Regulation of Nonprescription Drug Products

ODE-IV
What are OTC drugs?
Historical Development of OTC Drug Regulation

- Federal Food & Drug Act: adulteration/misbranding 1906
- Federal Food, Drug, and Cosmetic Act: safety pre-approval 1938
- Kefauver-Harris Amendments: efficacy pre-approval 1962
- Durham-Humphrey Amendement: prescription vs OTC 1951
- OTC Drug Review: Monograph process 1972
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”

- Specific Subject Matter Review Division (SSMRD) may review clinical trials
- ODE-IV/Div. of Nonprescription Clinical Evaluation reviews consumer behavior studies and postmarketing safety data

http://www.fda.gov/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/default.htm
## NDA vs. OTC Drug Monograph

<table>
<thead>
<tr>
<th>NDA Process</th>
<th>OTC Monograph Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-market approval</td>
<td>No pre-market approval</td>
</tr>
<tr>
<td>Confidential filing</td>
<td>Public process</td>
</tr>
<tr>
<td>Drug product-specific</td>
<td>Active ingredient-specific</td>
</tr>
<tr>
<td></td>
<td>■ OTC drug category</td>
</tr>
<tr>
<td>May require a user fee</td>
<td>No user fees</td>
</tr>
<tr>
<td>Potential for marketing exclusivity</td>
<td>No marketing exclusivity</td>
</tr>
<tr>
<td>Mandated FDA review timelines</td>
<td>No mandated timelines</td>
</tr>
<tr>
<td>May require clinical studies</td>
<td>May require clinical studies</td>
</tr>
<tr>
<td>■ label comprehension</td>
<td>■ label comprehension and actual use studies not required</td>
</tr>
<tr>
<td>■ actual use</td>
<td></td>
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</tbody>
</table>
OTC Drug Monograph
What is an OTC Drug Monograph?

- “Recipe book” for marketing an OTC drug

- A list and explanation of GRASE conditions
  GRASE = Generally Recognized As Safe and Effective

- Final monographs are published in
  Code of Federal Regulations: 21 CFR parts 331-358
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

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoyl peroxide 10% Acne treatment cream</td>
<td></td>
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</tbody>
</table>

**Uses**
- Treats acne
- Dries up acne pimples
- Helps prevent new acne pimples

**Warnings**
- For external use only
- Do not use on broken skin or on large areas of the body
- When using this product:
  - Do not use for children younger than 12 years of age
  - Do not use if there is redness or swelling in the area
  - Do not use on the eyes or other sensitive areas
  - Do not use if there is an open wound or sore
  - Do not use if there is skin irritation
- Stop use and ask a doctor if:
  - There is too much skin irritation or sensitivity develops
  - There is no improvement after 10 days of use

**Directions**
- Wash your hands before and after treatment
- Cover the entire affected area with a thin layer once daily
- If skin irritation occurs, discontinue use and ask a doctor
- If skin irritation occurs, wash off and ask a doctor
- If using a sunscreen, use a sunscreen that is not benzoyl peroxide

**Inactive Ingredients**
- Aluminum hydroxide gel, bentonite, carbomer-940, dimethicone, glyceryl stearate SE, isopropyl myristate, methylparaben, PEG-12, propylene glycol, propylparaben, purified water
§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 (max. rec. daily dosage) in a 24-hour period, or use the maximum dosage of this product for more than 2 weeks”
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
Category I: GRASE

Category II: not GRASE

Category III: cannot determine 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.
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
For More Information

internet site:
http://www.fda.gov/AboutFDA/CentersOffices/cder/ucm093452.htm