

to identify all safety reports previously filed for the bioavailability or bioequivalence study concerning a similar SADR and to analyze the SADR in light of previous similar reports, as required under proposed

§ 312.32(c)(1)(i) for IND safety reports.

An unexpected adverse drug experience is currently defined, under § 312.32(a), as:

Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. \* \* \*

For reporting purposes under proposed § 320.31(d), an unexpected SADR would be any SADR, the specificity or severity of which is not consistent with the U.S. labeling for the reference listed drug. FDA is proposing use of the U.S. labeling for the reference listed drug for this purpose because studies that are not subject to an IND are unlikely to have an investigator brochure for use as a reference document.

Under proposed § 312.32(c)(4), a sponsor of a clinical study under an IND for a drug marketed in the United States is only required to submit IND safety reports to FDA (review division that has responsibility for the IND) for SADRs that occur during the clinical study itself, whether from domestic or foreign study sites of the IND. Proposed § 312.32(c)(4) would apply to human bioavailability and bioequivalence studies that are the subject of proposed § 320.31(d). In these cases, the reference listed drug would be the marketed drug and persons conducting human bioequivalence and bioavailability studies that are not subject to an IND would only be required to submit safety reports to FDA from their studies.

### III.L. Proposed Implementation Scheme

FDA proposes that any final rule that may be issued regarding the proposal to require that SADRs in individual case safety reports be coded using MedDRA become effective 1 year after its date of publication in the **Federal Register**. FDA proposes that any final rule that may be issued based on all other proposals become effective 180 days after its date of publication in the **Federal Register**.

## IV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on

the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## V. Analysis of Impacts

### V.A. Background and Summary

FDA has examined the impacts of the proposed rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Title II of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million in any one year (adjusted annually for inflation). Section 205 of the Unfunded Mandates Reform Act also requires that the agency identify and consider a reasonable number of regulatory alternatives and from those alternatives select the least costly, most cost-effective, or least burdensome alternative that achieves the objective of the rule.

The following analysis, in conjunction with the remainder of this document, demonstrates that this proposed rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866 and in the other two statutes. The proposed rule would amend current safety reporting requirements for human drug and biological products. Based on the analysis below, as summarized in table 11, FDA projects that the annual benefits would exceed the costs if this proposed rule resulted in a 2 percent reduction in hospital-related SADRs. The agency believes that a reduction in hospital related SADRs of at least 2 percent is a reasonable and likely outcome of this rule. The agency has determined that the proposed rule is an economically significant rule as described in the Executive Order. As required by the Regulatory Flexibility

Act, the agency's Initial Regulatory Flexibility Analysis is included in this section. Because the rule may impose a mandate on the private sector that will result in a 1-year expenditure of \$110 million or more (the current inflation adjusted threshold), FDA has conducted a cost-benefit analysis according to the Unfunded Mandates Reform Act. The relationship of this proposed rule with other agency rulemaking is described in the background section (*e.g.*, reproposal of postmarketing periodic safety reporting requirements) (*see* section I of this document).

The proposed rule covers a small part of a broader based set of international initiatives (ICH and CIOMS) that, taken collectively, have the potential to generate substantial benefits, savings, and efficiencies for consumers, manufacturers, and regulators. The full benefits of this proposed rule will accrue when international regulatory inconsistencies are addressed, safety reporting submission requirements are harmonized internationally, and electronic information exchange is uniform and compatible for the major participants involved in monitoring drug safety. A primary objective of the proposed rule is the harmonization of FDA's safety reporting requirements with international initiatives. The proposed rule would also improve the quality of information contained in postmarketing individual case safety reports for human drug and biological products. By providing more complete information for individual case safety reports, the revised reports would enhance the ability of the drug and biologics manufacturers and the agency to identify, monitor, and communicate the risks and benefits of marketed drug and biological products. Monitoring these risks and benefits is especially critical for newly approved products introduced to large and diverse patient populations.

Specifically, the proposed rule would clarify and codify the agency's expectations for timely acquisition, evaluation, and submission of relevant safety information for marketed human drug and biological products. The proposed rule would expand postmarketing expedited safety reporting to include unexpected SADRs that cannot be classified as either serious or nonserious, information that is sufficient to consider changes in product administration, certain medically significant SADRs, and actual and potential medication errors as specified in the proposal. The proposed rule would require that each SADR in postmarketing individual case safety reports be coded using a single medical