



# REGULATION OF NONPRESCRIPTION DRUG PRODUCTS

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# TOPICS

- **Module 1:** FDA and OTC Drugs\*
- **Module 2:** Defining OTC Drugs
- **Module 3:** The Regulation of OTC Drugs
- **Module 4:** A Closer Look at OTC NDA Drug Products
- **Module 5:** A Closer Look at OTC Monograph Ingredients

\*Nonprescription Drug Products are also known as Over-the-Counter or (OTC) Drug Products



# MODULE 1: FDA AND OTC DRUGS

- FDA Core Functions
- FDA Organization Relevant to OTC Drugs
- FDA Primary Functions on OTC Regulation
- FDA OTC Review Staff

# FDA CORE FUNCTIONS

- The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services. It consists of the following four directorates overseeing the core functions of the agency:
  - Office of the Commissioner
  - Office of Medical Products and Tobacco
  - Office of Foods and Veterinary Medicine
  - Office of Global Regulatory Operations and Policy

# 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 Clinical Evaluation**
        - **Division of Nonprescription Regulation Development**
        - Division of Medical Imaging

# OFFICE OF DRUG EVALUATION IV

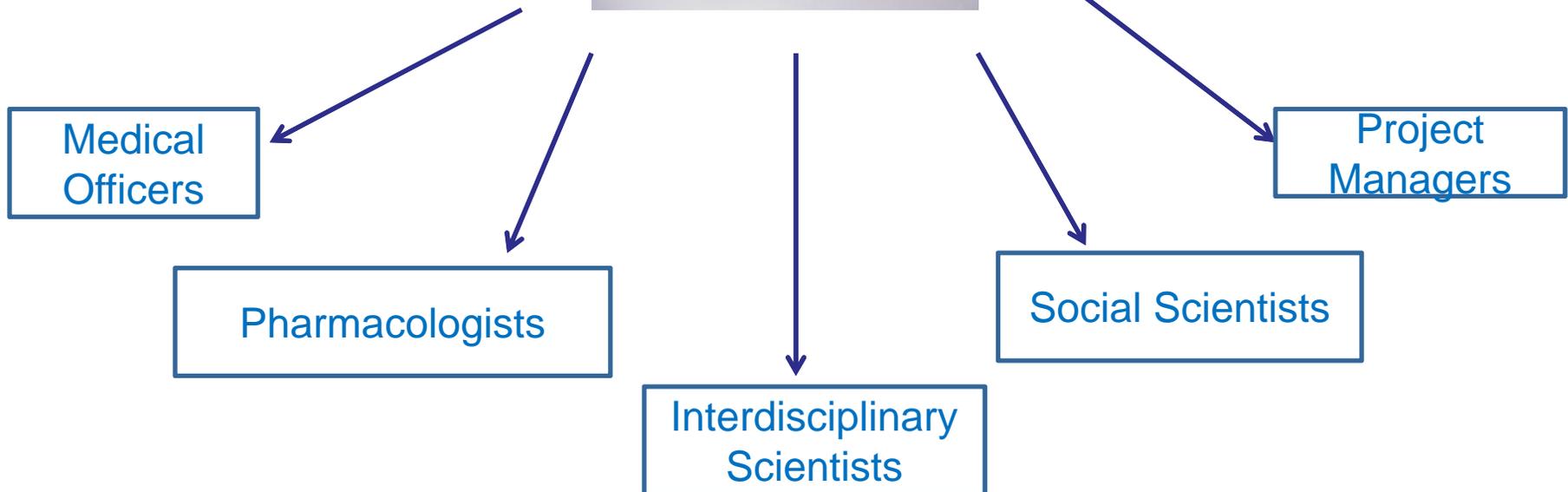
- Division of Nonprescription Clinical Evaluation (**DNCE**)
  - Oversight of OTC investigational new drug (IND)
  - Approval of OTCs marketed under New Drug Application (NDA)
- Division of Nonprescription Regulation Development (**DNRD**)
  - Development of OTC drug monographs
  - Review of OTC labels (marketed under an NDA)

# REVIEW STAFF



**DNCE**

**DNRD**



## MODULE 2: DEFINING AN OTC DRUG

- Food, Drug, and Cosmetic Act Definition of Drugs
- OTC Drugs vs. Dietary Supplements, Cosmetics, and Homeopathic Drugs
- OTC Drugs vs. Prescription Drug Products

# WHAT IS A DRUG?

## **Food, Drug, and Cosmetic Act** [FD&C Act, sec. 201(g)(1)]

- a drug is defined to include an article whose intended use is for the diagnosis, cure, mitigation, treatment, or prevention of disease or as an article that is intended to affect the structure or function of the body



# DIETARY SUPPLEMENTS

- A product taken by mouth that contains a "dietary ingredient" intended to supplement the diet
  - Examples include: vitamins, minerals, herbs or other botanicals, and amino acids
- Must be labeled as a dietary supplement
- Dietary supplements are not intended to treat, diagnose, prevent, or cure disease and cannot make such claims
- Regulated as a special category under foods

# COSMETICS

- Articles intended to be applied to the body for cleansing, beautifying, promoting attractiveness, or altering appearance
- Products can be both cosmetics and drugs. These products must meet the regulatory requirements of both cosmetics and drugs.

# HOMEOPATHIC DRUGS

A drug is homeopathic if it:

- is labeled as being homeopathic
- is listed in the Homeopathic Pharmacopeia of the United States (HPUS) or a HPUS addendum or supplement
- contains only homeopathic ingredients and diluents commonly used in homeopathic drugs

# WHEN IS A DRUG CONSIDERED A PRESCRIPTION DRUG PRODUCT?

- **FD&C Act:** A drug is regulated as a prescription drug product if it is not safe for use except under supervision of a practitioner licensed to administer the drug because of:
  - Toxicity or other potentially harmful effects
  - Method of use
  - Collateral measures necessary for use

## WHEN IS A DRUG CONSIDERED AN OTC DRUG PRODUCT?

- A drug can be over-the-counter if it can be used safely and effectively by a consumer guided by the product label - and none of the conditions that define a prescription drug are present.
- The product label is the only direction the consumer of an over-the-counter product has for safe and effective use. Therefore, the label is pivotal in determining whether a drug product can be sold over-the-counter.

# 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

# MODULE 3: THE REGULATION OF OTC DRUG PRODUCTS

- Overview of the OTC Regulatory Pathways
  - New Drug Applications (NDAs) for OTC Drugs
  - OTC Drug Review (Monograph Process)
- OTC Drug Facts Label



# NDA OR MONOGRAPH?





# NDA OR MONOGRAPH?



# OTC DRUG REGULATORY PATHWAYS

## New Drug Application

- Product specific (including formulation)
- Confidential filing
- Clinical development required
- Application submitted for approval
- Application fees (PDUFA)
- Mandated timelines
- Potential for marketing exclusivity
- Reporting requirements
- Comply with good manufacturing practices

## Monograph Process

- Ingredient and category specific regulations (CFR 330-358)
- Public process - No data confidentiality
- No clinical development
- May rely on existing data
- No user fees
- No mandated timelines
- No potential for marketing exclusivity
- Limited reporting requirements (SAEs)
- Comply with good manufacturing practices

# SAFETY REPORTING FOR OTC DRUGS

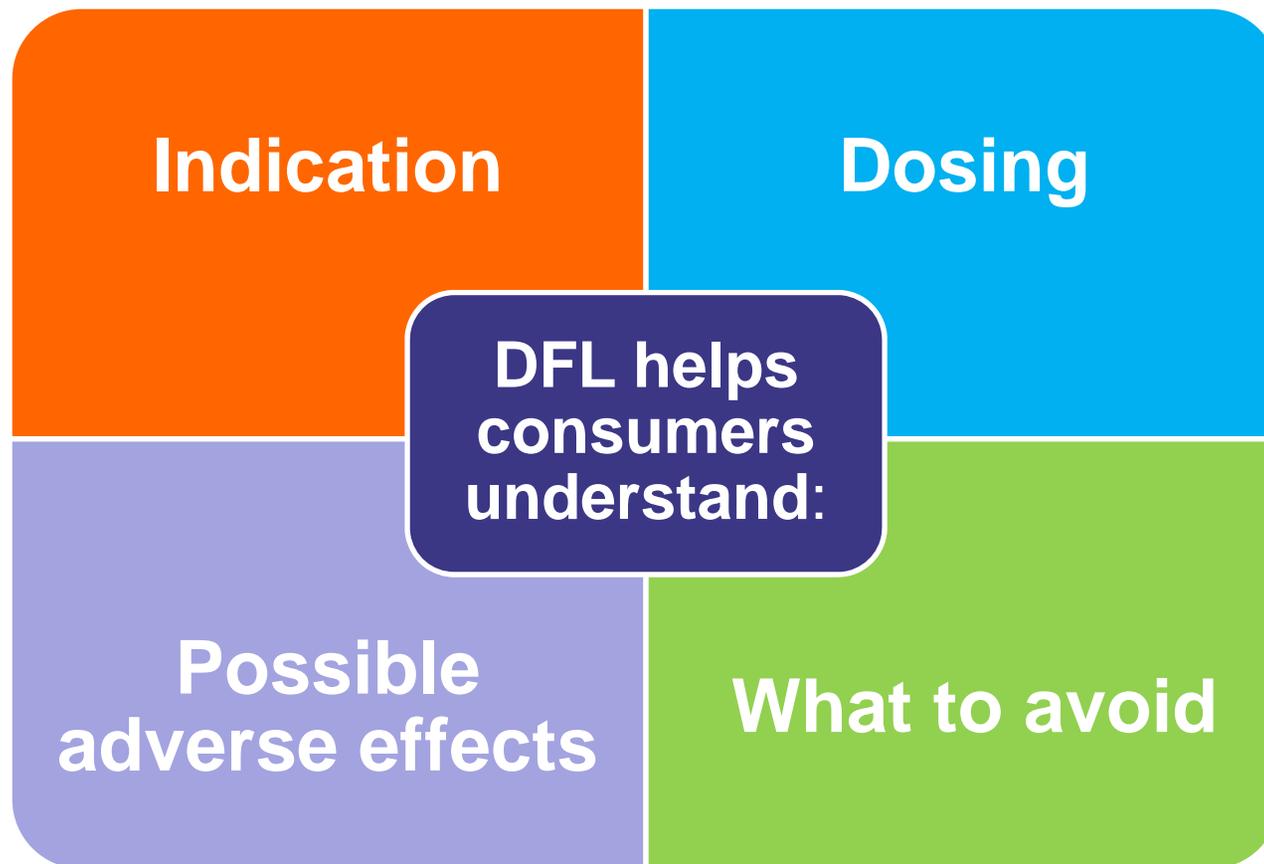
## **OTC products approved under an A/NDA**

- Subject to 21 CFR 314.80
- 15-day Alert reports and periodic reports
- Serious and non-serious adverse experiences (AEs) reported
- Foreign and domestic sources
- Follow up reports for any initial 15-day Alert reports

## **OTC monograph products**

- Subject to section 760 of the FD&C Act (effective in 2007)
- 15-day Alert reports – no periodic reporting
- Only serious AEs reported
- Domestic sources only
- Follow up reports for new medical information related to a submitted serious adverse event report that is received within 1 year of the initial report

# OTC DRUG FACTS LABEL (DFL)





# OTC DRUG FACTS LABEL EXAMPLE

<b>Drug Facts</b>	
<b>Active ingredient (in each tablet)</b>	<b>Purpose</b>
Chlorpheniramine maleate 2 mg	Antihistamine
<b>Uses</b> temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: ■ sneezing ■ runny nose ■ itchy, watery eyes ■ itchy throat	
<b>Warnings</b>	
<b>Ask a doctor before use if you have</b>	
■ glaucoma ■ a breathing problem such as emphysema or chronic bronchitis ■ trouble urinating due to an enlarged prostate gland	
<b>Ask a doctor or pharmacist before use if you are</b> taking tranquilizers or sedatives	
<b>When using this product</b>	
■ You may get drowsy ■ avoid alcoholic drinks ■ alcohol, sedatives, and tranquilizers may increase drowsiness ■ be careful when driving a motor vehicle or operating machinery ■ excitability may occur, especially in children	
<b>If pregnant or breast-feeding</b> , ask a health professional before use. <b>Keep out of reach of children.</b> In case of overdose, get medical help or contact a Poison Control Center right away.	
<b>Directions</b>	
adults and children 12 years and over	take 2 tablets every 4 to 6 hours; not more than 12 tablets in 24 hours
children 6 years to under 12 years	take 1 tablet every 4 to 6 hours; not more than 6 tablets in 24 hours
children under 6 years	ask a doctor
<b>Other information</b> store at 20-25° C (68-77° F) ■ protect from excessive moisture	
<b>Inactive ingredients</b> D&C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch	

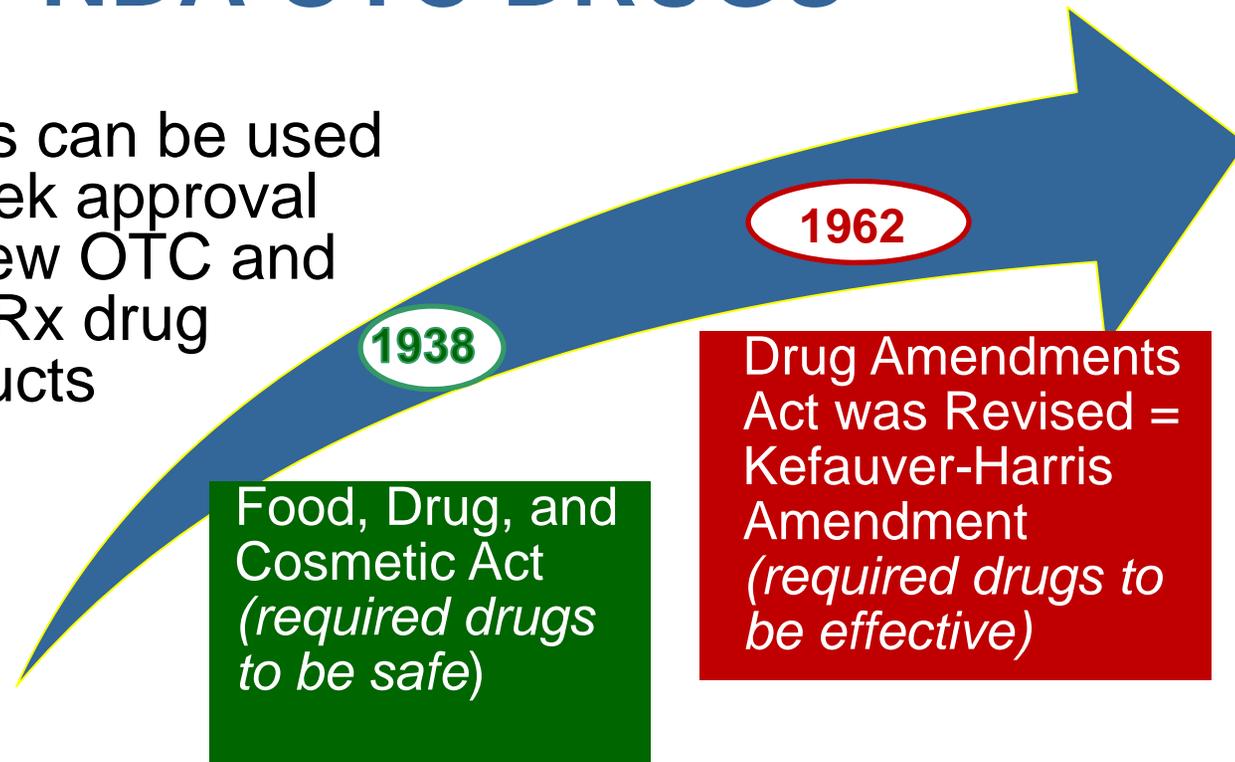
# MODULE 4: A CLOSER LOOK AT OTC NDA DRUG PRODUCTS

- Regulatory Overview of NDA Drug Products
- Comparing OTC NDAs with Prescription NDAs
- OTC Consumer Studies



# REGULATORY BACKGROUND: NDA OTC DRUGS

- NDAs can be used to seek approval for new OTC and new Rx drug products



- Abbreviated New Drug Applications (ANDAs) are used to seek approval for generic products

# Rx to OTC Switches

- **The Federal Food, Drug, and Cosmetic Act (FDCA)** does not permit Rx and OTC versions of the same drug product (e.g., same dosage form, strength, indication, and conditions of use) to be marketed at the same time. (21 U.S.C. 353(b))
- **Complete Rx-to-OTC switch**
  - Drug becomes available only OTC:
  - Example: Nicotine Replacement Therapy (gum, patch)
- **Partial Switch (most common)**
  - Drug is marketed as Rx and OTC depending on dosage form, strength, indication, etc.
  - Proton Pump Inhibitors
    - OTC Indication: Heartburn
    - Prescription Indication: Peptic Ulcer Disease, GERD

# REASONS FOR CONSUMER STUDIES

**Drug is first in its class to OTC market**

**New OTC Target Population**

**New OTC indication**

**Substantive labeling change to existing OTC Product**

**Directions not previously in the OTC marketplace**

# OTC Consumer Studies

## Label Comprehension Study

- Understanding the key label message

## Self- Selection Study

- Choosing the right product

## Actual Use Study

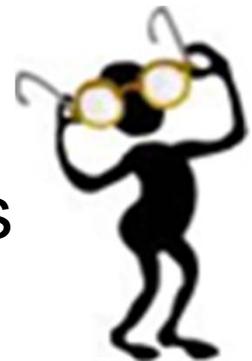
- Using according to labeled directions

## Human Factors Study

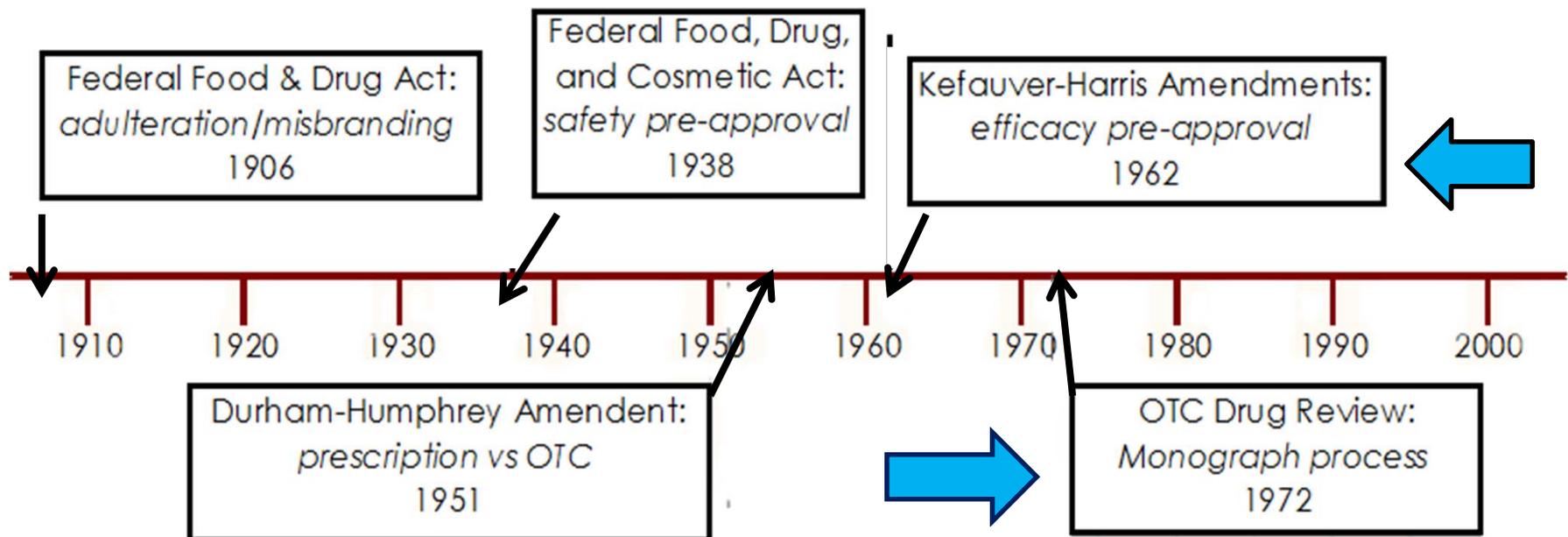
- Interacting with the product

# MODULE 5: A CLOSER LOOK AT THE OTC MONOGRAPH

- OTC Drug Review History
  - Conditions for Safety and Efficacy
  - Rulemaking Process
  - Amendments to the Monograph
- Description of a Monograph
- Time and Extent Applications
- Final Formulation Testing Requirements



# HISTORICAL DEVELOPMENT OF FDA DRUG REGULATION



## OTC DRUG REVIEW = MONOGRAPH PROCESS

- Result of 1962 Drug Amendments Act requirement that NDA products approved since 1938 needed to be shown to be not only safe, but also effective
  - Drug Efficacy Study Implementation (DESI) was implemented
  - Only 25% of 420 reviewed OTC drugs had evidence of effectiveness
  - Estimated 100,000 to 300,000 OTC products available
- Established in 1972 by FDA regulation (37 Fed Reg 85, Jan 5, 1972)

# OTC DRUG REVIEW



## Advisory Review Panel

- Comprised of expert scientists and clinicians
- Conducted reviews of existing data in the literature and submitted by industry
  - Different role than today's advisory committees
- Evaluated conditions of use for each active ingredient (dosage, indication, population, etc.)

# OTC DRUG REVIEW



Advisory Review Panel



- **Category I: GRASE (Generally Recognized as Safe and Effective)**
- **Category II: not GRASE**
- **Category III: insufficient data available to determine if Safe and Effective**

# MONOGRAPH PROCESS OVERVIEW

- Three-step public-notice and comment rulemaking process
  - Each step published in the *Federal Register*
  - Comments can be submitted and viewed at [www.regulations.gov](http://www.regulations.gov)



## 1. Advance Notice of Proposed Rulemaking

# MONOGRAPH PROCESS OVERVIEW

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1. Advance Notice of Proposed Rulemaking

2. Tentative Final Monograph



# THE REALITY OF THE MONOGRAPH PROCESS

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

# MONOGRAPH CATEGORIZATION

- Monograph categorizations can change over time based on new products and scientific developments
- Topical antiseptics for consumer use are an example
  - 1974 Advisory Panel defined ‘antimicrobial soap’
  - 1994 TFM defined ‘antiseptic handwash’
  - 2013 TFM ‘consumer antiseptics’ include:
    - antibacterial soaps
    - antibacterial wipes
    - antibacterial bodywashes
    - hand sanitizers



## EXAMPLES OF OTC DRUG CATEGORIES

- Antacids
- Laxatives
- Antidiarrheal products
- Emetics
- Antiemetics
- Antiperspirants
- Sunburn prevention/tx
- Antimicrobials
- Antitussives
- Stimulants
- Sedatives/sleep aids
- Analgesics
- Ophthalmics
- Hemorrhoidal products
- Dandruff products
- Oral hygiene aids
- Bronchodilator/asthma
- Allergies

# AMENDING AN OTC DRUG MONOGRAPH

- **FDA can initiate a change**
  - Safety
  - Effectiveness
- **Citizen Petition requesting change**
- **Time and Extent Application (TEA)**
  - A process in which a new condition is added to an existing monograph

# WHAT IS AN OTC DRUG MONOGRAPH?

- A “**rule book**” for GRASE conditions for a therapeutic category
- GRASE means generally recognized as safe and effective
- Final monographs are **regulations** published in the Code of Federal Regulations, Title 21, Parts 331 – 358 (citation example: 21 CFR 331)

# WHAT IS AN OTC DRUG MONOGRAPH?

- **GRASE 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)**
  - **Professional labeling, if appropriate for a specific ingredient and condition (not all monographs)**

# DIFFERENCE BETWEEN GRASE AND FINAL FORMULATION TESTING

- All active ingredients need to be shown to be GRASE for the specified intended use(s) before being included in a final monograph
- In addition, the monograph requires that some final formulations be tested
  - Example is sunscreen products, which often combine multiple active ingredients
  - The contribution of each active ingredient in a formulation must be demonstrated



↓

Drug Facts	
<b>Active Ingredients</b>	<b>Purpose</b>
Avobenzone 3% Homosalate 10% Octyl methoxycinnamate 7.5%	Sunscreen
<b>Uses</b>	
<ul style="list-style-type: none"> <li>• helps prevent sunburn</li> <li>• if used as directed with other sun protection measures (see <b>Directions</b>), decreases the risk of skin cancer and early skin aging caused by the sun</li> </ul>	
<b>Warnings</b>	
For external use only	
Do not use on damaged or broken skin	
When using this product keep out of eyes. Rinse with water to remove.	
Stop use and ask a doctor if rash occurs	
Keep out of reach of children. If product is swallowed, get medical help or contact a Poison Control Center right away.	
<b>Directions</b>	
<ul style="list-style-type: none"> <li>• apply liberally 15 minutes before sun exposure</li> <li>• reapply:                             <ul style="list-style-type: none"> <li>• after 40 minutes of swimming or sweating</li> <li>• immediately after towel drying</li> <li>• at least every 2 hours</li> </ul> </li> <li>• <b>Sun Protection Measures.</b> Spending time in the sun increases your risk of skin cancer and early skin aging. To decrease this risk, regularly use a sunscreen with a broad spectrum SPF of 15 or higher and other sun protection measures including:                             <ul style="list-style-type: none"> <li>• limit time in the sun, especially from 10 a.m. – 2 p.m.</li> <li>• wear long-sleeve shirts, pants, hats, and sunglasses</li> <li>• children under 6 months: Ask a doctor</li> </ul> </li> </ul>	
<b>Inactive ingredients</b>	
aloe extract, barium sulfate, benzyl alcohol, carbomer, dimethicone, disodium EDTA, jojoba oil, methylparaben, octadecane/MA copolymer, polyglyceryl-3 distearate, phenethyl alcohol, propylparaben, sorbitan isostearate, sorbitol, stearic acid, tocopherol (vitamin E), triethanolamine, water	
<b>Other information</b>	
<ul style="list-style-type: none"> <li>• protect this product from excessive heat and direct sun</li> </ul>	
<b>Questions or comments?</b>	
Call toll free 1-800-XXX-XXXX	

# A CLOSER LOOK AT TIME AND EXTENT APPLICATIONS (TEAs)

- A process to amend the OTC Monograph
- TEA data requirements

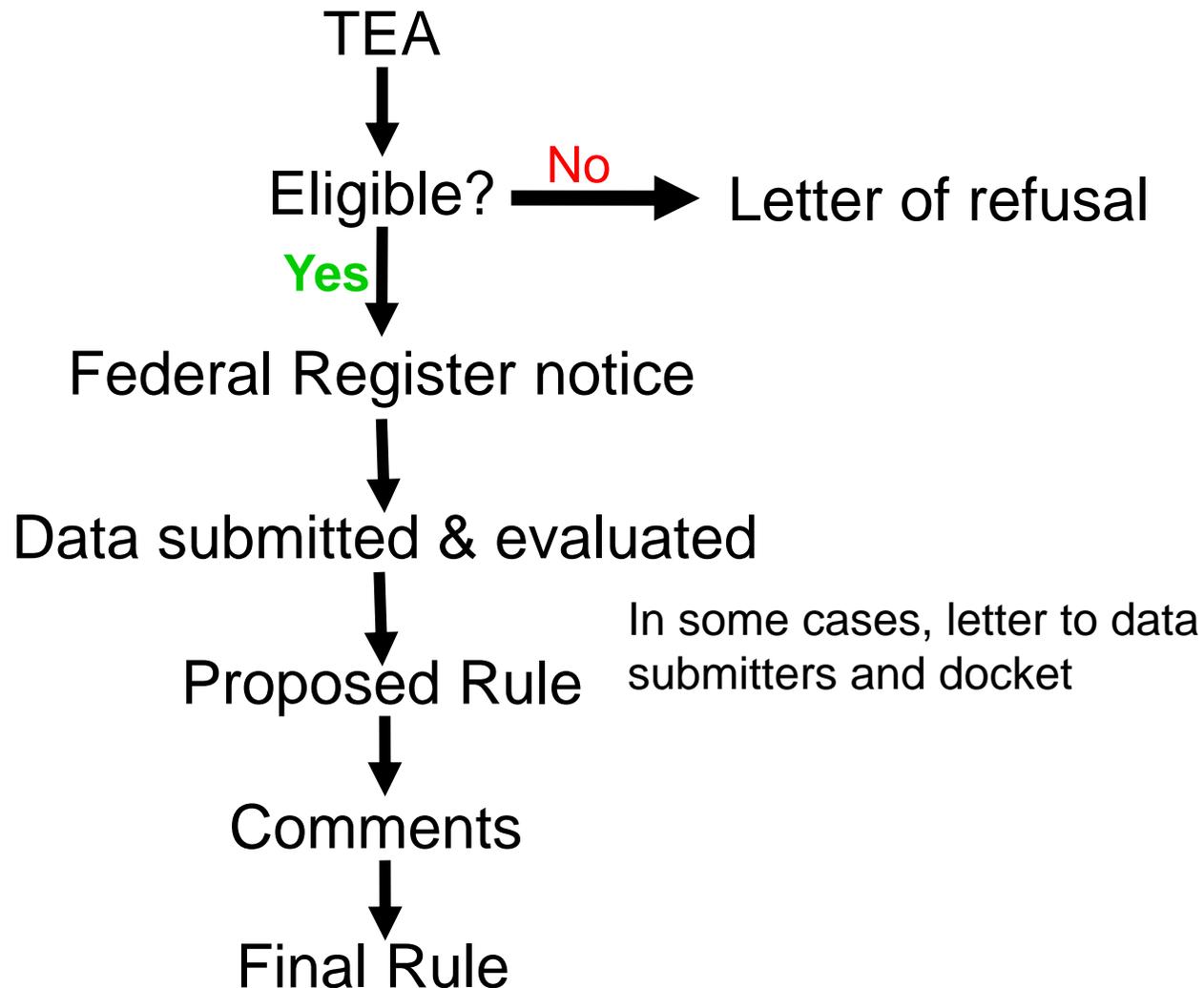
# TEAs

- Process allows active ingredients marketed elsewhere that meet certain conditions for duration and extent of marketing to be considered for inclusion in the monograph
- TEA process regulations were established in 2002
  - Can be found at 21 CFR 330.14
- Drugs that can be considered for TEAs are those:
  - Marketed in U.S. under a new drug application (NDA) after 1972
  - OR
  - With no U.S. marketing experience (21 CFR 330.14(a))
- Must have been marketed to a material extent and for a material time
- In addition to active ingredients, other ‘conditions’ may be considered under TEAs (dosage forms, dosage strength or route of administration)

## DETERMINING ELIGIBILITY

- FDA reviews applicant submission of marketing information
- To be eligible, a drug/condition must show marketing:
  - For OTC purchase by consumers
  - For at least 5 continuous years in the same country in sufficient quantity
  - In some cases, marketing history in more than one country may be necessary
- **If Eligible**, FDA makes a request to the public to submit safety and efficacy data
- **If Not Eligible**, a letter is sent to the applicant and the letter is placed in the public docket

# MULTI-STEP PROCESS





# FINAL REMARKS

# CONCLUSION

- DNRD and DNCE
  - OTC NDA drug products
  - OTC Monograph Ingredients
- OTC Drug Facts Label
  - Consumer use is paramount to OTC drug products
- OTC Drug Regulation (unique pathways)
  - Rx to OTC Switch, Time and Extent Applications
- OTC Evolution
  - Expect continued changes in the OTC realm!

# ADDITIONAL RESOURCES

- **Label Comprehension Study Guidance**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM143834.pdf>
- **Self-Selection Study Guidance**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM272122.pdf>
- **NSURE Initiative**  
<http://www.fda.gov/Drugs/ResourcesForYou/SpecialFeatures/ucm297128.htm>
- **Part 15 Hearing on Nonprescription Drug Safe Use Regulatory Expansion**  
<http://www.fda.gov/downloads/Drugs/NewsEvents/UCM301937.pdf>
- **FDA information on regulation of nonprescription products**  
<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm093452.htm>
- **Federal Dockets** <http://www.regulations.gov/>
- **Federal Register, Code of Federal Regulations, U.S. Code**  
<http://www.gpo.gov/fdsys/>