Table 8.--Proposed Reporting Frequency for Postmarketing Expedited Safety Reports

Submit as Soon as Possible	Submit Within 5 Calendar Days	Submit Within 7 Calendar Days	Submit Within 15 Calendar Days	Submit Within 30 Calendar Days	Submit Within 45 Calendar Days
• Blood safety report - telephone (fatality) (D.12)[1]	• Individual case safety reports from contractors to manufacturer (D.9) • Individual case safety reports from contractors and shared manufacturers to applicant (D.9)	• Blood safety report - written (fatality) (D.12)	• Serious and unexpected SADR Report (D.1) • Information sufficient to consider product administration changes (D.2) • Always expedited report (D.4) • Medication error report (D.5) • 15-day followup report (D.6)	• 30-day followup report (D.6)	• Unexpected SADR with unknown outcome (D.3) • Blood safety report - written (all serious SAR's except fatalities) (D.12)

[1]References in parentheses refer to location in section III of this document.

Table 9.--Proposed Reporting Frequency for Postmarketing Periodic Safety Reports

Persons with Reporting Responsibility	Submit Every 6 Months	Submit at 0.5, 1, 1.5, 2, 3, 4, and 5 Years	Submit at 7.5 and 12.5 Years	Submit at 10 Years and Every 5 Years Thereafter
Applicants with NDA's[1] or BLA's approved on or after 1/1/95 and applicants with approved pediatric use supplements	Individual case safety reports--semiannual submission (E.4)[2]	PSUR (E.2)	IPSR (E.3)	PSUR
Applicants with NDA's or BLA's approved before 1/1/95	Individual case safety reports--semiannual submission	NA	TPSR (E.1) or IPSR	TPSR or PSUR

[1]Applicants with approved ANDA's would determine the type of postmarketing periodic safety report required to be submitted to FDA (i.e., TPSR, PSUR, IPSR) and the frequency of submission for these reports based on the U.S. approval date of the application for the innovator NDA product (see section III.I of this document).

[2]References in parentheses refer to section III of this document.

FDA is also proposing to amend its postmarketing safety reporting regulations at §§ 314.80(c) and 600.80(c) to state that applicants who wish to submit postmarketing safety reports at times other than prescribed by these regulations may request a waiver for this purpose under §§ 314.90 or 600.90. This proposed revision does not represent a new provision, but rather provides a cross-reference to the existing waiver requirements under §§ 314.90 and 600.90.

FDA is also proposing to amend its postmarketing periodic safety reporting regulations at §§ 314.80(c)(2)(i) and 600.80(c)(2)(i) by removing the third and fourth sentences in these paragraphs. These sentences state that, upon written notice, FDA may request submission of periodic safety reports at different times than stated under §§ 314.80(c)(2)(i) and 600.80(c)(2)(i) (e.g., following the approval of a major supplement). FDA is proposing to remove these sentences because this information would now be stated under proposed §§ 314.80(c) and 600.80(c). This proposed revision represents an organizational change that clarifies that FDA may request a different time period for submission of not only postmarketing periodic safety reports, but also postmarketing expedited safety reports.

III.C.5. Determination of Outcome, Minimum Data Set, and Full Data Set

Proposed §§ 310.305(c)(1)(i)(A), 314.80(c)(1)(i)(A), and 600.80(c)(1)(i)(A) would amend FDA's postmarketing safety reporting regulations to require that manufacturers and applicants immediately, upon initial receipt of an SADR report, use active query to determine the outcome for the SADR (whether the SADR is serious or nonserious) and at least the minimum data set for the individual case safety report (i.e., identifiable patient, identifiable reporter, suspect drug or biological product, and SADR. FDA is proposing this change to clarify that timely acquisition of information is critical to determine whether an SADR must be submitted to FDA and, for those reactions that would be reported, whether the SADR would be submitted in a postmarketing expedited safety report or a postmarketing periodic safety report.

Proposed §§ 310.305(c)(1)(i)(A), 314.80(c)(1)(i)(A), and 600.80(c)(1)(i)(A) would also require manufacturers and applicants to report actual medication errors, even those that do not result in an SADR, and potential medication errors. Manufacturers and applicants would be required to immediately determine, using active query, the minimum information for the individual case safety report (minimum information described below and at proposed §§ 310.305(c)(1)(iii)(B) and (c)(1)(iii)(C), 314.80(c)(1)(iii)(B) and (c)(1)(iii)(C), and 600.80(c)(1)(iii)(B) and (c)(1)(iii)(C)).

Proposed §§ 310.305(c)(1)(ii), 314.80(c)(1)(ii), and 600.80(c)(1)(ii) would require manufacturers and applicants who are unable to immediately determine the outcome of an SADR (whether the SADR is serious or nonserious) to continue to use active query to attempt to determine the outcome within 30 calendar days after initial receipt of the SADR report by the manufacturer. The proposed rule would require that manufacturers and applicants maintain records of their efforts to obtain this information. These proposed revisions clarify that due diligence must be used to obtain the outcome for SADR's. Unknown outcomes should not be classified arbitrarily as nonserious SADR's. Instead, each of the outcomes in the definition of serious SADR should be considered as a possibility.

Under proposed §§ 310.305(c)(1)(iii)(A), 314.80(c)(1)(iii)(A), and 600.80(c)(1)(iii)(A), individual case safety reports for SADR's that do not contain a minimum data set would not be submitted to the agency. Instead, the proposed rule would require that manufacturers and applicants maintain records of any information received or otherwise obtained for the SADR along with a record of their efforts to obtain a minimum data set for the individual case safety report. These proposed amendments are consistent with proposed revisions to the premarketing safety reporting regulations at proposed § 312.32(c) (see section III.B.2.a of this document). This change would

clarify that, at a minimum, certain information must be submitted to FDA to provide the agency with enough information to allow an initial evaluation of the significance of an SADR.

Proposed §§ 310.305(c)(1)(iii)(B), 314.80(c)(1)(iii)(B), and 600.80(c)(1)(iii)(B) would require that reports of actual medication errors that do not result in an SADR be submitted to FDA even though the report does not contain a minimum data set (i.e., does not have an SADR). In these cases, individual case safety reports would be required to contain at least an identifiable patient, an identifiable reporter, and a suspect drug or biological product.

Proposed §§ 310.305(c)(1)(iii)(C), 314.80(c)(1)(iii)(C), and 600.80(c)(1)(iii)(C) would require that reports of potential medication errors be submitted to FDA even though the report does not contain a minimum data set (i.e., does not have an identifiable patient or an SADR). In these cases, individual case safety reports would be required to contain at least an identifiable reporter and a suspect drug or biological product.

FDA is requiring submission of individual case safety reports for actual medication errors that do not result in an SADR and potential medication errors because of their potential significance and the need for intervention to minimize future errors. For example, if an adult is given the wrong medication, no SADR may occur, but if the same error occurs with a child, an

SADR may occur. Also, if an error is prevented prior to administration of a product, this information could be used to prevent the error from occurring in other situations. For example, the proprietary name, label, labeling or packaging of the product could be changed if sufficient evidence suggests such a change is warranted, or education announcements could be communicated to health care professionals and/or consumers.

Proposed §§ 310.305(c)(1)(iv), 314.80(c)(1)(iv), and 600.80(c)(1)(iv) state that, for reports of serious SADR's, always expedited reports, and medication error reports, manufacturers and applicants would be required to use active query to obtain a full data set for the report (see section III.D.4 of this document for discussion of always expedited reports and section III.D.5 of this document for discussion of medication error reports). If a full data set cannot be obtained for these reports, manufacturers and applicants would provide the following information:

- All safety information, received or otherwise obtained, for the report;
- The reason(s) for their inability to acquire a full data set; and
- Documentation of their efforts to obtain a full data set (i.e., description of unsuccessful steps taken to obtain this information).

In some cases, the agency has received incomplete safety reports for serious SADR's, making interpretation of their significance difficult. This proposed amendment would require submission of complete information for reports of serious SADR's, always expedited reports, and medication error reports, which would facilitate their expeditious review.

Proposed §§ 310.305(c)(1)(v), 314.80(c)(1)(v), and 600.80(c)(1)(v) state that:

> For a serious SADR that was not initially reported to the manufacturer (applicant for proposed §§ 314.80(c)(1)(v) and 600.80(c)(1)(v)) by a health care professional (e.g., report from a consumer), active query must be used by the manufacturer (applicant for proposed §§ 314.80(c)(1)(v) and 600.80(c)(1)(v)) to contact the health care professional associated with the care of the patient to gather further medical perspective on the case and to acquire a full data set for the report.

The agency believes that contact with a health care professional is warranted for serious SADR's because of the critical nature of these reactions.

For nonserious SADR's with a minimum data set, proposed §§ 314.80(c)(1)(vi) and 600.80(c)(1)(vi) would require applicants to submit to FDA all safety information received or otherwise obtained. Applicants would not be required to acquire information in addition to the minimum data set, except that reports of nonserious SADR's resulting from a medication error would require a full data set. Thus, followup would not be required for reports of nonserious SADR's that contain a minimum data set and do not occur because of a medication error.

III.C.6. Spontaneous Reports and Reports From Clinical Trials

Proposed §§ 310.305(c)(1)(i)(B), 314.80(c)(1)(i)(B), and 600.80(c)(1)(i)(B) would require that, for spontaneous reports, manufacturers and applicants must always assume, for safety reporting purposes only, that there is at least a reasonable possibility, in the opinion of the initial reporter, that the drug or biological product caused the spontaneously reported event. Proposed §§ 310.305(c)(1)(i)(C), 314.80(c)(1)(i)(C), and 600.80(c)(1)(i)(C) state that, for a clinical trial, the possibility that the drug or biological product caused the SADR or that a medication error has occurred would be assumed if either the investigator or the applicant/manufacturer believes that such a reasonable possibility exists.

These proposed changes would clarify that all spontaneous reports received by manufacturers and applicants that contain a

minimum data set (minimum information for a report of a medication error that does not result in SADR) would be reported to FDA (i.e., as an individual case safety report and/or in a summary tabulation). These changes are consistent with the premarketing safety reporting requirements described in section III.B.2.b of this document (i.e., determination of the possibility of causality (attributability) of an SADR to the drug or biological product in a clinical investigation would be based on the opinion of either the applicant/sponsor or investigator). These proposed amendments are also consistent with the ICH E2A guidance (60 FR 11284 at 11286):

> Causality assessment is required for clinical investigation cases. All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADR's. For purposes of reporting, adverse event reports associated with marketed drugs (spontaneous reports) usually imply causality.

III.C.7. Lack of Efficacy Reports

With regard to reports of a lack of efficacy for an approved drug or biological product, the guidance of 1992 and guidance of 1993 advise applicants to submit all individual cases of such

reports that occur in the United States in postmarketing periodic safety reports. In this proposed rule, FDA would not require submission of individual case safety reports for reports of a lack of efficacy. Instead, applicants would be required to submit to FDA expedited reports of information sufficient to consider a product administration change, based upon appropriate medical judgement, for any significant unanticipated safety finding or data in the aggregate from a study that suggests a significant human risk. For example, applicants would be required to submit reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease (see section III.D.2 of this document). In addition, applicants would be required to include in postmarketing periodic safety reports (i.e., TPSR's, PSUR's, IPSR's) an assessment of whether it is believed that the frequency of lack of efficacy reports is greater than would be predicted by the premarketing clinical trials for the drug or biological product (see sections III.E.1.c, III.E.2.k.vi, and III.E.3 of this document). This assessment would be provided for reports of a lack of efficacy whether a serious SADR, nonserious SADR, or no SADR occurs. Applicants that submit PSUR's and IPSR's to FDA would also include in these reports a discussion of medically relevant lack of efficacy reports (e.g., might represent a significant hazard to the treated population) for a product(s) used to treat serious

or life-threatening diseases (see sections III.E.2.h and III.E.3 of this document).

III.D. Postmarketing Expedited Reports

Current postmarketing expedited safety reporting regulations at §§ 310.305(c), 314.80(c), and 600.80(c) require submission of "15-day Alert reports" to FDA. FDA is proposing to amend these regulations by removing the term "15-day Alert report" and replacing it with the term "expedited report" to be consistent with terminology used in the ICH E2A guidance. FDA is also proposing the following revisions to its postmarketing expedited safety reporting regulations.

III.D.1. Serious and Unexpected SADR's

Under the existing postmarketing expedited safety reporting regulations at § 310.305(c)(1)(i), persons subject to this requirement must report to FDA each adverse drug experience received or otherwise obtained that is both serious and unexpected as soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the person. Under the existing postmarketing expedited safety reporting regulations at §§ 314.80(c)(1)(i) and 600.80(c)(1)(i), persons subject to these requirements must report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible, but in no case later

than 15 calendar days of initial receipt of the information by the person.

FDA is proposing minor revisions to these regulations for consistency. Proposed § 310.305(c)(2)(i) would amend § 310.305(c)(1)(i) by adding the phrase "whether foreign or domestic" after the phrase "that is both serious and unexpected." Proposed §§ 314.80(c)(2)(i) and 600.80(c)(2)(i) would amend §§ 314.80(c)(1)(i) and 600.80(c)(1)(i) by adding the phrase "to FDA" after the word "report" and by adding the phrase "received or otherwise obtained" before the phrase "that is both serious and unexpected."

Proposed §§ 310.305(c)(2)(i), 314.80(c)(2)(i), and 600.80(c)(2)(i) would amend §§ 310.305(c)(1)(i), 314.80(c)(1)(i), and 600.80(c)(1)(i) by removing the phrase "of initial receipt of the information by the person whose name appears on the label ("by the applicant" for § 314.80(c)(1)(i), and "by the licensed manufacturer" for § 600.80(c)(1)(i)) and replacing it with the phrase "after receipt by the manufacturer ("applicant" for proposed §§ 314.80(c)(2)(i), and 600.80(c)(2)(i)) of the minimum data set for the serious, unexpected SADR." This proposed amendment is consistent with proposed revisions to the premarketing expedited safety reporting regulations at proposed § 312.32(c)(1)(i) (see section III.B.2.b of this document). The amendment would clarify that the 15 calendar day timeframe would

begin as soon as manufacturers and applicants have knowledge of the minimum data set for an SADR that is serious and unexpected. Manufacturers and applicants must use due diligence to acquire this information. For this purpose, they would be required, as described in section III.C.5 of this document, to use active query to determine the outcome for the SADR (whether the SADR is serious or nonserious) and acquire at least the minimum data set for the individual case safety report. Manufacturers and applicants should include in postmarketing expedited safety reports a chronological history of their efforts to acquire a minimum data set and to determine the seriousness and expectedness of an SADR if there is a delay in obtaining such information.

Proposed §§ 310.305(c)(2)(i), 314.80(c)(2)(i) and 600.80(c)(2)(i) state that if a full data set is not available for a serious and unexpected SADR report at the time of initial submission of the report to FDA, manufacturers and applicants must submit the information required under proposed §§ 310.305(c)(1)(iv), 314.80(c)(1)(iv) and 600.80(c)(1)(iv) as described in section III.C.5 of this document and also submit a 30-day followup report as described in section III.D.6 of this document. FDA is proposing this action to clarify the importance of acquiring complete information for serious SADR's.

III.D.2. Information Sufficient to Consider Product Administration Changes

Proposed §§ 310.305(c)(2)(ii), 314.80(c)(2)(ii), and 600.80(c)(2)(ii) would require that manufacturers and applicants submit to FDA information, received or otherwise obtained, whether foreign or domestic, that would be sufficient, based upon appropriate medical judgment, to consider changes in product administration. Manufacturers and applicants would be required to submit this information to the agency as soon as possible, but in no case later than 15 calendar days after the manufacturer or applicant determines that the information qualifies for expedited reporting. Examples of such information 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. The proposed rule would require that manufacturers and applicants maintain records of their efforts to determine whether information that they have received or otherwise obtained would qualify for expedited reporting under this proposed requirement. This proposed requirement is consistent with the proposed revisions to the premarketing expedited safety reporting

regulations at proposed § 312.32(c)(1)(ii) (see section III.B.2.c of this document) and with the ICH E2A guidance (60 FR 11284 at 11286). The proposed amendment would further clarify some of the types of safety information that must be submitted to FDA in an expedited manner.

III.D.3. Unexpected SADR's With Unknown Outcome

FDA expects that, in most cases, manufacturers and applicants will be able to determine the outcome for an SADR (whether the SADR is serious or nonserious). However, in those few cases where a determination may not be possible, FDA would require submission of unexpected SADR's with unknown outcome in an expedited manner (proposed §§ 310.305(c)(2)(iii), 314.80(c)(2)(iii), and 600.80(c)(2)(iii)). Expedited safety reports for unexpected SADR's with unknown outcome would be submitted to FDA within 45 calendar days after initial receipt by the manufacturer or applicant of the minimum data set for the unexpected SADR. FDA is proposing this action to expedite review of potentially serious SADR's.

The proposed rule would require that manufacturers and applicants reporting an unexpected SADR with unknown outcome include in the expedited safety report the reason(s) for their inability to classify an SADR as either serious or nonserious (i.e., unknown outcome). For this purpose, manufacturers and

applicants should include in the expedited report a chronological history of their efforts to determine the outcome of the SADR.

Manufacturers and applicants reporting an unexpected SADR with unknown outcome must exercise due diligence to determine the expectedness for the SADR and to acquire at least the minimum data set for the individual case safety report. For this purpose, these persons would be required to use active query to acquire this information (see section III.C.5 of this document). These persons should include in postmarketing expedited safety reports a chronological history of their efforts to acquire this information if there is a delay in obtaining it.

III.D.4. Always Expedited Reports

Proposed §§ 310.305(c)(2)(iv), 314.80(c)(2)(iv), and 600.80(c)(2)(iv) would require manufacturers and applicants to submit to FDA individual case safety reports for SADR's, received or otherwise obtained, whether foreign or domestic, that are the subject of an always expedited report. These always expedited reports would be submitted to the agency as soon as possible, but in no case later than 15 calendar days after receipt by the manufacturer ("applicant" for proposed §§ 314.80(c)(2)(iv), and 600.80(c)(2)(iv)) of the minimum data set for the report. The following medically significant SADR's, which may jeopardize the patient or subject and/or require medical or surgical

intervention to treat the patient or subject, would be subject to an always expedited report:

- Congenital anomalies,
- Acute respiratory failure,
- Ventricular fibrillation,
- Torsades de pointe,
- Malignant hypertension,
- Seizure,
- Agranulocytosis,
- Aplastic anemia,
- Toxic epidermal necrolysis,
- Liver necrosis,
- Acute liver failure,
- Anaphylaxis,
- Acute renal failure,
- Sclerosing syndromes,
- Pulmonary hypertension,
- Pulmonary fibrosis,
- Confirmed or suspected transmission of an infectious agent by a marketed drug or biological product,
- Confirmed or suspected endotoxin shock, and
- Any other medically significant SADR that FDA determines to be the subject of an always expedited report (i.e., may jeopardize the patient or subject

and/or require medical or surgical intervention to treat the patient or subject).

These SADR's would be submitted to the agency in an expedited manner whether unexpected or expected and whether or not the SADR leads to a serious outcome. The medical gravity of these SADR's requires expedited reporting.

The agency is proposing that a confirmed or suspected transmission of an infectious agent by a marketed drug or biological product would be the subject of an always expedited report. Examples of such transmissions include human immunodeficiency virus (HIV) transmission by anti-hemophilic factor, hepatitis C transmission by intravenous immunoglobulin, bacterial contamination of albumin leading to sepsis, and parvovirus contamination of anti-hemophilic factor causing an SADR. These SADR's indicate a public health problem that requires expedited review by the agency.

The proposal provides that the agency could make a new SADR the subject of an always expedited report. Such an SADR would only become the subject of these reports if FDA determines that the SADR is medically significant (i.e., may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject). New SADR's that become the subject of always expedited reports would be included in the agency's current guidance for industry on postmarketing

safety reporting for human drugs and licensed biological products.

Proposed §§ 310.305(c)(2)(iv)(B), 314.80(c)(2)(iv)(B), and 600.80(c)(2)(iv)(B) would require that if a full data set is not available for always expedited reports at the time of initial submission of the report to FDA, manufacturers and applicants would submit the information required under proposed §§ 310.305(c)(1)(iv), 314.80(c)(1)(iv) and 600.80(c)(1)(iv) as described in section III.C.5 of this document and also submit a 30-day followup report as described in section III.D.6 of this document. FDA is proposing this action to clarify the importance of acquiring complete information for medically significant SADR's that are the subject of always expedited reports.

III.D.5. Medication Errors

Proposed §§ 310.305(c)(2)(v)(A), 314.80(c)(2)(v)(A), and 600.80(c)(2)(v)(A) would require that each domestic report of an actual medication error, received or otherwise obtained, be submitted to the agency as soon as possible, but in no case later than 15 calendar days after receipt by the manufacturer ("applicant" for proposed §§ 314.80(c)(2)(v)(A) and 600.80(c)(2)(v)(A)) of the minimum data set for a report of an SADR or, if an SADR does not occur, the minimum information for the report as described in section III.C.5 of this document (i.e., an identifiable patient, an identifiable reporter, and a

suspect drug or biological product). For postmarketing safety reporting purposes, all reports of medication errors would be considered unexpected. FDA is proposing this new type of expedited report to protect public health.

Proposed §§ 310.305(c)(2)(v)(B), 314.80(c)(2)(v)(B), and 600.80(c)(2)(v)(B) would require that reports of potential medication errors, received or otherwise obtained, be submitted to the agency as soon as possible, but in no case later than 15 calendar days after receipt by the manufacturer ("applicant" for proposed §§ 314.80(c)(2)(v)(B) and 600.80(c)(2)(v)(B)) of the minimum information described in section III.C.5 of this document (i.e., an identifiable reporter and a suspect drug or biological product). FDA is proposing submission of this information to the agency in an expedited manner to attempt to prevent actual medication errors.

Proposed §§ 310.305(c)(2)(v)(C), 314.80(c)(2)(v)(C), and 600.80(c)(2)(v)(C) state that if a full data set is not available for an actual or potential medication error report at the time of initial submission of the report to FDA, manufacturers and applicants would submit the information required under proposed §§ 310.305(c)(1)(iv), 314.80(c)(1)(iv) and 600.80(c)(1)(iv) as described in section III.C.5 of this document and also submit a 30-day followup report as described in section III.D.6 of this document. FDA is proposing this action to clarify the importance

of acquiring complete information for reports of medication errors.

III.D.6. Followup Reports

Current postmarketing expedited safety reporting regulations at §§ 310.305(c)(2), 314.80(c)(1)(ii), and 600.80(c)(1)(ii) require persons subject to these regulations to promptly investigate all serious, unexpected adverse drug experiences that are the subject of expedited reports and to submit followup reports within 15 calendar days of receipt of new information or as requested by FDA. If additional information is not obtainable, records should be maintained of the unsuccessful steps taken to seek additional information.

Proposed §§ 310.305(c)(2)(vi), 314.80(c)(2)(vi), and 600.80(c)(2)(vi) would require manufacturers and applicants to use active query to obtain additional information for any serious and unexpected SADR submitted to FDA in an expedited report under proposed §§ 310.305(c)(2)(i), 314.80(c)(2)(i), and 600.80(c)(2)(i) that does not contain a full data set. The proposed amendment would also require these persons to use active query to obtain additional information for any always expedited report under proposed §§ 310.305(c)(2)(iv), 314.80(c)(2)(iv), and 600.80(c)(2)(iv) or any medication error report under proposed §§ 310.305(c)(2)(v), 314.80(c)(2)(v), and 600.80(c)(2)(v) that does not contain a full data set. This information would be

submitted to the agency in a followup report within 30 calendar days after initial submission of the expedited report to FDA by the manufacturer or applicant (30-day followup report). This proposed amendment would provide the agency with timely acquisition of more complete information for SADR's and medication errors that are the subject of these reports.

Proposed §§ 310.305(c)(2)(vi), 314.80(c)(2)(vi), and 600.80(c)(2)(vi) would also state that:

> * * * If a full data set is still not obtainable, the 30-day followup report must contain the information required under paragraph (c)(1)(iv) of this section. Any new safety information in the 30-day followup report must be highlighted. Any new information, received or otherwise obtained, after submission of a 30-day followup report must be submitted to FDA as a 15-day followup report under paragraph (c)(2)(vii) of this section.

This proposed amendment would clarify the information that would be required in a 30-day followup report if a full data set is still not available for the report. It would also clarify that FDA would require a 15-day followup report, as described in the paragraphs that follow, for any new information obtained or

otherwise received for the report after submission of the 30-day followup report. The proposed amendment would ensure that manufacturers and applicants would exercise due diligence to obtain complete information for SADR's that are the subject of 30-day followup reports.

Proposed §§ 310.305(c)(2)(vii), 314.80(c)(2)(vii), and 600.80(c)(2)(vii) would amend §§ 310.305(c)(2), 314.80(c)(1)(ii), and 600.80(c)(1)(ii) to clarify that manufacturers and applicants must submit 15-day followup reports to FDA of any new information received or otherwise obtained for any expedited or followup report (except for initial expedited reports under proposed §§ 310.305(c)(2)(i), (c)(2)(iv), and (c)(2)(v), 314.80 (c)(2)(i), (c)(2)(iv), and (c)(2)(v), and 600.80(c)(2)(i), (c)(2)(iv), and (c)(2)(v) that do not contain a full data set) within 15 calendar days of initial receipt of new information by the manufacturer or applicant. Proposed §§ 310.305(c)(2)(vii), 314.80(c)(2)(vii), and 600.80(c)(2)(vii) would also state that:

> * * * Expedited reports under paragraphs (c)(2)(i), (c)(2)(iv), and (c)(2)(v) of this section that do not contain a full data set at the time of initial submission of the report to FDA are subject to the 30-day followup reporting requirements under paragraph (c)(2)(vi) of this section rather

than the 15-day followup reporting requirements under this paragraph.

Thus, 15-day followup reports would be submitted for the following types of expedited and followup reports:

- Serious and unexpected SADR reports that contain a full data set,
- Information sufficient to consider product administration changes,
- Unexpected SADR's with unknown outcomes,
- Always expedited reports that contain a full data set,
- Actual and potential medication error reports that contain a full data set,
- 30-day followup reports, and
- 15-day followup reports.

These proposed revisions clarify the types of expedited reports that would be subject to the 15-day followup reporting requirements.

FDA notes that a 15-day followup report, rather than a serious and unexpected SADR report, should be submitted to FDA for an SADR that is initially reported to the agency as serious and expected or nonserious and unexpected, but is subsequently determined to be serious and unexpected. In these cases, manufacturers and applicants should include in the 15-day

followup report a chronological history describing the events that transpired which resulted in determination of the serious and unexpected character of the SADR.

FDA is proposing to amend its postmarketing expedited safety reporting regulations at §§ 310.305(c)(2), 314.80(c)(1)(ii), and 600.80(c)(1)(ii) by removing the second sentence in these paragraphs regarding maintaining records if additional information is not obtainable for a serious and unexpected adverse drug experience. The agency is proposing this amendment because postmarketing safety reporting requirements for serious and unexpected SADR reports that do not contain a full data set are now prescribed under proposed §§ 310.305(c)(1)(iv) and (c)(2)(vi), 314.80(c)(1)(iv) and (c)(2)(vi), and 600.80(c)(1)(iv) and (c)(2)(vi).

III.D.7. Supporting Documentation

Proposed §§ 310.305(c)(2)(viii)(A), 314.80(c)(2)(viii)(A), and 600.80(c)(2)(viii)(A) would require that manufacturers and applicants submit to FDA, if available, a copy of the autopsy report if the patient dies. If an autopsy report is not available, the proposed rule would require that manufacturers and applicants submit a death certificate to FDA. If an autopsy report becomes available after the manufacturer or applicant has submitted a death certificate to the agency, the manufacturer or applicant must submit the autopsy report to FDA. If the patient

was hospitalized, manufacturers and applicants would be required to submit to FDA, if available, a copy of the hospital discharge summary. If any of these documents is not in English, an English translation of the document would be required. FDA is proposing that manufacturers and applicants submit these documents to provide the agency with complete information for SADR's that result in a death or hospitalization.

Proposed §§ 310.305(c)(2)(viii)(A), 314.80(c)(2)(viii)(A), and 600.80(c)(2)(viii)(A) would require that manufacturers and applicants use active query to obtain the documents required to be submitted to FDA under this paragraph. These documents would be required to be submitted to FDA as 15-day followup reports (see section III.D.6 of this document) within 15 calendar days of initial receipt of the document by the manufacturer or applicant. In instances when a document is not submitted to FDA in a 15-day followup report within 3 months after submission of the initial expedited report for the death or hospitalization, the agency would assume that active query by the manufacturer or applicant did not result in access to these documents. In this case, a record of the reason(s) for the lack of documentation and the effort that was made to obtain the documentation would be required to be maintained by the manufacturer and applicant.

Proposed §§ 310.305(c)(2)(viii)(B), 314.80(c)(2)(viii)(B), and 600.80(c)(2)(viii)(B) would require that each expedited

report contain in the narrative a list of other relevant documents (e.g., medical records, laboratory results, data from studies) regarding the report that are maintained by manufacturers and applicants. FDA may require, when appropriate, that copies of one or more of these documents be submitted to the agency within 5 calendar days after receipt of the request. FDA would usually request such records in response to a suspected safety problem associated with the use of a drug or licensed biological product.

III.D.8. Scientific Literature

Current postmarketing expedited safety reporting regulations at §§ 314.80(d)(1) and 600.80(d)(1) require that expedited reports based on information from the scientific literature be accompanied by a copy of the published article. These regulations apply only to reports found in scientific and medical journals either as case reports or as the result of a formal clinical trial. Proposed §§ 314.80(c)(2)(ix) and 600.80(c)(2)(ix) would amend the current regulations by removing the phrase "either as case reports or as the result of a formal clinical trial" to clarify that all reports from the scientific literature, including case reports, and results of a formal clinical trial, epidemiological study, in vitro study, or animal study, that qualify for expedited reporting under proposed

§§ 314.80(c)(2) and 600.80(c)(2) would be required to be submitted to FDA.

The proposed rule would also remove §§ 314.80(d)(2) and 600.80(d)(2). These paragraphs provide that reports based on the scientific literature must be submitted on FDA Form 3500A or comparable format prescribed by the regulations and that, in cases where persons subject to the postmarketing safety reporting regulations believe that preparing the FDA Form 3500A constitutes an undue hardship, arrangements can be made with the agency for use of an acceptable alternative reporting format. FDA is proposing to remove these paragraphs because the reporting format for reports based on information in the scientific literature would be specified under proposed §§ 314.80(c)(4) and 600.80(c)(4) (see section III.F of this document).

For organizational purposes, FDA is proposing to move §§ 314.80(d) and 600.80(d), as revised by this proposed rule, to proposed §§ 314.80(c)(2)(ix) and 600.80(c)(2)(ix). Proposed § 310.305(c)(2)(ix) would amend § 310.305© by adding the paragraph:

> Scientific literature. An expedited report based on information from the scientific literature applies only to reports found in scientific and medical journals. These

expedited reports must be accompanied by a copy of the published article.

This proposed amendment would clarify for prescription drug products marketed for human use without an approved application the types of safety information found in scientific literature that would qualify for expedited reporting. The proposed amendment would also require that these reports include a copy of the published article that is the subject of the expedited report. The proposed amendment would provide the agency with more complete information for review of safety information from the scientific literature and would also provide uniformity between FDA's postmarketing expedited safety reporting requirements for prescription drugs marketed for human use without an approved application and marketed drugs with an approved application.

III.D.9. Contractors and Shared Manufacturers

Current regulations at §§ 310.305(c)(1)(i) and (c)(3), 314.80(c)(1)(iii), and 600.80(c)(1)(iii) require any person whose name appears on the label of a marketed drug product or licensed biological product as a packer or distributor to submit either expedited reports of serious and unexpected adverse drug experiences directly to FDA or reports of all serious adverse drug experiences to the manufacturer (§ 310.305(c)(3) or applicant (§§ 314.80(c)(1)(iii) and 600.80(c)(1)(iii)) instead of

FDA in 5 calendar days. This provision also applies to manufacturers for §§ 314.80(c)(1)(iii) and 600.80(c)(1)(iii) and to shared manufacturers, joint manufacturers, and any participants involved in divided manufacturing for § 600.80(c)(1)(iii). Proposed §§ 310.305(c)(2)(xi)(A), 314.80(c)(2)(x)(A), and 600.80(c)(2)(x)(A) would amend these regulations to require contractors, as defined in proposed §§ 310.305(a), 314.80(a) and 600.80(a) (see section III.A.4 of this document), to submit to the manufacturer (proposed § 310.305(c)(2)(xi)(A)) or applicant (proposed §§ 314.80(c)(2)(x)(A) and 600.80(c)(2)(x)(A)) safety reports of all SADR's (serious and nonserious) and medication errors for the manufacturer's (proposed § 310.305(c)(2)(xi)) or applicant's (proposed §§ 314.80(c)(2)(x) and 600.80(c)(2)(x)) drug or biological product, obtained or otherwise received, within 5 calendar days of initial receipt of the report by the contractor. This provision would also apply to shared manufacturers of licensed biological products for proposed § 600.80(c)(2)(x)(A) (i.e., all SAR's and medication errors would be required to be submitted to the applicant within 5 calendar days). The contractor would be required to submit a report of an SADR to the manufacturer (proposed § 310.305(c)(2)(xi)(A)) or applicant (proposed §§ 314.80(c)(2)(x)(A) and 600.80(c)(2)(x)(A)) even if the report does not contain a minimum data set. Contractors and

shared manufacturers would only be required to convey to manufacturers (proposed § 310.305(c)(2)(xi)(A)) or applicants (proposed §§ 314.80(c)(2)(x)(A) and 600.80(c)(2)(x)(A)) whatever safety information was obtained or otherwise received. They would not be required to use active query to acquire safety information, to conduct followup, or to submit postmarketing safety reports to FDA. Upon receipt of a safety report from a contractor or shared manufacturer, the manufacturer (proposed § 310.305(c)(2)(xi)(A)) or applicant (proposed §§ 314.80(c)(2)(x)(A) and 600.80(c)(2)(x)(A)) would be required to comply with the postmarketing safety reporting requirements under proposed §§ 310.305, 314.80 and 600.80 (e.g., use active query to acquire safety information, conduct followup, submit postmarketing safety reports to FDA). These proposed amendments would provide manufacturers and applicants with complete safety information regarding its products.

Proposed §§ 310.305(c)(2)(xi)(B), 314.80(c)(2)(x)(B), and 600.80(c)(2)(x)(B) would require that contracts between manufacturers and contractors (§ 310.305(c)(2)(xi)(B)) and applicants and contractors (§§ 314.80(c)(2)(x)(B) and 600.80(c)(2)(x)(B)) specify the postmarketing safety reporting responsibilities of the contractor. Although contractors and shared manufacturers have postmarketing safety reporting responsibilities, the manufacturer (proposed

§ 310.305(c)(2)(xi)(B)) or applicant (proposed §§ 314.80(c)(2)(x)(B) and 600.80(c)(2)(x)(B)) would be responsible for ensuring that the contractors and shared manufacturers of its products comply with these postmarketing safety reporting responsibilities. FDA believes that, in general, this proposal represents a practice that is already customary and usual in the pharmaceutical industry because contractors are typically considered agents of the manufacturer or applicant.

Proposed §§ 310.305(c)(2)(xi)(C), 314.80(c)(2)(x)(C), and 600.80(c)(2)(x)(C) would require that contractors and shared manufacturers maintain records of SADR reports and medication errors. This proposal is consistent with current postmarketing safety reporting requirements.

Proposed §§ 310.305(c)(2)(xi)(D), 314.80(c)(2)(x)(D), and 600.80(c)(2)(x)(D) state that the recordkeeping, written procedures, and disclaimer provisions under proposed §§ 310.305, 314.80 and 600.80 would apply to contractors and shared manufacturers. This proposal clarifies for contractors and shared manufacturers which of the postmarketing safety reporting provisions would apply to them.

III.D.10. Prescription Drugs Marketed for Human Use Without an Approved Application

Proposed § 310.305(c)(2)(x) would amend § 310.305(c)(1)(i) to require that expedited reports for prescription drugs marketed for human use without an approved application be accompanied by a list of the current addresses where all safety reports and other safety-related records for the drug product are maintained by manufacturers and contractors. In the October 1994 proposal, FDA proposed to include, under §§ 314.80(c)(2) and 600.80(c)(2), a section in its postmarketing periodic safety reports on location of adverse drug experience records (59 FR 54046 at 54061). FDA is now reproposing this amendment for its postmarketing periodic safety reports (see sections III.E.1.g, III.E.2.k.x, and III.E.3 of this document). The agency is also proposing to require the list of addresses in expedited reports for drugs covered under § 310.305 because manufacturers of these drugs are not required to submit postmarketing periodic safety reports to FDA. The list of addresses would provide rapid access to safety-related records for FDA inspections and for requests by FDA for additional information concerning safety issues.

III.D.11. Class Action Lawsuits

Manufacturers and applicants should not submit SADR's from class action lawsuits to FDA in an expedited report. The agency believes that SADR's from class action lawsuits would be submitted to FDA from other sources (e.g., spontaneous reports) prior to initiation of the class action lawsuit. Summary

tabulations of SADR's from class action lawsuits would be required in postmarketing periodic safety reports (see sections III.E.1.e and III.E.2.k.v of this document).

III.D.12. Blood and Blood Component Safety Reports

Current § 606.170(a) requires a blood establishment to thoroughly investigate any complaint of an adverse reaction arising as a result of blood collection or transfusion and to prepare and maintain a written report of the investigation, including followup and conclusions, as part of the record for that lot or unit of final product. If appropriate, the report must be forwarded to the manufacturer of the blood or blood component or the collection facility. Under § 606.170(b), a complication of a blood collection or blood transfusion resulting in a fatality must be reported to FDA as soon as possible by telephone or other rapid means of communication, and a written report of the investigation must be submitted to FDA within 7 days of the fatality. Each year, in accordance with § 606.170(b), FDA receives between 50 and 80 reports of fatalities.

Current § 600.171 requires licensed manufacturers of blood and blood components, unlicensed registered blood establishments and transfusion services to report biological product deviations. A biological product deviation is an event that represents either: (1) A deviation from current good manufacturing

practices, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of a product; or (2) an unexpected or unforseeable event that may affect the safety, purity, or potency of a product. In some cases, a biological product deviation reportable under § 606.171 may actually result in an adverse reaction in the transfusion recipient. In many other cases, the biological product deviation may be discovered before the affected products are administered or administration of the product may not result in an adverse reaction.

Although manufacturers of blood and blood components are currently exempt from the safety reporting requirements under § 600.80, FDA receives reports of fatal adverse reactions related to blood and blood components and may receive some additional information through biological product deviation reporting. However, the agency does not currently receive adequate information to monitor and assess safety-related information concerning the collection and transfusion of blood and blood components. Such information is essential for evaluating the agency's scientific and regulatory policies and for monitoring industry practices and their implications on blood safety. For these purposes, FDA is proposing to amend § 606.170 to require the reporting of all serious SAR's, in addition to fatalities, that are related to the collection or transfusion of blood and

blood components (e.g., red blood cells, plasma, platelets, and cryoprecipitate). For fatal SAR's, proposed § 606.170(c) would continue the current requirement that a fatal SAR be reported immediately by telephone, facsimile, express mail, or electronically transmitted mail and in a written report within 7 calendar days of the fatality. Because blood establishments are already required to investigate all complaints of an adverse reaction related to the collection and transfusion of blood and blood components and many of these reactions are well recognized and understood by blood establishments and by FDA, the agency is not proposing to require the submission of postmarketing periodic safety reports (i.e., TPSR's, PSUR's, IPSR's and individual case safety reports--semiannual submissions).

Specifically, FDA is proposing to amend § 606.170 by revising the title of the section to read "Suspected adverse reaction investigation and reporting"; by making editorial changes to § 606.170(a), which prescribes requirements for the investigation and recording of any complaint of an SAR related to the collection or transfusion of blood or blood components; by adding a new requirement for reporting of serious SAR's related to transfusion or collection procedures (proposed § 606.170(b)); and by redesignating current § 606.170(b) as § 606.170(c) and revising the paragraph as discussed below. FDA is also proposing that the terms "SAR" and "serious SAR," as used in proposed

§ 606.170, have the same meaning as defined in proposed § 600.80(a)(see sections III.A.1 and III.A.3 of this document).

In general, FDA believes that any SAR related to blood donation or transfusion that requires immediate medical intervention or followup medical attention should be reported. For the purpose of reporting serious SAR's related to blood collection, FDA interprets the term to include:

- Vasovagal reactions with syncope (hypotension and bradycardia) requiring medical intervention;
- Citrate reactions requiring significant medical intervention;
- Anaphylaxis or any major allergic reactions;
- Seizure of any type or duration;
- Cerebrovascular accidents;
- Cardiac arrhythmia, angina of any duration, myocardial infarction, or cardiac arrest;
- Clinically significant hypotension;
- Bronchospasm, respiratory insufficiency;
- Arterial puncture, air embolus;
- Phlebotomy-related nerve damage; and,
- Thrombophlebitis, phlebitis, or any procedure-related infection.

For SAR's related to donation, FDA interprets the term "serious SAR" not to include:

- Self-limited vasovagal reactions (hemodynamically stable);
- Self-limited citrate reactions;
- Localized hematoma, uncomplicated; and,
- Localized skin irritation, uncomplicated.

For the purposes of reporting serious SAR's related to receipt of a blood transfusion, FDA interprets the term to include:

- Any complication from the use of an unsuitable unit, including infusion of hemolyzed blood;
- Any complication from improper blood administration, including failure to use a standard blood filter (e.g., air embolism);
- Induced hemolysis, acute or delayed;
- Transmitted infections, including bacterial infections;
- Associated graft versus host disease;
- Related hypersensitivity with respiratory insufficiency and/or hypotension (e.g., anaphylaxis);
- Transfusion-related acute lung injury (TRALI);
- Induced alloimmunization which prevents effective transfusion therapy (e.g., posttransfusion purpura);
- Induced congestive heart failure; and
- Induced cardiac arrhythmias, including those resulting from metabolic imbalance.

For SAR's related to receipt of a blood transfusion, FDA interprets the term "SAR" not to include:

- Febrile nonhemolytic transfusion reactions;
- Related hypersensitivity without respiratory insufficiency nor hypotension;
- Induced alloimmunization which does not prevent effective transfusion therapy;
- Infections not clinically significant to the recipient, such as cytomegalovirus (CMV) infection in an immunocompetent adult; and,
- Induced hemochromatosis.

FDA is proposing to require that for a serious SAR related to blood collection, the establishment performing the blood collection be responsible for reporting the serious SAR to FDA, and for a serious SAR related to transfusion, the establishment responsible for the compatibility testing be responsible for reporting the serious SAR to FDA (proposed § 606.170(b)). FDA is proposing to require that reports of serious SAR's, including fatal SAR's under proposed § 606.170(c), be reported to FDA using the reporting format described in proposed § 600.80(c)(4). Thus the reporting facility would be required to submit a report for each individual patient on FDA Form 3500A or a computer-generated facsimile of FDA Form 3500A using the appropriate "preferred

term" in the latest version of MedDRA (see section III.F of this document).

Current § 606.171 requires reports of biological product deviations be submitted as soon as possible, but not to exceed 45 calendar days. Because there will be instances when an SAR occurs and a biological product deviation may have contributed to an SAR, FDA is proposing to require reporting of serious SAR's to the agency within 45 calendar days (for fatal SAR's, within 7 calendar days) of the determination that a serious SAR related to blood collection or transfusion has occurred. This will permit a blood establishment to investigate and report both a biological product deviation and an SAR related to the biological product deviation at the same time and will limit the reporting burden. In the case of a reported serious SAR that subsequently results in a fatality, FDA would not require two separate reports, one reporting the serious SAR and the other reporting the fatality. However, if the fatality occurs after the report of the serious SAR is submitted to the agency, the blood establishment should update the initial report to report the fatality.

III.E. Postmarketing Periodic Safety Reporting

The proposed rule would require all applicants to submit to FDA semiannually on an FDA Form 3500A (VAERS form for vaccines,

CIOMS I Form, if desired, for foreign SADR's) certain spontaneously reported SADR's (see tables 7 and 9 and section III.E.4 of this document regarding individual case safety reports--semiannual submissions). Applicants would also be required to submit other postmarketing periodic safety reports (i.e., TPSR's, PSUR's, or IPSR's) to FDA with a frequency as described in section III.E.5.a of this document (see tables 7 and 9). PSUR's, IPSR's, and TPSR's would provide FDA with an overview or summary of the safety profile of a drug or licensed biological product (excluding individual case safety reports). A TPSR would essentially contain the same format and content as the periodic safety report currently required by the agency's postmarketing periodic safety reporting regulations (see table 10 and section III.E.1 of this document). A PSUR would essentially be consistent with the format and content of the periodic safety report described in the ICH E2C guidance (see section III.E.2 of this document), and an IPSR would represent an abbreviated form of a PSUR (see section III.E.3 of this document). Applicants with drugs and licensed biological products approved prior to January 1, 1995, would have the option to submit either a TPSR or PSUR to FDA, whereas applicants with products approved on or after January 1, 1995, would be required to submit a PSUR (see tables 7 and 9 and section III.E.5.a of this document). FDA is proposing to require submission of periodic safety reports in a

PSUR format for products approved on or after January 1, 1995, to be consistent with the ICH E2C guidance. FDA is not proposing to require submission of PSUR's for products approved prior to January 1, 1995, because the agency recognizes that the most significant new safety information on a product is usually acquired in the first few years after it has been on the market. It is not necessary for applicants to reformat periodic safety reports for products approved prior to January 1, 1995. In addition, in some cases, it will be sufficient for FDA to review an abbreviated form of the PSUR (i.e., at 7.5 and 12.5 years after U.S. approval of a product). For these cases, the agency is proposing to require submission of an IPSR instead of a PSUR (see tables 7 and 9 and sections III.E.3 and III.E.5.a of this document).

III.E.1. Traditional Periodic Safety Reports (TPSR's)

Current regulations (§§ 314.80(c)(2)(ii)(a) through (c)(2(ii)(c) and 600.80(c)(2)(ii)(A) through (c)(2)(ii)(C)) require the submission of postmarketing periodic adverse drug experience reports that contain:

- A narrative summary and analysis of the information in the report and an analysis of the 15-day postmarketing Alert reports submitted during the reporting period (all 15-day Alert reports being appropriately referenced by the applicant's patient

identification number, adverse reaction term(s), and date of submission to FDA);

- An FDA Form 3500A describing each adverse drug experience not previously reported (with an index consisting of a line listing of the applicant's patient identification number and adverse reaction term(s)); and
- A history of actions taken since the last periodic report.

Proposed §§ 314.80(c)(3)(i) and 600.80(c)(3)(i) would amend these regulations by replacing the term "periodic adverse drug experience report" with the term "traditional periodic safety report (TPSR)." FDA is proposing this revision to differentiate the existing postmarketing periodic safety report from the proposed new postmarketing periodic safety reports (i.e., PSUR's and IPSR's, see sections III.E.2 and III.E.3 of this document).

III.E.1.a. Narrative summary and analysis of individual case safety reports. Proposed §§ 314.80(c)(3)(i)(A) and 600.80(c)(3)(i)(A) would amend §§ 314.80(c)(2)(ii)(a) and 600.80(c)(2)(ii)(A) by providing paragraph headings and reorganizing and revising these paragraphs. Proposed §§ 314.80(c)(3)(i)(A)(1) and 600.80(c)(3)(i)(A)(1) would amend §§ 314.80(c)(2)(ii)(a) and 600.80(c)(2)(ii)(A) by replacing the phrase "the information in the report" with the following:

> serious, expected SADR's and nonserious, unexpected SADR's occurring in the United States that were

submitted to the applicant during the reporting period from all spontaneous sources (i.e., health care professionals and other individuals) (with an index consisting of a line listing of the applicant's manufacturer report number and SADR term(s))

The narrative summary and analysis would include spontaneous reports submitted to the applicant by health care professionals and other individuals (e.g., consumers).

Proposed §§ 314.80(c)(3)(i)(A)(2) and 600.80(c)(3)(i)(A)(2) would amend §§ 314.80(c)(2)(ii)(a) and 600.80(c)(2)(ii)(A) by replacing the phrase "an analysis of the 15-day Alert reports * * * date of submission to FDA)" with the phrase:

> An analysis of the expedited reports submitted during the reporting period under paragraphs (c)(2)(i) through (c)(2)(vii) of this section (all expedited reports must be appropriately referenced by the applicant's manufacturer report number, SADR term(s), if appropriate, and date of submission to FDA),

Current regulations at §§ 314.80(c)(2)(iii) and 600.80(c)(2)(iii) state that periodic reporting, except for information regarding 15-day Alert reports, does not apply to adverse drug experience information obtained from postmarketing studies (whether or not conducted under an IND), from reports in

the scientific literature, and from foreign marketing experience. FDA is proposing to remove this statement because proposed §§ 314.80(c)(3)(i)(A)(1) and 600.80(c)(3)(i)(A)(1) specifies the type of information that FDA would require in a TPSR.

III.E.1.b. Individual case safety reports. FDA is also proposing to remove §§ 314.80(c)(2)(ii)(b) and 600.80(c)(2)(ii)(B) from these regulations. FDA is proposing this change because the requirement to submit individual case safety reports to FDA on FDA Form 3500A (VAERS form for vaccines) would be required in a separate submission on a semiannual basis (see section III.E.4 of this document).

III.E.1.c. Increased frequency reports. Proposed §§ 314.80(c)(3)(i)(A)(3) and 600.80(c)(3)(i)(A)(3) would amend §§ 314.80(c)(2)(ii)(a) and 600.80(c)(2)(ii)(A) to require applicants to include in TPSR's a discussion of any increased reporting frequency of serious, expected SADR's, including comments on whether it is believed that the data reflect a meaningful change in SADR occurrence. Even though the agency has revoked the requirement to submit increased frequency reports in an expedited manner (62 FR 34166), FDA is interested in reviewing periodically information on increased frequencies of serious, expected SADR's and is proposing that this type of information be submitted to the agency in TPSR's.

The proposed rule would also require that this section of the TPSR include an assessment of whether it is believed that the frequency of lack of efficacy reports, obtained or otherwise received during the reporting period, is greater than would be predicted by the premarketing clinical trials for the drug or biological product. This assessment would be provided whether a serious SADR, nonserious SADR, or no SADR occurs as a result of a lack of efficacy of the product.

III.E.1.d. Safety-related actions to be taken. Proposed §§ 314.80(c)(3)(i)(A)(4) and 600.80(c)(3)(i)(A)(4) would require applicants to include in TPSR's the applicant's conclusion as to what, if any, safety-related actions should be taken based on the analysis of the safety data in the TPSR (e.g., labeling changes, studies initiated). FDA is proposing this amendment to highlight safety-related actions that may be necessary.

III.E.1.e. Summary tabulations. Proposed §§ 314.80(c)(3)(i)(B), and 600.80(c)(3)(i)(B) would require that a new section of summary tabulations (i.e., lists of all SADR terms and counts of occurrences) be included in TPSR's for all serious, expected SADR's; nonserious, unexpected SADR's; nonserious, expected SADR's; and expected SADR's with unknown outcome occurring in the United States that are submitted to the applicant during the reporting period from all spontaneous sources (i.e., health care professionals and other individuals).

These tabulations would include SADR's that were previously submitted to FDA in an expedited report (i.e., serious, unexpected SADR's, unexpected SADR's with unknown outcome, and always expedited reports) and reports of SADR's not previously submitted to FDA by applicants (e.g., reports submitted to applicants by FDA; reports obtained from FDA from freedom of information requests at the discretion of applicants; reports from class action lawsuits). The proposed rule would require that cumulative data be provided for SADR's that are determined to be both serious and unexpected (i.e., all cases reported to date). These summary tabulations would be presented by body system or standard organ system classification scheme (e.g., cardiovascular, central nervous system, endocrine, renal). The proposed rule would also require summary tabulations for all domestic reports of actual medication errors (i.e., serious SADR's, nonserious SADR's, no SADR's) and potential medication errors (i.e., number of reports for specific errors) that were previously submitted to the agency as an expedited report.

In the guidance of 1992, FDA advises applicants to include in their postmarketing periodic safety reports a listing by body system of all adverse drug experience terms and counts of occurrences submitted during the reporting period. FDA is now proposing to clarify and codify this expectation.

III.E.1.f. History of safety-related actions taken. Proposed §§ 314.80(c)(3)(i)(C), and 600.80(c)(3)(i)(C) would amend §§ 314.80(c)(2)(ii)(c) and 600.80(c)(2)(ii)(C) by adding the phrase "safety-related" before the word "actions" and by removing the phrase "because of adverse drug experiences." FDA is proposing these changes because actions may be taken for safety-related reasons other than SADR's. The proposed rule would also amend these regulations by adding the phrase "periodic safety" before the word "report" for clarification.

III.E.1.g. Location of safety records. Proposed §§ 314.80(c)(3)(i)(D) and 600.80(c)(3)(i)(D) would require another new section in TPSR's that would contain a list of the current address(es) where all safety reports and other safety-related records for the drug product or licensed biological product are maintained. FDA is proposing to require a list of these addresses to provide rapid access to safety-related records for FDA inspections and for requests by FDA for additional information concerning safety issues.

III.E.1.h. Contact person. Proposed §§ 314.80(c)(3)(i)(E) and 600.80(c)(3)(i)(E) would require another new section in TPSR's that would contain the name and telephone number of the licensed physician or licensed physicians responsible for the content and medical interpretation of the data and information contained within the TPSR. The fax number and e-mail address for the licensed physician would also be included, if available.

This proposal would provide the agency with someone to contact with any questions that may arise during review of a TPSR. FDA is proposing that the contact persons be licensed physicians because of their crucial knowledge of the medical significance of the information provided in a TPSR.

Table 10 highlights the differences in content between the currently required postmarketing periodic adverse drug experience reports and proposed TPSR's.

Table 10.--Differences Between the Current Requirement for the Content of Postmarketing Periodic Adverse Drug Experience Reports and the Proposed Content of TPSR's.

Content of Periodic Adverse Drug Experience Report	Proposed Revisions to Content of Periodic Adverse Drug Experience Report (Proposed TPSR's)
Narrative summary and analysis of the information contained in the report.	Excludes nonserious expected SADR's.
	Includes discussion of increased frequency of serious expected SADR's and lack of efficacy reports.
	Includes applicant's recommendations for safety-related actions to be taken.
Analysis of expedited reports submitted to FDA during the reporting interval.	Not revised
FDA Form 3500A (VAERS form for vaccines) for each adverse drug experience not submitted to FDA as an expedited report.	Revoked requirement[1]
Index consisting of a line listing of the applicant's patient identification number and adverse reaction term(s).	Not revised
History of actions taken since the last report because of adverse drug experiences.	Not revised
----------	Codified requirement to submit summary tabulations.[2]
----------	New section added for location of safety records.
----------	New section added for contact information for licensed physician responsible for information in TPSR.

[1] Individual case safety reports would be submitted to FDA separately on a semiannual basis (see section III.E.4 of this document).

[2] Summary tabulations are currently requested (see the guidance of 1992) but not required for postmarketing periodic adverse drug experience reports.

III.E.2. Periodic Safety Update Reports (PSUR's)

Proposed §§ 314.80(c)(3)(ii) and 600.80(c)(3)(ii) would amend FDA's postmarketing periodic safety reporting regulations by adding a new type of postmarketing periodic safety report. This new report would be identified as a "periodic safety update report (PSUR)." The proposed content and format for the PSUR, as described below, are consistent with the ICH E2C guidance (62 FR 27470) and would enable applicants to submit a single core document (PSUR excluding appendices) to regulatory authorities worldwide. All dosage forms, formulations, and indications for which applicants hold an approved application (i.e., NDA, ANDA, BLA) for a given drug substance or licensed biological product should usually be covered in one PSUR. The PSUR may include separate presentations of these data as well as other data (e.g., populations) if such presentations would facilitate review of the PSUR. FDA is proposing that a PSUR contain the following information:

III.E.2.a. Title page, table of contents, and introduction. The title page would include, at a minimum, the following information:

- Name and international birth date of the drug substance or licensed biological product that is the subject of the PSUR,

- Various dosage forms and formulations of the drug substance or biological product covered by the PSUR,
- Name and address of the applicant,
- Reporting period covered by the PSUR, and
- Date of the PSUR.

The introduction would provide a brief description of how this PSUR relates to previous reports and circumstances, would reference relevant drug products, drug substances, or biological products reported in other periodic safety reports (e.g., a combination product reported in a separate PSUR), and would indicate any data duplication with other PSUR's. If two or more companies co-market the same drug substance or licensed biological product, the safety reporting responsibilities of each of the companies should be specified clearly in the introduction.

III.E.2.b. Worldwide marketing status. This section of the PSUR would contain a table of the chronological history of the worldwide marketing status of the drug or biological product(s) covered by the PSUR from the date the product was first approved (i.e., the international birth date) through its current status (i.e., cumulative information). The table would include:

- Dates of drug or biological product approval and renewal,
- Safety-related restrictions on product use,
- Indications for use and special populations covered by the drug or biological product approval,

- Lack of approval of the drug substance or biological product in any dosage form or for any indication for use by any regulatory authority(ies),
- Withdrawal of a pending drug or biological product marketing application by the applicant for safety- or efficacy-related reasons,
- Dates of market launches, and
- Trade name(s).

Drug or biological products that are approved in a country for a particular indication, population, or dosage form that may result in different types of patient exposure in that country should be identified, particularly if there are meaningful differences in the safety information reported in the PSUR due to the difference in patient exposures.

III.E.2.c. Actions taken for safety reasons. This section of the PSUR would contain details on regulatory authority-initiated (e.g., FDA) and/or applicant-initiated actions related to safety that were taken during the period covered by the PSUR and between the data lock point and PSUR submission (i.e., "late-breaking" safety concerns) including:

- Withdrawal or suspension of product approval or indication for use approval,
- Failure to obtain a marketing authorization renewal or to obtain an approval for a new indication for use,

- Restrictions on distribution (e.g., products recalled for safety reasons),
- Clinical trial suspension,
- Dosage modification,
- Changes in target population or indications, and
- Formulation changes.

This section of the PSUR would also contain a narrative identifying the safety-related reasons that led to these actions with relevant documentation appended when appropriate. Any communication with health care professionals (e.g., Dear Doctor letters) resulting from such actions would also be described with copies appended.

III.E.2.d. Changes to CCSI. This section of the PSUR would describe changes to the CCSI (e.g., new contraindications, precautions, warnings, SADR's, or interactions) made during the period covered by the PSUR. A copy of any modified section of the CCSI would be included. Applicants would use the CCSI in effect at the beginning of the reporting period for the PSUR. The revised CCSI would be used as the reference document for the next reporting period.

III.E.2.e. Worldwide patient exposure. This section of the PSUR would include, for the reporting period, an estimate of the worldwide patient exposure to the drug or biological product(s) covered by the PSUR (i.e., number of patients, average or median

dose received, and average or median length of treatment). In many cases, accurate patient exposure data for a reporting period may be difficult to obtain. However, applicants should exercise due diligence to obtain an estimate of this exposure. The method used to estimate patient exposure would always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions would be provided. If patient exposure is impossible to estimate, other measures of exposure, such as patient-days, number of prescriptions, or number of dosage units, could be used. If these or other more precise measures are not available and an adequate explanation for the lack of such information is provided, bulk sales could be used with estimates of what such numbers may mean in terms of patient exposure.

When possible, data broken down by gender and age (especially pediatric versus adult) would be provided. Data for the pediatric population would be reported, if possible, by age group (e.g., neonates, infants, children, adolescents). If these data are not available, an explanation for the lack of such information would be included. In addition, when a pattern of reports indicates a potential problem, details by country (with locally recommended dosage regimens) or other segmentation (e.g., indication, dosage form) would also be presented.

Patient exposure for clinical studies should also be provided when SADR data from these types of studies are included in the PSUR. For ongoing or blinded clinical studies, an estimate of patient exposure should be provided.

III.E.2.f. Individual case safety reports.

III.E.2.f.i. Line listings. Individual line listings of various data points from individual case safety reports are included as part of the format for international PSUR's agreed to by ICH (ICH E2C guidance, 62 FR 27470 at 27473 and 27474). FDA will not require submission of such line listings in PSUR's because, instead, the agency is proposing to require a separate semiannual submission of certain individual case safety reports on FDA Form 3500A (VAERS form for vaccines, CIOMS I form, if desired, for foreign SADR's) (see section III.E.4 of this document). However, FDA is willing to accept line listings in PSUR's as described in the ICH E2C guidance if applicants wish to include them. FDA believes that such an approach will help further the goal of harmonizing PSUR generation, formatting, and submission globally.

III.E.2.f.ii. Summary tabulations. This section of the PSUR would consist of summary tabulations of individual case safety reports (e.g., serious unlisted SADR's, serious listed SADR's, nonserious unlisted SADR's, nonserious listed SADR's) for

the following SADR's obtained or otherwise received during the reporting period:

- All serious and nonserious SADR's from spontaneous sources that were submitted to applicants by a health care professional,
- All serious SADR's from studies, individual patient IND's, or, in foreign countries, from named-patient "compassionate" use,
- All serious SADR's and nonserious unlisted SADR's from the scientific literature,
- All serious SADR's from regulatory authorities, and
- Serious SADR's from other sources such as reports created by poison control centers and epidemiological data bases.

These summary tabulations would be made up of lists by body system or standard organ system classification scheme (e.g., cardiovascular, central nervous system, endocrine, renal) of all SADR terms and counts of occurrences. For SADR's that are determined to be both serious and unlisted, cumulative data would also be provided (i.e., all cases reported to date). Applicants may provide information for this section of the PSUR in a narrative rather than a summary tabulation if the number of cases is small or the information is inadequate for any of the tabulations.

As noted previously, FDA would consider "study" information to include the following: safety information from company-sponsored patient support programs, disease management programs, patient registries, including pregnancy registries, or any organized data collection scheme (see section III.A.7 of this document). FDA is proposing to include summary tabulations for serious listed SADR's from study information in PSUR's to be consistent with the ICH E2C guidance (62 FR 27470 at 27474), even though the agency indicated in the clarification guidance of 1997 that only serious and unexpected adverse drug experiences for which there is a reasonable possibility that the drug or biological product caused the adverse drug experience should be reported to FDA from studies.

This section of the PSUR would also contain a brief discussion of the individual case data in the summary tabulations (e.g., discussion of medical significance or mechanism). This section of the PSUR should be used to comment on specific cases rather than to provide an overall assessment of the cases.

III.E.2.g. Safety studies. This section of the PSUR would contain a discussion (not just a listing of the studies) of nonclinical, clinical, and epidemiological studies concerning important safety information including:

- All applicant-sponsored studies newly analyzed during the reporting period;

- New studies specifically planned, initiated, or continuing during the reporting period that examine a safety issue, whether actual or hypothetical; and
- Published safety studies in the scientific and medical literature, including relevant published abstracts from meetings (provide citations for all reports from the literature).

As noted previously, FDA would consider "study" information to include the following: safety information from company-sponsored patient support programs, disease management programs, patient registries, including pregnancy registries, or any organized data collection scheme (see section III.A.7 of this document).

The study design and results of newly analyzed studies should be clearly and concisely presented with attention to the usual standards of data analysis and description that are applied to nonclinical and clinical study reports. Copies of full reports for these studies should be appended only if new safety issues are raised or confirmed. FDA may request copies of other studies, if necessary.

For new or ongoing studies, the objective, starting date, projected completion date, number of subjects (planned and enrolled), and protocol abstract for each study should be provided. When possible and relevant, interim results of ongoing studies should be presented.

III.E.2.h. Other information. This section of the PSUR would contain a discussion of medically relevant lack of efficacy reports (e.g., might represent a significant hazard to the treated population) for a product(s) used to treat serious or life-threatening diseases, or any important new information received after the data lock point (e.g., significant new cases).

III.E.2.i. Overall safety evaluation. This section of the PSUR would contain a concise, yet comprehensive, analysis of all of the safety information provided in the PSUR, including new information provided under the section entitled "Other Information." In addition, the section would include an assessment by applicants of the significance of the data collected during the reporting period, as well as from the perspective of cumulative experience. Applicants would highlight any new information on:

- Serious, unlisted SADR's;
- Increased reporting frequencies of listed SADR's, including comments on whether it is believed that the data reflect a meaningful change in SADR occurrence;
- A change in characteristics of listed SADR's (e.g., severity, outcome, target population); and
- Nonserious, unlisted SADR's.

As part of the overall safety evaluation, applicants would also explicitly address any new safety issue including but not limited to the following:

- Drug interactions;
- Experience with overdose, whether deliberate or accidental, and its treatment;
- Drug abuse or intentional misuse;
- Positive or negative experiences during pregnancy or lactation;
- Effects with long-term treatment; and
- Experience in special patient groups (e.g., pediatric population evaluated, if possible, by age group; geriatric; organ impaired).

Applicants would note a lack of significant new information for any of these categories.

III.E.2.j. Conclusion. This section of the PSUR would indicate new safety information that is not in accord with previous cumulative experience and with the CCSI in use at the beginning of the reporting period (e.g., new evidence that strengthens a possible causal relationship between the drug or biological product and an SADR, such as positive rechallenge, an epidemiological association, or new laboratory studies). This section of the PSUR would also specify and justify any action recommended or initiated, including changes in the CCSI.

III.E.2.k. Appendices. This section of the PSUR would include the following information as appendices:

III.E.2.k.i. Company core data sheet. A copy of the company core data sheet covered by the PSUR (i.e., in effect at the beginning of the period covered by the PSUR) would be provided. The company core data sheet would be numbered and dated and include the date of last revision. In addition, a copy of the company core data sheet for the next reporting period would be provided.

III.E.2.k.ii. U.S. labeling. A copy of the current approved U.S. labeling would be provided. Any safety information that is included in the CCSI but not in the U.S. labeling would be identified and an explanation for the discrepancy provided. Any safety-related changes or proposed changes to the U.S. labeling made during the reporting period would be described, including the supplement numbers and dates of submission for the supplements. Any suggested change or changes in the U.S. labeling that should be considered based on the safety analysis in the PSUR would also be described. (If appropriate, a supplemental application would be filed with FDA concerning those changes as prescribed under §§ 314.70 or 601.12.)

III.E.2.k.iii. Spontaneous reports submitted to the applicant by an individual other than a health care professional. This appendix would contain summary tabulations (e.g., serious

unlisted SADR's, serious listed SADR's, nonserious unlisted SADR's, nonserious listed SADR's) for all spontaneously reported serious SADR's, whether domestic or foreign, and all spontaneously reported nonserious SADR's occurring in the United States, obtained or otherwise received during the reporting period by the applicant from an individual other than a health care professional (e.g., SADR reports from consumers). These summary tabulations would consist of lists by body system or by standard organ system classification scheme (e.g., cardiovascular, central nervous system, endocrine, renal) of all SADR terms and counts of occurrences. For those SADR's that are determined to be both serious and unlisted, cumulative data (i.e., all cases reported to date by individuals other than a health care professional) would also be provided. The impact of these spontaneous reports on the overall safety evaluation would be discussed briefly. FDA may require applicants to submit to the agency, when appropriate, SADR reports (e.g., FDA Form 3500A's), within 5 calendar days after receipt of the request, for any or all of the SADR's contained within this appendix (see section III.H of this document).

III.E.2.k.iv. SADR's with unknown outcome. This appendix would contain summary tabulations for unlisted and listed SADR's with unknown outcome from all spontaneous sources (i.e., health care professionals and other individuals), obtained or otherwise

received by the applicant during the reporting period. These summary tabulations would consist of lists by body system or by standard organ system classification scheme of all SADR terms and counts of occurrences. The impact of these spontaneous reports on the overall safety evaluation would be discussed briefly. FDA may require applicants to submit to the agency, when appropriate, individual case safety reports (e.g., FDA Form 3500A's), within 5 calendar days after receipt of the request, for any or all of the listed SADR's with unknown outcome contained within this appendix (see section III.H of this document).

III.E.2.k.v. Class action lawsuits. This appendix would contain summary tabulations (e.g., serious unlisted SADR's, serious listed SADR's, nonserious unlisted SADR's, nonserious listed SADR's) for all SADR's obtained or otherwise received during the reporting period by the applicant from class action lawsuits. These summary tabulations would consist of lists by body system or by standard organ system classification scheme of all SADR terms and counts of occurrences. For SADR's that are both serious and unlisted, cumulative data would also be provided. The impact of these reports on the overall safety evaluation would be discussed briefly. FDA may require applicants to submit to the agency, when appropriate, individual case safety reports (e.g., FDA Form 3500A's), within 5 calendar days after receipt of the request, for any or all of the SADR's

contained within this appendix (see section III.H of this document).

III.E.2.k.vi. Lack of efficacy reports. This appendix would contain an assessment of whether it is believed that the frequency of lack of efficacy reports, obtained or otherwise received during the reporting period, is greater than would be predicted by the premarketing clinical trials for the drug or biological product. This assessment would be provided whether a serious SADR, nonserious SADR, or no SADR results from a lack of efficacy of the product.

III.E.2.k.vii. Information on resistance to antimicrobial drug products. This appendix would contain information, received or otherwise obtained by the applicant, on resistance to antimicrobial drug products intended to treat infectious diseases. Information would include:

- Changes in U.S. microbial in vitro susceptibility,
- The relationship of changes in U.S. microbial in vitro susceptibility and clinical outcomes,
- Therapeutic failure that may possibly be due to resistance to the antimicrobial drug product, and
- Whether the U.S. labeling should be revised because of the information on antimicrobial resistance learned during the period covered by the report.

III.E.2.k.viii. Medication errors. This appendix would contain summary tabulations for all domestic reports of medication errors submitted during the reporting period as an expedited report. For actual medication errors, summary tabulations would be provided for serious SADR's, nonserious SADR's, and no SADR's. For serious SADR's, cumulative data (i.e., all cases reported to date) would also be provided. For potential medication errors, the number of reports for specific errors would be provided. If an SADR occurs, the summary tabulations would consist of lists by body system or by standard organ system classification scheme of all SADR terms and counts of occurrences. The impact of these reports on the overall safety evaluation would be discussed briefly.

III.E.2.k.ix. U.S. patient exposure. This appendix would contain, for the reporting period, an estimate of the U.S. patient exposure to the drug product(s) or biological product(s) covered by the PSUR (i.e., number of patients, average or median dose received, and average or median length of treatment). The method used to estimate patient exposure would always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions would be provided. If patient exposure is impossible to estimate, other measures of exposure, such as patient-days, number of prescriptions, or number of dosage units, may be used.

If these or other more precise measures are not available and an adequate explanation for the lack of such information is provided, bulk sales may be used.

III.E.2.k.x. Location of safety records. This appendix would contain a list of the current address(es) where all safety reports and other safety-related records for the drug product or licensed biological product are maintained. The list of addresses would provide rapid access to safety-related records for FDA inspections and for requests by FDA for additional information concerning safety issues.

III.E.2.k.xi. Contact person. The name and telephone number of the licensed physician or licensed physicians responsible for the content and medical interpretation of the data and information contained within the PSUR would be provided. The fax number and e-mail address of the licensed physician would also be included, if available. This proposal would provide the agency with someone to contact with any questions that may arise during review of a PSUR. FDA is proposing that the contact persons be licensed physicians because of their crucial knowledge of the medical significance of the information provided in a PSUR.

The PSUR excluding appendices, as proposed in this rule, would represent a harmonized core document for worldwide

postmarketing periodic safety reporting for marketed drugs and licensed biological products.

III.E.3. Interim Periodic Safety Reports (IPSR's)

Proposed §§ 314.80(c)(3)(iii) and 600.80(c)(3)(iii) would amend FDA's postmarketing periodic safety reporting regulations by adding another new type of postmarketing periodic safety report. FDA is proposing that this new report be identified as an "interim periodic safety report (IPSR)." An IPSR would contain the same information as a PSUR, except that the following information would not be provided:

- Summary tabulations for individual case safety reports, obtained or otherwise received during the reporting period and brief discussion of the data concerning these reports (see section III.E.2.f.ii of this document),
- Any important new information received after the data lock point (e.g., significant new cases) (see section III.E.2.h of this document),
- Summary tabulations for spontaneous reports of SADR's submitted to the applicant by an individual other than a health care professional (see section III.E.2.k.iii of this document),
- Summary tabulations for spontaneous reports of SADR's with unknown outcome submitted to the applicant by health

care professionals and other individuals (see section III.E.2.k.iv of this document),

- Summary tabulations for reports of SADR's from class action lawsuits (see section III.E.2.k.v of this document),
- Summary tabulations of domestic reports of medication errors (see section III.E.2.k.viii of this document).

The IPSR would provide the agency with an overview of the safety profile of a drug product containing a drug substance or biological product without requiring summary information on individual case safety reports.

III.E.4. Semiannual Submission of Individual Case Safety Reports

Currently, postmarketing periodic safety reporting regulations (§§ 314.80(c)(2)(ii)(b) and 600.80(c)(2)(ii)(B)) require applicants to submit to FDA in periodic adverse drug experience reports an FDA Form 3500A (VAERS form for vaccines) for each spontaneously reported adverse drug experience occurring in the United States that has not been submitted to the agency as an expedited report. FDA is proposing to remove this requirement (see section III.E.1.b of this document). Instead, under proposed §§ 314.80(c)(3)(v) and 600.80(c)(3)(v), the agency would require applicants to submit semiannually a separate report to FDA consisting of a compilation of FDA Form 3500A's (VAERS forms for vaccines, CIOMS I forms, if desired, for foreign SADR's) for certain spontaneously reported individual case safety reports as

described below. This report would be identified as "Individual Case Safety Reports--Semiannual Submission."

The semiannual submission from applicants that submit TPSR's for a drug or licensed biological product would include an individual case safety report for each serious, expected SADR, whether domestic or foreign, and each nonserious, unexpected SADR occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources (i.e., health care professionals and other individuals). The semiannual submission for vaccines would also include an individual case safety report for each nonserious, expected SADR and each expected SADR with unknown outcome occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources.

The semiannual submission from applicants that submit PSUR's for a drug product containing a drug substance or licensed biological product would include an individual case safety report for each serious, listed SADR, whether domestic or foreign, and each nonserious, unlisted SADR occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources. The semiannual submission for vaccines would also include an individual case safety report for each nonserious, listed SADR and each listed SADR with unknown outcome occurring in the United States that is submitted to the

applicant during the reporting period from all spontaneous sources. The semiannual submission should not include individual case safety reports for serious, listed SADR's that were previously submitted to FDA as a serious, unexpected SADR in an expedited report (i.e., the agency does not want to receive duplicative reports for the same SADR).

The current approved U.S. labeling would be used as the reference document to determine whether an SADR is unexpected or expected, and the CCSI would be used to determine whether an SADR is unlisted or listed.

As described previously, a minimum data set would be required for all individual case safety reports of an SADR (see section III.C.5 of this document). In addition, a full data set would be required for reports of serious, expected SADR's and serious, listed SADR's. If a full data set is not available for these SADR reports, the information required under proposed §§ 314.80(c)(1)(iv) and 600.80(c)(1)(iv) would be provided. For nonserious SADR's with a minimum data set, the proposal would require that all safety information received or otherwise obtained be submitted. The proposal would not require that information in addition to the minimum data set be acquired. Thus, followup would not be required for nonserious SADR's that contain a minimum data set.

Followup information on SADR's submitted in an individual case safety report--semiannual submission may be submitted in the next individual case safety report--semiannual submission, unless such information changes the classification of the SADR to a serious, unexpected SADR. In these cases, the followup information would be submitted to FDA as an expedited 15-day followup report (see section III.D.6 of this document).

Applicants should not submit any reports of lack of efficacy in an individual case safety report--semiannual submission. As noted previously, applicants would be required to submit to FDA in an expedited manner information regarding certain lack of efficacy reports for the product (i.e., expedited reports of information sufficient to consider product administration changes) and also to provide in postmarketing periodic safety reports an assessment of all lack of efficacy reports for the product as compared to premarketing clinical trials for the product (see section III.C.7 of this document).

Applicants should not submit SADR's from class action lawsuits to FDA in an individual case safety report--semiannual submission. The agency believes, as noted previously, that SADR's from class action lawsuits would be submitted to FDA from other sources (e.g., spontaneous report) prior to initiation of the class action lawsuit (see section III.D.11 of this document). Summary tabulations of these SADR's would be required to be

included in postmarketing periodic safety reports (see sections III.E.1.e and III.E.2.k.v of this document).

Applicants should not submit reports of medication errors in an individual case safety report--semiannual submission. These reports would be submitted, as previously noted, as an expedited report (see section III.D.5 of this document).

III.E.5. Reporting Requirements

III.E.5.a. Reporting intervals. Current regulations (§§ 314.80(c)(2)(i) and 600.80(c)(2)(i)) require the submission of postmarketing periodic safety reports at quarterly intervals for 3 years from the date of approval of the application in the United States and then annually thereafter. Quarterly safety reports must be submitted within 30 days of the close of the quarter (the first quarter beginning on the date of U.S. approval of the application); annual safety reports must be submitted within 60 days of the anniversary date of U.S. approval of the application.

Products approved before January 1, 1995. Proposed §§ 314.80(c)(3)(i) and 600.80(c)(3)(i) would require applicants holding an NDA, ANDA, or BLA that was approved for initial marketing of a drug product containing a drug substance or licensed biological product before January 1, 1995, to submit either a TPSR or a PSUR every 5 years after U.S. approval of the application. The proposed rule would also require these

applicants to submit a TPSR or an IPSR 7.5 years and 12.5 years after U.S. approval of the application. Under proposed §§ 314.80(c)(3)(iii) and 600.80(c)(3)(iii), the reporting period for an IPSR would cover the period between the last PSUR or TPSR and the data lock point for the IPSR (e.g., between years 5 and 7.5 for an IPSR with a data lock point at 7.5 years after U.S. approval of the application).

Products approved on or after January 1, 1995. Under proposed §§ 314.80(c)(3)(ii) and 600.80(c)(3)(ii), applicants holding an NDA, ANDA, or BLA that was approved for initial marketing of a drug product containing a drug substance or licensed biological product on or after January 1, 1995, would be required to submit a PSUR to FDA with the following schedule:

- Semiannually (i.e., every 6 months) for 2 years after U.S. approval of the application,
- Annually for the next 3 years, and then
- Every 5 years thereafter.

The proposed rule would also require applicants to submit an IPSR 7.5 years and 12.5 years after U.S. approval of the application.

Products with approved pediatric use supplements. Proposed §§ 314.80(c)(3)(iv) and 600.80(c)(3)(iv) would require applicants holding an approved pediatric use supplement to an approved application (i.e., a supplement for use of the human drug or

biological product in the pediatric population) to submit a PSUR to FDA with the following schedule:

- Semiannually (i.e., every 6 months) for 2 years after U.S. approval of the supplement,
- Annually for the next 3 years, and
- Then every 5 years thereafter.

The proposed rule would also require these applicants to submit an IPSR 7.5 years and 12.5 years after U.S. approval of the supplement. These applicants would be required to submit PSUR's and IPSR's to FDA even if the pediatric use supplement or original application was approved prior to January 1, 1995. FDA is proposing this action to harmonize acquisition of new safety information regarding pediatric populations for timely review by the agency.

All products. Under proposed §§ 314.80(c)(3)(v) and 600.80(c)(3)(v), applicants holding an NDA, ANDA, or BLA would be required to submit an individual case safety reports--semiannual submission to FDA every 6 months after U.S. approval of an application. The 6-month interval for these reports would coincide with the reporting interval (6-month or multiples of 6 months) for TPSR's, PSUR's or IPSR's.

Alternative reporting frequency. Proposed §§ 314.80(c) and 600.80(c) would provide that, when appropriate, FDA may require in writing that applicants submit postmarketing periodic safety

reports at time intervals other than prescribed by the regulations (see section III.C.4 of this document). Usually such variations would occur if new safety concerns arose requiring more timely reporting (e.g., approval of a new indication or dosage form for the product, approval for use of the product in a new population, new safety issues in individual case safety reports submitted to FDA for the product). When anticipated, FDA would state the revised reporting interval in the approval letter for the new indication, new population, or new dosage form. In other cases, such revisions to the reporting interval would be conveyed to applicants in a written letter from the director of the responsible review division in FDA with an explanation of why such a new reporting time interval is required.

III.E.5.b. Submission date. Proposed §§ 314.80(c)(3) and 600.80(c)(3) would require that the data lock point for postmarketing periodic safety reports be the month and day of the international birth date of the drug product (proposed §§ 314.80(c)(3)(i) and 314.80(c)(3)(v)), drug substance (proposed §§ 314.80(c)(3)(ii), 314.80(c)(3)(iii), and 314.80(c)(3)(iv)) or licensed biological product (proposed §§ 600.80(c)(3)(i) through 600.80(c)(3)(v)) or any other month and day agreed on by the applicant and FDA. For example, applicants that are submitting PSUR's on an every 5 year basis may, in agreement with FDA, change the data lock point to facilitate international reporting

so long as there is never a time period of greater than 5 years in which FDA has not received a PSUR. Or, the applicant and FDA may agree to change the data lock point to the month and day of U.S. approval of the application if this date would result in better use of the applicant's resources.

Proposed §§ 314.80(c)(3) and 600.80(c)(3) would require that all postmarketing periodic safety reports be submitted to FDA within 60 calendar days after the data lock point for the report. As noted previously, the data lock point (i.e., month and day) for postmarketing periodic safety reports would be based on the month and day of the international birth date for the product and the frequency for submission of these reports would be based on the product's date (i.e., year) of U.S. approval (see section III.A.10 of this document).

III.E.5.c. Cover letter. Proposed §§ 314.80(c)(3) and 600.80(c)(3) would require that applicants include a cover letter with all postmarketing periodic safety reports (i.e., TPSR's, PSUR's, IPSR's, individual case safety reports--semiannual submission's). This cover letter would contain a list of the NDA and/or ANDA numbers for the human drug products or BLA numbers for the human biological products covered by the report.

III.E.5.d. International birth date for combination products. Proposed §§ 314.80(c)(3) and 600.80(c)(3) would also state that the international birth date for combination products

would be the international birth date of the human drug product containing the drug substance or licensed biological product that was most recently approved for marketing. For combination products that are also marketed individually, applicants may submit either a separate PSUR for the combination product or include information for the combination product as a separate presentation in the PSUR for one of the individual components.

III.F. Reporting Format

Current postmarketing safety reporting regulations at §§ 310.305(d)(1), 314.80(f)(1), and 600.80(f)(1) require persons subject to these requirements to submit an FDA Form 3500A (VAERS form for vaccines) for each report of an adverse drug experience. Foreign SADR's, including those associated with the use of vaccines, may be submitted on an FDA Form 3500A or, if preferred, on a CIOMS I form.

III.F.1. Forms versus Narrative Format

Proposed §§ 310.305(d)(1), 314.80(c)(4)(i), and 600.80(c)(4)(i) would amend the current postmarketing safety reporting format regulations by reorganizing these regulations and by adding new information. Proposed §§ 310.305(d)(1)(i) would prescribe, except as provided in the regulations, that:

> * * * the manufacturer must complete an FDA Form 3500A for each individual case safety report of an SADR. Reports based on

information about individual cases or case series in the scientific literature must be submitted on an FDA Form 3500A(s).

Proposed §§ 314.80(c)(4)(i)(A) and 600.80(c)(4)(i)(A) would prescribe the same requirements for submission of postmarketing individual case safety reports by applicants. Proposed § 600.80(c)(4)(i)(A) would also describe requirements for use of the VAERS form for vaccines. Proposed §§ 310.305(d)(1)(ii), 314.80(c)(4)(i)(B) and 600.80(c)(4)(i)(B) would prescribe that:

> Foreign SADR's may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form (foreign SAR's for vaccines, may be submitted either on a VAERS form, or, if preferred, on a CIOMS I form, for proposed § 600.80(c)(4)(i)(B)).

Proposed §§ 310.305(d)(1)(iii), 314.80(c)(4)(i)(C) and 600.80(c)(4)(i)(C) would prescribe that:

> Each domestic report of an actual or potential medication error must be submitted on an FDA Form 3500A (or, for vaccines, on a VAERS form for proposed § 600.80(c)(4)(i)(C)).

Proposed §§ 310.305(d)(1)(iv), 314.80(c)(4)(i)(D) and 600.80(c)(4)(i)(D) would prescribe that:

Reports of overall findings or data in the aggregate from published and unpublished in vitro, animal, epidemiological, or clinical studies must be submitted in a narrative format.

These proposed amendments would clarify the reporting format that would be required for individual case safety reports or other safety information (i.e., overall findings or data in the aggregate). Reports of actual and potential medication errors would be required to be submitted on an FDA Form 3500A (or VAERS form, as appropriate) because these reports describe an individual case even if an SADR does not occur or a patient is not identifiable. Reports of overall findings or data in the aggregate would be submitted in a narrative format rather than on FDA Form 3500A because FDA Form 3500A has been designed for reporting of data from an individual case.

III.F.2. Medical Dictionary for Regulatory Activities (MedDRA)

Most organizations currently use an international SADR terminology with a morbidity terminology to process regulatory data. In Europe, many users combine the World Health Organization's Adverse Reaction Terminology (WHOART) with the ninth revision of the International Classification of Diseases (ICD-9). In the United States, Coding Symbols for a Thesaurus of Adverse Reaction Terms with Clinical Modification of ICD-9 (ICD-

9-CM) is very commonly used, and Japan has developed its own version of these SADR terminologies, J-ART and MEDIS.

The established terminologies have been criticized for a number of reasons, including: Lack of specificity, limited data retrieval options, and an inability to effectively handle complex combinations of signs and symptoms (syndromes). Internationally, communication is impaired between regulatory authorities because of the delays and distortions caused by the translation of data from one terminology to another. Use of different terminologies also has significant consequences for pharmaceutical firms. Companies operating in more than one jurisdiction have had to adjust to subsidiaries or clinical research organizations that use different terminologies because of variations in data submission requirements.

ICH has developed an international medical terminology, MedDRA (the medical dictionary for regulatory activities), to support the computerization and transmission of information related to many aspects of the regulation of medical products (ICH M1). Use of a single medical terminology internationally would facilitate global communication of safety information for human drug and biological products.

Proposed §§ 310.305(d)(2), 314.80(c)(4)(ii), and 600.80(c)(4)(ii) would require that each SADR in an individual case safety report must be coded on the FDA Form 3500A, CIOMS I

Form, or VAERS Form using the appropriate "preferred term" in the latest version of MedDRA in use at the time the manufacturer or applicant becomes aware of the individual case safety report. FDA is proposing to require use of MedDRA to be consistent with ICH M1.

Proposed §§ 310.305(d)(2), 314.80(c)(4)(ii), and 600.80(c)(4)(ii) would also require that each individual case safety report of a medication error be coded both as a medication error and, if applicable, with the preferred term for any SADR's associated with the medication error. The proposal clarifies how actual and potential medication errors would be coded.

MedDRA must be licensed for a fee from an international MSSO. TRW was selected as the MSSO by ICH and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) through a contract process that involved bids from companies globally. FDA was involved in this process. The costs that would be imposed on industry to license MedDRA was a consideration in the selection of the MSSO.

Companies may license the latest version of MedDRA 3.3 by contacting TRW in Reston, VA, toll free number 877-258-8280 (703-345-7799 in Washington, DC area), FAX 703-345-7755, e-mail subscrib@meddramsso.com, Internet at www.meddramsso.com. Updated versions of MedDRA will be provided to subscribers as part of the annual licensing fee.

MedDRA is a hierarchical system composed of various levels of terminology (i.e., system organ class, high level group term, high level term, preferred term, lower level term). The agency is proposing to require use of the preferred term for reporting to FDA because each preferred term represents a unique medical concept accepted internationally, which will aid in the transmission and translation of reports from various parts of the world. The preferred term provides medically validated representations of colloquial terms, which will result in fewer misrepresentations and misunderstandings of colloquial reports from various parts of the world. The preferred term also provides medically validated representations of noncurrent terms in other previously widely used coding terminologies such as COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) and WHOART(?). Furthermore, the agency believes that the preferred term will be the accepted international standard for safety reporting because it is the level agreed to by ICH.

FDA believes that use of MedDRA, a standardized medical terminology, will be welcomed by most of industry. However, for some manufacturers and applicants (e.g., certain small businesses), use of MedDRA may result in a significant economic hardship. Applicants may request, under §§ 314.90 or 600.90, that FDA waive the requirement that each SADR in an individual case safety report be coded using MedDRA.

III.F.3. Single Form for Each Identifiable Patient

Current postmarketing safety reporting regulations, at §§ 310.305(d)(2), 314.80(f)(2), and 600.80(f)(2), state that each completed FDA Form 3500A, VAERS Form, or CIOMS I Form should refer only to an individual patient or a single attached publication. Under proposed §§ 310.305(d)(3), 314.80(c)(4)(iii), and 600.80(c)(4)(iii) FDA would remove the phrase "or a single attached publication" and replace the word "patient" with the word "case." This proposed amendment would clarify that an FDA Form 3500A should be completed for each identifiable patient described in a scientific article (e.g., six FDA Form 3500A's should be completed for an article describing six patients experiencing a particular SADR). This would also clarify that an FDA Form 3500A would be used to describe a potential medication error that does not involve a patient.

III.F.4. Contact Person

Proposed §§ 310.305(d)(4), 314.80(c)(4)(iv), and 600.80(c)(4)(iv) would state:

> Each completed FDA Form 3500A (VAERS Form for proposed § 600.80(c)(4)(iv)) or CIOMS I Form must include the name and telephone number (and fax number and e-mail address, if available) for the licensed physician responsible for the content and medical

interpretation of the data contained within the form (i.e., contact person for the company).

This information should be provided on FDA Form 3500A under the "contact office" box (box G1 on FDA Form 3500A). This proposed revision would provide FDA with a person to contact with any questions that may arise during review of an individual case safety report. The agency believes that the potential medical significance of these safety reports warrants oversight by a licensed physician.

III.F.5. Computer-Generated Facsimile of FDA Form 3500A or Vaccine Adverse Event Reporting System (VAERS) Form

Current §§ 310.305(d)(3), 314.80(f)(3), and 600.80(f)(3) state that instead of using an FDA Form 3500A, manufacturers and applicants may use a computer-generated FDA Form 3500A or other alternative format provided that the content of the alternative format is equivalent in all elements to those specified in FDA Form 3500A and the format is agreed to in advance by MedWatch: The FDA Medical Products Reporting Program. Alternative formats to the Center for Biologics Evaluation and Research's VAERS Form must be approved by the Division of Biostatistics and Epidemiology (§ 600.80(f)(3)).

Proposed §§ 310.305(d)(5), 314.80(c)(4)(v), and 600.80(c)(4)(v) would remove the use of alternative formats to

FDA Form 3500A and the requirement to obtain preapproval by MedWatch for use of a computer-generated FDA Form 3500A. Proposed § 600.80(c)(4)(v) would also remove the use of alternative formats to the VAERS Form and the requirement to obtain preapproval by the Division of Biostatistics and Epidemiology for use of a computer-generated VAERS Form. Instead, the proposed rule would permit manufacturers and applicants to use a computer-generated facsimile of FDA Form 3500A (or VAERS Form for vaccines) provided that it is readable, includes appropriate identifying information and contains all the elements (i.e., format, sections, blocks, titles, descriptors within blocks, text for disclaimer) of FDA Form 3500A (or the VAERS Form for vaccines) in the identical enumerated sequence of the form. The proposed rule would also permit use of a one-page FDA Form 3500A for individual case safety reports in which no suspect medical device is involved. For one-page reports, the box, Section D. Suspect Medical Device, on the front page of FDA Form 3500A would be replaced with the box, Section G. All Manufacturers, located on the back page of the form.

To be considered "readable" by FDA, the computer-generated facsimile should be formatted as follows.

- The facsimile should have at least a 1/4 inch margin around the entire form so that information is not lost during scanning, copying, or faxing of the document. The left-hand margin may be

increased up to ½ inch to permit binding (e.g., hole-punching) of the form; all other margins should continue to be at least 1/4 inch.

- The data and text that is contained within the boxes should be in a font size of not less than 10 point.
- The data and text that is contained within the boxes should be in a font type that is easy to read (e.g., CG Times, Arial) and not condensed, because the form may be copied or faxed multiple times. For visual contrast, the font type that is used for the data and text should, if possible, be different than the font type used to create the FDA Form 3500A or VAERS Form.
- All data and text should be contained within each of the boxes, e.g., an "x" mark should be centered within the box, and narratives should include margins so that letters of the text are not obscured or made ambiguous by lines defining a box.

FDA would consider "appropriate identifying information" to include:

- The name of the company centered on the top of the front page;
- In the lower left hand corner of the front page, the phrase "3500A Facsimile" instead of the phrase "FDA Form 3500A (date of form [e.g., 6/93])" or the phrase "VAERS facsimile" instead of the phrase "Form VAERS-1";

- The phrase "continued" at the end of each field that has additional information continued onto another page; and
- On each continuation page containing additional information, the page number identified as Page _ of _, the manufacturer report number in the upper right corner, the name of the company in the upper right corner, and the section and block number (e.g., Block B5) for each narrative entry.

This information is included in the draft guidance of 2001. Any revisions to these parameters would be included in updated versions of the guidance.

III.F.6. Other Revisions

The proposed rule would remove §§ 310.305(d)(4), 314.80(f)(4), and 600.80(f)(4). These paragraphs provide manufacturers and applicants with addresses for obtaining copies of FDA Form 3500A and instructions for completing the form. FDA is proposing to remove these paragraphs because the addresses are provided in the draft guidance of 2001.

The proposed rule would also remove §§ 314.80(e)(2) and 600.80(e)(2). These paragraphs state that persons subject to the postmarketing safety reporting regulations must separate and clearly mark reports of adverse drug experiences that occur during a postmarketing study as being distinct from those experiences that are being reported spontaneously to the person. FDA is proposing this revision because this information would be

submitted to the agency in a completed FDA Form 3500A under the box for "Report source" (box G3 on FDA Form 3500A).

III.G. Patient Privacy

Current postmarketing safety reporting regulations at §§ 310.305(e), 314.80(h), and 600.80(h) state that persons subject to these requirements should not include the names and addresses of individual patients in reports and, instead, should assign a unique code number to each report, preferably not more than eight characters in length. Proposed §§ 310.305(e), 314.80(e), and 600.80(e) would amend these regulations by removing the word "number." This proposed amendment would clarify that the code selected to identify a patient need not be limited to numbers (i.e., it could contain letters or a mixture of letters and numbers).

III.H. Recordkeeping

Current postmarketing safety recordkeeping regulations at § 314.80(I) require applicants to maintain for a period of 10 years records of all adverse drug experiences known to the applicant, including raw data and any correspondence relating to the adverse drug experiences. Under proposed § 314.80(f), FDA would amend these regulations to read:

> The applicant must maintain for a period of 10 years records of all safety information pertaining to its drug product, received or

otherwise obtained, including raw data, any correspondence relating to the safety information, and any reports of SADR's or medication errors not submitted to FDA or only provided to FDA in a summary tabulation. The applicant must also retain for a period of 10 years any records required to be maintained under this section. When appropriate, FDA may require an applicant to submit any or all of these records to the agency within 5 calendar days after receipt of the request.

This proposed revision clarifies the type of safety records that applicants would be required to maintain for its drug products. With regard to a request for these records by FDA, the agency would usually make such a request either in response to a suspected safety problem associated with the use of a drug or to determine a company's compliance with the postmarketing safety reporting requirements. Under proposed § 600.80(f), the agency is proposing similar revisions to the recordkeeping requirements for licensed biological products at § 600.80(i). FDA is proposing these revisions to clarify what types of postmarketing safety reporting records must be maintained.

Current § 310.305(f)(1) requires manufacturers, packers, and distributors to maintain for a period of 10 years records of all adverse drug experiences required under § 310.305, including raw data, any correspondence relating to adverse drug experiences, and the records required to be maintained under § 310.305. FDA is proposing to amend these regulations to be consistent with the postmarketing safety recordkeeping regulations at proposed §§ 314.80(f) and 600.80(f).

III.I. Abbreviated New Drug Application (ANDA) Products

Current § 314.98 requires applicants holding an approved ANDA to comply with the postmarketing safety reporting requirements under § 314.80. The proposed amendments to § 314.80 in this rule would apply to applicants holding an approved ANDA. For postmarketing periodic safety reporting purposes, proposed § 314.98(a) would require applicants holding an approved ANDA to determine the data lock point (i.e., month and day of the international birth date or any other month and day agreed by the applicant and FDA) for their periodic safety reports based on the data lock point of postmarketing periodic safety reports for other drug products containing the same drug substance (i.e., innovator NDA product that is the same drug product as the ANDA product or other ANDA products with the same drug substance if the innovator NDA product is no longer on the market). Thus, postmarketing periodic safety reports from different applicants

for drug products containing the same drug substance would be submitted to FDA at the same time. Applicants holding an approved ANDA may contact FDA, if necessary, for assistance in determining the data lock point for postmarketing periodic safety reports.

Proposed § 314.98(a) would also state that applicants holding an approved ANDA would determine the type of postmarketing periodic safety report that would be required to be submitted to FDA (i.e., TPSR, PSUR, or IPSR) 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, 1995, applicants holding an approved ANDA for the drug product would have the option of submitting either TPSR's or PSUR's and IPSR's to FDA. In these cases, an applicant holding an approved ANDA may choose to submit TPSR's to FDA even though other applicants with approved applications for the drug product submit PSUR's and IPSR's. If the innovator NDA product was approved for marketing on or after January 1, 1995, applicants holding an approved ANDA for the drug product would be required to submit PSUR's and IPSR's 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 TPSR's, PSUR's, and IPSR's for drug products with approved ANDA's 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 TPSR's, PSUR's, or IPSR's for drugs with approved ANDA's 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 § 601.37 requires, in accordance with the 1998 pediatric final rule, 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 (§ 601.37(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 (§ 601.37(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 601.37(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 also proposing to remove the requirement in §§ 314.81(b)(2)(vi) and 601.37(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, TPSR's, PSUR's, IPSR's, 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), PSUR's and IPSR's 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) PSUR's and IPSR's 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.

In the FEDERAL REGISTER of December 1, 1999 (64 FR 67207), FDA published a proposed rule to amend the status reports section of the postmarketing annual report requirements for approved drugs and licensed biological products to be consistent with section 130 of the Food and Drug Administration Modernization Act of 1997 (Public Law 105-115). These proposed amendments to the status reports section are beyond the scope of this proposed rule and will be addressed in separate rulemaking.

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