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IN FOCUS

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Regulation of Over-the-Counter (OTC) Drugs

The Food and Drug Administration (FDA) regulates the safety and effectiveness of drug products sold in the United States. FDA's regulatory authority covers both prescription and nonprescription (i.e., over-the-counter, or OTC) drugs, among other things.

Legislative Background

The Pure Food and Drug Act of 1906 prohibited the interstate commerce of adulterated and misbranded drugs, but it did not provide FDA with the authority to review and approve products before they enter the market. Thus, drugs introduced between 1906 and 1938 were considered "pure" but with unknown safety and effectiveness. In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act (FFDCA), which authorized FDA to regulate the safety of drug products sold in the United States. In 1951, the FFDCA was amended to include a prescription-only category of drugs. While prescription drugs require health practitioner supervision (due to drug toxicity, potential harmful effect, and/or method of use), OTC drugs can be used without a prescriber's authorization, provided that they have an acceptable safety margin, low potential for misuse or abuse, and are adequately labeled so that consumers can self-diagnose the condition, self-select the medication, and self-manage the condition.

Although the FFDCA of 1938 required a manufacturer to demonstrate that its drug product was safe, the law did not provide FDA the authority to require premarket evaluation of effectiveness. A safety tragedy with the drug Thalidomide and birth defects in other countries led to public support for stronger drug regulation in the United States. In 1962, the FFDCA was amended to require that a drug manufacturer demonstrate that its drug is effective, in addition to safe, for its intended use. This standard became the basis for the new drug application (NDA) process in place today (see CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*). Because drugs introduced between 1938 and 1962 were considered safe but with unknown effectiveness, FDA formed the Drug Efficacy Implementation Study (DESI), contracting with the National Academy of Science/National Research Council (NAS/NRC) to evaluate the effectiveness of those drugs approved on the basis of safety alone. However, the new requirement that a sponsor demonstrate the effectiveness of a drug product prior to marketing created a dilemma for FDA. It is estimated that in the early 1970s there were over 100,000 OTC drug products, made up of hundreds of different active ingredients, belonging to 26 broad therapeutic drug categories (as determined by FDA), which limited the feasibility of an FDA product-by-product review of effectiveness data.

The OTC Monograph Process

In 1972, FDA established the OTC Drug Review to evaluate the effectiveness of OTC drug products marketed in the United States prior to May 11, 1972. The OTC Drug Review is an ongoing, three-phase public rulemaking process.

Three-Phase Drug Review

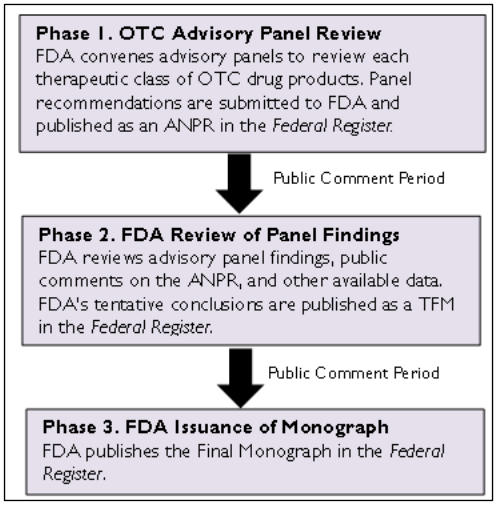
The first phase of the process is advisory panel review. When the OTC Drug Review first began, the FDA Commissioner convened an advisory panel for each drug category (e.g., antacids, sleep aids; drug categories are listed at 21 C.F.R. 330.5). The commissioner also published a notice in the *Federal Register* (FR) calling upon interested persons to submit for review by an advisory panel data and pertinent information for a category of drugs. Each panel was tasked with evaluating the active ingredients and existing labeling for a particular class of OTC drug products to determine what should be allowed to be classified as generally recognized as safe and effective (GRASE) for self-diagnosis, self-selection, and self-treatment. The advisory panel categorized the active ingredients in each drug category as GRASE, not GRASE, or more information needed. The panel then submitted their recommendations in a report to FDA, which was published in the FR as an advance notice of proposed rulemaking (ANPR) with a 90-day public comment period.

In the second phase of the OTC Drug Review, FDA evaluated the panel recommendations, public comments, and other available data. The agency published its tentative conclusions regarding the GRASE status of ingredients in that therapeutic class in the FR as a tentative final monograph (TFM), or proposed rule. If an advisory panel or FDA found no ingredients to be GRASE for a particular use, the agency issued a proposed rule to remove such ingredients from further consideration and to require approval of an NDA for that drug product. The public was once again provided with a comment period on the TFM.

The third phase of the review—monograph finalization—is ongoing, and a number of marketed OTC products are not yet covered by a final monograph (e.g., some external analgesic products). In this phase, FDA considers the public comments provided in response to a TFM and any new data the agency receives. FDA then publishes a final monograph in the FR as a final rule (and later in the *Code of Regulations*). The monograph functions as a sort of "rulebook." It establishes standards for each therapeutic category, addressing acceptable conditions (e.g., active ingredients, dosage strength, dosage form, route of administration). The final monographs are published in 21 C.F.R. parts 331-358. Provided that an OTC drug meets the specifications of the monograph, it is does not have to go through the FDA premarket approval process. Drug

products that do not meet the conditions of the monograph can apply for approval via the NDA process.

Figure 1. OTC Monograph Process



Source: Figure created by CRS based on FDA's website, http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM148055.pdf.

FDA continues to consult with its advisory committees (e.g., the Nonprescription Drugs Advisory Committee) on monograph-related issues.

Time and Extent Applications

The OTC monograph is a living document, as data and clinical understanding are constantly evolving. There are mechanisms to incorporate a new product or product condition into an existing monograph. A Citizen's Petition (CP) or a Time and Extent Application (TEA) may be used to request that FDA amend an OTC drug monograph to incorporate a new product or product condition. The CP may be used only to include an ingredient that would have been eligible for inclusion in the original TFM (i.e., the product must have been marketed in the United States prior to 1972), while the TEA applies to products initially marketed under an approved NDA after the OTC drug review began, or those without any U.S. marketing experience (21 C.F.R. 330.14(a)).

The TEA is a two-step process. The first step is *eligibility*—the interested party must demonstrate that the OTC drug has been marketed for a "material time" and to a "material extent." "Material time" is defined as marketing for a minimum of five continuous years in the same country, and "material extent" is defined as marketing a sufficient quantity as described in FDA regulation at 21 C.F.R. 330.14(c). These criteria have to be assessed for each specific product. If FDA determines that the drug is eligible for inclusion in the monograph, the second step is submission of *safety and effectiveness data*. FDA publishes a notice in the FR asking interested parties to submit data and pertinent information for that drug product. FDA or an advisory panel then reviews the data using the same safety and effectiveness standards as the OTC Drug Review. FDA has followed the TEA process to evaluate topical acne active ingredients, as well as sunscreen active ingredients prior to the enactment of the Sunscreen Innovation Act.

Summary of Regulatory Pathways

An OTC drug may enter the market via an approved NDA or abbreviated new drug application (which are product-specific) or by conforming to a monograph (which is ingredient-specific). Both pathways involve a scientific decision by FDA; however, there are some differences between the two mechanisms (see **Table 1**). Note that NDA-approved prescription drugs can switch to OTC status. The "Rx-to-OTC switch" is not discussed in this In Focus.

Table 1. Regulatory Pathways for OTC Drug Products

NDA Process	OTC Monograph
Premarket approval	No premarket approval
Confidential filing	Public, rulemaking process
Drug product-specific	Active ingredient-specific
May require a user fee	No user fees
Potential for marketing exclusivity	No marketing exclusivity
Mandated review timelines	No mandated timelines
Generally requires clinical studies	Generally does not require clinical studies
Reporting requirements	Limited reporting requirements (serious adverse events only)

Source: FDA, Regulation of Nonprescription Drug Products, http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM148055.pdf.

Issues for Congress

Although the OTC Drug Review began in the 1970s, many OTC monographs have not yet been finalized. FDA estimates that there are approximately 88 simultaneous rulemakings in 26 broad therapeutic categories, and approximately 800 active ingredients for over 1,400 different therapeutic uses. The Division of Non-Prescription Drug Products within FDA's Center for Drug Evaluation and Research (CDER) currently has 18 full-time employees devoted to overseeing the entire OTC market, which is about the same number of employees it takes to review one novel prescription drug application, according to CDER Director Janet Woodcock. Moreover, the agency's resources have been constrained by activities related to congressional mandates. On June 10, 2016, FDA held a public meeting to gather stakeholder input on the potential development of a user fee program for OTC monograph drugs. Such user fees would be used to support FDA review of the effectiveness and safety of ingredients to be included in a monograph. FDA is currently seeking input regarding the types of user fees (e.g., product listing fees, application fees) and performance goals that might be appropriate for a monograph user fee program.

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