

Congressional Report

Feasibility and Cost of a New Monograph System for

Marketed Unapproved Drugs

House Report 108 – 193 and

Senate Report 108 – 107

Food and Drug Administration

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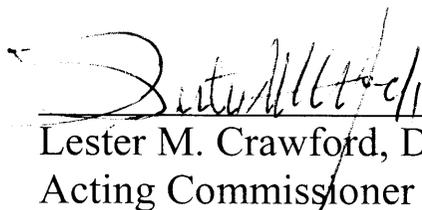
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Congressional Report

Feasibility and Cost of a New Monograph System for Marketed Unapproved Drugs

Report Language - House Report 108-193

“The Committee requests a report from FDA regarding the feasibility and cost of a new monograph system for prescription drug products that have been marketed to a material extent or for a material time without a premarket approval, provided such products are without apparent safety or efficacy problems. Enforcement resources regarding pharmaceutical products should be dedicated to activities that are most likely to improve public health.”

Report Language – Senate Report 108-107

“The Committee is aware of interest in the establishment of a monograph system for prescription drug products that have been marketed to a material extent and for a material time without apparent safety or efficacy problems and do not have premarket approval. FDA currently regards these products as “DESI” (Drug Efficacy Study implementation) or “DESI-II” products for compliance purposes. Such a monograph system would be modeled after the Agency’s system for over-the-counter pharmaceuticals that was established 30 years ago for products that were similarly generally recognized as safe and effective due to their long history of safe and effective marketing. The Committee is sympathetic to those who advocate such a monograph system, but recognizes that review of a proposal to establish such a system falls under the jurisdiction of the Health, Education, Labor, and Pensions Committee. However, in an effort to start the dialogue, the Committee directs FDA to prepare a report for the Committee on Appropriations and the Committee on Health, Education, Labor, and Pensions regarding the feasibility and cost of such a new monograph system for prescription drug products as described above. In the meantime, the Committee believes that enforcement resources regarding pharmaceutical products should be dedicated to activities that are most likely to improve the public health.”

Background

The Food and Drug Administration (FDA) routinely takes enforcement action against drugs that are marketed without FDA approval. The Agency issued a draft guidance entitled *Marketed Unapproved Drugs — Compliance Policy Guide* (October 2003), explaining how FDA intends to continue to exercise its enforcement discretion with regard to drugs that are marketed in the United States without required FDA approval. Public comments were solicited and received, and FDA is evaluating the comments and revising the draft guidance.

Despite past attempts to bring marketed unapproved drug products into compliance with the regulations, FDA estimates that several thousand prescription drug products are marketed

without FDA approval in the United States today.¹ It is difficult to obtain reliable estimates or lists of products because of reluctance on the part of manufacturers to report illegal activity and because of the ever changing nature of the marketplace. In some cases, these products remain on the market because the manufacturers of the products, some of whom also make approved products, assert that they were not required to demonstrate safety or efficacy under the amendments to the Federal Food, Drug, and Cosmetic Act in 1938 and 1962, and their status has never been adjudicated because of limited FDA resources for what are very time consuming and resource-intensive enforcement actions.^{2,3} In other cases, they are simply being marketed illegally without any alleged justification. Among the largest categories of marketed unapproved prescription drugs are cough and cold products and controlled substances, such as morphine and barbiturates.⁴

As described in the draft *Compliance Policy Guide*, to protect the public health from unsafe or ineffective unapproved prescription products, FDA's approach to date has been to give higher priority to enforcement actions involving products in the following categories:

- 1. Drugs with potential safety risks**
- 2. Drugs that lack evidence of effectiveness**
- 3. Health fraud drugs**

For prescription drugs, it appears that the application review process provides the most efficient mechanism for an expert review by FDA of the scientific data demonstrating safety and efficacy, as well as chemistry and bioavailability data, which must show that a quality product can be manufactured consistently. The application review process helps to ensure that patients receive the high-quality prescription medications they have come to expect. Once a drug that was previously marketed as unapproved becomes approved under a new drug application, allowing other unapproved versions of the drug to remain on the market undermines the integrity of the drug approval system and creates an uneven playing field. FDA's targeting of the above categories of drugs that undermine the drug approval system buttresses the integrity of this

¹ The rough estimate comprises several hundred drugs (different active ingredients) in various strengths, combinations, and dosage forms from multiple distributors and repackagers (draft guidance, *Marketed Unapproved Drugs — Compliance Policy Guide*, October 15, 2003). The *Compliance Policy Guide* provides a history of FDA marketing requirements and a description of unapproved marketed prescription drugs.

² Although some equate the universe of unapproved drugs with DESI drugs, only a small portion of the universe of the drugs marketed without approval remain on the market pending completion of the Drug Efficacy Study Implementation (DESI) review process. For additional information on the DESI program, see the Appendix to the draft guidance, *Marketed Unapproved Drugs — Compliance Policy Guide*, October 15, 2003.

³ These enforcement actions can be time consuming and resource intensive for FDA because of the many steps needed to complete them. Even before taking the matter to Court, the Agency generally will identify the subject(s) of the enforcement action; perform any necessary investigation and inspection; correspond with the subject(s), usually beginning with a warning letter; and prepare the enforcement action. This process is often followed by litigation, which, if contested, would involve multiple phases of discovery, briefing, and argument, as well as the possibility of a trial and one or more appeals to a higher court.

⁴ Some unapproved drugs that are currently marketed by prescription could be marketed under OTC monographs. For example, many cough and cold products might fall within this category.

system and makes it more likely that firms will comply with the new drug approval requirements, which, in turn, benefits the public health.⁵

Monograph System

The idea of using a monograph system as an alternative to full application review for prescription drugs is not new. Four times in the past 40 years, FDA, sometimes in conjunction with Congress, has considered whether a monograph system for prescription drugs could be used in place of, or in addition to, an application review. In 1968 and 1975, the Agency proposed monograph systems for “old” prescription drugs (those products that have been on the market without FDA approval). In 1978, Congress considered legislation that would have established a monograph system for certain prescription drugs. In 1991, FDA requested public comment on the merits of developing a monograph system for generic drugs. In each case, however, a monograph system was rejected for various scientific, cost, and feasibility reasons.

FDA has reviewed the monograph systems that were considered in the past and evaluated the applicability of the OTC monograph model (in which applicants would only need to satisfy the standards established in the monograph) to prescription drugs. This analysis included evaluation of developing monographs for classes of drugs, for unique formulations of drug ingredients, and for individual products. FDA also considered options for prioritizing the effort consistent with the Agency's enforcement priorities as noted above. Based on this assessment, FDA believes that a monograph system for old prescription drugs would be scientifically infeasible in many, if not all, instances. If, despite these concerns, FDA were to develop such a system, it would take many years to implement, and the costs would be prohibitive.

FDA has determined, for the following reasons, that it would not be feasible to establish safety, efficacy, quality, and appropriate labeling for prescription drugs by class, as is done under the OTC monograph system. FDA believes that prescription drug products have characteristics that, when taken together, do not lend themselves to marketing under monographs developed for classes of drugs without an application-specific review:

- Prescription products, by statutory definition, are not safe for use except under the supervision of a practitioner (21 U.S.C. 353(b)(1)(a)) and are typically used to treat diseases that cannot be self-diagnosed. Prescription product labeling is directed at practitioners and is very detailed to facilitate a thorough evaluation of the risks and benefits of taking the specific drug product. Accordingly, developing a label suitable to a class of drugs or maintaining a label appropriate to all products containing a single drug ingredient would be very difficult and, in some cases, impossible.
- Many prescription drugs are characterized as *high-risk drugs* because they pose unique and greater safety risks than other drugs (e.g., narrow therapeutic index drugs, drugs that affect metabolic parameters, drugs that affect mortality and morbidity), and the risks and benefits must be established individually for these drugs, in addition to adequate labeling and instructions for use.

⁵ Draft guidance, *Marketed Unapproved Drugs — Compliance Policy Guide*, October 15, 2003.

- Chemistry and bioavailability of prescription drugs are critical to their safe and effective use and must be evaluated for each individual product because differences in how products are manufactured can have major effects on their risks and benefits.⁶ For example, subtle variations in manufacturing can affect how an expected quantity of a drug is absorbed, which can determine whether the drug is safe and effective. Furthermore, because chemistry information often involves trade secrets, manufacturers would likely be reluctant to provide for use in a public forum the information necessary to establish monograph specifications for their products.

For these reasons, in most cases, it appears FDA could not establish conditions under which a class of prescription drugs could be deemed generally recognized as safe and effective without, at least some, individual application review. Therefore, a monograph system fashioned after the OTC or 1975 old drug monograph models would be infeasible for most prescription drug products. A monograph system that does not include individual application reviews of at least manufacturing and bioavailability data would not adequately ensure the safety and efficacy of prescription drugs sold to American consumers.

The OTC monograph model, with its emphasis on notice and comment rulemaking and multiple review cycles, has taken many years to implement and has been very resource intensive. Even if it were feasible to establish old drug prescription monographs by class, developing monographs for prescription drugs, which are by their very nature more scientifically complex, could be even more time consuming and resource intensive than under the OTC model.⁷ The time and resources involved is a function of both the quantity and complexity of the data that must be reviewed, the cumbersome nature of the notice and comment rulemaking process, and the need for external expert input through advisory panels and committees. To develop an OTC monograph, FDA must review safety and efficacy data, comparable to an NDA submission, to determine if the class of drugs (or unique formulation of ingredients) covered by the monograph is generally recognized as safe and effective. To develop monographs for prescription drugs, FDA would have to review the same type of data, in addition to reviewing bioavailability and chemistry data, neither of which is currently required for OTC monograph drugs.⁸

FDA estimates that developing and implementing a monograph system for many of the currently unapproved prescription drugs would cost the government at least \$300 million dollars over 10

⁶ OTC monographs do not establish standards for drug quality. Based on marketing history and evaluation of available reports and studies for OTC products, the Agency can conclude that drug quality parameters are relatively constant or vary in ways that do not affect safety and efficacy. In part, this is why OTC products have been determined safe for marketing without the need for a doctor's supervision (21 CFR 330.10).

⁷ Many of the currently marketed unapproved prescription products are combination products containing multiple active ingredients to treat multiple conditions. Establishing the safety and efficacy of combination products through a monograph process, if possible at all, would be even more complex and resource intensive than for single-ingredient products.

⁸ For OTC monographs, there is no requirement for all data to be submitted as there is for an NDA. As a result, sometimes data raising safety or efficacy questions about an ingredient may be selectively omitted. This would pose an increased public health risk for prescription drugs.

years.⁹ First, FDA would need to develop a regulatory framework for the system. We estimate this development effort would take 3 years and cost \$3.5 million.¹⁰ After that, it would cost, on average, \$7 million to develop an individual monograph for one category of simple, single-ingredient drug products (e.g., nasal decongestants). Developing monographs for more complex drugs, such as narcotics or combination products, would be significantly more costly than \$7 million per monograph. And, for the reasons described above, it might be necessary for these monographs to supplement, instead of replace, individual application reviews to ensure the safety and efficacy of these prescription medications. Even if resources were made available, FDA estimates that it would require more than a decade before a single product could be legally marketed under a monograph. This is the time we estimate it would take to establish the procedural framework through notice and comment rulemaking (estimated to take 3 years), put out a call for data, evaluate the data, publish a proposed monograph (estimated to take, collectively, 4 years), evaluate and incorporate comments, and publish a final monograph (estimated to take another 3 years). The actual time needed would depend on a number of factors including the number of monographs to be developed simultaneously, the complexity of the ingredients and products covered by the monographs, the amount of data to be reviewed, the number of comments received on the proposed monographs, and, of course, the resources available to do the work.

FDA believes that, in addition to the public health risks related to using such an approach for prescription drugs, the time, effort, and costs involved in developing and implementing a monograph system to establish the marketing conditions for unapproved, marketed prescription drugs far outweigh any potential benefits of such a system. FDA is currently in the process of revising the 2003 draft *Compliance Policy Guide* in response to comments that were submitted. The draft *Compliance Policy Guide* sets forth an enforcement approach that is preferable to a monograph system because, among other things:

- It will enable FDA to devote its resources to those actions most likely to improve the public health and protect against health fraud.
- It will allow FDA to proceed against an individual product or an entire class of products, as appropriate.
- It will not divert a significant amount of resources from the Agency's review and approval of new, innovative drugs.
- It will not require the Agency to await the resolution of a lengthy rulemaking process before removing potentially unsafe or ineffective products from the market.

Although the approach outlined in the draft *Compliance Policy Guide* will not remove all marketed unapproved drugs from the market quickly, it will give the Agency the flexibility to act

⁹ This is based on developing an estimated 40 separate monographs. These monographs would cover the cough/cold category of drugs, as well as many of the most common other marketed unapproved drugs, but would not include perhaps hundreds of unapproved drugs that fall into smaller miscellaneous categories. The estimates also do not include monographs for unapproved drugs that are in a category containing less than 10 products, nor do they include any DESI drugs subject to a final order prohibiting their continued marketing. If the entire universe of unapproved drugs were to be covered, many more monographs and commensurate resources would be needed.

¹⁰ Developing a regulatory framework would involve notice and comment rulemaking.

quickly in the event of significant public health risks. In revising the draft *Compliance Policy Guide* and planning enforcement actions, FDA will be mindful of the potential concerns that have been raised about our proposed enforcement approach. FDA will endeavor to proceed without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market.