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December 19, 2003

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

Re: Docket No. 2003D-0478
Request for Comment on Draft Guidance: Marketed Unapproved Drugs – Compliance Policy Guide

Dear Sir or Madam:

King Pharmaceuticals, Inc. (King) submits the following comments in response to the draft Compliance Policy Guide (CPG) regarding the marketing of unapproved drugs published by the Food and Drug Administration (FDA) on October 15, 2003 and announced in the *Federal Register* on October 23, 2003 (68 Fed. Reg. 60702). When final, the CPG will supersede CPG section 440.100, Marketed New Drugs Without Approved NDAs or ANDAs (CPG 7132c.02), as a description of the agency's enforcement priorities for unapproved drugs. As drafted, it expresses FDA's interest in encouraging drug manufacturers to obtain approved new drug applications (NDAs) for these products – many of which have been marketed for many years without FDA review or approval. And, FDA emphasizes its interest in doing so "without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market." FDA, *Draft Guidance, Marketed Unapproved Drugs – Compliance Policy Guide* (hereinafter "Draft Guidance") at 2.

King manufactures more than fifty branded prescription product lines, including Altace®, Levoxyl®, Skelaxin®, Sonata®, Synercid®, and Prefest®. We also have experience in obtaining FDA approval of an NDA for Tigan® Capsules (trimethobenzamide hydrochloride) – a drug previously marketed without approval. Despite the fact that two years have passed since the agency approved Tigan® Capsules, other oral trimethobenzamide HCl products continue to be illegally marketed by other companies. Thus, we believe we are well situated to offer an informed commentary to the proposed guidance as well as to suggest changes to FDA's proposed approach.

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COMMENTS

We appreciate the agency's interest in encouraging the initiation of much needed safety and efficacy studies on these products. We agree that the public benefits from companies' willingness to undertake clinical studies to evaluate the drugs' safety or effectiveness. We also support FDA's efforts to provide, through its enforcement discretion, an incentive for companies like King to invest in that lengthy and, often, costly research. And, we do not disagree that providing a short grace period – during which FDA will not pursue enforcement actions against unapproved products – is a reasonable step to allow doctors and patients to transition from unapproved to approved products.

King is convinced, however, that a grace period of one year from the date of approval of an NDA will not serve the agency's public health goals. A grace period triggered by the approval of an NDA offers, essentially, no period of market exclusivity to the innovator company and, therefore, provides no economic incentive to companies considering whether to undertake expensive clinical studies. As proposed, the draft guidance will not encourage companies like King to undertake these approval projects.

Instead, we believe that a grace period of one year from the date of filing of the first NDA for a particular marketed unapproved drug will better promote the goals of encouraging research concerning drugs' safety and effectiveness, providing patients with more approved drug alternatives, while avoiding undue disruptions in the market.

The proposed Compliance Policy Guide does not provide incentive for the initiation of clinical drug research.

In the Draft Guidance, FDA outlines its enforcement priorities regarding unapproved marketed drugs. This includes the agency's planned approach for the "special circumstance" that occurs when one company obtains approval of a new drug application (NDA) for a product that other companies are marketing without approval. Draft Guidance at 4. According to the agency, companies marketing these unapproved products after an NDA approval for the same product will receive a grace period of approximately one year from the date of approval before FDA will initiate enforcement action against them. The length of this normal grace period may vary depending on several factors that will be evaluated on a case-by-case basis. These factors include the effects on the public health of proceeding immediately to remove a medically necessary drug for which

there is no therapeutic alternative from the market, and the ability of the approved application holder to meet the needs of patients taking the drug, as well as the difficulty of conducting any required studies and obtaining approval of an NDA. *Id.*

As the agency recognizes, "[t]he 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." Draft Guidance at 5. FDA hopes that *de facto* exclusivity "will provide an incentive to firms to be the first to obtain approval to market a previously unapproved drug." *Id.* at 6. It is highly unlikely, however, that allowing a grace period for continued marketing of unapproved drugs for one year from the date of approval will provide such an incentive. And, in circumstances where the first applicant submits the results of clinical investigations essential for approval, any grace period will destroy an incentive created by statute. *See* 21 USC 355(c)(3)(D)(iii); 355(j)(5)(D)(iii).

It is important to note from the outset that, in light of the agency's more accelerated approval of abbreviated NDAs (ANDAs), a grace period of one year will create a very short period of market exclusivity. In the past decade, approval times for ANDAs have decreased dramatically – from a median of about twenty-seven months in 1994 to eighteen months in 2000, 2001, and 2002.1 Thus, companies illegally marketing unapproved products in the wake of an NDA application for the same drug will have ample opportunity to submit for review ANDAs covering their previously unapproved products, and the Office of Generic Drugs may be close to approving these ANDAs by the end of the one-year grace period. Indeed, if the agency's trend continues, ANDA approval times may drop to one year or less, so that the entire review process will fall within the one-year grace period. Similarly, an applicant could develop a section 505(b)(2) application based on published literature about the product, submit an application under the ten-month review period implemented under the Prescription Drug User Fee Act, and receive approval shortly after the end of the grace period.

In other words, under the approach set out in FDA's proposed guidance, the first company to file an NDA would immediately subsidize efficacy studies for all other companies in the market for that drug, with little hope of recouping its investment. Within a year of approval, its competitors will have filed for and perhaps received marketing approval, leaving FDA little reason to take enforcement actions following the one-year grace period. Obviously, this provides

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1 *See* Center for Drug Evaluation and Research, *The FDA Process for Approving Generic Drugs*, at 8 (Median Approval Times – Original ANDAs) (Oct. 29, 2002), available at http://www.fda.gov/cder/ogd/02-10_BCBS_gjb/sld008.htm.

no incentive whatsoever for any company to invest the substantial resources to become the innovator in the market. Indeed, by offering virtually no market exclusivity after a substantial investment in clinical studies and other application costs, FDA creates a distinct *disincentive* for the desired clinical investigations.2

Unfortunately, King's experience in the trimethobenzamide capsule market bears out this prediction. We worked closely with the agency to gain new drug approval of a trimethobenzamide capsule. We invested in a development program for Tigan® under an August 2001 agreement with the Acting Chief Counsel of FDA on behalf of the Commissioner. The clear expectation of this agreement was that FDA would move swiftly to remove unapproved products from the market once an approved product became available. After investing considerable resources in clinical trials, King attained approval for Tigan® capsules containing 300 mg of trimethobenzamide on December 13, 2001. Significantly, King's development program showed that an oral dose of 300 mg is required to achieve blood levels equivalent to those attained with an approved (and demonstrably effective) dosage of injectable trimethobenzamide HCl product. Regardless, today unapproved oral trimethobenzamide HCl products continue to be marketed at lesser strengths of 100 mg and 250 mg.

FDA approved Tigan® in December 2001. Not until one year later in December 2002 did FDA publish a notice that reviewed the regulatory history of trimethobenzamide products and stated categorically that unapproved products are in jeopardy of enforcement action. 67 Fed. Reg. 78476 (Dec. 24, 2002). Nonetheless, two years after King obtained approval of Tigan® and despite data indicating that the widely-available 250 mg dose is less than the approved effective dose, FDA has taken no enforcement action whatsoever to protect patients from these products, which are marketed by nearly a dozen firms and dominate today's marketplace.3/

2/ Where the statute creates exclusivity by barring FDA approval of later-filed applications, the agency's approach compounds this disincentive. In the face of a statutory bar on approval of later-filed applications, *see* 21 USC 355(c)(3)(D)(iii); 355(j)(5)(D)(iii), manufacturers of unapproved products are likely to do nothing at all. In these circumstances, FDA must take immediate enforcement action or risk undermining an incentive created by Congress.

3/ Notably, applying the factors the agency set out in the draft guidance for determining when the exercise of enforcement discretion is warranted, these unapproved trimethobenzamide products should be subject to enforcement actions. The proposed grace period of one year has expired (by more than a year). There are several non-therapeutically equivalent alternatives to Tigan®. King could easily meet the demand of patients taking trimethobenzamide HCl capsules. And, beyond the December 2002 notice, the companies currently marketing unapproved trimethobenzamide capsules have been on notice since 1979 that their products must obtain DESI approval. *See* 44 Fed. Reg. 2017, 2019-20 (Jan. 9, 1979).

Adding insult to injury, generic oral trimethobenzamide products based upon 300 mg Tigan® Capsules as the Reference Listed Drug were approved in August 2003.

As Congress has recognized, a manufacturer deciding whether to commence complex and lengthy research must balance the costs of drug development against the likelihood of revenue from the investment. In King's experience with Tigan® Capsules, the costs of the new drug approval process, including the conduct of clinical research, came close to a million dollars. Had we known that our competitors' unapproved products would be allowed to remain on the market for so long, King never would have initiated such a costly development program. Likewise, if FDA's Draft Guidance were to become final, no company similarly situated to King in 2001 would likely invest in similar development programs. Under FDA's policy, competitors may simply await final approval, file an ANDA or section 505(b)(2) application to cover their existing product once the proposed grace period expires, and stay on the market based on the innovator's research. Of course, all the while, consumers may be exposed to potentially ineffective and subpotent drugs when safe and effective alternatives are readily available.

Calculating the grace period from the date of the filing of the first NDA application will better promote innovative market behavior and public health.

Exclusivity has long been recognized as an effective way to advance public health needs. There are countless examples within the FDCA where market exclusivity is provided to the company that is willing to invest in research or other actions that might prove unsuccessful. Indeed, the first applicant to obtain approval of a drug marketed without approval could be eligible for statutory exclusivity if reports of new clinical investigations are essential to approval of the product. Through the proposed guidance and the exercise of its enforcement discretion, FDA has an opportunity to create a similar incentive to promote studies of additional marketed but unapproved drugs.

As discussed, however, King does not believe that FDA's proposed grace period of one year, beginning at the approval date of the innovator's NDA, will provide an effective incentive. We suggest, instead, a grace period beginning on the date FDA accepts the innovator's NDA for filing. Such a policy would increase the likelihood that the innovator will receive a true and reasonable period of market advantage. Under King's plan, the grace period would end at or around the time of NDA approval for the drug instead of one year later, by which time many competitors could have received ANDA approvals.

In fact, under King's proposal, most NDA-holders could, reasonably, receive one year of market advantage – which would approach FDA's stated objective. Our proposal strikes a balance between the interests of encouraging further study of unapproved marketed drugs without unduly disrupting the market or providing a windfall to the innovator. It is also more likely to promote the agency's goal of encouraging manufacturers to obtain evidence concerning the safety and effectiveness of their unapproved drugs, ultimately improving the public health.

Where the first NDA-holder is eligible for statutory exclusivity, FDA should provide no grace period whatsoever. Once all patients have had an opportunity to transition to the newly approved product, FDA should take swift action against all unapproved marketed products. Otherwise, the innovator has no opportunity to benefit from a period of exclusivity that Congress clearly envisioned when it enacted a bar to FDA's ability to approve a competing product.

The proposed exclusivity period will not disrupt the market or burden consumers.

The Draft Guidance seeks to create an incentive for certain behavior while avoiding unnecessary disruptions in the drug market or otherwise burdening consumers. Yet, King strongly believes that FDA's concerns of market disruption will not be borne out in the marketplace. Simply put, under King's plan, all manufacturers will receive adequate notice of any upcoming exclusivity period. With a published announcement in the *Federal Register* of the filing of the first NDA, the industry would be on notice as to the start of the grace period for the relevant drug.4/ *See* 21 CFR 310.6(c) (requiring manufacturers and distributors to review all relevant drug efficacy notices and assure full compliance).

We do not share FDA's concern that manufacturers of unapproved products will abandon the marketplace when one in a class receives NDA approval

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4/ Moreover, FDA easily could address any confidentiality concerns applicants may have about such publication. *See* 21 CFR 314.430. In such a context, manufacturers could agree to waive their rights to confidentiality in order to facilitate running of the grace period. *Id.* at 314.430(d)(1). Alternatively, if an innovator refused to do so, FDA should adjust the grace period to reflect, at a minimum, the shortest review period available for the competitor products. The statute prescribes a review period of 180 days for ANDAs, which would serve as an effective grace period in circumstances where competitors did not receive notice until approval of the first previously-unapproved product.

– leaving consumers without access to needed drugs. Instead of withdrawing product from the market, manufacturers of unapproved products may seek to fill the drug distribution pipeline, even in the face of heightened FDA enforcement scrutiny.5/ In those circumstances where FDA has reason to believe that a shortage will occur, it could take precautionary safeguards. For example, before medically necessary unapproved products for which there is no adequate substitute are entirely removed from the market, FDA could require evidence from the innovator company of its ability to meet the expected demand for the product. This type of approach will protect the public while affording consumers the benefit of an approved product.

We recognize the need for flexibility in applying any grace period, but urge FDA to weigh its discretion against the industry's need for predictable agency action. To that end, we urge the agency to consider the pendency of a generic approval and the innovator's eligibility for "new product" exclusivity when considering the factors that influence a decision whether and when to take enforcement action. Where generic approval is imminent after approval of the first NDA for a particular class of unapproved drugs, the agency should adjust its grace period to assure a *de facto* period of exclusivity.

Whatever the length of the grace period, we emphasize that it must be followed by swift, predictable, and comprehensive enforcement action by FDA. As our experience with Tigan® shows, lack of enforcement by the agency destroys any value to innovative conduct and, therefore, any incentive to initiate important medical research. Without assurances of predicable and real enforcement, manufacturers will, quite rationally, allocate their resources to more cost-effective activities – activities other than NDA approval studies for currently marketed, unapproved drug products. To be effective, FDA's final guidance must reflect these realties of economic behavior.

CONCLUSION

As written, the draft guidance has little hope of achieving its intended goals. By offering a one-year grace period from the time of NDA approval, the proposed compliance policy guide will discourage investment in needed safety and efficacy studies. King suggests that for most circumstances a one-year grace period from the date of the filing of the first NDA will produce a stronger economic

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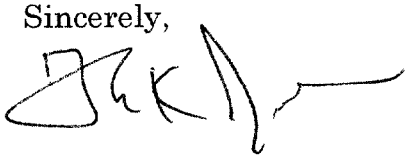
5/ *See* FDA Warning Letter to Howard Solomon, Chief Executive Officer of Forest Laboratories, Inc. (Aug. 7, 2003), available at http://www.fda.gov/foi/warning_letters/g4190d.pdf, at 2.

incentive for the desired behavior by creating a longer period of market exclusivity. We also respectfully recommend that a forceful and consistent enforcement approach is essential to give meaning to any *de facto* period of market exclusivity. Of course, where the first applicant is entitled to statutory exclusivity, FDA should provide no grace period whatsoever. Together, these policies will more effectively promote the desired results of increased efficacy studies and consumer access to tested drugs, without undue disruption to the market.

We thank FDA for its consideration of our comments and look forward to further dialogue on this issue.

Sincerely,



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cc: Meredith Manning
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