

carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate. “Alcohol Warning” [heading in boldface type]: “If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take [insert one nonsteroidal anti-inflammatory analgesic/antipyretic active ingredient] or other pain relievers/fever reducers. [Insert one nonsteroidal anti-inflammatory analgesic/antipyretic active ingredient] may cause stomach bleeding.”

(3) *Combinations of acetaminophen with nonsteroidal anti-inflammatory analgesic/antipyretic active ingredients—including but not limited to aspirin, carbaspirin calcium, choline salicylate, ibuprofen, ketoprofen, magnesium salicylate, naproxen sodium, and sodium salicylate.* “Alcohol Warning” [heading in boldface type]: “If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take [insert acetaminophen and one nonsteroidal anti-inflammatory analgesic/antipyretic active ingredient—including, but not limited to aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate] or other pain relievers/fever reducers. [Acetaminophen and (insert one nonsteroidal anti-inflammatory analgesic/antipyretic ingredient—including, but not limited to aspirin, carbaspirin calcium, choline salicylate, magnesium salicylate, or sodium salicylate)] may cause liver damage and stomach bleeding.”

(b) *Requirements to supplement approved application.* Holders of approved applications for OTC drug products that contain internal analgesic/antipyretic active ingredients that are subject to the requirements of paragraph (a) of this section must submit supplements under § 314.70(c) of this chapter to include the required warning in the product's labeling. Such labeling may be put into use without advance approval of FDA provided it includes the exact information included in paragraph (a) of this section.

(c) Any drug product subject to this section that is not labeled as required and that is initially introduced or initially delivered for introduction into interstate commerce after April 23,

1999, is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352) and is subject to regulatory action.

[63 FR 56801, Oct. 23, 1998]

§ 201.323 Aluminum in large and small volume parenterals used in total parenteral nutrition.

(a) The aluminum content of large volume parenteral (LVP) drug products used in total parenteral nutrition (TPN) therapy must not exceed 25 micrograms per liter (µg/L).

(b) The package insert of LVP's used in TPN therapy must state that the drug product contains no more than 25 µg/L of aluminum. This information must be contained in the “Precautions” section of the labeling of all large volume parenterals used in TPN therapy.

(c) The maximum level of aluminum present at expiry must be stated on the immediate container label of all small volume parenteral (SVP) drug products and pharmacy bulk packages (PBP's) used in the preparation of TPN solutions. The aluminum content must be stated as follows: “Contains no more than __ µg/L of aluminum.” The immediate container label of all SVP's and PBP's that are lyophilized powders used in the preparation of TPN solutions must contain the following statement: “When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than __ µg/L.” This maximum level of aluminum must be stated as the highest of:

(1) The highest level for the batches produced during the last 3 years;

(2) The highest level for the latest five batches, or

(3) The maximum historical level, but only until completion of production of the first five batches after January 26, 2001.

(d) The package insert for all LVP's, all SVP's, and PBP's used in TPN must contain a warning statement. This warning must be contained in the “Warnings” section of the labeling. The warning must state:

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral

administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

(e) Applicants and manufacturers must use validated assay methods to determine the aluminum content in parenteral drug products. The assay methods must comply with current good manufacturing practice requirements. Applicants must submit to the Food and Drug Administration validation of the method used and release data for several batches. Manufacturers of parenteral drug products not subject to an approved application must make assay methodology available to FDA during inspections. Holders of pending applications must submit an amendment under §314.60 or §314.96 of this chapter.

[65 FR 4110, Jan. 26, 2000]

EFFECTIVE DATE NOTE: At 65 FR 4110, Jan. 26, 2000, §201.323 was added, effective Jan. 26, 2001. At 66 FR 7864, Jan. 26, 2001, the effective date was delayed until Jan. 26, 2003.

APPENDIX A TO PART 201—EXAMPLES OF GRAPHIC ENHANCEMENTS USED BY FDA

I. SECTION 201.66 STANDARD LABELING FORMAT

A. Overall

1. The “Drug Facts” labeling is set off in a box or similar enclosure by the use of a barline with all black type printed on a white, color contrasting background.

B. Typeface and size

1. “Drug Facts” is set in 14 point Helvetica Bold Italic, left justified.

2. “Drug Facts (continued)” is set in 8 point Helvetica Bold Italic for the words “Drug Facts” and 8 point Helvetica Regular for the word “(continued)” and is left justified.

3. The headings (e.g., “Directions”) are set in 8 point Helvetica Bold Italic, left justified.

4. The subheadings (e.g., “Ask a doctor or pharmacist before use if you are”) are set in 6 point Helvetica Bold, left justified.

5. The information is set in 6 point Helvetica Regular with 6.5 point leading, left justified.

6. The heading “Purpose” is right justified.

7. The bullet is a 5-point solid square.

8. Two em spacing separates bullets when more than one bullet is on the same line.

9. A table format is used for 3 or more dosage directions.

10. A graphic appears at the bottom of the first panel leading the reader to the next panel.

C. Barlines and hairlines

1. A 2.5-point horizontal barline extends to each end of the “Drug Facts” box (or similar enclosure), providing separation between each of the headings.

2. A 0.5-point horizontal hairline extends within 2 spaces on either side of the “Drug Facts” box (or similar enclosure), immediately following the title and immediately preceding the subheadings.

3. A 0.5-point horizontal hairline follows the title, immediately preceding the heading, when a heading appears on a subsequent panel immediately after the “Drug Facts (continued)” title.

D. Box or Enclosure

1. All information is enclosed by a 2.5-point barline.

II. SECTION 201.66 MODIFIED LABELING FORMAT

A. Overall

1. The “Drug Facts” labeling is presented in all black type printed on a white color contrasting background.

B. Typeface and size

1. “Drug Facts” is set in 9 point Helvetica Bold Italic, left justified.

2. The headings (e.g., “Directions”) are set in 8 point Helvetica Bold Italic, left justified.

3. The subheadings (e.g., “Ask a doctor or pharmacist before use if you are”) are set in 6 point Helvetica Bold, left justified.

4. The information is set in 6 point Helvetica Regular with 6.5 point leading, left justified.

5. The heading “Purpose” is right justified.

6. The bullet is a 5-point solid square.

7. Bulleted information may start on same line as headings (except for the “Warnings” heading) and subheadings, with 2 em spacing separating bullets, and need not be vertically aligned.

C. Barlines and hairlines

1. A 2.5-point horizontal barline extends to each end of the “Drug Facts” box (or similar enclosure), providing separation between each of the headings.

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2. A 0.5-point horizontal hairline extends within 2 spaces on either side of the “Drug Facts” box (or similar enclosure), immediately following the title and immediately preceding the subheadings.

D. Box or Enclosure

1. All information is set off by color contrast. No barline is used.

III. EXAMPLES OF § 201.66 STANDARD LABELING AND MODIFIED LABELING FORMATS

A. SECTION 201.66 STANDARD LABELING FORMAT

Title:
14 pt. Helvetica Bold
Italic, left justified

Body text:
6 pt. Helvetica Regular with
6.5 pts. leading, left justified

Subheadings:
6 pt. Helvetica Bold,
left justified

Bullet: 5 pt.
Solid square

Headings:
8 pt. Helvetica Bold
Italic, left justified

Right justified

2.5 point barline

2.5 point box barline

0.5 point hairline

Table format for
3 or more dosages

Graphic leading to
next panel

8 pt. Helvetica Regular

Title for
continued panel:
8 pt. Helvetica Bold Italic

Drug Facts

Active ingredient (in each tablet) **Purpose**
Chlorpheniramine maleate 2 mg.....Antihistamine

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory
allergies: ■ sneezing ■ runny nose ■ itchy, watery eyes ■ itchy throat

Warnings
Ask a doctor before use if you have
■ glaucoma ■ a breathing problem such as emphysema or chronic bronchitis
■ trouble urinating due to an enlarged prostate gland
Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives
■ you may get drowsy ■ avoid alcoholic drinks
■ alcohol, sedatives, and tranquilizers may increase drowsiness
■ be careful when driving a motor vehicle or operating machinery
■ excitability may occur, especially in children
If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison
Control Center right away.

Directions

adults and children 12 years and over	take 2 tablets every 4 to 6 hours; not more than 12 tablets in 24 hours
children 6 years to under 12 years	take 1 tablet every 4 to 6 hours; not more than 6 tablets in 24 hours
children under 6 years	ask a doctor

Other information ■ store at 20-25° C (68-77° F) ■ protect from excessive moisture

Inactive ingredients D&C yellow no. 10, lactose, magnesium stearate, microcrystalline
cellulose, pregelatinized starch

B. SECTION 201.66 MODIFIED LABELING FORMAT

Title:
9 pt. Helvetica Bold
Italic, left justified

Body text:
6 pt. Helvetica Regular with
6.5 pts. leading, left justified

Bullet: 5 pt.
Solid square

Subheadings:
6 pt. Helvetica Bold,
left justified

Headings:
8 pt. Helvetica Bold
Italic, left justified

Right justified

2.5 point barline

0.5 point hairline

Bulleted information may
start on same line as headings
(except Warnings) and subheadings
and need not be vertically aligned

Dark type on light background

Box barline omitted; color
contrast used to highlight
Drug Facts information

Drug Facts

Active ingredients (in each tablet) **Purpose**
Aluminum hydroxide gel 200 mg.....Antacid
Magnesium hydroxide 200 mg.....Antacid
Simethicone 25 mg.....Antigas

Uses
■ relieves symptoms referred to as gas
■ relieves: ■ heartburn ■ acid indigestion ■ sour stomach
■ upset stomach due to these symptoms

Warnings
Ask a doctor before use if you have kidney disease
Ask a doctor or pharmacist before use if you are taking a
prescription drug. Antacids may interact with certain
prescription drugs.
Stop use and ask a doctor if symptoms last for more
than 2 weeks
Keep out of reach of children.

Directions ■ chew 1 to 4 tablets 4 times daily
■ do not take more than 16 tablets in 24 hours or use the
maximum dosage for more than 2 weeks

Inactive ingredients D&C red no. 30, D&C yellow no. 10,
dextrose, FD&C blue no. 1, glycerin, magnesium stearate,
mannitol, saccharin sodium, sorbitol, starch, sugar, talc