Monograph Reform is Here!

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May 29, 2020

OTC Monograph Reform

- On March 27, 2020, the President signed into law H.R. 748, the "Coronavirus Aid, Relief, and Economic Security Act" (CARES Act)
- The CARES Act includes an important legislative initiative that reforms and modernizes the way 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

- OTC monograph system prior to the CARES Act
  - OTC drugs
  - Regulatory pathways for marketing OTC drugs
  - Historic OTC drug review
  - Generally recognized as safe and effective
- OTC monograph system after the CARES Act
  - Overview of OTC Monograph Reform
  - Considerations for industry
  - How FDA is preparing

What are Over-The-Counter (OTC) Drugs?

- OTC drugs
  - Available to consumers without a prescription (nonprescription drugs)
  - Self-selected and used safely and effectively by the consumer without the supervision of a health care practitioner
  - Low potential for abuse
  - Benefits of OTC availability outweigh the risks

Regulatory Pathways for Marketing OTC Drugs

- New Drug Application/Abbreviated New Drug (NDA/ANDA)
  - Application submitted to FDA for premarket approval
  - Safety and effectiveness testing is required
  - Marketed after NDA is approved
  - Product specific
- OTC Monograph
  - Marketed without an approved drug application if the drug complies with the requirements in section 505G of the Federal Food, Drug, and Cosmetic Act (FD&C Act), including any applicable conditions in an OTC Monograph
  - Safety and effectiveness data on the individual drug product is not required
    - Except final formulation testing when specified in certain OTC monographs
  - Therapeutic category specific based on active ingredients and other conditions

OTC Monograph

- A “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 generally recognized as safe and effective (GRASE)

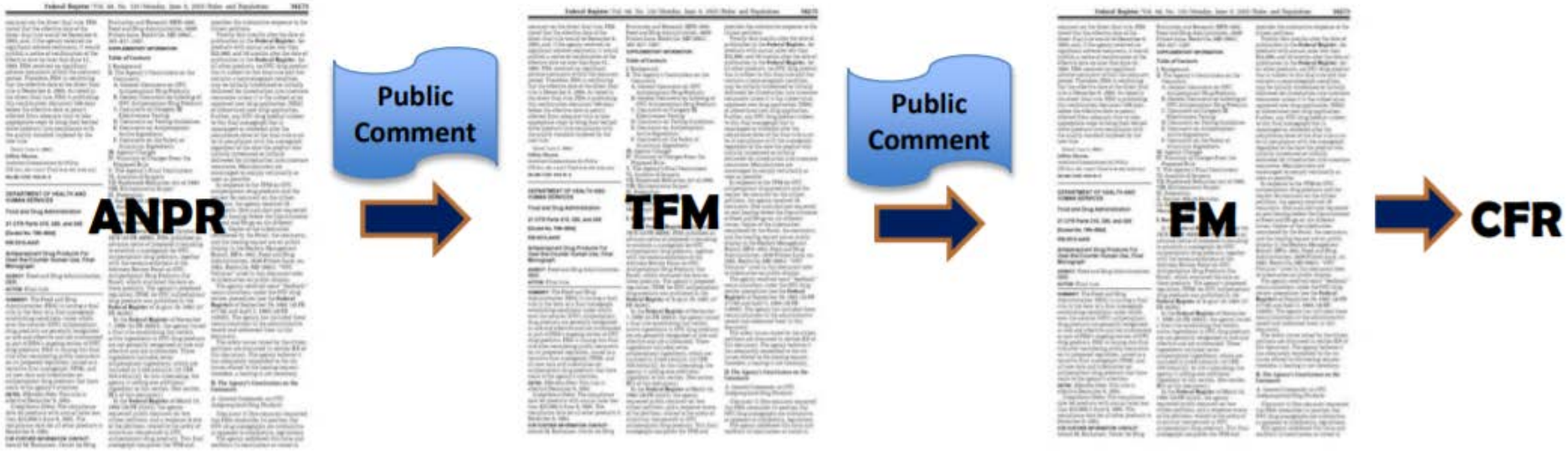
- OTC monographs cover ~ 800 active ingredients for over 1,400 different uses, authorizing over 100,000 drugs

OTC Drug Review Prior to CARES Act

- Began in 1972 to evaluate the safety and effectiveness of OTC drug products marketed in the United States before May 11, 1972
- Established GRASE conditions for each OTC therapeutic drug class in the form of OTC monographs
- Three-phase public rulemaking process to establish the OTC monographs
- In effect until the CARES Act was passed in March 2020

OTC Monograph Rulemaking Process Under OTC Drug Review Prior to CARES Act

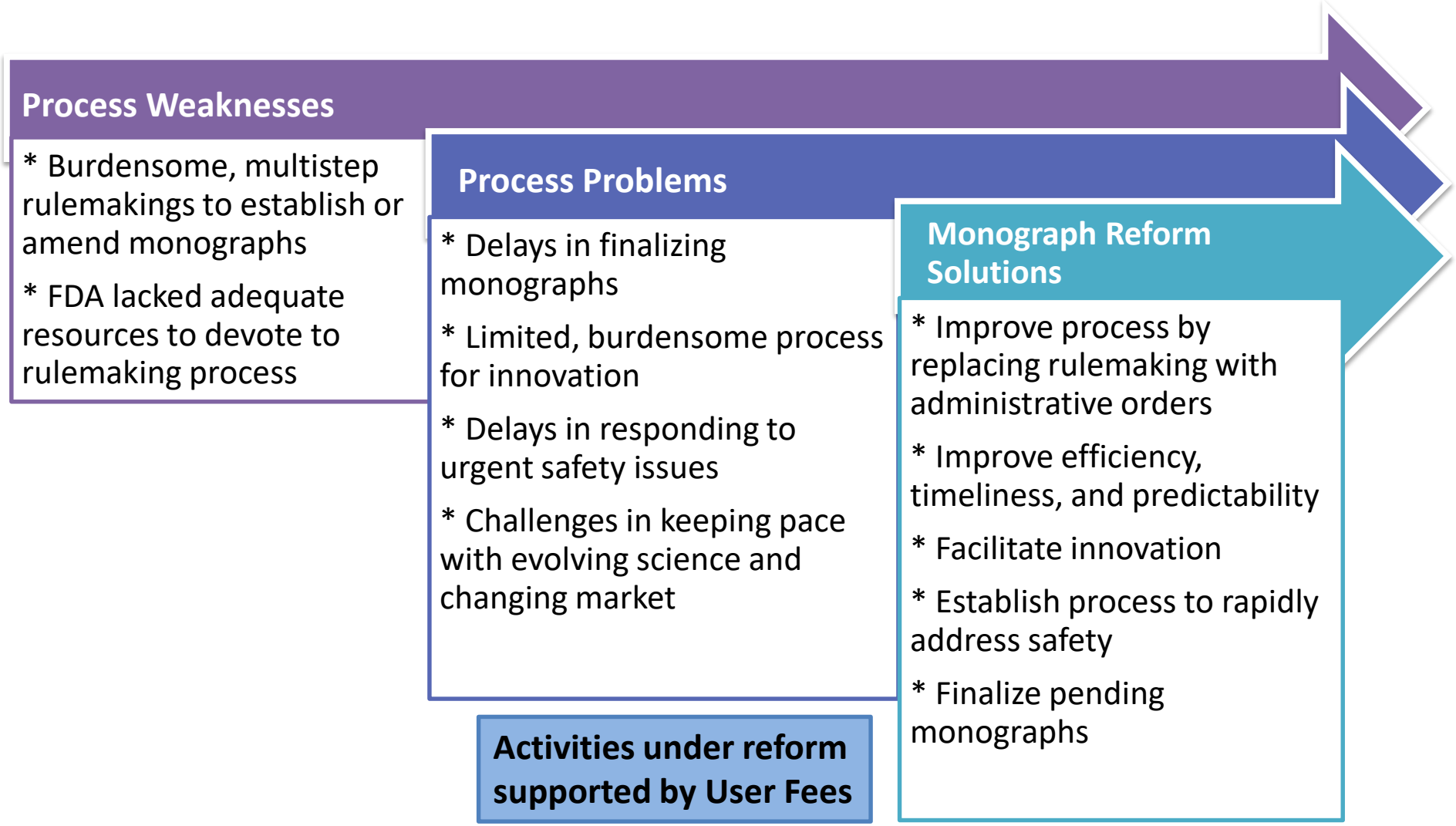
- Three-phase public notice-and-comment rulemaking process
  - Phase 1: Advance Notice of Proposed Rulemaking (ANPR)
  - Phase 2: Tentative Final Monograph (TFM)
  - Phase 3: Final Monograph → Code of Federal Regulations (CFR)



GRASE Categories

- Active ingredients and other conditions evaluated in the OTC Drug Review were categorized into three categories in an ANPR and TFM
  - Category I: GRASE
  - Category II: not GRASE
  - Category III: insufficient data available to determine if GRASE
- Only GRASE conditions, including active ingredients, are included in published final monographs
  - Category I, II, and III designations are not used in the final monograph
  - “Negative Monograph” listed non-GRASE conditions

Challenges with the OTC Drug Review Prior to CARES Act



CARES Act

- The CARES Act amends the FD&C Act to
  - Modernize the OTC drug review and OTC monograph drug development process
  - Provide FDA with the authority to collect user fees dedicated to OTC monograph drug activities
- Over-the-Counter Monograph User Fee Program Performance Goals and Procedures Document
  - Specifies FDA and industry mutually agreed upon timelines

OTC Monograph Reform

- For simplicity, we will refer to the OTC monograph reform provisions under the CARES Act as OTC Monograph Reform

- We will refer to the monograph system as the OTC Drug Review

- We will refer to the OTC user fee program authorized under the CARES Act as the Over-the-Counter Monograph User Fee program (or “OMUFA”)
  - Referenced in the Performance Goals and Procedures document developed by FDA and industry to accompany the user fee legislation

OTC Monograph Drug Regulation Before and After CARES Act

What Stays the Same?

- Ingredient based review
- Active ingredients grouped by therapeutic category
- GRASE determination
- Drugs complying with OTC monograph and other applicable requirements may be marketed without FDA approval
- Process includes public comment period

What's New?

- Administrative order process
- OTC monograph order request (OMOR)
- Clarification of status of existing OTC monograph drugs, including drugs that were previously subject to TFMs and ANPRs
- Process for minor changes in dosage forms
- Exclusivity period for certain OTC monograph drugs
- OTC monograph user fees
- Formal meetings

Overview of OTC Monograph Reform

- Administrative Order Process
- Status of Final Monograph Regulations
- Status of Existing OTC Monograph Products
- Minor Changes in Dosage Form
- Exclusivity
- Treatment of Sunscreen Innovation Act
- User Fees (OMUFA)
- Formal Meetings with FDA
- Confidential Information
- OTC Monograph Reform Required Guidances

Administrative Order Process

- Replaces the rulemaking process with an administrative order process
- Gives FDA the authority to issue an administrative order that adds, removes or changes GRASE conditions for an OTC drug monograph
- Establishes an expedited process to address safety issues
- Either industry or FDA can initiate the administrative order process

Industry-Initiated Order

- A requestor can request for FDA to issue an administrative order
- This request is called an “OTC monograph order request” (OMOR)
- Two types of OMORs
  - Tier 1 OMORs
  - Tier 2 OMORs

Tier 1 OMOR

A Request For:

- Any request not determined to be a Tier 2 OMOR
- Examples of Tier 1 OMORs
  - 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
  - Addition of a new monograph therapeutic category (each ingredient proposed for the new therapeutic category will be a separate OMOR)

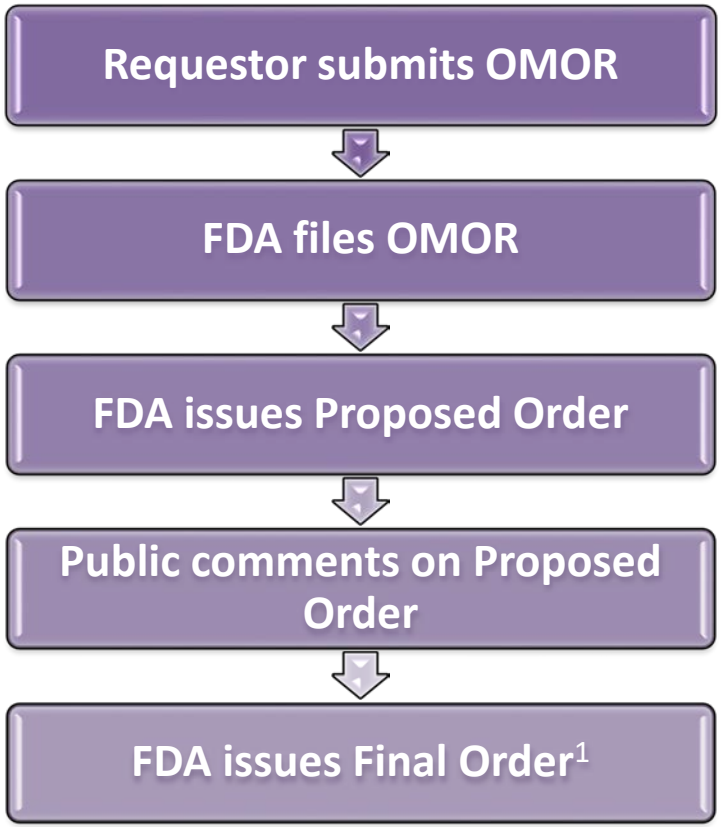
Tier 2 OMOR

A Request For:

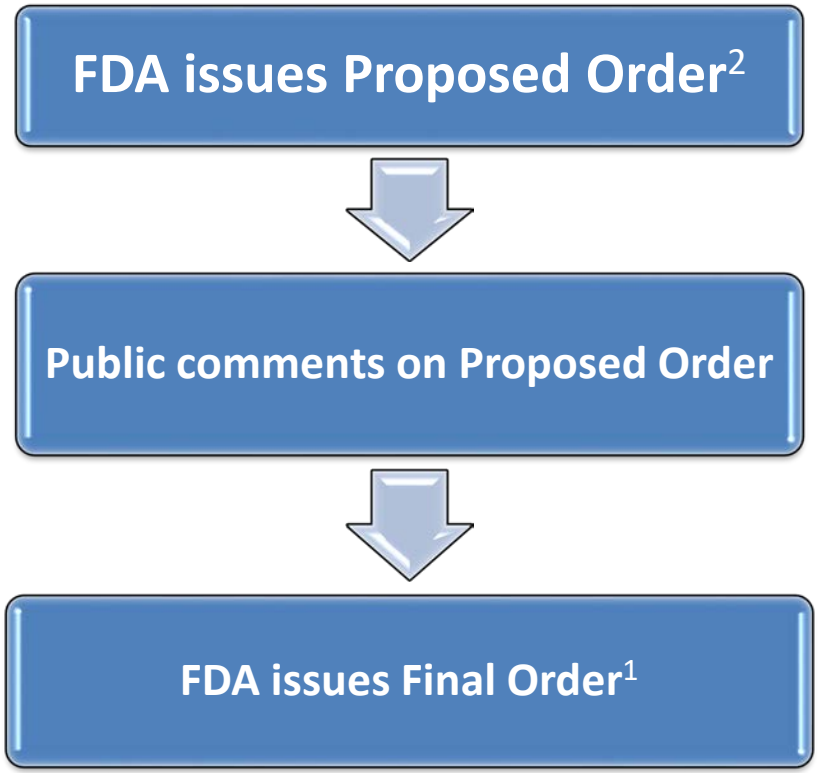
- Reordering of existing information in the Drug Facts label (DFL)
- Addition of information to the “Other Information” section of the DFL
- Modification to the “Directions for Use” section of the DFL, consistent with a minor dosage form change
- Standardization of the concentration or dose of a specific finalized ingredient within a particular finalized monograph
- Change to ingredient nomenclature to align with nomenclature of a standards-setting organization
- Addition of an interchangeable term consistent with 21 C.F.R. § 330.1 (or any successor regulations)

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

Expedited FDA-Initiated Order

- FDA can initiate an expedited procedure for issuing an order when
  - A drug poses an imminent hazard to public health
  - 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
- FDA will issue an interim final order that becomes effective before public comment
  - After public comment, FDA will issue a final order

OMOR Review Timeline

	Tier 1 - GRASE Finalization	Tier 1[1]	Tier 2	Tier 1 - Specified Safety Labeling Change
Filing determination	60 calendar days after receipt of OMOR	60 calendar days after receipt of OMOR	60 calendar days after receipt of OMOR	60 calendar days after receipt of OMOR
Proposed Order Issued	12 months after receipt of OMOR	12 months after receipt of OMOR	10 months after receipt of OMOR	6 months after receipt of OMOR
Public Comment Period	45 calendar days	45 calendar days	45 calendar days	45 calendar days
Assessment of comments	60 calendar days	60 calendar days	60 calendar days	60 calendar days
Comment review extension[2]	6 months[2]	5 months[2]	3 months[2]	3 months[2]
Final Order Issued	17.5 months after receipt of OMOR (or 23.5 months[3])	17.5 months after receipt of OMOR (or 22.5 months[3])	15.5 months after receipt of OMOR (or 18.5 months[3])	11.5 months after receipt of OMOR (or 14.5 months[3])

[1] Except Tier 1 OMORs for GRASE Finalization and Specified Safety Labeling Changes

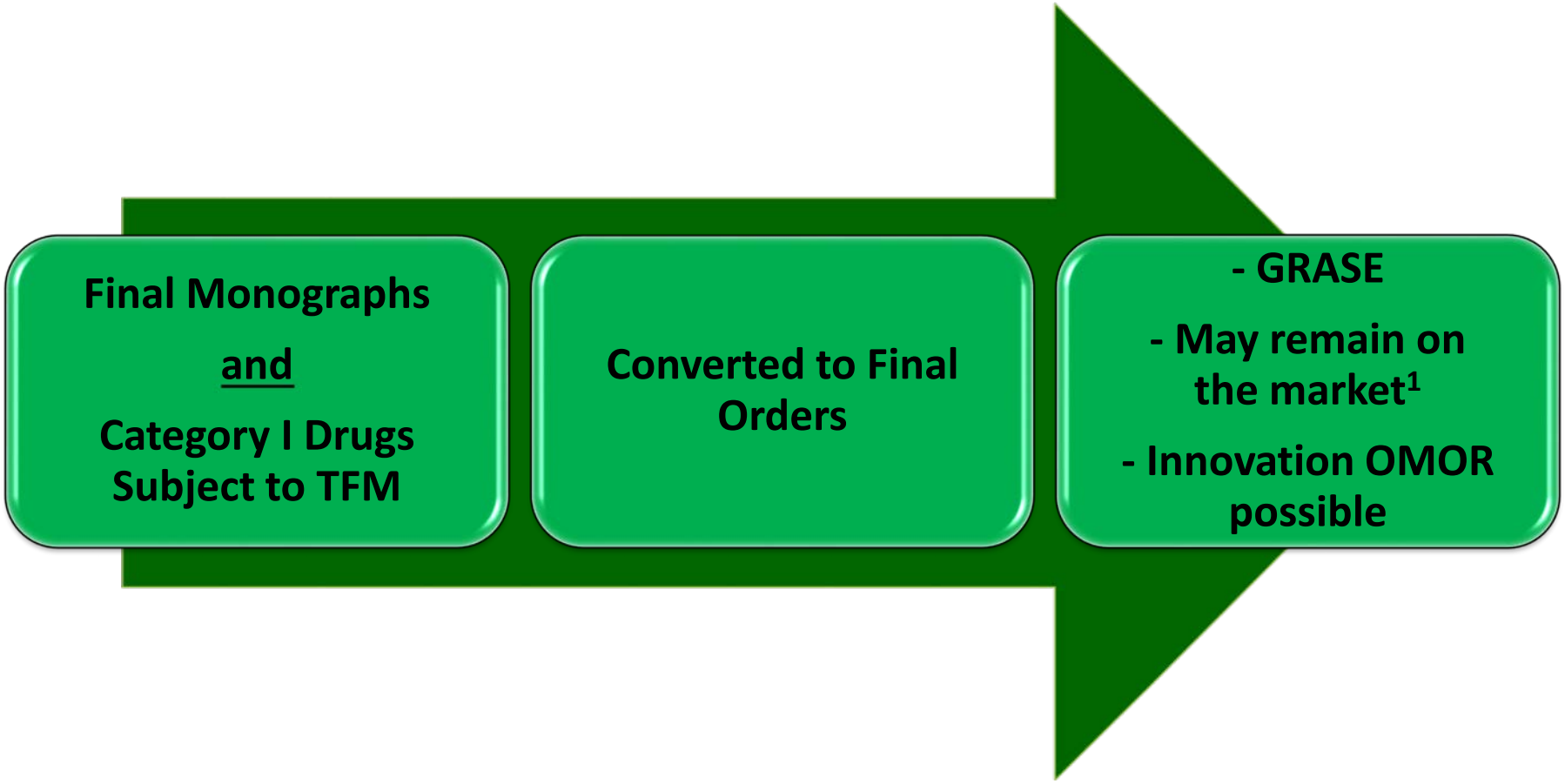
[2] If comments received by FDA are numerous or substantive, there will be an extension of the comment review period which will extend the final order goal date.

[3] The final order goal date if comment review extension is necessary.

Overview of Regulatory Status for Monograph Regulations

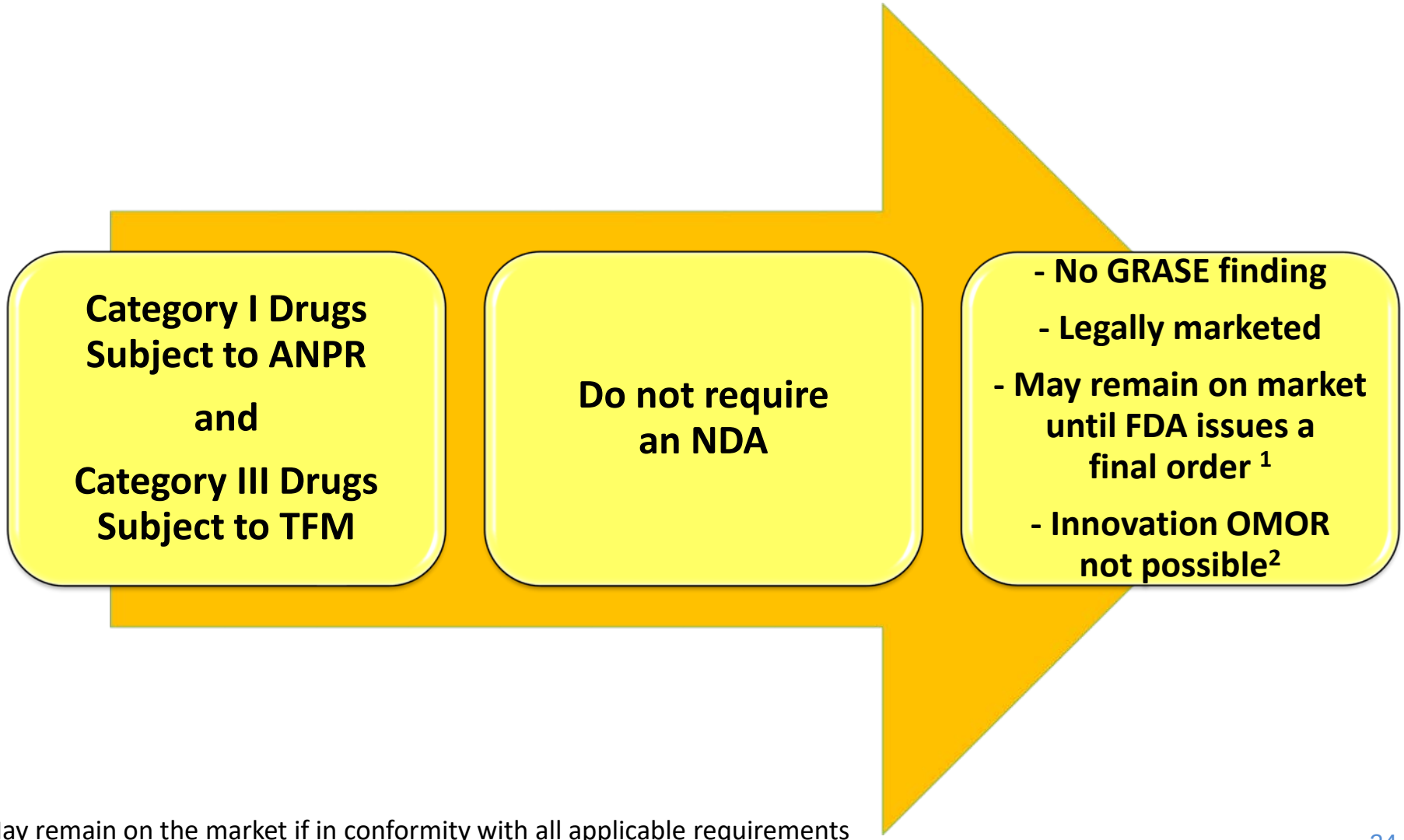
- Clarification of status of existing OTC monograph drugs, including drugs that were previously subject to TFMs and ANPRMs
- Final orders will be posted on FDA's public website
- Existing final monographs will be removed from CFR
- 21 CFR 310.545 ("negative monograph") is deemed a final administrative order
  - 21 CFR 310.545 lists ingredients for specific uses that were determined to be not GRASE and new drugs

What Products Can Remain on the Market?



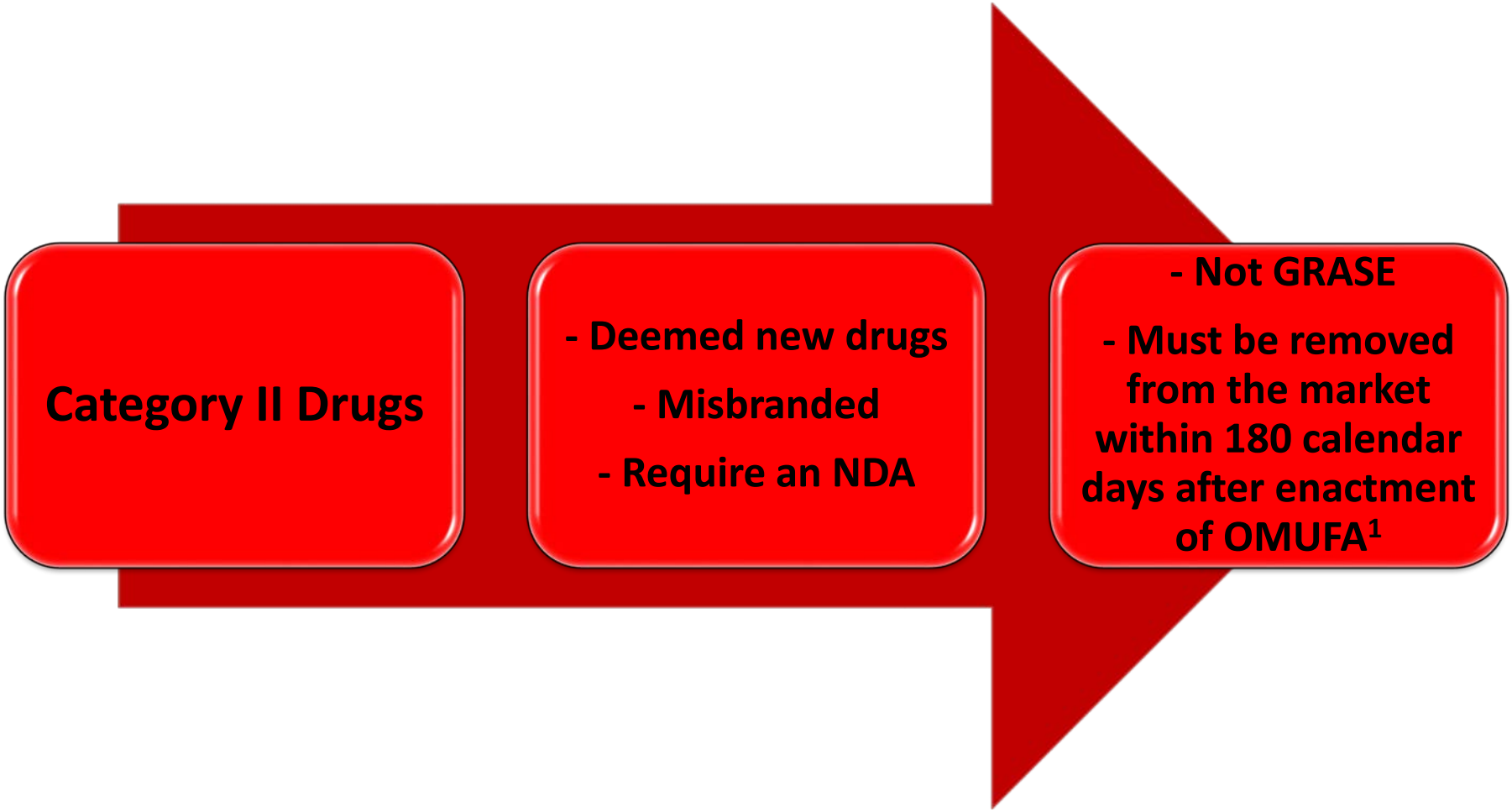
[1]May remain on the market if in conformity with all applicable requirements

What Products Can Remain on the Market?



[1]May remain on the market if in conformity with all applicable requirements
[2]Unless a GRASE finalization occurs at the same time

Category II Drugs Cannot Remain on the Market



[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

Establishes a Process for Minor Changes in Dosage Forms

- In the future, sponsors will be able to make minor dosage form changes without the issuance of an order if
  - Drug is GRASE
  - Change follows FDA order on determining whether a minor change affects the safety, efficacy, absorption, or other exposure
  - Sponsor retains sufficient data on file to support change
  - Data are available at FDA request
- Process begins when
  - FDA issues order/guidance pair regarding types of minor changes that can be made without submitting an OMOR
  - Under the goals document, FDA is scheduled to issue the solid oral dosage forms order/guidance pair by April 1, 2025

Exclusivity Period for Certain OTC Monograph Drugs

- A requestor may be granted 18 months of exclusivity for a change subject to a final order issued in response to an OMOR, that provides for
  1. A drug to contain an active ingredient (including any ester or salt of the active ingredient), not previously included in certain nonprescription drugs sold without NDAs **OR**
  2. A change in conditions of use of a drug, for which new human data studies that were conducted or sponsored by the requestor were essential to issuance of the order

No Exclusivity Period

- Safety-related changes, as defined by FDA, or any other changes FDA determines are necessary to assure safe use
- Changes which are the subject of a Tier 2 OMOR (as defined in section 744L)
- Changes related to methods of testing safety or efficacy

Addresses the Sunscreen Innovation Act (SIA)

- OTC Monograph Reform sunsets the Sunscreen Innovation Act (SIA) on September 30, 2022
  - But, while SIA remains in effect, provides potential for exclusivity under it
  - Any final sunscreen order under SIA will be deemed a final order under 505G
- Requires FDA to issue a proposed order no later than 18 months after enactment of OTC Monograph Reform

Addresses the SIA (cont'd)

- A sponsor of an OTC sunscreen active ingredient, or a combination of ingredients, that is subject to a proposed sunscreen order issued pursuant to the SIA may elect to
  - Transition the review of such ingredient or combination of ingredients to the new administrative order process by providing written notification to the Secretary within 180 calendar days of the enactment of OTC Monograph Reform
- If no election is made, review of the ingredient continues under the process set forth in SIA

Establishes an OTC User Fee Program (OMUFA)

- FDA will collect two types of user fees
  - Facility fees
    - Due annually
  - OTC Monograph Order Request (OMOR) fees
    - Due upon submission of OMOR

Amends Misbranding Provisions

- An OTC monograph drug is misbranded if it
  - Does not comply with the requirements under section 505G of FD&C Act
  - Is manufactured, prepared, propagated, compounded, or processed in a facility for which fees have not been paid under section 744M

Formal Meetings with FDA

- Allows for formal meetings between sponsors or requestors and FDA to discuss, for example
  - Advice on studies or other information necessary to support submissions
  - Matters relevant to regulation of OTC monograph drugs
  - Matters relevant to the development of new OTC monograph drugs

OTC Monograph Reform Required Guidances

- Formal meetings
- Format and content of data submissions
- Format of electronic submissions
- Consolidated proceedings and procedures for appeal
- Minor changes in dosage forms without an OMOR

Considerations for Industry

- ✓ Familiarize yourself with the new law
  - Understand the current status of OTC monograph drugs that you have interest in
- ✓ Review the drug registration and listing requirements
  - Update facility registrations in eDRLS
  - Look for FDA correspondence about updating facility registration
- ✓ Frequently check FDA's website
  - OMUFA User Fee information
  - Interim OTC Monograph Reform website
  - Deemed final administrative orders
  - Guidance documents

How FDA is Preparing

- Implementing the changes set forth under the OTC Monograph Reform
- Developing outreach for external stakeholders
- Implementing the OMUFA user fee program performance goals and procedures
  - Setting up tracking for OMUFA timelines
  - Hiring additional staff
  - Building IT infrastructure
  - Drafting required guidances
- Setting up procedures for user fee collection
- Preparing the deemed final administrative orders for public posting

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
  - 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.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