DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance

Sent via e-mail in .pdf format
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Dear Mr. Cole and Mr. Noble:

Thank you very much for meeting with representatives of the Office of Compliance of FDA's Center for Drug Evaluation and Research (CDER) on March 28, 2006. We appreciated the opportunity to hear your perspective and to share some of our own thoughts. I wanted to follow-up on a few points.

First, as promised, I am providing information about CDER's unapproved drugs coordinator. Her name is Dr. Sally Loewke, and she works in CDER's Office of New Drugs (the office that reviews new drug applications (NDAs)). She can be reached at 301-796-0710. CDER recommends that any firm marketing an unapproved drug contact the coordinator and, at the same time, schedule a meeting with the relevant review division to discuss what data would be required to support an application for approval. We want to reassure you that we will not target a firm or a marketed unapproved drug for enforcement action simply because the firm has scheduled this meeting or is pursuing approval of a marketed unapproved drug.

In preparation for the meeting, we recommend that the company do a survey of available literature and other accessible data on the product and provide to the division a short summary of the studies and data that are available to support the safety and efficacy of the drug for the proposed indication.

At the meeting, CDER would expect the division to discuss whether enough is known about the specific product to be marketed to obviate the need for pre-clinical work (e.g., carcinogenicity or reproductive toxicity studies), depending on the proposed indication. CDER also would expect

the division to provide advice on the quality and amount of data that it would expect in the NDA, based on a review of the summary of the studies in the literature and other available data that the company would provide before the meeting.

Regarding the amount and quality of data that would be necessary to obtain approval of a marketed unapproved drug, the agency issued a guidance in 1998 concerning the amount and type of evidence needed to support effectiveness in an NDA (Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, May, 1998, at http://www.fda.gov/cder/guidance/1397fnl.pdf). That guidance was issued as a result of the Food and Drug Administration Modernization Act and described in some detail how we interpret the statutory requirements for adequate and well-controlled studies. Of note, the guidance indicated that the agency is willing in some cases to consider studies from the literature when the applicant does not have access to primary data. An applicant seeking approval to market a previously unapproved drug should be familiar with this guidance as it describes the principles we will use to examine available data proposed for inclusion in an NDA. In general, the guidance indicates that some further data (i.e., beyond a published report), such as the protocol, is better than none and that multiple published studies are generally more credible than a single report. The pharmacologic properties of the drug could also influence the usefulness of published controlled studies. Information about the safety of the product will not generally be available from published reports, but may be determined from marketing history, both here and in countries with reasonable surveillance systems. For example, published studies of a drug from a familiar class with many members (e.g., narcotics), if they showed results similar to studies we had reviewed, might have enhanced credibility.

CDER would like to work with companies seeking approval to market previously unapproved marketed drugs, and the Center is willing to be flexible in applying statutory requirements, to the extent possible, while still maintaining adequate controls to ensure that drugs are safe and effective for the conditions of use proposed in the labeling.

Second, because you stated that user fees (PDUFA fees) may deter your members from seeking required FDA approval for their drugs, I wanted to clarify some of the circumstances in which your members may not be required to pay those fees. As we discussed, there are no user fees for abbreviated new drug applications (ANDAs) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Therefore, if your members' drugs are eligible for approval as generics via an ANDA (as may be the case for unapproved versions of an already approved drug), no fees would be assessed. In addition, applications submitted under section 505(b)(2) of the FD&C Act will not be assessed fees if they do not request approval of: (1) a molecular entity that has not been approved under a 505(b) application; or (2) an indication for a use that has not been approved under a 505(b) application.* See section 735(1)(B) of the FD&C Act.

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* A sponsor would qualify for a fee if, for example, it seeks a different use of the drug, a different dosing regime, a different route of administration, or a use in a new population, or if its labeling compares the sponsor's product to other products.

Any application submitted under section 505(b)(1) or 505(b)(2) of the FD&C Act that does not require clinical data for approval would only be assessed a half fee. Bioavailability and bioequivalence data are not considered clinical data for purposes of assessing user fees. See FDA's guidance for industry, *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees.*

There may also be no application fee if a drug is designated as an "orphan drug." According to section 736(a)(1)(E) of the FD&C Act, a sponsor that submits an application for a prescription drug product that has been designated as a drug for a rare disease or condition pursuant to section 526 of the FD&C Act is not subject to the application fee. However, if the application includes an indication that is not orphan-designated it would be eligible for the user fee.

A sponsor of an application that would be assessed either a full fee or a half fee may qualify for waiver under several provisions of PDUFA. For example, a sponsor may be eligible for a small business waiver, which provides for a complete waiver of the application fee for any company with less than 500 employees (including affiliated companies) for the first application that the company (including its affiliates) submits. See section 736(d)(3) of the FD&C Act. A sponsor may also be eligible for a public health or barrier to innovation waiver, which provides for waiver of the application fee, as well as annual product and establishment fees, if a company meets the criteria. See sections 736(d)(1)(A) and (B) of the FD&C Act; FDA's *Attachment G – Draft Interim Guidance for Waivers of and Reductions in User Fees*. FDA evaluates requests for these waivers on a case-by-case basis.

This is just an informal summary of some of the relevant provisions. For authoritative information on user fees and waivers, please consult CDER's user fee staff in the Office of Regulatory Policy at 301-594-2041. More information on user fees is also available on the Internet at http://www.fda.gov/cder/pdufa/default.htm.

Third, I am enclosing for your information a copy of the agency's October 2003 draft Compliance Policy Guide on Marketed Unapproved Drugs. The appendix to this draft guidance describes the various kinds of unapproved drugs that are on the market. As we discussed at our meeting, it explains why it is not accurate to label all of these drugs as "DESI drugs." As discussed, many marketed unapproved drugs are not "DESI drugs" and were never the subject of any kind of FDA approval.

Finally, the slides that you provided before our meeting imply that FDA approval makes drugs less safe because the drugs may become over the counter (OTC), resulting in a "loss of physician supervision." Whether a drug is approved as a prescription or OTC product depends on the safety of that specific drug. By definition, FDA would not approve a drug as an OTC drug if it could not be used safely without physician supervision. See sections 505(d) and 503(b)(1) of the FD&C Act. While it is true that insurers are unlikely to reimburse patients for the cost of buying an OTC drug, it is also correct that patients would not have to spend the time and money to see a physician before buying an OTC drug.

Mr. Cole, please consider sharing this information with your members. Thank you again to both of you for taking the time to meet with us.

Sincerely,

Deborah M. Autor / ET

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Cc: Sally A. Loewke, M.D.