May 30, 2014

Notice

Regulatory cooperation initiative (RCI) over-the-counter (OTC) products

Release of final labelling standards

Health Canada and the Australian Therapeutic Goods Administration (TGA) have initiated the Regulatory Cooperation Initiative (RCI) project to explore various ways of work sharing between the two regulatory agencies. Two labelling standards have been developed (*nonprescription topical nasal decongestants* and *nonprescription oral adult expectorant cough and cold*) because they meet the goals of aligning the ongoing work of both regulators and reducing unnecessary differences.

The proposed *nonprescription topical nasal decongestants labelling standard* describes the requirements necessary to receive marketing authorization for non-prescription topical nasal decongestant products containing oxymetazoline hydrochloride or xylometazoline hydrochloride as a single ingredient for use in adults to relieve nasal congestion.

The proposed *nonprescription oral adult expectorant cough and cold labelling standard* describes the requirements necessary to receive marketing authorization for oral expectorant non-prescription products containing guaifenesin as a single ingredient for use in adults to relieve symptoms of common cold.

This initiative is the first of its kind between Health Canada and the TGA. This is one step in the ongoing collaboration between Health Canada and the TGA to work toward greater regulatory convergence and harmonization where feasible. Both regulators will continue to explore if there may be additional opportunities for future OTC monograph initiatives.

Health Canada Santé Canada

GUIDANCE DOCUMENT

Nonprescription oral adult expectorant cough and cold labelling standard

Published by authority of the
Minister of Health

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Health Products and Food Branch

Canada

Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	The Health Products and Food Branch's mandate is to take an integrated approach to the management of the risks and benefits to health related 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*

Également disponible en français sous le titre : Ligne directrice : Norme d'étiquetage des médicaments adults contre la toux Expectorant et le rhume, administrés par voie orale et vendus sans ordonnance

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.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

Table of contents

1. Introduction

This labelling standard describes the requirements necessary to receive marketing authorization (Drug identification number (DIN)) for oral expectorant nonprescription product containing guaifenesin as a single ingredient for use in adults and children 12 years of age and older to relieve symptoms of common cold. This labelling standard does not apply to products for use by children under 12 years of age.

2. Medicinal ingredient

Table 1: Drug medicinal ingredient

Therapeutic class	Medicinal ingredient Preferred name
Expectorant	Guaifenesin

3. Pharmaceutical forms

3.1 Acceptable:

- Immediate release solid oral dosage forms such as tablets, caplets, capsules, chewable tablets, effervescent tablets, powders.
- Oral liquid formulations such as suspension, syrup, elixir.

3.2 Unacceptable:

- Modified dose release (e.g. liquid extended release, solid oral sustained release, bi-layer formulations or enteric coated products).
- Products that require evaluation of animal sourced ingredients (e.g. animal tissue based gelatin capsules, where valid EDQM Certificates of suitability is not provided).
- Other dosage forms: e.g., chewable liquid filled capsule, powder dosage form intended for direct application to the mouth, thin strips, lollipops, popsicles/freezer pops etc.

4. Indications

4.1 Acceptable indications

- Expectorant / cough expectorant.
- Relief of wet cough or wet chest cough due to common colds.[1]
- Helps loosen phlegm (mucous) and makes coughs more productive. [1, 2, 3]
- Relief of chest congestion due to common colds. [1, 2]

[1] Robinson, Cummings and Deffenbaugh, 1977.
[2] Kuhn et al, 1982.
[3] Thomson, Pavia and McNichol, 1973.

- Helps thin mucous/bronchial secretions. [1], [2]

4.2 Unacceptable indications

The following indications for expectorant products are excluded and would require a review outside of the standard. These include but are not limited to:

- treat lower respiratory tract conditions (including infections and asthma).
- bronchitis.
- coughs due to allergies or inhaled irritants.
- influenza/flu.
- allergy/hay fever symptoms
- relief of dry cough.

5. Dosage directions

5.1 Dosage for adults and children 12 years of age and older[4]

Table 2:

Therapeutic class	Medicinal ingredient preferred name	Recommended single dose[5]	Dose interval	Maximum daily dose
Expectorant	Guaifenesin	200-400 mg	every 6 hours	1600 mg

5.2 Dosing considerations

1. The quantitative declaration of the medicinal ingredients on any panel of the inner and outer labels should be prominently displayed and should be further identified by the therapeutic class or indication listed under **Section 4.1**, e.g.: "Active ingredient: Guaifenesin (expectorant) 200mg"; “Active ingredient: Guaifenesin (relief of wet cough) 200mg”.

2. The labels should declare the recommended single and maximum daily dose, as well as the dosing interval for the product. Maximum daily dose may be expressed in terms of dosage units (e.g. do not exceed X tablets per day).

3. For liquid formulations, the following statement should be included with the directions for use: “Use only the measuring device provided.”

[4] Doses and dosing frequency are those recommended by the Expert advisory committee on nonprescription cough and cold remedies (Second report, April 1989).

[5] For liquid formulations, the single dose must be contained and labelled in standard units (e.g., millilitres).

5.3 Combinations

Applicants can apply outside of the labelling standard should they wish to combine guaifenesin with other medicinal ingredients.

6. Warnings

For outer and inner labels

- Keep out of reach of children.
- Do not take more than the recommended dosage.
- Read the complete label *[and package insert if applicable]* prior to use and follow all label instructions.
- Do not use this product in children under 12 years of age.

Ask a doctor or pharmacist before use if you:

- have persistent or chronic cough, difficulty breathing, asthma or other chronic lung conditions.
- are pregnant or breastfeeding.[4]
- Consult a doctor if symptoms worsen, last for more than a week or are accompanied by a high fever (>38^{o} C), persistent headache, rash or the production of thick yellow/green phlegm.

- **In case of overdose:** Call a poison control centre or doctor immediately, even if you do not notice any signs or symptoms.

Optional warnings that may appear on other outer panels or package insert or inner panels of a peel-back / accordion label:

- Do not use with any other cough and cold medications since harm may occur, unless recommended by a doctor or pharmacist.
- Do not use longer than 7 days
- Do not use if you have an allergy to any of the listed ingredients.
- Stop use if allergic reactions such as wheezing, rash, or itching develops

7. Other labelling requirements

For all products:

- **Declaration of ingredients:**
  - Single ingredient products and/or ones for which a compendial standard exists must declare the proper name of the finished product on the front panel of all labels, immediately preceding or following the brand name in a font size not less than ½ the size of the brand name. (C.01.004)
  - All products must declare the active ingredients on the inner and outer labels, and clearly label these as "active" or "medicinal" ingredients. (C.01.004)
  - Nonprescription products must provide a qualitative listing of "non medicinal" ingredients on the outer label. (C.01.004)
- ***Guidance document - Labelling of pharmaceutical drugs for human use*:** This guidance document should be consulted for applicable labelling requirement.

Legibility:

Although no specific type size is mentioned in the *Regulations*, Section *A.01.016* specifies that all information required to appear on a label must be:

- Clearly and prominently displayed, and
- Readily discernible to the purchaser or consumer under the customary conditions of purchase and use.

A person with normal vision, or those with corrective glasses that restore normal vision, should be able to read the information without straining. The colour, contrast, the position, and the spacing of the information are all to be taken into consideration in complying with these requirements.

8. Specifications

This labelling standard describes those requirements that are specific to this class of drug.

Products must comply with the requirements in the *Food and Drugs Act* and associated *Regulations*. It is also noted that all products are subject to Part C, Division 2 of the *Food and Drug Regulations*.

All ingredient (medicinal and non-medicinal) and finished product specifications must meet or exceed the standards described in the publications referred to in Schedule B to the *Food and Drugs Act*, or equivalent standards. Where no Schedule B monograph exists for the dosage form, specifications should be similar to those of a comparable compendial dosage form. In the absence of a Schedule B standard for any dosage form, testing must be adequate to demonstrate the product's identity, potency, purity and quality.

Finished product specifications should include tests for identification and an assay with suitable limits for the medicinal ingredient(s). The specifications for all dosage forms should include a description of the dosage form, including organoleptic properties as well as physico-chemical testing e.g., pH, specific gravity, viscosity, appropriate to the dosage form. Where antimicrobial preservatives are added, an assay with suitable limits should be included. Antimicrobial preservative effectiveness should be determined in order to establish that the product is capable of resisting microbial contamination.

Any change to the manufacturing process that impacts the safety and efficacy of the ingredients, such as the use of novel technology (e.g. nanotechnology), requires supporting data and will be reviewed outside the labelling standard.

9. Non-medicinal ingredients

Non-medicinal ingredients must be restricted to those substances, necessary for the formulation of the dosage form. Their concentration must not exceed the minimum required to provide their intended effect. They must be harmless in the amounts used, their presence must not affect the therapeutic efficacy or safety of the medicinal ingredients and they must not interfere with assays and tests for the medicinal ingredients and, if present, antimicrobial preservatives. Sponsors should be aware that ingredients of botanical origin added as non-medicinal ingredients must comply with the Health Canada policy, *Herbs used as non-medicinal ingredients in nonprescription drugs for human use* (1995).

10. References

1. American Hospital Formulary Service®. AHFS Drug Information 2009®. Published by Authority of the Board of the American Society of Health-System Pharmacists®, Bethesda, Maryland.

2. Coughs suppressants, expectorants mucolytics and nasal decongestants: Sweetman SC (ed), Martindale: The Complete Drug Reference. [online] London: Pharmaceutical Press <http://www.medicinescomplete.com/> (Accessed on Oct 12, 2012).

3. First report of the expert advisory committee on nonprescription cough and cold remedies. *Heath and Welfare Canada, August 1988*.

4. *Guidance document: Labelling of pharmaceutical drugs for human use*. Health Canada, January 10, 2014.

5. *Guidance for industry: Impurities in existing drug substances and products*. Health Canada, September 2005.

6. *Guidance to industry: Product monograph*. Health Canada, October, 2004.

7. *Herbs used as non-medicinal ingredients in nonprescription drugs for human use*. Health Canada, September 1995.

8. Kuhn JJ, Hendley JO, Adams KF, Clark JW, Gwaltney JM Jr. Antitussive effect of guaifenesin in young adults with natural colds. *Chest* 1982; **82**(6):713–8.

9. Robinson RE, Cummings WB, Deffenbaugh ER. Effectiveness of guaifenesin as an expectorant: a cooperative double-blind study. *Current Therapeutic Research* 1977; **22** (2):284–96.

10. Second report of the expert advisory committee on nonprescription cough and cold remedies. *Health and Welfare Canada, April 1989*.

11. Thomson, M.L., Pavia, D. and McNichol, M.W. A preliminary study of the effect of guaifenesin on mucociliary clearance from the human lung. Thorax. 1973; **28**: 742-747.

12. Third report of the expert advisory committee on nonprescription cough and cold remedies. *Health and Welfare Canada, September 1989*.

13. United States Food and Drug Administration: Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products For Over-The-Counter Human Use Code of Federal

Regulations Part 341, Title 21, Volume 5 Revised as of April 1, 2012. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=341&showFR=1