

February 6, 2009

NOTICE

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Release of the Final Guidance Document: *Nonprescription Oral Paediatric Cough and Cold Labelling Standard*

The final version of this Health Canada *Guidance Document – Nonprescription Oral Paediatric Cough and Cold Labelling Standard* is now available. Comments and suggestions received from the consultation on the draft version of the guidance were reviewed and considered in the finalization of this document.

This Labelling Standard reflects Health Canada's decision as described in the December 18, 2008 Notice: To Market Authorization Holders: Health Canada's Decision on Labelling of Certain Paediatric (0 to under 12 years) Nonprescription Cough and Cold Products in Canada regarding: (1) Enhanced labelling, including a prohibition to not use for children under 6 years; (2) Child resistant packaging; and (3) Inclusion of dosing devices for all liquid formulations for products that have labelling for use in children aged 6 to under 12 years. The Labelling Standard also finalizes additional aspects that were published for comment, such as the permitted ingredients, doses, indications for use, font size, directions for use and ingredient-specific warning statements that will be required to appear on the product labels.

As with any Guidance Document or Labelling Standard, alternate approaches to the requirements, as described in these documents, may be acceptable provided they are supported by adequate justification and data. In these cases, an application outside of the Labelling Standard may be submitted.

Should you have any questions or comments regarding the content of the guidance, please contact

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GUIDANCE DOCUMENT

Nonprescription Oral Paediatric Cough and Cold Labelling Standard

Published by authority of the
Minister of Health

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Health Products and Food Branch

Canada

<p>Our mission is to help the people of Canada maintain and improve their health.</p> <p><i>Health Canada</i></p>	<p>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:</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><i>Health Products and Food Branch</i></p>
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Également disponible en français sous le titre : Ligne directrice : Norme d'étiquetage des médicaments pédiatriques en vente libre contre la toux et le rhume, administrés par voie orale

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	1
2. MEDICINAL INGREDIENTS.....	1
3. PHARMACEUTICAL FORMS	2
4. INDICATIONS.....	2
4.1 Acceptable Indications.....	2
4.2 Unacceptable Indications	2
5. DOSAGE DIRECTIONS.....	3
5.1 Dosage for Children 6 to under 12 years	3
5.2 Dosing Considerations	4
5.3 Combinations	4
6. WARNINGS	5
6.1 For outer and inner labels of all products	5
6.2 For products containing an antihistamine	6
6.3 For products containing an antitussive	6
6.4 For products containing a decongestant.....	6
7. OTHER LABELLING REQUIREMENTS	6
8. SPECIFICATIONS.....	7
9. NON-MEDICINAL INGREDIENTS.....	8
10. SPECIAL NOTES	8
11. REFERENCES	9

1. INTRODUCTION

This Labelling Standard describes the requirements necessary to receive marketing authorization (a Drug Identification Number (DIN)) for single and multiple-ingredient orally administered nonprescription paediatric products for use in children 6 to under 12 years of age to provide relief of symptoms associated with the common cold. This Standard does not apply to products solely for use by adults (over 12 years of age). These products should not be used in children under 6 years of age.

2. MEDICINAL INGREDIENTS

The medicinal ingredients of a product complying with this Standard consist of the following ingredients when used singly or in acceptable combinations within the established limits specified in Table 2.

TABLE 1:
Drug medicinal ingredients

Therapeutic Class	Medicinal Ingredient Preferred Name
Antihistamine	Brompheniramine maleate
	Chlorpheniramine maleate
	Dexbrompheniramine maleate
	Diphenhydramine hydrochloride
	Doxylamine succinate
	Pheniramine maleate
	Triprolidine hydrochloride
Antitussive	Diphenhydramine hydrochloride
	Dextromethorphan
	Dextromethorphan hydrobromide
Decongestant	Phenylephrine hydrochloride and sulphate
	Pseudoephedrine hydrochloride and sulphate ¹
Expectorant	Guaifenesin (glyceryl guaiacolate)

¹ When present as a single active ingredient, pseudoephedrine is regulated as a natural health product and requires a Natural Health Product Number (NPN) for market authorization. Please consult the Natural Health Products Directorate (NHPD) monograph for this ingredient. When pseudoephedrine is combined with cough and cold ingredients listed in this standard, the product is regulated by the Therapeutic Products Directorate (TPD) and requires a DIN for market authorization. This standard will only be applicable to pseudoephedrine in combination products.

3. PHARMACEUTICAL FORMS

The acceptable dosage forms are as follows:

- Immediate release solid oral dosage forms such as tablets, caplets, chewable tablets, effervescent tablets, powders.
- Oral liquid formulations such as suspension, syrup, elixir, tincture or drops.
- Single ingredient thin strips.

Unacceptable dosage forms are as follows:

- 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).
- Novel dosage forms: e.g., multiple ingredient thin strips, lollipops, popsicles/freezer pops.

4. INDICATIONS

4.1 Acceptable Indications

For all products:

- to temporarily relieve the symptoms of the common cold.

For products containing an antihistamine:

- temporary symptomatic relief of sneezing and /or runny nose (sniffles) due to common colds.

For products containing an antitussive:

- temporary relief of dry cough due to common colds.

For products containing a decongestant:

- temporary relief of nasal congestion/pressure due to common colds.
- temporary relief of stuffiness due to common colds.

For products containing an expectorant:

- relief of wet cough due to common colds.
- helps loosen phlegm (mucous).
- for the relief of chest congestion.

4.2 Unacceptable Indications

- relief of nasal symptoms other than runny nose and sneezing (for antihistamine)
- alleviate nasal congestion (for antihistamine)
- treat lower respiratory tract conditions (including infections and asthma)

- bronchitis
- sinusitis
- relief of sinus pressure/congestion (for decongestant)
- promote sinus drainage
- coughs due to allergies or inhaled irritants (for antitussives and expectorants)
- chest coughs (for antitussives and expectorants)
- influenza/flu
- allergy/hay fever symptoms
- relief of wet cough (for antitussives)
- relief of dry cough (for expectorant)
- sleep aid (e.g., relieves sneezing, runny nose and helps you get to sleep)

5. DOSAGE DIRECTIONS

5.1 Dosage for Children 6 to under 12 years²

TABLE 2:

Therapeutic Class	Medicinal ingredient preferred name	Recommended Single Dose ³	Dose Interval	Maximum Daily Dose
Antihistamine	Brompheniramine Maleate	2mg	every 4-6 hours	12mg
	Chlorpheniramine Maleate	2mg	every 4-6 hours	12mg
	Dexbrompheniramine Maleate	1mg	every 4-6 hours	6mg
	Diphenhydramine hydrochloride	12.5-25 mg	every 4-6 hours	100mg
	Doxylamine succinate	3.75-6.25 mg	every 4-6 hours	37.5mg
	Pheniramine maleate	6.25-12.5 mg	every 4-6 hours	75mg
	Triprolidine hydrochloride	1.25mg	every 4-6 hours	5mg
Antitussive	Diphenhydramine hydrochloride	12.5 mg	every 4 hours	75mg
	Dextromethorphan OR Dextromethorphan hydrobromide	5-10 mg	every 4 hours	60mg
		15 mg	every 6-8 hours	

² Doses and dosing frequency are those recommended by the Expert Advisory Committee on Nonprescription Cough and Cold Remedies (First Report, August 1988; Second Report, April 1989; Third Report September 1989).

³ For liquid formulations, the single dose must be contained and labelled in standard units (e.g. mL) and a measuring device shall be provided that accurately delivers this dose.

Decongestant	Phenylephrine hydrochloride and sulphate ⁴	5mg	every 4 hours	30mg
	Pseudoephedrine hydrochloride and sulphate ⁴	30mg	every 4-6 hours	120mg
Expectorant	Guaifenesin (glyceryl guaiaacolate)	100mg	every 6 hours	400mg

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, e.g.: “Active Ingredient: Guaifenesin (expectorant) 100mg”. Alternate wording for therapeutic class may be acceptable provided they are listed under **Section 4.1** of this Labelling Standard.
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.”

5.3 Combinations

Acceptable Combinations:

TABLE 3^{5, 6}

Therapeutic Class	Antihistamine ⁷	Antitussive ⁷	Decongestant	Antitussive ⁷ and Decongestant	Expectorant
Antihistamine ⁷		X ⁸	X	X ⁸	
Antitussive ⁷	X ⁸		X		
Decongestant	X	X			X
Antitussive ⁷ and	X ⁸				

⁴ Doses for phenylephrine and pseudoephedrine are expressed in terms of the salt.

⁵ Acceptable combinations are only for **single** ingredients from each therapeutic class. Combinations of more than two therapeutic classes are only permitted for antitussive, antihistamine and decongestant products.

⁶ Combinations are acceptable only when there are compatible dosing intervals and provided the daily maximum dosage of each ingredient is not exceeded.

⁷ Diphenhydramine can be both an antitussive and antihistamine (see Unacceptable Combinations below).

⁸ It is not acceptable to combine diphenhydramine **antitussive** with another antihistamine or combine diphenhydramine **antitussive** with another antitussive.

Decongestant					
Expectorant			X		

Unacceptable Combinations:

- Any antihistamine active ingredient in combination with the oral expectorant active ingredient.
- A combination of diphenhydramine **antitussive** with another antihistamine or a combination of diphenhydramine **antitussive** with another antitussive.
- Any antitussive active ingredient in combination with the oral expectorant active ingredient.
- Combinations with:
 - two or more ingredients from the same therapeutic class.
 - ingredients from different therapeutic classes if any ingredient is present at less than the minimum effective dose; OR
 - an ingredient specifically intended to counteract a side effect of another ingredient in the product.

6. WARNINGS

6.1 For outer and inner labels of all products

- Keep out of reach of children.
- Read the complete label [*and package insert if applicable*] prior to use and follow all label instructions.
- Do not use this cough and cold product in children under 6 years of age.
- Do not exceed the single and maximum daily dose. Do not use for longer than 7 days. Overdose may result in serious harm.
- DO NOT** give with any other cough and cold medications since harm may occur, unless recommended by a healthcare practitioner.
- Consult a healthcare practitioner prior to combining with other medications, including natural health products, prescription drugs or nonprescription drugs.

All of the following warnings may appear on an insert or other panels if it can be demonstrated that space is limited on the packaging. Note that the packaging must carry clear instructions to access the insert or other panels:

- Consult a healthcare practitioner if symptoms worsen, last for more than a week or are accompanied by a high fever ($>38^{\circ}\text{C}$) or the production of thick yellow/green phlegm.
- Do not use if the child is allergic to any of the ingredients.
- Discontinue use if allergic reactions such as wheezing, rash or itching develop.
- Side effects may include: allergic reaction, breathing difficulties, convulsions, drowsiness, hallucinations, and rapid heart rate.

- **In Case of Overdose:** Call a Poison Control Centre or doctor immediately, even if you do not notice any signs or symptoms.

6.2 For products containing an antihistamine

- May cause drowsiness or excitability.
- Do not use when child is engaged in activities requiring mental alertness.
- Consult a healthcare practitioner prior to use if the child has:
 - chronic lung disease.
 - difficulty in urination.
 - glaucoma.
- For products containing diphenhydramine:
 - Do not use with a topically applied product that also contains diphenhydramine.

6.3 For products containing an antitussive

- Consult a healthcare practitioner prior to use if the child has asthma or other chronic lung conditions.
- For Product containing dextromethorphan:
 - Do not use with a monoamine oxidase inhibitor (MAOI) or for 2 weeks after stopping the MAOI drug.
- For products containing diphenhydramine:
 - the warning statements appropriate for oral antihistamine should also appear (see section 6.2).

6.4 For products containing a decongestant

- Consult a healthcare practitioner prior to use if the child has:
 - heart or thyroid disease.
 - high blood pressure.
 - diabetes.
 - glaucoma.

7. OTHER LABELLING REQUIREMENTS

For all products:

1. All products intended for use in children 6 to under 12 years of age should be in child resistant containers that comply with sections C.01.001 (2), (3) and (4) of the *Food and Drug Regulations*.

2. 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:

- a) *Clearly and prominently displayed, and*
- b) *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. A type size of 10 point for text and 9 point minimum for tables are recommended for any cough and cold product package inserts, in keeping with section 2.2 of Health Canada's *Guidance to Industry: Product Monograph*. It is recommended that cough and cold product labels have a minimum of font size 9.

8. SPECIFICATIONS

This Labelling Standard describes those requirements that are specific to this class of drugs.

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. SPECIAL NOTES

Sponsors are requested to take note of the following combinations of cough and cold products since additional data could be required in support of the appropriate use of such a proposed product. Health Canada could also recommend that an application outside of the Standard be submitted. When applicable, a review outside of the Standard would be appropriate as noted below. Please note that if the conditions of Section C.08.001 of the *Food and Drug Regulations* are met, a New Drug Submission will be required.

- Combinations of cough and cold products that include an analgesic. The *Nonprescription Drugs Analgesics Labelling Standard* should be consulted since it provides relevant information related to the use of analgesics, which could be applicable for these combinations.
- Combinations that contain codeine, codeine phosphate and codeine sulphate. Codeine should not be administered to children except on the advice of a health care professional. Section 36 of the *Narcotic Control Regulations* should be consulted for the conditions of acceptability of codeine in nonprescription medications. Should a sponsor have sufficient supporting data for the appropriate use of such a proposed product, an application outside of the Standard may be submitted.
- Combinations with an active ingredient regulated as a natural health product other than pseudoephedrine (e.g. vitamins, echinacea, menthol, camphor, caffeine, eucalyptus). Should a sponsor have sufficient supporting data for the appropriate use of such a proposed product, an application outside of the Standard may be submitted.
- Combinations with a dosage form identified as unacceptable for submission under this Labelling Standard as per Section 3 (e.g. modified dose release, products that require evaluation of animal sourced ingredients, and, novel dosage forms). Should a sponsor have sufficient supporting data for the appropriate use of such a proposed product, an application outside of the Standard may be submitted.

- Chemical interactions between phenylephrine and maleate under common storage conditions may occur (Marín, et al. 2005; Wong, et al. 2006), resulting in an impurity whose identity has been elucidated (Wong, et al. 2006). For combination products containing the ingredients phenylephrine and brompheniramine/ chlorpheniramine/ dexbrompheniramine/ pheniramine maleate, sponsors should add an additional test(s) in their specifications to identify this impurity and provide a summary of a risk management plan for any drug product batches potentially identified as exceeding the threshold limits for this impurity. Sponsors should refer to the recommended limits for impurities outlined in Draft Guidance for Industry - Impurities in Existing Drug Substances and Products (dated 2005/09/06).

11. REFERENCES

1. First report of the expert advisory committee on nonprescription cough and cold remedies. *Heath and Welfare Canada, August 1988.*
2. Second report of the expert advisory committee on nonprescription cough and cold remedies. *Heath and Welfare Canada, April 1989.*
3. Third report of the expert advisory committee on nonprescription cough and cold remedies. *Heath and Welfare Canada, September 1989.*
4. *Guidance for Industry - Impurities in Existing Drug Substances and Products.* Health Canada, September 2005.
5. *Guidance to Industry: Product Monograph.* Health Canada, October, 2004.
6. *Herbs Used as Non-Medicinal Ingredients in Nonprescription Drugs for Human Use.* Health Canada, September 1995.
7. Marín A, Espada A, Vidal P., Barbas C. A major degradation product identified in several pharmaceutical formulations against the common cold. *Analytical Chemistry* 2005: 77(2):, 471-477
8. Scientific Advisory Panel On Nonprescription Paediatric Cough & Cold Medication (SAP-NPCCM). Health Canada, March 2008.
9. Wong J, Wiseman L, Al-Mamoon S, Cooper T, Zhang L-K, Chan T-M. A major degradation product identified in several pharmaceutical formulations against the common cold. *Analytical Chemistry* 2006: 78(22): 7891-7895.