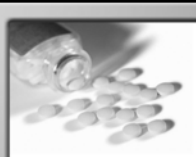
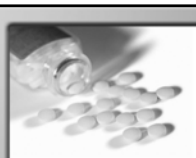


Introduction to Nonprescription Products

Leah Christl, Ph.D.
Supervisory Project Manager
Division of Nonprescription Clinical Evaluation
Acting Associate Director for Regulatory Affairs
Office of Nonprescription Products

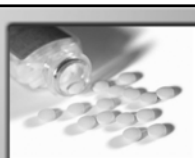


What is the Office of Nonprescription Products (ONP)?

- Formerly Division of Over-the-Counter Drug Products
- Report directly to Office of New Drugs
- Over-the-counter (OTC) drug products are those drugs that are available to consumers without a prescription.

ONP Continued

- 2 Divisions within ONP
  - Division of Nonprescription Clinical Evaluation (DNCE)
    - INDs and NDAs
  - Division of Nonprescription Regulation Development (DNRD)
    - OTC drug monographs

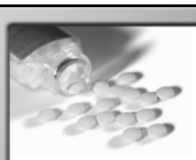


Examples of OTC Drugs

- Antiperspirants (not deodorants)
- Toothpastes (not whitening only)
- Antiplaque/Antigingivitis Mouthrinses
- Acne Remedies
- Hair Regrowth Aids
- Contraceptives
- Hospital-use topical antimicrobials
- Sunscreens

Characteristics of an OTC Drug

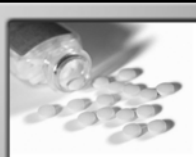
- Acceptable safety margin
- Low misuse and abuse potential
- Consumer can self-recognize, self-diagnose, self-treat
- Can be adequately labeled
- Health practitioner not needed for safe and effective use of the product



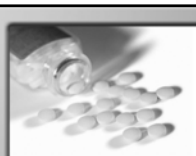
Marketing Options for an OTC

- Two Regulatory Systems
  - New Drug Applications (NDA)
  - OTC Drug Monographs
- General OTC Drug Lifecycle

Rx NDA → **OTC NDA** → **OTC Drug Monograph**



Marketing Under an NDA

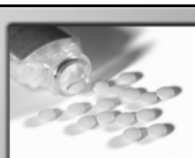


The NDA Process

- Requires a pre-approved application
- Confidential filing
- Drug product-specific
- May require clinical studies (clinical development costs)
- May require a user fee under PDUFA
- Post-approval NDA maintenance
- Individual license to market
- Potential for marketing exclusivity
- Mandated FDA review timelines

Where to Begin for an NDA

- An IND (Investigational New Drug) for trials in human subjects
- Typical “milestone” development meetings with FDA
  - Pre-IND
  - End of Phase 2
  - Pre-NDA

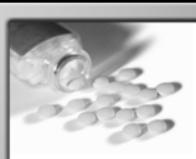


NDA references

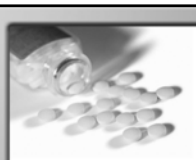
- For the pre-IND Meeting:

  Guidance entitled “Formal Meetings With Sponsors and Applicants for PDUFA Products”
- For the NDA review process:

  Guidance entitled “Good Review Management Principles for PDUFA Products”
- For IND requirements: 21 CFR 312
- For NDA requirements: 21 CFR 314



Marketing Under an OTC Drug Monograph



Why Did We Create Monographs?

- 1962 Amendments to FD&C Act
  - Kefauver-Harris Amendment
    - All new drugs must demonstrate effectiveness as well as safety
  - FDA began Drug Efficacy Study Implementation (DESI) for all Rx and OTC Drugs
- 420 OTC drug products deferred (under NDAs)
- Hundreds of thousands of non-NDA OTC drugs

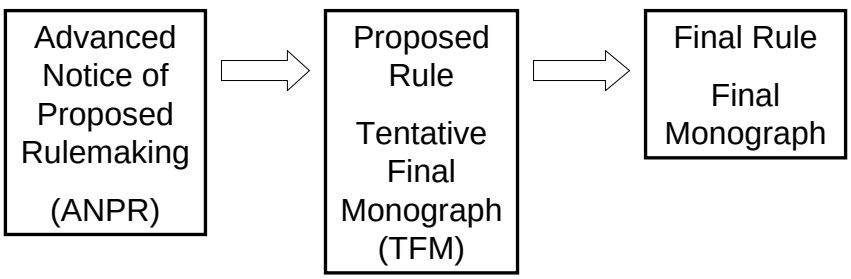
What are OTC Drug Monographs?

- 1972 – OTC Drug Review
  - Advisory Panel convened for each therapeutic category of OTC drug products
  - Developed monographs by therapeutic class (rather than individual product review) for efficiency
  - Results in the creation of a regulation – an OTC drug Monograph
- Established conditions under which an OTC drug is Generally Recognized As Safe and Effective (GRASE) and not misbranded
- NDA regulations (Part 314) do not apply

Just the Basics

How is a Monograph Established?

- See 21 CFR 330
- Three Step Rulemaking Process



The Monograph Process

- Public process
- Class-specific regulations (CFR 330-358)
  - by therapeutic class
- No data confidentiality
- No potential for marketing exclusivity
- No necessary clinical development costs
- No user fees under PDUFA
- No mandated FDA review timelines

Required Conditions

- Active ingredients
  - Category I: GRASE
  - Category II: Not GRASE
  - Category III: GRAS or GRAE
- Dosage or concentration
- Dosage Forms
- Required labeling
- Packaging and/or testing requirements (if necessary)
- “The product is manufactured in compliance with current good manufacturing practices, as established by parts 210 and 211 of this chapter.”
- “The establishment(s) in which the drug product is manufactured is registered, and the drug product is listed, in compliance with part 207 of this chapter.”

Just the Basics

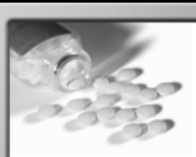
Can I Add to the Monographs?

- Citizen Petition, IF
  - Product was marketed prior to 1975
- Time and Extent Application (TEA) under 21 CFR 330.14, IF
  - Product marketed OTC outside of U.S.
  - Product marketed OTC inside U.S. after 1975
- Both are preliminary to a Proposed Rule

Just the Basics

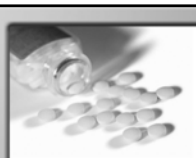
How are NDAs and Monographs Different?

NDA	**Monograph**
Pre-approval Required	Pre-approval Not Required
Clinical studies and user fees may be necessary	Clinical studies not necessary and no user fees
Approved labeling is unique to your drug	Labeling is the same for all similar drugs
Possible marketing exclusivity	No marketing exclusivity
Approved NDA is your license to market	Final monograph is open to anyone



How are NDAs and Monographs the Same?

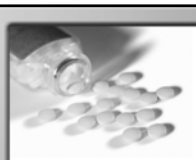
- Standards for safety and effectiveness
- Manufacturing and GMP inspections
- Labeling under 21 CFR 201 Subpart C
- Advertising regulations



ALL OTC DRUGS

Standards for Effectiveness for All OTC Products

- OTC drugs are not candy
- Same standards as prescription drugs



Standards for Safety for All OTC Products

Consumers can…

- Self-Diagnose
- Self-Treat
- Self-Manage

Without Professional Guidance

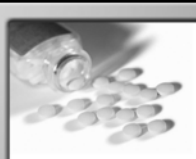
- Label Comprehension Studies
- Actual Use Studies
- U.S. and Worldwide adverse event data

Label Comprehension Study

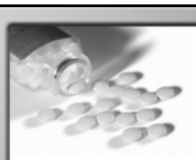
- Survey - Not clinical data
- Test consumers' ability to:
  - determine whether drug is appropriate for them
  - use medication accurately
  - recognize when to see a physician or seek emergency assistance

Actual Use Study

- Clinical data
- Patients screened for entry
- Given supply of drug and sent home
- Record use, adverse events, and outcomes
- Report on consumers' ability to follow label directions for use, warnings, etc.



Labeling
OTC Drug Products



Labeling Regulations
OTC Drug Products

- 21 CFR 201 Subpart C
  - Labeling Requirements for Over-the-Counter Drugs
    - 201.60 Principal display panel.
    - 201.61 Statement of identity.
    - 201.62 Declaration of net quantity of contents.
- 21 CFR 201.66
  - Format and content requirements for over-the-counter (OTC) drug product labeling.
  - Final Rule: 64 FR 13254 (March 17, 1999)
  - Effective May 16, 2005
- 21 CFR 211.132
  - Tamper-evident packaging requirements for over-the-counter (OTC) human drug products.

OTC Labeling

- "Drug Facts" Format
  - Standard format for labeling of OTC drugs that consumers become accustomed to
  - Mimic successful "Nutrition Facts" for foods and "Supplement Facts" for dietary supplements
- Enhance consumers' understanding of OTC drug labels to increase safe and effective use of these products
- 21 CFR 201.66
- Final Rule: 64 FR 13254 (March 17, 1999)
  - Effective May 16, 2005

What labeling is required?

- Uses
- Warnings
  - Do Not Use
  - Ask a Doctor
  - Ask a Doctor or Pharmacist
- Directions
- Professional labeling
  - **The labeling provided to health professionals (but not to the general public)**

Before Drug Facts

TAVIST-D®
Antihistamine/Nasal Decongestant

12 Hour Relief of Sinus & Nasal Congestion

NEW DOSAGE FORM

Indications: For the temporary relief of nasal congestion associated with upper respiratory allergies or sinusitis when accompanied by other symptoms of hay fever or allergies, including runny nose, sneezing, itching of the nose or throat, or itchy watery eyes.

Directions:	
Age	Dose
Adults and children 12 years of age and over	Swallow 1 caplet whole every 12 hours, not to exceed 2 caplets in 24 hours or as directed by a doctor.
Children under 12 years of age	Consult a Doctor

Warnings: Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately. May cause drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery. May cause excitability especially in children.

Do not exceed recommended dosage. If nervousness, dizziness, or sleeplessness occur, discontinue use and consult a doctor. If symptoms do not improve within 7 days, or are accompanied by fever, consult a doctor. Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, glaucoma, a breathing problem such as emphysema or chronic bronchitis, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

Drug Interaction Precaution: Do not take this product if you are presently taking another product containing phenylpropanolamine. Do not use this product if you are now taking a prescription monoamine oxidase inhibitor [MAOI] (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you are uncertain whether your prescription drug contains an MAOI, consult a health professional before taking this product.

Active Ingredients: Each Tavist-D Caplet contains clemastine fumarate, USP, 1.34 mg (equivalent to 1 mg clemastine) immediate release and phenylpropanolamine hydrochloride, USP, 75 mg extended release.

Inactive Ingredients: Carnauba wax, hydroxypropyl methylcellulose, lactose monohydrate, methylparaben, polydextrose, polyethylene glycol, silicon dioxide (colloidal), starch (pregelatinized), stearic acid, titanium dioxide, triacetin.

Sodium free.

Store at Controlled Room Temperature, 20°- 25°C (68°-77°F).

3 0043-0131-08 5

After Drug Facts

Drug Facts

Active Ingredients (in each caplet) — **Purpose**
Clemastine fumarate 1.34 mg (equivalent to 1 mg clemastine) ..... Antihistamine
Phenylpropanolamine HCl 75 mg extended release ..... Nasal Decongestant

Uses temporarily relieves these symptoms of the common cold, hay fever, or other upper respiratory allergies:
- nasal congestion • runny nose • sneezing • itchy, watery eyes • itching of the nose or throat
- temporarily relieves nasal congestion associated with sinusitis

Warnings

Do not use if you are now taking • another product containing phenylpropanolamine
- a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have • high blood pressure • heart disease • glaucoma • thyroid disease • diabetes
• 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 sedatives or tranquilizers

When using this product • do not use more than directed • avoid alcoholic drinks • drowsiness may occur
• alcohol, sedatives, and tranquilizers may increase drowsiness • be careful when driving a motor vehicle or operating machinery
• excitability may occur, especially in children

Stop use and ask a doctor if • nervousness, dizziness, or sleeplessness occurs • new symptoms occur
• symptoms do not get better within 7 days or occur with a fever

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 • do not crush or chew caplet
• adults and children 12 years of age and over: take 1 caplet every 12 hours; not more than 2 caplets in 24 hours unless directed by a doctor • children under 12 years of age: consult a doctor

Other information • sodium free • store at controlled room temperature 20°-25°C (68°-77°F)

Drug Facts (continued)

Inactive ingredients carnauba wax, hydroxypropyl methylcellulose, lactose monohydrate, methylparaben, polydextrose, polyethylene glycol, silicon dioxide (colloidal), starch (pregelatinized), stearic acid, titanium dioxide, triacetin

OTC Advertising

- Federal Trade Commission
  - FTC has regulatory authority over advertising of OTC drugs
  - FDA has regulatory authority over labeling of OTC drugs
- Definition of Labeling vs. Advertising
  - What is labeling?
    - Legal definition in FD&C Act
    - 201(m) “Labeling”
    - **“The term “labeling” means all labels, and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.”**
    - Physical attachment not necessary
    - Textual relationship is significant
- No “fair balance” requirements
- Use of the Internet

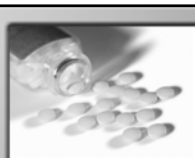
Questions and Answers

Question 1

I am a newcomer to FDA regulation of OTC drugs. Where do I begin?

Answer:

1. http://www.fda.gov/cder/Offices/OTC/industry.htm
2. Under “Other Regulatory Information”
3. See “Frequently Asked Questions”
4. Call ONP and Compliance



Question 2

I want to market my product as a cosmetic. Can I do that?

Answer:

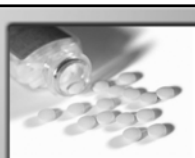
1. http://www.fda.gov/cder/Offices/OTC/industry.htm
2. Under “Other Regulatory Information”
3. See “Is It a Drug, a Cosmetic, or Both”
4. Call ONP and Compliance

Question 3

I have a competitor making claims that are not supported by the monograph or an approved NDA. Can I make the same claims?

Answer: NO.

Contact CDER Office of Compliance.



Question 4

I want to market a 1% tolnaftate for the treatment of athlete's foot (tinea pedis). What do I have to do?

Answer: Is it allowed under a monograph?

1. http://www.fda.gov/cder/Offices/OTC/industry.htm
2. Milestone listing for FR date
3. Rulemaking History for OTC Drug Products
4. Categorical listing to look up publication
5. CFR for allowed concentrations and uses
6. Registration and Listing