
Guidance for FDA Staff and Industry

Marketed Unapproved Drugs — Compliance Policy Guide

Sec. 440.100 Marketed New Drugs Without Approved NDAs or ANDAs

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 2006**

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Guidance for FDA Staff and Industry¹

Marketed Unapproved Drugs — Compliance Policy Guide

Chapter - 4

Subchapter - 440

Sec. 440.100 Marketed New Drugs Without Approved NDAs or ANDAs

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This compliance policy guide (CPG) describes how we intend to exercise our enforcement discretion with regard to drugs marketed in the United States that do not have required FDA approval for marketing. This CPG supersedes section 440.100, Marketed New Drugs Without Approved NDAs or ANDAs (CPG 7132c.02). It applies to any drug required to have FDA approval for marketing, including new drugs covered by the Over-the-Counter (OTC) Drug Review, except for licensed biologics and veterinary drugs.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Reason for This Guidance

For historical reasons, some drugs are available in the United States that lack required FDA approval for marketing. A brief, informal summary description of the various categories of these drugs and their regulatory status is provided in Appendix A as general background for this document. The manufacturers of these drugs have not received FDA approval to legally market

¹ This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

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their drugs, nor are the drugs being marketed in accordance with the OTC drug review. The new drug approval and OTC drug monograph processes play an essential role in ensuring that all drugs are both safe and effective for their intended uses. Manufacturers of drugs that lack required approval, including those that are not marketed in accordance with an OTC drug monograph, have not provided FDA with evidence demonstrating that their products are safe and effective, and so we have an interest in taking steps to either encourage the manufacturers of these products to obtain the required evidence and comply with the approval provisions of the Federal Food, Drug, and Cosmetic Act (the Act) or remove the products from the market. We want to achieve these goals without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market.

The goals of this guidance are to (1) clarify for FDA personnel and the regulated industry how we intend to exercise our enforcement discretion regarding unapproved drugs and (2) emphasize that illegally marketed drugs must obtain FDA approval.

B. Historical Enforcement Approach

FDA estimates that, in the United States today, perhaps as many as several thousand drug products are marketed illegally without required FDA approval.² Because we do not have complete data on illegally marketed products, and because the universe of such products is constantly changing as products enter and leave the market, we first have to identify illegally marketed products before we can contemplate enforcement action. Once an illegally marketed product is identified, taking enforcement action against the product would typically involve one or more of the following: requesting voluntary compliance; providing notice of action in a *Federal Register* notice; issuing an untitled letter; issuing a Warning Letter; or initiating a seizure, injunction, or other proceeding. Each of these actions is time-consuming and resource intensive. Recognizing that we are unable to take action immediately against all of these illegally marketed products and that we need to make the best use of scarce Agency resources, we have had to prioritize our enforcement efforts and exercise enforcement discretion with regard to products that remain on the market.

In general, in recent years, FDA has employed a risk-based enforcement approach with respect to marketed unapproved drugs. This approach includes efforts to identify illegally marketed drugs, prioritization of those drugs according to potential public health concerns or other impacts on the public health, and subsequent regulatory follow-up. Some of the specific actions the Agency has taken have been precipitated by evidence of safety or effectiveness problems that has either come to our attention during inspections or been brought to our attention by outside sources.

III. FDA'S ENFORCEMENT POLICY

In the discussion that follows, we intend to clarify our approach to prioritizing our enforcement actions and exercising our enforcement discretion with regard to the universe of unapproved, illegally marketed drug products in all categories.

² This rough estimate comprises several hundred drugs (different active ingredients) in various strengths, combinations, and dosage forms from multiple distributors and repackagers.

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A. Enforcement Priorities

Consistent with our risk-based approach to the regulation of pharmaceuticals, FDA intends to continue its current policy of giving higher priority to enforcement actions involving unapproved drug products in the following categories:

Drugs with potential safety risks. Removing potentially unsafe drugs protects the public from direct and indirect health threats.

Drugs that lack evidence of effectiveness. Removing ineffective drugs protects the public from using these products in lieu of effective treatments. Depending on the indication, some ineffective products would, of course, pose safety risks as well.

Health fraud drugs. FDA defines health fraud as "[t]he deceptive promotion, advertisement, distribution or sale of articles . . . that are represented as being effective to diagnose, prevent, cure, treat, or mitigate disease (or other conditions), or provide a beneficial effect on health, but which have not been scientifically proven safe and effective for such purposes. Such practices may be deliberate or done without adequate knowledge or understanding of the article" (CPG Sec. 120.500). Of highest priority in this area are drugs that present a direct risk to health. Indirect health hazards exist if, as a result of reliance on the product, the consumer is likely to delay or discontinue appropriate medical treatment. Indirect health hazards will be evaluated for enforcement action based on section 120.500, Health Fraud - Factors in Considering Regulatory Action (CPG 7150.10). FDA's health fraud CPG outlines priorities for evaluating regulatory actions against indirect health hazard products, such as whether the therapeutic claims are significant, whether there are any scientific data to support the safety and effectiveness of the product, and the degree of vulnerability of the prospective user group (CPG Sec. 120.500).

Drugs that present direct challenges to the new drug approval and OTC drug monograph systems. The drug approval and OTC drug monograph systems are designed to avoid the risks associated with potentially unsafe, ineffective, and fraudulent drugs. The drugs described in the preceding three categories present direct challenges to these systems, as do unapproved drugs that directly compete with an approved drug, such as when a company obtains approval of a new drug application (NDA) for a product that other companies are marketing without approval (*see* section III.C., Special Circumstances – Newly Approved Product). Also included are drugs marketed in violation of a final and effective OTC drug monograph. Targeting drugs that challenge the drug approval or OTC drug monograph systems buttresses the integrity of these systems and makes it more likely that firms will comply with the new drug approval and monograph requirements, which benefits the public health.

Unapproved new drugs that are also violative of the Act in other ways. The Agency also intends, in circumstances that it considers appropriate, to continue its policy of enforcing the preapproval requirements of the Act against a drug or firm that also violates another provision of the Act, even if there are other unapproved versions of the drug

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made by other firms on the market. For instance, if a firm that sells an unapproved new drug also violates current good manufacturing practice (CGMP) regulations, the Agency is not inclined to limit an enforcement action in that instance to the CGMP violations. Rather, the Agency may initiate a regulatory action that targets both the CGMP violation *and* the violation of section 505 of the Act (21 U.S.C. 355). This policy efficiently preserves scarce Agency resources by allowing the Agency to pursue all applicable charges against a drug and/or a firm and avoiding duplicative action. *See United States v. Sage Pharmaceuticals, Inc.*, 210 F.3d 475, 479-80 (5th Cir. 2000).

Drugs that are reformulated to evade an FDA enforcement action. The Agency is also aware of instances in which companies that anticipate an FDA enforcement action against a specific type or formulation of an unapproved product have made formulation changes to evade that action, but have not brought the product into compliance with the law. Companies should be aware that the Agency is not inclined to exercise its enforcement discretion with regard to such products. Factors that the Agency may consider in determining whether to bring action against the reformulated products include, but are not limited to, the timing of the change, the addition of an ingredient without adequate scientific justification (*see, e.g.*, 21 CFR 300.50 and 330.10(a)(4)(iv)), the creation of a new combination that has not previously been marketed, and the claims made for the new product.

B. Notice of Enforcement Action and Continued Marketing of Unapproved Drugs

FDA is not required to, and generally does not intend to, give special notice that a drug product may be subject to enforcement action, unless FDA determines that notice is necessary or appropriate to protect the public health.³ The issuance of this guidance is intended to provide notice that any product that is being marketed illegally is subject to FDA enforcement action at any time.⁴ The only exception to this policy is, as set forth elsewhere, that generally products subject to an ongoing DESI⁵ proceeding or ongoing OTC drug monograph proceeding (i.e., an OTC product that is part of the OTC drug review for which an effective final monograph is not yet in place) may remain on the market during the pendency of

³ For example, in 1997, FDA issued a *Federal Register* notice declaring all orally administered levothyroxine sodium products to be new drugs and requiring manufacturers to obtain approved new drug applications (62 FR 43535, August 14, 1997). Nevertheless, FDA gave manufacturers 3 years (later extended to 4 (65 FR 24488, April 26, 2000)) to obtain approved applications and allowed continued marketing without approved new drug applications because FDA found that levothyroxine sodium products were medically necessary to treat hypothyroidism and no alternative drug provided an adequate substitute.

⁴ For example, FDA may take action at any time against a product that was originally marketed before 1938, but that has been changed since 1938 in such a way as to lose its *grandfather* status (21 U.S.C. 321(p)).

⁵ The Drug Efficacy Study Implementation (DESI) was the process used by FDA to evaluate for effectiveness for their labeled indications over 3,400 products that were approved only for safety between 1938 and 1962. DESI is explained more fully in the appendix to this document.

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that proceeding⁶ and any additional period specifically provided in the proceeding (such as a delay in the effective date of a final OTC drug monograph).⁷ However, once the relevant DESI or OTC drug monograph proceeding is completed and any additional grace period specifically provided in the proceeding has expired, all products that are not in compliance with the conditions for marketing determined in that proceeding are subject to enforcement action at any time without further notice (*see, e.g.*, 21 CFR 310.6).

FDA intends to evaluate on a case-by-case basis whether justification exists to exercise enforcement discretion to allow continued marketing for some period of time after FDA determines that a product is being marketed illegally. In deciding whether to allow such a grace period,⁸ we may consider the following factors: (1) the effects on the public health of proceeding immediately to remove the illegal products from the market (including whether the product is medically necessary and, if so, the ability of legally marketed products to meet the needs of patients taking the drug); (2) the difficulty associated with conducting any required studies, preparing and submitting applications, and obtaining approval of an application; (3) the burden on affected parties of immediately removing the products from the market; (4) the Agency's available enforcement resources; and (5) any special circumstances relevant to the particular case under consideration.

C. Special Circumstances — Newly Approved Product

Sometimes, a company may obtain approval of an NDA for a product that other companies are marketing without approval.⁹ We want to encourage this type of voluntary compliance with the new drug requirements because it benefits the public health by increasing the assurance that marketed drug products are safe and effective — it also reduces the resources that FDA must expend on enforcement. Thus, because they present a direct challenge to the drug approval system, FDA is more likely to take enforcement action against remaining unapproved drugs in this kind of situation. However, we intend to take into account the circumstances once the product is approved in determining how to exercise our enforcement discretion with regard to the unapproved products. In exercising enforcement discretion, we intend to balance the need to provide incentives for voluntary compliance against the implications of enforcement actions on the marketplace and on consumers who are accustomed to using the marketed products.

⁶ OTC drugs covered by ongoing OTC drug monograph proceedings may remain on the market as provided in current enforcement policies. *See, e.g.*, CPG sections 450.200 and 450.300 and 21 CFR part 330. This document does not affect the current enforcement policies for such drugs.

⁷ Sometimes, a final OTC drug monograph may have a delayed effective date or provide for a specific period of time for marketed drugs to come into compliance with the monograph. At the end of that period, drugs that are not marketed in accordance with the monograph are subject to enforcement action and the exercise of enforcement discretion in the same way as any other drug discussed in this CPG.

⁸ For purposes of this guidance, the terms *grace period* and *allow a grace period* refer to an exercise of enforcement discretion by the Agency (i.e., a period of time during which FDA, as a matter of discretion, elects not to initiate a regulatory action on the ground that an article is an unapproved new drug).

⁹ These may be products that are the same as the approved product or somewhat different, such as products of different strength.

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When a company obtains approval to market a product that other companies are marketing without approval, FDA normally intends to allow a grace period of roughly 1 year from the date of approval of the product before it will initiate enforcement action (e.g., seizure or injunction) against marketed unapproved products of the same type. However, the grace period provided is expected to vary from this baseline based upon the following factors: (1) the effects on the public health of proceeding immediately to remove the illegal products from the market (including whether the product is medically necessary and, if so, the ability of the holder of the approved application to meet the needs of patients taking the drug); (2) whether the effort to obtain approval was publicly disclosed;¹⁰ (3) the difficulty associated with conducting any required studies, preparing and submitting applications, and obtaining approval of an application; (4) the burden on affected parties of removing the products from the market; (5) the Agency's available enforcement resources; and (6) any other special circumstances relevant to the particular case under consideration. To assist in an orderly transition to the approved product(s), in implementing a grace period, FDA may identify interim dates by which firms should first cease *manufacturing* unapproved forms of the drug product, and later cease *distributing* the unapproved product.

The length of any grace period and the nature of any enforcement action taken by FDA will be decided on a case-by-case basis. Companies should be aware that a Warning Letter may not be sent before initiation of enforcement action and should not expect any grace period that is granted to protect them from the need to leave the market for some period of time while obtaining approval. Companies marketing unapproved new drugs should also recognize that, while FDA normally intends to allow a grace period of roughly 1 year from the date of approval of an unapproved product before it will initiate enforcement action (e.g., seizure or injunction) against others who are marketing that unapproved product, it is possible that a substantially shorter grace period would be provided, depending on the individual facts and circumstances.¹¹

The shorter the grace period, the more likely it is that the first company to obtain an approval will have a period of de facto market exclusivity before other products obtain approval. For example, if FDA provides a 1-year grace period before it takes action to remove unapproved competitors from the market, and it takes 2 years for a second application to be approved, the first approved product could have 1 year of market exclusivity before the onset of competition. If FDA provides for a shorter grace period, the period of effective exclusivity could be longer.

¹⁰ For example, at the Agency's discretion, we may provide for a shorter grace period if an applicant seeking approval of a product that other companies are marketing without approval agrees to publication, around the time it submits the approval application, of a *Federal Register* notice informing the public that the applicant has submitted that application. A shortened grace period may also be warranted if the fact of the application is widely known publicly because of applicant press releases or other public statements. Such a grace period may run from the time of approval or from the time the applicant has made the public aware of the submission, as the Agency deems appropriate.

¹¹ Firms are reminded that this CPG does not create any right to a grace period; the length of the grace period, if any, is solely at the discretion of the Agency. For instance, firms should not expect any grace period when the public health requires immediate removal of a product from the market, or when the Agency has given specific prior notice in the *Federal Register* or otherwise that a drug product requires FDA approval.

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FDA hopes that this period of market exclusivity will provide an incentive to firms to be the first to obtain approval to market a previously unapproved drug.¹²

D. Regulatory Action Guidance

District offices are encouraged to refer to CDER for review (with copies of labeling) any unapproved drugs that appear to fall within the enforcement priorities in section III.A. Charges that may be brought against unapproved drugs include, but are not limited to, violations of 21 U.S.C. 355(a) and 352(f)(1) of the Act. Other charges may also apply based on, among others, violations of 21 U.S.C. 351(a)(2)(B) (CGMP), 352(a) (misbranding), or 352(o) (failure to register or list).

¹² The Agency understands that, under the Act, holders of NDAs must list patents claiming the approved drug product and that newly approved drug products may, in certain circumstances, be eligible for marketing exclusivity. Listed patents and marketing exclusivity may delay the approval of competitor products. If FDA believes that an NDA holder is manipulating these statutory protections to inappropriately delay competition, the Agency will provide relevant information on the matter to the Federal Trade Commission (FTC). In the past, FDA has provided information to the FTC regarding patent infringement lawsuits related to pending abbreviated new drug applications (ANDAs), citizen petitions, and scientific challenges to the approval of competitor drug products.

APPENDIX

BRIEF HISTORY OF FDA MARKETING APPROVAL REQUIREMENTS AND CATEGORIES OF DRUGS THAT LACK REQUIRED FDA APPROVAL¹³

Key events in the history of FDA's drug approval regulation and the categories of drugs affected by these events are described below.

A. 1938 and 1962 Legislation

The original Federal Food and Drugs Act of June 30, 1906, first brought drug regulation under federal law. That Act prohibited the sale of adulterated or misbranded drugs, but did not require that drugs be approved by FDA. In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act (the Act), which required that new drugs be approved for safety. As discussed below, the active ingredients of many drugs currently on the market were first introduced, at least in some form, before 1938. Between 1938 and 1962, if a drug obtained approval, FDA considered drugs that were identical, related, or similar (IRS) to the approved drug to be covered by that approval, and allowed those IRS drugs to be marketed without independent approval. Many manufacturers also introduced drugs onto the market between 1938 and 1962 based on their own conclusion that the products were generally recognized as safe (GRAS) or based on an opinion from FDA that the products were not new drugs. Between 1938 and 1962, the Agency issued many such opinions, although all were formally revoked in 1968 (*see* 21 CFR 310.100).

B. DESI

In 1962, Congress amended the Act to require that a *new drug* also be proven effective, as well as safe, to obtain FDA approval. This amendment also required FDA to conduct a retrospective evaluation of the effectiveness of the drug products that FDA had approved as *safe* between 1938 and 1962 through the new drug approval process.

FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. The NAS/NRC created 30 panels of 6 professionals each to conduct the review, which was broken down into specific drug categories. The NAS/NRC reports for these drug products were submitted to FDA in the late 1960s and early 1970s. The Agency reviewed and re-evaluated the findings of each panel and published its findings in *Federal Register* notices. FDA's administrative implementation of the NAS/NRC reports was called the Drug Efficacy Study Implementation (DESI). DESI covered the 3,400 products specifically reviewed by the NAS/NRCs as well as the even larger number of IRS products that entered the market without FDA approval.

Because DESI products were covered by approved (pre-1962) applications, the Agency concluded that, prior to removing products not found effective from the market, it would follow

¹³ This brief history document should be viewed as a secondary source. To determine the regulatory status of a particular drug or category of drugs, the original source documents cited should be consulted.

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procedures in the Act and regulations that apply when an approved new drug application is withdrawn:

- All initial DESI determinations are published in the *Federal Register* and, if the drug is found to be less than fully effective, there is an opportunity for a hearing.
- The Agency considers the basis of any hearing request and either grants the hearing or denies the hearing on summary judgment and publishes its final determination in the *Federal Register*.
- If FDA's final determination classifies the drug as effective for its labeled indications, as required by the Act, FDA still requires approved applications for continued marketing of the drug and all drugs IRS to it – NDA supplements for those drugs with NDAs approved for safety, or new ANDAs or NDAs, as appropriate, for IRS drugs. DESI-effective drugs that do not obtain approval of the required supplement, ANDA, or NDA are subject to enforcement action.
- If FDA's final determination classifies the drug as ineffective, the drug and those IRS to it can no longer be marketed and are subject to enforcement action.

1. Products Subject to Ongoing DESI Proceedings

Some unapproved marketed products are undergoing DESI reviews in which a final determination regarding efficacy has not yet been made. In addition to the products specifically reviewed by the NAS/NRC (i.e., those products approved for safety only between 1938 and 1962), this group includes unapproved products identical, related, or similar to those products specifically reviewed (*see* 21 CFR 310.6). In virtually all these proceedings, FDA has made an initial determination that the products lack substantial evidence of effectiveness, and the manufacturers have requested a hearing on that finding. It is the Agency's longstanding policy that products subject to an ongoing DESI proceeding may remain on the market during the pendency of the proceeding. *See, e.g., Upjohn Co. v. Finch*, 303 F. Supp. 241, 256-61 (W.D. Mich. 1969).¹⁴

2. Products Subject to Completed DESI Proceedings

Some unapproved marketed products are subject to already-completed DESI proceedings and lack required approved applications. This includes a number of products IRS to DESI products for which approval was withdrawn due to a lack of substantial evidence of effectiveness. This group also includes a number of products IRS to those DESI products for which FDA made a

¹⁴ Products first marketed after a hearing notice is issued with a different formulation than those covered by the notice are not considered subject to the DESI proceeding. Rather, they need approval prior to marketing. Under longstanding Agency policies, a firm holding an NDA on a product for which a DESI hearing is pending must submit a supplement prior to reformulating that product. The changed formulation may not be marketed as a related product under the pending DESI proceeding; it is a new drug, and it must be approved for safety and efficacy before it can be legally marketed. *See, e.g., "Prescription Drugs Offered for Relief of Symptoms of Cough, Cold, or Allergy"* (DESI 6514), 49 FR 153 (January 3, 1984) (Dimetane and Actifed); *"Certain Drugs Containing Antibiotic, Corticosteroid, and Antifungal Components"* (DESI 10826), 50 FR 15227 (April 17, 1985) (Mycolog). *See also* 21 U.S.C. 356a(c)(2)(A). Similarly, firms without NDAs cannot market new formulations of a drug without first getting approval of an NDA.

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final determination that the product is effective, but applications for the IRS products have not been both submitted and approved as required under the statute and longstanding enforcement policy (*see* 21 CFR 310.6). FDA considers all products described in this paragraph to be marketed illegally.

C. Prescription Drug Wrap-Up

As mentioned above, many drugs came onto the market before 1962 without FDA approvals. Of these, many claimed to have been marketed prior to 1938 or to be IRS to such a drug. Drugs that did not have pre-1962 approvals and were not IRS to drugs with pre-1962 approvals were not subject to DESI. For a period of time, FDA did not take action against these drugs and did not take action against new unapproved drugs that were IRS to these pre-1962 drugs that entered the market without approval.

Beginning in 1983, it was discovered that one drug that was IRS to a pre-1962 drug, a high potency Vitamin E intravenous injection named E-Ferol, was associated with adverse reactions in about 100 premature infants, 40 of whom died. In November of 1984, in response to this, a congressional oversight committee issued a report to FDA expressing the committee's concern regarding the thousands of unapproved drug products in the marketplace.

In response to the E-Ferol tragedy, CDER assessed the number of pre-1962 non-DESI marketed drug products. To address those drug products, the Agency significantly revised and expanded CPG section 440.100 to cover all marketed unapproved prescription drugs, not just DESI products. The program for addressing these marketed unapproved drugs and certain others like them became known as the *Prescription Drug Wrap-Up*. Most of the Prescription Drug Wrap-Up drugs first entered the market before 1938, at least in some form. For the most part, the Agency had evaluated neither the safety nor the effectiveness of the drugs in the Prescription Drug Wrap-Up.

A drug that was subject to the Prescription Drug Wrap-Up is marketed illegally, unless the manufacturer of such a drug can establish that its drug is grandfathered or otherwise not a *new drug*.

Under the 1938 grandfather clause (*see* 21 U.S.C. 321(p)(1)), a drug product that was on the market prior to passage of the 1938 Act and which contained in its labeling the same representations concerning the conditions of use as it did prior to passage of that Act was not considered a *new drug* and therefore was exempt from the requirement of having an approved new drug application.

Under the 1962 grandfather clause, the Act exempts a drug from the effectiveness requirements if its composition and labeling has not changed since 1962 and if, on the day before the 1962 Amendments became effective, it was (a) used or sold commercially in the United States, (b) not a new drug as defined by the Act at that time, and (c) not covered by an effective application. *See* Pub. L. 87-781, section 107 (reprinted following 21 U.S.C.A. 321); *see also* *USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655, 662-66 (1973).

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The two grandfather clauses in the Act have been construed very narrowly by the courts. FDA believes that there are very few drugs on the market that are actually entitled to grandfather status because the drugs currently on the market likely differ from the previous versions in some respect, such as formulation, dosage or strength, dosage form, route of administration, indications, or intended patient population. If a firm claims that its product is grandfathered, it is that firm's burden to prove that assertion. *See* 21 CFR 314.200(e)(5); *see also United States v. An Article of Drug (Bentex Ulcerine)*, 469 F.2d 875, 878 (5th Cir. 1972); *United States v. Articles of Drug Consisting of the Following: 5,906 Boxes*, 745 F.2d 105, 113 (1st Cir 1984).

Finally, a product would not be considered a *new drug* if it is generally recognized as safe and effective (GRAS/GRAE) and has been used to a material extent and for a material time. *See* 21 U.S.C. 321(p)(1) and (2). As with the grandfather clauses, this has been construed very narrowly by the courts. *See, e.g., Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); *United States v. 50 Boxes More or Less Etc.*, 909 F.2d 24, 27-28 (1st Cir. 1990); *United States v. 225 Cartons . . . Fiorinal*, 871 F.2d 409 (3rd Cir. 1989). *See also* Letter from Dennis E. Baker, Associate Commissioner for Regulatory Affairs, FDA, to Gary D. Dolch, Melvin Spigelman, and Jeffrey A. Staffa, Knoll Pharmaceutical Co. (April 26, 2001) (on file in FDA Docket No. 97N-0314/CP2) (finding that Synthroid, a levothyroxine sodium product, was not GRAS/GRAE).

As mentioned above, the Agency believes it is not likely that any currently marketed prescription drug product is grandfathered or is otherwise not a *new drug*. However, the Agency recognizes that it is at least theoretically possible. No part of this guidance, including the Appendix, is a finding as to the legal status of any particular drug product. In light of the strict standards governing exceptions to the approval process, it would be prudent for firms marketing unapproved products to carefully assess whether their products meet these standards.

D. New Unapproved Drugs

Some unapproved drugs were first marketed (or changed) after 1962. These drugs are on the market illegally. Some also may have already been the subject of a formal Agency finding that they are new drugs. *See, e.g.,* 21 CFR 310.502 (discussing, among other things, controlled/timed release dosage forms).

E. Over-the-Counter (OTC) Drug Review

Although OTC drugs were originally included in DESI, FDA eventually concluded that this was not an efficient use of resources. The Agency also was faced with resource challenges because it was receiving many applications for different OTC drugs for the same indications. Therefore, in 1972, the Agency implemented a process of reviewing OTC drugs through rulemaking by therapeutic classes (e.g., antacids, antiperspirants, cold remedies). This process involves convening an advisory panel for each therapeutic class to review data relating to claims and active ingredients. These panel reports are then published in the *Federal Register*, and after FDA review, tentative final monographs for the classes of drugs are published. The final step is the publication of a final monograph for each class, which sets forth the allowable claims, labeling, and active ingredients for OTC drugs in each class (*see, e.g.,* 21 CFR part 333). Drugs marketed in accordance with a final monograph are considered to be generally recognized as safe and effective (GRAS/GRAE) and do not require FDA approval of a marketing application.

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Final monographs have been published for the majority of OTC drugs. Tentative final monographs are in place for virtually all categories of OTC drugs. FDA has also finalized a number of *negative monographs* that list therapeutic categories (*e.g.*, OTC daytime sedatives, 21 CFR 310.519) in which no OTC drugs can be marketed without approval. Finally, the Agency has promulgated a list of active ingredients that cannot be used in OTC drugs without approved applications because there are inadequate data to establish that they are GRAS/GRAE (*e.g.*, phenolphthalein in stimulant laxative products, 21 CFR 310.545(a)(12)(iv)(B)).

OTC drugs covered by ongoing OTC drug monograph proceedings may remain on the market as provided in current enforcement policies (*see, e.g.*, CPG sections 450.200 and 450.300, and 21 CFR part 330). This document does not affect the current enforcement policies for such drugs.

OTC drugs that need approval, either because their ingredients or claims are not within the scope of the OTC drug review or because they are not allowed under a final monograph or another final rule, are illegally marketed. For example, this group would include a product containing an ingredient determined to be ineffective for a particular indication or one that exceeds the dosage limit established in the monograph. Such products are new drugs that must be approved by FDA to be legally marketed.