FDA Regulation of Over-the-Counter Drug Products

Presented By:
Carolina Wirth, Of Counsel
Arnall Golden Gregory LLP
Carolina.Wirth@agg.com

Genevieve Razick, Associate
Arnall Golden Gregory LLP
Genevieve.Razick@agg.com

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FDLI

Over-the-Counter Drug Products

- OTC drugs play a big role in our healthcare system with more consumers leaning towards self-medication.
- The global OTC drug market revenue is expected to exceed $178B by 2024.
- More than 80 therapeutic categories for OTC drugs products.
- Over 300,000 marketed OTC drugs products.

Polling Question #1

Prescription vs. OTC Drugs

- 1951 Durham-Humphrey Amendments to the Federal Food, Drug and Cosmetic Act (FD&C Act).
- Defines a prescription drug as:

A drug intended for use by man which

(A) 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 ...

21 U.S.C. § 353(b)(1)

Prescription vs. OTC Drugs

- Statute does not define OTC Drugs
  - anything that does not meet the Rx definition could potentially be sold as an OTC drug
- 1962 Kefauver-Harris Amendments to the FD&C Act
  - established a framework that required drug manufacturers to prove scientifically that a medication was not only safe, but also effective.

Requirements for all OTC Drugs

- Standards for safety and efficacy
  - same as for Rx drugs but requires adequate labeling so consumers are able to self-diagnose, self-treat, and self-manage
- Have low potential for abuse or misuse
- Compliance with Good Manufacturing Practices (inspections)
- Labeling must adhere to 21 C.F.R. § 201.66

Two current regulatory pathways

(1) OTC Monograph Reform (Formerly OTC Drug Review)

- Established in March 2020 after the enactment of the CARES Act
- Based on the determination made under the OTC Drug Review Process (1972-2020) as to whether certain active ingredients and indications were Generally Recognized As Safe and Effective (GRASE) for use in OTC drugs products.

(2) OTC New Drug Application (NDA)

- the FD&C Act does not differentiate between prescription and OTC drugs with respect to new drug status

New Drug Application (NDA) Process

- Product specific
- Confidential
- Clinical development required
- Application for approval + fee
- Adverse event reporting requirements
- Good manufacturing practices

OTC Drug Review (1972-2020)

- Most OTC drugs are marketed pursuant to the OTC Drug Review (started in 1972 and was never completed)
- Utilizing independent panels of experts, FDA tentatively classified OTC drugs into one of three categories:
  - Category I, GRASE, and not misbranded
  - Category II, not GRASE or unacceptable indications
  - Category III, insufficient data for final classification

OTC Drug Review

- The administrative process generally included three steps:

  (1) publication of the expert panel's report as a proposed monograph

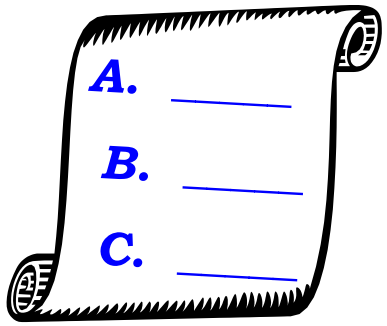
  (2) publication of FDA's own review of the report and public comments, known as a "tentative final monograph" (notice-and-comment rulemaking)

  (3) publication of a final regulation, known as the final "monograph," which prescribes the ingredients and labeling for OTC drugs in the category which are GRASE and not misbranded and, therefore, do not require FDA premarket approval

Monographed Drugs

- Once a monograph was final, any drug within the category could only be marketed in compliance with the monograph
- Think of it as a recipe or formula -- if a firm follows the recipe, it can market the product without an NDA or FDA approval
- Established for therapeutic classes of drugs, not individual products

Monographs



- Monographs Included:
  - Active ingredients that are GRASE; specific indications, directions for use, and warnings; any required finished formulation testing; usually states in general terms the dosage form required
    - e.g., antacid products must be "in a form suitable for oral administration."
  - Some monographs addressed more specific dosage forms
  - Final monographs were published in the Code of Federal Regulations: 21 C.F.R. parts 331-358

Monographs

(cont'd)

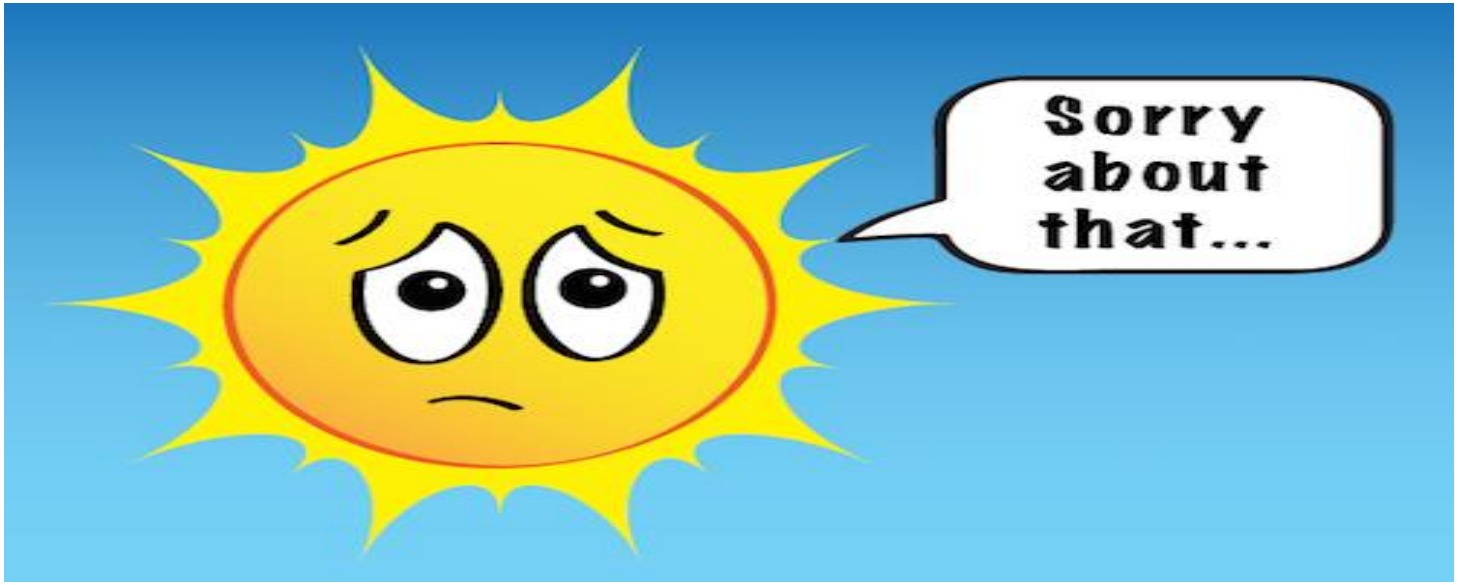
When the Final Monograph was published, only products containing ingredients and claims included in the monograph could be marketed

- other OTC drugs required NDA approval or an amendment to the monograph to be marketed (This has been modified by the CARES Act)

OTC Drug Categories – Some Examples

- Antacids
- Sleep aids
- Wart removers
- Cough and cold products
- Dandruff products
- Antiperspirants
- Analgesics

OTC Drugs: Some Unexpected Products



Sunscreen Drug Claims

- to help prevent sunburn
- decrease the risks of skin cancer caused by the sun
- other examples: toothpaste and hand sanitizer

Issues with old OTC Monograph Process

- Slow and cumbersome rulemaking process
- Limited/lack of resources (e.g., funding/personnel)
- Agency backlog and slow responses (e.g., responding to urgent safety issues)
- Final Monographs delayed
- Limited opportunities for innovation

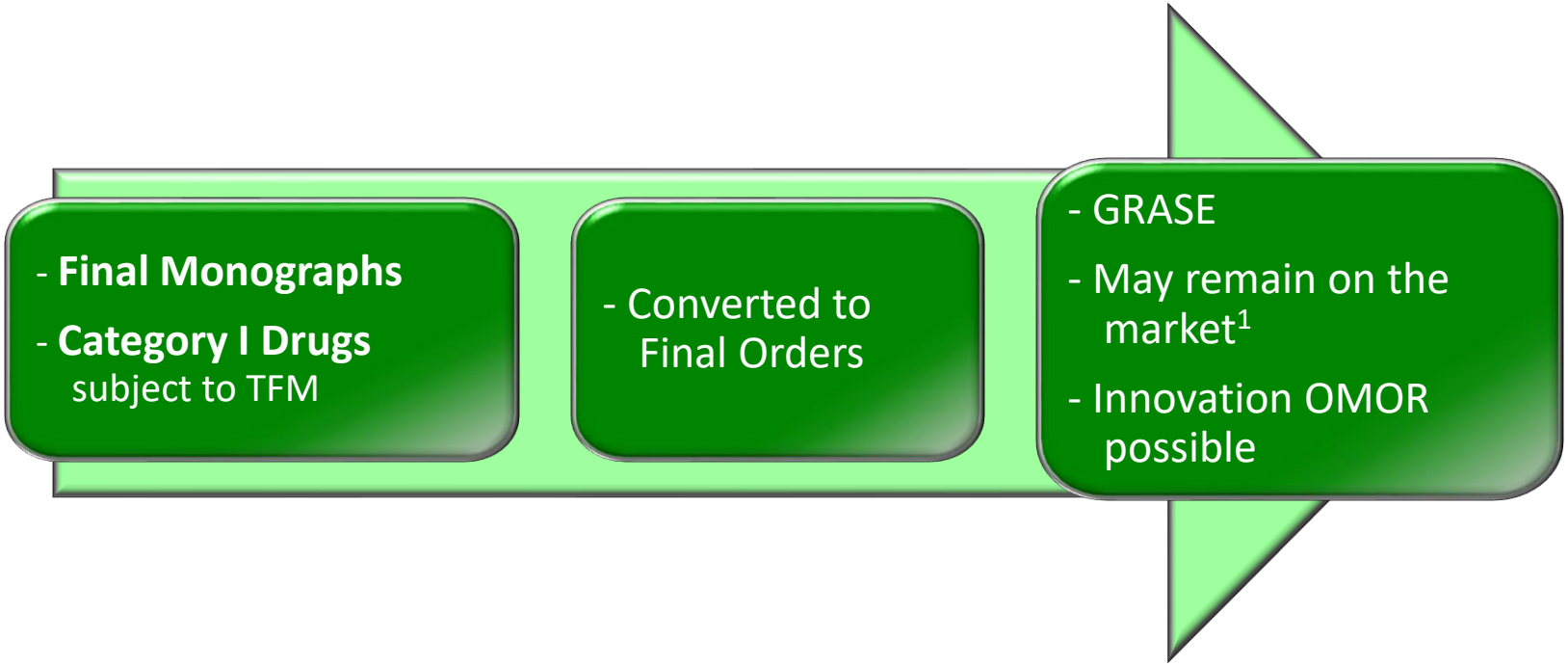
The CARES Act

- On March 27, 2020, the President signed into law the Coronavirus Aid, Relief, and Economic Security Act, or "CARES" Act (Pub. Law 116-136).
  - modernizes the OTC Drug Review process
  - includes new provisions related to OTC user fees and 18-month exclusivity
  - utilizes final administrative orders instead of notice-and-comment rulemaking
  - Establishes the **OTC Monograph User Fee Act** (OMUFA) (User fee section of OTC Monograph Reform in CARES Act)
    - OMOR Fees
    - OTC Monograph Facility Fees

Modernized OTC Drug Review

- FDA may issue a final administrative order to add, remove or change a GRASE condition for an OTC drug monograph
  - Can be initiated by FDA or industry
- Expedited process to address safety issues
- Maintained the GRASE determinations and allows certain drugs in compliance with an OTC monograph and other requirements to continue to be marketed

Modernized OTC Drug Review



[1]**May remain on the market if in conformity with all applicable requirements**

Source: FDA Webinar, Monograph reform is here!

Modernized OTC Drug Review

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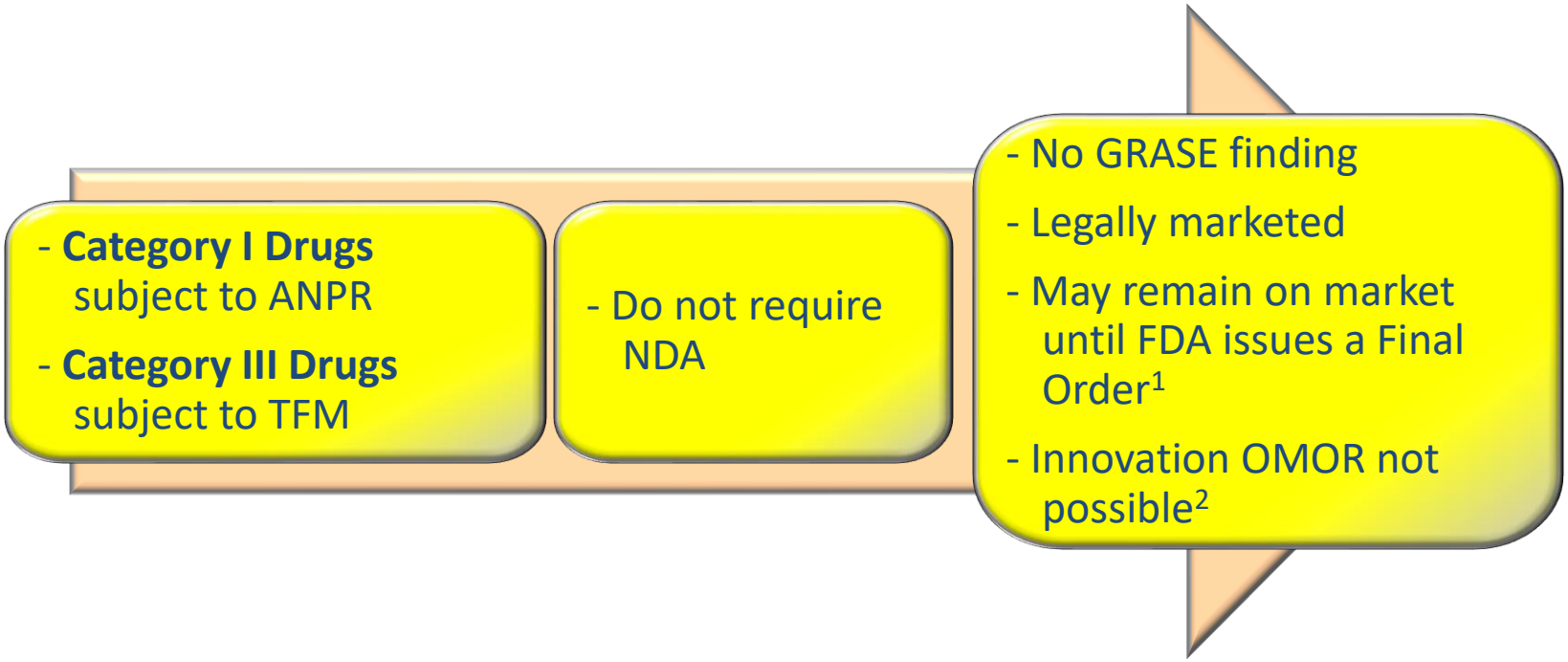

[1] May remain on the market if in conformity with all applicable requirements

[2] Unless a GRASE finalization occurs at the same time

Source: FDA Webinar, Monograph reform is here!

Modernized OTC Drug Review

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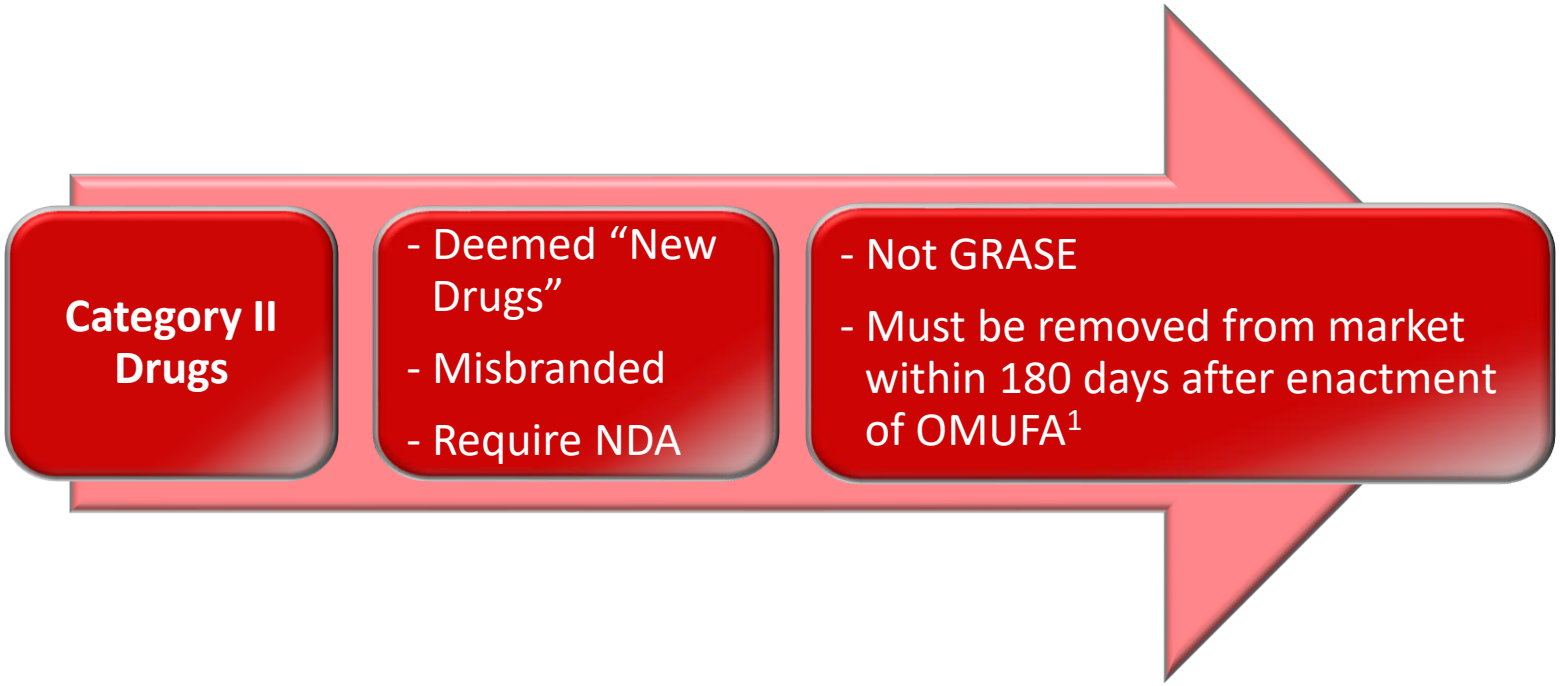


[1] Unless FDA determines that it is in the interest of public health to extend the period during which the drug may be marketed without an approved NDA

Source: FDA Webinar, Monograph reform is here!

Modernized OTC Drug Review

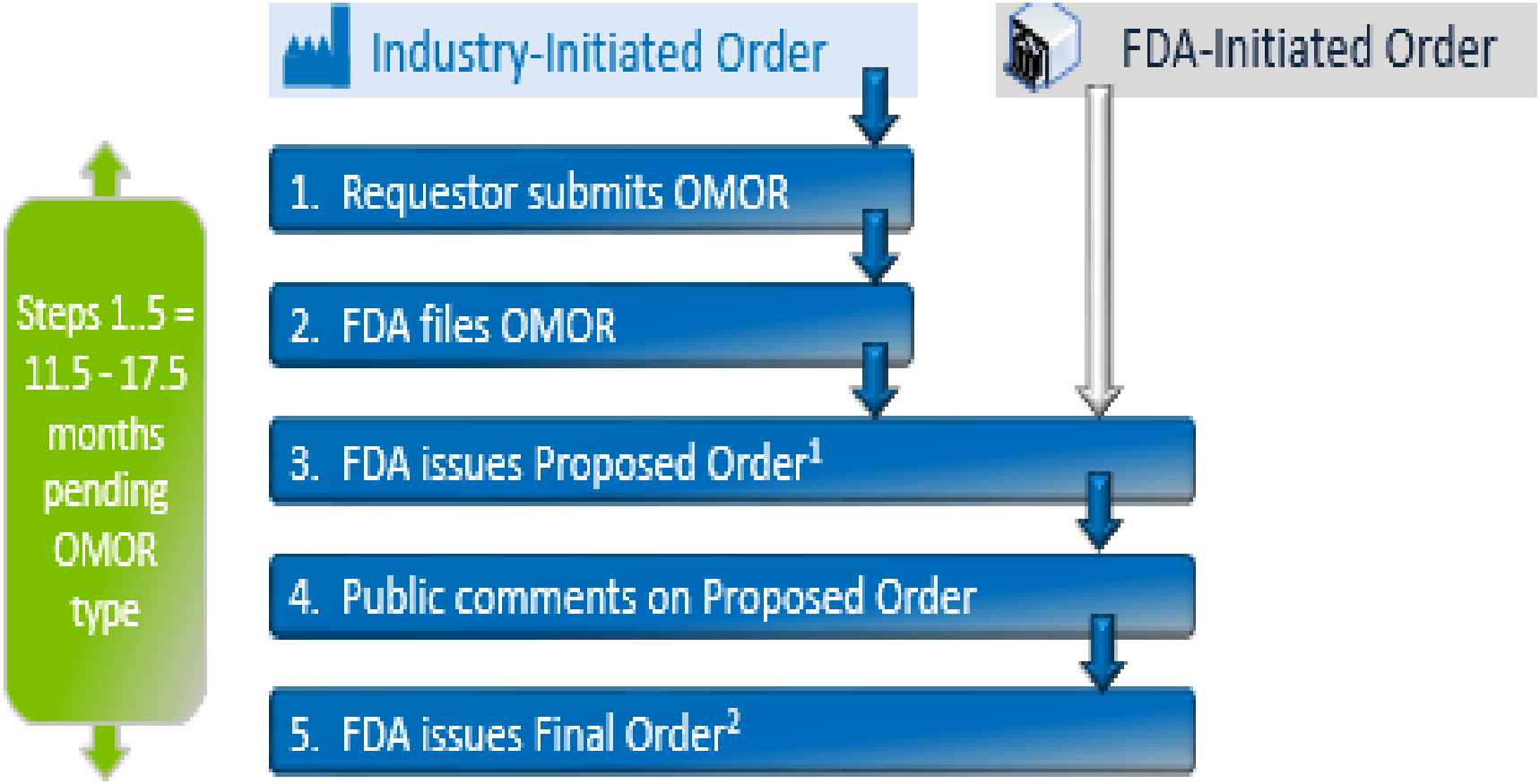
(cont'd)

The OTC monograph order request (OMOR) is used to request FDA to issue an administrative order. There are two types of OMORs:

- Tier 1 OMOR
  - Addition of a new ingredient to a monograph that already has one or more ingredients that have been found to be GRASE
  - Addition of a new indication to a monograph that already has one or more ingredients that have been found to be GRASE, and the new indication applies to one or more of the GRASE ingredients
- Tier 2 OMOR
  - Reordering of existing information in the Drug Facts label (DFL)
  - Modification to the "Directions for Use" section of the DFL

Administrative Order Process

(Source: FDA webinar, Monograph reform is here!)



Expedited Administrative Order

- FDA can initiate expedited procedures when:
  - (1) a drug poses an imminent hazard to the public health, or
  - (2) there is a change in the labeling of a drug, class of drugs, or combination of drugs that is reasonably expected to mitigate a significant or unreasonable risk of a serious adverse event associated with use of the drug

- FDA issues an interim final order and, after public comment, a final order.

- FDA is currently drafting guidance documents to implement OTC Monograph Reform.

Polling Question #2

OTC Monograph Facility Fees

- FDA will collect an OTC Monograph Facility Fee starting with fiscal year 2021.
- The CARES Act required FDA to establish the facility fees by the second Monday in May, and the fees were due on the later of the first business day of July 2020, or 45 calendar days after publication of a Federal Register Notice.
- The Federal Register Notice has not been published as of November 11, 2020.
- For subsequent fiscal years after 2021, the facility fees will be due on the later of the first business day of June, or the first business day after the enactment of an appropriations act providing for the collection and obligation of fees for the year

Rx to OTC Switch Process

FDA Considerations

- Can the condition be adequately self-diagnosed?
- Can the condition be successfully self-treated?
- Is the self-treatment product safe and effective for consumer use, under conditions of actual use?
- How long has the drug been marketed as Rx?

Example: Claritin vs. Mevacor

Claritin – Successful Rx to OTC Switch

- temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:
  - runny nose
  - itchy
  - watery eyes
  - sneezing
  - itching of the nose or throat

Example: Claritin vs. Mevacor

Mevacor – Unsuccessful Rx to OTC Switch

- used for the primary prevention of Coronary Heart Disease
- in individuals without symptomatic cardiovascular disease, average to moderately elevated total-C and LDL-C, and below average HDL-C, MEVACOR is indicated to reduce the risk of:
  - Myocardial infarction
  - Unstable angina
  - Coronary revascularization procedures

Polling Question #3

OTC Drug Studies

- Label comprehension studies
  - assesses the extent to which consumers understand the information on OTC drug product labeling and how well they apply this information when making drug product-use decisions in a hypothetical situation
- Actual use studies
  - is the product being used in accordance with labeled directions

OTC Drug Studies

- Self selection studies
  - test whether consumers can apply the label information to their personal medical situations and make correct decisions about whether it is appropriate for them to use or not use the drug product
- Human factors study
  - interacting with the product

"Forced" Rx to OTC Switch

- Only one historical example of FDA attempting the switch of a Rx drug to OTC status on its own initiative and over the objections of the product's sponsor.
  - 1982, FDA issued a tentative final monograph which included metaproterenol for asthma (sulfate metered-dose inhalers)
  - due to extensive negative comments, the agency rescinded its decision shortly thereafter
- FDA has indicated its preference now to "stimulate," switches rather than force them.

Rx to OTC Switch by NDA

- sNDA (efficacy supplement): if there are no changes to the dosage form, route of administration, and indication
- New NDA: if there are differences between the marketed product and proposed OTC product
- 505(b)(2) NDA: if the sponsor is using a study not conducted by the sponsor (and no right of reference)

Partial OTC Switches

- Partial OTC Switches: prescription versions of Rx-to-OTC products
  - e.g., topical antifungals for athlete's foot, ringworm, and jock itch (treatment of Tinea versicolor is still an Rx indication)
- The FD&C Act does not permit both Rx and OTC versions of a drug to be marketed simultaneously, this does not apply to different dosage forms, strengths, indications, and so forth
- Partial switch will require a new NDA

The Switch Regulation

- Following enactment of the Durhman-Humprhrey Amendments to the FD&C Act, FDA switched a number of drugs to OTC status using a rulemaking approach (the "switch regulation"), authorized under section 503(b)(3) of the FD&C Act, codified at 21 C.F.R. § 310.200
  - used in the 1950s and 60s when certain drugs were marketed by different companies under different conditions, some "Rx" and some OTC, even if the drugs had identical dosage and indications
  - FDA has not used the "switch regulation" to switch a drug since 1971

OTC Drug Labeling Requirements

- Drug Facts labeling
  - intended to make it easier for consumers to read and understand OTC drug product labeling
  - helps consumers use OTC drug products safely and effectively
- Applicable regulation: 21 C.F.R. § 201.66

OTC Drug Labeling Requirements

(cont'd.)

- Title (Drug Facts or Drug Facts (continued))
- Active Ingredients
- Purpose(s)
- Use(s)
- Warning(s)
- Directions
- Other information
- Inactive ingredients
- Questions? Or Questions or comments: (optional)

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

OTC Advertising

- The Federal Trade Commission regulates OTC drug advertising
    - truthful
    - substantiation
    - fair
- FDA regulates the Labeling of OTC Drugs – Office of Nonprescription Drugs (OND)
- The Office of Prescription Drug Promotion (OPDP) regulates Rx drug advertising and labeling

"Behind-the-Counter" OTC Drugs

- Sold only in pharmacies
- Requires intervention of pharmacist before dispensing
- Regulated by FDA through OTC drug monographs
  - proponents: pharmacist counseling helps with patient safety
  - opponents: pharmacist counseling will not benefit the consumer
- As an example, the sale of cold medicine containing pseudoephedrine is limited to behind the counter


QUESTIONS