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The Pharmacy Drug Company

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RE: Docket No. 2003N-0241

Eon Labs, Inc. would like to comment on the proposed rule, "*Requirements for Submission of In Vivo Bioequivalence Data*" Docket No. 2003N-0341 that appeared in the Federal Register, Vol68, No. 209, Wednesday, October 29, 2003, p. 61640.

Although we support the proposed rule, we are very much concerned that the proposed requirement for the submission of all bioequivalence (BE) studies would prolong the review time by the Agency, delay the entry to market of low cost generic alternatives, and increase personnel requirements by the Agency.

FDA is proposing to amend its regulations to require "*applicants to submit data from all bioequivalence studies (BE studies) that the applicant conducts on a drug product formulation for approval.*"

The Agency proposes in Section §314.96, that "*the applicant must submit either a complete or summary report.*" In many cases, the sponsor may request only a summary report from the contract research laboratory (CRO) when the test product has failed to meet standard BE criteria. A complete report for the failed BE study may not be generated for the sponsor. If complete study reports for failed BE studies are submitted with the ANDA, more time will be required by the Agency to review this information. If the Agency requests a complete report for a failed BE study after review of the summary report, the sponsor will need time to have the CRO generate the complete report which will incur additional costs and time to the applicant.

We agree with FDA's position that "*an understanding of how changes in components, composition, and methods of manufacturer may affect formulation performance*" is important. However, the Agency review of the ANDA submission should focus on the to-be-marketed formulation that has demonstrated in vivo performance by passing the requisite BE studies along with the appropriate in vitro and CMC data. ANDA applicants already put together a *product development report* that includes the rationale for the development of the to-be-marketed formulation. This report includes the justification for the final formulation and manufacturing process. Generally, the results from preliminary pilot studies or pivotal bioequivalence studies that fail to meet the current bioequivalence criteria are reviewed and the formulation is changed accordingly. Therefore, the product

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development report may be the most appropriate place to put a small summary of the results for all bioequivalence studies performed on the product prior to ANDA submission.

Retention of samples for each failed BE study – Is it necessary to retain samples for every failed BE study? This places a burden on both the applicant and the contract research organization (CRO). The proposal does not address this issue.

Burden estimate – We feel that that there will be significantly more FDA review time and resources required to assess all failed studies. If the Agency wants to gain “*an understanding of how changes in components, composition, and methods of manufacturer may affect formulation performance*” for every ANDA submission using failed BE studies, then each BE study should be submitted in detail along with formulation (CMC) and in vitro drug release data that must be critically reviewed and evaluated. We feel that the focus of the bioequivalence review should be on the final to-be-marketed formulation. However, we feel that the burden can be reduced for both the Agency and the sponsor by providing a brief summary of all bioequivalence studies in the product development report in the ANDA submission.

Disputes – Occasionally, failed and passing BE studies may appear to be in conflict or there may be other issues that need resolution. The time needed to resolve these issues will delay the approval process. We suggest that there should be an efficient mechanism in place that quickly addresses disputes in a timely manner.

Failed BE studies required for SUPAC – The proposal does not address failed BE studies that are required by certain SUPAC changes on approved drug products. Since SUPAC is a requirement for both NDA and ANDA holders, the same BE requirements should be for all FDA approved drug products.

In conclusion, we support the proposed rule. However, we feel that there are several areas stated above that need further clarification. In addition, we would like to suggest that a simple tabulated and graphical summary of each bioequivalence study performed on the test product could be placed into the product development report that is included with the ANDA submission.

We appreciate your consideration of our comments. We hope that our comments are clear and welcome any questions that you may have.

Sincerely,



Leon Shargel, Ph.D.
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