

also proposing to remove the requirement in §§ 314.81(b)(2)(vi) and 601.28(b) to submit safety-related information in the clinical data section of approved NDA and BLA annual reports. FDA is proposing these changes because this safety-related information for a drug or licensed biological product would be provided to the agency in postmarketing safety reports (*i.e.*, expedited reports, TPSRs, PSURs, IPSRs, individual case safety reports—semiannual submissions). For example, proposed §§ 314.80(c)(2)(ii) and 600.80(c)(2)(ii) would require postmarketing expedited reports for certain information that would be sufficient, based on appropriate medical judgment, to consider changes in product administration (*e.g.*, any significant unanticipated safety finding or data in the aggregate from an *in vitro*, animal, epidemiological, or clinical study, whether or not conducted under an IND, that suggests a significant human risk such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease). Under proposed §§ 314.80(c)(3)(ii)(E), 314.80(c)(3)(iii)(E), 600.80(c)(3)(ii)(E), and 600.80(c)(3)(iii)(E), PSURs and IPSRs would contain a section on worldwide patient exposure that includes, when possible, data broken down by gender and age (especially pediatric versus adult). Under proposed §§ 314.80(c)(3)(ii)(G), 314.80(c)(3)(iii)(F), 600.80(c)(3)(ii)(G) and 600.80(c)(3)(iii)(F), PSURs and IPSRs would include a section on safety studies that would contain a discussion of nonclinical, clinical, and epidemiological studies that contain important safety information. This safety studies section would include all applicant-sponsored studies newly analyzed during the reporting period; new studies specifically planned, initiated, or continuing during the reporting period; and published safety studies in the scientific and medical literature.

III.K. Safety Reporting for In Vivo Bioavailability and Bioequivalence Studies

FDA's existing *in vivo* bioavailability and bioequivalence study regulations, under § 320.31(a), require submission of an IND, as prescribed under part 312, for certain studies in humans (*i.e.*, studies that involve a new chemical entity, a radioactively labeled drug product, or a cytotoxic drug product). Section 320.31(b) requires an IND for certain studies in humans using a drug

product that contains an already approved, non-new chemical entity (*i.e.*, a single-dose study where either the maximum single or total daily dose exceeds that specified in the approved labeling for the drug product, a multiple-dose study where either the single or total daily dose exceeds that specified in the approved labeling of the drug product, a multiple-dose study on a controlled release product on which no single-dose study has been completed). Section 320.31(d) exempts all other *in vivo* bioavailability and bioequivalence studies in humans from the requirements of part 312 if certain conditions are satisfied (*i.e.*, samples of any test article and reference standard are reserved by the person conducting the study and released to FDA upon request, studies are conducted in compliance with the requirements for institutional review set forth in 21 CFR part 56 and informed consent set forth in 21 CFR part 50).

FDA believes that drug products that are being investigated in human bioavailability and bioequivalence studies that are not subject to an IND are, in general, safe. However, as noted in section II.B.4 of this document, FDA receives some safety information periodically regarding drugs in these studies, thus making the agency uncertain whether it is receiving all necessary safety information regarding the specificity and severity of SADR related to these drugs or any new SADR that may be related to them. FDA has determined that a more comprehensive and orderly system for collecting safety information for these studies is needed. For this purpose, the agency is proposing to require persons conducting human bioavailability and bioequivalence studies that are not subject to an IND to submit expedited safety reports to FDA to alert the agency to potential safety problems quickly. The proposed rule would not require these persons to submit an IND to FDA for the studies.

FDA believes that this new proposed safety reporting requirement will result in submission of minimal reports to the agency (~ 200/year; *see* table 13 for estimate). FDA seeks comment on the reasonableness of this estimate and requests that comments provide information to support any alternative estimates.

The act provides authority to FDA to require safety reports for human bioavailability and bioequivalence studies that are not subject to an IND. Section 505(i) of the act provides broad authority for FDA to issue regulations governing the clinical investigation of new drugs to protect the rights, safety,

and welfare of human subjects and otherwise to protect the public health. In addition, section 701 of the act (21 U.S.C. 371) provides that the agency has authority to issue regulations for the efficient enforcement of the act.

FDA is proposing to amend its regulations at § 320.31(d) to require persons conducting human bioequivalence and bioavailability studies that are not subject to an IND to submit safety reports to FDA as prescribed under § 312.32 for drug products subject to an IND. Under proposed § 312.32(c)(1), a written safety report must be submitted within 15 calendar days to FDA and all participating investigators for any SADR that, based on the opinion of the investigator or sponsor, is both serious and unexpected and for information that, based upon appropriate medical judgment, might materially influence the benefit-risk assessment of an investigational drug, or that would be sufficient to consider changes in either product administration or in the overall conduct of a clinical investigation. Examples of reportable information would include any significant unanticipated safety finding or data in the aggregate from an *in vitro*, animal, epidemiological, or clinical study, whether or not conducted under an IND, that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease. In addition, under proposed § 312.32(c)(2), a telephone or facsimile transmission safety report must be submitted within 7 calendar days to FDA for any unexpected fatal or life-threatening SADR.

Proposed § 320.31(d)(3) would require that these safety reports be transmitted to all participating investigators and the appropriate FDA division in the Center for Drug Evaluation and Research. Thus, safety reports for the reference listed drug would be sent to the new drug review division responsible for that drug; safety reports for the investigational drug product would be sent to the Director, Division of Bioequivalence, Office of Generic Drugs. The proposed rule would also require that each written notification bear prominent identification of its contents, *i.e.*, "Bioavailability/Bioequivalence Safety Report." Each report should clearly identify the sponsor of the bioavailability or bioequivalence study and the contract research organization, if applicable. In each written Bioavailability/Bioequivalence Safety Report, the sponsor would be required