Health Canada Santé Canada

Guidance Document

Acetylsalicylic Acid Labelling Standard

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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*

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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 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.

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1 Introduction

This Labelling Standard describes the requirements necessary to receive marketing authorization (a Drug Identification Number (DIN)) for oral analgesics containing acetylsalicylic acid (ASA) as a single medicinal ingredient or in combination with: caffeine; caffeine and codeine; buffering agents or antacids when formulated within the specified combinations and limits for nonprescription self-care use. This Labelling Standard does not apply to products used by children under 12 years of age, or for products used for cardioprotection and stroke prevention.

2 Medicinal ingredients

Table 1: Drug medicinal ingredients and dosage

Medicinal ingredient (preferred name)	Dosage units[a]	Specific regulatory requirement
Acetylsalicylic acid	325 mg	C.09.030.(1), (2); C.09.035 of the *Food and Drug Regulations (FDR)*
	500 mg	C.09.032 (2)(a) The label must state this is not a standard dosage unit product if the product is in a solid dosage form.
	650 mg	C.09.032 (3)(a) The label must state that each individual dosage form contains two adult standard dosage units.
Caffeine	15 to 65 mg	Acetylsalicylic acid and caffeine are acceptable in combination products. C.09.031(1)(b) and (d)
Codeine	8 mg (solid) 20 mg/30 mL (liquid)[b]	May be combined with an adult dosage of 15-65 mg caffeine per dosage unit[c]

Acceptable combinations

Acetylsalicylic acid in combination with:

[a] An acetylsalicylic acid product in the form of a liquid shall contain one adult standard dosage unit per teaspoon (5 millilitres).C.09.033 (1). For liquid formulations, the single dose must be contained and labelled in standard units (for example, millilitres) and a measuring device shall be provided that accurately delivers this dose.

[b] Section 36(1)(a)(i) of the *Narcotic Control Regulations subject to the Controlled Drugs and Substances Act.*

[c] Codeine may be combined with caffeine (15-65 milligram) and a dosage unit of acetylsalicylic acid. Caffeine in the range of 15 milligram to 65 milligram can be combined with a dosage unit of acetylsalicylic acid.

- Caffeine [15-65 milligram (mg)] (C.09.031(1)(b) and (d));
- Codeine [8 mg; 20 mg/30 millilitre (ml)] and Caffeine (15-65 mg);
- one or more buffering agents;
- Caffeine and one or more buffering agents.

Buffered acetylsalicylic acid products

The term "buffered" is acceptable for acetylsalicylic acid products that provide at least 1.9 milliequivalents (mEq) of acid neutralizing capacity per adult standard dosage unit (325 mg of ASA) or equivalent. (C.09.034)

Unacceptable combinations:

- combination of two different salicylates (C.09.010(a));
- combination of acetaminophen with a salicylate (C.09.010(b));
- combination of salicylates with herbal ingredients (I.L. 659).

3 Pharmaceutical forms

3.1 Acceptable

The following dosage forms for acetylsalicylic acid products are acceptable:

Tablets or chewable tablets, caplets, powder-filled capsules, effervescent tablets, suspensions, solutions, syrups or liquids.

3.2 Unacceptable

The following dosage forms for acetylsalicylic acid products require a review outside of the Labelling Standard:

- 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).

- Liquid filled capsules, powder and granules.

- Novel dosage forms.

Note that this list is not exhaustive. Dosage forms other than the traditional dosage forms (listed above under Acceptable dosage forms) may require supporting data and will be reviewed outside the Labelling Standard.

4 Indications

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

- both adults and children (≥ 12 years), and for adults ≥ 18 years

4.1 Acceptable indications for adults and children 12 years and older (American Hospital Formulary Service (AHFS) 2011; Schrör 2009)

Antipyretic:

- fever.

- **Analgesic to relieve:**

- mild to moderate aches and pains [for example (e.g.), minor muscle pain, minor backache];
- headache, tension headache;
- mild to moderate pain due to arthritis or rheumatism;
- pain of mild or moderate migraine;
- pain of menstrual cramps;
- mild to moderate pain following dental work or intervention, toothache;
- mild to moderate pain due to muscle sprains and strains.

4.2 Acceptable indications for adults 18 years and older recommendation by the scientific advisory committee on nonprescription drugs on May 30, 2013

- Relieve fever and pain due to cold and flu[d]

4.3 Unacceptable indications

The following indications for acetylsalicylic acid products are excluded and require a review outside of the Labelling Standard. These include but are not limited to:

- any mention of antiplatelet action or prevention of heart attacks or blood clots;
- severe pain;
- inflammation, to relieve inflammation;
- treatment of arthritis, rheumatism;
- rheumatic fever;
- relief/treatment of migraine and associated symptoms (nausea, sensitivity to light and/or sound, etc.);
- neuralgia;
- pain relief adjuvant/enhancer;
- mental alertness/prevents drowsiness/stimulant;
- sleep aid;

5 Dosage directions

For all products (except effervescent), take with a glass [250 millilitre (mL)] of water, or milk. (AHFS 2011).

For effervescent products: dissolve in one glass (250 mL) of water.

[d] Included because of concern surrounding the association between acetylsalicylic acid (ASA) use in children and teenagers and brain/liver damage (Reye's Syndrome), Canadian Paediatric Society [www.caringforkids.ca]

5.1 Dosage for adults and children 12 years and older

Table 2: Dosages for adults and children 12 years and older

Standard dosage unit[e]	Single dose	Dose interval[f]	Maximum[g] daily dose	Maximum daily dosage units
325 mg	1 or 2 x 325 mg	every 4-6 hours	4000 mg	12
500 mg[h]	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

6 Warnings and precautions

6.1 For outer and inner labels of all acetylsalicylic acid containing products

- **Keep out of the reach of children.** C.01.029(1)(a)[i,j]

- **Do not** take more than the recommended dose unless advised by your doctor. Use the smallest effective dose. C.09.011(b)

- **Do not take if you** are in your last trimester of pregnancy.

- **Do not give** to children and teenagers less than 18 years of age who have chicken pox, cold or flu symptoms before a physician or pharmacist is consulted about Reye's Syndrome, a rare serious illness reported to be associated with acetylsalicylic acid C.01.028 (1)(e) (Recommendation by the Scientific Advisory Committee on Nonprescription Drugs on May 30, 2013).

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:

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[e] C.01.024, C.09.022 (1),(2) of the *Food and Drug Regulations*.

[f] AHFS 2011; Repchinsky 2010. Health Canada Product Monograph, Aspirin, Oct 5, 2007.

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

[h] **Acetylsalicylic acid and caffeine:**
- *Single dose (1 or 2 dosage units)***:** 65 milligram caffeine in combination with 500 milligram acetylsalicylic acid every 4-6 hours (Hersh et al, 2000; Sawynok & Yaksh 1993; Zhang 2001).
- *Maximum daily dose***:** 520 mg caffeine/day.

[i] 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)

[j] Note that Section C.01.029(1)(a) does not apply if the product is in an effervescent or suppository 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)

- **Do not take if you:**
  - are allergic to salicylates or any of the non-medicinal ingredients in the formulation;
  - are allergic to any other non-steroidal anti-inflammatory drugs (NSAIDs) or other pain relievers/fever reducers;
  - have an ulcer or a history of ulcers;
  - are prone to bleeding;
  - have active or severe liver or kidney disease;
  - have a history of asthma induced by salicylates or other NSAIDs;
  - are using methotrexate at doses of 15 mg/week or more;

- **Do not use** with other drugs containing acetylsalicylic acid or other salicylates, or other NSAIDs (e.g. ibuprofen, naproxen) (Gaziano & Gibson 2006).

- **Stomach bleeding warning:** This product contains a nonsteroidal anti-inflammatory drug (NSAID) which **may cause severe stomach bleeding**. (Federal Register/ Vol. 74, No. 81/ April 29, 2009),

- **Consult a doctor or pharmacist before use if you:**

  - have a history of stomach problems such as heartburn;
  - have asthma, high blood pressure, heart disease, liver or kidney disease, gout, severe anemia or any other serious condition;
  - are taking acetaminophen, anticonvulsants, blood thinners (anticoagulants), diuretics, medication for arthritis, diabetes or gout, methotrexate, steroids, or any other medication;
  - have 3 or more alcoholic drinks per day;
  - are trying to conceive, pregnant or nursing (Briggs et al 2011);
  - are having surgery in 5 to 7 days;
  - are 60 years or older [Kuehn 2009, United States Food and Drug Administration (FDA) Questions and Answers on Final Rule for Labelling Changes to Over-the-Counter Pain Relievers].

- **Consult a doctor or pharmacist if :**

  - your pain lasts more than 5 days, or fever lasts more than 3 days (C.09.011(a)), (Berardi RR et al, 2006);
  - new symptoms occur or if redness or swelling is present.

Serious side effects and what to do about them

- **Stop use and consult a doctor** if any of the following occur:

- an allergic reaction which may include itching, skin rashes or hives, wheezing or trouble breathing, swelling in the face ;
- You experience any of the following signs of stomach bleeding:
  - feel faint, vomit blood, have bloody or black stools;
  - have stomach pain that does not get better;
- any loss of hearing or ringing or buzzing in the ears;

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

6.2 Additional warnings for combination products with 65 milligram caffeine

- **Do not take if you**:
  - **Are allergic to caffeine**

- Avoid other caffeine-containing products. Too much caffeine may cause rapid heart rate, nervousness or sleeplessness. (Deiner et al, 2005)

- Consult a doctor or pharmacist before use if you have glaucoma or overactive bladder syndrome.

6.3 Additional warnings for combination products with codeine

- **Do not take if you**:

  - are allergic to codeine or other opioids (warning will also include other active ingredients);
  - are in your last trimester of pregnancy or nursing. Codeine may cause serious harm to a breastfed baby (FDA Alert, August 17, 2007; Gashe et al, 2004; Health Canada Advisory October 8, 2008; Madadi et al 2009);
  - have difficulty breathing, have asthma or other chronic lung disease;
  - have suffered head injury;
  - are at risk of blocked intestines;
  - suffer from seizures.

- The following warning must be legibly and conspicuously printed 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 physician or dentist" (Section 36(1)(b) of the *Narcotic Control Regulations*).

- Consult your doctor if you feel sedated or drowsy, confused, have shallow breathing or have severe constipation (AHFS 2011).

- Consult your doctor before use if you are taking other medications that can make you sleepy or less alert, for example: narcotic analgesics or sedating antihistamines, or you are currently taking anti-depressants, other prescription drugs or natural health products or 3 or more alcoholic beverages per day, or if you have recently had surgery under general anaesthesia.

7 Other labelling 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 acetylsalicylic acid 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)

    - As of May 13, 2012, non-prescription products must provide a qualitative listing of "non-medicinal" ingredients on the outer label.

- 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)[k]

- The inner and outer labels of a drug that contains more than 2 g of acetylsalicylic acid or the equivalent quantity of its salts or derivatives shall carry a statement to the effect that there is enough drug in the package to seriously harm a child C.01.029(2)(b)

- 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 inner and outer labels must carry a caution that the product is to be used only on the advice of a physician. (C.01.025).

Legibility

[k] 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)

Although no specific type size is mentioned in the *Regulations*, Section A.01.016 [http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/]specifies that all information required to appear on a label must be:

- Clearly and prominently displayed on the label; 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 Therapeutic Products Directorate's *Guidance to Industry: Product Monograph[*http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/monograph/pm_mp-eng.php]. 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 ingredients (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[*http://laws-lois.justice.gc.ca/eng/acts/F-27/page-15.html#h-22], 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 Therapeutic Products Directorate 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*.

Submissions for combinations of various strengths of acetylsalicylic acid, codeine and 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 (MacDonald and Macleod 2010, Martell 2007). As such, combinations other than those listed under section 2 of this Labelling Standard will be required to file an application outside the current Labelling Standard.

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