

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.

Based on a weighted-average calculation using the information presented above, the submission of each additional BE study is expected to cost \$2,880 ($[120 \times \$40 \times 0.2] + [60 \times \$40 \times 0.8]$). Thus, the overall impact on the industry of reporting an additional 35 BE studies per year would be \$100,800 ($2,880 \times 35$).

Assuming it is equally likely that each of the 35 additional BE studies would be conducted by any of the 57 applicants, a binomial distribution can be used to predict how many firms would submit additional studies. Based on this distribution, 19 firms would incur costs of \$2,880 for 1 additional BE study, 6 firms would incur costs of \$5,760 ($2 \times \$2,880$) for two additional studies, and 1 firm would incur costs of \$8,640 ($3 \times \$2,880$) for 3 additional studies (the total number of studies in the calculation does not equal 35 because of rounding). Thus, the maximum expected annual cost burden for any one firm would be \$8,640. More than half (31 of 57, or 54 percent) of all firms would be expected to incur no additional annual costs under the proposed rule.

D. Impact on Small Entities

FDA recognizes that some of the establishments that would be required to submit additional BE study reports would be small entities with limited resources. As shown in the following paragraphs, the agency estimates that the maximum expected cost of the proposed rule for any one small entity would be between 0.58 percent and 1.9 percent of the total cost of preparing and submitting an ANDA, and that the maximum expected burden for any one of these small entities would be 0.005 percent of average revenues. Although FDA does not believe it likely that the proposed rule would have a significant economic impact on a substantial number of small entities, the agency acknowledges the uncertainty of its estimates with respect to the number of additional BE studies that would be submitted, their distribution among large and small entities, and the number of small entities affected. As a result, the agency has prepared this Initial Regulatory Flexibility Analysis and requests detailed public comment regarding the number of small entities affected by the proposed rule as well as its economic impact.

FDA also recognizes that requiring submission of all BE study results may result in a longer total application review time if these additional BE study results suggest that a generic product is not bioequivalent to the RLD. In these situations, firms would be required to submit additional data that demonstrate bioequivalence in order to obtain marketing approval. Marketing approval may be denied if evidence from the additional BE studies fails to establish bioequivalence. The agency does not know how frequently these situations might occur.

According to standards established by the Small Business Administration (SBA), a small pharmaceutical preparation manufacturer (NAICS Code 325412) employs fewer than 750 employees (Ref. 3). An FDA review of ANDAs submitted during the 3-year period from October 1996 to September 1999 found that 32 percent of the applications (322 of 1,007) were from small entities and that 39 percent of ANDA sponsors (64 of 164) were small entities. Thus, the majority of ANDAs are neither submitted nor sponsored by small entities. Assuming these proportions continue to hold, there would be 22 small entities (0.39×57) submitting ANDAs annually. FDA also assumes that this group of small entities would submit 11 of the additional 35 BE studies ($0.10 \times 0.32 \times 346$) per year.

Assuming it equally likely that each of the 11 additional BE studies would be reported by any of the 22 small entities, a binomial distribution can be used to predict how many firms would submit additional studies. Based on this distribution, seven small entities would incur costs of \$2,880 for one additional BE study, and two firms would incur costs of \$5,760 ($2 \times \$2,880$) for two additional BE studies. Thus, the maximum expected burden for any one small entity would be \$5,760. More than half (13 of 22, or 59 percent) of all small entities would be expected to incur no additional annual costs under the proposed rule.

The cost of preparing and submitting an ANDA is believed to be between \$300,000 (Ref. 4) and \$1 million (Ref. 5). Based on this information, the maximum expected cost burden of the proposed rule on any one firm would be between 0.86 percent and 2.9 percent of the total cost of preparing and submitting an ANDA. The maximum expected cost burden for any one small entity would be between 0.58 percent and 1.9 percent of the total cost of preparing and submitting an ANDA.

A year 2000 survey of 26 public generic drug companies revealed 15 firms with fewer than 750 employees

(Ref. 5). These 15 small entities had an average of 331 employees and average annual revenues of \$115 million. The maximum expected burden of this proposed rule for any one of these small entities therefore would be only 0.005 percent of average revenues. The agency believes this cost could be recovered through drug sales after marketing approval.

In recognition of the potential economic impact on small entities, the agency has structured the rule to minimize the reporting burden. For example, the agency believes that summary reports of additional BE studies would suffice 80 percent of the time provided that complete results are available to FDA upon request. The agency believes that a summary report would require only 60 hours of staff time per BE study, or half the time and expense required to prepare and submit a complete report. This provision should prove particularly beneficial for small entities.

Furthermore, no specific educational or technical skills are required to complete and submit the additional BE study reports. Trained and qualified employees of an establishment who are involved in normal operations generally complete similar activities. Also, FDA has reviewed related Federal rules and has not identified any rules that duplicate, overlap, or conflict with the proposed rule.

FDA has evaluated only two regulatory options: (1) Continuing the current practice of requiring the submission of only pivotal BE study results, or (2) requiring the submission of results from all BE studies conducted by an applicant on a final drug product formulation. Under the first option, firms would incur no additional reporting costs, although some firms might experience significant costs if their product were initially approved and subsequently recalled or had approval withdrawn because the product is found not to be bioequivalent to the RLD. The agency believes that the second option, requiring that results from all BE studies conducted on the final drug product formulation be submitted for approval, is important for assessing bioequivalence. The proposed rule would require reporting of all BE studies, but would permit summary reports for nonpivotal BE studies except where full reports are specifically requested by the agency. The agency believes that the proposed rule therefore addresses the perceived regulatory need in the least intrusive and most cost effective way. FDA specifically requests public comment regarding any other viable alternatives to this proposed rule.