Regulation of Over-the-Counter (OTC) Drug Products

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http://www.fda.gov/cder/otcmonographs/rulemaking_index.htm: OTC Monograph

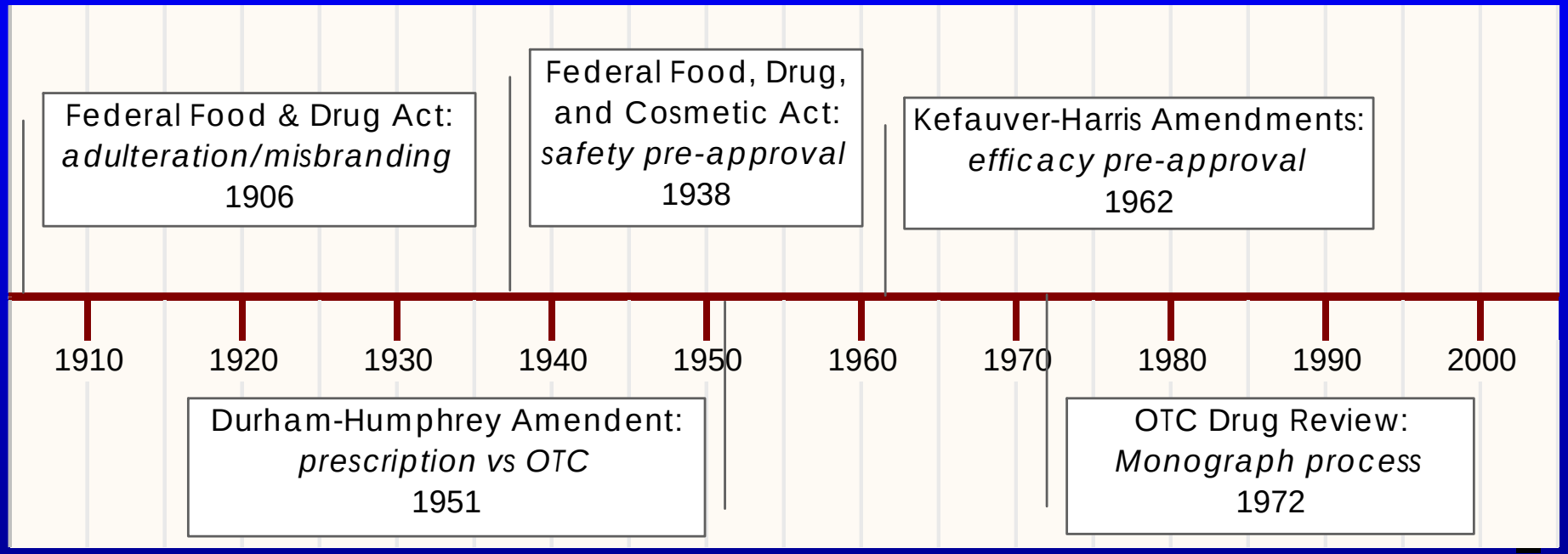
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm: NDA

What are OTC drugs?

New Drug Application (NDA)

OTC Drug Monograph

Historical Development of OTC Drug Regulation



Office of Nonprescription Products (ONP)

Division of Nonprescription Clinical Evaluation (DNCE)

- NDAs *mostly*

Division of Nonprescription Regulation Development (DNRD)

- OTC Monographs *mostly*

Medical Officers

Interdisciplinary Scientists

Melissa Furness — Project Managers — *Walt Ellenberg*

Social Scientists

Toxicologist

Outline

- Requirements for all OTC drug products
- Two regulatory pathways:
  - OTC New Drug Application (NDA)
  - OTC Drug Monograph

What are the requirements for all OTC drug products?

- Standards for safety and efficacy
- Good Manufacturing Practices (inspections)
- Labeling under 21 CFR 201.66

Safety & Effectiveness Standards for OTC Products

- Same standards as prescription drugs

Also, consumers must be able to…

- Self-diagnose
- Self-treat
- Self-manage

Which can be assessed through…

- Label comprehension studies
- Actual use studies

OTC Labeling

- "Drug Facts"
  - Standardized labeling format
  - Similar to "Nutrition Facts" & "Supplement Facts"
- 21 CFR 201.66
- Required as of May 2005

OTC Labeling & Advertising

- FDA regulates OTC drug labeling
  - FD&C Act: "labeling" means all labels, and other written, printed, or graphic matter…
    1. upon any article or any of its containers, or
    2. accompanying such article

    (physical attachment not necessary)

- FTC regulates OTC drug advertising
  - No *fair balance* requirement:

    benefits vs. warnings/contraindications

OTC NDA

Types of NDAs

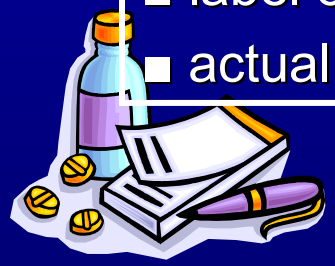
- Rx-to-OTC switches
  - full switch (NDA supplement)
  - partial switch (new NDA)
- Direct-to-OTC
- NDA deviation (§ 330.11)
- Generic (ANDA)

Review of NDAs for Nonprescription Drugs

- MAPP 6020.5R "Good Review Practice: OND Review Management of INDs and NDAs for Nonprescription Drug Products"
  - http://www.fda.gov/cder/mapp.htm
- We (ONP) may collaborate with Specific Subject Matter Review Divisions (SSMRDs)
  - SSMRD reviews clinical trials
  - ONP reviews consumer behavior studies and postmarketing safety data

NDA vs. OTC Drug Monograph

NDA Process	OTC Monograph Process
Pre-market approval	No pre-market approval
Confidential filing	Public process
Drug product-specific	Active ingredient-specific ■ OTC drug category
May require a user fee	No user fees
Potential for marketing exclusivity	No marketing exclusivity
Mandated FDA review timelines	No mandated timelines
May require clinical studies ■ label comprehension ■ actual use	May require clinical studies ■ label comprehension and actual use studies not required



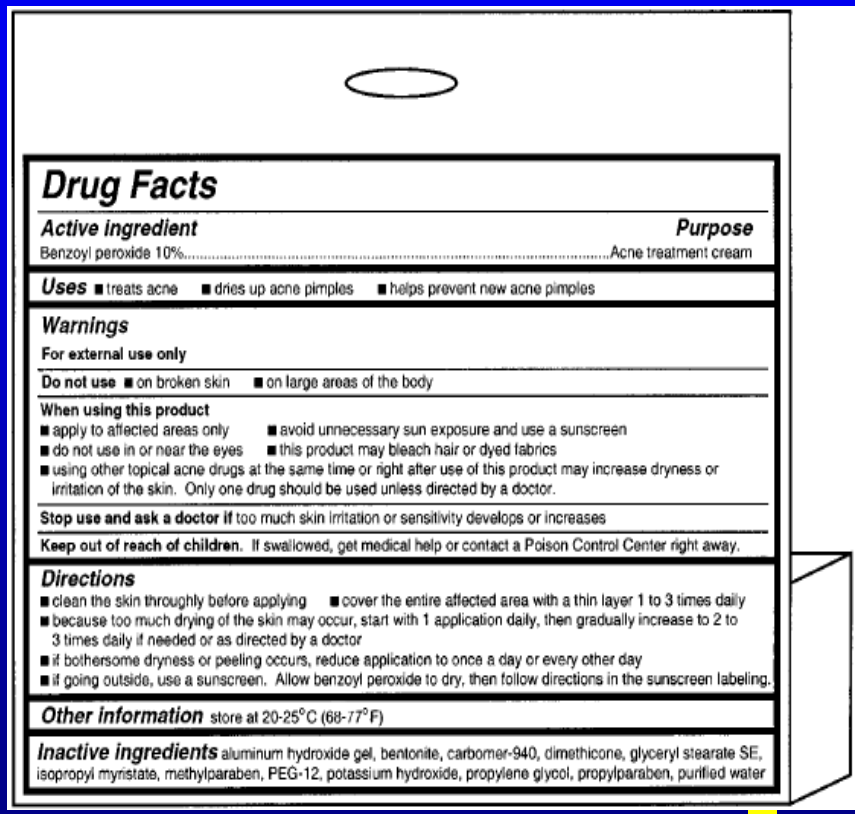
OTC Drug Monograph

What is an OTC Drug Monograph?

- "Recipe book" for marketing an OTC drug
- Required GRASE conditions → GRASE product
  GRASE: Generally Recognized As Safe and Effective
- Final monographs are published in
  Code of Federal Regulations (CFR)
  - 21 CFR parts 331-358
  - http://www.fda.gov/cder/Offices/OTC/industry.htm

What is included in an OTC Drug Monograph?

- GRASE active ingredients
  - dosage strength
  - dosage form
- Labeling requirements
  - indications
  - warning & directions for use
- Final formulation testing



Drug Facts

Active ingredient ***Purpose***

Benzoyl peroxide 10%..... Acne treatment cream

Uses ■ treats acne ■ dries up acne pimples ■ helps prevent new acne pimples

Warnings

For external use only

Do not use ■ on broken skin ■ on large areas of the body

When using this product

■ apply to affected areas only ■ avoid unnecessary sun exposure and use a sunscreen
■ do not use in or near the eyes ■ this product may bleach hair or dyed fabrics
■ using other topical acne drugs at the same time or right after use of this product may increase dryness or irritation of the skin. Only one drug should be used unless directed by a doctor.

Stop use and ask a doctor if too much skin irritation or sensitivity develops or increases

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Directions

■ clean the skin throughly before applying ■ cover the entire affected area with a thin layer 1 to 3 times daily
■ because too much drying of the skin may occur, start with 1 application daily, then gradually increase to 2 to 3 times daily if needed or as directed by a doctor
■ if bothersome dryness or peeling occurs, reduce application to once a day or every other day
■ if going outside, use a sunscreen. Allow benzoyl peroxide to dry, then follow directions in the sunscreen labeling.

Other information store at 20-25°C (68-77°F)

Inactive ingredients aluminum hydroxide gel, bentonite, carbomer-940, dimethicone, glyceryl stearate SE, isopropyl myristate, methylparaben, PEG-12, potassium hydroxide, propylene glycol, propylparaben, purified water

Example of a Final OTC Drug Monograph: Antacid

§331.10 *Active ingredients*…Calcium, as carbonate or phosphate; maximum daily dosage limit 160mEq. calcium (e.g., 8 grams calcium carbonate)

§331.30(b) *Indications*…‘‘For the relief of’’ (optional, any or all of the following:) ‘‘heartburn,’’ ‘‘sour stomach,’’and/or ‘‘acid indigestion’’

§331.30(c) *Warnings*…‘‘Do not take more than (maximum recommended daily dosage) in a 24–hour period, or use the maximum dosage of this product for more than 2 weeks,

Drug Facts

Active ingredient(s) — **Purpose**
Calcium carbonate USP 750mg. ..... Antacid

Use(s) relieves ■acid indigestion ■heartburn ■sour stomach

Warnings
Ask a doctor or pharmacist before use if you are taking a prescription drug. Antacids may interact with certain prescription drugs.

When using this product
■do not take more than 10 tablets in 24 hours
■do not use the maximum dosage for more than 2 weeks

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions
chew 2-4 tablets as symptoms occur, or as directed by a doctor

Other information store at room temperature

Inactive ingredients sucrose, corn starch, talc, mineral oil, natural and artificial flavors, adipic acid, sodium polyphosphate, red 40 lake, yellow 6 lake, yellow 5 lake, blue 1 lake

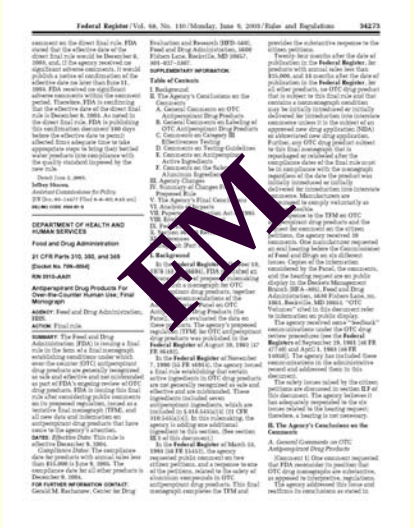
Questions or comments? 1-800-xxx-xxxx

How is an OTC Monograph established?

- "The OTC Drug Review" (1972 – present)
  - Overview in 21 CFR 330
- Advisory review panels → expert recommendations
- Three-step rulemaking process
  - Federal Register publications

1. Advance Notice of Proposed Rulemaking

2. Tentative Final Monograph



3. Final Monograph

How is an OTC monograph established? (cont.)

- 17 advisory review panels created
  - Antacid Panel, Antimicrobial Panel, Antiperspirant Panel, Dental Panel, Cough/Cold Panel…
- 9 member panels
  - Physicians, pharmacists, toxicologist, industry representative, consumer representative
- Reviewed 14,000 volumes of data submitted by industry, healthcare professionals, and consumers
- Held public meetings

OTC Drug Review

Advisory Review Panel

- Category I: GRASE
- Category II: not GRASE
- Category III: cannot determine if safe and effective

OTC Drug Review

- Category I: GRA
- Category II: not C
- Category III: can e if safe and effective

OTC Drug Review

Comments

OTC Drug Review

Comments

Data

Mechanisms to Amend an OTC Drug Monograph

- Citizen Petition
- Time and Extent Application (TEA)

Citizen Petition

- 21 CFR 10.30
- Can be used to amend OTC drug monograph at any stage
- Limited to pre-1975 marketing conditions
  - “conditions”: active ingredient, dosage form, indication, etc.

Citizen Petition

Example: Request amend External Analgesic Monograph

- 10% trolamine salicylate
- Indication: muscle pain relief (external analgesic)
- Marketed OTC in U.S. before 1975

OTC Monograph for External Analgesics:

- Trolamine salicylate not included (e.g., not GRASE)

TEA

- 21 CFR 330.14 (Effective in 2002)
- Can be used to amend OTC drug monograph for products marketed:
  - under an approved NDA after OTC Drug Review began
  - outside the United States
- Meets "material time" and "material extent" requirements of 21 CFR 330.14(b)
  - ≥5 continuous years in the same country
  - 10s of millions of dosage units sold

Time and Extent Application (cont.)

Step 1: Sponsor submits marketing data

FDA publishes of Notice of Eligibility (Call for data)

Step 2: FDA reviews safety and efficacy data to determine GRASE

Example: Request to amend Pediculicide Monograph

- >5 years continuous marketing in a foreign country
- ≤½ million bottles sold in 3 countries

Did not meet "material extent" requirement (i.e., 10s millions units sold); not eligible for TEA

For More Information

internet site:

http://www.fda.gov/cder/Offices/OTC/default.htm

intranet site:

http://inside.fda.gov/CDER/Office of New Drugs/Office of Nonprescription Products

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