Over-the-Counter Drug Monograph

United States Food and Drug Administration Approach

Theresa M. Michele, MD
Director, Division of Nonprescription Drug Products
Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
OUTLINE

• Organizational Structure
• U.S. Regulatory Frameworks for Over-the-Counter (OTC) Drugs
  – New Drug Application
  – OTC Drug Monograph
• Origins of the OTC Drug Monograph
• OTC Monograph Review Process
• Future of the OTC Monograph
FDA ORGANIZATION RELEVANT TO OTC DRUGS

• Office of Medical Products and Tobacco
  • Center for Drug Evaluation and Research
    • Office of New Drugs
      • Office of Drug Evaluation IV
        • Division of Nonprescription Drug Products
OTC DRUG PRODUCTS

OTC drug products generally have these characteristics:

• Can be adequately labeled such that
  – The consumer can self-diagnose, self-treat, and self-manage the condition being treated
  – No health practitioner is needed for the safe and effective use of the product
• Drug has low potential for misuse and abuse
• Safety margin is such that the benefits of OTC availability outweigh the risks
# TWO REGULATORY PATHWAYS

<table>
<thead>
<tr>
<th>New Drug Application</th>
<th>OTC Monograph</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product specific (including formulation and labeling)</td>
<td>Therapeutic category-specific regulations (product can contain permissible active ingredients in a monograph compliant formulation)</td>
</tr>
<tr>
<td>Certain subsequent labeling and formulation changes require prior approval through supplemental application</td>
<td>Changes do not require approval when in compliance with monograph</td>
</tr>
<tr>
<td>Confidentiality during the approval process</td>
<td>Public process for monograph changes</td>
</tr>
<tr>
<td>Safety and effectiveness testing required for each individual product</td>
<td>Safety and effectiveness testing of each individual product not required if compliant with monograph</td>
</tr>
<tr>
<td>Application submitted for premarket approval</td>
<td>No FDA product-specific premarket application or preapproval</td>
</tr>
<tr>
<td>Application fees (i.e., user fees)</td>
<td>No user fees</td>
</tr>
<tr>
<td>Adverse event and other reporting requirements</td>
<td>Limited reporting requirements (serious adverse events only)</td>
</tr>
<tr>
<td>Comply with good manufacturing practices</td>
<td>Comply with good manufacturing practices</td>
</tr>
<tr>
<td>A period of market exclusivity (if certain conditions are met)</td>
<td>No market exclusivity</td>
</tr>
</tbody>
</table>
New Drug Application OR MONOGRAPH?
EXAMPLES OF OTC MONOGRAPH DRUG CATEGORIES

• Antacids
• Laxatives
• Antidiarrheal products
• Antiemetics
• Antiperspirants
• Sunscreens
• Cough and cold products
• Wart removers

• Sedatives/Sleep aids
• Stimulants
• Ophthalmic products
• Hemorrhoidal products
• Dandruff products
• Anticaries products
• Otic products
• Analgesics
• Allergies
ORIGINS OF THE OTC MONOGRAPH
HISTORICAL DEVELOPMENT OF FDA DRUG REGULATION

- **Federal Food & Drug Act**
  - **adulteration/misbranding**
  - **1906**
- **Federal Food, Drug, & Cosmetic Act**
  - **safety**
  - **1938**
- **Durham-Humphrey Amendment**
  - *prescription versus OTC*
  - **1951**
- **Kefauver-Harris Amendment**
  - *efficacy*
  - **1962**
- **OTC Drug Review Monograph process**
  - **1972**
CURRENT OTC MONOGRAPH PROCESS

• OTC drug review established in 1972
  – Implemented 1962 Congressional directive to review the safety and effectiveness of drugs

• Rather than review hundreds of thousands of individual OTC products, FDA began issuing monographs establishing conditions under which OTC drugs are generally recognized as safe and effective (GRASE)
  – Monographs are “rulebooks” establishing indications, strengths, dosing information, warnings, etc., for OTC products containing the covered ingredients to be GRASE
  – Each monograph generally provides for the marketing of hundreds or thousands of products
  – Products meeting the specifications of a monograph are not required to be reviewed by FDA before marketing

• The monographs cover some 800 active ingredients for over 1,400 different uses and over 100,000 products

• Each monograph is established by regulation
  – There are >150 final rules related to OTC drugs
  – Approximately 88 ongoing rulemakings in 26 broad therapeutic categories
WHAT GOES IN A MONOGRAPh?

• Conditions include:
  – Active ingredients (must comply with a USP drug monograph)
  – Dosage strength and form and route of administration
  – Patient population (age, gender) and indications for use
  – Required labeling: • Uses • Warnings • Directions
  – Final formulation testing, if required for the specific product (not all monographs)
### Drug Facts

<table>
<thead>
<tr>
<th>Active ingredient (in each dosage unit)</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>xxxxxxxxxxxxxxxxxxxxxxx mg.............</td>
<td>xxxxxxx</td>
</tr>
</tbody>
</table>

#### Uses
- xxxxxxxxxxxxxxxx
- xxxxxxxxxxxxxxxx

#### Warnings
- Do not use xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
- Ask a doctor before use if you have
  - xxxxxxxxxxxxxxxx
  - xxxxxxxxxxxxxxxx
- Ask a doctor or pharmacist before use if you are xxxxxxxxxxxxxxxx
- When using this product
  - xxxxxxxxxxxxxxxx
  - xxxxxxxxxxxxxxxx
- Stop use and ask a doctor if
  - xxxxxxxxxxxxxxxx
  - xxxxxxxxxxxxxxxx
- 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.

### Drug Facts (continued)

#### Directions
- xxxxxxxxxxxxxxxx
- xxxxxxxxxxxxxxxx

#### Other information
- xxxxxxxxxxxxxxxx
- xxxxxxxxxxxxxxxx

#### Inactive ingredients
- xxxxxxxxxxxxxxxx

#### Questions?
- 123-555-1234
THE OTC MONOGRAPH REVIEW PROCESS
GRASE CATEGORIES

• In 1970s, Advisory Review Panels reviewed therapeutic classes of OTC drugs and put products into three categories:
  – **Category I**: GRASE (Generally Recognized as Safe and Effective)
  – **Category II**: not GRASE
  – **Category III**: insufficient data available to determine if generally recognized as safe and effective

• Monograph products using original ingredients may stay on the market until FDA makes a final determination of ingredient status
CURRENT OTC MONOGRAPH RULEMAKING PROCESS

Requires a three-step public notice and comment rulemaking process

– Advance Notice of Proposed Rulemaking
– Tentative Final Monograph
– Final Monograph → Code of Federal Regulations
# REALITY OF THE MONOGRAPH PROCESS

<table>
<thead>
<tr>
<th>Published</th>
<th>Fed Reg citation</th>
<th>Topic</th>
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<tbody>
<tr>
<td>12-4-79</td>
<td>44FR69768</td>
<td>ANPR for External Analgesic Drug Products</td>
</tr>
<tr>
<td>2-5-80</td>
<td>45FR7820</td>
<td>Correction</td>
</tr>
<tr>
<td>9-26-80</td>
<td>45FR63878</td>
<td>Reopening of administrative record</td>
</tr>
<tr>
<td>9-7-82</td>
<td>47FR39412</td>
<td>Reopening of administrative record</td>
</tr>
<tr>
<td>12-7-82</td>
<td>47FR54981</td>
<td>Correction</td>
</tr>
<tr>
<td>12-28-82</td>
<td>47FR57738</td>
<td>Extension of comment and reply periods</td>
</tr>
<tr>
<td>2-8-83</td>
<td>48FR5852</td>
<td>TFM (Tentative Final Monograph = Proposed Rule)</td>
</tr>
<tr>
<td>3-11-83</td>
<td>48FR10373</td>
<td>Correction</td>
</tr>
<tr>
<td>10-2-85</td>
<td>50FR40260</td>
<td>Amend TFM to add male genital desensitizer indication</td>
</tr>
<tr>
<td>7-30-86</td>
<td>51FR27360</td>
<td>Amend TFM to add seborrheic dermatitis and psoriasis indication</td>
</tr>
<tr>
<td>8-25-88</td>
<td>53FR32592</td>
<td>Amend TFM warnings and directions for external anal conditions</td>
</tr>
<tr>
<td>4-3-89</td>
<td>54FR13490</td>
<td>Amend TFM to remove astringent drug products</td>
</tr>
<tr>
<td>10-3-89</td>
<td>54FR40818</td>
<td>Amend TFM to add poison ivy, poison oak, and insect bite indications</td>
</tr>
<tr>
<td>1-31-90</td>
<td>55FR3370</td>
<td>Amend TFM to address fever blister and cold sore indications</td>
</tr>
<tr>
<td>2-27-90</td>
<td>55FR6932</td>
<td>Amend TFM to make hydrocortisone 1% OTC</td>
</tr>
<tr>
<td>3-27-90</td>
<td>55FR11291</td>
<td>Correction</td>
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<tr>
<td>6-20-90</td>
<td>55FR25234</td>
<td>Amend TFM to address treatment and prevention</td>
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<tr>
<td>8-30-91</td>
<td>56FR43025</td>
<td>Hydrocortisone; Notice of Enforcement Policy</td>
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<tr>
<td>6-19-92</td>
<td>57FR27654</td>
<td>FR (Final Rule) Male genital desensitizer</td>
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<tr>
<td>12-18-92</td>
<td>57FR60426</td>
<td>FR (Final Rule) Diaper rash labeling</td>
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<tr>
<td>8-29-97</td>
<td>62FR45767</td>
<td>Amend TFM to add warning about diphenhydramine</td>
</tr>
<tr>
<td>11-19-97</td>
<td>62FR61710</td>
<td>Reopening of administrative records to consider new data</td>
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FUTURE OF THE MONOGRAPH
BENEFITS AND CHALLENGES OF THE MONOGRAPH SYSTEM

• Well-functioning OTC drug market should promote self-care, patient choice, and industry innovation

• But the current process is not working well
  – Burdensome, multi-step rulemakings take years to complete
    • Even urgent safety issues are subject to lengthy rulemakings, frustrating FDA, industry and patient groups
    • The difficulty in staying up-to-date impairs consumer confidence
  – Process is backward-looking
    • Intended to cover products on the market in 1972
    • Innovation has stalled
  – Program not supported by user fees
    • Significantly under-resourced
  – Status quo does not serve public health or industry well
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OTC DRUG REFORM PROPOSAL
(Under Consideration by Congress)

**Process Weaknesses**
- Burdensome, multistep rulemakings
- Limitations on innovation
- Inadequate resources

**Current Problems**
- Delays in finalizing monographs
- Limited, burdensome process for innovation
- Challenges in responding quickly to urgent safety issues
- Challenges in keeping pace with evolving science and changing market

**FDA and Industry Supported Solutions**
- Improve process by replacing rulemaking with administrative orders
- Make innovation process more nimble and flexible
- Help speed response to urgent safety issues through interim final orders
- Finalize proposed monographs by statute

**Resources for reform supported by user fees**