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Roxane Laboratories

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January 13, 2004

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

Subject:
Written Comments:
Proposed Rule: Requirements for Submission of In Vivo Bioequivalence Data

[Docket No. 2003N-0341]

Dear Madam or Sir:

Enclosed are written comments on the above-referenced Proposed Rule.

Thank you for the opportunity to participate in a dialog with the Agency via submission of these written comments.

If there are any questions or concerns you may reach me at: 614-272-4785.

Sincerely,

A handwritten signature in black ink, appearing to read 'Elizabeth A. Ernst', with a large flourish extending to the right.

Elizabeth A. Ernst
Associate Director, Regulatory Affairs
DRA-Multisource Products for Roxane Laboratories

Enclosure: Comments from Roxane Laboratories, Inc, concerning the Proposed Rule:
Requirements for Submission of In Vivo Bioequivalence Data

2003N-0341

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(Note: italicized paragraphs represent language directly from the Proposed Rule)

Supplementary Information

IV. Description of the Proposed Rule

The proposed rule would amend and clarify current BE (bioequivalence) study submission requirements to specifically require applicants to submit data on all BE studies, including studies that do not meet passing bioequivalence criteria, performed on a drug product formulation submitted for approval under an ANDA or an amendment or supplement to an ANDA that contains BE studies.

Comment: The proposed rule is not explicitly clear as to whether *all* studies conducted during the development of a formulation, whether or not BE is an objective, would be required to be submitted. A full development program for a generic formulation includes studies not designed to evaluate BE. The objective of these studies may be to elicit information related to the performance of prototype drug formulations but are not powered or expected to pass BE statistical criteria. In other cases, the objective of the study may be to determine if a drug entity can be reliably measured in the media chosen, i.e. plasma or serum. While such studies aid in the development of a bioequivalent formulation, they are not BE studies and therefore should not have to be submitted.

In addition, if all studies are subject to FDA submission, will firms be required to follow retention guidelines for clinical drug supplies? Rigorous regulatory requirements necessary for pivotal studies are currently not required for pilot, exploratory, or research and development studies.

The Agency should more precisely clarify the types of studies subject to this rule.

A. Proposed Requirements for the Submission of Data From All BE Studies Conducted on the Same Drug Product Formulation Submitted for Approval in ANDAs, Supplements, and Amendments.

1. *[in part]. The applicant would continue to be required to submit complete reports of the BE studies upon which the applicant relies for approval. For all other BE studies on the same drug product formulation, the applicant would be required to submit a summary report. FDA plans to issue guidance on the format of a summary report. If a summary report is submitted and the agency believes that there may be bioequivalence issues or concerns with the product, the agency may require that a complete report be prepared and submitted to FDA.*

Comment: Clarification and guidance is needed to determine the meaning of *bioequivalence issues or concerns* as referenced in the above paragraph. The Agency is urged to clarify how this would be consistently applied across products and reviewers, and whether or not it will be the reviewer's discretion only. While it

is recognized that not all potential issues or concerns with BE studies can be identified prospectively, some general guidelines or discussion is warranted.

The Agency may be confronted with situations where an applicant submits 1 study that passes, and another study that fails. Or, 1 study passes by a very close margin, and one fails by a similar close margin. What will represent assurance to the Agency that the product is either bioequivalent or not? What additional data will be required to provide this assurance? Will additional studies be required, and is this at the reviewer's discretion? The Agency does not know how frequently situations such as this may occur, and there is no objective criteria given to determine what constitutes a "situation". These points should be clarified before they present themselves to the Agency.

In lieu of this, it can be anticipated that many companies will proactively compile complete reports for *all* submissions in anticipation of inconsistent application or interpretation of this statement by different reviewers, potentially increasing review time and costs.

C. Proposed Requirement for the Submission of Data From All Postmarketing BE Studies Conducted or Otherwise Obtained by the Applicant on the Same Drug Product Formulation That Has Been Approved.

Under Sec.314.81(b)(2)(vi), an ANDA applicant is required to submit, in an annual report, the results of "biopharmaceutic, pharmacokinetic, and clinical pharmacology studies conducted by or otherwise obtained by the applicant" during the annual reporting period. All BE studies would fall into one or more of the categories of studies (i.e., biopharmaceutic, pharmacokinetic, and clinical pharmacology) required to be submitted under this section. As a result, the agency is proposing to interpret this section to require ANDA applicants with approved ANDAs to submit postmarketing reports of all BE studies, both passing and nonpassing, conducted or obtained by the applicant during the annual reporting period on the same drug product formulation that has been approved. FDA believes that the language in current Sec. 314.81(b)(2)(vi) is sufficient to accomplish this purpose. Therefore, FDA is not amending this language, but is clarifying through this rulemaking that it intends to interpret the section to require submission of postmarketing reports of all BE studies conducted or otherwise obtained by ANDA applicants. Under this section, applicants may submit either complete or summary reports of the BE studies conducted or otherwise obtained during the annual reporting period. If a summary report is submitted for a BE study and FDA believes that there may be bioequivalence issues or concerns with the product the agency may require that a complete study report be prepared and submitted to FDA.

Comment: The proposed rule further states that "*In particular, the agency believes that an applicant would rarely, if ever, conduct a postmarketing BE study other than one required for an ANDA supplement*". The FDA correctly assumes that it would be highly unusual for an ANDA applicant to conduct a postmarketing BE study. However, a BE study may be initiated not by the applicant, but by another concern outside of its jurisdiction. For example, a competitor may conduct a BE study with an applicant's drug formulation intended to raise questions about

issues or circumstances related to BE status (i.e., “challenge studies”). The Proposed Rule states that “*Under this section, applicants may submit either complete or summary reports of the BE studies conducted or otherwise obtained during the annual reporting period. If a summary report is submitted for a BE study and FDA believe that there may be bioequivalence issues or concerns with the product, the agency may require that a complete study report be prepared and submitted to FDA*”. In the instance whereby the study is conducted outside of the applicant’s immediate jurisdiction, summary or complete reports will not be available to satisfy this requirement on the part of the applicant. The burden in this case should not be placed on the applicant to obtain and submit information from studies purporting to contain “bioequivalence issues or concerns with the product”.

IX Analysis of Economic Impacts

B. Affected Entities

The proposed rule would affect establishments that submit ANDAs containing BE studies. FDA does not know the precise number of entities, either large or small, that will submit ANDAs in the future. In the year 2000, there were 346 BE studies submitted by 57 applicants in 197 ANDAs, amendments, and supplements. FDA estimates that this proposed rule would result in a 10 percent increase in the number of BE studies submitted annually or 35 (346 x 0.10) additional studies. This estimate is based on information suggesting that approximately 20 percent of all BE studies conducted produce results that do not meet bioequivalence limits and that approximately 50 percent of these studies are conducted on formulations that are not submitted for approval.

Comment: The estimate given is too conservative and static, and not reflective of recent data trends available to the FDA. Receipts of original ANDA applications have shown a dramatic increase in recent years. In fact, there were 449 original ANDA applications in (fiscal) year 2003, a 25% increase from 2002 (which increased 18% from 2001). Controlled correspondence documents have also increased precipitously, with a 36% increase between FY 2003-2003. Full and tentative approvals of ANDAs have increased every year since 1998.¹ It is not unreasonable to suspect that this trend will continue as the Congress, Administration, and the public strive to encourage and remove barriers to generic drug development.

Current and future estimated workload, in conjunction with the Division of Bioequivalence staffing and hiring status, does not support review of additional BE studies without seriously impacting an already stressed system. Adequate hiring and retention should be firmly established and in place before any implementation of a Final Rule.

¹ Gary J. Buehler, R.Ph. Director, Office of Generic Drugs. Presentation: *Office of Generic Drugs Update*. Generic Pharmaceutical Association, 2003 Fall Technical Workshop (Bethesda, MD). October 16, 2003

C. Compliance Requirements and Cost

The main cost of complying with this proposed rule would be staff time. This analysis assumes a weighted average wage rate of \$40 per hour. FDA estimates it would require approximately 120 hours of staff time to prepare and submit each additional complete BE study report, and approximately 60 hours of staff time for each additional BE study summary report. The agency believes that a complete report would be required approximately 20 percent of the time, while a summary would suffice approximately 80 percent of the time.

Comment: The analysis is flawed in that other costs are not considered in addition to the “main cost” of staff time. Many generic firms utilize the services of Contract Research Organizations (CROs) to conduct various activities related to the design, initiation, conduct, and report generation of clinical trials. Thus, other significant direct and indirect costs related to report generation would increase the total beyond that based only on a staff time x wage rate model.

Without guidelines or guidance on what might constitute “bioequivalence issues or concerns with the product”, and how this would be interpreted in a consistent manner by different FDA reviewers, it is difficult to evaluate how the Agency calculates that complete reports would be required approximately 20 percent of the time, vs. a summary only 80 percent of the time. In fact, even if accurate, many firms may proactively compile complete reports in efforts to streamline efficiency and development (however maximizing costs) because of perceived latitude in interpretation by the FDA, and recognizing that they must be made available upon request.