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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
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Re: **Draft Guidance for Industry on Applications Covered by Section 505(b)(2)**
Docket No. 99D-4809
64 Fed. Reg. 68697
(December 8,1999)

The Pharmaceutical Research and Manufacturers of America (PhRMA) submits these comments on the draft guidance that the Food and Drug Administration (FDA) made available on December 8, 1999, concerning new drug applications covered by section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act).[1] PhRMA is a voluntary, nonprofit association that represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to research on medicines that allow patients to lead longer, healthier, and more productive lives. PhRMA's member companies invest approximately $24 billion annually to discover and develop new medicines. These companies are the source of nearly all new drugs that are discovered and marketed throughout the world.

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[1] *Guidance for Industry: Applications Covered by Section 505(b)(2) (the "Draft Guidance")*, available at http://www.fda.gov/OHRMS/DOCKETS/98F/994809gd.pdf

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I. Introduction

The issuance of this procedural guidance signals FDA's intention to encourage and facilitate broader use of 505(b)(2) applications. However, PhRMA is concerned that FDA's efforts to expand the use of such applications will undermine the public health and intellectual property protections built into the new drug application (NDA) and abbreviated new drug application (ANDA) processes. Accordingly, for the reasons set forth below, PhRMA requests that FDA withdraw and reissue the draft guidance document to make clear that the Agency will not approve under section 505(b)(2) of the Act an NDA that relies on a prior agency finding of safety and efficacy or that in any fashion relies on an unauthorized reference to proprietary and trade secret safety and efficacy data contained in an innovator manufacturer's NDA that is otherwise not available in the public domain. To the extent that the draft guidance document reflects FDA's interpretation of 21 C.F.R. § 314.54, PhRMA also requests that FDA initiate rulemaking to modify that regulation in a similar manner.

Upon FDA recognition and acceptance of the above position, PhRMA does believe a 505(b)(2) guidance document would be useful. Much of the current draft provides a meaningful start. However, PhRMA has identified additional issues that must be given consideration and incorporated into any final guidance document. ***First,*** insofar as 505(b)(2) applications may be used for proposed modifications to approved drugs, the guidance document should define clearly the types of data needed to demonstrate that a modified drug is safe and effective. ***Second,*** as a practical matter,

there are likely to be few circumstances in which a 505(b)(2) applicant will rely on data that do not pertain to a listed drug. Thus, to ensure that drug manufacturers are able to protect their intellectual property rights, FDA should adopt a presumption that a 505(b)(2) application relies on data for a listed drug unless the applicant demonstrates otherwise.

II. Section 505(b)(2) Does Not Authorize FDA to Approve a New Drug Application Based On the Agency's Prior Finding of Safety and Efficacy

In FDA's draft guidance document, the Agency has stated that it will accept and approve 505(b)(2) applications for new drug products that rely on "the Agency's finding of safety and effectiveness for an approved drug, without regard to a right to rely on such data." See Guidance Document, at 2. PhRMA submits that section 505(b)(2) does not authorize FDA to follow this course of action.

Section 505(b)(2) was enacted in 1984 as part of the Hatch-Waxman generic drug amendments. The legislative history of the Hatch-Waxman Amendments indicates that section 505(b)(2) was intended only to codify FDA's "paper NDA" policy, which permitted approval of certain drugs based on published studies.[2] See H.R. 98-857, Part I, 98th Cong., 2d Sess. 32, *reprinted in* 1984 U.S.C.C.A.N. 2647, 2665 (noting that section 505(b)(2) addresses filing of "Paper NDAs").

FDA is incorrect in interpreting section 505(b)(2) as authorizing the agency to approve a new drug by reference to a prior finding of safety and efficacy based on

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[2] The policy was limited to copies of drug products (or closely related forms) marketed after 1962 and offered for the same indications.

another company's proprietary data. The safety and effectiveness data a company submits when its seeks approval of an NDA are highly confidential, and thus are protected against unauthorized disclosure and use. See 18 U.S.C. § 1905, 21 U.S.C. § 331(j). The *only* circumstances in which FDA can rely on those data to approve another drug are the circumstances set forth in section 505(j), which provides for approval of generic drugs. Section 505(j) expressly authorizes FDA to approve a generic drug based on a prior finding of safety and efficacy for a pioneer drug, if the generic drug is "the same as" the pioneer drug in specified ways, and bioequivalent to it. Section 505(b)(2), by contrast, says nothing to authorize approval of a proposed new drug based on comparison with a previously approved product. Rather, section 505(b)(2) merely authorizes an NDA applicant to rely on published literature—as was permitted under the paper NDA policy—to satisfy the "full reports" requirement applicable to all NDAs. See H.R. 98-857, at 16, *reprinted in* 1984 U.S.C.C.A.N. at 2649 ("under the Paper NDA procedure, the generic manufacturer may submit scientific reports, instead of clinical trials, to support findings of safety and efficacy"). Thus, approval of 505(b)(2) applications based on prior findings of safety and efficacy is not authorized by section 505(b)(2) or any other provision of the Act, and would violate proprietary rights in the data.

III. Clear Procedural Guidance is needed for 505(b)(2) NDAs

The NDA (505(b)(1) and 505(b)(2)) and ANDA procedures are distinguished by the levels of clinical and non clinical data they require and the exclusivity protections for

which they are eligible. Recent FDA practices have blurred these distinctions, and this guidance does not clarify them. For example, FDA has approved versions of certain complex drug products under both 505(b)(2) and ANDA procedures. In 1998, FDA treated Ferring's Repronex as the "generic" equivalent of Serono's Pergonal through the ANDA process.[3] One year later, FDA approved Duramed's Cenestin under a 505(b)(2) application; however, Cenestin originally had been the subject of an ANDA referencing Wyeth-Ayerst's Premarin.[4]

In fact, an FDA representative has been quoted as stating that FDA's "generic" approval process for recombinant molecules will rely on the 505(b)(2) NDA "paper" mechanism: *"We are postulating a path for the recombinant molecule that gets an AB rating in the Orange Book, that does not come in under the [ANDA] route, it comes in under the (b)(2) route."*[5] This statement, in PhRMA's view, reflects a substantial and impermissible change in FDA policy. The pharmaceutical industry has long held the view that A ratings are reserved for generic copies approved through the ANDA process and simply are not available to modified drugs approved by 505(b)(2). PhRMA believes that the notion that modified drugs will be deemed substitutable is not what Congress intended when it enacted 505(b)(2).

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3 *Orange Book, at 3-216 (19th ed. 1999); Generic Recombinant Protein "Paper" NDA Approval Process Outlined by FDA,* THE PINK SHEET, at 32 (April 5, 1999).

4 *Id.*

5 *FDA Generic Recombinant Protein Approval Process Will Use "Paper" NDAs,* HEALTH NEWS DAILY, at 1 (March 30, 1999)(quoting Roger Williams, then Director, FDA Office of Pharmaceutical Science)(Emphasis added)> Subsequently, after leaving FDA, Dr. Williams, speaking as Acting Executive Vice President and CEO of U.S. Pharmacopoeia, suggested that 505(b)(2) procedures also could be applied to biological drugs related under the Public Health Service Act. *USP Monograph Could Substitute For ANDA Chemistry Review, Williams Says,* THE PINK SHEET, February 14, 2000, at 35.

Precisely because it is not clear how 505(b)(2) applications will be used, there is concern within the industry that the 505(b)(2) process might become a vehicle for the approval of a vast array of different salts and other chemical variants of approved small-molecule drugs in addition to its use with respect to certain large-molecule and other complex drugs. The experiences discussed above underscore the need for substantive as well as procedural guidance from FDA on this subject before FDA embarks further down this path.

1. FDA must ensure that 505(b)(2) applicants submit sufficient data to support all aspects of the safety and efficacy of the modified drug product.

As noted above, a section 505(b)(2) application is an NDA under 505(b) and as such, it must contain full reports to demonstrate that the new drug in question is safe and effective. Even when the 505(b)(2) application seeks minor modifications to an approved drug, significant questions of safety and effectiveness may arise. Because a 505(b)(2) application serves the same purpose as an NDA with respect to the modification to the drug or other proposed change (e.g., a change to the active ingredient), the same showing of safety and efficacy as is required for a full or supplemental NDA under section 505(b)(1) is also required to support a 505(b)(2) modification.

FDA has not yet advised the regulated industry what data will be required to support specific types of 505(b)(2) changes. FDA should address the substantive aspects of the 505(b)(2) process – specifically, the kinds of studies needed to prove the

safety and effectiveness of a 505(b)(2) modification – in this guidance document. The review of the clinical and other data supporting a 505(b)(2) application should be conducted pursuant to a clearly enunciated policy expressed in a publicly available guidance document.

Rather than establishing uniform substantive data requirements, the draft guidance indicates that a 505(b)(2) applicant should submit a plan to FDA before submitting the application. This plan should identify the components of the application to be supported by publicly available information (not previous FDA findings which as noted above are not permitted) and should describe any additional studies to be conducted. The guidance indicates that FDA "will critique the plan and provide guidance."[6] This suggests that the clinical studies and other data needed to support the 505(b)(2) application will be determined in large part by direction provided by FDA staff to individual applicants. This ad hoc approach suggests that FDA could apply a variable standard to such applications that would not necessarily track the rigorous uniform standards applied to full NDAs.

2. FDA should presume that a 505(b)(2) applicant is relying on data involving a listed drug unless the applicant demonstrates otherwise.

From the standpoint of the pioneer manufacturer, the significant problem with the 505(b)(2) is the "mismatch" between the publicly available data that the applicant may rely on and the patent protections that the pioneer manufacturer (which generated the data) can claim. This is best understood in comparison to the ANDA process. An

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[6] *Draft Guidance. at 9*

ANDA application may rely on data concerning a listed drug but remains subject to the patent and exclusivity protections for the same listed drug. A 505(b)(2) application, on the other hand, because it seeks approval of a drug that is different from a listed drug, might not provide meaningful patent and data exclusivity protection(s) to the pioneer.

As a practical matter, it is unlikely a 505(b)(2) application will rely on publicly available research that was *not* performed in connection with a listed drug. Thus, it would be reasonable for the FDA to presume that a 505(b)(2) applicant is relying on publicly available data involving a listed drug, notwithstanding that the drug under review is a modified drug or even a new chemical entity. A 505(b)(2) applicant who fails to identify one or more listed drugs should be required to demonstrate the reason why the data it relies on to support a finding of safety and/or efficacy for the modified drug has not been submitted in connection with a previously approved NDA or ANDA.

IV. Conclusion

The Act is clear that FDA must require the same scope and quality of evidence of safety and efficacy for a drug approval under 505(b)(2) as that required under 505(b)(1). Nothing in the Act allows FDA to short circuit that requirement by relying on data and prior findings of safety and efficacy which it has no right to divulge or reference. For the foregoing reasons, therefore, and to avoid engaging further in improper and statutorily unsupported action that will significantly adversely affect research-based companies, the FDA should withdraw and/or reissue the 505(b)(2) draft guidance document and should not apply 21 C.F.R. § 314.54 to approve NDAs that rely without authorization on non-public proprietary data. Reissuance of any revised

guidance must take into account additional substantive and procedural safeguards as discussed above to further ensure proper implementation of section 505(b)(2).

Sincerely yours,

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