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December 22, 2003

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DEC 22

VIA HAND-DELIVERED

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

Re: Docket # 2003D-0478 -- Draft Compliance Policy Guide On Marketed Unapproved Drugs, 68 Fed. Reg. 60702 (Oct. 23, 2003)

Dear Sir or Madam:

These comments are submitted on behalf of PFab LP, d/b/a/ PharmaFab®, with regard to the above-referenced draft compliance policy guide. PharmaFab is a contract manufacturer of solid dose and liquid formulations for the branded and generic pharmaceutical industry.

PharmaFab requests FDA take several actions with respect to this docket, for reasons that are further explained below. *First*, PharmaFab joins in the comments filed by the Branded Pharmaceutical Association (BPA) and that organization's request that FDA issue a revised solicitation for comments on this draft Compliance Policy Guide (CPG) on marketed unapproved drugs. As BPA requested, the revised solicitation should present both the draft CPG and the prescription drug monograph system that Congress has directed FDA to consider. Thereby, the public comment period may assist FDA in assessing the relative merits of its proposed CPG and a prescription drug monograph system that would allow certain prescription drugs to be marketed without FDA premarket approvals. The comment period should also be extended to allow for more meaningful public input.

Second, PharmaFab respectfully requests that the entire docket 02P-0483 be assumed into and cross-referenced with the docket for this draft CPG. PharmaFab respectfully submits that the perspective of the regulated industry regarding the marketing of older prescription pharmaceuticals outside of the current drug approval process cannot be understood in the absence of this information.

Third, in the event that the draft CPG is adopted, it should be revised to eliminate the presumption that a grace period between the approval of an older prescription pharmaceutical

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outside of the current premarket approval scheme and the initiation of enforcement action against competitive products should be set at one-year. PharmaFab agrees that a grace period should be utilized, and that the policy considerations outlined in the draft CPG are sound, but that a presumptive one-year grace period does not serve those policy considerations well.

BACKGROUND

The draft Compliance Policy Guide (CPG) by its own terms is designed to supersede section 440.100, Marketed New Drugs With Approved NDAs or ANDAs (CPG 7132c.02). The impetus for revisiting CPG began in October 2002, when FDA issued 70 Warning Letters to manufacturers and distributors of prescription single entity sustained release guaifenesin products based on the "new drug" status of the products. These letters followed the July 2002 approval of a New Drug Application (NDA) for an over-the-counter single entity sustained release guaifenesin product. In several prior instances of so-called "old drugs" marketed without approved NDAs or Abbreviated New Drug Applications (ANDAs), when FDA determined that such products should have approval, the agency has provided notice through the Federal Register of its determination, and has provided time for manufacturers to file NDAs/ANDAs and obtain approval. *E.g.*, levothyroxine sodium tablets (1997 notice; 2001 cut-off date for approvals), digoxin (2000 proposal to revoke regulation governing conditions for marketing; 2002 final rule revoking regulation). The industry reasonably expected that if the agency decided to change its practice with respect to other products (such as single entity sustained release guaifenesin) and to require approval applications, it would announce the new policy and give the affected companies an opportunity to comply.

Representatives from affected companies met in November 2002with the Chief Counsel and the Director of the Center for Drug Evaluation and Research's Office of Compliance to discuss the Warning Letters. At that meeting, these FDA officials explained that FDA would now consider -- in the event of an NDA approval for a drug that had previously been marketed without objection from FDA albeit without approval – that all unapproved versions of the drug will have to be immediately withdrawn from the market. The rationale for refusing to provide for an orderly transition from unapproved to approved status was that the potential to force competitors off the market by obtaining an unexpected approval would "incentivize" companies to seek such approvals. That policy has now been more formally enunciated in the draft CPG, albeit with the admission that there may be circumstances under which a grace period would allow continued marketing of the competitive products, with a presumptive length of one year.

FDA SHOULD REVISE THE SOLICITATION FOR COMMENTS ON THIS DRAFT CPG TO INCLUDE COMMENTS ON A PRESCRIPTION DRUG MONOGRAPH

The far-reaching effects of FDA's focus on older prescription pharmaceuticals marketed outside the current drug approval process led to broader inquiries on the part of regulated industry, consumers, and the Congress. As a result, both the Senate and House of Representatives Agriculture

Subcommittees of their respective Appropriations Committees made a request of the agency with respect to a report on the development of an alternative model for regulating older prescription pharmaceuticals marketed outside of the current drug approval process. The Senate appropriators framed their request in the following language:

> PRESCRIPTION DRUG MONOGRAPH SYSTEM. – 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.

Senate Agriculture Appropriations Report 108-107 (July 17, 2003) at 157.

The House Committee request paralleled the Senate's:

> PRESCRIPTION DRUG MONOGRAPH SYSTEM. – 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.

House Agriculture Appropriations Report 108-193 (July 9, 2003) at 86.

As noted in BPA's comments on the draft CPG, FDA's "Questions and Answers" (Q&A) (http://www.fda.gov/cder/compliance/CPG_QandA.htm) that accompanied the draft revised CPG contained the following exchange:

> **Has FDA considered a monograph system that would allow certain prescription drugs to be marketed without individual FDA approvals for each?**
>
> FDA is examining whether any class or classes of prescription drugs might be regulated under a monograph system in lieu of requiring individual applications. The Agency will be preparing a report to Congress, in the coming months, that considers the feasibility and cost of such a system. Although FDA has considered and declined this approach on several past occasions, the agency will consider whether new, relevant factors affect our analysis as we re-visit the question.

PharmaFab concurs with BPA that the agency itself perceives a connection between the draft CPG on drugs marketed outside of the present drug approval process, and the possible development of a Prescription Drug Monograph (PDM) system.

PharmaFab acknowledges that FDA retains the authority, indeed the obligation, to take enforcement action against products that present potential safety risks, ineffective drugs, and health fraud drugs. That authority does not depend on finalization of the draft CPG. In that case, there is no untoward effect on the agency from reissuing the solicitation for comment on the draft CPG to include comments on the development of a PDM. Such a course can only assist FDA in the development of the reports requested by Congress.

FDA SHOULD ASSUME THE DOCKET IN 02P-0483 INTO THE DOCKET ON THE DRAFT CPG

The November 12, 2002, Citizen Petition regarding FDA enforcement activity over single entity, extended release guaifenesin has a clear and acknowledged nexus with the draft CPG. Superseding CPG 7132c.02 (1987) with the present draft would effectively respond to the Citizen Petition. The dockets for this draft CPG and the Citizen Petition in 02P-0483 should therefore be assumed into each other and cross-referenced.

THE DRAFT CPG SHOULD BE REVISED TO ELIMINATE THE PRESUMPTION OF A ONE-YEAR GRACE PERIOD BUT RETAIN THE CONSIDERATIONS FOR THE SETTING OF A GRACE PERIOD

PharmaFab agrees that when a company obtains approval of an NDA for a product that other companies are marketing outside of the current drug approval process, FDA should set a grace period for those competing products to obtain their own approvals or leave the market. The draft CPG provides that FDA "normally intends to allow a grade period of roughly 1 year from the date of approval of the product before it will initiate enforcement action" against competing products. The draft CPG also provides that this presumptive one-year grace period

> 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; (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.

Draft CPG at 5, lines 172-180.

FDA should retain all of these considerations in the event of finalization of the draft CPG. In addition, FDA should consider that the "effects on the public health" include not merely the availability of a particular drug under these circumstances, but the costs imposed on consumers as well. For example, when a broad competitive market for single entity, extended release guaifenesin was replaced with a single over-the-counter (OTC) product, not only was there an approximately 700% increase in the cost of the product, but insurance reimbursability was lost in the prescription to OTC switch. For some members of the patient population, the practical availability of a product is very closely tied to its affordability. "Effect on the public health" must be read to include whether affected patient populations can afford and safely use the approved product.

There may also be other matters that should be considered in determining "effect on the public health" which may vary according to the particular products at issue. For example, with respect to single entity, extended release guaifenesin, the sole product allowed to remain on the market bears a label warning against use in patients under 12 years old, thus leaving those patients with no available product. In addition, the sole product allowed to remain on the market contains

excipients that make the product unusable by many affected patients, and switching to available OTC products, which requires more frequent dosing, has presented patient management issues in some settings. FDA should therefore read "effect on the public health" broadly in each case.

FDA should, however, dispense with the presumptive one-year grace period. Such a presumption will likely become a default period, and supersede the more important considerations outlined above. Moreover, from the regulated industry's perspective, the time necessary to obtain FDA approval for a competitive product, *i.e.*, the period from the filing of an NDA or ANDA to agency approval, is not the sole consideration. There may also be issues regarding business planning in deciding to devote the resources to seek approval for a product or discontinue the currently marketed form, inventory reductions (which affect not only manufacturers but distributors as well), and planning for marketing after approval. Ultimately, "changes in the market" are changes in therapy instituted by physicians and their patients. Affected patient populations, physicians, and the regulated industry should all be given an opportunity to assist FDA in determining an appropriate grace period, and the presumption of a one-year grace period is contrary to reasoned decision-making in this regard.

PharmaFab also wishes to express its significant concerns with FDA's assumption of the authority to manage the drug approval process to grant market exclusivity. That authority is not generally granted the agency under the Food, Drug, and Cosmetic Act; authority to make grants of market exclusivity are very specifically granted under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman), Pub. L. No. 98-417, 98 STAT.1585. The Hatch-Waxman Amendments represent a legislative compromise between the competing interests of innovator and generic drug companies. *Abbott Labs. v. Young*, 920 F.2d 984, 991 (D.C. Cir. 1990) (Edwards, J., dissenting); *Mylan Pharm. Inc. v. Henney*, 94 F. Supp. 2d 36, 53 (D.D.C. 2000); *see also Zeneca Ltd. v. Pharmachemie B.V.*, No. 96-12413-RCL, 1998 U.S. Dist. LEXIS 12842, at *9-10 (D. Mass. July 8, 1998). Wholly different concerns are under consideration here, and the agency should not presume to exercise authority similar to its administration of Hatch-Waxman with regard to the exercise of enforcement discretion.

* * * * *

PharmaFab has been keenly involved in all of the issues that led to the development of the draft CPG, and appreciates the opportunity to provide comment. As the agency moves forward in this area, it should continue to keep as its primary object preservation of the public health. PharmaFab considers the development of a Prescription Drug Monograph to be a key component of these efforts.

Respectfully submitted,

David L. Durkin
Counsel to PharmaFab

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