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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20857

Re: Docket No. 2003N-0341
Proposed Rule Regarding Requirements for Submission of* In Vivo *Bioequivalence Data

Dear Sir or Madam:

We submit the following comments in response to the notice published by the Food and Drug Administration (FDA) on October 29, 2003 regarding the agency's proposed rule concerning the submission of certain *in vivo* bioequivalence (BE) data. 68 FR 61640. The proposed rule would require an applicant of an abbreviated new drug application (ANDA) to submit data from all bioequivalence studies, including those that do not meet passing bioequivalence criteria, that the applicant conducts on the drug product formulation submitted for approval. FDA seeks this change because additional BE data may be important in making individual bioequivalence determinations and in the agency's evaluation of ANDAs in general. The agency also believes the proposed rule will lead to increased knowledge regarding the impact of changes in components, composition, and methods of manufacture on bioequivalence and drug performance.

COMMENTS

Hogan and Hartson L.L.P. (Hogan & Hartson) fully supports FDA's goal of increasing access to additional bioequivalence data. As the agency recognized, "additional bioequivalence data on the same drug product formulation . . . can be important, even critical, to the agency's bioequivalence

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determination." 68 FR at 61643. Furthermore, we agree that a more complete understanding of bioequivalence and generic drug performance will "promote[] further development of science-based bioequivalence policies." *Id.* at 61641. Indeed, because of this crucial role of bioequivalence data in individual cases and in the agency's development of broader policy, we believe it is imperative that the final rule be as comprehensive and effective as possible. And, we believe that with the following modifications, the proposed rule will better promote FDA's intended goals.

1. FDA should require the submission of BE data related to different formulations of the same drug, particularly where the chemical or physical properties of the proposed drug may affect bioavailability.

As drafted, the proposed rule would require ANDA applicants to submit data on all BE studies performed on the "final formulation" or the "same drug product formulation" of a drug product submitted for approval. 68 FR at 61641. The same drug formulation "would include formulations that have minor differences in composition or method of manufacture from the formulation submitted for approval, but are similar enough to be relevant to the agency's determination of bioequivalence." *Id.* at 61643. This proposed language is problematic in two ways.

First, clarification is needed regarding which formulations are "similar enough" such that sponsors would be required to submit BE data for those formulations. If FDA chooses to retain this language, as opposed to requiring the submission of BE data for all formulations, it must clearly define the meaning of the phrase "similar enough." Otherwise, the rule will be open to subjective and varying interpretations by sponsors – resulting in inconsistent compliance across ANDA submissions.

Second, this language defining the "final formulation" may not capture all relevant bioequivalence data. For example, formulations containing an active ingredient with a particle size or morphic form that differs from the drug for which the ANDA is submitted would not be considered the "final formulation" of the drug. Thus, ANDA sponsors would not be required to submit bioequivalence data performed on these formulations, although such differences might affect the drug's pharmacokinetic profile, safety, and effectiveness.

Members of the Advisory Committee for Pharmaceutical Science recognized this problem at a meeting in November 2000. There, Chairman Stephen Byrn highlighted the importance of having access to *all* bioequivalence data:

> Even the innovator may not know the effect of slight changes in the formulation on product variability, because they may have made it the same way all the time, and so we could have a situation where you start changing and adjusting just a little bit, and you get a very variable product, and there is no way to know that unless you report essentially all the experiments that showed how variable it was.

Transcript of Advisory Committee for Pharmaceutical Science Meeting at 216-17 (Nov. 16, 2000) ("AC Transcript"), available at http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3657t2.pdf. At the same meeting, one doctor also warned that even changes in dyes "can change the performance of the [drug] product" because of known interactions between dyes and active ingredients. *Id.* at 216.

Similarly, FDA recognized the critical role of even small variations in chemical and physical properties of drugs in its *Guide to Inspections of Oral Solid Dosage Forms*:

> Characterization of the chemical and physical properties of the drug substance is one of the most important steps in the development of a solid dosage form. . . . [T]he physical properties of the BPC such as solubility, polymorphism, hygroscopicity, particle size, density, etc. must be addressed. *The literature, and actual experience demonstrates, that the physical quality, e.g., particle size of raw materials, can sometimes produce a significant impact on the availability and clinical effect of a dosage form drug.*

Guide to Inspections of Oral Solid Dosage Forms – Pre/Post Approval Issues for Development and Validation (Jan. 1994) at 3-4 (emphasis added), available at http://www.fda.gov/ora/inspect_ref/igs/solid.html.

This principle is indeed borne out in experience. For example, drugs composed of smaller particle sizes are often more readily absorbed than those composed of larger particles, resulting in greater potency, increased incidence of adverse events, and different types of adverse events. Thus, the particle size of many innovator products is integral to the potency and safety profile of those drugs. Furthermore, because the physical characteristics of many innovator products – including particle size – often are protected by patents, generic companies tend to develop versions of innovator products that differ in these characteristics. Such variations, although indisputably relevant to the drug's bioequivalence and perhaps safety and efficacy, would not be captured by the proposed rule. As a result, BE studies revealing such important data likely would never be presented to FDA.

Furthermore, FDA states that formulation or manufacturing changes of the type that qualify as level 1 or level 2 changes in the current guidances on scale up and postapproval changes (SUPAC) would render the original and modified products the "same" drug product formulation for purposes of the proposed rule. 68 FR 61643. In other words, when an applicant makes changes qualifying as SUPAC level 3 changes, the drug products would not be considered the "same" formulations, and only BE studies related to the final version of the product would need to be submitted. Level 3 changes include certain changes to an excipient such as a filler, binder, lubricant, or film coat; 1/ certain changes in the amount of preservative, or use of a different preservative; 2/ and a change in manufacturing site from one "campus" to another. 3/

1/ *See* SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation (Nov. 1995) (SUPAC-IR) at 7,12; SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation (Sept. 1997) (SUPAC-MR) at 14.

2/ *See* SUPAC-SS: Nonsterile Semisolid Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation (May 1997) (SUPAC-SS) at 9.

3/ *See* SUPAC-IR at 15 (defining a different campus as "one that is not on the same original contiguous site or where the facilities are not in adjacent city blocks"); SUPAC-MR at 18 (same). Notably, in such a situation, the equipment, standard operating procedures, environmental conditions, and controls would remain the same at the new site. *Id.*

Thus, an ANDA applicant may make certain changes to a filler, lubricant, preservative, or other excipient, or change manufacturing sites from one building to another, create a SUPAC level 3 change, and thereby avoid BE reporting requirements under the proposed rule. This is troubling because, as FDA and its experts have observed, such changes may affect the drug's performance. As drafted, the proposed rule could encourage ANDA sponsors to build such changes into their drug development plan in order that the sponsor have the ability to circumvent the requirement of submitting failed study results. Such conduct would certainly undermine the intended goals of the proposed rule. In those circumstances, FDA would not gain additional expertise regarding changes to drug formulations or BE study conditions that might influence the performance of the final drug formulation.

For these reasons, we respectfully suggest that FDA revise the proposed rule to require the submission of *all* bioequivalence studies performed on various formulations of a drug for which an ANDA is ultimately submitted, particularly when the physical properties of the proposed drug (*e.g.* particle size, dissolution/disintegration, density) may affect bioavailability. Complete reports for each bioequivalence study would not be warranted unless requested by the agency. We believe that complete reports on all passing bioequivalence studies and summary reports on all failed studies would capture changes to formulation or manufacturing that qualify as level 3 changes pursuant to the SUPAC guidances, and even certain cosmetic changes that may affect the drug's performance. 4/ At minimum, FDA should examine summaries of these studies and clarify which information should be included in the summary reports. Any other approach would leave too many loopholes through which sponsors could avoid the reporting requirements intended by the proposed rule, and would detract from the rule's aim of promoting sound science-based BE policy. 5/

4/ *See* AC Transcript at 216 (urging that cosmetic changes to a drug formulation "certainly should be included" in the agency's consideration of any "final formulation").

5/ The submission of all BE data could also serve useful ancillary purposes. For instance, FDA could use information collected from these studies to refine the SUPAC levels, which are currently based on minimum in vivo data. BE data could also guide the agency in establishing chemistry, manufacturing and controls specifications to assure post-approval product quality.

2. FDA should further explain the factors it will apply when evaluating additional BE studies.

FDA proposes to require that sponsors submit full reports of those BE studies performed on the final product formulation proposed for marketing. When these reports indicate one or more nonpassing BE study, the agency will evaluate the significance of the passing and nonpassing data. 68 FR at 61641. In this evaluation, FDA proposes to apply four "critical" factors: "(1) [t]he statistical power of each study, (2) minor differences in the formulation used in each study, (3) whether the product was administered consistent with the RLD's labeling in every study, and/or (4) various other study design issues." *Id.* We believe that this information is so critical that the rule should require the submission of that information for all drug formulations.

The statistical power of BE studies is crucial to determining whether product variability exists. When drug products are highly variable, greater study power is required to determine bioequivalence. *See* AC Transcript at 217 (observing same); *see also* Summary Minutes of the Opthalmic Devices Panel Meeting (Nov. 8, 2000) at 22 (noting that "[s]tatistical power is a key measure of confidence in product safety); Preface, *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") (discussing significance of statistical power in bioequivalence determinations). When testing such products, generic manufactures may fail to establish bioequivalence with their first study and, perhaps legitimately, re-test the drug with a larger sample size of subjects in an attempt to achieve bioequivalence through an adequately powered study. At some point, however, additional studies of larger size or different formulations may become problematic. Without reviewing reports of all BE studies on both the final and earlier, experimental formulations, FDA may be unable to determine whether the ANDA sponsor is achieving bioequivalence by reformulating the drug product or by "testing into compliance" through tests of increasing sample sizes.

We believe that requiring summary reports for failed BE studies on all drug formulations will also address FDA's apparent inconsistent treatment of "minor" formulation changes in the proposed rule. As drafted, the proposed rule requires information only on BE studies conducted on the same formulation submitted for approval. "Same formulation" would include "minor differences in composition or method of manufacture" from the final formulation. 68 FR at 61643. The proposed rule offers only one example of acceptable "minor" differences—Level 1 or 2 SUPAC changes, which range from changes that are *unlikely* to have any

detectable impact on quality and performance to those that *could* have a significant impact. 6/ Studies involving level 3 SUPAC changes, which are those that are *likely* to have a significant impact on quality and performance, need not be submitted.

Yet, a "critical" factor for evaluating submitted BE studies (failed and passing) is "minor differences in the formulations used in each study." 68 FR at 61641. This suggests that FDA anticipates, or at least acknowledges, that certain "minor" formulation differences are likely to have a significant impact on bioequivalence. Yet, this information is more likely to emerge from the submission of BE study results for a broad range of formulations. Arguably, the proposed rule requests data that will not yield the "critical" information FDA seeks to evaluate. Because the term "minor" appears to mean different things in different parts of the proposed rule, it is not clear what information must be submitted. FDA should clarify these inconsistencies by requiring the submission of complete reports on passing BE studies and summary reports on failed BE studies on all formulations. This approach would better allow agency reviewers the information necessary to evaluate the impact of formulation changes on bioequivalence and, ultimately, the drug's performance in the body.

In order to provide further guidance to applicants, it also would be helpful if FDA were to explain in more detail the nature of the "other study design issues" it may wish to examine in its evaluation of BE data. For example, is the agency primarily interested in conditions under which the drug was administered, or the rationale for the selection of certain types of study design characteristics? If the purpose is to account for differences in studies that were arguably designed to affect BE results such that they fall within a certain confidence interval, FDA should ensure that the bioequivalence reports contain information necessary to uncover such practices.

This can be accomplished by clarifying the contents of complete and summary reports. FDA could, for instance, require a detailed description of the protocol for the passing BE studies (e.g., study design, pharmacokinetic information, dissolution data, and analytical and statistical methods). Summary reports on failed BE studies that briefly describe and offer possible explanations for the differences between the passing and failed protocols would then provide FDA with

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6/ *See, e.g.,* SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation (Nov. 1995).

sufficient information about potential study design issues. Without more transparent standards, certain study design issues crucial to patient safety may not come to light until after approval – undermining the rule's purpose. Thus, FDA should take steps to ensure that it receives information necessary to fully evaluate the physicochemical factors that influence the proposed drug proposed drug product's pharmacokinetic profile before making final bioequivalence determination.

3. FDA should create means for enforcing and monitoring compliance with the proposed rule.

In the proposed rule, the agency asserts that failure to submit certain study results could constitute a false statement sufficient to allow non-approval of the application. 68 FR at 61643. Nonetheless, the proposed rule provides no specific enforcement mechanism. Thus, we suggest an amendment to 21 C.F.R. § 314.127(b) to reflect that failure to submit all required BE study reports is grounds for receiving an unapprovable letter. In addition, FDA may consider a mechanism, beyond existing pre-approval inspectional authority, to monitor ANDA applicants to verify that they are indeed submitting all appropriate study results.

To this end, FDA should not rely on field investigators acting under the direction of FDA's Office of Compliance to discover the existence of BE studies or to monitor compliance with the rule. Unless FDA investigators are specifically directed to look for failing study results, it is unlikely that such studies will be found during an inspection. 7/ Moreover, for narrow therapeutic index drugs or the top 200 prescribed drugs, the agency may not even have an opportunity to discover BE studies during an inspection because pre-approval inspections are not mandated. *See* http://www.fda.gov/cder/dmpq/CPGM7346832.htm.

In any case, even if such studies are targeted by investigators, those officials are not the appropriate experts to make scientific determinations regarding the significance of the data to a proposed product's bioequivalence. Instead, this evaluation should occur during the ANDA review process. The Office of Generic Drugs (OGD), not the Office of Compliance, is responsible for establishing that the proposed generic drug is bioequivalent to the reference drug. The OGD's pharmaceutical scientists are therefore the proper experts to evaluate whether

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7/ *See, e.g.*, AC Transcript at 218 (reflecting Dr. Conner's comments that in his experience with inspectors, "only in rare cases do they happen to stumble over something, but if they don't know something exists, the chances are they probably won't find it").

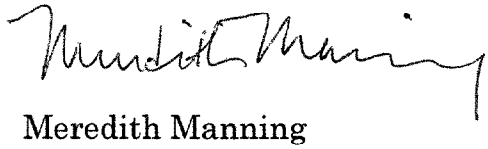
submitted data demonstrates bioequivalence. Unless and until generic manufacturers submit full reports of passing BE studies and summary reports for failed BE studies, FDA's process of reviewing and determining bioequivalence will be incomplete and disjunctive.

CONCLUSION

Hogan & Hartson supports the goals of increasing FDA's access to bioequivalence data and improving the agency's understanding of these data. As such, we welcome the changes represented in the proposed rule. Indeed, because we agree that data produced by bioequivalence studies may prove very important in the ANDA process, we support an expansion of the proposed rule to require the submission of all BE data for all formulations of a drug, particularly when the physical properties of the proposed drug may affect bioequivalence. We also look forward to increased discussion of the factors FDA will use to evaluate the data, and encourage the creation of explicit monitoring and enforcement mechanisms. With these additions to the proposed rule, we are convinced it will effectively promote increased understanding of many of the scientific issues implicated by the generic drug approval process.

We thank the agency for considering our comments and look forward to future collaboration on this important topic.

Sincerely,



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