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# THE ORANGE BOOK PROTOCOL FOR HANDLING THE DISCONTINUED DRUG

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## 1. ABSTRACT

The Orange Book Protocol for handling discontinued drugs is an important resource for healthcare professionals, pharmacists, and patients. When a drug is discontinued, it can have significant implications for patient care, drug availability, and regulatory compliance. The Orange Book Protocol guides how to manage the discontinuation of drugs in a way that ensures patient safety and continuity of care. Our review article examines the process of adding drugs to the discontinued section, focusing on recent additions and with their identification, monitoring, and reporting according to FDA guidelines. We explore how manufacturers can access this information and provide practical guidelines for navigating the discontinuation process. By addressing gaps and challenges, our work contributes to a better understanding of drug availability and patient safety. One of the key aspects of the Orange Book Protocol is the identification of discontinued drugs. This involves regularly checking the FDA's Orange Book, which lists approved drug products with therapeutic equivalence evaluations. Once a drug has been **identified** as discontinued, the Orange Book Protocol guides how to manage existing supplies of the drug. In addition to **managing existing supplies**, the Orange Book Protocol also addresses the communication of discontinuation to healthcare providers and patients. Another important aspect of the Orange Book Protocol is the **reporting** of drug discontinuations to the FDA. By reporting discontinuations, healthcare professionals and drug manufacturers contribute to the overall safety and effectiveness of the drug supply chain. The Orange Book Protocol also emphasizes the importance of **post-discontinuation monitoring**. Healthcare professionals are encouraged to monitor patients who were previously taking the discontinued drug to assess their response to alternative treatments and identify any adverse effects. This ongoing monitoring is essential for ensuring that patients continue to receive high-quality care following the discontinuation of a drug.

**KEYWORDS:** FDA, Orange Book, drug discontinuation, guidelines.

## 2. INTRODUCTION

The FDA manages the Orange Book, which lists approved drugs and their details. They keep updating, based on user feedback to make it more useful. By linking data sources to help generic drug makers find information easily.[6] FDA officials recognize the benefits of proposed improvements but also note challenges due to labor and data accessibility.[7] The Orange Book, mandated under the FD&C Act, serves as a regulatory resource for drug marketing availability, bioequivalence, drug substitution, and patent and exclusivity data. It helps applicants for generic drugs by providing essential information for their submissions.[8] FDA guidance on the Orange Book answers common questions, clarifying its content and format. The guidance highlights that "should" indicates recommendations, not requirements.[9]

The Orange Book is a listing of medication and prescription drugs that the U.S. Food and Drug Administration (FDA) has accredited as each secure and effective. Although it is commonly called the Orange Book, its formal name is Approved Drug Products with Therapeutic Equivalence Evaluations. However, a drug that is currently subject to regulatory action may still appear in the Orange Book.

The Orange Book was first proposed in January 1979 and published in October 1980, with the name derived from the orange-colored cover of the printed book.

### 2.1 The Orange Book has four main sections

- Prescription Drug Product List: Approved prescription drugs with therapeutic equivalence evaluations.

- OTC Drug Product List: Approved over-the-counter drugs.
- Drug Products with Approval under Section 505: Administered by the Center for Biologics Evaluation and Research.

Discontinued Drug Product List: Cumulative list of approved drugs that are no longer marketed or have been withdrawn for various reasons.[10]

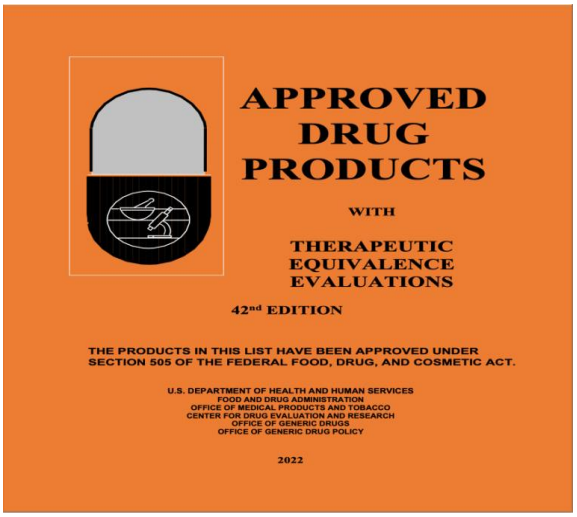


**Fig1: Orange Book of Usfda.**

**2.2 The Orange Book serves several purposes**.

1. Provides crucial information like application and approval dates, patents, and expiry dates.
2. Identifies innovator drugs and their approved generic versions.
3. Helps pharmaceutical companies make strategic decisions and safeguard innovations through patent filings.
4. Identifies exclusivity periods for approved drugs, aiding in understanding market competition timelines.
5. Helps identify polymorphs of patented drugs and allows for challenges to these patents.
6. Allows easy search for approved drugs based on various criteria like name, ingredient, and dosage form.[10]

**2.3Hatch-Waxman Act**

Orange book work on an called, Hatch-Waxman Act, also called the Drug Price Competition and Patent Term Restoration Act, is a federal law passed in 1984. It's crucial for the Orange Book because it changed how generic drugs are regulated and what's in the book. Here how.

**2.3.1Abbreviated New Drug Application (ANDA)**

The Hatch-Waxman Act created the ANDA pathway for generic drugs, making it easier for manufacturers to get FDA approval by showing their drug is as effective as a brand-name one.

**2.3.2Patent Listing Requirements**

Under the Act, brand-name drug makers must give patent information to the FDA, which is listed in the Orange Book, helping generics makers identify barriers.

**2.3.3Patent Certification**

Generics makers must certify to the FDA about patents listed in the Orange Book. There are different certifications depending on the patent status.

There are several types of certifications, including:

1. Paragraph I Certification: The patent information has expired.
2. Paragraph II Certification: The patent is invalid or will not be infringed by the generic drug.
3. Paragraph III Certification: The generic manufacturer will begin marketing after the patent expires.
4. Paragraph IV Certification: The generic manufacturer asserts that the patent is invalid or not infringed and seeks immediate approval.
5. The Orange Book database published by the U.S. Drug and Food Administration (FDA) was analyzed for the frequency of occurrence of different counterions used for the formation of pharmaceutical salts.[11]

**2.3.4Exclusivity and Generic Delay**

The Act provides market exclusivity periods for some brand-name drugs, listed in the Orange Book, delaying generic versions' approval.

**2.3.5Bioequivalence and Therapeutic Equivalence**

The Act emphasizes that generic drugs should be as effective as brand-name ones. The Orange Book includes evaluations of this, helping identify interchangeable generics.

**2.3.5 Overall Impact**

The Hatch-Waxman Act changed generic drug regulation significantly, closely linked to the Orange Book's content and purpose.[12][13][14]

## 3. MATERIALS AND METHODS

**3.1Literature Search Strategy**

We conducted a comprehensive literature search to identify relevant studies, documents, and regulatory information pertaining to the Orange Book protocol for handling discontinued drugs. The search was performed using several electronic databases and search engines, including but not limited to PubMed, Web of Science, Scopus, and Google Scholar.

Keywords used in the search included "Orange Book protocol," "discontinued drugs," "FDA regulations," "Hatch-Waxman Act," "generic drug regulation," and related terms. Boolean operators such as AND, OR, and NOT were employed to refine the search and broaden the scope of relevant literature.

Additionally, we manually searched the reference lists of relevant articles and reviews to identify additional sources not captured through electronic searches.

The inclusion criteria for selecting literature encompassed documents discussing the regulatory framework of the Orange Book, FDA guidelines and policies related to discontinued drugs, implications of the Hatch-Waxman Act on generic drug regulation, and any relevant case studies or analyses of discontinued drug products. Exclusion criteria included non-English publications, duplicates, and studies not directly related to the Orange Book protocol or discontinued drugs.

The search strategy aimed to capture a comprehensive overview of the regulatory landscape and practical implications of handling discontinued drugs within the framework of the Orange Book protocol.

This search strategy ensured the thorough identification and retrieval of pertinent literature to inform the review of the Orange Book protocol for discontinued drugs.

## 4. DISCONTINUED DRUG PRODUCT

Products indexed in Drugs@FDA as "discontinued" are accepted merchandise which have in no way been marketed, were discontinued from marketing, are for navy use, are for export only, or have had their approvals withdrawn for reasons other than safety or efficacy after being discontinued from marketing.[15]

### 4.1Discontinued Section

Drug products in the discontinued section of the Orange Book are annotated with a footnote indicating they were not withdrawn due to safety or effectiveness concerns.

These annotations are based on determinations made since 1995 and published in the Federal Register.

The purpose of identifying these drug products in the Discontinued Drug Product List is to prevent multiple citizen petitions requesting the same determination.
Approved products are added to the Discontinued Drug Product List when the applicant informs the Division of Orange Book Publication and Regulatory Assessment (DOBPRA) that they are no longer being marketed.

Products may also be added if annual reports or other submissions to the FDA indicate they are not being marketed, or due to other administrative actions by the Agency.

Changes to the Orange Book are not influenced by the drug registration and listing requirements of Section 510 of the FD&C Act.

### 4.2.Changes To The Orange Book To Add Drug In Discontinued Section

- Applicants are asked to notify the Division of Orange Book Publication and Regulatory Assessment (DOBPRA) of any changes or corrections to the Orange Book, such as changes in ownership or a product's marketing status.
- This notification helps keep the Orange Book current and accurate.
- According to Section 506I(a) of the FD&C Act, applicants must inform the FDA in writing at least 180 days before withdrawing a drug product from sale. If 180 days is not feasible, they should notify the FDA by the date of withdrawal.
- Similarly, Section 506I(b) of the FD&C Act requires applicants to inform the FDA in writing within 180 days of a drug product's approval if it will not be available for sale within the next 180 days.
- If a newly approved product is intended to be discontinued rather than listed in parts 1 or 2 of the Orange Book, a request must be submitted to DOBPRA by the end of the month in which the product is approved. This ensures the product is not listed as "active" in the next published Orange Book update.
- The notification allows the FDA sufficient time to react and take necessary actions.
- If providing 180 days' notice is not feasible, the company should inform the FDA by the date of withdrawal from sale.
- This ensures the FDA is informed promptly if circumstances prevent the full 180-day notice.
- During the 180 days before withdrawal, all remaining product should be unexpired.
- This ensures that any product available for sale during this period is still within its expiration date.
- Companies should adhere to all procedures regarding resupply and receiving back any expired product.
- Following these procedures helps maintain the integrity of the supply chain and ensures compliance with regulations.
- It's essential for companies to regularly check Federal Register notices.
- This helps companies stay informed about any updates or changes in regulations or requirements issued by the FDA.[16]

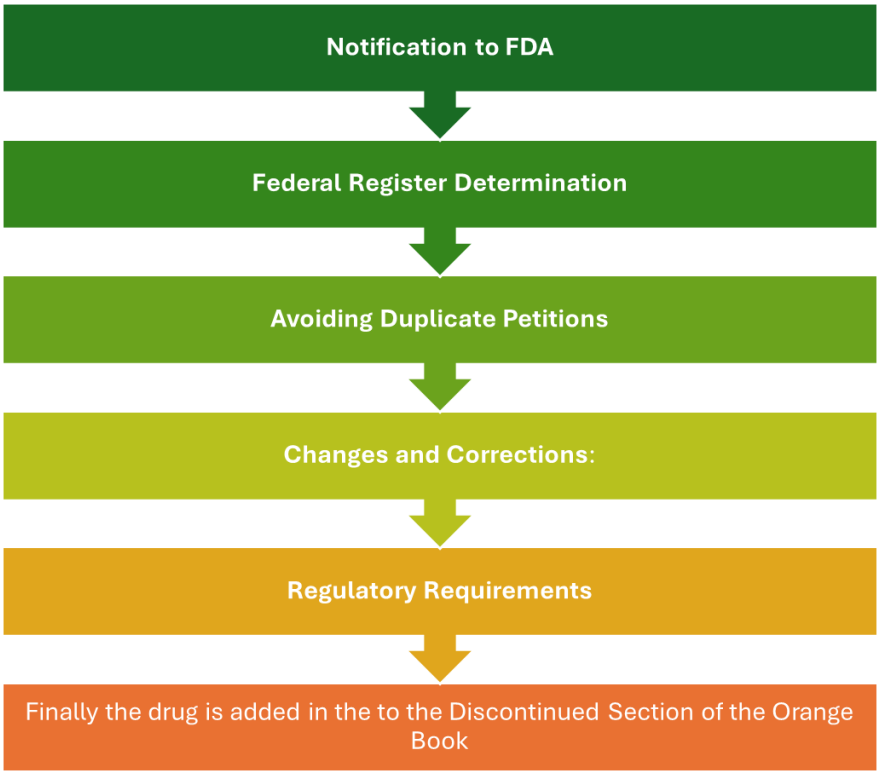


**Fig 2: Protocol For Drug To Added In Discontinued Section of Orange Book.**

**4.3. Protocol For Drug To Added In Discontinued Section**.

The process for a drug to be added to the Discontinued Section of the Orange Book involves several steps as outlined in the provided sources.

- **Notification to FDA**: Generally, approved products are added to the Discontinued Drug Product List when the applicant notifies the Division of Orange Book Publication and Regulatory Assessment (DOBPRA) of the product's not-marketed status. This notification can be made through annual reports or other submissions to the Agency indicating that the product is not being marketed or as a result of other Agency administrative actions.
- **Federal Register Determination**: For drug products in the Discontinued Section for which a determination has been made that they were not withdrawn for safety or effectiveness reasons, an annotation is added following the product strength stating, "Federal Register determination that product was not discontinued or withdrawn for safety or effectiveness reasons." These determinations listed in the Orange Book reflect determinations made since 1995 and published in the Federal Register.
- **Avoiding Duplicate Petitions**: The identification of drug products in the Discontinued Drug Product List aims to prevent the submission of multiple citizen petitions requesting determinations for the same drug product.
- **Changes and Corrections**: Applicants are encouraged to inform DOBPRA of any changes or corrections, including changes in ownership or marketing status that would result in the product being moved to the Discontinued Drug Product List.
- **Regulatory Requirements**: Changes to the Orange Book are not affected by the drug registration and listing requirements of Section 510 of the FD&C Act. Applicants must notify the Agency in writing 180 days prior to withdrawing a drug product from sale, or within 180 days of approval if the drug product will not Be to be had on the market inside a hundred and eighty days of approval. In the process for a drug to be added to the Discontinued Section of the Orange Book involves notification to the FDA, Federal Register determinations, avoiding duplicate petitions, informing DOBPRA of changes or corrections, and compliance with regulatory requirements regarding drug withdrawals and marketing status.

**4.4 Notification To Fda**

Under Section 506C: Certain persons are required to notify FDA of:

Permanent discontinuance in manufacturing certain finished drug and biological products.

Interruption in manufacturing certain finished drug and biological products likely to lead to a meaningful disruption in supply.

Permanent discontinuance in manufacturing API for certain finished drugs and biological products.

Interruption in manufacturing API for certain finished drugs and biological products likely to lead to a meaningful disruption in API supply.

#### 4.4.1. Notification Requirements

Notifications must disclose reasons for discontinuation or interruption.

Timely, informative notifications recommended to aid FDA in preventing or mitigating shortages.

#### 4.4.2. Assessment by FDA

FDA assesses potential public health impact upon receiving notifications.

Further discussion may be requested with the reporting manufacturer if deemed appropriate.

#### 4.4.3. Assessment Criteria

Analysis focuses on whether a change in production will significantly reduce supply.

Manufacturer should not base assessment on competitors' capacities or market demand.

#### 4.4.4. Timely Notification

Manufacturers advised not to delay notifying FDA until after production cessation.

FDA should be notified well in advance to prevent supply decline.

This outlines the essential points regarding the notification process to FDA concerning permanent discontinuance or interruptions in manufacturing of certain drug and biological products.

### 4.5. NOTIFICATION TO FDA DRAFT GUIDANCE

#### 4.5.1. PURPOSE OF THE GUIDANCE

FDA released a draft guidance on February 5, 2024, to aid applicants and manufacturers in notifying the agency about changes in the production of drugs, biologics, and APIs.

The guidance aims to prevent drug shortages and outlines how FDA communicates with the public about such shortages.

#### 4.5.2. REQUIREMENTS UNDER SECTION 506C OF THE FD&C ACT

Section 506C mandates applicants and manufacturers to notify FDA of:

Permanent discontinuance or interruption in manufacturing of certain finished drug and biological products.

Permanent discontinuance or interruption in manufacturing of API for such products.

Notifications should disclose reasons for the discontinuation or interruption.

#### 4.5.3. WHO MUST NOTIFY FDA AND WHICH PRODUCTS ARE SUBJECT

Manufacturers covered under the notification requirement include:

Applicants with accredited BLAs for positive completed organic products.

Manufacturers of positive completed drug merchandise advertised with out accredited NDAs or ANDAs.

Other entities in the supply chain for drugs, such as third-party API manufacturers, are not obligated to notify FDA.

#### 4.5.4. TIMING OF NOTIFICATION

Manufacturers must notify FDA at least six months before a discontinuance or interruption.

If six months' notice is not feasible, notification should be made as soon as possible.

Notifications for discontinuances or interruptions must be submitted no later than 5 business days after occurrence.

#### 4.5.5. INFORMATION TO INCLUDE IN NOTIFICATIONS

Notifications must include.

Product name, applicant/manufacturer details, and reason for discontinuation or interruption.

For API-related issues, disclose API source and any alternatives known by the manufacturer.

Additional information recommended includes supply disruption details, market share, inventory status, and potential impact on public health.

#### 4.5.6. HOW TO NOTIFY FDA

Manufacturers should submit initial notifications via email or FDA's NextGen Portal.

Separate notifications are required for each discontinuance or interruption.

Failure to notify FDA may result in noncompliance letters and public disclosure of noncompliance.

#### 4.5.7. COMMUNICATION OF SHORTAGE INFORMATION BY FDA

FDA maintains public lists of drug and biological products in shortage, including product details and reasons for shortage.

Updates are provided regularly to ensure stakeholders have current information on shortages.

FDA evaluates market conditions to determine when a shortage is resolved and removes products from the shortage list accordingly.

This draft guidance aims to streamline the notification process, facilitate effective communication between manufacturers and FDA, and ensure timely and accurate information is available to prevent and address drug shortages.[18][23]

**4.6. However, the protocol for different product and API differ from each other slightly. there are.**

1 permanent discontinuance or interruption in manufacturing biological product.
2 permanent discontinuance or interruption in manufacturing prescription and otc drug product.
3 permanent discontinuance or interruption in manufacturing api permanent discontinuance or interruption in manufacturing of certain drug or biological products.

**4.6.1. Biological Products**

The FDA is focusing on notifying them about shortages of medical products like plasma-based medicines, vaccines, and blood for transfusions.

For plasma-based medicines, direct notifications from all manufacturers are preferred to ensure better tracking of shortages.

Vaccine manufacturers are encouraged to inform the FDA directly about supply issues, as not all vaccines are reported to the CDC, and the information shared might not be detailed enough for the FDA's needs.

Regarding blood for transfusions, although systems exist to monitor supply, the FDA wants direct notifications from major blood suppliers to predict significant shortages.

**NOTIFICATION**

Permanent Discontinuance: If a manufacturer decides to stop making a drug indefinitely, they must tell the FDA.

**Interruption in Manufacturing**: Manufacturers must inform the FDA if there's a problem in making a drug that could lead to a significant shortage in the United States. This doesn't include routine issues like maintenance.

**Timing and Submission**: Manufacturers should notify the FDA at least 6 months before a discontinuance or interruption happens, or as soon as possible if 6 months' notice isn't possible. Notifications should be sent electronically to specific FDA email addresses.

**Contents of the Notification:** Notifications should include details like the name of the drug, why it's being discontinued or.

**Failure to Notify**

Manufacturers who don't notify the FDA on time will receive a warning letter. They have 30 days to respond, explaining why they didn't notify on time. If the FDA finds their reasons.

**Method of Notification:** Notifications should be submitted electronically to designated FDA email addresses, ensuring prompt and efficient communication.

**Consequences of Non-compliance:** Failure to comply with the notification requirements may result in FDA action, including issuing warning letters to the manufacturer.

**Estimated Costs and Benefits:** The implementation of this rule is estimated to cost drug and biological product manufacturers up to $40.54 million annually.

The FDA is expected to spend up to $6.38 million annually to prevent shortages.

Despite these costs, the benefits of avoiding expensive alternative products and improving patient care could outweigh them, ranging from $30.45 million to $98.65 million annually over 20 years.[21]

**4.6.2. PRESCRIPTION AND OTC DRUG PRODUCT DISCONTINUATION IN ORANGE BOOK**

Over the counter(OTC) drugs are medicines that can be purchased without a doctor's prescription, while prescription drugs, often referred to as Rx drugs, require a doctor's prescription. OTC drugs are intended for general use and are safe when used as directed, while prescription drugs are more heavily regulated and are prescribed for specific individuals and conditions. Prescription drugs are prescribed by a doctor and bought at a pharmacy, while OTC drugs can be bought off-the-shelf in stores. The FDA regulates both types of drugs, but through different processes: prescription drugs go through the New Drug Application (NDA) process, while OTC drugs are regulated through OTC Drug monographs, which cover acceptable ingredients, doses, formulations, and labeling. The process for discountinuation for Prescription and OTC Drug Product flow the same process as mention above topics.

**Re-Marketing of Drug Products**

Occasionally, drug products listed as discontinued may reappear with the notation "CMFD" in the Orange Book Cumulative Supplement, indicating a change in marketing status.

**Reasons for re-marketing may include**

Transfer of ownership in the NDA or ANDA, with the purchasing company intending to reintroduce the drug to the market.

Approval withdrawal for products in the discontinued list, signaling that they will not be re-marketed.

**Implications of Re-Marketing**

Re-marketed drugs may offer opportunities for new manufacturers to enter the market through ANDA applications, especially if the original brand-name drug is no longer available.

However, FDA must ensure that re-marketed drugs meet safety and effectiveness standards before being reintroduced to the market.

Before, it was easy for companies to move a drug from the "Discontinued Drug Product List" to the "Prescription Drug Product List" or the "OTC Drug Product List."

But something happened a few years ago with a drug that was put back on the market after being discontinued, and the FDA made the process more formal.

**Process**
Now, when a company tells the FDA they want to sell a drug again, the FDA asks some questions.

The company needs to send a letter to the FDA with details and also copy it to the Orange Book inbox.

**Timing**
It's better to send this information to the FDA at least two months before planning to sell the drug again, so they have time to process the request.[17]

**4.6.3.API DISCONTINATION IN ORANGE BOOK**
Active Pharmaceutical Ingredients (APIs) are essential chemical compounds primarily manufactured in key regions such as the USA, Europe, China, and India. These compounds serve as the backbone of various medications, playing crucial roles in diagnosing, curing, mitigating, and treating a wide range of diseases. In recent years, there has been a notable shift in the pharmaceutical industry towards embracing microbial-based fermentation methods for API production. This transition has been fueled by growing concerns over the environmental impact of traditional chemical-based manufacturing processes.

The pharmaceutical industry is shifting towards microbial-based fermentation methods for making Active Pharmaceutical Ingredients (APIs) due to environmental concerns. This method is economically viable and shows promise for reducing pollution.

Challenges persist in environmental sustainability as chemical-based API production contributes to pollution and contaminates water sources.

Using biomass, especially lignocellulosic biomass, is gaining interest as a renewable resource for API production, but there are challenges like pretreatment and economic barriers.
Advancements in genetic and metabolic engineering offer solutions for producing APIs sustainably from renewable biomass sources.

The FDA's guidance covers both permanent discontinuances and temporary interruptions in drug manufacturing, including over-the-counter drugs, and aims to inform the public about shortages while collaborating with manufacturers to mitigate risks to public health The scope of the guidance includes both permanent discontinuances and temporary interruptions in drug manufacturing, including over-the-counter drugs (OTC) and products manufactured without an NDA or ANDA. It addresses interruptions in both drug production and the supply of APIs.

The FDA aims to keep the public informed of drug shortages and collaborate with manufacturers to mitigate risks to public health. This guidance reflects the agency's efforts to address and manage disruptions in drug supply to ensure continued access to essential medications.[18][19][20][21]

**5. SYMBOL FOR ADDITION AND DELETION OF PRESCRIPTION AND OTC DRUG PRODUCT IN ORANGE BOOK**
The FDA Provides, Prescription and OTC Drug Products list of the new additions and new deletions to the Prescription and OTC Drug Product Lists for a specific month.

Additions and deletions are identified in this document by the symbols >ADD> and >DLT>, respectively. Products which have in no way been marketed, had been discontinued from advertising or which have had their approvals withdrawn for apart from protection or efficacy reasons, could be flagged in this Cumulative Supplement with the "@" image to designate their non-advertised status.

All merchandise having a "@" image withinside the twelfth Cumulative Supplement of the modern Edition List will then be brought to the "Discontinued Drug Product List" of the subsequent Edition.

- >ADD> or >A> indicates Addition
- >DLT> or >D> indicates Deletion
- @ indicates drugs that have been discontinued from marketing or that have had their approvals withdrawn for other than safety or efficacy reasons[22]

**5.1 PROCESS TO ACCESS UPDATED AND NEW LIST OF DISCONTINUED DRUGS ON FDA WEBSITE**
The FDA contain a staff which on regular bases called as the Drug Shortages Staff (DSS) determines that the market is covered, based on information collected from all manufacturers. It checks the market covered that is when supply is available from at least one manufacturer to cover total market demands. However, sometimes manufacturers may not have all resources available. DSS keep in check the supply of products with Resolved status. For the most recent supply information, contact the manufacturers.[28]


**Fig 4: Flow Chart Represting Steps To Acess Updated And New List Of Discontinued Drugs On Fda Website.**

#### 5.1.1. Resolved Status

A drug receives "Resolved" status when the Drug Shortages Staff (DSS) determines that the market is covered and there is enough supply to meet the total demand.

#### 5.1.2. Market Coverage

The market is considered "covered" when supply is available from at least one manufacturer to meet the total market demand.

However, not all manufacturers may have all presentations (e.g., different strengths, formulations) of the drug available.

#### 5.1.3. Monitoring Supply

The DSS continues to monitor the supply of products with Resolved status.

#### 5.1.4. Obtaining Current Supply Information

For the most up-to-date information on the supply of a drug with Resolved status, users should contact the manufacturers directly.

However, the availability of all product presentations may vary across different manufacturers. The DSS monitors the supply, and users should reach out to the manufacturers for the latest information on product availability.

**Table 1: Recently Updated And New List Of Discontinued Drugs.**

| S.No | DISCOUNTINUE DRUG NAME | DATE /MONTH/YEAR |
|---|---|---|
| 1 | Lacosamide Tablet | 15 APRIL2024 |
| 2 | Cisatracurium Besylate Injection | 15 APRIL 2024 |
| 3 | Evolocumab Injection | 12 APRIL 2024 |
| 4 | Clobetasol Propionate Cream | 03 APRIL 2024 |
| 5 | Morphine Sulfate Tablet, Extended Release | 03 APRIL 2024 |
| 6 | Fluconazole Tablet | 28 MARCH 2024 |
| 7 | Linezolid Tablet | 28 MARCH 2024 |
| 8 | Amifostine Injection | 16 APRIL 2024 |

### 5.2 STEPS TO ACCESS THE DISCOUNTINUE DRUG LIST FROM THE OFFICIAL WEBSITE OF FDA (US FOOD AND DRUG ADMINISTRATION

STEP 1: On US FDA OFFICIAL site home page, search on drug data base.
STEP 2: Then select drug short age, the drug shortage provides Current and Resolved Drug Shortages and Discontinuations Reported to FDA.
STEP 3: From the options given one can access the Current and Resolved Drug Shortages and Discontinuations, therapeutic category of shortage.
STEP 4: Select on to the option new and update, the following data on the Current and Resolved Drug Shortages and Discontinuations can be accessed .the list get updated frequently.

## 6. CASE STUDIES

### 6.1TROGLITAZONE (REZULIN)

**Title**: Withdrawal of Troglitazone (Rezulin) from the Market Due to Liver Toxicity: A Case Study.

#### Introduction

Troglitazone, marketed under the brand name Rezulin, was introduced in 1997 as a promising treatment for type 2 diabetes. It belonged to the thiazolidinedione class of drugs and was hailed for its ability to effectively lower blood glucose levels in diabetic patients. Initial clinical trials showed promising results, leading to its approval by the United States Food and Drug Administration (FDA) for use in diabetic management.

#### CASE STUDY

However, post-marketing surveillance soon revealed alarming safety concerns associated with troglitazone use. Reports of serious liver damage, including instances of liver failure and death, emerged, prompting regulatory action. In response to mounting evidence, the FDA mandated a black box warning on the drug's label in 1997, alerting healthcare providers and patients to the potential risks of liver toxicity. Despite this precautionary measure, reports of liver-related adverse events continued to surface.

The FDA's concerns escalated in 2000 when the agency requested the manufacturer, Parke-Davis, to voluntarily withdraw troglitazone from the market due to the unacceptable risk of liver injury associated with its use. The decision to withdraw the drug was not limited to the United States; it also extended to other countries, including Germany, where similar safety concerns were

raised. The withdrawal of troglitazone marked the end of its brief but troubled tenure in the pharmaceutical market, underscoring the importance of stringent safety monitoring and regulatory oversight in drug approval and post-market surveillance.

**SUMMARY**

The withdrawal of troglitazone from the market serves as a cautionary tale highlighting the potential pitfalls of pharmaceutical development and regulation. Despite initial promise, the drug's association with severe liver toxicity ultimately outweighed its therapeutic benefits, leading to its removal from circulation. The troglitazone case underscores the importance of robust post-market surveillance mechanisms and the need for prompt regulatory action in response to emerging safety concerns. It also underscores the ethical imperative of prioritizing patient safety above commercial interests in drug development and marketing decisions.[1][2][3]

**6.2ALISKIREN (RASILEZ, TEKTURNA)**

**Title:** Discontinuation of Aliskiren (Rasilez, Tekturna) Due to Safety Concerns: A Case Study.

**Introduction:** Aliskiren, a direct renin inhibitor, emerged as a promising treatment for hypertension, offering a novel mechanism of action targeting the renin-angiotensin system. Marketed under the brand names Rasilez and Tekturna, it represented a first-in-class drug in its category.

Key points about the aliskiren case.

- Aliskiren was developed as a first-in-class direct renin inhibitor and demonstrated efficacy in lowering blood pressure.
- During clinical trials, aliskiren was generally well-tolerated, with the most common side effects being mild gastrointestinal issues like diarrhea.
- However, in 2011, Novartis terminated the ALTITUDE study, which was evaluating aliskiren in high-risk patients with diabetes and renal impairment.
- The ALTITUDE study was stopped early due to an increased rate of adverse events when aliskiren was added to an ACE inhibitor or ARB drug in this high-risk patient population.
- Following the termination of the ALTITUDE study, Novartis announced it would be discontinuing the development and marketing of aliskiren-based products due to safety concerns.

**SUMMARY**

While aliskiren demonstrated efficacy as an antihypertensive medication, its discontinuation stemmed from safety issues that surfaced during the ALTITUDE study, particularly in high-risk patients with coexisting diabetes and renal impairment. The decision underscores the critical importance of ongoing safety monitoring and evaluation throughout the lifecycle of pharmaceutical products. It serves as a reminder of the pharmaceutical industry's ethical obligation to prioritize patient safety above commercial interests.[4][5]

**Table 2: Differences Between Withdrawn & Discontinued Drugs.**

| Aspect | Withdrawn Drugs | Discontinued Drugs |
|---|---|---|
| Definition | Drugs that have been removed from the market due to safety concerns or lack of efficacy | Drugs that have been halted from further development or production for various reasons |
| Reason | Safety concerns (e.g., adverse effects, risks outweigh benefits) or lack of efficacy | Lack of efficacy, safety concerns, commercial reasons, strategic shifts, or market demand |
| Regulatory Action | Usually mandated by regulatory agencies | Decision made by the pharmaceutical company |
| Timing | Can occur at any stage post-approval | Typically occurs during clinical development or before approval |
| Legal Implications | Often accompanied by regulatory investigations, lawsuits, and recalls | May involve financial losses and redirection of resources, but usually fewer legal implications |
| Impact on Market | Generally has a significant impact on public health and healthcare systems | May impact the company's financial performance and reputation, but often has a lesser public health impact |

Offend the discontinued drug misunderstood as withdrawal drug here are the difference between both to get better understanding.

**7. CONCLUSION**

The Orange Book is an important resource for healthcare providers, patients, and drug manufacturers. The discontinued section of the Orange Book provides information about drugs that have been withdrawn from the market or are no longer being manufactured. The process for adding a drug to the discontinued section is relatively straightforward and involves notifying the FDA of the discontinuation and providing the necessary information. The discontinued section of the Orange Book is a valuable resource for identifying drugs that are no longer available and for making informed treatment decisions.

**8. ACKNOWLEDGEMENT**

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Sure, I can help format the references you provided. Since there are quite a few references and they vary in format, I'll format each one individually.

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