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APRIL 22, 2021

Regulation of Over-the-Counter (OTC) Drugs

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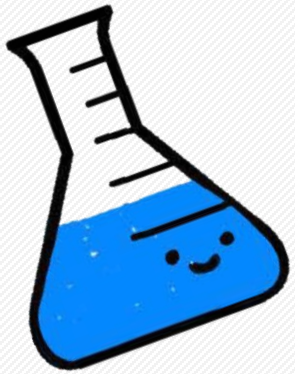
SHOOK
HARDY & BACON



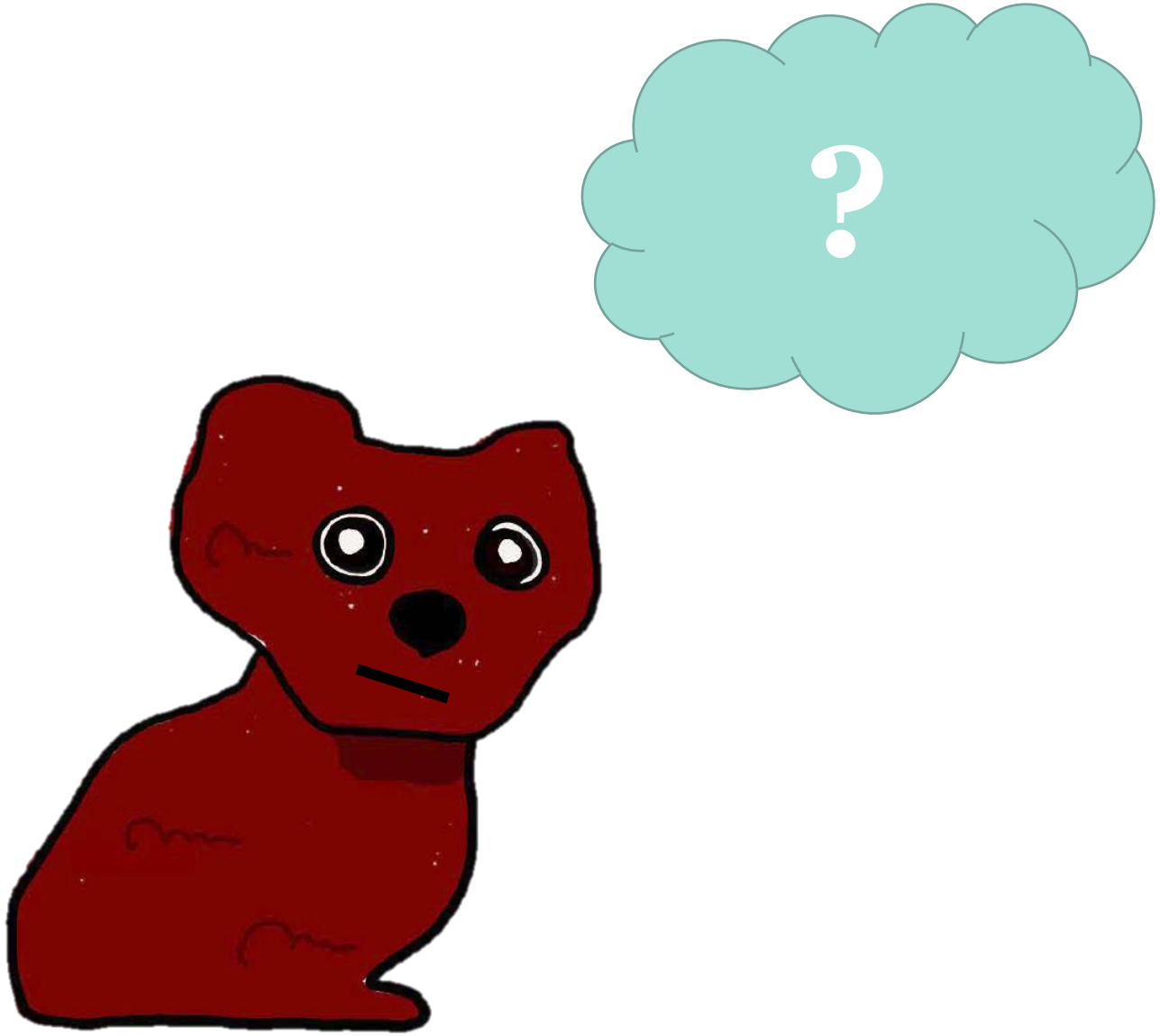
01 What's a Drug, and an OTC Drug?

02 OTC Monographs … Administrative Orders

03 OTC NDAs

04 "Behind-the-Counter" OTC Drugs

What's your favorite OTC drug flavor?



1

What's a Drug, and an OTC Drug?

A Drug is an …

- article[] intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals
- article[] (other than food) intended to affect the structure or any function of the body of man or other animals

FDCA, Section 201(g)(1)

A Cosmetic is an …

article[] intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance

FDCA, Section 201(i)(1)

A Food is an …

article[] used for food or drink for man or other animals, chewing gum

FDCA, Section 201(f)

Why did we review these definitions?

Combinations:

Cosmetic-Drug:

- Toothpaste, anticaries
- Moisturizer sunscreens

Food-Drug:

- Mentholated cough drop
- Baking soda (sodium bicarbonate)

Fun Fact!

A “food” OTC drug (such as mentholated cough drops and baking soda) are subject to food cGMPs and the Preventive Control Rule, not drug cGMPs.

21 C.F.R. 211.1(c)

More Definitions

Prescription

- Not safe unless under a practitioner's supervision because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use
- Limited by the approval

Adequate Directions

Directions under which the layman can use a drug safely and for the purposes for which it is intended.

What is “OTC” really about …

OTC = how the drug is sold

OTC ≠ how the product gets to market

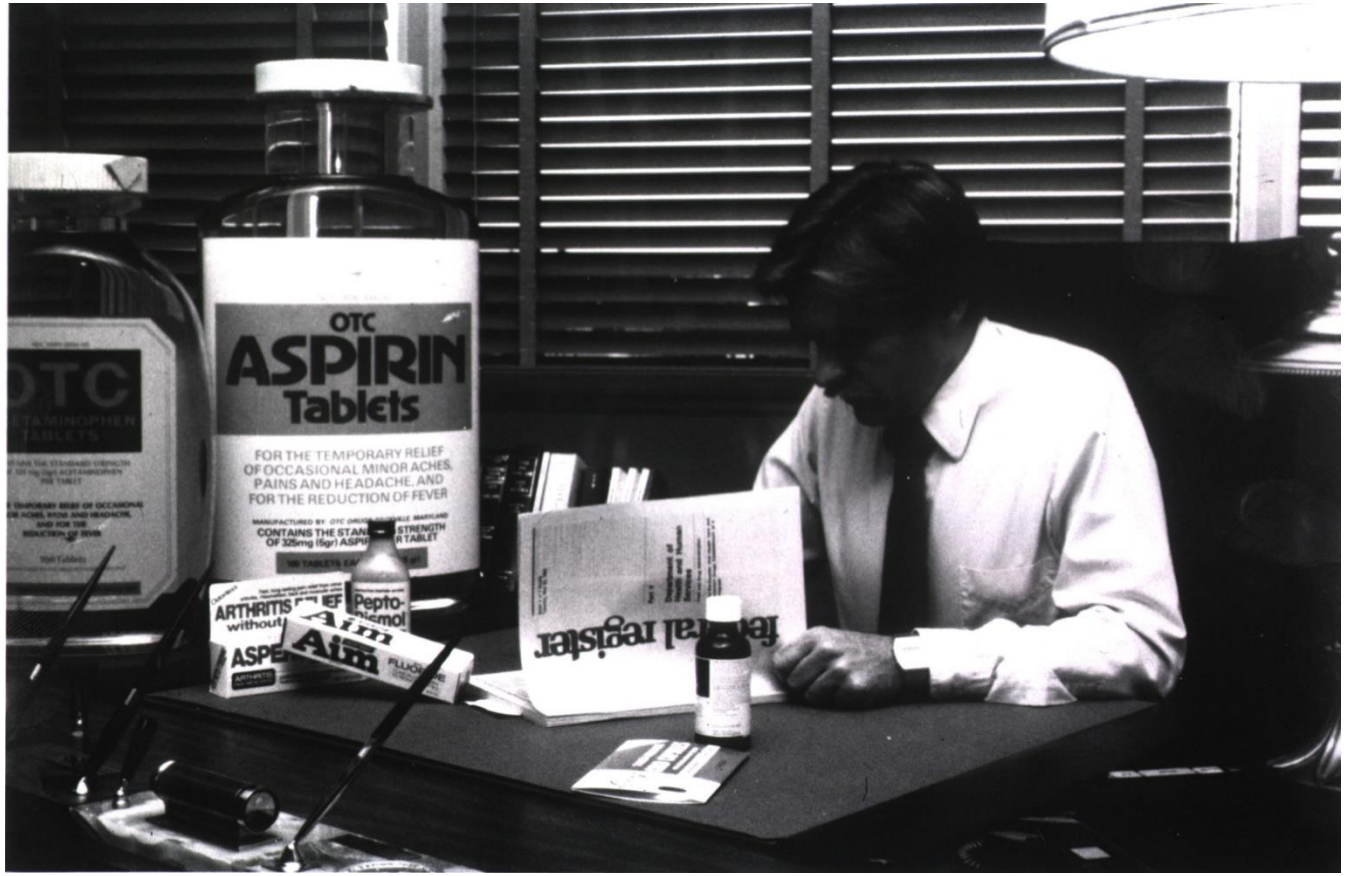
2

OTC Monographs … Administrative Orders

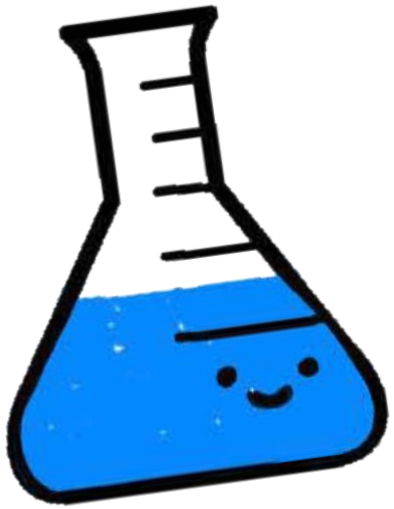
Requirements Solved by OTC Monographs

When is *premarket approval not required*, because the drug is **G**enerally **R**ecognized as **S**afe and **E**ffective (GRASE or GRAS/E) under the conditions on the label

What are *adequate directions for use*



OTC Monograph Equation



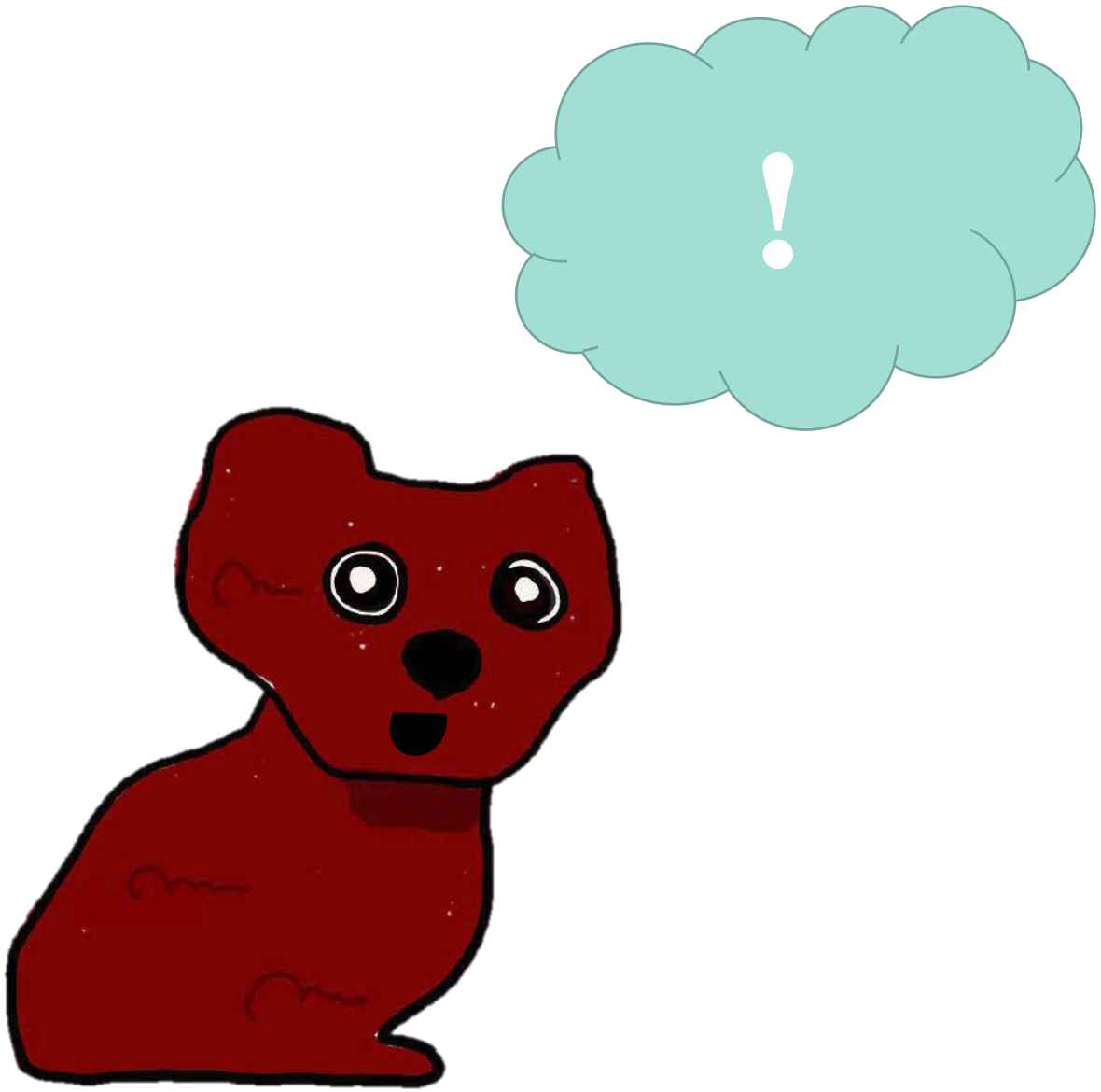
Condition(s) for Use

Active Ingredient(s)

\+ [Testing?]

OTC Monograph Drug

I’m going to market an antacid!



Step 1: Find the Monograph

Monographs are arranged by drug categories

Food and Drug Administration, HHS §331.10

(2) Number and percent of filing determinations issued within 90 days of submission of a safety and effectiveness data submission;
(3) If applicable, number and percent of feedback letters issued within 730 days from the date of filing;
(4) Number and percent of notices for proposed rulemaking issued within 1,095 days from the date of filing;
(5) Number and percent of final rules issued within 912 days of closing of the docket of the proposed rulemaking; and
(6) Total number of TEAs submitted under §330.14.
(c) *Timelines for FDA review and action.* FDA will review and take an action within the following timelines:
(1) Within 180 days of submission of a TEA under §330.14(c), FDA will issue a notice of eligibility or post to the docket a letter of ineligibility, in accordance with §330.14(d) and (e).
(2) Within 90 days of submission of a safety and effectiveness data submission, in accordance with §330.14(j), FDA will issue a filing determination. The date of filing begins the FDA timelines in paragraphs (c)(3) and (4) of this section.
(3) Within 730 days from the date of filing, if the condition is initially determined not to be GRASE for OTC use in the United States, FDA will inform the sponsor and other interested persons who have submitted data of its determination by feedback letter in accordance with §330.14(g)(4).
(4) Within 1,095 days from the date of filing of a safety and effectiveness data submission, FDA will issue a notice of proposed rulemaking to either:
(i) Include the condition in an appropriate OTC monograph(s), either by amending an existing monograph(s) or establishing a new monograph(s), if necessary; or
(ii) Include the condition in §310.502 of this chapter.
(5) Within 912 days of the closing of the docket of the proposed rulemaking under paragraph (c)(4) of this section, FDA will issue a final rule.

[81 FR 84477, Nov. 23, 2016]

PART 331—ANTACID PRODUCTS FOR OVER-THE-COUNTER (OTC) HUMAN USE

Subpart A—General Provisions

Sec.
331.1 Scope.

Subpart B—Active Ingredients

331.10 Antacid active ingredients.
331.11 Listing of specific active ingredients.
331.15 Combination with nonantacid active ingredients.

Subpart C—Testing Procedures

331.20 Determination of percent contribution of active ingredients.
331.21 Test Modifications.

Subpart D—Labeling

331.30 Labeling of antacid products.
331.80 Professional labeling.

AUTHORITY: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

SOURCE: 39 FR 19874, June 4, 1974, unless otherwise noted.

Subpart A—General Provisions

§331.1 Scope.

An over-the-counter antacid product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in §330.1 of this chapter.

Subpart B—Active Ingredients

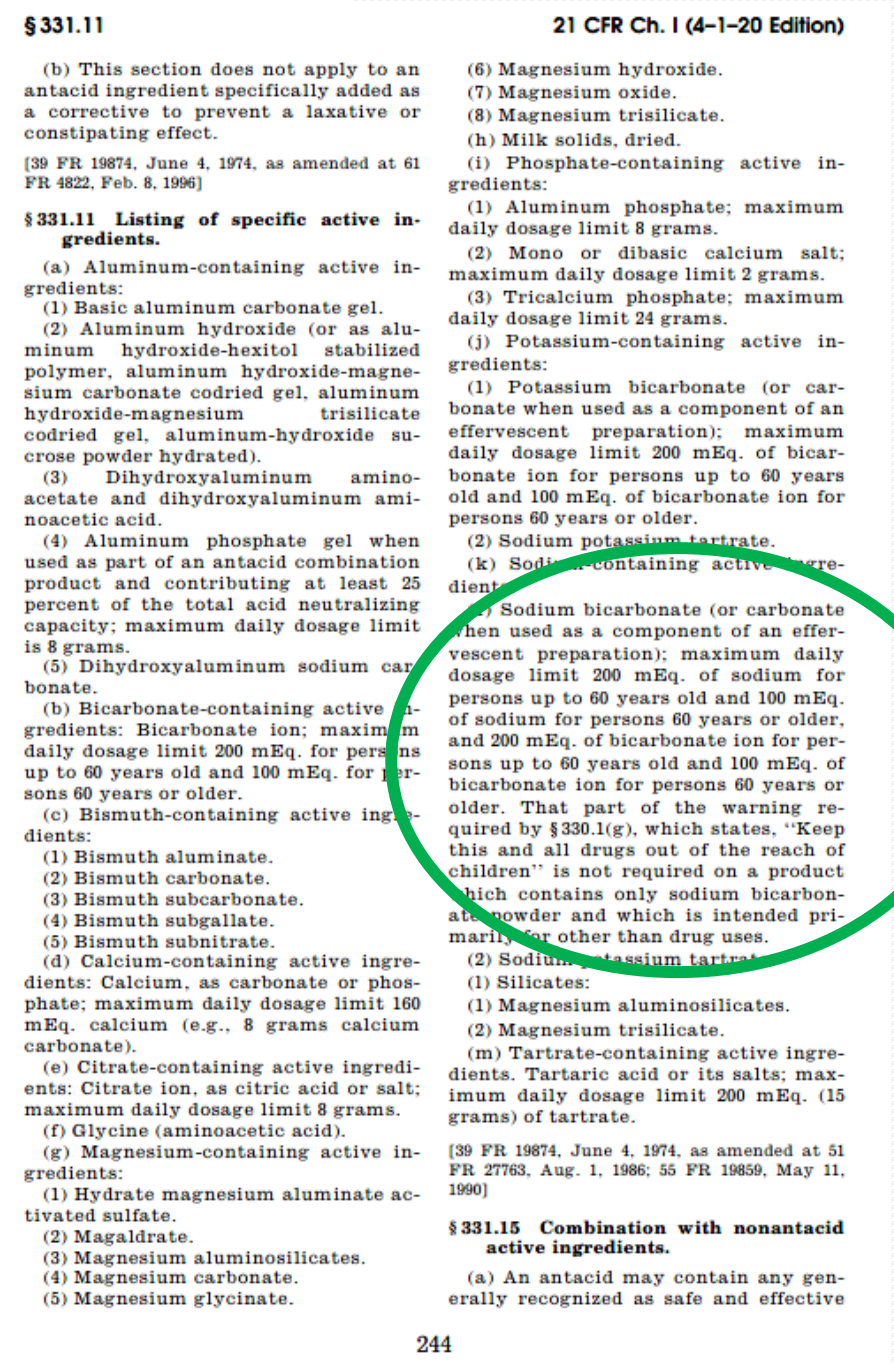
§331.10 Antacid active ingredients.

(a) The active antacid ingredients of the product consist of one or more of the ingredients permitted in §331.11 within any maximum daily dosage limit established, each ingredient is included at a level that contributes at least 25 percent of the total acid neutralizing capacity of the product, and the finished product contains at least 5 meq of acid neutralizing capacity as measured by the procedure provided in the United States Pharmacopeia 23/National Formulary 18. The method established in §331.20 shall be used to determine the percent contribution of each antacid active ingredient.

243

Step 2: Identify the Active Ingredients

Not only important to identify relevant ingredient(s), but also the concentration (usually) and other useful information



§ 331.11 21 CFR Ch. I (4–1–20 Edition)

(b) This section does not apply to an antacid ingredient specifically added as a corrective to prevent a laxative or constipating effect.

[39 FR 19874, June 4, 1974, as amended at 61 FR 4822, Feb. 8, 1996]

§ 331.11 Listing of specific active ingredients.

(a) Aluminum-containing active ingredients:
(1) Basic aluminum carbonate gel.
(2) Aluminum hydroxide (or as aluminum hydroxide-hexitol stabilized polymer, aluminum hydroxide-magnesium carbonate codried gel, aluminum hydroxide-magnesium trisilicate codried gel, aluminum-hydroxide sucrose powder hydrated).
(3) Dihydroxyaluminum aminoacetate and dihydroxyaluminum aminoacetic acid.
(4) Aluminum phosphate gel when used as part of an antacid combination product and contributing at least 25 percent of the total acid neutralizing capacity; maximum daily dosage limit is 8 grams.
(5) Dihydroxyaluminum sodium carbonate.
(b) Bicarbonate-containing active ingredients: Bicarbonate ion; maximum daily dosage limit 200 mEq. for persons up to 60 years old and 100 mEq. for persons 60 years or older.
(c) Bismuth-containing active ingredients:
(1) Bismuth aluminate.
(2) Bismuth carbonate.
(3) Bismuth subcarbonate.
(4) Bismuth subgallate.
(5) Bismuth subnitrate.
(d) Calcium-containing active ingredients: Calcium, as carbonate or phosphate; maximum daily dosage limit 160 mEq. calcium (e.g., 8 grams calcium carbonate).
(e) Citrate-containing active ingredients: Citrate ion, as citric acid or salt; maximum daily dosage limit 8 grams.
(f) Glycine (aminoacetic acid).
(g) Magnesium-containing active ingredients:
(1) Hydrate magnesium aluminate activated sulfate.
(2) Magaldrate.
(3) Magnesium aluminosilicates.
(4) Magnesium carbonate.
(5) Magnesium glycinate.
(6) Magnesium hydroxide.
(7) Magnesium oxide.
(8) Magnesium trisilicate.
(h) Milk solids, dried.
(i) Phosphate-containing active ingredients:
(1) Aluminum phosphate; maximum daily dosage limit 8 grams.
(2) Mono or dibasic calcium salt; maximum daily dosage limit 2 grams.
(3) Tricalcium phosphate; maximum daily dosage limit 24 grams.
(j) Potassium-containing active ingredients:
(1) Potassium bicarbonate (or carbonate when used as a component of an effervescent preparation); maximum daily dosage limit 200 mEq. of bicarbonate ion for persons up to 60 years old and 100 mEq. of bicarbonate ion for persons 60 years or older.
(2) Sodium potassium tartrate.
(k) Sodium-containing active ingredients:
(1) Sodium bicarbonate (or carbonate when used as a component of an effervescent preparation); maximum daily dosage limit 200 mEq. of sodium for persons up to 60 years old and 100 mEq. of sodium for persons 60 years or older, and 200 mEq. of bicarbonate ion for persons up to 60 years old and 100 mEq. of bicarbonate ion for persons 60 years or older. That part of the warning required by § 330.1(g), which states, "Keep this and all drugs out of the reach of children" is not required on a product which contains only sodium bicarbonate powder and which is intended primarily for other than drug uses.
(2) Sodium potassium tartrate.
(l) Silicates:
(1) Magnesium aluminosilicates.
(2) Magnesium trisilicate.
(m) Tartrate-containing active ingredients. Tartaric acid or its salts; maximum daily dosage limit 200 mEq. (15 grams) of tartrate.

[39 FR 19874, June 4, 1974, as amended at 51 FR 27763, Aug. 1, 1986; 55 FR 19859, May 11, 1990]

§ 331.15 Combination with nonantacid active ingredients.

(a) An antacid may contain any generally recognized as safe and effective

244

Step 3: Identify the Labeling

submitted will be subject to the disclosure rules in part 20 of this chapter.

[61 FR 4823, Feb. 8, 1996]

Subpart D—Labeling

§ 331.30 Labeling of antacid products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antacid."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: "For the relief of" (optional, any or all of the following:) "heartburn," "sour stomach," and/or "acid indigestion" (which may be followed by the optional statement:) "and upset stomach associated with" (optional, as appropriate) "this symptom" or "these symptoms." Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in §330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(c) *Warnings.* The labeling of the product contains the following warnings, under the heading "Warnings", which may be combined but not rearranged to eliminate duplicative words or phrases if the resulting warning is clear and understandable:

(1) "Do not take more than (maximum recommended daily dosage, broken down by age groups if appropriate, expressed in units such as tablets or teaspoonfuls) in a 24-hour period, or use the maximum dosage of this product for more than 2 weeks, except under the advice and supervision of a physician."

(2) For products which cause constipation in 5 percent or more of persons who take the maximum recommended dosage: "May cause constipation."

(3) For products which cause laxation in 5 percent or more of persons who

take the maximum recommended dosage: "May have laxative effect."

(4) For products containing more than 5 gm per day lactose in a maximum daily dosage: "Do not use this product except under advice and supervision of a physician if you are allergic to milk or milk products."

(d) *Drug interaction precaution.* The labeling of the product contains the following statement "Ask a doctor or pharmacist before use if you are [bullet][1] presently taking a prescription drug. Antacids may interact with certain prescription drugs."

(e) *Directions for use.* The labeling of the product contains the recommended dosage, under the heading "Directions", per time interval (e.g., every 4 hours) or time period (e.g., 4 times a day) broken down by age groups if appropriate, followed by "or as directed by a physician."

(f) *Exemption from the general accidental overdose warning.* The labeling for antacid drug products containing the active ingredients identified in §331.11(a), (b), and (d) through (m); permitted combinations of these ingredients provided for in §331.10; and any of these ingredients or combinations of these ingredients in combination with simethicone (identified in §332.10 of this chapter and provided for in §331.15(c)), are exempt from the requirement in §330.1(g) of this chapter that the labeling bear the general warning statement "In case of accidental overdose, seek professional assistance or contact a poison control center immediately." With the exception of sodium bicarbonate powder products identified in §331.11(k)(1), the labeling must continue to bear the first part of the general warning in §330.1(g) of this chapter, which states, "Keep this and all drugs out of the reach of children."

(g) [Reserved]

(h) The word "doctor" may be substituted for the word "physician" in any of the labeling statements in this section.

[39 FR 19874, June 4, 1974, as amended at 47 FR 38484, Aug. 31, 1982; 51 FR 16266, May 1, 1986; 51 FR 27763, Aug. 1, 1986; 52 FR 7830, Mar. 13, 1987; 55 FR 11581, Mar. 29, 1990; 58 FR 45208, Aug. 26, 1993; 59 FR 60556, Nov. 25, 1994; 61 FR 17806, Apr. 22, 1996; 64 FR 13295, Mar. 17, 1999; 69 FR 13734, Mar. 24, 2004]

§ 331.80 Professional labeling.

(a) The labeling of the product provided to health professionals (but not to the general public):

(1) Shall contain the neutralizing capacity of the product as calculated using the procedure set forth in United States Pharmacopeia 23/National Formulary 18 expressed in terms of the dosage recommended per minimum time interval or, if the labeling recommends more than one dosage, in terms of the minimum dosage recommended per minimum time interval.

(2) May contain an indication for the symptomatic relief of hyperacidity associated with the diagnosis of peptic ulcer, gastritis, peptic esophagitis, gastric hyperacidity, and hiatal hernia.

(3) *For products containing basic aluminum carbonate gel identified in §331.11(a)(1)—Indication.* "For the treatment, control, or management of hyperphosphatemia, or for use with a low phosphate diet to prevent formation of phosphate urinary stones, through the reduction of phosphates in the serum and urine."

(4) *For products containing aluminum identified in §331.11(a)—Warnings.* (i) Prolonged use of aluminum-containing antacids in patients with renal failure may result in or worsen dialysis osteomalacia. Elevated tissue aluminum levels contribute to the development of the dialysis encephalopathy and osteomalacia syndromes. Small amounts of aluminum are absorbed from the gastrointestinal tract and renal excretion of aluminum is impaired in renal failure. Aluminum is not well removed by dialysis because it is bound to albumin and transferrin, which do not cross dialysis membranes. As a result, aluminum is deposited in bone, and dialysis osteomalacia may develop when large amounts of aluminum are ingested orally by patients with impaired renal function.

[1] See §201.66(b)(4) of this chapter.

Step 3a: Identify the Labeling

Don't forget other labeling requirements appear in 21 C.F.R. Part 201 and elsewhere, including guidances

associated with the product without indicating each active ingredient (the established name and quantity of each active ingredient are not required); the dosage form; and the price charged for a prescription for a specific quantity of the drug product.

(3) The reminder advertisement or reminder labeling may also include other written, printed, or graphic matter, e.g., identification of professional or convenience services provided by the pharmacy: *Provided*, That such information is neither false nor misleading and contains no representation or suggestion concerning the drug product's safety, effectiveness, or indications for use.

(4) The price stated in the reminder advertisement or reminder labeling as that charged for a prescription shall include all charges to the consumer including, but not limited to, the cost of the drug product, professional fees, and handling fees, if any. Mailing fees and delivery fees, if any, may be stated separately and without repetition.

(b) This exemption from §§ 201.100 and 202.1 of this chapter is applicable to all prescription drug reminder labeling and reminder advertisements solely intended to provide consumers with information regarding the price charged for prescriptions including price lists, catalogs, and other promotional material, whether mailed, posted in a pharmacy, placed in a newspaper, or aired on radio or television.

(c) Any reminder advertisement or reminder labeling intended to provide consumers with prescription price information which is not in compliance with this section shall be the subject of appropriate regulatory action. Such action may be taken against the product and/or the responsible person.

[40 FR 58799, Dec. 18, 1975]

PART 201—LABELING

Subpart A—General Labeling Provisions

Sec.

Subpart B—Labeling Requirements for Prescription Drugs and/or Insulin

Subpart C—Labeling Requirements for Over-the-Counter Drugs

Subpart D—Exemptions From Adequate Directions for Use

PART 330—OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED

Subpart A—General Provisions

Sec.

Step 4: Identify Other Requirements

Don't forget sometimes there are other requirements, like testing

Food and Drug Administration, HHS § 331.30

nonantacid laxative ingredient to correct for constipation caused by the antacid. No labeling claim of the laxative effect may be used for such a product.

(b) An antacid may contain any generally recognized as safe and effective analgesic ingredient(s), if it is indicated for use solely for the concurrent symptoms involved, e.g., headache and acid indigestion, and is marketed in a form intended for ingestion as a solution.

(c) An antacid may contain any generally recognized as safe and effective antiflatulent ingredient if it is indicated for use solely for the concurrent symptoms of gas associated with heartburn, sour stomach or acid indigestion.

Subpart C—Testing Procedures

§ 331.20 Determination of percent contribution of active ingredients.

To determine the percent contribution of an antacid active ingredient, place an accurately weighed amount of the antacid active ingredient equal to the amount present in a unit dose of the product into a 250-milliliter (mL) beaker. If wetting is desired, add not more than 5 mL of alcohol (neutralized to an apparent pH of 3.5), and mix to wet the sample thoroughly. Add 70 mL of water, and mix on a magnetic stirrer at 300 ±30 r.p.m. for 1 minute. Analyze the acid neutralizing capacity of the sample according to the procedure provided in the United States Pharmacopeia 23/National Formulary 18 and calculate the percent contribution of the antacid active ingredient in the total product as follows:

Percent contribution = (Total mEq. Antacid Active Ingredient × 100)/(Total mEq. Antacid Product).

[61 FR 4823, Feb. 8, 1996]

§ 331.21 Test modifications.

The formulation or mode of administration of certain products may require a modification of the United States Pharmacopeia 23/National Formulary 18 acid neutralizing capacity test. Any proposed modification and the data to support it shall be submitted as a petition under the rules established in § 10.30 of this chapter. All information submitted will be subject to the disclosure rules in part 20 of this chapter.

[61 FR 4823, Feb. 8, 1996]

Subpart D—Labeling

§ 331.30 Labeling of antacid products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "antacid."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: "For the relief of" (optional, any or all of the following:) "heartburn," "sour stomach," and/or "acid indigestion" (which may be followed by the optional statement:) "and upset stomach associated with" (optional, as appropriate) "this symptom" or "these symptoms." Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(c) *Warnings.* The labeling of the product contains the following warnings, under the heading "Warnings", which may be combined but not rearranged to eliminate duplicative words or phrases if the resulting warning is clear and understandable:

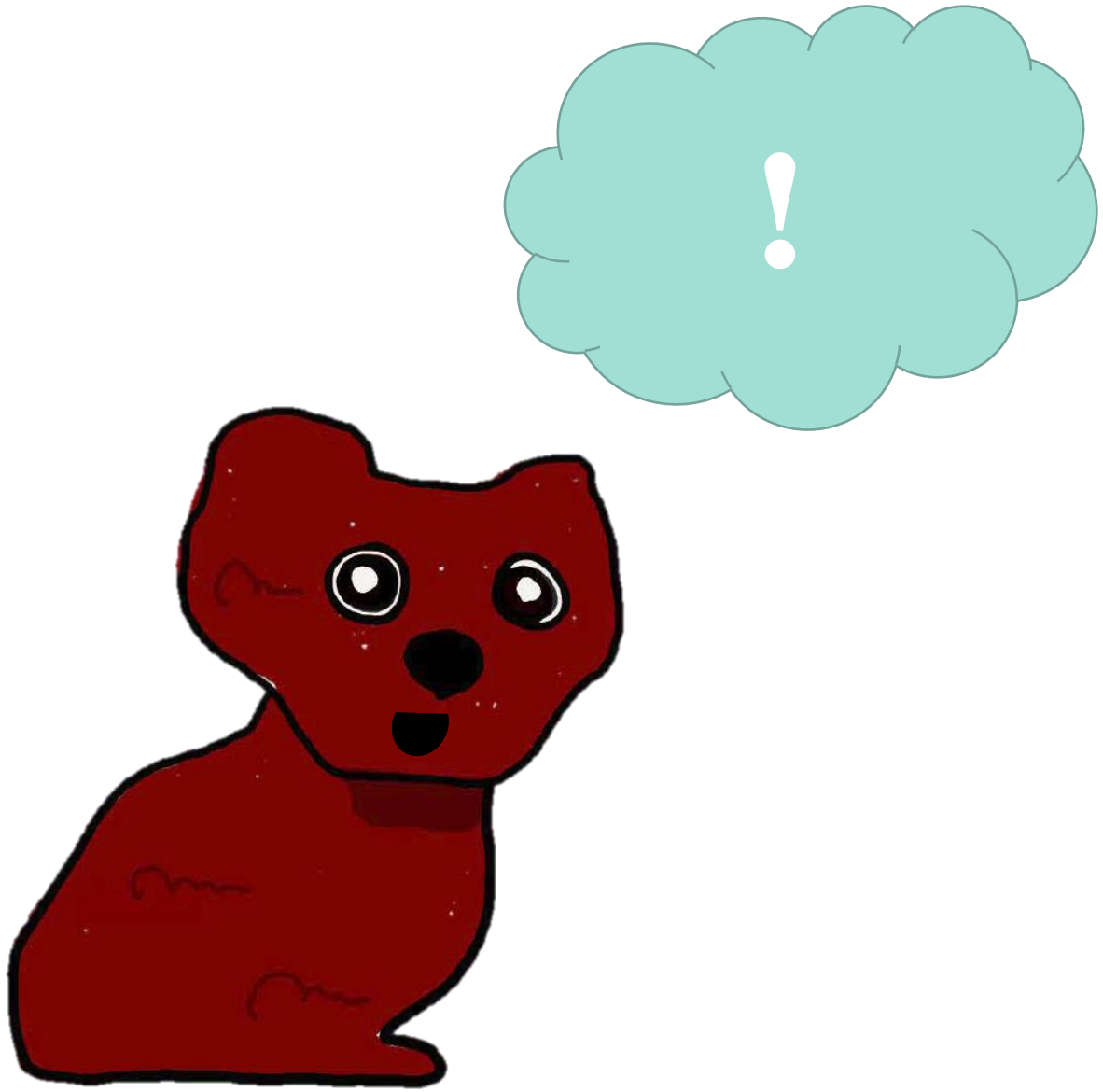
(1) "Do not take more than (maximum recommended daily dosage, broken down by age groups if appropriate, expressed in units such as tablets or teaspoonfuls) in a 24–hour period, or use the maximum dosage of this product for more than 2 weeks, except under the advice and supervision of a physician."

(2) For products which cause constipation in 5 percent or more of persons who take the maximum recommended dosage: "May cause constipation."

(3) For products which cause laxation in 5 percent or more of persons who

245

What if I make an antacid (sodium bicarbonate) and cough drop (menthol)?



No go

Can only make a combination if the Monograph allows for it.

Otherwise makes it an unapproved new drug

§ 331.15 Combination with nonantacid active ingredients.

(a) An antacid may contain any generally recognized as safe and effective nonantacid laxative ingredient to correct for constipation caused by the antacid. No labeling claim of the laxative effect may be used for such a product.

(b) An antacid may contain any generally recognized as safe and effective analgesic ingredient(s), if it is indicated for use solely for the concurrent symptoms involved, e.g., headache and acid indigestion, and is marketed in a form intended for ingestion as a solution.

(c) An antacid may contain any generally recognized as safe and effective antiflatulent ingredient if it is indicated for use solely for the concurrent symptoms of gas associated with heartburn, sour stomach or acid indigestion.

Product Development: Cough Drop

What if I say in my advertising L
“takes your cough & runny/stuffy nose!”
“Only Natural flavors; most refreshing”

(b) *Oral antitussive drug.* A drug that either is taken by mouth or is dissolved in the mouth in the form of a lozenge and acts systemically to relieve cough.

(b) *Topical antitussives.* (1) Camphor. (2) Menthol.

(1) ‘‘Temporarily’’ (select one of the following: ‘‘alleviates,’’ ‘‘calms,’’ ‘‘controls,’’ ‘‘decreases,’’ ‘‘quiets,’’ ‘‘reduces,’’ ‘‘relieves,’’ or ‘‘suppresses’’) ‘‘cough due to’’ (select one of the following: ‘‘minor bronchial irritation’’ or ‘‘minor throat and bronchial irritation’’) (select one of the following: ‘‘as may occur with,’’ ‘‘associated with,’’ or ‘‘occurring with’’) (select one of the following: ‘‘A cold’’ or ‘‘the common cold’’) ‘‘or inhaled irritants.’’

(2) ‘‘Temporarily’’ (select one of the following: ‘‘alleviates,’’ ‘‘calms,’’ ‘‘controls,’’ ‘‘decreases,’’ ‘‘quiets,’’ ‘‘reduces,’’ ‘‘relieves,’’ or ‘‘suppresses’’) ‘‘cough’’ (select one of the following: ‘‘as may occur with,’’ ‘‘associated with,’’ or ‘‘occurring with’’) (select one of the following: ‘‘A cold,’’ ‘‘the common cold,’’ or ‘‘inhaled irritants’’).

So can I?

RUNNY/STUFFY NOSE

No go: makes it an unapproved new drug

(g) *Topical nasal decongestant drug.* A drug that when applied topically inside the nose, in the form of drops, jellies, or sprays, or when inhaled intranasally reduces nasal congestion caused by acute or chronic rhinitis.

NATURAL FLAVORS AND MOST REFRESHING

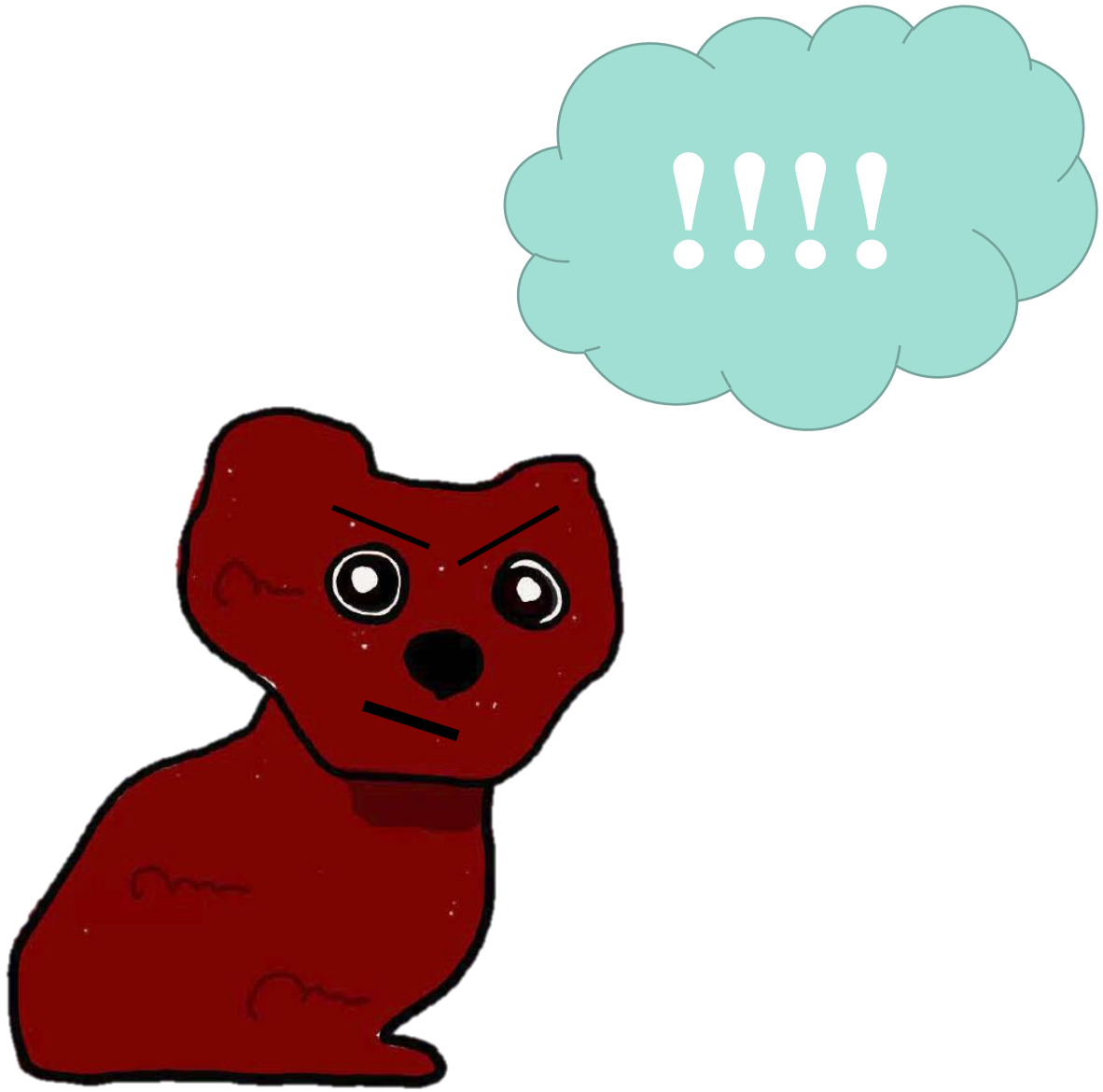
Better be true (natural flavors), but not a Monograph issue

Product Development: Cough Drop

(b) *For products containing menthol identified in §§ 341.14(b)(2) and 356.12(f) of this chapter.* The product contains 5 to 10 milligrams menthol. The labeling of the product contains the established name of the drug, if any, and identifies the product as a "cough suppressant/oral anesthetic" or "antitussive (cough suppressant)/oral anesthetic." The indications shall be combined from § 341.74(b) and part 356 of this chapter. The warnings shall be combined from § 341.74(c)(1), (c)(2), and (c)(3) and part 356 of this chapter. The directions shall be: "Directions [in bold type] [bullet][1] adults and children 2 years and over: dissolve lozenge slowly in the mouth. Repeat every 2 hours as needed or as directed by a doctor. [bullet] children under 2 years of age: ask a doctor".

350	350.1 to 350.60	ANTIPERSPIRANT DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE
352	352.1 to 352.77	SUNSCREEN DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE [STAYED INDEFINITELY]
355	355.1 to 355.70	ANTICARIES DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE
357	357.101 to 357.850	MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE
358	358.101 to 358.760	MISCELLANEOUS EXTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE
361	361.1	PRESCRIPTION DRUGS FOR HUMAN USE GENERALLY RECOGNIZED AS SAFE AND EFFECTIVE AND NOT MISBRANDED: DRUGS USED IN RESEARCH

Why can’t I find the oral anesthetic Monograph in the C.F.R.?!



Backstory:

Kefauver Amendment (1962): Drugs must be safe “and effective”

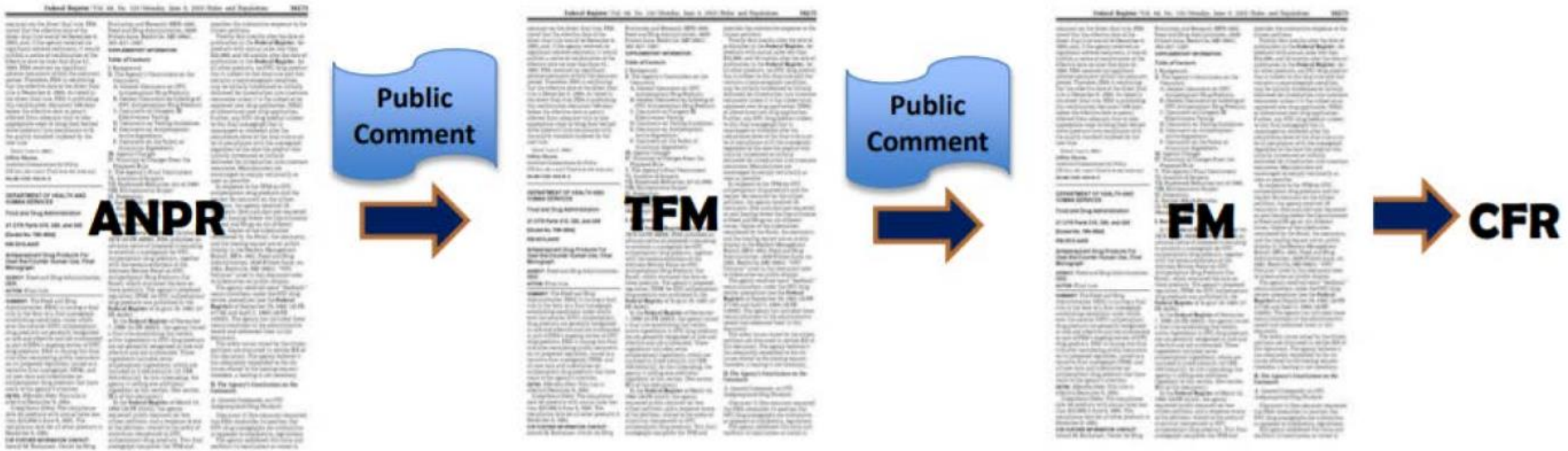
Issue: How to determine that OTC drugs are effective [and appropriately labeled]?

Backstory Cont.

Solution: OTC Monograph Review

- Identify ~300,000 OTC drugs in the market ***in 1972*** and categorize them
- Analyze the effectiveness by active ingredient (~700 actives) and conditions for use
- Establish regulations that specify the active ingredient and labeling

The Monograph's 3 Step Plan



Advance Notice of Proposed Rulemaking

Tentative Final Monograph

Final Monograph

Source: FDA, Monograph Reform is Here! (5/20/2020), slide 8

What do the three categories mean?

Category I: GRASE

Category II: Not GRASE (usually not effective)

Category III: More data needed to determine if GRASE

Backstory Cont.

FDA to Congress in 1977:

> "Panel Reports with Proposed Monographs" for 17 additional categories are scheduled for publication during fiscal year 1978, along with the tentative publication of ten final monographs. Monographs for all categories are scheduled for completion by fiscal year 1983 and should lead to definitive federal standards on ingredients and labeling claims for all non-prescription drugs. As the final monographs are published, FDA will begin to examine marketed products to assure compliance and will take enforcement action as appropriate.

FDA to Congress in 2017:

> Approximately one third of the monographs are not yet final, and several hundred individual ingredients (monographs can include multiple ingredients) do not have a final determination of safety and effectiveness. In addition, a number of planned safety labeling changes for monograph ingredients have not yet taken place while similar changes have already been made to prescription drugs containing the same ingredient. Finally, restrictions in the monograph system may discourage manufacturers from innovating.

Practical implications of no final

Home / Drugs / Development & Approval Process | Drugs / How Drugs are Developed and Approved / Over-the-Counter OTC | Nonprescription Drugs / Status of OTC Rulemakings

Status of OTC Rulemakings

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Status of OTC Rulemakings

On March 27, 2020, the President signed the Over-the-Counter Monograph Safety, Innovation, and Reform Act into law. This act is intended to modernize the process by which FDA regulates over-the-counter monograph drugs. The FDA is in the process of implementing the changes set forth in the act and will update the public and this webpage as we have additional information.

Content current as of:
03/30/2020

Regulated Product(s)
Drugs
Over-the-Counter Drugs

The Over-the-Counter (OTC) drug category web site contains *Federal Register* notices organized by therapeutic category subtopics. Each web page also links to therapeutic category pages organized chronologically.

This rulemaking history site is intended as a research aid and is not an official FDA record. We have tried to make these histories accurate and complete. Should you find an error, however, please let us know so that we can correct it.

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

A
Acne
Administrative Procedures
Alcohol
Allergy
Analgesic, External
Analgesic, Internal
Anorectal

L
Labeling
Laxative
Leg Muscle Cramps

M
Male Genital Desensitizers
Menstrual

N
Nailbiting
Nasal Decongestant
Nighttime Sleep Aid

O

69768 Federal Register / Vol. 44, No. 234 / Tuesday, December 4, 1979 / Proposed Rules

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Food and Drug Administration
21 CFR Part 348
[Docket No. 78N-0301]
External Analgesic Drug Products for Over-the-Counter Human Use; Establishment of a Monograph and Notice of Proposed Rulemaking

AGENCY: Food and Drug Administration.
ACTION: Proposed Rule.
SUMMARY: This proposed rule would establish conditions under which over-the-counter (OTC) external analgesic drug products are generally recognized as safe and effective and not misbranded. The proposed rule, based on the recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products, is part of the ongoing review of OTC drug products conducted by the Food and Drug Administration (FDA).
DATES: Comments by March 6, 1980 and reply comments by April 3, 1980.
ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.
FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.
SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on May 29, 1978, a report of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products. Under § 330.10(a)(6) (21 CFR 330.10(a)(6)), the agency issues (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC external analgesic drug products are generally recognized as safe and effective and not misbranded; (2) a statement of conditions excluded from the monograph because the Panel determined that data were insufficient to classify these conditions as either (1) or (2) above; and (3) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, comment on the full evaluation, and comment on the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document as a formal proposal to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members but does not necessarily reflect the agency's position on any particular matter contained in it. The Panel recommended classification of the ingredient methapyrilene hydrochloride in Category I for topical use as an external analgesic. Subsequent to this recommendation, studies, not available to the Panel, provided data from which the agency concluded that methapyrilene is a potent carcinogen in animal and must be considered a potential human carcinogen. These data are on file in the office of the Hearing Clerk (address given above) under Docket No. 78N-0244. In June 1979, the agency initiated a recall of all oral and topical products containing methapyrilene. These products are considered misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act. The Panel's report and proposed monograph, however, have not been changed to reflect these subsequent events.

FDA is aware of the recommendation to make low concentrations of OTC use, hydrocortisone available for OTC use. Without addressing the merits of this recommendation, the agency merely wishes to point out that no final decision will be made without careful thorough evaluation of [illegible] which are submitted [illegible]

analgesic drug products submitted for consideration by the Advisory Review Panel. All the submitted information will be put on public display at the office of the Hearing Clerk, Food and Drug Administration, after January 3, 1980, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 16 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address given above).

Based upon the conclusions and recommendations of the Panel, the agency proposes the following:

1. That the conditions included in the monograph, under which the drug products would be generally recognized as safe and effective and not misbranded (Category I), be effective 30 days after the date of publication of the final monograph in the Federal Register.

2. That the conditions excluded from the monograph because they would cause the drug to be not generally recognized as safe and effective or to be misbranded (Category II), be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the Federal Register, regardless of whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph, because the available data are insufficient (Category III) to classify such conditions either as Category I or Category II, will be the subject of a later notice. The status of Category III conditions after publication of a final order is the subject of a recent decision in Cutler v. Kennedy, No. 77-0734 (D.D.C. [illegible] case, the [illegible]

5852 Federal Register / Vol. 48, No. 27 / Tuesday, February 8, 1983 / Proposed Rules

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
21 CFR Part 348
[Docket No. 78N-0301]
External Analgesic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.
ACTION: Notice of proposed rulemaking.
SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) external analgesic drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after [illegible]ering the report and [illegible]ions of the Advisory [illegible]n OTC Topical [illegible]ntirheumatic, Otic, Burn, [illegible] Prevention and Treatment [illegible]ts and public comments on [illegible] notice or proposed [illegible]g that was based on those [illegible]ndations. This proposal is part [illegible]going review of OTC drug [illegible]s conducted by FDA.
[illegible]: Written comments, objections, or [illegible]st for oral hearing before the [illegible]missioner of Food and Drugs on the [illegible]posed regulation by April 11, 1983. [illegible]w data by February 8, 1984. [illegible]comments on the new data by April 9, 1984. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the Federal Register of September 29, 1981 (46 FR 47730). Written comments on the agency's economic impact determination by June 8, 1983.
ADDRESS: Written comments, objections, or request for oral hearing to the Docket Management Branch (HFA-305), Food and Drug Administration , Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857. New data and comments on new data should also be addressed to the Dockets Management Branch.
FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, National Center for Drugs and Biologics (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.
SUPPLEMENTARY INFORMATION: In the Federal Register of December 4, 1979 (44 FR 69768) FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC external analgesic drug products, together with the recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by March 6, 1980. Reply comments in response to comments filed in the initial comment period could be submitted by April 3, 1980.

In a notice published in the Federal Register of September 29, 1980 (45 FR 63878), the agency advised that it had reopened the administrative record for OTC external analgesic drug products to allow for consideration of recommendations on camphor-containing drug products that had been received from the Advisory Review Panel on OTC Miscellaneous External Drug Products after the date the administrative record previously had officially closed. The agency concluded that the Miscellaneous External Panel's recommendations should be available to the agency in developing a proposed regulation on external analgesic drug products in the form of a tentative final monograph.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. Data and information received after the administrative record was reopened have also been put on display in the Dockets Management Branch.

The advance notice of proposed rulemaking, which was published in the Federal Register on December 4, 1979 (44 FR 69768), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule), FDA states for the first time its position on the establishment of a monograph for OTC external analgesic drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC external analgesic drug products.

In response to the advance notice of proposed rulemaking, 1 trade association, 10 drug manufacturers, 36 health professionals, and 4 consumers submitted comments. In response to the notice of reopening the administrative record to allow for consideration of recommendations on camphor-containing drug products, one trade association, six drug manufacturers, and one drug marketer submitted comments. Copies of the comments received are also on public display in the Dockets Management Branch.

This proposal to establish Part 348 (21 CFR 348) constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC external analgesic drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

FDA published in the Federal Register of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established.

Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety and effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph (46 FR 47738).

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not

Amending a Monograph

Requires engaging in the notice and comment process:

- Proposed rule
- Final rule

New Acetaminophen Warnings

NDA/ANDA

FDA notified the NDA/ANDA holders, either requiring or requesting the change

Monograph

Encouraged including the warning through a guidance document, despite the Monograph being unfinished (TFM Nov. 16, 1988)

Time and Extent Applications

- Different mechanism to update the Monograph, primarily to incorporate conditions outside of the U.S.

- Two step process:
  - Step 1: material time ***and*** material extent?
  - Step 2: prove GRASE

Why learn about the Monographs aren't they outdated?

Not quite.

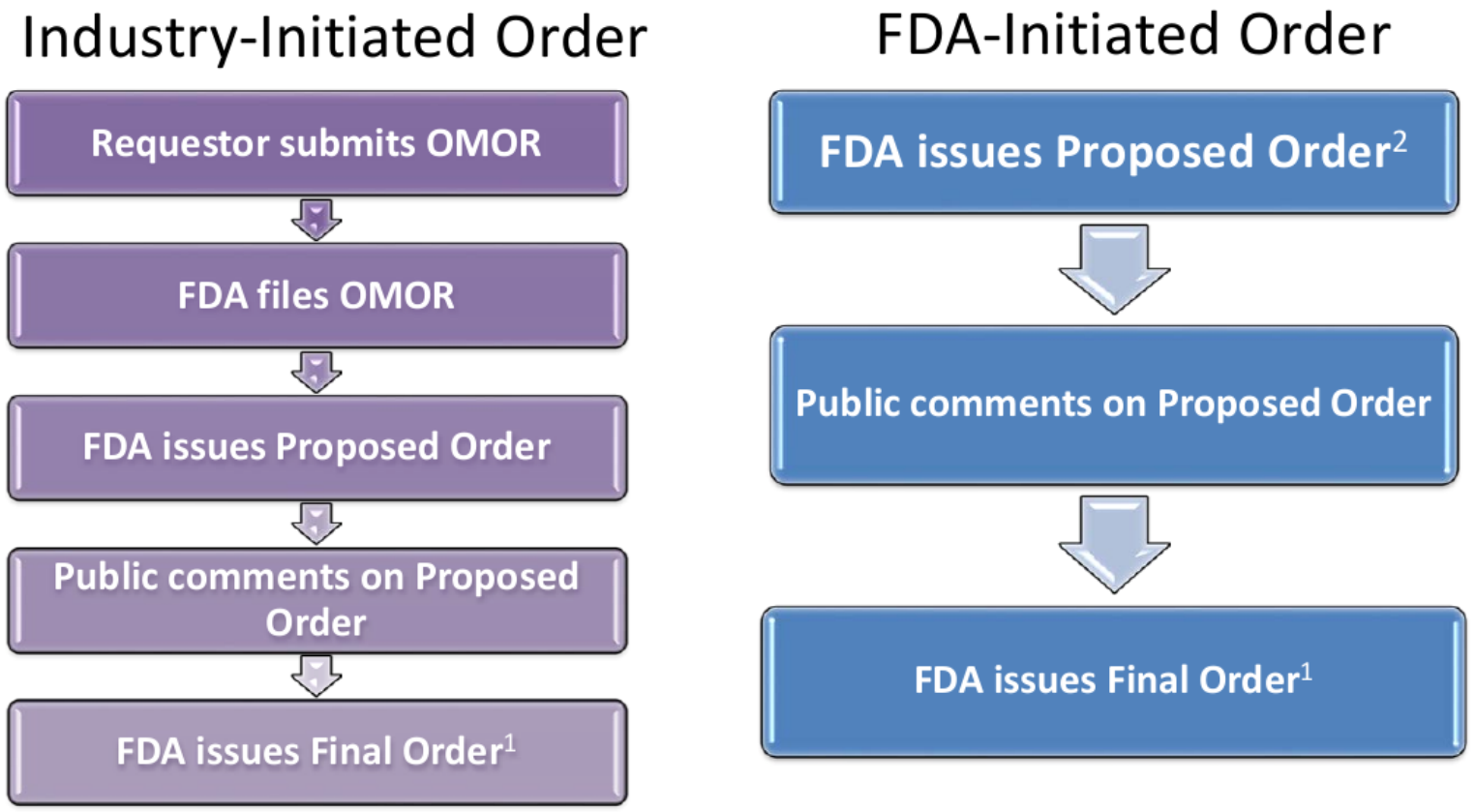
The CARES Act transition to Administrative Orders is built on the Monograph process.

Administrative Orders

Monographs become Administrative Orders

- Active ingredient-based system
- Specifies conditions (such as labeling) to market the drug without approval

Administrative Orders in Process



[1] Final orders are final Agency actions subject to dispute resolution, administrative hearings, and judicial review.
[2] Or interim final order under an expedited procedure

Exclusivity

18 month exclusivity when:

- A new active ingredient not previously included in certain non-prescription drugs without an NDA
- A change in use that required new human data studies

OTC User Fees

Created under the CARES Act, called “Over-the-Counter Monograph User Fee Act” (OMUFA)

- Manufacturer Fees:
  - Monograph Drug Facility (MDF) Facility Fee
  - Contract Manufacturing Organization (CMO) Facility Fee
- OTC Monograph Order Requests (OMOR)
  - Tier 1
  - Tier 2

The Meantime

Converted to Final Orders and thus can be marketed:

- Final Monographs
- Category I subject to a TFM

Not under a Final Order, but can be marketed:

- Category I subject to ANPR
- Category III subject to TFM

No longer allowed: Category II

3

OTC NDAs, Including Rx to OTC Switch

Another Route – New Drug Approval

- For not GRASE
- Approaches:
  - Full NDA
  - NDA [Monograph] Deviation

- Many common OTC drugs require an NDA/ANDA
  - Ibuprofen (brand name, Advil or Motrin)
  - Fexofenadine (brand name Allegra)
  - Ranitidine (brand name Zantac)

The Switch

- A prescription drug switches to over-the-counter
- How:
  - NDA holder files a supplement
  - Citizen petition to force a switch (see Section 503(b)(3))
    - FDA theoretically could do it on its own
- Examples (yes that's the same list):
  - Ibuprofen (brand name, Advil or Motrin)
  - Fexofenadine (brand name Allegra)
  - Ranitidine (brand name Zantac)

4

Behind-the-Counter

A Third-Option?

- Not a prescription drug, but requires interacting with a medical professional prior to purchase
- Behind the Counter:
  - Pseudoephedrine (not for FDA reasons, but limit methamphetamine production)
  - Plan B (previously)
- FDA Draft Guidance: Innovative Approaches for Nonprescription Drug Products (2018)

Wiley: The Orange Popcorn Cat

Help to lead to the Color Additive Amendment of 1960

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