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December 22, 2003

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Ln., Room 1061
Rockville, MD 20852

**RE: {DOCKET NO. 2003D-0478} DRAFT GUIDANCE ON MARKETED
UNAPPROVED DRUGS; COMPLIANCE POLICY GUIDE; AVAILABILITY**

To Whom It May Concern:

We submit the following comments in response to the Draft Guidance dated October 2003, entitled "Marketed Unapproved Drugs; Compliance Policy Guide".

Adams Laboratories, Inc. (Adams) believes both that this Guidance is important and that the principles and procedures it outlines are generally workable. The Guidance demonstrates the agency's commitment to regulate the marketing of unapproved drugs appropriately and to carry out the mission of the Center for Drug Evaluation and Research to "Protect the public health by ensuring that human drugs are safe and effective." FDA's NDA review and approval, and the OTC monograph system, ensure that human drugs are safe and effective. Adams fully supports the goal expressed in the compliance policy -- aggressive protection of the integrity of this system.

In our view, one important aspect of this goal is to assure that any period of enforcement discretion (grace period) provided to manufacturers of unapproved drugs after a new product has obtained approval to market is minimized. Any grace period, regardless of its length, benefits manufacturers of illegal drugs and is damaging to companies who have taken steps to secure approval, and thereby to market drugs that conform to FDA laws and regulations. A grace period allows manufacturers of illegal drugs to maintain their market share and fill their distribution channels to maximum levels. For example, under current industry standards for inventory control, a grace period of one year allows a company manufacturing illegal drugs at least five to six inventory turnovers of the unapproved product.

The situation for extended-release guaifenesin is illustrative. First, the agency delayed taking any action for 6 months, and then implemented an approximately 1-year grace period for manufacturers of illegal guaifenesin. For Adams, which had secured FDA approval, this delay and subsequent grace period had a significant negative impact. Adams was committed and prepared to manufacture drug supplies sufficient to meet the market demand following FDA approval of our product. To achieve that goal, Adams built inventory based on our expectation that continued marketing of unapproved drugs

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would no longer be allowed. The extended grace period provided to the manufacturers of unapproved products perturbed the market expectation and forced Adams to destroy substantial quantities of the initially manufactured product that would have exceeded its expiration date. We urge the agency to take steps, in the final guidance, to address this outcome through establishment of firm and more appropriate grace periods.

Notwithstanding our concern about the length of time unapproved guaifenesin products remained on the market, Adams endorses the step-wise approach the agency took in this situation. However, we strongly recommend a grace period of no longer than 6 months. This length of time is both reasonable for current manufacturers of unapproved products and more fair to the manufacturer of the new approved product. We urge the agency to set, in step-wise fashion: an absolute date when all manufacturing of illegal products must stop; an absolute date when these products can no longer be distributed; and an absolute date when these products can no longer be dispensed. A 6-month grace period still will provide manufacturers of the unapproved drugs roughly two to three inventory turns and minimal inventory losses.

The draft Guidance recognizes there are perhaps thousands of unapproved drugs marketed illegally in the United States and that FDA cannot take immediate enforcement action against all of these products because of scarce agency resources. However, it is clear that manufacturers of unapproved drugs fully understand the illegal status of these drugs and that they also know how to conform to NDA and/or monograph requirements. If FDA wishes to “encourage” the manufacturers of these products to provide evidence demonstrating that their products are safe and effective “without ... unnecessarily disrupting the market,” the most effective way to do this is to put these manufacturers on notice as to the certainty and speed of FDA compliance action. Adams urges FDA to firm up this notice in the final Compliance Policy Guide. Specifically, these manufacturers are on notice, through this Guide, that once FDA has approved a product that other companies are marketing without approval, the agency will initiate compliance action.

The length of any grace period after FDA approval furthermore should not be pegged to the date of submission of an NDA, which places the burden of determining the grace period on the company submitting the application. This is inappropriate. FDA cannot release information about NDA submission publicly, but FDA’s use of that date to calculate the length of any grace period essentially forces a company to release the information, whether it is in the company’s interest or not. We suggest that, instead, FDA’s own action – the publication of this Guidance – serve as the official notification to the industry of possible FDA enforcement action, to occur shortly after the approval of any currently marketed unapproved drug.

Compliance with the approval provisions of the Federal Food, Drug, and Cosmetic Act (the “Act”) requires a manufacturer to develop consistent formulation and stability testing, submit data periodically to FDA, follow imposed manufacturing controls, and limit labeling and promotional claims. Manufacturers who choose not to comply have essentially unrestricted marketing and a very low risk of any disruption by the agency.

The disparity is more troubling in a case where a manufacturer has received approval of an NDA for an OTC product. Allowing the unapproved prescription drug to remain on the market is truly an unprecedented challenge to the drug approval system. Indeed there is a major benefit to manufacturers of the non-approved prescription drug not only because they are not required to comply with marketing limitations, formulation performance, etc., but also because their products have a misleading mantle of "legitimacy" through their prescription-only labeling. FDA should deal more quickly with this type of situation because it poses a very serious threat to the drug approval system.

In the case of single-ingredient, extended-release guaifenesin products, for example, there were approximately 20 manufacturers and approximately 50 re-packagers and private label distributors of unapproved products. Although Mucinex[®] (guaifenesin) Extended-Release Tablets, 600 mg and 1200 mg, were approved in July 2002 and December 2002 respectively, FDA action against competitors was not effective until November 30, 2003. This allowed the continued marketing of illegal products for up to 17 months. Sustained release guaifenesin continued to be marketed as a prescription therapy for Fibromyalgia and any other indication the manufacturer chose because it was not regulated under an NDA. Not only did this garner sales in favor of the manufacturers of unapproved products, but it also served to confuse prescribing physicians, pharmacists, and consumers, who believed that the formulations were legal, since the drugs were still available. Consumers, in particular, were allowed continued exposure to products for uses that have never been proven to be safe or effective. FDA enforcement action must quickly end this type of marketing. Protecting the public against these types of representations is a fundamental element of the drug approval system.

Adams strongly urges FDA to take a firm position that continued marketing of unapproved drugs, especially after approval of a product, is illegal and subject to enforcement action. To act otherwise is to encourage non-compliance with the Act and also will lead to a larger number of illegal products being introduced into the U.S. market. Clearly notifying manufacturers of swift and certain enforcement action will encourage companies to conform to the existing drug approval system. Quickly removing unapproved drugs from the market after a company obtains approval to market a product will provide incentives for companies to comply appropriately with new drug requirements.

Sincerely,



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DJK/tc