound within the crystal structure.

**Anhydrous form**
A solid form which does not include water bound within the crystal structure and does not include water associated loosely with the molecules of the crystal.

**Clathrate**
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.

**Complex**
A compound which is formed by the equilibrium association of two or more interacting molecules or ions. Complexes may be formed in solution or in the solid state.

**Drug substance (or Active Pharmaceutical Ingredient (API))**
Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

**Hydrate**
A compound that contains water within its crystal structure.

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

**Polymorph**
Different crystalline or amorphous forms of the same drug substance. This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms.

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

**Solvate**
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 general class of solvates where the solvent is water.