

Marketed, Unapproved Drugs

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**Division of New Drugs and Labeling Compliance
Office of Compliance
Center of Drug Evaluation and Research
Food and Drug Administration**

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Objectives

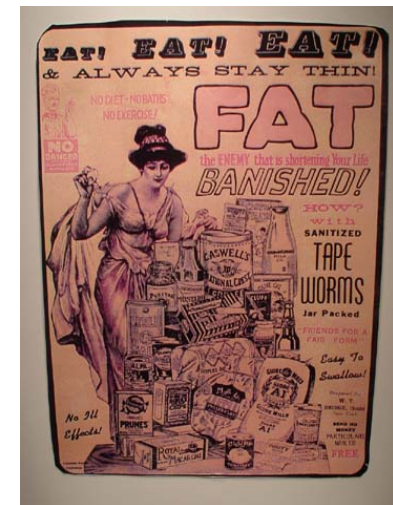
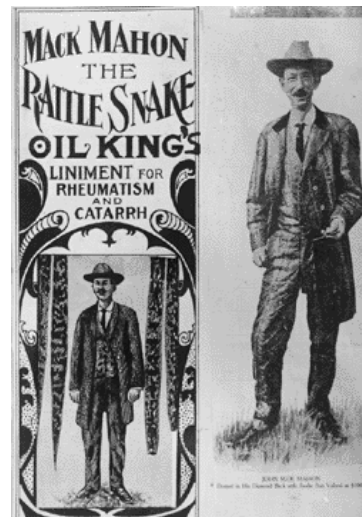
- Become familiar with the history of drug regulation in the U.S.
- Understand the public health risk associated with marketed, unapproved drugs.
- Learn about FDA's Marketed, Unapproved Drug Initiative.
- Learn how to utilize FDA resources to determine the approval status of drugs.
- Understand the role of the pharmacist with respect to marketed, unapproved drugs

History of Drug Regulation in the United States

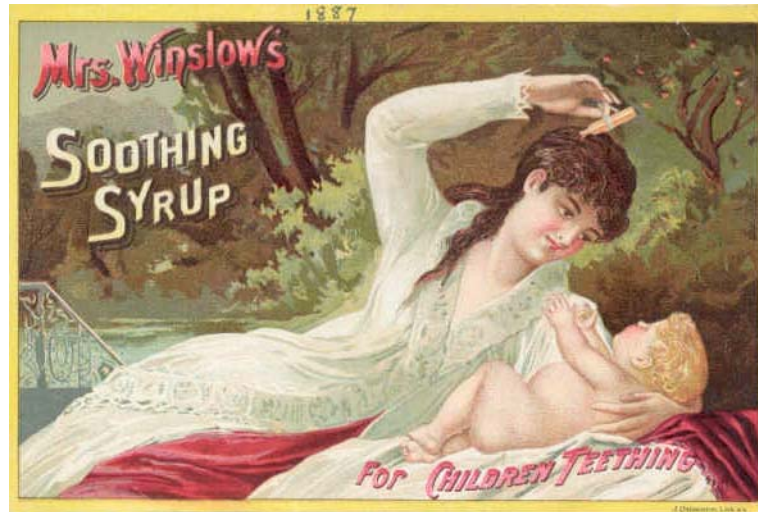


History of Drug Regulation in the United States-continued

Prior to 1906 – anything went!

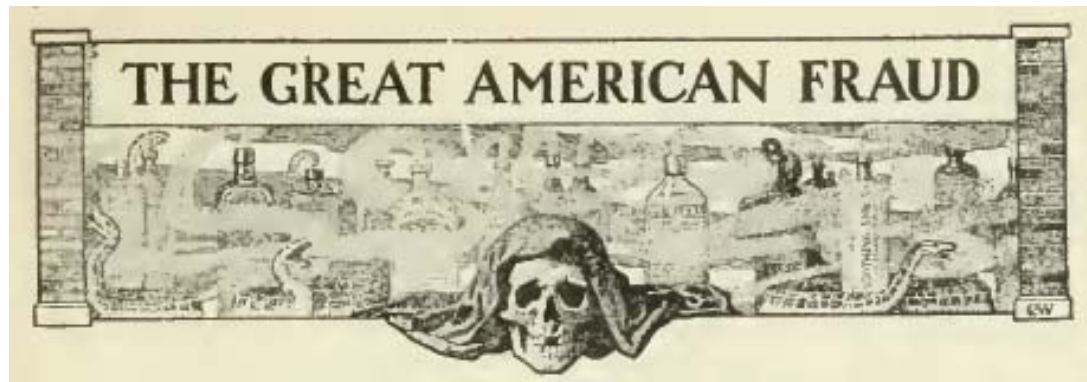


History of Drug Regulation in the United States-continued



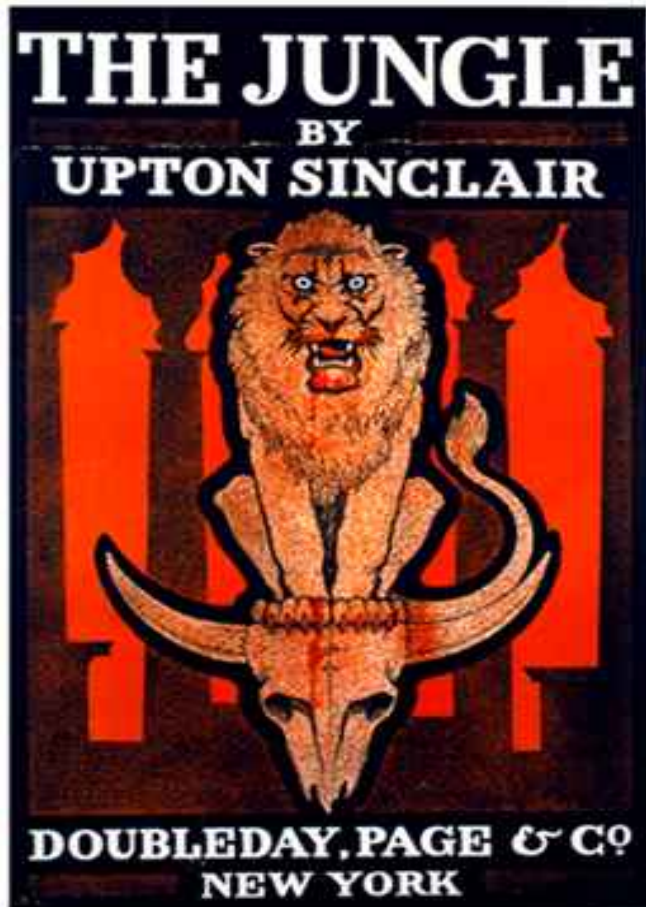
“For children teething. Greatly facilitates the process of Teething, by softening the gums, reducing all inflammation; will allay ALL PAIN and spasmodic action, and is SURE TO REGULATE THE BOWELS. Depend on it, Mothers, it will give rest to yourselves and RELIEF AND HEALTH TO YOUR INFANTS. Sold by chemists, at 1s 1/2d per bottle.”

History of Drug Regulation in the United States-continued



- 1905: The 10-part series titled “The Great American Fraud” by Samuel Hopkins Adams was published in Collier’s.
 - Exposed fraud in the patent medicine industry, medical quackery, and described the harmful effects of these malpractices on the American public

1905



Federal Food and Drugs Act of 1906 (Pure Food and Drugs Act; The Wiley Act)

- Complete freedom to market
- No requirement for testing or approval
- Failed to regulate medical devices or cosmetics
- Gave the Bureau of Chemistry the authority to test food and drugs for adulteration or misbranding
- Promotes accurate labeling and purity of food and drugs

Federal Food and Drugs Act of 1906 -continued

- Identified the United States Pharmacopeia (USP) and National Formulary (NF) as the official standards for drugs
- Prohibited the manufacture and interstate shipment of “adulterated” and “misbranded” drugs
- Defined two bases for seizing a drug
 - Adulteration
 - Misbranding

The Elixir Sulfanilamide Disaster-1937

- 107 deaths, mostly children
- Product seized because it was misbranded (it was labeled as an elixir, yet it contained no alcohol!)



Photo courtesy of FDA.

Federal Food, Drug and Cosmetic Act (FD&C Act) of 1938

- Requires proof of safety prior to marketing
- Requires submission of a New Drug Application
- Creates category called “new drugs”
 - Not generally recognized as safe (GRAS) for use in the conditions prescribed, recommended, or suggested in the labeling, and
 - Has not been used to a material extent or time under such conditions

Federal Food, Drug and Cosmetic Act (FD&C Act) of 1938 -continued

- Required that drugs be labeled with adequate directions for safe use
- Formally authorized FDA to conduct factory inspections
- Required that safe tolerance levels be set for necessary poisonous substances
- Prohibited false therapeutic claims

Federal Food, Drug and Cosmetic Act (FD&C Act) of 1938

-continued

- Retains ability to seize drugs that are:
 - Misbranded
 - Adulterated
- “Grandfathered Drugs”
- Still no distinction between prescription and nonprescription drugs

Humphrey-Durham Amendment - 1951



Caution:
Federal law
prohibits
dispensing
without
prescription

"... because of its toxicity or other potential for harmful effect or because the method of collateral measures necessary to its use, it may safely be sold and used only under the supervision of a practitioner."

Thalidomide Disaster - 1961

FDA medical officer Frances Kelsey refused to recommend approval of the NDA for Kevadon, a brand of thalidomide that a company hoped to market in the U.S., because of insufficient safety data.



Kefauver-Harris Amendments - 1962

- Established rules for new drug investigation, including informed consent for study subjects in clinical trials
- Established Good Manufacturing Practices (GMPs)
- Adverse event reporting
- Transferred regulation of **prescription** drug advertising from the Federal Trade Commission to the FDA

Kefauver-Harris Amendments – 1962

...continued

- Required that drugs be proven **effective**, as well as safe, prior to marketing
 - ***The definition of the term “new drug” was amended to “any drug...not generally recognized as safe **and effective** (GRASE) for use under the conditions prescribed, recommended or suggested in the labeling...”
- Required a retrospective evaluation of efficacy of drugs approved for safety between 1938 and 1962

Waxman-Hatch Act of 1984

- Created the generic drug industry
- Birth of the ANDA –Abbreviated New Drug Application
- Allowed generic firms to rely on findings of safety and efficacy of innovator drug after expiration of patents and exclusivities (do not have to repeat expensive clinical and pre-clinical trials)
- Common misconception that Unapproved Drugs are Generic Drugs—this is NOT TRUE!!!

Note: Unapproved Drugs are NOT Generic Drugs!!!

Legal Description: Bottom Line

All drugs **must** have FDA approval or comply with an Over the Counter (OTC) monograph, unless...

1. DESI pending
2. OTC drug subject to a tentative final monograph
3. “Grandfathered”
4. Generally recognized as Safe/Effective (GRASE)

Legal Description: Bottom Line

1. DESI pending

- National Academy of Sciences/National Research Council (NAS/NRC) contracted to make an initial evaluation of effectiveness for all drugs approved as safe between 1938 and 1962
- According to the Act, all drugs reviewed under DESI are considered “new drugs.” They are not considered GRASE or grandfathered.
- Over 3,400 products evaluated, as well as an even larger number of identical, related, or similar (IRS) drugs
- FDA reviewed and reevaluated the NAS/NRC reports and published the findings in Federal Register notices

Legal Description: Bottom Line

DESI pending (continued)...

- If final determination classified a drug as **Effective** for one or more indications, that drug and those Identical, Related, or Similar (IRS) to it can be marketed for such indications, ***provided*** each product is the subject of an application approved for safety AND effectiveness.
- If the final DESI determination classified one or more indications for a drug and those IRS to it as **Lacking Substantial Evidence of Effectiveness (LSEE)**, a Notice of Opportunity of Hearing (NOOH) was published in the Federal Register. Firms could either submit a Hearing Request to contest the DESI classification of LSEE for the affected indication(s) or discontinue marketing of the drug for the LSEE indication(s).

Legal Description: Bottom Line -continued

2. Tentative Final Monographs

- Tentative Final Monograph
 - OTC drugs covered by ongoing monograph proceedings may remain on the market, subject to current enforcement policies
- OTC Final Monograph
 - Monograph = “Recipe” for an OTC drug; lists the acceptable ingredients, permissible claims, doses, formulations, and labeling.
 - Drugs marketed under a final OTC monograph are considered GRASE and do not require FDA approval
 - OTC monographs have been finalized for the majority of OTC drugs

Legal Description: Bottom Line -continued

3. “Grandfathered” drugs

- **1938 Clause**: Drug must have been marketed prior to 6/25/1938 and no change in formulation, dosage, strength, manufacture, indications, etc., since that time in order to be considered “grandfathered”
- **1962 Clause**: Drugs marketed prior to 10/10/1962 are exempt from the effectiveness requirements if...
 - Composition and labeling have not changed since that date
 - Used or sold commercially in US
 - Not a “new drug” as defined at that time
 - Not covered by an effective application

*****FDA believes that it is not likely that any currently marketed drugs are entitled to grandfather status.***

Legal Description: Bottom Line ...continued

4. GRASE (Generally Recognized As Safe and Effective)

- Requires a consensus among experts that the product is safe and effective based on published scientific literature regarding the finished drug product of the same quality and quantity needed to approve a drug.
- The Agency believes it is not likely that any currently marketed prescription drug is GRASE.



Categories of Unapproved Drugs on the Market

1. DESI pending drugs and those drugs that are identical, related, or similar (IRS) to them
2. Pre-1938 and pre-1962 drugs not subject to DESI review.
 - Drugs that claim to be marketed pre-1938 or IRS to such a drug
 - Drugs on the market pre-1962 without FDA approval for safety and those drugs that were IRS to them
3. Post 1962 Drugs
 - First marketed after 1962
 - Drugs marketed before 1962, but were changed after 1962

Why Are Unapproved Drugs a Public Health Problem?

1. Unapproved Drugs may be unsafe.
 - There may not always be a documented safety risk: the absence of proof of a problem is not proof of the absence of a problem
 - Affirmative safety problems
E.g., E-Ferol, Quinine, Carbinoxamine



Why Are Unapproved Drugs a Public Health Problem (cont'd)?

2. Unapproved Drugs may be **ineffective.**
 - E.g., Trimethobenzamide Hydrochloride suppositories
 - Final DESI determination: Found to lack sufficient evidence of effectiveness (LSEE)
 - FDA withdrew approval for this product (5/2007)

Why Are Unapproved Drugs a Public Health Problem (cont'd)?

3. The product labeling for Unapproved Drugs is not FDA-approved.
 - Important information meant to ensure safe use, such as information about drug interactions and adverse events, may be omitted or modified.
 - Unapproved drugs may be labeled for use in populations for which there is not scientific support (e.g., pediatrics)

E.g., Unapproved Hydrocodone drug products
(11/2007)

Why Are Unapproved Drugs a Public Health Problem (cont'd)?

4. Concerns regarding the manufacturing processes for unapproved drugs and changes in the formulations of these products- the potential for drug quality deficiencies exists.

E.g., Unapproved sublingual nitroglycerin tablets

Why Are Unapproved Drugs a Public Health Problem (cont'd)?

5. No opportunity for FDA to review and approve trade names to minimize potential safety issues caused by name confusion between marketed drugs.

E.g.

Rynatan dispensed in place of Artane

Rythmol dispensed in place of Rynatan

Why Are Unapproved Drugs a Public Health Problem (cont'd)?

6. Challenge the integrity of the drug approval system

E.g., Unapproved Codeine sulfate tablets

7. Limited post-market surveillance; no periodic reporting

Why Are Unapproved Drugs a Public Health Problem (cont'd)?

8. There is a common **misconception** amongst healthcare practitioners and consumers, that all marketed drugs are FDA-approved, and therefore, are assumed to be safe and effective.
 - Misconception that all drugs listed in commonly used references are FDA-approved.
 - Misconception that assignment of an NDC number is equivalent to FDA approval.

Scope of the Unapproved Universe

- Thousands of prescription drugs are marketed without approval
 - Approximately 2% of the 3.6 billion prescriptions filled in the U.S. annually (2006 estimate)
 - Relatively broad range of drugs
 - Some firms specialize in marketing unapproved drugs

What is FDA doing about Unapproved Drugs??

- Unapproved Drugs Initiative: June 2006
- Eliminate all unapproved drugs from the market
- Marketed Unapproved Drugs-Compliance Policy Guide (CPG* 440.100) published in 2006.

*Compliance Policy Guide



Unapproved Drugs Initiative

CPG 440.100 - Marketed Unapproved Drugs -2006

- Improve the safety of the drug supply by enforcement and by encouraging the manufacturers of unapproved products to obtain the required evidence and submit marketing applications for their unapproved drugs
- FDA wants to achieve these goals without adversely affecting the public health, imposing undue burdens on consumers, or unnecessarily disrupting the market
- Provide notice that any product that is being marketed illegally is subject to FDA enforcement action at any time

Enforcement Priorities in the CPG

For all unapproved drugs:

- Drugs with potential **safety risks**
- Drugs that **lack evidence of effectiveness**
- **Fraudulent** drugs
- Unapproved drugs that **directly compete with an approved drug product**
- Drugs from manufacturers that are **otherwise violating the Act** (e.g. GMP violations, ADE reporting violations)
- Drugs with **formulation changes** made to avoid enforcement action

Enforcement Actions – Drug Class

- **Carbinoxamine** (June 8, 2006)
- **Quinine** (December 15, 2006)
- **Ergotamine** (March 1, 2007)
- **Trimethobenzamide** suppositories (April 9, 2007)
- Timed-Release **Guaifenesin** (May 29, 2007)
- **Hydrocodone** (September 28, 2007)
- **Colchicine** for Injection (February 6, 2008)
- **Balanced Salt Solution (BSS)** (Sept. 23, 2008)
- Topical drug products containing **Papain** (Sept. 22, 2008)
- **Narcotics** (Morphine Sulfate, Hydromorphone, Oxycodone) (March 31, 2009)
- **Codeine Sulfate Tablets** (October 13, 2009)
- **Nitroglycerin** Sublingual Tablets (March 16, 2010)
- **Epinephrine** 0.3 mg prefilled single dose syringe (June 6, 2010)
- **Colchicine** Oral Products (October 1, 2010)
- **Cough, Cold, and Allergy** Products (March 3, 2011)

How can you determine the approval status of a drug??

- Don't assume that just because a drug is listed in commonly used references, such as LexiComp, Facts and Comparisons, and American Hospital Formulary Service Drug Information (AHFS DI), that it is approved!!!
- FDA provides various resources that list approved drugs, such as Drugs@FDA, the Orange Book, and the NDC Directory

How can you determine the approval status of a drug??

- **Drugs@FDA:**

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda>

Contains a listing of most FDA-approved drug products, including:

- Prescription and over-the-counter human drugs with an approved drug marketing application (NDA or ANDA).
- Most therapeutic biologic products (approved BLA)



Drugs@FDA

U.S. Department of Health & Human Services

www.hhs.gov

FDA U.S. Food and Drug Administration

A-Z Index Search go

Home | Food Drugs | Medical Devices | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Radiation-Emitting Products | Tobacco Products

Drugs@FDA

FDA Approved Drug Products

Start Over Back to Search Results

FAQ | Instructions | Glossary | Contact Us

Overview

Drug Name

Active Ingredient(s)

Form(s) and Strength(s) Available

PROZAC

• FLUOXETINE HYDROCHLORIDE

• CAPSULE; ORAL: EQ 10MG BASE ; EQ 20MG BASE ; EQ 40MG BASE
• SOLUTION; ORAL: EQ 20MG BASE/5ML **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**
• TABLET; ORAL: EQ 10MG BASE ; EQ 20MG BASE

Details about drugs are organized by FDA Application Number (NDA or ANDA or BLA).
Click on a drug name or application number to view drug details:
Click on a column header to re-sort the table:

<u>Drug Name and FDA Application Number</u>	<u>Dosage Form/Route</u>	<u>Strength</u>	<u>Marketing Status</u>	<u>Company</u>
<u>PROZAC (NDA # 018936)</u>	CAPSULE; ORAL	Multiple Strengths	Prescription	LILLY
<u>PROZAC (NDA # 020101)</u>	SOLUTION; ORAL	EQ 20MG BASE/5ML **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**	Discontinued	LILLY
<u>PROZAC (NDA # 020974)</u>	TABLET; ORAL	Multiple Strengths	Discontinued	LILLY

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Disclaimer

How can you determine the approval status of a drug?? (continued)

- **Drugs@FDA**

Drug products not included are:

- Over-the-counter (OTC) products marketed under a final or pending monograph
- Biologic products regulated by the Center for Biologics Evaluation and Research (CBER)
- Dietary supplements (do not require FDA approval)
- Animal Drugs
- Unapproved Drugs, e.g., Phenobarbital Tablets



Drugs@FDA

The screenshot shows the Drugs@FDA website interface. At the top, there's a blue header with the U.S. Department of Health & Human Services logo and the website URL www.hhs.gov. Below this, the FDA logo and 'U.S. Food and Drug Administration' are displayed. A navigation bar includes links for Home, Food Drugs, Medical Devices, Vaccines, Blood & Biologics, Animal & Veterinary, Cosmetics, Radiation-Emitting Products, and Tobacco Products. The main content area features the 'Drugs@FDA' logo, 'FDA Approved Drug Products', and a 'Start Over' button. A search bar with 'A-Z Index' and a 'go' button is present. The search results for 'phenobarbital' are shown, indicating that no results were found. A red oval highlights the message: 'Search Results for 'phenobarbital'' and 'Your search term did not return any results.' Below this, there are links for 'Modify Your Search' and a list of troubleshooting tips for search problems. At the bottom, there are links for 'Back to Top', 'Back to Previous Page', and 'Back to Drugs@FDA Home', along with a 'Disclaimer' section.

U.S. Department of Health & Human Services www.hhs.gov

FDA U.S. Food and Drug Administration

Home Food Drugs Medical Devices Vaccines, Blood & Biologics Animal & Veterinary Cosmetics Radiation-Emitting Products Tobacco Products

Drugs@FDA
FDA Approved Drug Products

Start Over

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Search Results for 'phenobarbital'

Your search term did not return any results.
[Modify Your Search](#)

- **Spelling or Formatting Problems**
 - If you are not sure of the spelling, try "Browse by Drug Name."
 - Try putting in part of the Drug Name or Active Ingredient. You must enter at least three letters or numbers.
 - A drug name containing a combination of letters, punctuation, and spaces has to be formatted exactly as it appears in the database. Examples: H.P. ACTHAR gel or X-TROZINE L.A. Try entering just part of the name, such as "acthar" or "trozine."
- For Application Number searches, you must enter five digits for NDAs and ANDAs, and six digits for BLAs.
[More about searching](#)
- Dietary supplements, most biologic products, animal drugs, and certain drug products are not in Drugs@FDA.
[More information about the contents of Drugs@FDA](#)

[Modify Your Search](#)

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FDA/Center for Drug Evaluation and Research
Office of Communications
Division of Information Services
Update Frequency: Daily

How can you determine the approval status of a drug?? (Continued)

- **Orange Book**

(Approved Drug Products with Therapeutic Equivalence Evaluations)

<http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>

- Contains a listing of Rx and OTC drug products with approved NDAs and ANDAs
- Discontinued products



Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Proprietary Name Search Results from "OB_Rx" table for query on "celexa."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N021046	AA	Yes	CITALOPRAM HYDROBROMIDE	SOLUTION; ORAL	EQ 10MG BASE/5ML	CELEXA	FOREST LABS
N020822	AB	No	CITALOPRAM HYDROBROMIDE	TABLET; ORAL	EQ 10MG BASE	CELEXA	FOREST LABS
N020822	AB	No	CITALOPRAM HYDROBROMIDE	TABLET; ORAL	EQ 20MG BASE	CELEXA	FOREST LABS
N020822	AB	Yes	CITALOPRAM HYDROBROMIDE	TABLET; ORAL	EQ 40MG BASE	CELEXA	FOREST LABS

[Return to Electronic Orange Book Home Page](#)

- **Orange Book**

Drug products not included are:

- pre-1938 drugs (e.g., Phenobarbital Tablets)
- DESI pending drugs (e.g., Donnatal Tablets and Librax Capsules)
- Products withdrawn from the market for safety or efficacy reasons, e.g., Seldane.
- Animal drug products
- Biologic drug products



Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

No matching records found. Use your browser's Back button to go back and enter a new search criteria.

How can you determine the approval status of a drug?? (Continued)

- **DailyMed**

<http://dailymed.nlm.nih.gov/dailymed/about.cfm>

- Public service provided by the National Library of Medicine (do not accept advertising)
- Contains up-to-date drug labeling for marketed drugs
- Provides approval status for drugs, Rx and OTC: approved, not approved, OTC monograph final, OTC monograph not final



DailyMed: About DailyMed - Windows Internet Explorer

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=41564

Back to DailyMed: Search (Alt+Left)

File Edit View Favorites Tools Help

Skip to DrugLabel content | Skip to DrugLabel sections



**Daily
Current
Medication
Information**

Options

- Home
- E-mail Label Information
- Downloads
- SPL History
- Print this Label
- Download this Label (PDF)
- Notify of Updates
- Contact Us

Additional Resources

- Report Adverse Event
- MedlinePlus Information

Search : GO

Limits: ☐ Drug Name ☐ NDC Code ☐ Drug Class

MORPHINE SULFATE injection
[Physicians Total Care, Inc.]

RxNorm Names

Not yet provided

Category	DEA Schedule	Marketing Status
HUMAN PRESCRIPTION DRUG LABEL	CII	unapproved drug other

Disclaimer: This drug has not been found by FDA to be safe and effective, and this labeling has not been approved by FDA. For further information about unapproved drugs, click here.

Drug Label Sections

- Description
- Clinical Pharmacology
- Indications & Usage
- Contraindications
- Warnings
- Precautions
- Adverse Reactions
- Overdosage
- Dosage & Administration
- How Supplied
- Patient Counseling Information
- Supplemental Patient Material
- Boxed Warning
- Patient Package Insert
- Highlights
- Full Table of Contents
- Medication Guide

How can you determine the approval status of a drug?? (Continued)

- **The National Drug Code (NDC) Directory**

<http://www.accessdata.fda.gov/scripts/cder/ndc/default.cfm>

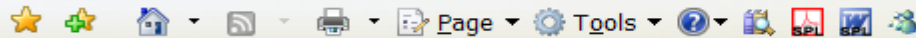
- Contains a listing of all human prescription drugs and insulin products in commercial distribution
- NDC number \neq FDA approval !!!



NDC Get Active Ingredient - Windows Internet Explorer

http://www.accessdata.fda.gov/scripts/cder/ndc/getai.cfm

File Edit View Favorites Tools Help



NDC Search Results on phenobarbital

Ingredient Name	NDC Number	Appl No	Strength	Trade Name
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PHENOBARBITAL	61392-*984	Other	60MG	PHENOBARBITAL TABLETS
PHENOBARBITAL	63739-*200	Other	16.2MG	PHENOBARBITAL TABLETS
PHENOBARBITAL	63739-*201	Other	32.4MG	PHENOBARBITAL TABLETS
PHENOBARBITAL	64125-*903	Other	100MG	PHENOBARBITAL TABLETS
PHENOBARBITAL	66267-*388	Other	30MG	PHENOBARBITAL TABLETS
PHENOBARBITAL	66466-4225	Other	16.2MG	PHENOBARBITAL TABLETS
PHENOBARBITAL	66466-4226	Other	32.4MG	PHENOBARBITAL TABLETS
PHENOBARBITAL	66466-4227	Other	64.8MG	PHENOBARBITAL TABLETS
PHENOBARBITAL	66466-4228	Other	97.2MG	PHENOBARBITAL TABLETS
PHENOBARBITAL	67228-9016	Other	60MG	PHENOBARBITAL TABLETS

What can YOU do about Unapproved Drugs??

- Know your state's pharmacy laws. Are there laws in the state in which you plan to practice pharmacy that regulate the dispensing of Unapproved Drugs??
- Check to see if a drug product is approved prior to dispensing it.
- Consult with healthcare providers that prescribe an unapproved drug; work to find an approved alternative whenever possible.

What can YOU do about Unapproved Drugs??

- Work with your employer to eliminate or minimize the number of unapproved drugs on your pharmacy's shelves or on your institution's formulary, to the extent possible
 - Increase awareness/knowledge to formulary decision makers regarding unapproved drugs
 - Evaluate drugs for approval status when considering addition to formulary

Resources

Unapproved Drugs Website

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/default.htm>

Electronic Code of Federal Regulations (e-CFR)

<http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&tpl=%2Findex.tpl>

FDA>Drugs: www.fda.gov/Drugs/default.htm

Drugs@FDA: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>

Orange Book: <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>

DailyMed: <http://dailymed.nlm.nih.gov/dailymed/about.cfm>

NDC Directory: <http://www.accessdata.fda.gov/scripts/cder/ndc/default.cfm>

Questions



For additional Information, contact: druginfo@fda.hhs.gov