

based on the U.S. approval date of the application for the innovator NDA product. If the innovator NDA product (even if no longer on the market) was approved for marketing before January 1, 1998, applicants holding an approved ANDA for the drug product would have the option of submitting either TPSRs or PSURs and IPSRs to FDA. In these cases, an applicant holding an approved ANDA may choose to submit TPSRs to FDA even though other applicants with approved applications for the drug product submit PSURs and IPSRs. If the innovator NDA product was approved for marketing on or after January 1, 1998, applicants holding an approved ANDA for the drug product would be required to submit PSURs and IPSRs to FDA.

Proposed § 314.98(a) also provides that applicants holding an approved ANDA would determine the frequency of submission for postmarketing periodic safety reports based on the U.S. approval date of the application for the innovator NDA product. For example, if the innovator NDA product is the first human drug product containing the drug substance approved in the world and the application is approved for marketing on June 15, 1980, applicants of the innovator NDA product and all ANDA products with the same drug product would either submit a TPSR or PSUR to FDA every 5 years based on the U.S. approval date of the innovator NDA product (e.g., data lock point of June 15, 2000, June 15, 2005). In this case, an applicant with an ANDA approved on January 1, 1999, would have a data lock point of June 15, 2000, even though the reporting period for the drug product is less than 5 years; the next reporting period for the drug product would cover a 5-year period (i.e., June 16, 2000 through June 15, 2005). If the first human drug product containing the drug substance was approved for marketing in Europe on February 1, 1980, and the same drug product was approved in the United States on June 15, 1980, applicants of this drug product and all ANDA products with the same drug product would either submit a TPSR or PSUR to FDA with a 5-year frequency based on the U.S. approval date and with a date lock point based on the European approval date (e.g., February 1, 2000, February 1, 2005).

All applicants holding an approved NDA or ANDA would be required to submit postmarketing individual case safety reports—semiannual submissions to FDA every 6 months (see section III.E.4 in this document). Thus, even though the agency would not be receiving TPSRs, PSURs, and IPSRs for drug products with approved ANDAs

frequently after approval of the product, FDA would receive in a timely manner individual case safety reports for the product (i.e., expedited reports, individual case safety reports—semiannual submission) that would identify any potential problems associated with the formulation of the product. It is not necessary to receive TPSRs, PSURs, or IPSRs for drugs with approved ANDAs more frequently because the innovator NDA product has been evaluated for a number of years.

III.J. Postmarketing Approved New Drug Application (NDA) and Biologics License Application (BLA) Annual Reports

Current § 314.81(b)(2) requires applicants of marketed drug products subject to an NDA to submit an annual report to FDA within 60 days of the anniversary date of U.S. approval of the application. This annual report must contain a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product and a description of actions the applicant has taken or intends to take as a result of new information, such as submitting a labeling supplement, adding a warning to the labeling, or initiating a new study (§ 314.81(b)(2)(i)). This summary section must also contain, in accordance with the 1998 pediatric final rule, a statement of whether labeling supplements for pediatric use were submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population were initiated. The 1998 pediatric final rule also requires that the summary section include, where possible, an estimate of the patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents), including dosage form. The annual report also must contain a section on nonclinical laboratory studies that includes copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (e.g., mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the ingredients in the drug product (§ 314.81(b)(2)(v)). The applicant must submit a copy of a published report if requested by FDA. The annual report also must contain a section on clinical data that includes, among other data, published clinical trials on safety of the drug (or abstracts of them) and reports of clinical experience pertinent to safety (for example, epidemiological studies or

analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the applicant (§ 314.81(b)(2)(vi)). The clinical data section also must contain, in accordance with the 1998 pediatric final rule, an analysis of available safety and efficacy data in the pediatric population, changes proposed in the labeling based on this information, and an assessment of data needed to ensure appropriate labeling for the pediatric population.

Current § 601.28 requires applicants of licensed biological products to submit an annual report to FDA within 60 days of the anniversary date of U.S. approval of the application. This annual report must contain, among other information, a brief summary stating whether labeling supplements for pediatric use were submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population were initiated (§ 601.28(a)). This summary section also must contain, where possible, an estimate of the patient exposure to the product, with special reference to the pediatric population (neonates, infants, children, and adolescents), including dosage form. The annual report also must contain a section on clinical data that includes an analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information (§ 601.28(b)). This clinical data section also must contain an assessment of data needed to ensure appropriate labeling for the pediatric population.

As noted in section I of this document, FDA received comments on the October 1994 proposal that noted that the proposed amendments to the agency's postmarketing safety reporting requirements would duplicate certain information required in postmarketing approved NDA annual reports. In light of these comments, FDA is proposing to revoke the requirement for safety-related information in postmarketing approved NDA and BLA annual reports to eliminate duplicative reporting.

FDA is proposing to remove the requirement in § 314.81(b)(2)(i) to report safety information or safety-related labeling changes in the summary section of approved NDA annual reports. FDA is also proposing to remove the requirement in §§ 314.81(b)(2)(i) and 601.28(a) to submit an estimate of patient exposure to the drug product with special reference to the pediatric population. FDA is also proposing to remove the requirement in § 314.81(b)(2)(v) to include the section on nonclinical laboratory studies in approved NDA annual reports. FDA is