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January 7, 2004

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

Re: Docket No. 2003N-0341  
Proposed Rule: Requirements for Submission of In Vivo Bioequivalence Data;  
Proposed Rule, 68 Fed. Reg. 61640 (Oct. 29, 2003)

Dear Sir or Madam:

**Background**

On October 29, 2003, the Food and Drug Administration (FDA) published a Proposed Rule

to amend its regulations on submission of bioequivalence data to require an abbreviated new drug application (ANDA) applicant to submit data from all bioequivalence studies (BE studies) that the applicant conducts on a drug product formulation submitted for approval. In the past, ANDA applicants have submitted BE studies demonstrating that a generic product meets bioequivalence criteria for FDA to approve the ANDA, but have not typically submitted additional BE studies conducted on the same drug product formulation, such as studies that do not show that the product meets these criteria. FDA is proposing this change because we now believe that data from additional BE studies may be important in our determination of whether the proposed formulation is bioequivalent to the reference listed drug (RLD) and are relevant to our evaluation of ANDAs

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in general. In addition, such data will increase our understanding of how changes in components, composition, and methods of manufacture may affect formulation performance. 68 Fed. Reg. 61640 (Oct. 29, 2003).

### Clarification of Terms

The acceptability and the impact of this proposed rule depends on the term "Same Drug Product Formulation" for the purposes of required BE study submission. As stated in the proposal

FDA intends that the terminology "same drug product 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. For example, where an applicant makes formulation or manufacturing changes of the type that qualify as level 1 or level 2 changes in FDA's current guidances on scale up and post approval changes (SUPAC) . . . the agency would consider the original and modified products to be similar enough to constitute the same drug product formulation for the purposes of the proposed rule. *Id.* at 61643.

This definition is not clear. For example, the proposed rule suggests that if a BE pilot study

- is performed which is underpowered with regard to number of subjects, and/or
- is performed only to confirm that the formulation is appropriate, and/or
- is used to estimate the number of subjects required for a definitive BE study, and/or
- is used to determine the appropriateness of properly defining the plasma concentration time curves,

at least summary reports must be submitted to FDA for review if only Level 1 or Level 2 changes differentiated this formulation from the actual formulation submitted in the application. It is difficult to see the value these pilot studies would have to FDA or anyone else other than the formulator even though these types of studies are routinely performed by the pharmaceutical industry.

In addition, basing FDA's definition of "same drug" on what is permissible under SUPAC for Level 1 and Level 2 changes creates an apparent inconsistency on how changes are treated pre- and post-approved. In effect, the scientific rationale that permits a post-approval change which does not require a BE study under SUPAC would no longer apply under the proposed rule simply because the application is not yet FDA approved. This implies that the time when FDA approves a

drug product, rather than a consistent scientific rationale, determines whether certain studies need to be reported to FDA. This approach does not support FDA's need to ensure decisions are science-based.

We suggest that the "same drug product formulation" definition for determining what BE studies are submitted to FDA for review be limited to studies which are statistically powered correctly and have a batch size of at least 100,000 packaged units. Proper clinical conduct of the study and an adequate sample size are crucial when meeting the bioequivalence requirements. This statistical restriction would eliminate all pilot studies and focus the review on scientifically valid studies.

Based on this proposed definition of "same drug product formulation," pharmaceutical companies could concur with FDA that all definitive bioequivalence studies on the same formulation and same manufacturing process of test product should be reported to FDA consistent with a company's pro-active scientific and regulatory responsibilities.

#### **Additional Comments**

1. FDA proposes that the submission of all BE studies (pilot and definitive) in the form of summary reports or final reports for unapproved applications will provide valuable scientific information that will increase FDA's knowledge and understanding of bioequivalence and generic drug development. This knowledge will promote further development of scientific-based bioequivalence policies. No one can deny that this is a worthwhile goal.

Unfortunately, valuable resources will be misdirected both by FDA and applicants to resolve differences in interpretations of failed BE studies. Significant industry and FDA resources will be spent in summarizing/reviewing all the BE studies. This also raises the potential for additional delays in application approval. At what point does an issue become only "an interesting academic question to explore"? If FDA does not agree with the applicant's explanation why the failed BE study is not relevant and/or asks additional questions, how will these issues be resolved? Will this delay the approval of the application? Will FDA need to establish a separate administrative procedure to resolve these questions?

2. The Proposed Rule states that "FDA may inspect the sites of the different studies to determine whether there were technical flaws" (*Id.* at 61641). What if a pilot study (pass or fail) is conducted by a CRO in a foreign country while the definitive study is conducted in the United States? Will this delay approval of the application if FDA does not have the resources to investigate the site in a timely manner, especially those in a foreign country? The same concerns surface to a lesser degree if the CRO for the pilot study is located in this country. Each inspection takes resources, and FDA lacks adequate resources to perform its existing functions. Such resource constraints will not support an expanded ANDA review process without an inevitable slowdown in approvals.

3. FDA has stated that an applicant “would rarely, if ever, conduct a post-marketing BE study other than one required for an ANDA supplement” (Id. at 61643). The additional requirement for submitting failed BE studies will not increase industry’s desire to consider ways to improve manufacturing processes and/or formulation. This appears to be contrary to FDA’s desire to raise the quality of approved drug products.

4. It is unclear from the proposal how FDA intends to apply the Freedom of Information (FOI) Act to requests for the release of failed bio studies that have been submitted to FDA under the terms of the proposed rule. FOI access to information about failed BE studies (pilot and/or definitive) may add a new negative dimension to the safety/effectiveness of generic drugs debate and may generate deeper concerns for state formularies about generic drugs. Unwanted suspicion of inferiority could be promoted by some companies that may try to limit the use of generic drugs as an alternative to contain soaring healthcare costs. Similarly, generic drug companies themselves may inappropriately use such information to disparage other companies and their products. FDA must place proper controls on the release and use of such information.

Sincerely,



Robert A. Dormer

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