Health Canada Santé Canada

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Notice

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Release of Final Guidance Document*: Acetaminophen Labelling Standard*

The final version of this Health Canada *Guidance Document - Acetaminophen Labelling Standard* is now available. Comments and suggestions received from the consultation between January to March 2009 on the draft version of the guidance were reviewed and considered in the finalization of this document.

This labelling standard replaces the acetaminophen portion of the December 2, 1994 *Analgesics Labelling Standard*. It identifies the permitted ingredients, doses, and indications for use for these products, as well as the font size, the directions for use and ingredient-specific warning statements which will be required to appear on the product labels. Of note, this labelling standard now reflects strengthened safety labelling regarding acetaminophen overdosing, the risks to infant health posed by codeine use in nursing mothers and provides weight-based dosing information for children.

This new labelling standard is effective immediately for all submissions seeking a new market authorization. Holders of market authorizations for existing products are strongly encouraged to effect any necessary labelling changes as soon as possible by submitting an updated label for review via a Post-authorization Division 1 Change. By Fall 2010, Health Canada expects all products to comply with the new labelling standard and will take appropriate regulatory measures, as circumstances warrant, to deal with any products that remain on the market without updated labelling.

This standard should also be used to inform the labelling of products that contain acetaminophen in addition to other ingredients (other than caffeine and codeine as specified in the standard), but which would not be submitted to Health Canada under the Labelling Standard stream.

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

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

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Health Canada Santé Canada

GUIDANCE DOCUMENT

Acetaminophen Labelling Standard

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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 pour l'acétaminophène*

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 (a Drug Identification Number (DIN)) for oral analgesics containing acetaminophen as a single ingredient and in combination with caffeine and/or with codeine, when formulated within the specified combinations and limits for nonprescription self-care use. Paediatric preparations containing codeine are not acceptable under this labelling standard.

2 MEDICINAL INGREDIENTS

Table 1: Drug Medicinal Ingredients and Dosage

Medicinal ingredient preferred name	Dosage Units (adult ≥12years)[a]	Dosage Units (children <12 years)[b]	Specific Regulatory Requirement
Acetaminophen	325 mg	80mg/mL or 160 mg/5mL	• C.09.020(1), (2) of the *Food and Drug Regulations (FDR)*; • A liquid dosage form is to be either of the children's standard dosage units per mL for drops, or per teaspoon (5 mL) for other liquid formulations. C.09.022 (4), (5); • An accurate measuring device shall be provided and must be capable of accurately delivering 0.5 millilitres of the children's drops. C.09.022 (6)
	500 mg		The label must state this is not a standard dosage unit.[c]
	650 mg		The label must state this is not a standard dosage unit.[c]
Caffeine	15 or 65 mg[d]	Not applicable	Acetaminophen and caffeine are acceptable in combination products. C.09.021(1) of the *Food and Drug Regulations (FDR)*

[a] Note that for a liquid dosage form, a standard adult dosage unit is 325 milligram per teaspoon (5 millitre). C.09.022(7).

[b] C.09.024 of the *Food and Drug Regulations.*

[c] C.09.022(1),(2) of the *Food and Drug Regulations.*

[d] Codeine may be combined with Caffeine (15 milligram) and a dosage unit of acetaminophen. Caffeine at 65 milligram can be combined with a dosage unit of acetaminophen. Any other combination will be reviewed outside the Labelling Standard.

Codeine[e]	8 mg (solid) 20 mg/30 mL (liquid)[e]	0 mg	May be combined with adult dosage of acetaminophen + 15 mg caffeine per dosage unit[f]

3 PHARMACEUTICAL FORMS

The acceptable dosage forms are as follows: tablets, caplets, capsules, effervescent tablets, liquid, syrup, elixir, drops, granules or powder. **(Does not apply to modified release, bi-layer formulations or products that require evaluation of animal-sourced ingredients.)**

4 INDICATIONS

To help prevent dosing errors, acetaminophen-containing products may not be concurrently labeled for:

- both adults (≥12 years) and children (<12 years); **OR**
- infants (<2 years) and children (≥2 years).

4.1 Acceptable Indications

Antipyretic:

- fever;
- fever due to colds and flu;
- fever due to immunization.

Analgesic to Relieve:

- mild to moderate aches and pains (for example [e.g.] minor muscle pain, minor backache) (Prescott LF, 1996), (Gaziano MJ and Gibson MC, 2006);
- headache, tension headache (Migliardi et al, 1994);
- pain of mild to moderate migraine;
- mild to moderate pain due to arthritis, or rheumatism (Temple et al, 2006), (Bradley et al, 1991);
- pain of menstrual cramps (Ali et al, 2007);
- mild to moderate pain following dental work or intervention, toothache (McQuay HJ and Moore RA, 2002);
- teething pain (paediatric-only products);
- pain due to minor muscle sprains and strains (AHFS® 2009);
- pain (aches) due to cold and flu;
- pain due to immunization.

[e] Pediatric preparations containing codeine are not acceptable under this labelling standard.
[f] Section 36(1) of the *Narcotic Control Regulations*

4.2 Unacceptable Indications

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

- severe pain;
- treatment of arthritis, rheumatism;
- rheumatic fever;
- migraine and associated symptoms (nausea, sensitivity to light and/or sound, etc.);
- neuralgia;
- pain relief adjuvant/ enhancer;
- mental alertness/prevents drowsiness/stimulant;
- enhancement of motor/cognitive performance;
- sleep aid;
- sedation.

5 DOSAGE DIRECTIONS

5.1 Dosage for Adults and Children 12 years and older

Table 2: Dosages for Adults and Children 12 years and older[g]

Dosage Unit[g]	Single Dose	Dose Interval[h]	Maximum[i] Daily Dose	Maximum Daily Dosage Units
325 mg	1 or 2 x 325 mg	every 4 -6 hours	4000 mg	12
500 mg[j]	1 or 2 x 500 mg	every 4 - 6 hours	4000 mg	8
650 mg	1 x 650 mg	every 4 - 6 hours	4000 mg	6

Adult dosage directions must state:

a) For all doses:

- Take 1 [*caplet/tablet/etc.*] every 4-6 hours.

[g] C.01.024, C.01.025, C.09.022(1),(2) of the *Food and Drug Regulations*. All other recommended doses or dosage units fall outside the scope of this Labelling Standard.

[h] AHFS® 2009; Hersh et al, 2000; Moore et al, 2008; Repchinsky et al., 2002.

[i] C.01.021 of the *Food and Drug Regulations.*

[j] **Acetaminophen and caffeine:**

- *Single dose (1 or 2 dosage units)***:** 65 milligrams caffeine in combination with 500 milligrams acetaminophen every 4 - 6 hours (Hersh et al, 2000; Ali et al, 2007; Sawynok J and Yaksh TL, 1993; Zhang Wei-Ya, 2001).
- *Maximum daily dose***:** 520 milligrams caffeine/day.

b) For doses where more than 1 dosage unit is recommended (e.g. 325 and 500mg strengths):

- If pain or fever does not respond to 1 [*caplet/tablet/etc.*], take 2 [*caplets/tablets/etc*] at next dose.

5.2 Dosages for Children under 12 years

The age-related dosing is provided as per the *Food and Drug Regulations* (C.01.024) for use when the weight of a child is unknown. The weight-related dosing is also provided.

Table 3: Dosages for Children Under 12 years of Age[k,l,m]

Age (Years)	Single Dose				Maximum Daily Dose		
	mg	X 80 mg	X 160 mg	X 325 mg	mg	X 80 mg	X 160 mg
11 to under12	480	6	3	1 ½	2400	30	15
9-10	400	5	2 ½	1 ¼	2000	25	12 ½
6-8	320	4	2	1	1600	20	10
4-5	240	3	1 ½		1200	15	7½
2-3	160	2	1		800	10	5
Age (Months)							
12-23	120	1 ½			600	7 ½	
4-11	80	1			400	5	
0-3	40	½			200	2½	

Table 4: Dosages for Children based on Weight[n]

Body Weight		Single Dose (mg)	Maximum Daily Dose (mg)
Pounds (lbs)	Kilograms (kg)		
72 – 95	32.0 – 43.9	480	2400
60 – 71	27.0- 31.9	400	2000
48 – 59	22.0- 26.9	320	1600
36 – 47	16.0- 21.9	240	1200
24 – 35	11.0- 15.9	160	800
18 – 23	8.0 - 10.9	120	600
12 – 17	5.5 - 7.9	80	400
6 – 11	2.0 – 5.4	40	200

[k] C.01.024 of the *Food and Drug Regulations.*

[l] **Dosing interval:** Every 4-6 hours. (AHFS, 2009; Repchinsky et al., 2002)

[m] Solid dosage forms for which 1/2 or 1/4 doses are recommended must be adequately scored to ensure proper dosage.

[n] Temple, 1983.

6 WARNINGS

6.1 For outer and inner labels of all acetaminophen products

- **KEEP OUT OF THE REACH OF CHILDREN.** C.01.029(1)[o,p]
- This package contains enough drug to seriously harm a child (if greater than 3.2 grams of acetaminophen in the package). C.01.029(2)(c)[o, p]
- **DO NOT USE** with other drugs containing **acetaminophen**.

- **[For adult use products only]:**

    - **ADULT USE ONLY. DO NOT** take more than the recommended dose unless advised by your doctor. Use the smallest effective dose. Taking more than the maximum daily dose may cause **severe or possibly fatal liver damage.** C.09.011(b), C.01.024(3)(b), (Fontana et al, 2001; Kaplowitz N, 2004; Lee WM, 2007; Larson et al, 2005).

- **[For children and infants' (<12 years) products only]:**

    - **DO NOT** take more than the recommended dose unless advised by your doctor. Taking more than the maximum daily dose may cause **severe or possibly fatal liver damage.** C.09.011(b), C.01.024(3)(b), (Fontana et al, 2001; Kaplowitz N, 2004; Lee WM, 2007; Larson et al, 2005).

All of the following warnings may appear on an insert or inner 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 inner panels:

- Do not take if allergic to acetaminophen.
- **Consult a doctor if:**
    - you develop allergic reactions such as wheezing, rash or itching;
    - your symptoms last for more than five days, or fever lasts more than 3 days. (Berardi RR et al, Handbook of Nonprescription Drugs 15th, 2006), C.09.011(a).
- **In Case of Overdose:** call a Poison Control Centre or doctor immediately, even if you do not notice any signs or symptoms. Within the first 24 hours you may experience increased sweating, nausea, vomiting, stomach pain, and loss of appetite.

[o] Must be preceded by a prominently displayed symbol that is octagonal in shape, conspicuous in colour and on a background of a contrasting colour. C.01.029(3)

[p] Above highlighted items do not apply if the product is in an effervescent, suppository or powder form; or packaged in a non-reclosable package containing not more than two adult standard dosage units per package. C.01.031.2(c),(d),(f)

- Ask a doctor or a pharmacist before use if you:
  - **[For adult use products only]:**
    - are pregnant or breastfeeding (Koniman et al, 2007; Federal Register: 21 CFR, Part 201.63, 1999);
    - have chronic alcoholism (Draganov et al, 2000; Zimmerman HJ and Maddrey WC, 1995)
  - have a serious liver or kidney disease (Bennett et al, 1994; Curhan et al, 2004; Medicines and Healthcare products Regulatory Agency, Paracetamol; Federal Register: 21 CFR parts 201 and 343, 2006; USP-DI 2007);
  - use any other medications including natural health products, prescription drugs, salicylates or other pain and fever relief medications (nonsteroidal anti-inflammatory drugs (NSAIDS)) (Hersh, Pinto and Moore, 2007);

6.2 Additional Warnings For combinations with 65 mg caffeine

- Avoid other caffeine containing products. Too much caffeine may cause rapid heart rate, nervousness or sleeplessness (Deiner et al, 2005; Renner et al, 2007).
- Ask a doctor or pharmacist before use if you have high blood pressure, glaucoma, or overactive bladder syndrome.

6.3 Additional Warnings For combinations with codeine

- **Do not take if you**:
  - are allergic to codeine or other opioids;
  - have suffered head injury;
  - are at risk of blocked intestines;
  - suffer from seizures;
- The following warning must appear conspicuously on the inner and outer main panel of the label:
  "This preparation contains codeine and should not be administered to children except on the advice of a doctor or a dentist." (Section 36(1) of the *Narcotic Control Regulations*).
- Codeine may cause harm to a breast fed baby.
- **Contact your doctor immediately** if you are breastfeeding and your baby is having difficulty breathing or feeding, or is very sleepy or limp (*Use of Codeine Products by Nursing Mothers. Health Canada Advisory* October 8, 2008; *Information for Healthcare Professionals: Use of Codeine Products in Nursing Mothers.* United States Food and Drug Administration (FDA) Alert August 17, 2007; Gashe et al, 2004; Koren et al, 2006).
- Consult your doctor if you feel sedated or drowsy, confused, have shallow breathing or have severe constipation (Meyer D and Tobias JS, 2005; AHFS® 2009).
- Consult your doctor before use if you have difficulty breathing, have asthma or other chronic lung disease.
- Consult your doctor before use if you are taking tranquilizers, sedatives, sedating antihistamines or other depressants, or 3 or more alcoholic beverages per day.

7 OTHER REQUIREMENTS

7.1 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)

    - Multiple ingredient products for which there is no compendial standard must state the following on the front panels of all labels:
        - Contains acetaminophen and other ingredients

    - 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)

- At least one of the package sizes available for sale must be provided in a child resistant package and the outer label of all containers that are not child resistant shall carry a statement that the drug is also available in a child resistant package. C.01.031(a)(ii),(b)[p]

- For adult use only products containing more than two or three times the standard adult dosage unit or for products that recommend dosages in excess of 650 mg per single dose, and/or 4 grams per day, the label must state that the product is to be used only on the advice of a doctor. (C.01.025)

- **For children's use only products**:
    - the drug is to be packaged in a child resistant container C.01.031(a)(i);

    - the package size is limited to no more than 1.92 grams in the 80 mg dosage units or 3.2 grams in the 160 mg dosage units. C.01.037(c)(d);

    - the word "Children" or "Infants" must be bolded on the front panel of all labels to help prevent dosing errors.

- **Legibility of labels:**

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

7.2 For products containing codeine

- The active ingredients of products containing codeine must appear conspicuously on the inner and outer main panel of the label (Section 36(1) of the *Narcotic Control Regulations*).
- The inner and outer labels shall show on the upper left quarter of the main panel of the label, the symbol "N" in a colour contrasting with the rest of the label or in type not less than half the size of any other letters used thereon.

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 Divisions 1, 2 and 9 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.

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 should be restricted to those substances, necessary for the formulation of the dosage form. Their concentration should not exceed the minimum required to provide their intended effect. The benefits of their use should exceed any risk associated with these ingredients, their presence should not affect the therapeutic efficacy or safety of the medicinal ingredients and they should 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 should comply with the Health Canada's Policy, *Herbs Used as Non-Medicinal Ingredients in Nonprescription Drugs for Human Use* (1995).

10 SPECIAL NOTES

Codeine, although meeting the definition of a Natural Health Product under Schedule 1 of the *Natural Health Products Regulations (NHPR),* is excluded (under Schedule 2 of the *NHPR*) since it is subject to the *Controlled Drugs and Substances Act*.

Products making different dosing recommendations or using different dosage units of acetaminophen other than those listed in Tables 1-4 will require an application to be filed outside the labelling standard. Sufficient supporting data demonstrating the safe and effective use of such a product will need to be submitted for assessment.

Submissions for combinations of various strengths of acetaminophen, codeine and/or caffeine may require additional supporting data to demonstrate that the combination has a therapeutic advantage over existing products and that the enhanced benefit justifies the potential increased risk that may be associated with the new combination (Zhang WY and Po AL, 1996; Mitchell et al, 2008; Martell BA, 2007). As such, combinations other than those listed under section 2 will require an application to be filed outside the labelling standard.

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