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OTC drug filing and review process in the US

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Abstract

The Over-the-Counter (OTC) Drug Monograph System in the United States (US) serves as a vital regulatory framework for non-prescription medications. Through the monograph review process there is a low regulatory burden for industry to market OTC drugs and that helps to keep OTC drug costs low to consumers. As, this process is applicable only in the US the OTC drug filing and review process becomes streamline and due to its limited time exposure this process is not time consuming.

There are mainly two pathways to bring a OTC drug in the US: (a) NDA, (b) OTC drug review process. By comparing both the procedures NDA submission is time consuming process and as of that for OTC review process, if drugs meet the conditions specified in the monograph OTC drug can be marketed in a more streamline process. Administrative order process provides sponsor or requestors and the FDA to issue an order. As, the three phase rulemaking process is removed after the enactment of CARES act, the OTC monograph reform encountered several challenges and is beneficial. OTC Monograph System, serves as a cornerstone for ensuring the accessibility, safety, and efficacy of a diverse range of OTC drugs.

The proposed study is based on review process for various OTC monograph drugs. This research is focused on the regulatory pathway that facilitates the approval of non-prescription medications, the study explores the historical evolution and current functioning of the OTC Monograph System.

Keywords: Over the counter (OTC) drug review process, OTC Monograph Order Request (OMOR), Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER)

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1. Introduction

OTC Drugs are drugs that do not require a doctor's prescription and can be bought off-the-shelf in stores. In the United States (US), Food and Drug Administration (FDA) regulates the OTC drugs. FDA decides whether a medicine is safe and effective enough to sell over-the-counter. Over-the-counter medication is a way of self-medication. (1)

There are two regulatory pathways to bring a nonprescription drug to market in the U.S.: (1) The drug application process (NDA) and (2) OTC Drug Review (OTC monograph) process. Both pathways represent two different mechanisms. A primary difference between the pathways for approval is that NDA results in the approval to sell a specific finished drug product whereas the OTC drug monograph process focuses on the safety and effectiveness of one or more active ingredients within a drug category. For the purposes of FDA marketing approval, the NDA process generally requires submitting data from clinical trials demonstrating the safety and effectiveness of a drug. If an OTC drug product complies with a monograph, it does not need approval from FDA for NDA prior to marketing.

OTC drugs are not required to go through the premarket approval process, they are required to comply with various other statutory and regulatory requirements. For example: (a) Manufacturers of OTC drugs are required to register their facilities and list the OTC drugs

manufactured there, to comply with current good manufacturing practices (CGMPs), (b) To meet labeling requirements, (c) To report serious adverse events to FDA.

In addition, OTC drugs may contain only those inactive ingredients that are safe in the amounts administered and that do not interfere with the effectiveness of the preparation. FDA may inspect OTC drug manufacturing facilities and take enforcement action against violative OTC drugs through issuance of warning letters, import alerts, and voluntary recalls. FDA can, with DOJ (Department of Justice) assistance, pursue more stringent actions, such as product seizure or injunction. (2)

On March 27, 2020, the Coronavirus Aid, Relief, and Economic Security Act (CARES Act) was signed into law. The CARES Act added section 505G to the Federal Food, Drug and Cosmetic (FD&C) Act. Section 505G reforms and modernizes the framework for the regulation of OTC monograph drugs.

OTC monograph drugs may be marketed without an approved drug application under section 505 of the FD&C Act if they meet the requirements of section 505G of the FD&C Act, including the OTC drug monograph (OTC monograph) and other applicable requirements.

An OTC drug monograph establishes conditions, such as active ingredients, uses (indications), doses, routes of administration, labeling, and testing, under which an OTC drug in a given therapeutic category (e.g., sunscreen, antacid) is generally recognized as safe and effective (GRASE) for its intended use.

Under the process set forth in section 505G(b) of the FD&C Act, FDA has the authority to issue an administrative order (proposed and final) that adds, removes, or changes generally recognized as safe and effective (GRASE) conditions for an OTC drug monograph. Either FDA or a requestor can initiate the administrative order process. (3,4)

2. OTC Monograph System

An OTC monograph drug is a nonprescription or OTC drug that may be marketed without an approved drug application under section 505 of the FD&C Act if it meets the requirements of section 505G of the FD&C Act, as well as other applicable requirements.

OTC A monograph establishes conditions, such as active ingredients and related conditions (e.g., dosage level, combination of active ingredients, labeled indications, warnings and adequate directions for use), under which an OTC drug in a given therapeutic category (e.g., sunscreen, antacid) is generally recognized as safe and effective (GRASE) for its intended use and thus may be marketed without an approved NDA. FDA assesses monograph compliance as part of its inspection process.

The FDA classifies OTC drugs into different therapeutic categories based on their intended uses and active ingredients. These categories represent a broad classification of OTC drugs, and each category has specific monographs outlining the acceptable ingredients (considered to be GRASE), doses, formulations, labeling, and conditions for use. Examples of OTC monograph drug categories are given in the following table:

Table 1: OTC monograph drug categories

Sr. No.	Drug Categories
1	Antacids
2	Laxatives
3	Antidiarrheal products
4	Antiemetics
5	Antiperspirants
6	Sunscreens
7	Cough and cold products
8	Wart removers
9	Sedatives/Sleep aids
10	Stimulants
11	Ophthalmic products
12	Hemorrhoidal products
13	Dandruff products
14	Anticaries products
15	Otic products
16	Analgesics
17	Allergies

Content of OTC Monograph

The following conditions are included in an OTC monograph for a drug, conditions include:

- Active ingredients (must comply with a USP drug monograph)
- Dosage strength and form and route of administration
- Patient population (age, gender) and indications for use
- Required labeling:
  - Uses
  - Warnings
  - Directions
- Final formulation testing, if required for the specific product (not all monographs)

The following example is of OTC monograph for the first aid antibiotic drug product for OTC human use, it includes:

Part A—General Provisions

- Scope
- Definitions

Part B—Active Ingredients

- First aid antibiotic active ingredients
- Permitted combinations of active ingredients

Part C—Labeling

- Labeling of first aid antibiotic drug products

- Labeling of permitted combinations of active ingredients (5)

3. OTC Drug Review Process

The OTC drug review process is a regulatory framework implemented by the U.S. FDA for the evaluation and approval of non-prescription drugs in the U.S. The FDA periodically reviews and updates existing monographs. This process results in the development of OTC monographs for specific drug categories.

The OTC drug monograph process or drug review process does not require a manufacturer to submit clinical trial data demonstrating safety and effectiveness of an individual drug product, nor does it require an OTC drug product to be approved by FDA before marketing. This is because FDA had already evaluated the safety and effectiveness evidence as part of its monograph rulemaking. As long as the drug product complies with the conditions of the monograph, premarket approval is not necessary.

Background

FDA established the OTC drug monograph process through rulemaking in 1972, for the purpose of evaluating the safety and effectiveness of OTC drug products that were marketed in the US prior to May 11, 1972.

FDA in 1972 established GRASE (Generally Recognized as Safe and Effective) conditions for each OTC therapeutic drug class in the form of OTC Monographs. Advisory Review Panels reviewed therapeutic classes of OTC drugs and put products into three categories:

- Category I: GRASE. Category I includes conditions considered to be safe and effective on the basis of existing data and information.
- Category II: Not GRASE. Category II includes conditions that are not GRASE.
- Category III: Insufficient data. Category III includes conditions for which there is not enough information to place them in Category I or II.

Conditions: Include active ingredients, dosage strength, dosage form and route of administration, patient population, indications for use, required labeling (e.g., warnings). Before the enactment of CARES (Coronavirus Aid, Relief, and Economic Security) Act, 2020 FDA established three-phase public rulemaking process to establish each OTC monograph.

Phase 1: Advance Notice of Proposed Rulemaking (ANPR) followed by public comment.

Phase 2: Tentative Final Monograph (TFM) followed by public comment.

Phase 3: Final Monograph that is published in the Code of Federal Regulations (CFR).

Several challenges were faced before the CARES Act such that some monographs remained unfinalized for decades, resulting in OTC monograph drugs on the market that were not subject to a final determination regarding their safety and effectiveness and FDA's ability to respond to safety concerns with OTC monograph drugs in a timely and efficient manner was limited under the rulemaking process.

To overcome the challenges, on march 27, 2020, the Coronavirus Aid, Relief, and Economic Security Act (CARES Act) was signed into law. The CARES Act includes provisions that govern the way certain OTC drugs are regulated in the United States. The CARES Act added section 505G to the Federal Food, Drug and Cosmetic Act (FD&C Act). Section 505G reforms and modernizes the OTC drug review process. The act created a new process for issuing monographs through administrative orders rather than the three phase rulemaking process. CARES Act also added section 744M to the FD&C Act authorizing FDA to assess and collect user fees dedicated to OTC monograph drug activities. The CARES Act establishes a user fee program for OTC monograph drugs, including facility fee and an OTC monograph order request fee (for administrative orders requested by requestors). A key provision to OTC monograph reform is that it gives an 18-month exclusivity period for certain administrative order.

Administrative Order Process

Under the process set forth in section 505G(b) of the FD&C Act, FDA has the authority to issue an administrative order (proposed and final) that adds, removes, or changes generally recognized as safe and effective (GRASE) conditions for an OTC drug monograph. The administrative order process to add, remove, or change a monograph can be initiated by either industry (any person or group of persons marketing, manufacturing, processing, or developing a drug) or FDA. There are mainly two types of administrative order: (1) Industry Initiated Order and (2) FDA Initiated Order. The figure given below explains the administrative order process:-

(1) Industry Initiated order:

Industry can request that FDA issue an administrative order by submitting an OTC monograph order request (OMOR) to FDA. FDA will determine if the OMOR is acceptable for filing. If FDA accepts the OMOR for filing, FDA will the review the OMOR and issue a proposed order. The public will receive at least 45 calendar days to submit comments on the proposed order. After reviewing and considering the comments, FDA will issue a final order which is the final OTC monograph. All final orders are subject to dispute resolution, an administrative hearing, and judicial review.

(2) FDA Initiated Order:

FDA issues a proposed order. The public will receive at least 45 calendar days to submit comments on the proposed order. After reviewing and considering the comments, FDA will issue a final order which is the final OTC monograph. All final orders are subject to dispute resolution, an administrative hearing, and judicial review.

The OTC Monographs@FDA portal provides a resource for the public to view Administrative Orders

(Proposed, Final, and Interim Final Orders) for OTC Monograph Drugs and view OTC Monographs. This portal also facilitates the ability for the public to submit, search, and view comments and data for Proposed and Interim Final Administrative Orders. The comment period for both the industry & FDA initiated order will be of 45 calendar days. (6)

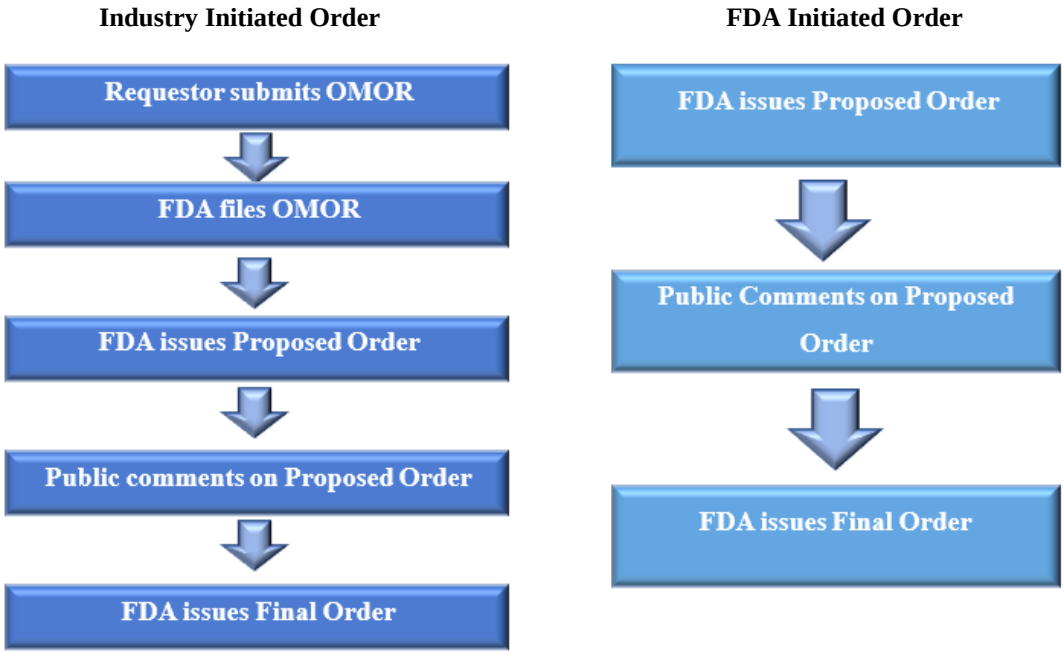

Figure 1. Administrative Order Process

4. OTC Monograph Order Request (OMOR)

OMOR is a request for the issuance of an administrative order initiated by the industry determining whether a drug is generally recognized as safe and effective (GRASE) or whether a change to a condition of use of a drug is GRASE. The requestor will submit an OMOR for the issuance of administrative order by the FDA. There are two types of OMORs. The below table (Table 2) describes the types and fee rate for OMORs:

Table 2. Types of OMORs and Fee Rate FY 2024

Sr. No.	Types of OMORs	OMOR Fee Rate FY 2024
1	Tier One OMORs	$537,471
2	Tier Two OMORs	$107,494

Tier One OMORs:

Most Innovation OMORs will be Tier One OMORs. Examples include the following:

- 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 fixed-dose combination of ingredients to a monograph that already has one or more ingredients that have been found to be GRASE
- Addition of a new test method for a monograph that already has one or more ingredients that have been found to be GRASE, and the new test method applies to one or more of the GRASE ingredients

Tier Two OMORs:

Requests for the following will be limited to Tier Two Innovation OMORs:

- Reordering of existing information in the Drug Facts label (DFL)
- Standardization of the concentration or dose of a specific finalized ingredient within a particular finalized monograph
- An ingredient nomenclature change to align with nomenclature of a standards-setting organization
- Addition of an interchangeable term under 21 CFR 330.1(i)
- Modification to existing DFL Directions for Use, in order to be consistent with a final order/guidance pair on minor dosage form changes
- Addition of information (either required or optional) to be included under the "Other Information" section of Drug Facts labeling,
- Other specific items may be added by FDA later as FDA gains experience with Tier Two OMORs

The following table outlines the timelines for Innovation OMOR review

Table 3. Timelines for OMOR Review

Parameters	Tier One OMORs	Tier Two OMORs
Filing Determination	FDA makes file ability determination 60 calendar days after receipt of OMOR	FDA makes file ability determination 60 calendar days after receipt of OMOR
Issuance of proposed order	If OMOR is filed, FDA issues proposed order 12 months after receipt of OMOR	If OMOR is filed, FDA issues proposed order 10 months after receipt of OMOR
Public comment period	Begins on the date of issuance of the proposed order, and lasts 45 calendar days	Begins on the date of issuance of the proposed order, and lasts 45 calendar days
Assessment of volume and substantiveness	Begins one calendar day after the end of the comment period, and lasts 60 calendar days	Begins one calendar day after the end of the comment period, and lasts 60 calendar days
Issuance of final order	17.5 months after receipt of OMOR	15.5 months after receipt of OMOR

If significant number of comments are received or the comments received during the comment period are numerous or substantive, there will be an extension of the final order goal date. For Tier One OMORs: the extension will be 5 months and for Tier Two OMORs: the extension will be 3 months.

After submitting an OMOR, if any deficiencies are identified then FDA may "Refuse to File" an OMOR. FDA will make a filing determination within 60 calendar days after receipt of an OMOR. FDA will issue a letter (a "Day 74 Letter") to requestors within 74 calendar days after receipt of an OMOR. The Day 74 Letter includes FDA's filing decision and any filing issues that were identified. (7)

OMOR Content and Format (8)

OMORs must be submitted in electronic format. An OMOR should be organized into five modules as follows:

Module 1: Administrative Information

Module 2: Summaries

Module 3: Quality

Module 4: Nonclinical Study Reports

Module 5: Clinical Study Reports

The below table describes the sections included in CTD Modules for an OMOR:

Table 4. CTD format for OMOR

Module 1: Administrative Information
Table of Content (TOC)
Cover letter
Administrative Information
References
Meetings
Labeling
Module 2: Summaries
TOC
Introduction to Summary Documents
Quality Overall Summary (QOS)
Nonclinical Overview
Clinical Overview
Nonclinical Written and Tabulated Summaries
Module 3: Quality Data
TOC
Body of Data
Literature References
Module 4: Non Clinical Study Reports
TOC
Study Reports
Literature References
Module 5: Clinical Study Reports
TOC
Tabular Listing of all Clinical Studies
Literature References

General Considerations for an OMOR

The OMOR should be in English language. If any portion of a submission is in a foreign language, the requestor should provide a complete and accurate English translation, including English translations of any references. Font size for text and tables should be of a style and size that is large enough to be easily legible and narrative text should be submitted in Times New Roman 12 point font. For footnotes 10 point font is acceptable.

The requestor should format an OMOR to standard U.S. letter size paper (8.5 by 11 inches). To present a floor plan, synthesis diagram, batch formula, or manufacturing instructions the requestor can format individual pages larger than standard paper size. Page numbering should be at the document level and not at the module level. Requestors should place hyperlinks to scientific articles and other published materials in the relevant sections by subject.

An Environmental Assessments (EAs) must be submitted as part of applications or petitions that request FDA action, unless the action qualifies for categorical exclusion. Because an OMOR is a request for agency action analogous to an application or petition, the requestor must accompany such a request with either an EA or a claim of categorical exclusion. An adequate EA is one that contains sufficient information to enable FDA to determine whether the proposed action may significantly affect the quality of the human environment. (8)

5. OTC Monograph Submissions in Electronic Format

Section 505G(j) of the FD&C Act requires that all OTC monograph submissions under section 505G should

be in electronic format. Examples of OTC monograph submissions include the following:

- OMORs
- Public comments to a proposed administrative order (issued either on FDA's initiative or at the request of one or more requestors) or interim final administrative order
- Formal meeting requests and meeting packages
- Formal dispute resolution requests related to a final administrative order
- Administrative hearing requests related to a final administrative order
- Responses to record requests by FDA relating to minor changes
- Updates to drug listing information for the drug in accordance with section 510(j) of the FD&C Act when a change is made to a drug subject to section 505G.

OMORs, formal meeting requests and meeting packages, formal dispute resolution requests related to a final administrative order, administrative hearing requests related to a final administrative order, and responses to record requests by FDA relating to minor changes should be electronically submitted through the CDER NextGen Portal.

Submissions related to updating drug listing information should be electronically submitted consistent with the Electronic Drug Registration and Listing System (eDRLS) process and instructions.

FDA's CDER NextGen Portal is a website for users to report information to the FDA, including certain OTC monograph submissions. Submitters need to have a CDER NextGen Portal account to submit OTC monograph submissions in electronic format through the CDER NextGen Portal. (9)

6. User Fees for OTC Monograph Drug

OTC Monograph drug user fee program referred to as "OMUFA," is structured based on the Prescription Drug User Fee Act (PDUFA). Under the OMUFA program, industry-paid fees help support FDA's regulatory activities related to OTC monograph drugs. Additionally, the FDA commits to meeting performance objectives that are mutually agreed upon between the FDA and the industry, including specific time frames for conducting certain OTC monograph activities. (10)

There are two types of OMUFA User Fee:

- Facility Fee
- OMOR Fee

Facility Fees

FDA assess and collect annual facility fees from qualifying manufacturers of OTC monograph drugs. FDA will collect facility fees with respect to the two types of OTC monograph drug facilities: Monograph Drug Facility (MDF) and Contract Manufacturing Organization (CMO) facilities.

MDF is a foreign or domestic business or other entity that, in addition to meeting other criteria, is engaged in manufacturing or processing the finished dosage form of an OTC monograph drug.

CMO facility is an OTC monograph drug facility where neither the owner nor any affiliate of the owner or facility sells the OTC monograph drug produced at such facility directly to wholesalers, retailers, or consumers in the United States. (10)

The facility fee rate for MDF and CMO for FY 2024 is outlined below in the table:

Table 4: FY 2024 Facility User Fee Rates (10)

Fee Category	FY 2024 Fee Rates
Facility Fees:	
MDF	$34,166
CMO	$22,777

Payment of user fees

Payment must be made in U.S. currency by electronic check or wire transfer, payable to the order of the Food and Drug Administration. The preferred payment method is online using electronic check (Automated Clearing House (ACH) also known as eCheck) or credit card for payments under $25,000 (Discover, VISA, MasterCard, American Express). Payments must be made using U.S. bank accounts and by using U.S. credit cards. (11)

7. Conclusion

By not requiring premarket approval, there is a low regulatory burden for industry to market OTC drugs and that helps to keep OTC drug costs low to consumers. FDA is able to evaluate the safety and efficacy of thousands of OTC drug products by therapeutic category, instead of reviewing NDAs for each drug product. In addition, consistent with the lower regulatory burden provided under the previous monograph rulemaking process, the modifications made by the CARES Act do not require a product-by-product review of OTC drug products. The flexibility of the administrative order process allows for extensions to final order goal dates in response to numerous or substantive comments, demonstrating a commitment to thorough and thoughtful decision-making.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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