Regulation of Over-the-Counter (OTC) Drugs

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Introduction to US Drug Law and Regulation

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FDLI

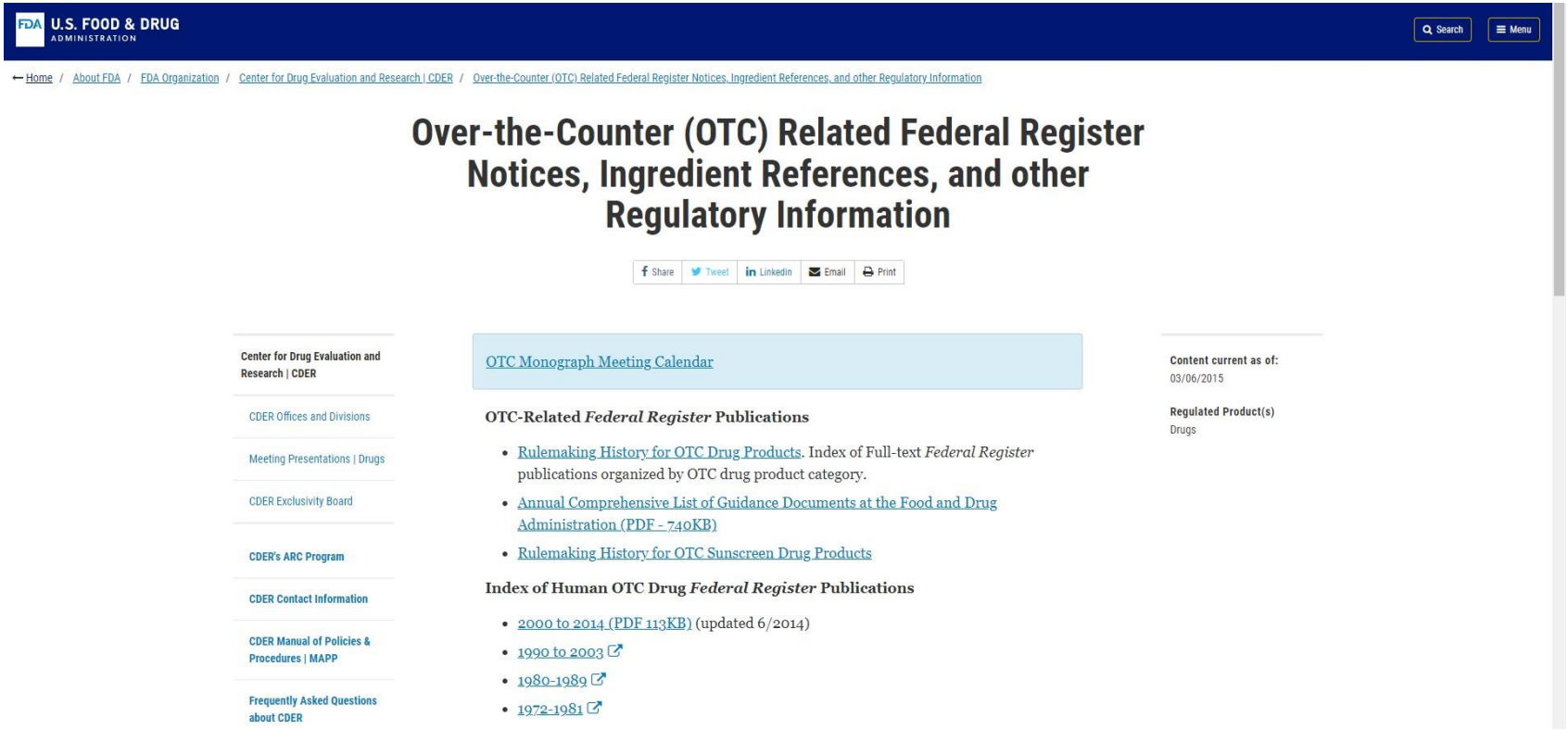
Agenda

A. Rx vs. OTC Status
B. FDA's OTC Review and Monograph Process
C. "OTC by NDA"
D. Rx-to-OTC Switches
E. Behind-the-Counter (BTC) Drugs

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, there was no statutory language or regulation that allowed for an OTC drug status
- OTC status is increasingly being sought as a way to alleviate various burdens on the U.S. health care system and to reduce out-of-pocket costs to consumers

  E.g., January 17, 2019 FDA announcement supporting switch to OTC naloxone



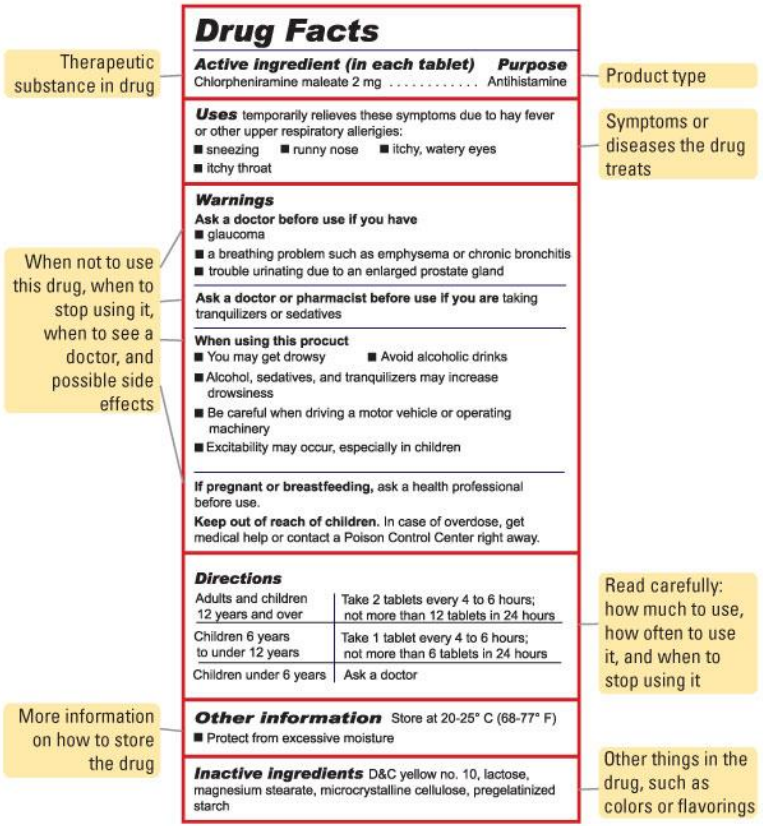
https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/over-counter-otc-related-federal-register-notices-ingredient-references-and-other-regulatory

A. Rx vs. OTC Considerations

- All OTC drugs are “drugs” and are regulated accordingly by FDA/CDER.
- Subject to the same standards for safety and efficacy, but 2 possible pathways available to market (Monograph or NDA/ANDA)
- Subject to the same regulatory requirements that apply to all drug products, including:
  - ✓ CGMP manufacturing and FDA inspections
  - ✓ Facility registration and product listing
  - ✓ Labeling in compliance with Part 201
  - ✓ Adverse event reporting

OTC Labeling: Drug Facts Label (DFL)

Criteria set forth in 21 C.F.R. § 201.66



OTC Drug Marketing: Additional Regulators

- FDA oversees OTC drug labels, while the Federal Trade Commission polices the “truth or falsity” of all advertising for this product class (under 1971 interagency agreement)
- “Advertising” regulated by the FTC is a broad concept that includes traditional media ads, websites, social media accounts owed or operated by the drug marketer, endorsements/testimonials from product users that have a material connection to the marketer, and more
- Can be anything that is intended to induce purchase of a product – whether directed to consumers or otherwise

OTC Drug Marketing: FTC Requirements

- All express and implied claims, including pictorial representations or vignettes, require appropriate substantiation
- No “fair balance” as for Rx drug advertising, but FTC looks at the “net impression” of the ad, which considers its context
- Historical development by case law/enforcement action of what is adequate to support certain types of claims:
  - “Doctor recommended”
  - Survey-based claims, e.g., “9 out of 10 consumers say”
  - Comparative claims, e.g., “our product is better than X”

  (If X is not specified, comparison is assumed to be to all competitors)

Drug Definition (FD&C Act § 201(g)(1))

"Drug" means an article:

(A) recognized in the official USP, HPUS, or NF, or any supplement;

(B) intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in mean or other animals;

(C) (other than food) intended to affect the structure or any function of the body of man or other animals;

(D) intended for use as a component of any article specified in clause (A), (B), or (C)

“New Drug” Definition (FD&C Act § 201(p))

- Any drug that is:

  (1) Not “generally recognized as safe and effective” (GRASE)

  or

  (2) Lacks a significant history of use under the conditions for which it is promoted (“material extent” or “material time”)

*Section 505(a): All new drugs must be approved under an NDA before introduction into interstate commence

1951 Durham-Humphrey Amendment

- Defined the kinds of drugs that cannot be used safely without medical supervision, and limited the sale of those drugs to prescription only by a licensed medical professional.
- Required “Rx Only” statement to be included in product labeling.
- “Prescription only” limitations (FD&C Act § 503(b)):
  - Need for a physician’s supervision due to:
    - Toxicity or other potential for harm
    - Method of use
    - Condition is not readily self-diagnosed
  - Or, such limitation has been set forth in an approved NDA
- Can “**adequate directions**” be written for layperson use? (FD&C § 502(f))

Characteristics of OTC Drugs Today

- Consumers must be able to:
  - ✓ Self diagnose (Is this the right OTC medication for me?)
  - ✓ Self-treat (How much do I take? When/how often?)
  - ✓ Self-manage (It's been 14 days, now what?)
- No health care practitioner is needed for the safe and effective use of the product.
- The drug has a low potential for misuse and abuse.
  - ➢ Case study: OTC pseudoephedrine for nasal and sinus congestion

The First Test for GRASE

- The drug must be “generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof”; and
- Such general recognition is based on adequate published data demonstrating the drug’s safety and efficacy.

The First Test for GRASE (cont'd)

- "General recognition of safety"
  - Low incidence of adverse reactions or significant side effects under adequate direction for use/warnings, and
  - Low potential for harm that may result from abuse under conditions of widespread availability
- "General recognition of effectiveness"
  - Reasonable expectation that in a significant portion of the target population, pharmacological effect of the drug when used under adequate directions for use/warnings against unsafe use will provide clinically significant relief of the type claimed

Second Test for GRASE (Time & Extent Application)

- The drug must have been used “to a material extent” and “for a material time” under the labeled conditions.
- Available for products initially marketed in the U.S. after 1972 or products with no U.S. marketing experience (i.e. foreign product)
- To be eligible for TEA consideration, the product must meet criteria:
  - ✓ The specific product (AI, dosage form, strength, intended use) must have been marketed as an OTC drug
  - ✓ Marketing must be continuous years for at least 5 years in the same country, although more than one country may be necessary
- FDA determines if product/condition in TEA is eligible for inclusion in an OTC Monograph, then safety and effectiveness review begins …

B. OTC Review and Monograph Process

- Efficacy requirement was added to the FD&C Act in 1962 (Kefauver-Harris Drug Amendments)
- That led first to the Drug Efficacy Study Implementation (DESI) program, launched in 1968, to carry out recommendations from the National Academies re. how to measure effectiveness for >4,000 marketed drugs approved on the basis of safety alone between 1938 and 1962
- DESI estimated 100,000 – 500,000 OTC drug products on the market
- Impossible to do a product-by-product review!

OTC Monograph Process: Legal Basis

- Instead, FDA determined that the majority of marketed OTC drugs contained ~200 AIs and could be grouped into 26 therapeutic categories
- A “therapeutic category” based system was established in order to create an efficient review process; kicked off in 1972 with 26 categories (but more have been added, many with sub-categories)
  - *E.g.*, Acne, Antihistamines, External/Internal Analgesics, Laxatives, Sleep Aids
- Within each therapeutic category, ingredients were grouped by more specific use or indication
  - E.g., within Oral Healthcare: anticaries, toothache relief, antigingivitis/antiplaque

Monograph Process Vision: “Efficient Review”

- OTC Drug Review officially kicked off on May 11, 1972 with FDA publication in the *Federal Register* of the final procedures, list of 26 therapeutic categories, and a “call for data” to support GRASE finding
- Developing each Monograph requires a separate, multi-step public rulemaking process to determine conditions that are GRASE (or not). It has proven quite cumbersome and expensive to implement.
- End product is a Final Monograph or regulation that can be used as a “rule book” for marketing certain OTC drug products **without prior marketing approval from FDA**.

Phase 1: Advisory Review Panels

- FDA assembles expert panels to review active ingredients and claims, and the available data supporting them, as submitted by industry.
- Expert panels are charged with determining the conditions under which OTC drugs in each therapeutic category would be considered GRASE and not misbranded. Panel report is published for feedback in the form of an Advanced Notice of Proposed Rulemaking (ANPR).
  - Category I = GRASE for the claimed therapeutic indication
  - Category II = not GRASE
  - Category III = insufficient data to determine if GRASE

Phase 2: FDA Review and Monograph Proposal

- Panel recommendations and all public feedback are considered by FDA to make final decisions about GRASE and Monograph conditions.
- FDA publishes a proposed rule/Tentative Final Monograph (TFM) that provides another opportunity for public comment or additional industry data submissions in response.
- Many products currently marketed under TFM – FDA exercises enforcement discretion and doesn't prioritize action when an OTC drug product is marketed under a TFM.
  - CPG 450.200 ("*Prior to the final publication of a proposed monograph, it would not be in the agency's interest to pursue regulatory action unless failure to do so poses a potential health hazard to the consumer.*")

Phase 3: Final Monograph Published

- After all data and comments have been reviewed, FDA publishes the final regulations for the particular drug category in the form of a Final Monograph, which is then codified in the *Code of Federal Regulations*.
- Each rule establishes all the conditions under which the covered OTC drug products are GRASE and therefore not subject to enforcement under the FD&C Act as unapproved new drugs or misbranded drugs.
- Many different reasons that not all of these are “Final” yet

Final Monograph Contents

- Each Final Monograph (in the form of regulations codified in 21 C.F.R. Parts 331-358) lays out detailed “conditions” or requirements for marketing drugs under that particular therapeutic class, including:
  - ✓ Active ingredients
  - ✓ Strength
  - ✓ Directions for use
  - ✓ Indications/uses
  - ✓ Dosing
  - ✓ Warnings*

**Not all Monographs contain required warnings; some contain other conditions*

Complying with a Final Monograph

- 21 C.F.R. Part 330 “OTC Human Drugs Which are GRAS/E and Not Misbranded”
- General provisions that apply across the board to all drugs marketed via the Monograph pathway:

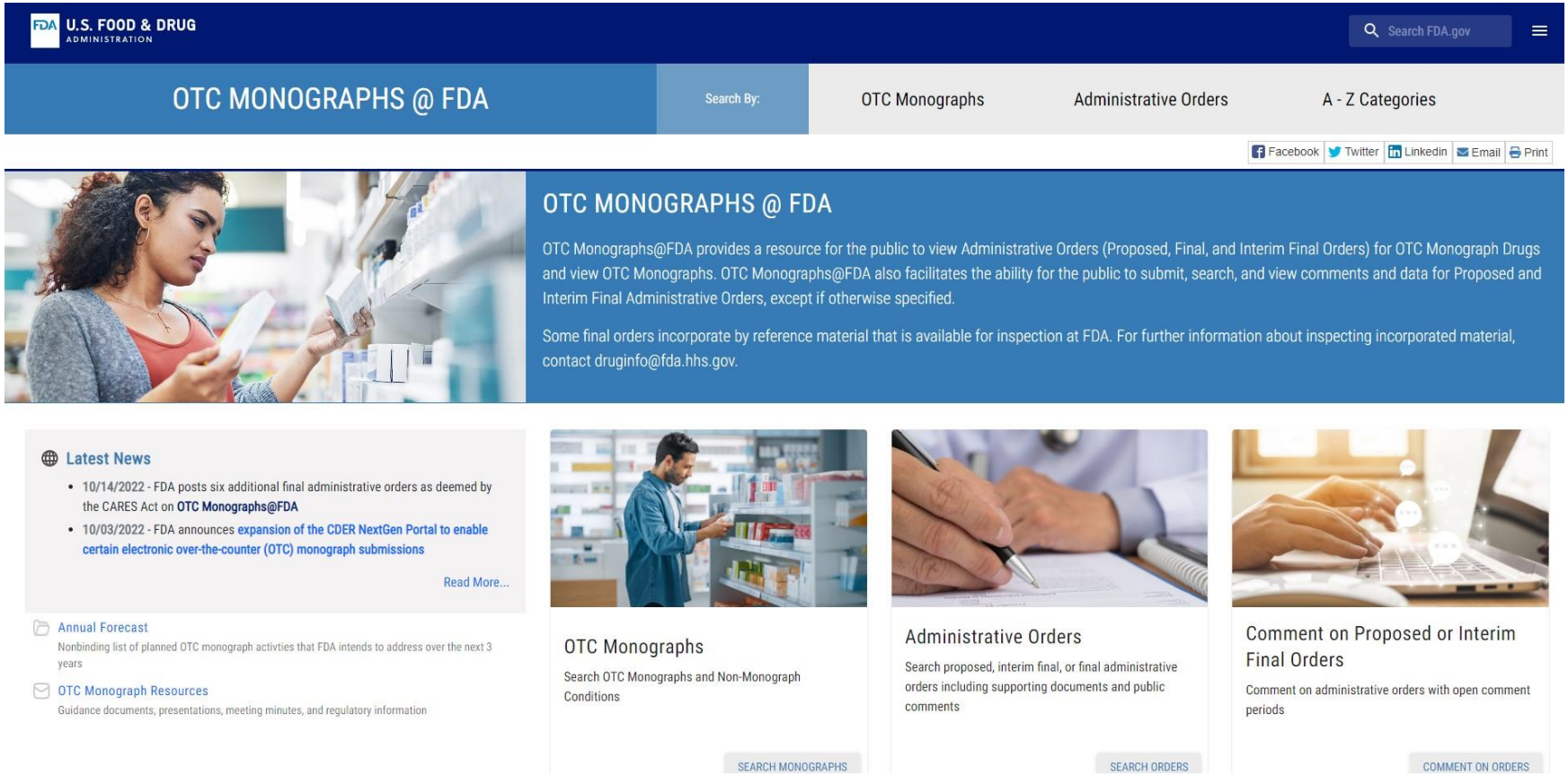
  “An over-the-counter (OTC) drug listed in this subchapter is generally recognized as safe and effective and is not misbranded if it meets each of the conditions contained in this part and each of the conditions contained in any applicable monograph. Any product which fails to conform to each of the conditions contained in this part and in an applicable monograph is liable to regulatory action.”

Monograph Challenges

- Must go through multistep rulemakings to create or amend monographs
- Inadequate FDA resources
- Delays in review and finalizing
- Limits to innovation and responding to changes in science and the industry
- Lacks process to respond to safety issues

OTC Monograph Reform

- The Coronavirus Aid, Relief, and Economic Security (CARES) Act became law in March 2020
  - Included amendments to the FDCA to modernize OTC drug regulation
- Added Section 505G to the FDCA:
  - Deemed final monographs and tentative final monographs to be final administrative orders
  - “Negative monograph” (21 CFR 310.545) also deemed a final administrative order



Final administrative orders can be found on FDA's web-portal OTCMonographs@FDA

Administrative Order Process

- Replaces the rulemaking process and gives FDA more flexibility
- Industry or FDA can initiate the administrative order process
- Expedited process for safety-related changes

Industry-Initiated Process

- Called an “OTC monograph order request,” or OMOR

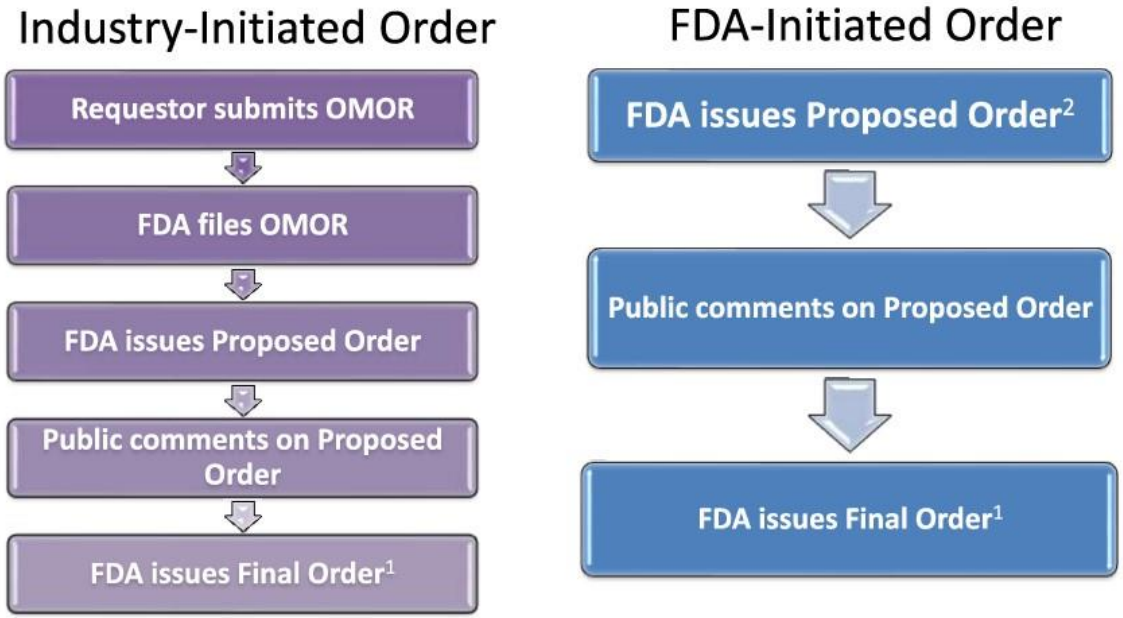
Tier 1 OMOR	Tier 2 OMOR

• Any request that is not a Tier 2 OMOR
• Examples:
  • Addition of a new ingredient to an existing monograph
  • Addition of a new indication to an existing monograph
  • Addition of a new monograph therapeutic category
	• Reordering Drug Facts label information
	• Addition of information to “Other Information” section of Drug Facts label
	• Modification to the “Directions for Use”
	• Standardization of concentration or dose
	• Change to ingredient nomenclature
	• Addition of an interchangeable term consistent with 21 CFR 330.1

FDA-Initiated Process

- Expedited procedure circumstances:
  - A drug poses an imminent public health hazard
  - A change in labeling is reasonably expected to mitigate a significant or unreasonable risk of serious adverse events
- Interim final order becomes effective prior to public comment
  - FDA issues final order after public comment

Administrative Order Process



[1] Final orders are final Agency actions subject to dispute resolution, administrative hearings, and judicial review.
[2] Or interim final order under an expedited procedure

Effect of Reform on Certain OTC Drugs

Type of OTC Drug	Impact of OTC Reform
Drugs under final monograph ***and*** Category I drugs subject to TFM	• Able to remain on the market • Innovation OMOR possible
Category I drugs subject to ANPR ***and*** Category III drugs subject to TFM	• Do not require an NDA • Able to remain on the market until FDA issues a final order • Innovation OMOR not possible, unless GRASE determination is finalized
Category II drugs	• Removed from market • Require an NDA

Exclusivity for Certain OTC Drugs

- 18-month exclusivity available to manufacturer's that request a change through an OMOR subject to a final order, providing for:
  - A drug containing an active ingredient not previously included in nonprescription drugs sold without NDAs; **OR**
  - A change in conditions of use of a drug, for which new human studies were essential to issuance of the final order
- Not available for:
  - necessary safety-related changes
  - Tier 2 OMORs
  - changes relating to methods of testing safety or efficacy

OTC Drug User Fees

- CARES Act included the Over-the-Counter Monograph User Fee Act, or OMUFA
  - New user fee program requiring OTC drug manufacturers to pay fees to fund FDA's regulatory activities

FY 2022 Facility User Fee Rates	
MDF Facility Fee	$24,178
CMO Facility Fee	$16,119

FY 2022 OMOR Fee Rates	
Tier 1	$507,021
Tier 2	$101,404

Formal Meetings with FDA

- OTC monograph drug manufacturers may request meetings with FDA to discuss topics such as:
  - Studies or other information necessary to support submissions
  - Regulation of OTC monograph drugs
  - Development of new OTC monograph drugs

Types of Meetings

	Purpose	FDA Response Time	Scheduling Time
Type X	• Necessary for an otherwise stalled OTC monograph order development program to proceed • Necessary to address an important safety issue	14 days	30 days

Type Y	• Milestone discussions during OTC monograph order development program, such as
	  • Overall data recommendations meeting
	  • Pre-OMOR submission meeting
		14 days	70 days

Type Z	• Any meeting that is not Type X or Y	21 days	75 days

OTC Monograph Reform Guidance

- Draft guidances
  - Formal Meetings Between FDA and Sponsors or Requestors of Over-the-Counter Monograph Drugs (February 2022)
  - Providing OTC Monograph Submissions in Electronic Format (September 2022)
  - Assessing User Fees Under the OTC Monograph Drug User Fee Program (October 2022)

Additional Considerations for Nonprescription Use

- New proposed rule creating conditions for a manufacturer to bring a nonprescription drug to market through NDA/ANDA process
- When labeling alone cannot ensure safe consumer self-selection and use, may propose an additional condition for nonprescription use
- Must submit a NEW NDA/ANDA (not a supplement) proposing an additional condition
  - E.g., an applicant could propose that consumers must respond to a set of self-selection screening questions via mobile app or automated telephone system

C. “OTC by NDA”

- When an OTC Monograph “recipe book” is not available for your new product, the drug must be approved before market launch via an NDA (or ANDA) that authorizes non-prescription sale of the drug. Post 1971-innovations are all approved this way due to lack of a Monograph!
  - Ibuprofen
  - Nicotine replacement therapy
  - Colgate Total toothpaste
  - Allergy medications
  - Miconazole anti-fungal
- Standard NDA requirements apply + an additional requirement to demonstrate the drug can be used safely OTC and doesn’t meet the prescription criteria in Section 503(b).

NDA vs. OTC Monograph

New Drug Application	Vs.	OTC Monograph
Product specific (inc. formulation)	✗	Ingredient/therapeutic cat. specific orders
Premarketing approval required	✗	No premarketing approval or application
Application submitted to FDA	✗	Initial OMOR for monograph
Confidential filing	✗	Relies upon submission of adequate data
Clinical development required	✗	Typically no clinical development
Application fees (PDUFA)	✓	Application fees (OMUFA)
Mandated timelines	✓	Mandated timelines for OMOR
Potential for marketing exclusivity	✓	**Limited** potential for marketing exclusivity
Reporting requirements/CGMPs	✓	**Limited** reporting requirements SAE/CGMP

D. Rx to OTC "Switches"

- When a drug originally approved as a prescription product is subsequently approved for OTC use
- Can be a "full" or "partial" switch
  - Full switch – for all the approved indications or uses
  - Partial switch – for some but not all
- If a partial switch is sought, the Rx and OTC products must have clinically meaningful differences (*e.g.*, dose, indication, length of use)
  - Rx ibuprofen is approved at a greater dose than what's available OTC

"Switch" Procedures

- By submission/FDA approval of an Efficacy Supplement to an existing NDA for the Rx product (often requires consumer studies)
  - Allergy drugs, *e.g.* "Claritin"; "Zytec"; "Allegra"; "Xyzal" (most recent 1/2017)
  - Emergency contraception, *e.g.* "Plan B"
  - Yeast infection/antifungals, *e.g.* "Monistat"; "Lamisil"; "Lotrimin"
- By Creation or Amendment of a New or Existing Monograph
- By Citizen Petition (with full data to support the switch)

Need to be able to "translate" key elements of Rx drug label into consumer-friendly terms and the DFL

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 a combo product with a device)?

Clinical Studies

- May be required in a Switch Application, depending on the changes from the approved prescription version
- Modifications to indication, patient population, or dose may require clinical trials
- Note – actual use studies are considered clinical trials, allowing for the possibility of 3-year NDA exclusivity. There's lots of interesting case law/administrative history involving challenges to 3-year exclusivity for supplemental NDAs that contained "new clinical investigations" necessary to support the switch decision.

E. Behind-the-Counter (BTC) Drugs

- Congress has authority to regulate a particular drug or class of drugs in a more restrictive way than FDA may have done – *e.g.*, PSE history
- Certain conditions are placed on the otherwise unrestricted OTC availability of the drug, such as requiring the pharmacist to check ID or provide specific information prior to sale. In many ways, the proposed rule for ACNU has displaced the push to simply expand BTC category
- Arguments in favor of an in-between category of BTC products include:
  - ✓ Pharmacist education and an increased interaction with patients to ensure safe and effective use
  - ✓ Increased patient access to drugs that might otherwise be underutilized, especially in patients without health insurance

Questions?

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