

not be as therapeutically effective as the RLD. Where the relative bioavailability of a test product is too high, the concern with the product generally is not therapeutic efficacy but rather its safety relative to the RLD. In some cases, bioequivalence will not be demonstrated because of inadequate numbers of subjects in the study relative to the magnitude of intrasubject variability rather than either significantly high or low relative bioavailability of the product.

II. Not All BE Studies Are Currently Being Submitted

The act and FDA regulations require that an ANDA applicant submit information demonstrating bioequivalence of a proposed drug to the RLD, but they do not specify the type or quantity of information that must be submitted to demonstrate bioequivalence. It has been the practice of ANDA applicants to submit evidence of bioequivalence consisting of studies demonstrating that the rate and extent of absorption of the test product meets bioequivalence limits. Thus, ANDA applicants that have conducted multiple studies on a final formulation producing passing and nonpassing results have generally not submitted the results of the nonpassing study or studies to FDA. Similarly, ANDA applicants that have conducted multiple studies on a final formulation producing more than one passing result have generally not submitted the results of all of the passing studies to FDA. As a result, FDA only infrequently sees data from additional studies and is generally unaware of the existence of such studies. In rare instances, ANDA applicants have submitted additional BE studies or the agency has learned about such studies through other means. As discussed in section III of this document, information from additional BE studies conducted on a product can be important in assessing bioequivalence for that product.

III. Need for Submission of All Studies

In recent years, there have been certain cases where applicants did not submit all of the BE studies conducted on the final formulation of an ANDA product prior to approval, and FDA discovered postapproval that the submission of such studies could have been important in assessing bioequivalence. The agency is not aware of any adverse public health consequences associated with products for which studies were not submitted. Moreover, the agency is not aware of any information regarding any generic product currently on the market that

would suggest that the product is not bioequivalent to a reference listed drug to which it has been designated as therapeutically equivalent. However, the agency now believes that it is necessary for the purposes of evaluating a drug product submitted for approval under an ANDA to have data obtained from all additional BE studies conducted on the final formulation. This view was supported by FDA's Advisory Committee for Pharmaceutical Science, which recommended in a recent meeting that FDA review all BE studies conducted by the applicant on the final formulation (Ref. 1). The agency is proposing that ANDA applicants submit information from all BE studies for the following reasons:

1. Data contained in additional passing and nonpassing BE studies can be important to FDA's assessment of bioequivalence for a specific product.

2. Even when additional BE studies are not critical to the agency's bioequivalence determination for the specific product being reviewed, the data provide valuable scientific information that increases the agency's knowledge and understanding of bioequivalence and generic drug development and promotes further development of science-based bioequivalence policies.

The agency's experience with evaluating additional passing and nonpassing BE studies has shown that information from such studies can be important in assessing whether a formulation is bioequivalent to the RLD. For example, in one recent case, the ANDA applicant conducted an additional BE study on the final formulation prior to submission of its ANDA, but did not submit the results of the study to FDA. The agency found out about the results of the additional study after approval of the ANDA. The additional study indicated that the bioequivalence of the approved product was questionable. Based on the information in the additional study, the agency reconsidered its decision to approve the drug and requested that the firm voluntarily withdraw the product from the market. The firm withdrew the product from the market and withdrew its ANDA. Although cases such as this may occur relatively infrequently, it is imperative that FDA be aware of the additional BE studies and have the information necessary to evaluate their significance.

When FDA receives an ANDA that contains one or more nonpassing BE studies for the final formulation, the agency will evaluate the significance of both the passing and nonpassing BE studies. As an initial matter, for each

study submitted in summary report form, FDA will consider whether it is necessary to request a full report from the applicant. Regardless of the form of the report, however, FDA anticipates that a number of factors will be critical in evaluating both the passing and nonpassing BE studies. For example, FDA may consider: (1) The 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. In addition, FDA may inspect the sites of the different studies to determine whether there were technical flaws in how the studies were conducted. For example, the reliability of a particular study's results could be undermined by flaws in: (1) Its inclusion and exclusion criteria, (2) an investigator's compliance with standard operating procedures and/or the study protocol, (3) its analytical or assay methodologies, (4) the storage of samples, (5) how between treatment washout periods were carried out, and/or (6) various other flaws in how the study was conducted. The goal of FDA's evaluation will be to determine: (1) The importance and reliability of the data collected in the different studies and (2) how the studies should be weighed in making a bioequivalence determination. Ultimately, however, the responsibility to demonstrate that the ANDA product is bioequivalent to the RLD rests with the applicant. Therefore, if conflicting BE studies are submitted, it will ultimately be the applicant's responsibility to demonstrate why the nonpassing study or studies should not undermine a determination that the ANDA product is bioequivalent to the RLD.

Even in cases where information from additional BE studies is not critical to the agency's bioequivalence determination for a specific product, the data will provide valuable scientific information that increases our knowledge and understanding of bioequivalence and generic drug development issues. Data from additional BE studies also provide FDA with useful and relevant information about drug products submitted for approval, including how minor formulation or composition changes, or changes in study design, affect the performance of a formulation. FDA anticipates that further experience with data from additional passing and nonpassing BE studies will facilitate a more focused and efficient ANDA review process and enhance FDA's