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);

(2) All serious unexpected SADR's, unexpected SADR's with unknown outcome, and always expedited reports that were previously submitted to FDA in an expedited report under paragraphs (c)(2)(i), (c)(2)(iii), and (c)(2)(iv) of this section (include cumulative data for serious unexpected SADR's, i.e., all cases reported to date);

(3) All reports of SADR's not previously submitted to FDA by the applicant (e.g., reports submitted to applicants by FDA, reports obtained from FDA from freedom of information requests at the discretion of the applicant, reports from class action lawsuits); and

(4) All domestic reports of medication errors previously submitted to FDA under paragraph (c)(2)(v) of this section. For actual medication errors, provide summary tabulations of serious SADR's, nonserious SADR's, and no SADR's. For potential medication errors, provide the number of reports for specific errors;

(C) History of safety-related actions taken. This section of the TPSR includes a history of safety-related actions taken since the last periodic safety report (e.g., labeling changes, studies initiated);

(D) Location of safety records. This section of the TPSR includes a list of the current address(es) where all safety reports and other safety-related records for the drug product are maintained; and

(E) Contact person. This section of the TPSR includes the name and telephone number for the licensed physician(s) responsible for the content and medical interpretation of the information contained within the TPSR. Include, if available, the fax number and e-mail address for the licensed physician(s).

(ii) Periodic safety update report (PSUR). An applicant holding an application for a human drug product approved under section 505(c) of the act on or after January 1, 1998, must submit a PSUR to FDA according to 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 data lock point for the PSUR is the month and day of the international birth date of the drug substance or any other month and day agreed on by the applicant and FDA. Each PSUR must contain:

(A) Title page, table of contents, and introduction. (1) The title page includes, at a minimum, the following information:

(i) Name and international birth date of the drug substance that is the subject of the PSUR,

(ii) Various dosage forms and formulations of the drug substance covered by the PSUR,

(iii) Name and address of the applicant,

(iv) Reporting period covered by the PSUR, and

(v) Date of the PSUR.

(2) The introduction:

(i) Provides a brief description of how the PSUR relates to previous reports and circumstances;

(ii) References relevant drug products or substances reported in other periodic safety reports (e.g., a combination product reported in a separate PSUR); and

(iii) Indicates any data duplication with other PSUR's.

(B) Worldwide marketing status. This section of the PSUR contains a table of the chronological history of the worldwide marketing status of the drug product(s) covered by the PSUR from the date the product(s) was first approved (i.e., the international birth date) through its current status (i.e., cumulative information). The table consists of:

(1) Dates of drug approval and renewal;

(2) Safety-related restrictions on product use;

(3) Indications for use and special populations covered by the drug approval;

(4) Lack of approval of the drug substance in any dosage form or for any indication for use by any regulatory authority(ies);

(5) Withdrawal of a pending marketing application for the drug product by the applicant for safety- or efficacy-related reasons;

(6) Dates of market launches; and

(7) Trade name(s).

(C) Actions taken for safety reasons. (1) This section of the PSUR includes details on the following types of regulatory authority-initiated (e.g., by 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):

(i) Withdrawal or suspension of drug product approval or indication for use approval;

(ii) Failure to obtain a marketing authorization renewal or to obtain an approval for a new indication for use;

(iii) Restrictions on distribution (e.g., products recalled for safety reasons);

(iv) Clinical trial suspension;

(v) Dosage modification;

(vi) Changes in target population or indications; and

(vii) Formulation changes.

(2) This section of the PSUR also contains a narrative identifying the safety-related reasons that led to these actions with relevant documentation appended when appropriate.

(3) Any communication with health care professionals (e.g., Dear Doctor letters) resulting from such actions must also be described with copies appended.

(D) Changes to CCSI. This section of the PSUR describes 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 must be included. The applicant must use the CCSI in effect at the beginning of the reporting period for the PSUR. The revised CCSI is to be used as the reference document for the next reporting period.

(E) Worldwide patient exposure. (1) This section of the PSUR includes, for the reporting period, an estimate of the worldwide patient exposure to the drug 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 must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must 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.

(2) When possible, data broken down by gender and age (especially pediatric versus adult) must be provided. For the pediatric population, data must be reported, if possible, by age group (e.g., neonates, infants, children, adolescents). If these data are not available, an explanation must be included.

(3) 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) must be presented.

(F) Individual case safety reports. (1) This section of the PSUR includes 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:

(i) All serious and nonserious SADR's from spontaneous sources that were submitted to applicants by a health care professional;

(ii) All serious SADR's from studies, individual patient IND's, or, in foreign countries, from named-patient "compassionate" use;

(iii) All serious SADR's and nonserious unlisted SADR's from the scientific literature;

(iv) All serious SADR's from regulatory authorities; and

(v) Serious SADR's from other sources such as reports created by poison control centers and epidemiological data bases.

(2) The summary tabulations must be made up 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 determined to be both serious and unlisted, include cumulative data (i.e., all cases reported to date).

(3) The applicant must conclude this section with a brief discussion of the data concerning the individual case safety reports in the PSUR (e.g., discussion of medical significance or mechanism).

(G) Safety studies. This section of the PSUR contains a discussion of nonclinical, clinical, and epidemiological studies that contain important safety information, as follows:

(1) All applicant-sponsored studies newly analyzed during the reporting period (copies of full reports should be appended only if new safety issues are raised or confirmed; FDA may request copies of other studies, if necessary);

(2) New studies specifically planned, initiated, or continuing during the reporting period that examine a safety issue, whether actual or hypothetical; and

(3) Published safety studies in the scientific and medical literature, including relevant published abstracts from meetings (provide literature citation).

(H) Other information. This section of the PSUR includes:

(1) 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; and

(2) Any important new information received after the data lock point (e.g., significant new cases).

(I) Overall safety evaluation. This section of the PSUR contains a concise, yet comprehensive, analysis of all of the safety information provided in the PSUR, including new information provided under paragraph (c)(3)(ii)(H)(2) of this section. In addition, this section of the PSUR includes an assessment by the applicant of the significance of the data collected during the reporting period, as well as from the perspective of cumulative experience.

(1) The applicant must highlight any new information on:

(i) Serious, unlisted SADR's;

(ii) Increased reporting frequencies of listed SADR's, including comments on whether it is believed that the data reflect a meaningful change in SADR occurrence;

(iii) A change in characteristics of listed SADR's (e.g., severity, outcome, target population); and

(iv) Nonserious, unlisted SADR's.

(2) As part of the overall safety evaluation, the applicant must also explicitly address any new safety issue including but not limited to the following (lack of significant new information for each of the following must be mentioned):

(i) Drug interactions;

(ii) Experience with overdose, whether deliberate or accidental, and its treatment;

(iii) Drug abuse or intentional misuse;

(iv) Positive or negative experiences during pregnancy or lactation;

(v) Effects with long-term treatment; and

(vi) Experience in special patient groups (e.g., pediatric, geriatric, organ impaired). For the pediatric population, data must be evaluated, if possible, by age group (e.g., neonates, infants, children, adolescents).

(J) Conclusion. This section of the PSUR:

(1) Indicates 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

product and an SADR such as positive rechallenge, an epidemiological association, or new laboratory studies); and

(2) Specifies and justifies any action recommended or initiated, including changes in the CCSI.

(K) Appendices. This section of the PSUR includes:

(1) Company core data sheet. Provide a copy of the company core data sheet covered by this PSUR (i.e., in effect at the beginning of the period covered by the PSUR) as well as the company core data sheet for the next reporting period. Company core data sheets must be numbered and dated and include the date of last revision.

(2) U.S. labeling. Provide a copy of the current approved U.S. labeling. Specify any safety information that is included in the CCSI but not in the U.S. labeling and provide an explanation for the discrepancy. Describe any safety-related changes or proposed changes to the U.S. labeling made during the reporting period (include the supplement number(s) and date(s) of submission for the supplement(s)) and any suggested change(s) that should be considered based on the safety analysis in the PSUR.

(3) Spontaneous reports submitted to the applicant by an individual other than a health care professional. Provide 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., reports from consumers). These summary tabulations must consist of lists by body system or by standard organ system classification scheme of all SADR terms and counts of occurrences. For those SADR's that are determined to be both serious and unlisted, include cumulative data (i.e., all cases reported to date by individuals other than a health care professional). Include a brief discussion of the impact of the spontaneous reports described in this appendix on the overall safety evaluation.

(4) SADR's with unknown outcome. Provide 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 must consist of lists by body system or by standard organ system classification scheme of all SADR terms and counts of occurrences. Include a brief discussion of the impact of the spontaneous reports described in this appendix on the overall safety evaluation.

(5) Class action lawsuits. Provide 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 must consist of lists by body system or by standard organ system classification scheme of all SADR terms and counts of occurrences. For those SADR's that are determined to be both serious and unlisted, include cumulative data. Include a brief discussion of the impact of the reports described in this appendix on the overall safety evaluation.

(6) Lack of efficacy reports. Provide 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 product.

(7) Information on resistance to antimicrobial drug products. Provide information, received or otherwise obtained by the applicant, on resistance to antimicrobial drug products intended to treat infectious diseases. Include information on 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 this PSUR.

(8) Medication errors. Provide summary tabulations of all domestic reports of medication errors submitted during the reporting period under paragraph (c)(2)(v) of this section. For actual medication errors, provide summary tabulations for serious SADR's, nonserious SADR's, and no SADR's (for serious SADR's include cumulative data, i.e., all cases reported to date). For potential medication errors, provide the number of reports for specific errors. If an SADR occurs, the summary tabulations must consist of lists by body system or by standard organ system classification scheme of all SADR terms and counts of occurrences. Include a brief discussion of the impact on the overall safety evaluation of these reports.

(9) U.S. patient exposure. Provide, for the reporting period, an estimate of the U.S. patient exposure to the drug 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 must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must 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.

(10) Location of safety records. Provide a list of the current address(es) where all safety reports and other safety-related records for the drug product(s) are maintained.

(11) Contact person. Provide the name and telephone number of the licensed physician(s) responsible for the content and medical interpretation of the data and information contained within the PSUR. Include, if available, the fax number and e-mail address of the licensed physician(s).

(iii) Interim periodic safety report (IPSR). An applicant holding an application for a human drug product approved under section 505(c) of the act on or after January 1, 1998, must submit an IPSR to FDA 7.5 years and 12.5 years after U.S. approval of the application. The data lock point for the IPSR is the month and day of the international birth date of the drug substance or any other month and day agreed on by the applicant and FDA. The reporting period for the IPSR covers 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 7.5 years after U.S. approval of the application). Each IPSR must contain:

(A) Title page, table of contents, and introduction. (1) The title page includes, at a minimum, the following information:

(i) Name and international birth date of the drug substance that is the subject of the IPSR,

(ii) Various dosage forms and formulations of the drug substance covered by the IPSR,

(iii) Name and address of the applicant,

(iv) Reporting period covered by the IPSR, and

(v) Date of the IPSR.

(2) The introduction:

(i) Provides a brief description of how the IPSR relates to previous reports and circumstances,

(ii) References relevant drug products or substances reported in other periodic safety reports (e.g., a combination product reported in a separate IPSR), and

(iii) Indicates any data duplication with other IPSR's.

(B) Worldwide marketing status. This section of the IPSR contains a table of the chronological history of the worldwide marketing status of the drug product(s) covered by the IPSR from the date the product(s) was first approved (i.e., the international birth date) through its current status (i.e., cumulative information). The table consists of:

(1) Dates of drug approval and renewal;

(2) Safety-related restrictions on product use;

(3) Indications for use and special populations covered by the drug approval;

(4) Lack of approval of the drug substance in any dosage form or for any indication for use by any regulatory authority(ies);

(5) Withdrawal of a pending marketing application for a drug product by the applicant for safety or efficacy related reasons;

(6) Dates of market launches; and

(7) Trade name(s).

(C) Actions taken for safety reasons. (1) This section of the IPSR includes details on the following types of regulatory authority-initiated (e.g., by FDA) and/or applicant-initiated actions related to safety that were taken during the period covered by the IPSR and between the data lock point and IPSR submission (i.e., "late-breaking" safety concerns):

(i) Withdrawal or suspension of drug product approval or indication for use approval;

(ii) Failure to obtain a marketing authorization renewal or to obtain an approval for a new indication for use;

(iii) Restrictions on distribution (e.g., products recalled for safety reasons);

(iv) Clinical trial suspension;

(v) Dosage modification;

(vi) Changes in target population or indications; and

(vii) Formulation changes.

(2) This section of the IPSR also contains a narrative identifying the safety-related reasons that led to these actions with relevant documentation appended when appropriate.

(3) Any communication with health care professionals (e.g., Dear Doctor letters) resulting from such actions must also be described with copies appended.

(D) Changes to CCSI. This section of the IPSR describes changes to the CCSI (e.g., new contraindications, precautions, warnings, SADR's, or interactions) made during the period covered by the IPSR. A copy of any modified section of the CCSI must be included. The applicant must use the CCSI in effect at the beginning of the reporting period for the IPSR. The revised CCSI is to be used as the reference document for the next reporting period.

(E) Worldwide patient exposure. (1) This section of the IPSR includes, for the reporting period, an estimate of the worldwide patient exposure to the drug product(s) covered by the IPSR (i.e., number of patients, average or median dose received, and average or median length of treatment). The method used to estimate patient exposure must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must 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.

(2) When possible, data broken down by gender and age (especially pediatric versus adult) must be provided. For the pediatric population, data must be reported, if possible, by age group (e.g., neonates, infants, children, adolescents). If these data are not available, an explanation must be included.

(3) 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) must be presented.

(F) Safety studies. This section of the IPSR contains a discussion of nonclinical, clinical, and epidemiological studies that contain important safety information, as follows:

(1) All applicant-sponsored studies newly analyzed during the reporting period (copies of full reports should be appended only if new safety issues are raised or confirmed; FDA may request copies of other studies, if necessary);

(2) New studies specifically planned, initiated, or continuing during the reporting period that examine a safety issue, whether actual or hypothetical; and

(3) Published safety studies in the scientific and medical literature, including relevant published abstracts from meetings (provide literature citation).

(G) Other information. This section of the IPSR includes 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.

(H) Overall safety evaluation. This section of the IPSR contains a concise, yet comprehensive, analysis of all of the safety information provided in the IPSR. In addition, this section of the IPSR must include an assessment by the applicant of the significance of the data collected during the reporting period, as well as from the perspective of cumulative experience.

(1) The applicant must highlight any new information on:

(i) Serious, unlisted SADR's;

(ii) Increased reporting frequencies of listed SADR's, including comments on whether it is believed that the data reflect a meaningful change in SADR occurrence;

(iii) A change in characteristics of listed SADR's (e.g., severity, outcome, target population); and

(iv) Nonserious, unlisted SADR's.

(2) As part of the overall safety evaluation, the applicant must also explicitly address any new safety issue including but not limited to the following (lack of significant new information for each of the following must be mentioned):

(i) Drug interactions;

(ii) Experience with overdose, whether deliberate or accidental, and its treatment;

(iii) Drug abuse or intentional misuse;

(iv) Positive or negative experiences during pregnancy or lactation;

(v) Effects with long-term treatment; and

(vi) Experience in special patient groups (e.g., pediatric, geriatric, organ impaired). For the pediatric population, data must be evaluated, if possible, by age group (e.g., neonates, infants, children, adolescents).

(I) Conclusion. This section of the IPSR:

(1) Indicates 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 product and an SADR such as positive rechallenge, an epidemiological association or new laboratory studies); and

(2) Specifies and justifies any action recommended or initiated, including changes in the CCSI.

(J) Appendices. This section of the IPSR includes:

(1) Company core data sheet. Provide a copy of the company core data sheet covered by this IPSR (i.e., in effect at the beginning of the period covered by the IPSR), as well as the company core data sheet for the next reporting period. Company core data sheets must be numbered and dated and include the date of last revision.

(2) U.S. labeling. Provide a copy of the current approved U.S. labeling. Specify any safety information that is included in the CCSI but not in the U.S. labeling and provide an explanation for the discrepancy. Describe any safety-related changes or proposed changes to the U.S. labeling made during the reporting period (include the supplement number(s) and date(s) of submission for the supplement(s)) and any suggested change(s) that should be considered based on the safety analysis in this IPSR.

(3) Spontaneous reports submitted to the applicant by an individual other than a health care professional. Provide a brief discussion of the impact on the overall safety evaluation of any spontaneously reported serious SADR's, whether domestic or foreign, and any 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., reports from consumers).

(4) SADR's with unknown outcome. Provide a brief discussion of the impact on the overall safety evaluation of any spontaneously reported unlisted and listed SADR's with unknown outcome obtained or otherwise received during the reporting period by the applicant from health care professionals and other individuals.

(5) Class action lawsuits. Provide a brief discussion of the impact on the overall safety evaluation of any safety information obtained or otherwise received during the reporting period by the applicant from class action lawsuits.

(6) Lack of efficacy reports. Provide an assessment of whether it is believed that the frequency of any 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 product.

(7) Information on resistance to antimicrobial drug products. Provide information, received or otherwise obtained by the applicant, on resistance to antimicrobial drug products intended to treat infectious diseases. Include information on 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 this IPSR.

(8) Medication errors. Provide a brief discussion of the impact on the overall safety evaluation of all domestic reports of medication errors submitted during the reporting period under paragraph (c)(2)(v) of this section.

(9) U.S. patient exposure. Provide, for the reporting period, an estimate of the U.S. patient exposure to the drug product(s) covered by the IPSR (i.e., number of patients, average or median dose received, and average or median length of treatment). The method used to estimate patient exposure must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must 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.

(10) Location of safety records. Provide a list of the current address(es) where all safety reports and other safety-related records for the drug product are maintained.

(11) Contact person. Provide the name and telephone number for the licensed physician(s) responsible for the content and medical interpretation of the information contained within the IPSR. Include, if available, the fax number and e-mail address for the licensed physician(s).

(iv) Pediatric use supplements. After approval of a pediatric use supplement to an approved application (i.e., a supplement for use of the human drug product in the pediatric population), the applicant must submit PSUR's to FDA as prescribed under paragraph (c)(3)(ii) of this section according to the following schedule: Semiannually for 2 years after U.S. approval of the supplement, annually for the next 3 years, and then every 5 years thereafter. These applicants must also submit IPSR's to FDA as prescribed under paragraph (c)(3)(iii) of this section at 7.5 years and 12.5 years after U.S. approval of the supplement. The data lock point for the PSUR and IPSR is the month and day of the international birth date of the drug substance or any other month and day agreed on by the applicant and FDA.

(v) Semiannual submission of individual case safety reports. (A) An applicant holding an application for a human drug product

approved under section 505(c) of the act must submit to FDA semiannually (i.e., every 6 months) after U.S. approval of the application a separate report that consists of individual case safety reports for certain spontaneously reported SADR's for the human drug product. The individual case safety reports must be submitted to FDA on the form designated by the agency under paragraph (c)(4) of this section. The data lock point for the report is the month and day of the international birth date of the drug product or any other month and day agreed on by the applicant and FDA. This report must be identified as "individual case safety reports--semiannual submission."

(B) Applicants that submit TPSR's to FDA for the drug product must submit 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). Applicants that submit PSUR's to FDA for the drug product must submit 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. If a full data set is not available for a

serious SADR, the applicant must submit the information required under paragraph (c)(1)(iv) of this section.

(C) 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 must be submitted to FDA as a 15-day followup report (see paragraph (c)(2)(vii) of this section).

(4) Reporting format. (i)(A) Except as provided in paragraphs (c)(4)(i)(B), (c)(4)(i)(D), and (c)(4)(v) of this section, the applicant 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).

(B) Foreign SADR's may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form.

(C) Each domestic report of an actual or potential medication error must be submitted on an FDA Form 3500A.

(D) 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.

(ii) Each SADR in an individual case safety report must be coded on the FDA Form 3500A or CIOMS I form using the appropriate

"preferred term" in the latest version of MedDRA (the medical dictionary for regulatory activities) in use at the time the pplicant becomes aware of the individual case safety report. For individual case safety reports of medication errors, the report must be coded both as a medication error and, if applicable, with the preferred term for any SADR's associated with the medication error.

(iii) Each completed FDA Form 3500A or CIOMS I form should refer only to an individual case.

(iv) Each completed FDA Form 3500A 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).

(v) Instead of using FDA Form 3500A, the applicant may use a computer-generated facsimile of FDA Form 3500A 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 in the identical enumerated sequence of the form. For individual case safety reports in which no suspect medical device is involved, a one-page FDA Form 3500A is acceptable.

(d) Multiple reports. An applicant should not include in reports under this section any SADR's that occurred in clinical trials if they were previously submitted as part of the approved

application. If a report applies to a drug for which an applicant holds more than one approved application, the applicant should submit the report to the application that was first approved. If a report refers to more than one drug marketed by an applicant, the applicant should submit the report to the application for the drug listed first in the report.

(e) Patient privacy. The names and addresses of individual patients should not be included in reports under this section; instead, the applicant and its contractors should assign a unique code to each report, preferably not more than eight characters (i.e., numbers and/or letters) in length. The name of the reporter from whom the information was received should be included. Names of patients, individual reporters, health care professionals, hospitals, and geographic identifiers in safety reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter.

(f) Recordkeeping. Each 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. Each 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.

(g) Written procedures. Each applicant must develop and maintain written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing safety information to FDA.

(h) Withdrawal of approval. If an applicant fails to establish and maintain records and make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

(i) Disclaimer. A report or information submitted by an applicant under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the drug caused or contributed to an SADR. An applicant need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the drug caused or contributed to an SADR.

8. Section 314.81 is amended by removing paragraph (b)(2)(v), by redesignating paragraphs (b)(2)(vi) and (b)(2)(vii) as paragraphs (b)(2)(v) and (b)(2)(vi), respectively, and by revising paragraph (b)(2)(i) and newly redesignated paragraph (b)(2)(v) to read as follows:

§ 314.81 Other postmarketing reports.

* * * * *

(b) * * *

(2) * * *

(i) Summary. A brief summary of significant new information from the previous year that might affect the effectiveness of the drug product or the sections of the drug product labeling that are not related to safety. The report must also contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit an efficacy labeling supplement or initiate a new study. The summary must briefly state whether supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated.

* * * *

(v) Clinical data. (A) Published clinical trials of the drug (or abstracts of them), including clinical trials on effectiveness; clinical trials on new uses; and biopharmaceutic, pharmacokinetic, and clinical pharmacology studies conducted by or otherwise obtained by the applicant. Review articles, papers describing safety related information or the use of the drug product in medical practice, papers and abstracts in which the drug is used as a research tool, promotional articles, press

clippings, and papers that do not contain tabulations or summaries of original data should not be reported.

(B) Summaries of completed unpublished clinical trials, or prepublication manuscripts if available, conducted by, or otherwise obtained by, the applicant. Supporting information should not be reported. (A study is considered completed 1 year after it is concluded.)

(C) Analysis of available efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population must be included.

* * * * *

9. Section 314.98 is amended in paragraph (a) by adding the abbreviation "(ANDA)" after the phrase "abbreviated new drug application", by removing the citation "§ 314.94" and by adding in its place the phrase "section 505(j) of the act", by removing the phrase "adverse drug experiences" and by adding in its place the phrase "suspected adverse drug reactions", and by adding two sentences to the end of the paragraph; and in paragraph (b) by removing the phrase "Division of Epidemiology and Surveillance (HFD-730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857" and by adding in its place the word "FDA" to read as follows:

§ 314.98 Postmarketing reports.

(a) * * * For purposes of postmarketing periodic safety reporting, applicants must 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 new drug application (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). Applicants must determine the type of postmarketing periodic safety report required to be submitted to FDA (i.e., traditional periodic safety report (TPSR), periodic safety update report (PSUR) or interim periodic safety report (IPSR)) and the frequency of submission for these reports based on the U.S. approval date of the application for the innovator NDA product.

* * * * *

PART 320--BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

10. The authority citation for 21 CFR part 320 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 355, 371.

11. Section 320.31 is amended by revising paragraph (d) to read as follows:

§ 320.31 Applicability of requirements regarding an "Investigational New Drug Application."

* * * *

(d) A bioavailability or bioequivalence study in humans other than one described in paragraphs (a) through (c) of this section is exempt from the requirements of part 312 of this chapter, except for the safety reporting requirements under § 312.32 of this chapter, if the following conditions are satisfied:

(1) If the study is one described under § 320.38(b) or § 320.63, the person conducting the study, including any contract research organization, must retain reserve samples of any test article and reference standard used in the study and release the reserve samples to FDA upon request in accordance with and for the period specified in § 320.38;

(2) An in vivo bioavailability or bioequivalence study in humans must be conducted in compliance with the requirements for institutional review set forth in part 56 of this chapter and informed consent set forth in part 50 of this chapter; and

(3) Safety reports as prescribed under § 312.32 of this chapter must be transmitted to all participating investigators and the appropriate FDA division in the Center for Drug Evaluation and Research (i.e., safety reports for the reference listed drug must be sent to the new drug review division that has

responsibility for that drug, safety reports for the investigational drug product must be sent to the Director, Division of Bioequivalence, Office of Generic Drugs). Each written notification under this paragraph must bear prominent identification of its contents, i.e., "bioavailability/bioequivalence safety report." For reporting purposes under this paragraph, an unexpected suspected adverse drug reaction (SADR) is any SADR, the specificity or severity of which is not consistent with the U.S. labeling for the reference listed drug.

PART 600--BIOLOGICAL PRODUCTS: GENERAL

12. The authority citation for 21 CFR part 600 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 360i, 371, 374; 42 U.S.C. 216, 262, 263, 263a, 264, 300aa-25.

13. Section 600.80 is revised to read as follows:

§ 600.80 Postmarketing reporting of suspected adverse reactions.

(a) Definitions. The following definitions of terms apply to this section:

Active query means direct verbal contact (i.e., in person or by telephone or other interactive means such as a video conference) with the initial reporter of a suspected adverse reaction (SAR) or medication error by a health care professional (e.g., physician, physician assistant, pharmacist, dentist,

nurse) representing the applicant. For SAR's, active query entails, at a minimum, a focused line of questioning designed to capture clinically relevant information associated with the licensed biological product and the SAR, including, but not limited to, information such as baseline data, patient history, physical exam, diagnostic results, and supportive lab results.

Actual medication error means a medication error that involves an identifiable patient whether the error was prevented prior to administration of the product or, if the product was administered, whether the error results in a serious SAR, nonserious SAR, or no SAR.

Blood component means as defined in § 606.3(c) of this chapter.

Company core data sheet means a document prepared by the applicant containing, in addition to safety information, material relating to indications, dosing, pharmacology, and other information concerning the biological product. The only purpose of this document is to provide the company core safety information (CCSI) for periodic safety update reports (PSUR's), interim periodic safety reports (IPSR's), and certain individual case safety reports--semiannual submissions (i.e., if PSUR's are submitted for the product).

Company core safety information (CCSI) means all relevant safety information contained in the company core data sheet that

the applicant proposes to include in the approved product labeling in all countries where the applicant markets the biological product. It is the reference information by which an SAR is determined to be "listed" or "unlisted" for PSUR's, IPSR's, and certain individual case safety reports--semiannual submissions (i.e., if PSUR's are submitted for the product).

Contractor means any person (e.g., manufacturer, joint manufacturer, packer, or distributor whether or not its name appears on the label of the product; licensee; contract research organization) that has entered into a contract with the applicant (includes participants involved in divided manufacturing) to manufacture, pack, sell, distribute, or develop the licensed biological product or to maintain, create, or submit records regarding SAR's or medication errors.

Data lock point means the date designated as the cut-off date for data to be included in a postmarketing periodic safety report.

Disability means a substantial disruption of a person's ability to conduct normal life functions.

Full data set means completion of all the applicable elements on FDA Form 3500A or the vaccine adverse event reporting system (VAERS) form (or on a Council for International Organizations of Medical Sciences (CIOMS) I form for reports of foreign SAR's), including a concise medical narrative of the case

(i.e., an accurate summary of the relevant data and information pertaining to an SAR or medication error).

International birth date means the date the first regulatory authority in the world approved the first marketing application for a human biological product.

Life-threatening SAR means any SAR that, in the view of the initial reporter, places the patient at immediate risk of death from the SAR as it occurred. It does not include an SAR that, had it occurred in a more severe form, might have caused death.

Listed SAR means an SAR whose nature, specificity, severity, and outcome are consistent with the information in the CCSI.

Medication error means any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: Prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Minimum data set means the report includes an identifiable patient, an identifiable reporter, a suspect biological product, and an SAR.

Nonserious SAR means any SAR that is determined not to be a serious SAR.

Potential medication error means an individual case safety report of information or complaint about product name, labeling, or packaging similarities that does not involve a patient.

SAR with unknown outcome means an SAR that cannot be classified, after active query, as either serious or nonserious.

Serious SAR means any SAR that results in any of the following outcomes: Death, a life-threatening SAR, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious SAR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Spontaneous report means a communication from an individual (e.g., health care professional, consumer) to a company or regulatory authority that describes an SAR or medication error. It does not include cases identified from information solicited by the applicant, shared manufacturer, or contractor, such as

individual case safety reports or findings derived from a study, company-sponsored patient support program, disease management program, patient registry, including pregnancy registries, or any organized data collection scheme. It also does not include information compiled in support of class action lawsuits.

Suspected adverse reaction (SAR) means a noxious and unintended response to any dose of a biological product for which there is a reasonable possibility that the product caused the response. In this definition, the phrase "a reasonable possibility" means that the relationship cannot be ruled out.

Unexpected SAR means any SAR that is not included in the current U.S. labeling for the licensed biological product. Reactions that may be symptomatically and pathophysiologically related to a reaction included in the U.S. labeling, but differ from the labeled reaction because of greater severity or specificity, would be unexpected. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the U.S. labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the U.S. labeling only included cerebral vascular accidents. "Unexpected," as used in this definition, refers to an SAR that has not been previously observed (i.e., included in the U.S. labeling); it does not refer

to an SAR that might be anticipated from the pharmacological properties of the licensed biological product. SAR's that are mentioned in the U.S. labeling as occurring with a class of products but not specifically mentioned as occurring with the particular product are considered unexpected.

Unlisted SAR means an SAR whose nature, specificity, severity, or outcome is not consistent with the information included in the CCSI.

(b) Review of safety information. (1) Any person having a biologics license under § 601.20 of this chapter must promptly review all safety information pertaining to its product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiology/surveillance studies, animal or in vitro studies, electronic communications with applicants via the Internet (e.g., e-mail), reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not been previously reported to the Food and Drug Administration (FDA) by the applicant.

(2) Individual case safety reports that are forwarded to the applicant by FDA must not be resubmitted to the agency by the applicant; however, applicants must include information from

these individual case safety reports in any comprehensive safety analysis subsequently submitted to FDA. In addition, applicants must submit to FDA all followup information for these individual case safety reports.

(c) Reporting requirements. For nonvaccine biological products, the applicant must submit to FDA two copies of each postmarketing expedited report (described under paragraphs (c)(2)(i) through (c)(2)(vii) of this section) and each postmarketing periodic safety report of an individual case safety reports--semiannual submission (described under paragraph (c)(3)(v) of this section) pertaining to its product. For nonvaccine biological products, the applicant must also submit to FDA one copy of a PSUR, IPSR, or traditional periodic safety report (TPSR) along with one copy for each approved application or a human licensed biological product covered by the report. For vaccines, the applicant must submit to VAERS two copies of each safety report pertaining to its product and required under this section. FDA may waive the requirement for multiple copies in appropriate instances. Upon written notice, FDA may require, when appropriate, that the applicant submit reports under this section to the agency at times other than those stated. An applicant that wishes to submit reports under this section at different intervals must submit to FDA a request for a waiver under § 600.90.

(1) Determination of outcome, minimum data set, and full data set--(i)(A) Initial determinations. Upon initial receipt of an SAR report, the applicant must immediately determine ~~using active query~~ the outcome for the SAR (whether the SAR is serious or nonserious) and at least the minimum data set for the individual case safety report. For reports of actual medication errors that do not result in an SAR and potential medication errors, the applicant must immediately determine ~~using active query~~ the minimum information for the individual case safety report (minimum information described under paragraphs (c)(1)(iii)(B) and (c)(1)(iii)(C) of this section).

If the applicant is not able to immediately determine the information in this paragraph, active query must be used to obtain it as soon as possible.

(B) Spontaneous reports. For spontaneous reports, the applicant must always assume, for safety reporting purposes under this section, that there is at least a reasonable possibility, in the opinion of the initial reporter, that the biological product caused the spontaneously reported event.

(C) Clinical trials. For a clinical trial, the possibility that the biological product caused the SAR or that a medication error has occurred must be assumed if either the investigator or the applicant believes that such a reasonable possibility exists.

(ii) SAR's with unknown outcome. For an SAR with unknown outcome that cannot be immediately determined, the applicant must continue to use active query to attempt to determine the outcome of the SAR within 30 calendar days after initial receipt of the

SAR report by the applicant. The applicant must maintain a record of its efforts to determine the outcome for an SAR with nknown outcome.

(iii)(A) Minimum data set for SAR reports. The applicant must not submit an individual case safety report for an SAR to FDA if the report does not contain a minimum data set; instead, the applicant must maintain records of any information received or otherwise obtained for the SAR along with a record of its efforts to obtain a minimum data set.

(B) Minimum information for reports of actual medication errors that do not result in an SAR. For reports of actual medication errors that do not result in an SAR, an individual case safety report must be submitted to FDA even though the report does not contain a minimum data set (i.e., does not have ı SAR). These reports must contain at least an identifiable patient, an identifiable reporter, and a suspect biological product.

(C) Minimum information for potential medication error reports. For reports of potential medication errors, an individual case safety report must 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 SAR). These reports must contain at least an identifiable reporter and a suspect biological product.

(iv) Full data set. For reports of serious SAR's, always expedited reports (see paragraph (c)(2)(iv) of this section), and medication error reports (see paragraph (c)(2)(v) of this section), the applicant must ~~use active query to obtain~~ submit a full data set. If a full data set is not available for the report, ~~cannot be obtained~~, the applicant must use active query to obtain this information. If a full data set is not obtainable after active query, the applicant must:

(A) Submit all safety information, received or otherwise obtained, for the report;

(B) Indicate the reason(s) for its inability to acquire a full data set; and

(C) Document its efforts to obtain a full data set (i.e., description of unsuccessful steps taken to obtain this information).

(v) Serious SAR's not initially reported by a health care professional. For a serious SAR that was not initially reported to the applicant by a health care professional (e.g., report from a consumer), ~~active query must be used by~~ the applicant must ~~to~~ contact the health care professional associated with the care of the patient using active query to gather further medical perspective on the case and to acquire a full data set for the report.

(vi) Nonserious SAR's. For reports of nonserious SAR's with a minimum data set, except for those resulting from a medication error, all safety information received or otherwise obtained by the applicant must be submitted to FDA even though

If the manufacturer is unable to contact the health care professional, it must include in the report for the serious SADR: (A) the reason(s) for its inability to contact the health care professional and (B) a description of its efforts to contact the health care professional.

information in addition to the minimum data set is not required to be acquired. Reports of nonserious SAR's resulting from a medication error require a full data set under paragraph (c)(1)(iv) of this section.

(2) Postmarketing "expedited reports"--(i) Serious and unexpected SAR. The applicant must report to FDA each SAR, received or otherwise obtained, that is both serious and unexpected, whether foreign or domestic, as soon as possible, but in no case later than 15 calendar days after receipt by the applicant of the minimum data set for the serious, unexpected SAR. If a full data set is not available for the serious and unexpected SAR report at the time of initial submission of the report to FDA, the applicant must submit the information required under paragraph (c)(1)(iv) of this section and also submit a 30-day followup report as required by paragraph (c)(2)(vi) of this section.

(ii) Information sufficient to consider product administration changes. The applicant must also report 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. The applicant must submit this information to FDA as soon as possible, but in no case later than 15 calendar days after determination by the applicant that the information qualifies for

expedited reporting. Examples of such information include any significant unanticipated safety finding or data in the aggregate rom an in vitro, animal, epidemiological, or clinical study, whether or not conducted under an investigational new drug application (IND), that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a biological product used in treating a life-threatening or serious disease. The applicant must maintain a record of its efforts to determine whether the information required to be reported under this paragraph qualifies for expedited reporting.

(iii) Unexpected SAR with unknown outcome. The applicant must also report to FDA each SAR that is unexpected and for which the determination of an outcome is unattainable (i.e., SAR with unknown outcome) within 45 calendar days after initial receipt by the applicant of the minimum data set for the unexpected SAR. The applicant must document in the expedited report the reason(s) for the inability to determine the outcome.

(iv) Always expedited report. (A) The applicant must also report to FDA each SAR, received or otherwise obtained, whether foreign or domestic, that is the subject of an always expedited report. These reports must be submitted to FDA as soon as possible, but in no case later than 15 calendar days after receipt by the applicant of the minimum data set for the report.

The following medically significant SAR's, which may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject, are subject to an always expedited report:

(1) Congenital anomalies,

(2) Acute respiratory failure,

(3) Ventricular fibrillation,

(4) Torsades de pointe,

(5) Malignant hypertension,

(6) Seizure,

(7) Agranulocytosis,

(8) Aplastic anemia,

(9) Toxic epidermal necrolysis,

(10) Liver necrosis,

(11) Acute liver failure,

(12) Anaphylaxis,

(13) Acute renal failure,

(14) Sclerosing syndromes,

(15) Pulmonary hypertension,

(16) Pulmonary fibrosis,

(17) Confirmed or suspected transmission of an infectious agent by a marketed drug or biological product,

(18) Confirmed or suspected endotoxin shock, and

(19) Any other medically significant SAR that FDA determines to be the subject of an always expedited report (i.e., ay jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject).

(B) SAR's that are the subject of an always expedited report must be submitted to FDA whether unexpected or expected and whether or not the SAR leads to a serious outcome. If a full data set is not available for an always expedited report at the time of initial submission of the report to FDA, the applicant must submit the information required under paragraph (c)(1)(iv) of this section and also submit a 30-day followup report as required by paragraph (c)(2)(vi) of this section.

(v) Medication error--(A) Actual medication error. The applicant must also submit to FDA each domestic report of an ctual medication error, received or otherwise obtained, as soon as possible, but in no case later than 15 calendar days after receipt by the applicant of the minimum data set for a report of an SAR or, if an SAR does not occur, the minimum information described under paragraph (c)(1)(iii)(B) of this section (i.e., identifiable patient, identifiable reporter, and suspect biological product).

(B) Potential medication error. The applicant must also submit to FDA each domestic report of a potential medication error, received or otherwise obtained, as soon as possible, but

in no case later than 15 calendar days after receipt by the applicant of the minimum information described under paragraph (c)(1)(iii)(C) of this section (i.e., identifiable reporter and suspect biological product).

(C) Full data set. 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, the applicant must submit the information required under paragraph (c)(1)(iv) of this section and also submit a 30-day followup report as required by paragraph (c)(2)(vi) of this section.

(vi) The 30-day followup report. The applicant must use active query to obtain additional information for any expedited report under paragraphs (c)(2)(i), (c)(2)(iv), and (c)(2)(v) of this section that does not contain a full data set and must submit a followup report to FDA within 30 calendar days after initial submission of the expedited report to FDA by the applicant. 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.

(vii) The 15-day followup report. The applicant must report to FDA any new information, received or otherwise obtained, for any expedited or followup report (except for initial 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) within 15 calendar days of initial receipt of the new information by the applicant. 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.

(viii) Supporting documentation. (A) If the patient dies, the applicant must submit a copy of the autopsy report to FDA, if it is available. If an autopsy report is not available, the applicant must submit a death certificate to FDA. If an autopsy report becomes available after the applicant has submitted a death certificate to the agency, the autopsy report must be submitted to FDA. If the patient was hospitalized, the applicant must submit a copy of the hospital discharge summary to FDA, if it is available. If any of these documents is not in English, the document must be accompanied by an English translation. Applicants must use active query to obtain these documents.

These documents must be submitted to FDA as 15-day followup reports (see paragraph (c)(2)(vii) of this section) within 15 calendar days of initial receipt of the document by the applicant. If these documents are 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 will assume that active query by the applicant has not resulted in access to these documents. In this case, a record of the reason(s) for the lack of such documentation and the effort that was made to obtain the documentation must be maintained by the applicant.

(B) Each expedited report must contain in the narrative a list of other relevant documents (e.g., medical records, laboratory results, data from studies) for the report that are maintained by the applicant. When appropriate, FDA may require an applicant to submit copies of one or more of these documents to the agency within 5 calendar days after receipt of the request.

(ix) 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.

(x) Submission of safety reports by contractors and shared manufacturers. (A) Contractors and shared manufacturers must submit to the applicant (includes participants involved in divided manufacturing) safety reports of any SAR's or medication errors for the applicant's biological product, obtained or otherwise received, within 5 calendar days of initial receipt of the report by the contractor or shared manufacturer. The contractor and shared manufacturer must submit a safety report for an SAR to the applicant even if the report does not contain a minimum data set. Upon receipt of the safety report from a contractor or shared manufacturer, the applicant must comply with the postmarketing safety reporting requirements of this section.

(B) A contract between the applicant and a contractor must specify the postmarketing safety reporting responsibilities of the contractor. The applicant is responsible for ensuring that the contractors and shared manufacturers of its licensed biological products comply with these postmarketing safety reporting responsibilities.

(C) The contractor and shared manufacturer must maintain a record of each submission to the applicant under paragraph (c)(2)(x)(A) of this section that includes:

(1) A copy of each safety report;

(2) The date the report was initially received by the contractor or shared manufacturer;

(3) The date the report was submitted to the applicant; and

(4) The name and address of the applicant.

(D) The recordkeeping, written procedures, and disclaimer provisions under paragraphs (f), (g), and (j) of this section apply to contractors and shared manufacturers.

(xi) Report identification. Each expedited report submitted to FDA under paragraphs (c)(2)(i) through (c)(2)(vii) of this section must bear prominent identification as to its contents, e.g., "expedited report--serious and unexpected SAR," "expedited report--30-day followup report." Each type of report (e.g., serious and unexpected SAR reports, 30-day followup reports) must be submitted to FDA under separate cover. Reports of medication errors must indicate whether the error is actual or potential and if actual, whether a serious SAR, nonserious SAR, or no SAR occurred, e.g., "expedited report--actual medication error--nonserious SAR," "expedited report--potential medication error."

(3) Postmarketing periodic safety reports. The applicant must submit postmarketing periodic safety reports under this section (i.e., TPSR's, PSUR's, IPSR's, individual case safety reports--semiannual submission) to FDA within 60 calendar days after the data lock point for the report. The applicant must include a cover letter containing a list of the biologics license application number(s) (i.e., BLA number(s)) for the human

biological product(s) covered by the postmarketing periodic safety report. The international birth date for combination products is the international birth date of the human licensed biological product most recently approved for marketing.

(i) Traditional periodic safety reports (TPSR's). Each applicant holding a biologics license under § 601.20 of this chapter for a human biological product approved before January 1, 1995, must submit either a PSUR as prescribed under paragraph (c)(3)(ii) of this section or a TPSR as described under this paragraph every 5 years after U.S. approval of the application. In addition, these applicants must submit either an IPSR as described under paragraph (c)(3)(iii) of this section or a TPSR as described under this paragraph 7.5 years and 12.5 years after U.S. approval of the application. The data lock point for the PSR, PSUR, or IPSR is the month and day of the international birth date of the licensed biological product or any other month and day agreed on by the applicant and FDA. Each TPSR must contain:

(A) Summary. This section of the TPSR includes:

(1) A narrative summary and analysis of serious, expected SAR's and nonserious, unexpected SAR'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 SAR term(s));

(2) 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, SAR term(s), if appropriate, and date of submission to FDA);

(3) A discussion of any increased reporting frequency of serious, expected SAR's, including comments on whether it is believed that the data reflect a meaningful change in SAR occurrence, and 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 biological product; and

(4) 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).

(B) Summary tabulations. This section of the TPSR includes summary tabulations (i.e., lists of all SAR terms and counts of occurrences) presented by body system or by standard organ system classification scheme for:

(1) All serious expected SAR's, nonserious unexpected SAR's, nonserious expected SAR's, and expected SAR'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);

(2) All serious unexpected SAR's, unexpected SAR's with unknown outcome, and always expedited reports that were previously submitted to FDA in an expedited report under paragraphs (c)(2)(i), (c)(2)(iii), and (c)(2)(iv) of this section (include cumulative data for serious unexpected SAR's, i.e., all cases reported to date);

(3) All reports of SAR's not previously submitted to FDA by the applicant (e.g., reports submitted to applicants by FDA, reports obtained from FDA from freedom of information requests at the discretion of the applicant, reports from class action lawsuits); and

(4) All domestic reports of medication errors previously submitted to FDA under paragraph (c)(2)(v) of this section. For actual medication errors, provide summary tabulations of serious SAR's, nonserious SAR's, and no SAR's. For potential medication errors, provide the number of reports for specific errors;

(C) History of safety-related actions taken. This section of the TPSR includes a history of safety-related actions taken

since the last periodic safety report (e.g., labeling changes, studies initiated);

(D) Location of safety records. This section of the TPSR includes a list of the current address(es) where all safety reports and other safety-related records for the licensed biological product(s) are maintained; and

(E) Contact person. This section of the TPSR includes the name and telephone number for the licensed physician(s) responsible for the content and medical interpretation of the information contained within the TPSR. Include, if available, the fax number and e-mail address for the licensed physician(s).

(ii) Periodic safety update report (PSUR). An applicant holding a biologics license under § 601.20 of this chapter for a human biological product approved on or after January 1, 1998, must submit a PSUR to FDA according to 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 data lock point for the PSUR is the month and day of the international birth date of the licensed biological product or any other month and day agreed on by the applicant and FDA. Each PSUR must contain:

(A) Title page, table of contents, and introduction. (1) The title page includes, at a minimum, the following information:

(i) Name and international birth date of the licensed biological product(s) that is the subject of the PSUR,

(ii) Various dosage forms and formulations of the biological product(s) covered by the PSUR,

(iii) Name and address of the applicant,

(iv) Reporting period covered by the PSUR, and

(v) Date of the PSUR.

(2) The introduction:

(i) Provides a brief description of how the PSUR relates to previous reports and circumstances;

(ii) References relevant biological products reported in other periodic safety reports (e.g., a combination product reported in a separate PSUR); and

(iii) Indicates any data duplication with other PSUR's.

(B) Worldwide marketing status. This section of the PSUR contains a table of the chronological history of the worldwide marketing status of the biological product(s) covered by the PSUR from the date the product(s) was first approved (i.e., the international birth date) through its current status (i.e., cumulative information). This table consists of:

(1) Dates of biological product approval and renewal;

(2) Safety-related restrictions on product use;

(3) Indications for use and special populations covered by the biological product approval;

(4) Lack of approval of the biological product in any dosage form or for any indication for use by any regulatory authority(ies);

(5) Withdrawal of a pending marketing application for the biological product by the applicant for safety- or efficacy-related reasons;

(6) Dates of market launches; and

(7) Trade name(s).

(C) Actions taken for safety reasons. (1) This section of the PSUR includes details on the following types of regulatory authority-initiated (e.g., by 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):

(i) Withdrawal or suspension of biological product approval or indication for use approval;

(ii) Failure to obtain a marketing authorization renewal or to obtain an approval for a new indication for use;

(iii) Restrictions on distribution (products recalled for safety reasons);

(iv) Clinical trial suspension;

(v) Dosage modification;

(vi) Changes in target population or indications; and

(vii) Formulation changes.

(2) This section of the PSUR also contains a narrative identifying the safety-related reasons that led to these actions th relevant documentation appended when appropriate.

(3) Any communication with health care professionals (e.g., Dear Doctor letters) resulting from such actions must also be described with copies appended.

(D) Changes to CCSI. This section of the PSUR describes changes to the CCSI (e.g., new contraindications, precautions, warnings, SAR's, or interactions) made during the period covered by the PSUR. A copy of any modified section of the CCSI must be included. The applicant must use the CCSI in effect at the beginning of the reporting period for the PSUR. The revised CCSI is to be used as the reference document for the next reporting period.

(E) Worldwide patient exposure. (1) This section of the PSUR includes, for the reporting period, an estimate of the worldwide patient exposure to the 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 must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must 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.

(2) When possible, data broken down by gender and age (especially pediatric versus adult) must be provided. For the pediatric population, data must be reported, if possible, by age group (e.g., neonates, infants, children, adolescents). If these data are not available, an explanation must be included.

(3) 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) must be presented.

(F) Individual case safety reports. (1) This section of the PSUR includes summary tabulations of individual case safety reports (e.g., serious unlisted SAR's, serious listed SAR's, nonserious unlisted SAR's, nonserious listed SAR's) for the following SAR's obtained or otherwise received during the reporting period:

(i) All serious and nonserious SAR's from spontaneous sources that were submitted to applicants by a health care professional,

(ii) All serious SAR's from studies, individual patient IND's, or, in foreign countries, from named-patient "compassionate" use,

(iii) All serious SAR's and nonserious unlisted SAR's from the scientific literature,

(iv) All serious SAR's from regulatory authorities, and

(v) Serious SAR's from other sources such as reports created by poison control centers and epidemiological data bases.

(2) The summary tabulations must be made up of lists by body system or by standard organ system classification scheme of all SAR terms and counts of occurrences. For SAR's that are determined to be both serious and unlisted, include cumulative data (i.e., all cases reported to date).

(3) The applicant must conclude this section with a brief discussion of the data concerning the individual case safety reports in the PSUR (e.g., discussion of medical significance or mechanism).

(G) Safety studies. This section of the PSUR contains a discussion of nonclinical, clinical, and epidemiological studies that contain important safety information, as follows:

(1) All applicant-sponsored studies newly analyzed during the reporting period (copies of full reports should be appended only if new safety issues are raised or confirmed; FDA may request copies of other studies, if necessary);

(2) New studies specifically planned, initiated, or continuing during the reporting period that examine a safety issue, whether actual or hypothetical; and

(3) Published safety studies in the scientific and medical literature, including relevant published abstracts from meetings (provide literature citation).

(H) Other information. This section of the PSUR includes:

(1) 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; and

(2) Any important new information received after the data lock point (e.g., significant new cases).

(I) Overall safety evaluation. This section of the PSUR contains a concise, yet comprehensive, analysis of all of the safety information provided in the PSUR, including new information provided under paragraph (c)(3)(ii)(H)(2) of this section. In addition, this section of the PSUR includes an assessment by the applicant of the significance of the data collected during the reporting period, as well as from the perspective of cumulative experience.

(1) The applicant must highlight any new information on:

(i) Serious, unlisted SAR's;

(ii) Increased reporting frequencies of listed SAR's, including comments on whether it is believed that the data reflect a meaningful change in SAR occurrence;

(iii) A change in characteristics of listed SAR's (e.g., severity, outcome, target population); and

(iv) Nonserious, unlisted SAR's.

(2) As part of the overall safety evaluation, the applicant must also explicitly address any new safety issue including but not limited to the following (lack of significant new information for each of the following must be mentioned):

(i) Drug interactions;

(ii) Experience with overdose, whether deliberate or accidental, and its treatment;

(iii) Drug abuse or intentional misuse;

(iv) Positive or negative experiences during pregnancy or lactation;

(v) Effects with long-term treatment; and

(vi) Experience in special patient groups (e.g., pediatric, geriatric, organ impaired). For the pediatric population, data must be evaluated, if possible, by age group (e.g., neonates, infants, children, adolescents).

(J) Conclusion. This section of the PSUR:

(1) Indicates 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 biological product and an SAR, such as positive rechallenge, an epidemiological association, or new laboratory studies); and

(2) Specifies and justifies any action recommended or initiated, including changes in the CCSI.

(K) Appendices. This section of the PSUR includes:

(1) Company core data sheet. Provide a copy of the company core data sheet covered by this PSUR (i.e., in effect at the beginning of the period covered by the PSUR), as well as the company core data sheet for the next reporting period. Company core data sheets must be numbered and dated and include the date of last revision.

(2) U.S. labeling. Provide a copy of the current approved U.S. labeling. Specify any safety information that is included in the CCSI but not in the U.S. labeling, and provide an explanation for the discrepancy. Describe any safety-related changes or proposed changes to the U.S. labeling made during the reporting period (include the supplement number(s) and date(s) of submission for the supplement(s)) and any suggested change(s) that should be considered based on the safety analysis in this PSUR.

(3) Spontaneous reports submitted to the applicant by an individual other than a health care professional. Provide

summary tabulations (e.g., serious unlisted SAR's, serious listed SAR's, nonserious unlisted SAR's, nonserious listed SAR's) for all spontaneously reported serious SAR's, whether domestic or foreign, and all spontaneously reported nonserious SAR'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., reports from consumers). These summary tabulations must consist of lists by body system or by standard organ system classification scheme of all SAR terms and counts of occurrences. For those SAR's that are determined to be both serious and unlisted, include cumulative data (i.e., all cases reported to date by individuals other than a health care professional). Include a brief discussion of the impact of the spontaneous reports described in this appendix on the overall safety evaluation.

(4) SAR's with unknown outcome. Provide summary tabulations for unlisted and listed SAR'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 must consist of lists by body system or by standard organ system classification scheme of all SAR terms and counts of occurrences. Include a brief discussion of the impact of the spontaneous

reports described in this appendix on the overall safety evaluation.

(5) Class action lawsuits. Provide summary tabulations (e.g., serious unlisted SAR's, serious listed SAR's, nonserious unlisted SAR's, nonserious listed SAR's) for all SAR's obtained or otherwise received during the reporting period by the applicant from class action lawsuits. These summary tabulations must consist of lists by body system or by standard organ system classification scheme of all SAR terms and counts of occurrences. For those SAR's that are determined to be both serious and unlisted, include cumulative data. Include a brief discussion of the impact of the reports described in this appendix on the overall safety evaluation.

(6) Lack of efficacy reports. Provide 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 biological product.

(7) Medication errors. Provide summary tabulations of all domestic reports of medication errors submitted during the reporting period under paragraph (c)(2)(v) of this section. For actual medication errors, provide summary tabulations of serious SAR's, nonserious SAR's, and no SAR's (for serious SAR's, include cumulative data, i.e., all cases reported to date). For

potential medication errors, provide the number of reports for specific errors. If an SAR occurs, the summary tabulations must consist of lists by body system or by standard organ system classification scheme of all SAR terms and counts of occurrences. Include a brief discussion of the impact on the overall safety evaluation of these reports.

(8) U.S. patient exposure. Provide, for the reporting period, an estimate of the U.S. patient exposure to the 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 must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must 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.

(9) Location of safety records. Provide a list of the current address(es) where all safety reports and other safety-related records for the licensed biological product(s) are maintained.

(10) Contact person. Provide the name and telephone number for the licensed physician(s) responsible for the content and medical interpretation of the data and information contained within the PSUR. Include, if available, the fax number and e-mail address for the licensed physician(s).

(iii) Interim periodic safety report (IPSR). An applicant holding a biologics license under § 601.20 of this chapter for a human biological product approved on or after January 1, 1998, must submit an IPSR to FDA 7.5 years and 12.5 years after U.S. approval of the application. The data lock point for the IPSR is the month and day of the international birth date of the licensed biological product or any other month and day agreed on by the applicant and FDA. The reporting period for the IPSR covers 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 7.5 years after U.S. approval of the application). Each IPSR must contain:

(A) Title page, table of contents, and introduction. (1) The title page includes, at a minimum, the following information:

(i) Name and international birth date of the licensed biological product(s) that is the subject of the IPSR,

(ii) Various dosage forms and formulations of the biological product(s) covered by the IPSR,

(iii) Name and address of the applicant,

(iv) Reporting period covered by the IPSR, and

(v) Date of the IPSR.

(2) The introduction: I) Provides a brief description of how the IPSR relates to previous reports and circumstances,

(ii) References relevant biological products reported in other periodic safety reports (e.g., a combination product reported in a separate IPSR), and

(iii) Indicates any data duplication with other IPSR's.

(B) Worldwide marketing status. This section of the IPSR contains a table of the chronological history of the worldwide marketing status of the biological product(s) covered by the IPSR from the date the product(s) was first approved (i.e., the international birth date) through its current status (i.e., cumulative information). This table consists of:

(1) Dates of biological product approval and renewal;

(2) Safety-related restrictions on product use;

(3) Indications for use and special populations covered by the biological approval;

(4) Lack of approval of the biological product in any dosage form or for any indication for use by any regulatory authority(ies);

(5) Withdrawal of a pending marketing application for the biological product by the applicant for safety- or efficacy-related reasons;

(6) Dates of market launches; and

(7) Trade name(s).

(C) Actions taken for safety reasons. (1) This section of the IPSR includes details on the following types of regulatory authority-initiated (e.g., by FDA) and/or applicant-initiated actions related to safety that were taken during the period covered by the IPSR and between the data lock point and IPSR submission (i.e., "late-breaking" safety concerns):

(i) Withdrawal or suspension of biological product approval or indication for use approval;

(ii) Failure to obtain a marketing authorization renewal or to obtain an approval for a new indication for use;

(iii) Restrictions on distribution (products recalled for safety reasons);

(iv) Clinical trial suspension;

(v) Dosage modification;

(vi) Changes in target population or indications; and

(vii) Formulation changes.

(2) This section of the IPSR also contains a narrative identifying the safety-related reasons that led to these actions with relevant documentation appended when appropriate.

(3) Any communication with health care professionals (e.g., Dear Doctor letters) resulting from such actions must also be described with copies appended.

(D) Changes to CCSI. This section of the IPSR describes changes to the CCSI (e.g., new contraindications, precautions, warnings, SAR's, or interactions) made during the period covered by the IPSR. A copy of any modified section of the CCSI must be included. The applicant must use the CCSI in effect at the beginning of the reporting period for the IPSR. The revised CCSI is to be used as the reference document for the next reporting period.

(E) Worldwide patient exposure. (1) This section of the IPSR includes, for the reporting period, an estimate of the worldwide patient exposure to the biological product(s) covered by the IPSR (i.e., number of patients, average or median dose received, and average or median length of treatment). The method used to estimate patient exposure must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must 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.

(2) When possible, data broken down by gender and age (especially pediatric versus adult) must be provided. For the

pediatric population, data must be reported, if possible, by age group (e.g., neonates, infants, children, adolescents). If these data are not available, an explanation must be included.

(3) 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) must be presented.

(F) Safety studies. This section of the IPSR contains a discussion of nonclinical, clinical, and epidemiological studies that contain important safety information, as follows:

(1) All applicant-sponsored studies newly analyzed during the reporting period (copies of full reports should be appended only if new safety issues are raised or confirmed; FDA may request copies of other studies, if necessary);

(2) New studies specifically planned, initiated, or continuing during the reporting period that examine a safety issue, whether actual or hypothetical; and

(3) Published safety studies in the scientific and medical literature, including relevant published abstracts from meetings (provide literature citation).

(G) Other information. This section of the IPSR includes 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.

(H) Overall safety evaluation. This section of the IPSR contains a concise, yet comprehensive, analysis of all of the safety information provided in the IPSR. In addition, this section of the IPSR includes an assessment by the applicant of the significance of the data collected during the reporting period, as well as from the perspective of cumulative experience.

(1) The applicant must highlight any new information on:

(i) Serious, unlisted SAR's;

(ii) Increased reporting frequencies of listed SAR's, including comments on whether it is believed that the data reflect a meaningful change in SAR occurrence;

(iii) A change in characteristics of listed SAR's (e.g., severity, outcome, target population); and

(iv) Nonserious, unlisted SAR's.

(2) As part of the overall safety evaluation, the applicant must also explicitly address any new safety issue including but not limited to the following (lack of significant new information for each of the following must be mentioned):

(i) Drug interactions;

(ii) Experience with overdose, whether deliberate or accidental, and its treatment;

(iii) Drug abuse or intentional misuse;

(iv) Positive or negative experiences during pregnancy or lactation;

(v) Effects with long-term treatment; and

(vi) Experience in special patient groups (e.g., pediatric, geriatric, organ impaired). For the pediatric population, data must be evaluated, if possible, by age group (e.g., neonates, infants, children, adolescents).

(I) Conclusion. This section of the IPSR:

(1) Indicates 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 biological product and an SAR, such as positive rechallenge, an epidemiological association or new laboratory studies); and

(2) Specifies and justifies any action recommended or initiated, including changes in the CCSI.

(J) Appendices. This section of the IPSR includes:

(1) Company core data sheet. Provide a copy of the company core data sheet covered by this IPSR (i.e., in effect at the beginning of the period covered by the IPSR), as well as the company core data sheet for the next reporting period. Company core data sheets must be numbered and dated and include the date of last revision.

(2) U.S. labeling. Provide a copy of the current approved U.S. labeling. Specify any safety information that is included in the CCSI but not in the U.S. labeling and provide an explanation for the discrepancy. Describe any safety-related changes or proposed changes to the U.S. labeling made during the reporting period (include the supplement number(s) and date(s) of submission for the supplement(s)) and any suggested change(s) that should be considered based on the safety analysis in this IPSR.

(3) Spontaneous reports submitted to the applicant by an individual other than a health care professional. Provide a brief discussion of the impact on the overall safety evaluation of any spontaneously reported serious SAR's, whether domestic or foreign, and any spontaneously reported nonserious SAR'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., reports from consumers).

(4) SAR's with unknown outcome. Provide a brief discussion of the impact on the overall safety evaluation of any spontaneously reported unlisted and listed SAR's with unknown outcome obtained or otherwise received during the reporting period by the applicant from health care professionals and other individuals.

(5) Class action lawsuits. Provide a brief discussion of the impact on the overall safety evaluation of any safety information obtained or otherwise received during the reporting period by the applicant from class action lawsuits.

(6) Lack of efficacy reports. Provide an assessment of whether it is believed that the frequency of any 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 biological product.

(7) Medication errors. Provide a brief discussion of the impact on the overall safety evaluation of all domestic reports of medication errors submitted during the reporting period under paragraph (c)(2)(v) of this section.

(8) U.S. patient exposure. Provide, for the reporting period, an estimate of the U.S. patient exposure to the biological product(s) covered by the IPSR (i.e., number of patients, average or median dose received, and average or median length of treatment). The method used to estimate patient exposure must always be described. If the patient exposure is impossible to estimate or is meaningless, an explanation of and justification for such conclusions must 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.

(9) Location of safety records. Provide a list of the current address(es) where all safety reports and other safety-related records for the licensed biological product(s) are maintained.

(10) Contact person. Provide the name and telephone number for the licensed physician(s) responsible for the content and medical interpretation of the information contained within the IPSR. Include, if available, the fax number and e-mail address for the licensed physician(s).

(iv) Pediatric use supplements. After approval of a pediatric use supplement to an approved application (i.e., a supplement for use of the human biological product in the pediatric population), the applicant must submit PSUR'S to FDA as prescribed under paragraph (c)(3)(ii) of this section according to the following schedule: Semiannually for 2 years after U.S. approval of the supplement, annually for the next 3 years, and then every 5 years thereafter. These applicants must also submit IPSR'S to FDA as prescribed under paragraph (c)(3)(iii) of this section at 7.5 years and 12.5 years after U.S. approval of the supplement. The data lock point for the PSUR and IPSR is the month and day of the international birth date of the licensed

biological product or any other month and day agreed on by the applicant and FDA.

(v) Semiannual submission of individual case safety reports. (A) An applicant holding a biologics license under § 601.20 of this chapter for a human biological product must submit to FDA semiannually (i.e., every 6 months) after U.S. approval of the application a separate report that consists of individual case safety reports for certain spontaneously reported SAR's for the biological product. The individual case safety reports must be submitted on the form designated by the agency under paragraph (c)(4) of this section. The data lock point for the report is the month and day of the international birth date of the licensed biological product or any other month and day agreed on by the applicant and FDA. This report must be identified as "individual case safety reports--semiannual submission."

(B) Applicants that submit TPSR's to FDA for the licensed biological product must submit an individual case safety report for each serious, expected SAR, whether domestic or foreign, and each nonserious, unexpected SAR 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). Reports for vaccines must include an individual case safety report for each nonserious, expected SAR

and each expected SAR with unknown outcome occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources. Applicants that submit PSUR's to FDA for the licensed biological product must submit an individual case safety report for each serious, listed SAR, whether domestic or foreign, and each nonserious, unlisted SAR occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources. Reports for vaccines must include an individual case safety report for each nonserious, listed SAR and each listed SAR with unknown outcome occurring in the United States that is submitted to the applicant during the reporting period from all spontaneous sources. If a full data set is not available for a report of a serious SAR, the applicant must submit the information required under paragraph (c)(1)(iv) of this section.

(C) Followup information to SAR'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 SAR to a serious, unexpected SAR. In these cases, the followup information must be submitted to FDA as a 15-day followup report (see paragraph (c)(2)(vii) of this section).

(4) Reporting format. (i)(A) Except as provided in paragraphs (c)(4)(i)(B), (c)(4)(i)(D), and (c)(4)(v) of this

section, the applicant must complete the reporting form designated by FDA for each individual case safety report of an SAR (FDA Form 3500A or, for vaccines, a VAERS form). Reports based on information about individual cases or case series in the scientific literature must be submitted on an FDA Form 3500A(s) or, for vaccines, on a VAERS form(s).

(B) Foreign SAR'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.

(C) 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.

(D) 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.

(ii) Each SAR in an individual case safety report must be coded on the FDA Form 3500A, VAERS form, or CIOMS I form using the appropriate "preferred term" in the latest version of MedDRA (the medical dictionary for regulatory activities) in use at the time the applicant becomes aware of the individual case safety report. For individual case safety reports of medication errors, the report must be coded both as a medication error and, if

applicable, with the preferred term for any SAR's associated with the medication error.

(iii) Each completed FDA Form 3500A, VAERS form, or CIOMS I form should refer only to an individual case.

(iv) Each completed FDA Form 3500A, VAERS form 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).

(v) Instead of using FDA Form 3500A (or a VAERS form for vaccines), the applicant may use a computer-generated facsimile of FDA Form 3500A (or the 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. For individual case safety reports in which no suspect medical device is involved, a one-page FDA Form 3500A is acceptable.

(d) Multiple reports. An applicant should not include in reports under this section any SAR's that occurred in clinical trials if they were previously submitted as part of the license application. If a report refers to more than one biological

product marketed by an applicant, the applicant should submit the report to the license for the product listed first in the report.

(e) Patient privacy. For nonvaccine biological products, the names and addresses of individual patients should not be included in reports under this section; instead, the applicant, shared manufacturer and contractors should assign a unique code to each report, preferably not more than eight characters (i.e., numbers and/or letters) in length. The name of the reporter from whom the information was received should be included. Names of patients, individual reporters, health care professionals, hospitals, and geographic identifiers in safety reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter. For vaccine SAR reports, these data will become part of the CDC Privacy Act System 09-20-0136, "Epidemiologic Studies and Surveillance of Disease Problems." Information identifying the person who received the vaccine or that person's legal representative will not be made available to the public, but may be available to the vaccinee or legal representative.

(f) Recordkeeping. Each applicant must maintain for a period of 10 years records of all safety information pertaining to its product, received or otherwise obtained, including raw data, any correspondence relating to the safety information, and any reports of SAR's or medication errors not submitted to FDA or

only provided to FDA in a summary tabulation. Each 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.

(g) Written procedures. Each applicant must develop and maintain written procedures for the surveillance, receipt, evaluation, and reporting off safety information to FDA.

(h) Revocation of license. If an applicant fails to establish and maintain records and make reports required under this section with respect to a licensed biological product, FDA may revoke the license for such a product in accordance with the procedures of § 601.5 of this chapter.

(i) Exemptions. Manufacturers of the following listed products are not required to submit safety reports under this section:

(1) Whole blood or components of whole blood. These products are subject to the reporting requirements for blood and blood components in § 606.170 of this chapter.

(2) In vitro diagnostic products, including assay systems for the detection of antibodies or antigens to retroviruses. These products are subject to the reporting requirements for devices.

(j) Disclaimer. A report or information submitted by an applicant under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the applicant or FDA that the report or information constitutes an admission that the biological product caused or contributed to an SAR. An applicant need not admit, and may deny, that the report or information submitted under this section constitutes an admission that the biological product caused or contributed to an SAR.

PART 601--LICENSING

14. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: 15 U.S.C. 1451-1561; 21 U.S.C. 321, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263; sec. 122, Pub. L. 105-115, 111 Stat. 2322 (21 U.S.C. 355 note).

§ 601.37 [AMENDED]

15. Section 601.37 Annual reports of postmarketing pediatric studies is amended by removing the second sentence in paragraph (a) and the phrase "safety and" in the first sentence in paragraph (b).

PART 606--CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS

16. The authority citation for 21 CFR part 606 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 355, 360, 360j, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

17. Section 606.170 is revised to read as follows:

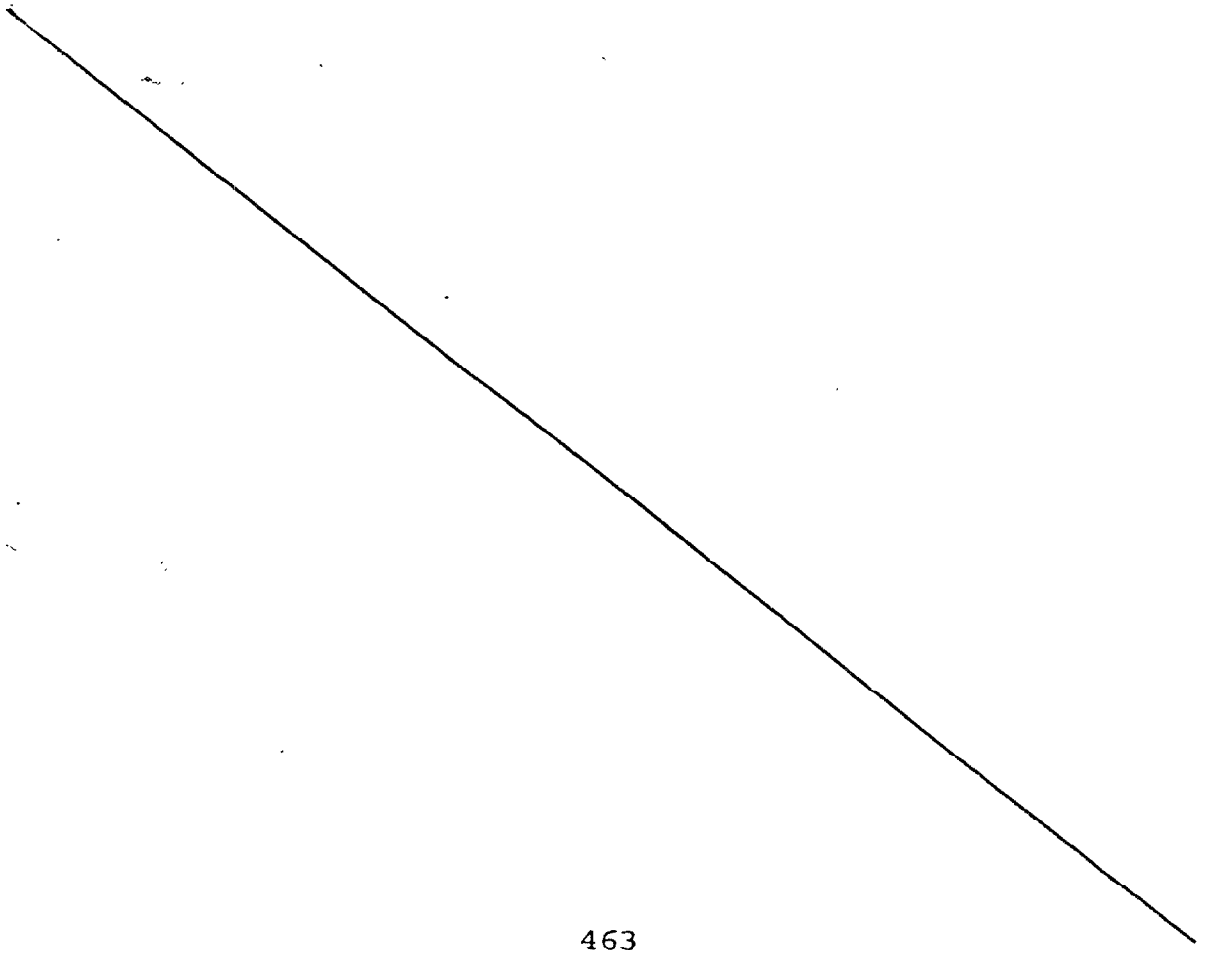
§ 606.170 Suspected adverse reaction investigation and reporting.

(a) Any reports of complaints of suspected adverse reactions (SAR's), as defined in § 600.80(a) of this chapter, regarding each unit of blood or blood product arising as a result of blood collection or transfusion must be investigated promptly and thoroughly. Records of the complaint and investigation must be maintained. The collection or transfusing facility must prepare and maintain a written report of the investigation of SAR's, including followup and conclusions, as part of the record for that lot or unit of final product. If it is determined that there was an SAR related to transfusion or possibly related to the collection procedure, then copies of all such reports must be forwarded to and maintained by the manufacturer or collection facility.

(b) For any serious SAR, as defined in § 600.80(a) of this chapter, except for a fatality, the facility performing the compatibility testing (if the SAR is related to transfusion) or the collecting facility (if the SAR is related to the blood

collection procedure), must submit a written report to the Center for Biologics Evaluation and Research (CBER), at FDA within 45 calendar days after determination of the serious SAR. The written report must be submitted using the reporting format provided in § 600.80(c)(4) of this chapter.

(c) For an SAR that results in a fatality, the Director, Office of Compliance and Biologics Quality, at CBER must be notified by telephone, facsimile, express mail, or electronically transmitted mail as soon as possible. Within 7 calendar days after the fatality, the collection facility (if the fatality is related to blood collection) or the facility performing the



compatibility tests (if the fatality is related to transfusion) must submit a written report to CBER, FDA, using the reporting format provided in § 600.80(c)(4) of this chapter.

(Information collection requirements approved by the Office of Management and Budget under control number 0910-0116)

Dated: _____

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