



ECR PHARMACEUTICALS

ECR PHARMACEUTICALS

P.O. BOX 71600

RICHMOND, VIRGINIA 23255

Tel: (804) 527-1950 Fax: (804) 527-1959

December 15, 2003

Division of Dockets Management
HFA-305
US Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Dear Sir or Madam:

This letter is submitted to comment on the draft "Guidance: Marketed Unapproved Drugs – Compliance Policy Guide" that appeared in the Federal Register on October 23, 2003. (68 Federal Register 60,702, Docket number 2003D-0478) I am the operating officer of ECR Pharmaceuticals, Richmond, Virginia. Our firm markets branded, prescription pharmaceutical products and has approximately 80 employees.

The background information noted in the above draft guidance I believe appropriately outlines the issue at hand, i.e., there are a large number of products which have long been marketed in the US which fall outside the specific new drug approval process. These drugs are largely comprised of components which are approved entities under another format (OTC Monograph, etc.) or may be drugs subject to ongoing DESI review. These drugs are widely and generally accepted as safe and effective. Many of these drugs fall outside the approval process because they are extended release preparations of approved immediate release entities, and hence subject to classification as a new drug product under provisions which date to 1959. Not noted in the overview is that these drugs are widely utilized by physicians and patients, are very competitively priced, and because of the latter exert significant pressure on the market to maintain low and reasonable prescription drug costs. If these drugs do not continue to be available, or are not available at a reasonably low cost, the US consumer will be adversely affected.

We also concur with the intent of the guidance to review and formalize the approval of these long established products. We were pleased to see the substantial thought and sound reasoning prevailing in approaching this matter. Appropriately and correctly accomplishing a format for approving these products will benefit patients, physicians, the FDA and industry. I must however caution that a format which does not provide that these products continue to be widely available and competitively priced, would not benefit the US public, and would harm physicians and the industry, notably small pharmaceutical firms which contribute so significantly toward maintaining the supply of affordable drug products. I believe a mutually beneficial format which resolves this matter is available and achievable, and which will have the support of all parties.

Two particular issues need to be examined: (1) the current format for granting exclusivity to encourage the submission of new drug applications for the types of products noted above, and (2) the requirement of a new drug application for extended release formulations of approved immediate release products.

2003D-0478

CS7

Though well intended, and superficially logical, the granting of exclusivity to firms which submit an NDA for a product noted above is not reasonably functional and the result is often adverse to the public interest. This format will not often be undertaken by a firm currently marketing these products because of the high cost of doing the NDA. Small firms generally market these types of products and these businesses simply do not have the assets to undertake the very expensive task of an NDA. Additionally, in most cases the submission will not at the end of the day enhance the scientific body of knowledge for the drug. Further, this format decreases competition within the industry which results in substantially higher prices for the product. Almost nothing good results from this high cost approach for the US public, physicians, the FDA, or industry.

When codified in 1959, the requirement that an extended release formulation of an approved, immediate release drug be treated as a new drug product, and hence subject to submission of an NDA, was reasonable and soundly based. At that point the technology was new, consistent drug release profiles were not well established, and substantial questions regarding the overall effects of extended release formulations were poorly known. However, some 40 years later extended release technology which provides well-controlled and reliable drug release profiles is widely available in industry and is well accepted. As indicated earlier, many of the products noted as falling outside the current approval process are long marketed extended release formulations of approved immediate release drugs. The long-term actual use of these products has provided insight into their safety and efficacy well beyond that which could be demonstrated in small, very expensive clinical trials. Appropriate guidance and parameters can be effectively established to regulate these extended release products without requiring the costly submission of an NDA. Certain product categories, notably those drug products with long half-lives or those which have significant inter-subject variations, may need to be excepted from this general approach and an NDA required. The latter should however be identified and treated as exceptions, and not be the rule for all extended release products. I believe these exceptions could be readily identified during a public comment period, and/or by the FDA in response to a sponsors future request for consideration and guidance.

To demonstrate certain deficiencies intrinsic in the proposed draft compliance policy guide format, I use the example of Adams' recently approved NDA for Mucinex, 600 mg extended release guaifenesin.

Guaifenesin has been available since the 1940's in the US market as an immediate release product and is classified as a category I expectorant. This immediate release drug and its dosing guidelines are listed in the OTC Cough/Cold Monograph. Extended release formulations of guaifenesin have been available in the US market since the 1980's without the benefit of an NDA. These fall outside the approval process, on the basis of the 1959 regulations that extended release products are new drugs and hence subject to an NDA. By the year 2000, these extended release guaifenesin formulations were widely prescribed by physicians and were being used safely and effectively in tens of thousands of patients. Approximately 20 manufacturers, and many more distributors, both branded and generic, made this product available in the US market with virtually no safety or efficacy concerns or complaints. The product was available at a pharmacy cost of about 8 cents per single 600 mg tablet.

In 2002, using the regulatory incentive which provides exclusivity for submitting an NDA for this type of marketed but unapproved product, Adams submitted and received approval for Mucinex.

As noted earlier, this regulatory provision is well intended, but may clearly yield results adverse to the public good. In the case of Mucinex, the granted exclusivity ultimately forced the more than 20 firms manufacturing and marketing the product out of the market. This absence of competition raised the pharmacy price of the 600 mg guaifenesin tablet from 8 cents to 60 cents. The FDA also classified the product as OTC, in opposition to the sponsor's request and the previously marketed status of the drug. This classification resulted in most insurance programs and Medicare dropping this as a covered drug. The latter is a policy matter of different origin which needs to be addressed in a different forum, as inclusion here detracts from the central issue at hand - formalizing an approval process for long established, marketed products.

In summary, the approval of the Mucinex product (1) added substantially nothing to the body of science regarding the product or its safety and effectiveness, (2) provided one company with a monopoly for a long established and widely used product, displacing some 20 other manufacturers or distributors, and (3) raised the price of the product over 700%, hence making an affordable widely used product potentially unavailable to many patients. While well intended, the results clearly indicate an adverse outcome. Continuation of this format for long marketed prescription products which are currently outside the approval process will negatively effect the public good as well as those manufacturers who produce these beneficial pharmaceuticals. It also may bring common sense into question.

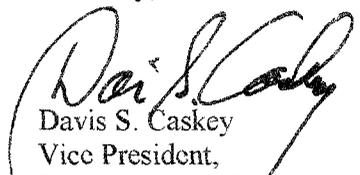
We currently have available only three mechanisms for prescription drug product approval: a 505 (b) (1) NDA, the full NDA process which involves several million dollars of investment and hence is only reasonably available to large firms; the 505 (b) (2) NDA which essentially applies to new formulations of previously approved products whose patents have expired and which some data from the innovator can be used, and which again requires millions of dollars of investment; and the ANDA process which provides for the precise duplication of a product whose patent and/or exclusivity has expired.

There is a better way to accomplish FDA's objectives and formalize the status of these many useful drugs which have long been marketed but fall outside the specific approval process. The Branded Pharmaceutical Association (BPA) has proposed a format similar in construction to the previously implemented OTC monograph for these products. This approach is referenced as a Prescription Drug Monograph and would provide guidance regarding acceptable limits and parameters for specific prescription drug substances and categories, notably acceptable extended release drug profiles. This format would help the FDA assure that these products are appropriately manufactured within the devised limits. It provides for multiple companies to concurrently come into compliance, thus providing continued competition to maintain affordable prices. It benefits the general public in that these products will continue to be available at reasonable prices. The evaluation process in devising a prescription drug monograph should be open to public comment and hence transparent in its development. We believe this approach to have wide support within the pharmaceutical industry as well as with our elected legislative representatives. We encourage your review and support of this format. We want to work with FDA to add clarity and stability to the process of formalizing approval of these products as we are certain that such will yield a good outcome for all parties. We also want to reinforce that we do not in any manner wish to detract from the FDA's mandate and efforts to assure a US drug supply which is safe and effective. To the contrary, we want to support and help assure these efforts.

Division of Documents Management
US Food and Drug Administration
Page Four

Please be advised that I will make myself available for your questions and comments, which may include visiting your offices in person. We believe that appropriate resolution of this issue via the development of a Prescription Drug Monograph, or similar format, can have a substantial positive impact on the US consumer of prescription products and FDA oversight. It can also have an equally negative effect if not handled correctly. We look forward to working with you.

Sincerely,



Davis S. Caskey
Vice President,
Pharmaceutical Operations
ECR Pharmaceuticals

cc: The Honorable John Warner
The United States Senate
By FAX 202-224-6295

Mr. Christopher J. Yianilos
Deputy Legislative Director/Legislative
Counsel

The Honorable George Allen
The United States Senate
By FAX 202-224-5432

Mr. Robert Turner, II
Legislative Assistant

The Honorable Eric Cantor
The United States House of Representatives
202-225-0011

Ms. Colleen Maloney
Legislative Assistant

Dr. Mark McClellan
Commissioner,
US Food and Drug Administration
301-443-3100

Mr. David Horowitz, Esq.
Director,
Office of Compliance, CDER
US Food and Drug Administration
301-827-8901