OTC Monograph Reform in the CARES Act: FDA-Initiated Safety Orders

Valerie Pratt, MD & Evelyn Mentari, MD, MS
Office of Nonprescription Drugs
Center for Drug Evaluation and Research

Over-the-Counter Monograph Reform

- On March 27, 2020, the President signed into law P.L. 116-136, the “Coronavirus Aid, Relief, and Economic Security Act” (CARES Act)
- The CARES Act includes important statutory provisions that reform and modernize the way over-the-counter (OTC) monograph drugs are regulated in the United States
- For simplicity, we will refer to the regulatory framework under the CARES Act as OTC Monograph Reform

Objectives

- Provide an overview of nonprescription drugs
- Provide an overview of OTC Monograph Reform
- Discuss how FDA identifies, evaluates, and responds to safety issues, including for OTC monograph drugs
- Provide an overview of FDA-initiated administrative orders to address safety issues
- Provide an overview of OTC Monographs@FDA and comment submission

What are Over-the-Counter Drugs?

Also known as nonprescription drugs

- Safe and effective without health care provider supervision
- Low misuse and abuse potential
- Self-diagnosable medical condition
- Consumers read the Drug Facts label to
  - Self-select
  - Self-treat
  - Self-administer

Regulatory Pathway for Marketing Nonprescription Drugs

- **New Drug Application/Abbreviated New Drug (NDA/ANDA)**
  - Application submitted to FDA for premarket approval

- **OTC Drug Review (OTC Monograph)**
  - Marketed without an approved drug application if the drug complies with statutory and regulatory requirements
  - Began in 1972 to evaluate the safety and effectiveness of OTC drug products marketed in the United States before May 11, 1972
  - Established conditions under which an OTC drug is generally recognized as safe and effective (GRASE) in the form of OTC monographs

OTC Monograph

- “Rule book” for each therapeutic category establishing conditions, such as active ingredients, uses (indications), doses, route of administration, labeling, and testing under which an OTC drug is GRASE
- OTC monographs include ~ 800 active ingredients for more than 1,400 different uses, authorizing more than 100,000 drugs

OTC Drug Review Prior to CARES Act

- 1962 Kefauver-Harris amendment required drugs to be effective via a new drug application
- OTC Drug Review began in 1972 to evaluate OTC drug products marketed before May 11, 1972
- Expert panels reviewed therapeutic categories of drugs by active ingredient for safety and efficacy
- Established GRASE conditions for OTC therapeutic drug classes in the form of OTC monograph regulations
- Multi-step, public rulemaking process to establish or revise OTC monographs in the form of regulations
- In effect until the CARES Act passed in March 2020

Challenges with the OTC Drug Review Prior to CARES Act: Safety

Process Weaknesses

* **Burdensome, multistep rulemakings to establish or amend monograph regulations**
* **FDA lacked adequate resources to devote to rulemaking process**

Process Problems

* Delays in finalizing monograph regulations
* Limited, burdensome process for innovation
* **Delays in responding to urgent safety issues**
* **Delays in updating labeling to address safety issues**
* Challenges in keeping pace with evolving science and changing market

Activities under reform supported by User Fees

Monograph Reform Solutions

* **Improve process by replacing rulemaking with administrative orders**
* **Improve efficiency, timeliness, and predictability**
* Facilitate innovation
* **Establish process to rapidly address safety**
* Finalize pending monographs

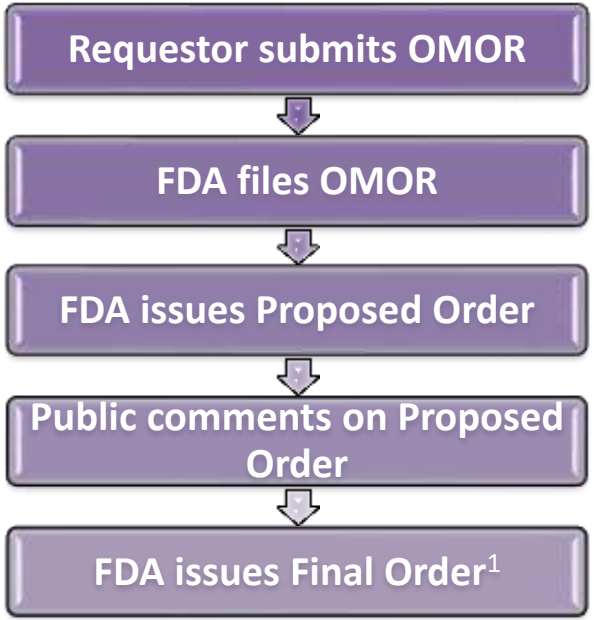
OTC Drug Review After CARES Act

- Administrative Order Process
  - Replaces rulemaking process with more expeditious administrative order process
  - An administrative order can add, remove, or change GRASE conditions for an OTC monograph
  - Can be initiated by either industry or FDA
    - A requestor can submit an OTC Monograph Order Request (OMOR) to request FDA initiate the administrative order process

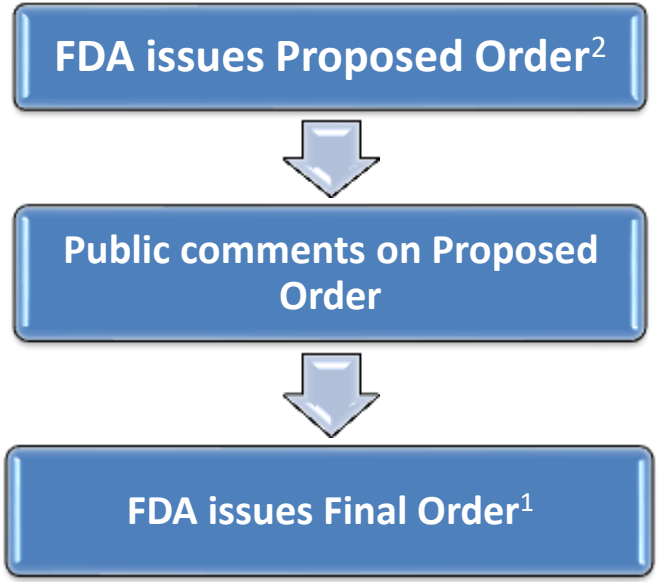
- Expedited process to address safety issues

Overview of Administrative Order Process

Industry-Initiated Order



FDA-Initiated Order



[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

Drug Safety

- Science constantly evolves
- FDA is constantly:
  - Identifying and tracking safety issues
  - Evaluating safety issues
  - Responding to safety issues

Identifying a Safety Issue

- Potential risks associated with drugs are identified from various sources including:
  - Published medical journals
  - Media reports
  - Foreign regulatory agencies
  - Required safety reporting from responsible persons for the nonprescription drug or related prescription drug
  - FDA Adverse Event Reporting System (FAERS)
  - Citizen Petitions

Newly Identified Safety Signal (NISS) Process

- In April 2020, FDA introduced a new process for identifying, evaluating, and responding to newly identified safety signals.[1]
- FDA prioritizes newly identified safety signals based on severity
  - Potential risk: 12 months
  - Important potential risk: 6 months
  - Emergency: Timeframe determined by CDER leadership

[1] Food and Drug Administration, Office of the Center Director, Manual of Policies and Procedures 4121.3: Collaborative Identification, Evaluation, and Resolution of a Newly Identified Safety Signal (NISS) (Silver Spring, Md.: 2020), accessed November 18, 2020, https://www.fda.gov/media/137475/download.

Newly Identified Safety Signal (NISS) Process

FDA may consider the following activities, among others, to evaluate a safety issue:

- Complete a full FAERS review
- Complete a substantial literature review
- Request a new site inspection
- Request new product testing
- Review clinical trial data

Newly Identified Safety Signal (NISS) Process

- The evaluation of safety issues is the same for monograph and NDA drugs
- However, the tools to address safety issues differ between the monograph and NDA regulatory processes
- Monograph reform has added new tools to address monograph drug safety issues

Addressing an OTC Monograph Safety Issue

FDA can now address an OTC monograph safety issue by initiating the administrative order process

- For example
  - FDA may change labeling language that is included in the Drug Facts label (DFL)
  - FDA may issue certain administrative orders with packaging requirements to encourage use in accordance with labeling
- In certain circumstances, FDA may expedite the administrative order process

Expedited Administrative Orders

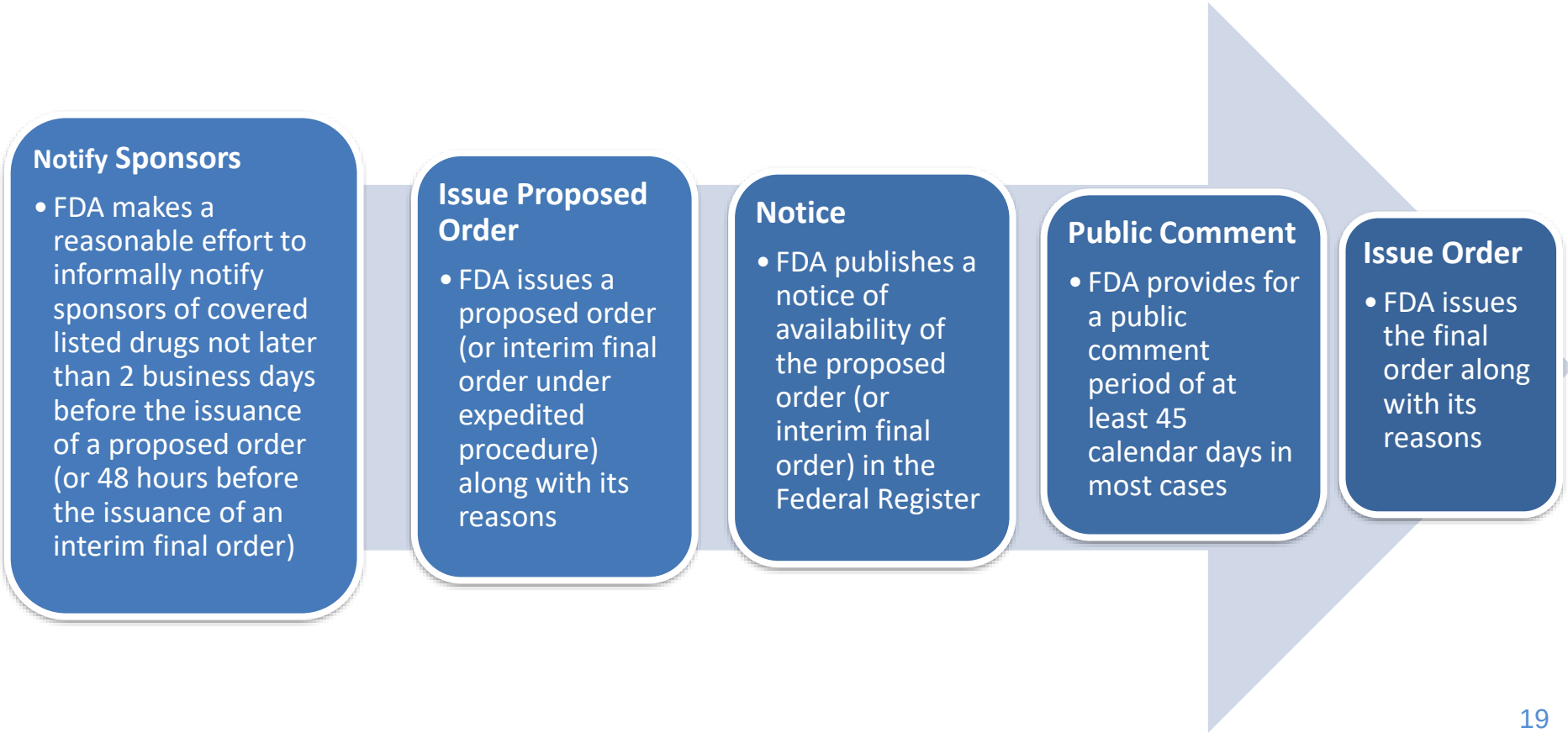
FDA or the U.S. Department of Health and Human Services (HHS) can initiate an expedited procedure and issue an interim final administrative order when there is

- Imminent hazard to public health
  - The HHS Secretary determines that "a drug, class of drugs, or combination of drugs … poses an imminent hazard to the public health"
  - HHS Secretary cannot delegate authority to issue an imminent hazard interim final order
- Safety labeling change
  - FDA determines that "a change in the labeling of a drug, class of drugs, or combination of drugs … is reasonably expected to mitigate a significant or unreasonable risk of a serious adverse event associated with use of the drug"

Standard versus Expedited Administrative Orders

- Standard administrative order process
  - Involves public comment followed by issuance of a final administrative order
  - Becomes effective once the time for requesting judicial review has expired
- Expedited administrative order process
  - Involves interim final administrative order issued before public comment
  - Becomes effective on date specified
  - After public comment, FDA will issue a final order

FDA-Initiated Administrative Order Process



How Can the Public Provide Comments on Administrative Orders?

OTC Monographs@FDA, a public, web-based portal that allows public to

- View proposed and final administrative orders and supporting documents
- Submit comments (including data) to proposed administrative orders

OTC Monographs@FDA

Two-Phase Roll Out

- 1st Phase
  - Interim (transitional) system with limited capabilities and content
    - View proposed and final administrative orders and supporting documents
    - Submit comments (including data) to proposed administrative orders
- 2nd Phase
  - Enhanced capabilities and content
    - Search a repository of OTC monographs, administrative orders and supporting documents
    - Link to Federal Register (FR) notices
  - Expected in 2022

FDA Forecast of Planned OTC Monograph Activities

- Each year, FDA will publish a nonbinding listing of OTC monograph issues FDA intends to address in the coming three years, including safety labeling changes
- For issues that FDA anticipates the submission of data will likely be needed, FDA will include a date by which it will expect these data to be submitted
- FDA will publish the first forecast by October 1, 2021
- FDA will publish subsequent forecasts no less frequently than annually

Contact Us

- For Questions on
  - OTC Monograph Reform druginfo@fda.hhs.gov
  - User fees (OMUFA) CDERCollections@fda.hhs.gov
  - Meeting requests monograph-meeting-requests@fda.hhs.gov
  - Small business and industry assistance cdersbia@fda.hhs.gov
- Resources
  - OTC Monograph Reform in the CARES Act https://www.fda.gov/drugs/over-counter-otc-nonprescription-drugs/over-counter-otc-drug-review-otc-monograph-reform-cares-act
  - Registration and Listing https://www.fda.gov/industry/structured-product-labeling-resources/business-operation-qualifier

We will take a brief break and then return to answer your questions.


FDA
U.S. FOOD & DRUG
ADMINISTRATION