Regulation of Over-the-Counter Drugs

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FDLI's Introduction to Drug Law and Regulation
November 9-10, 2021

Hyman, Phelps & McNamara PC

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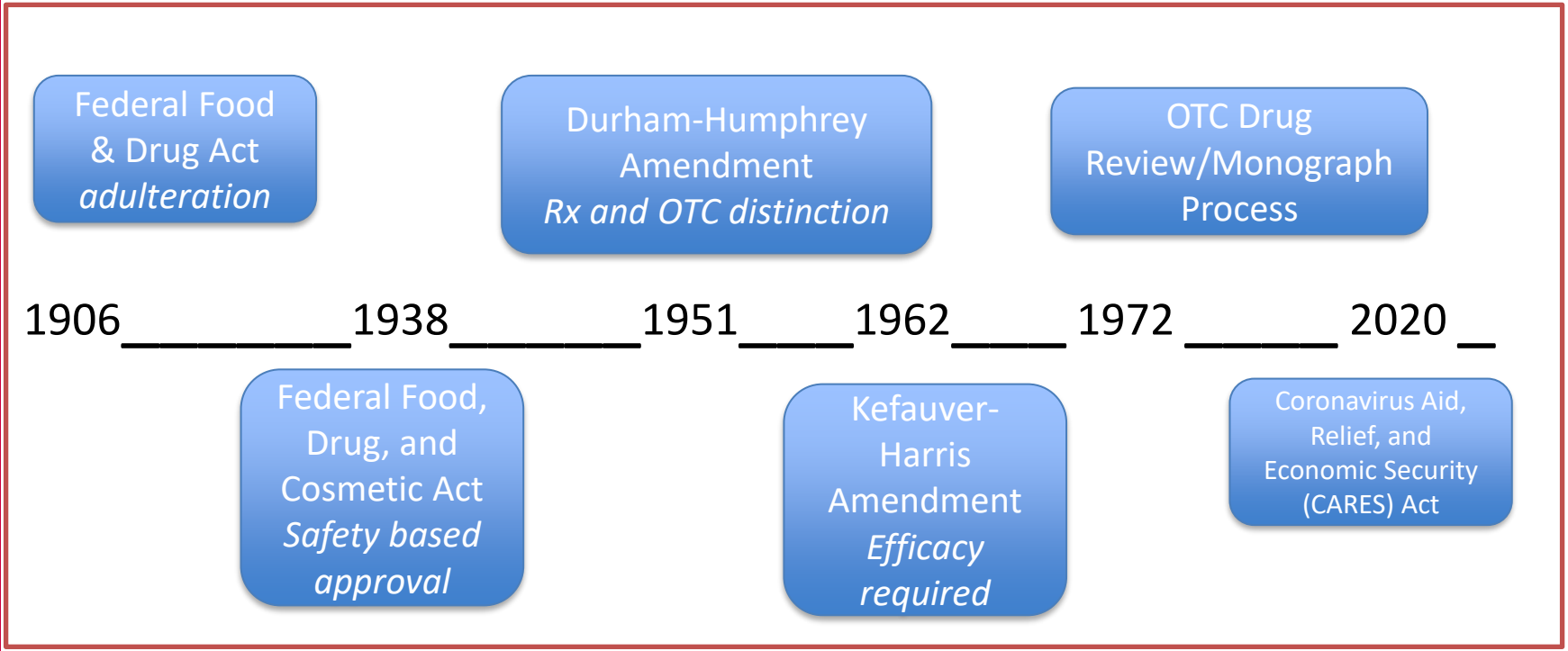
The Wide World of OTC Drugs

- Drugs are either prescription or nonprescription (OTC)
- Over 300,000 OTC drugs available in the U.S.
- Prior to 1951, no statutory provision or regulation dictated status

A Short History of OTC Drugs



What makes a drug Rx or OTC?

- Nonprescription **unless** meets criteria in FDCA § 503(b)
- Prescription drug is one that either
  - because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug; or
  - is limited by an approved application under section 505 to use under the professional supervision of a practitioner licensed by law to administer such drug.

Poll #1

What distinguishes an OTC drug from a prescription drug?

a. An OTC drug is safe enough that it can't hurt someone if they don't follow the directions.
b. A doctor does not need to examine a patient in order to tell them to use the drug.
c. The patient has to be able to figure out if they should take it.
d. It can be offered at a price that people can afford even if insurance doesn't cover it.
e. All of the above.

Characteristics of OTC Drugs

- Consumers must be able to
  - Self-diagnose (Is this the right OTC med for me?)
  - Self-treat (How much do I take? When?)
  - Self-manage (It's been 14 days, now what?)
- No health care practitioner is needed for the safe and effective use of the product
- Drug has low potential for misuse and abuse

Pathways to Market

- New Drug Application/Abbreviated New Drug Application (NDA/ANDA)

- OTC Drug Review or Monograph Process

New Drug Applications

- For single product
- Covers all ingredients, CMC, labeling

Approved Applications

- Direct to OTC NDA
  - Typically not a NCE because FDA wants some history of use prior to making it OTC
- OTC Switch
  - After some period of use as a prescription drug
- ANDA

OTC Switch

- Drug originally approved as a prescription approved for OTC use
- Full or partial switch
  - Full switch – for all the approved indications and doses
  - Partial switch – for some, but not all
    - If partial, the Rx and OTC products have to have a *clinically meaningful difference* (e.g., dose, indication, length of use)
- Can be by original sponsor or new sponsor

OTC Consumer Studies

- Label Comprehension Study
  - Can the consumer understand the key label messages?
- Self-selection Study
  - Can the consumer choose the correct product?
- Actual Use Study
  - Can the consumer use the drug safely and effectively according to the labeled instructions?
- Human Factors Study
  - Can the consumer interact with the product correctly (especially if combination product with device)?

Clinical Studies

- May be required depending on the changes from the approved Rx version
- Modifications to indication, patient population, dose may require clinical trials
- Note – actual use studies are considered clinical trials allowing for the possibility of 3-year exclusivity

OTC NDA Review

- ONDP is the lead office; reviews consumer studies
- Specific subject matter review division consulted (e.g., division responsible for dermatology or allergy drugs)
- MaPP 6020.5 (Division names are out of date)
- May go to Advisory Committee

NSURE INITIATIVE

Nonprescription Drug Safe Use Regulatory Expansion

- Initiative launched in 2012 to find ways to make more drugs currently available only by Rx available for OTC switch (i.e., expand access)
- Make more prescription drugs available OTC through the use of new technologies or other conditions of safe use

Innovative Approaches for Nonprescription Drug Products

- Draft guidance issued July 2018
- Modest in scope
- Identifies two “innovative approaches” for instances in which the Drug Facts Labeling (DFL) alone is not sufficient for OTC use

Innovative Approaches

- Labeling in addition to DFL
  - Information leaflets or other documents inside the carton or container
  - Text or images on a video display, including interactive displays for consumer review
  - Information on websites
  - Statements or questions in mobile app
- Additional conditions for safe and effective use
  - Requirement for consumer to answer self-selection questions in mobile app and "the outcome of the self-selection test affirmatively indicates that the consumer is an appropriate candidate . . . ."
  - Prior to purchase, consumer required to view and affirm they viewed text or images in a video describing how to use the product.

FDA, Draft Guidance for Industry, Innovative Approaches for Nonprescription Drug Products, 3 (July 2018)

FDA working on proposed rule to facilitate (UA Spring 2021)

OTC Drug Review

OTC Drug Review

- Efficacy requirement added in 1962
- FDA tackled the prescription drugs under the DESI program (still not completely done)
- 100,000-300,000 OTC drugs on market
- Insurmountable task to review product by product

OTC Drug Review

- OTC drugs divided into therapeutic categories
  - acne
  - antihistamines
  - external and internal analgesics
  - laxative
  - sunscreens
  - sleep aids
- Started with 26 therapeutic categories
  - more categories now, many with multiple subcategories

OTC Drug Review

Within each therapeutic category

- Grouped by more specific use or indication

  E.g., within Oral Healthcare: anticaries, toothache relief, antigingivitis/antiplaque

- Reviewed by active ingredient

OTC Drug Review/OTC Monographs

- A multistep ~~rulemaking~~ administrative order process the end product of which is a final monograph or ~~regulation~~ order which can be used as a "rule book" for marketing certain OTC drug products **without prior marketing approval from FDA**

- Through the process, a determination of conditions under which use of a drug containing identified active ingredient is "generally recognized as safe and effective" (or GRAS/E, GRASE, GRAS/GRAE)

- Each final monograph (in the form of ~~regulations in 21 C.F.R. Parts 331-358~~ administrative orders) lays out the "conditions" or requirements for marketing under that monograph, including:

active ingredients	indication/use
strength	dosing
directions for use	warnings*

*not all monographs include all these conditions and some include others

OTC Drug Regulatory Pathways

New Drug Application

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

Monograph Process

- Ingredient and therapeutic category specific regulations (21 C.F.R. §§ 330-358)
- No premarketing approval or application required
- Public process - no data confidentiality
- Typically no clinical development (no clinical trials)
- Relies upon adequate data being submitted
- No user fees (yet)
- No mandated timelines (yet)
- Limited reporting requirements (serious adverse events only)
- Comply with good manufacturing practices

Curious Concept

Eligibility for the monograph – was tied to May 11, 1972

- Only OTC drugs that were on the market before this date are eligible to be covered by a monograph
  - ingredient, use, strength

Poll #2

How to get to market – NDA or monograph?

Pain reliever works faster than aspirin for ordinary headaches. No risks of stomach issues, addiction (not an opioid), etc.

a. Monograph
b. NDA
c. Not enough info to advise

Creation of a Final Monograph (The Theory)

Beginning in early 1970s

- Advisory review panels convened for each therapeutic category (more or less)
- Industry invited to provide information about products currently on the market
  - Labels, ingredients, safety and efficacy information
- Panels were to determine if ingredients could be generally recognized as safe and effective for self-treatment, and to review claims, indications, dosing, warnings

The Theory (cont'd)

- **ANPR:** Advisory Panel Report published as an Advanced Notice Proposed Rulemaking discussing what was submitted, what the Panel concluded about the indications and ingredients. Categories for safety and for effectiveness
  - Cat I – generally recognized as safe and effective for the claimed therapeutic indication
  - Cat II – not generally recognized as safe and effective
  - Cat III – insufficient data available to determine if safe and effective

  (safety and effectiveness evaluated separately – e.g., Panel could find Cat I for safety and Cat III for effectiveness)
- **Public comment period and FDA review**
- **TFM:** FDA's proposed rule or regulation based on its evaluation of the panel report and public comments; includes proposed determination of GRAS and GRAE status for each ingredient for each use and the proposed rule
- **Public comment period**
- **FM:** Final monograph (rule) establishing conditions under which certain OTC products are GRASE

The Reality
The Long and Winding Road
Rulemaking History for OTC Topical Antimicrobial Drug Products

Topical Antimicrobial Drug Products: First Aid Antiseptic

- ANPR: 9/13/1974
- Extension of Comment Period: 10/17/1974
- TFM: 1/6/1978
- Extension of Comment Period: 2/3/1978
- Reopening of Administrative Record: 3/9/1979, 10/26/1979, 3/21/1980
- Amended TFM: Establishes first aid separate from healthcare antiseptics: 7/22/1991
- Correction: 1/9/1992
- Call for Data: Miscellaneous products: 12/31/2003

The (Very) Long, etc. (cont'd)

Topical Antimicrobial Drug Products: Healthcare Antiseptic

- Advance Notice of Proposed Rulemaking: **9/13/1974**
- Extension of Comment Period: 10/17/1974
- TFM: 1/6/1978
- Extension of Comment Period: 2/3/1978
- Proposed Rule- Establishes healthcare separate from first aid antiseptics: 6/17/1994
- Extension of Comment Period: 11/15/1994
- Reopening of Administrative Record: 5/29/2003
- Call for Data: Miscellaneous products: 12/31/2003
- Notice: Public Hearing and Request for Comment: 11/21/2012
- Amendment to TFM: Establishes GRAS/E conditions for healthcare antiseptics: 5/1/2015
- Final Rule: Finalizes rulemaking for healthcare antiseptics: **12/20/2017**

Topical Antimicrobial Drug Products: Consumer Antiseptic

- ANPR: **9/13/1974**
- Extension of Comment Period: 10/17/1974
- TFM: 1/6/1978
- Extension of Comment Period: 2/3/1978
- Reopening of Administrative Record: 3/9/1979, 10/26/1979
- Reopening of Administrative Record: Proposed Rule: Establishes healthcare separate from first aid antiseptics: 6/17/1994
- Extension of Comment Period: 11/15/1994
- Reopening of Administrative Record: 5/29/2003
- Call for Data: Miscellaneous products: 12/31/2003
- Amended TFM: Establishes consumer antiseptic washes separate from healthcare antiseptics: 12/17/2013
- Amended TFM: (Consumer Antiseptic Rubs); Tentative Final Monograph: 6/29/2016
- Final Rule: (Consumer Antiseptic Washes); Tentative Final Monograph: **9/2/2016**

40 Years Later

- Over 50 monograph categories
- 26 Final Monographs, but many only TFMs
- 15 “Negative Monographs” (final rule saying no GRAS/E conditions for that category)
- Many products marketed under TFMs with FDA exercising enforcement discretion

Shortcomings

- Takes too long to make changes
- No way to revise quickly in response to new safety information – all changes through multi-step/year rulemaking
- Products that can be marketed limited to those that were on the market in 1972; no ability to innovate

OTC Monograph Reform

- FDA and industry agreed the monograph system is “broken.”
- Over the course of several years and with public input industry and the agency worked together on a regulatory system that would address the shortcomings of the monograph system and provide funding through user fees for the new program.
- Bills pending in Congress for several years until **finally** included in the CARES Act in March 2020.

Major Changes

- Rulemakings out/administrative orders in
- New methods to (try to) make changes to monographs
- OMUFA Fees – annual facility fees and for requests for change to a monograph
- Exclusivity
- Goals Letter – Process and Timelines

Deemed Final Orders

- CARES provided that final monographs would automatically become “deemed final orders”
- FDA has started posting on website
  - OTC Monographs@FDA https://www.accessdata.fda.gov/scripts/cder/omuf/
- Will no longer appear in CFR. Only place to find on FDA’s website.
- Preambles to Fed Reg notices not included

Status of Drugs Covered by Unfinished Monographs (TFM or ANPR)

- Category I under TFM and conforms to requirements of that TFM/ANPR – not a new drug
- Category III TFM/Cat I ANPR and conforms to conditions established for Cat I – not a new drug
- Category II under TFM or ANPR = new drug needing premarket approval
- Sunscreens

OMUFA Fees

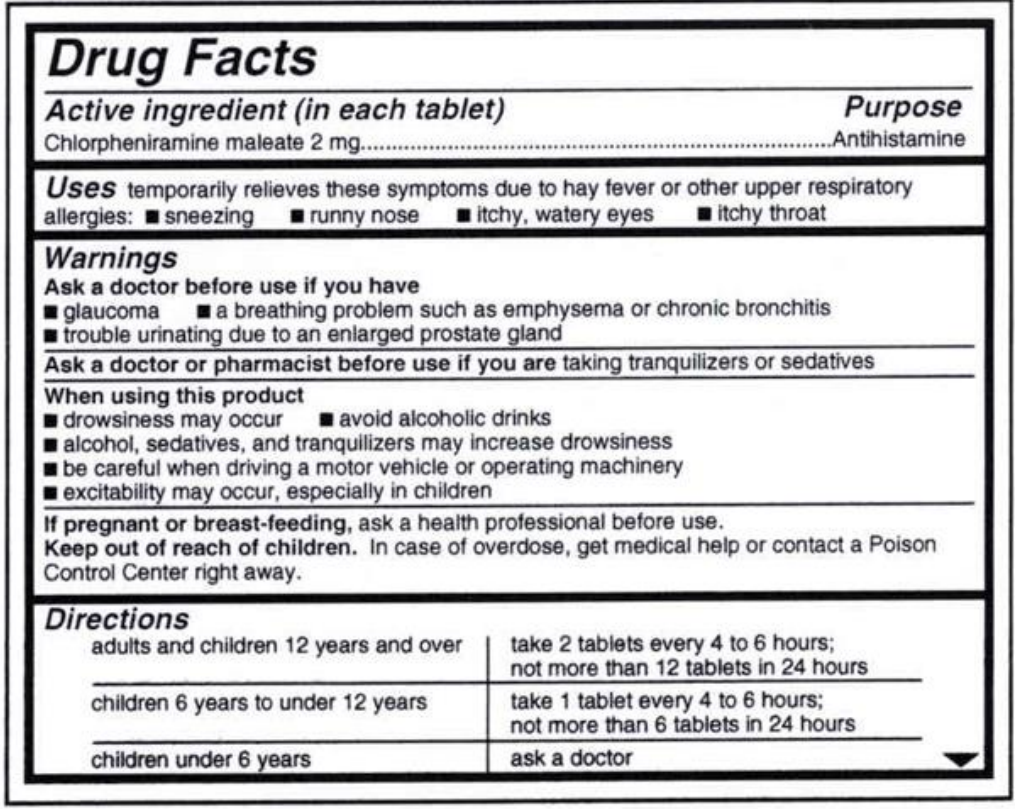
Fiscal Year (FY) 2021 User Fee Rates

FY 2021 Facility User Fee Rates	
Monograph Drug Facility (MDF) Facility Fee	$20,322
Contract Manufacturing Organization (CMO) Facility Fee	$13,548

FY 2021 OMOR Fee Rates	
Tier 1	$500,000
Tier 2	$100,000

OTC Drug Labeling

- All OTC drugs must use Drug Facts Labeling (DFL) (21 C.F.R. § 201.66)
- Substantive and format – font size, placement
- NDA drugs have label approved as part of the application approval
- OTC monograph drugs must use information in the regulations (or TFM) to craft DFL
- Also subject to labeling regs in Part 200 about net quantity, statement of identity, font size, etc.



Drug Facts

Active ingredient (in each tablet) — **Purpose**

Chlorpheniramine maleate 2 mg ..... Antihistamine

Uses temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: ■ sneezing ■ runny nose ■ itchy, watery eyes ■ itchy throat

Warnings

Ask a doctor before use if you have

■ glaucoma ■ 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 tranquilizers or sedatives

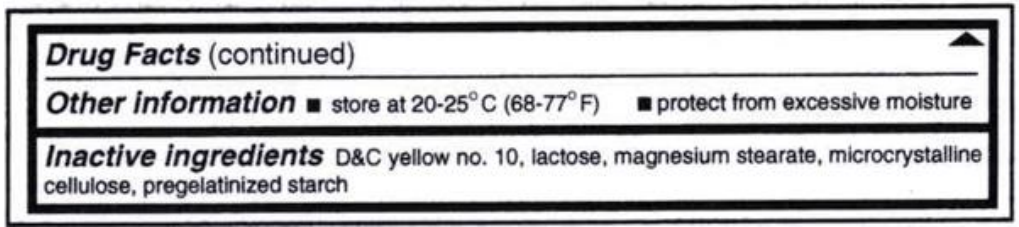
When using this product

■ drowsiness may occur ■ 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

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

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



Drug Facts (continued)

Other information ■ store at 20-25° C (68-77° F) ■ protect from excessive moisture

Inactive ingredients D&C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch

Poll #3

Which of the following are conditions that are likely to be covered in a monograph? Check all that apply.

a. Required Active ingredients
b. Permitted Inactive ingredients
c. Indication
d. Dosage
e. Directions for Use
f. Warnings

FTC Regulation of OTC Drugs

- FDA regulates labeling of OTC drugs
- FTC regulates truth or falsity of advertising (other than labeling) of **OTC** drugs
- MOU 225-71-8003 (April 27, 1971)
- Many FTC limitations and requirements related to the claims made by text/pictures outside the DFL
  - Works faster, best ever, doctor recommended
- Claims can be express or implicit, by words or pictures

Other Requirements

- **Manufacturing**: All drugs – Rx, OTC, NDA, monograph must be manufactured in compliance with current Good Manufacturing Practice requirements (cGMPs)
- **Reporting:** OTC drugs with approved applications must comply with post market report requirements in 21 C.F.R. §§ 314.80 and 314.81; monograph drugs only must report "serious adverse events" under FDCA § 760(a)(3)

Who regulates OTC drugs within FDA?

- Within CDER's Office of New Drugs
  - In Office of Drug Evaluation IV (ODEIV)
    - Office of Nonprescription Drug Products (ONDP)
      - DNDP I and DNDP II – divided by therapeutic area

- Within CDER's Office of Compliance
  - Office Unapproved Drug and Labeling Compliance (OUDLC) for OTC drugs that do not have an approved NDA or ANDA

OTC Links

- Rx to OTC Switch List
  https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm106378.htm

- OTC Monographs@FDA
  https://www.accessdata.fda.gov/scripts/cder/omuf/

- Information About OTC Monograph Reform
  https://www.fda.gov/drugs/over-counter-otc-nonprescription-drugs/over-counter-otc-drug-review-otc-monograph-reform-cares-act

Questions?

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