estimated SADR's are prevented, then the benefits of this proposed rule will exceed the compliance costs that it imposes on the U.S. economy. In addition, the agency has considered other alternatives as discussed in section V.E.4 of this document and determined that the proposed rule is the least burdensome and the most cost effective alternative that would meet the objectives of this rule.

V.G. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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16. Bates, David W. et al., "The Costs of Adverse Drug Events in Hospitalized Patients," Journal of the American Medical Association , 277:307-311, 1997.

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28
29. → VI. Paperwork Reduction Act of 1995

This proposed rule contains collections of information which are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes agency requests or requirements that members of the public obtain, maintain, retain, or report information to the agency, or disclose information to a third party or to the public. The title, description, and respondent description of the information collection are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, gathering

Ref 28 is "International Reporting of Periodic Drug Safety Update Summaries," Final Report of the CIOMS Working Group II, 1992.

Ref 29 is "Current Challenges in Pharmacovigilance: Pragmatic Approaches," Final Report of the CIOMS Working Group V, 2001.

and maintaining the data needed, and completing and reviewing the collection of information.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Safety Reporting Requirements for Human Drug and Biological Products

Description: The proposed rule would amend FDA's safety reporting regulations for human drug and biological products to implement definitions, and reporting formats and standards as recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and by the World Health Organization's Council for International Organizations of Medical Sciences (CIOMS); codify the agency's expectations for timely acquisition, evaluation, and submission of relevant safety information for

marketed drugs and licensed biological products; require that certain information, such as domestic reports of medication errors, be submitted to the agency in an expedited manner; clarify certain safety reporting requirements; and make other minor revisions. The proposed rule would also amend FDA's postmarketing annual reports regulations for human drugs and licensed biological products by revising the content for these reports. These changes would further worldwide consistency in the collection of safety information and submission of safety reports, increase the quality of safety reports, expedite FDA's review of critical safety information, and enable the agency to protect and promote public health.

VI.A. Expedited Safety Reporting

OMB

Proposed §§ 310.305(c)(2)(i), 314.80(c)(2)(i), and 600.80(c)(2)(i) would require manufacturers and applicants to submit a report to FDA for each SADR, 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 manufacturer or applicant of the minimum data set for the serious, unexpected SADR. Based on data concerning the number of expedited reports currently received by the agency, FDA estimates that approximately 350 expedited reports of serious and unexpected SADR's will be submitted annually under proposed § 310.305(c)(2)(i);

The estimates provided in this section are not only attributed to the new proposed requirements in this rulemaking but also include burdens associated with our current safety reporting requirements.

approximately 50,000 reports will be submitted annually under proposed § 314.80(c)(2)(i); and approximately 3,000 reports will be submitted annually under proposed § 600.80(c)(2)(i). FDA estimates that approximately 14 manufacturers under proposed § 310.305(c)(2)(i) will submit these reports; approximately 282 applicants under proposed § 314.80(c)(2)(i) will submit these reports; and approximately 69 applicants under proposed § 600.80(c)(2)(i) will submit these reports. Based on the agency's familiarity with the content of expedited reports for serious and unexpected SADR's, FDA estimates that it will take an average of 16 hours for manufacturers and applicants to prepare and submit one of these reports to FDA. Preparation of an expedited report for a serious and unexpected SADR would include gathering information (proposed §§ 310.305(b) and (c)(1), 314.80(b) and (c)(1), and 600.80(b) and (c)(1)), providing attachments, if applicable (proposed §§ 310.305(c)(2)(ix) and (c)(2)(x), 314.80(c)(2)(ix), and 600.80(c)(2)(ix)), and formatting information (proposed §§ 310.305(c)(2)(xii), (d), and (e), 314.80(c)(2)(xi), (c)(4), and (e), and 600.80(c)(2)(xi), (c)(4), and (e)).

Proposed §§ 310.305(c)(2)(ii), 314.80(c)(2)(ii), and 600.80(c)(2)(ii) would require manufacturers and applicants to submit a report to FDA concerning information, received or otherwise obtained, whether foreign or domestic, that would be

sufficient, based upon appropriate medical judgment, to consider product administration changes (e.g., any significant unanticipated safety finding or data in the aggregate from an in vitro, animal, epidemiological, or clinical study, whether or not conducted under an IND, that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease). Manufacturers and applicants would be required to submit this information to FDA as soon as possible, but in no case later than 15 calendar days after determination by the manufacturer or applicant that the information qualifies for expedited reporting. Expedited reports containing information that would be sufficient to consider changes in product administration are a new type of safety report. Based on data concerning voluntary reporting of this type of information to the agency, FDA estimates that approximately 5 expedited reports concerning information sufficient to consider product administration changes will be submitted annually under proposed § 310.305(c)(2)(ii); approximately 300 reports will be submitted annually under proposed § 314.80(c)(2)(ii); and approximately 4 reports will be submitted annually under proposed § 600.80(c)(2)(ii). FDA estimates that approximately 5 manufacturers under proposed § 310.305(c)(2)(ii) will submit

these expedited reports; approximately 50 applicants under proposed § 314.80(c)(2)(ii) will submit these expedited reports; and approximately 4 applicants under proposed § 600.80(c)(2)(ii) will submit these expedited reports. Based on the content of the voluntary reports submitted to the agency, FDA estimates that it will take an average of 8 hours for manufacturers and applicants to prepare and submit an expedited report to FDA concerning information sufficient to consider product administration changes. Preparation of these expedited reports would include gathering information (proposed §§ 310.305(b) and (c)(1), 314.80(b) and (c)(1), and 600.80(b) and (c)(1)), providing attachments, if applicable (proposed §§ 310.305(c)(2)(ix) and (c)(2)(x), 314.80(c)(2)(ix), and 600.80(c)(2)(ix)), and formatting information (proposed §§ 310.305(c)(2)(xii), (d), and (e), 314.80(c)(2)(xi), (c)(4), and (e), and 600.80(c)(2)(xi), (c)(4), and (e)).

Proposed §§ 310.305(c)(2)(iii), 314.80(c)(2)(iii), and 600.80(c)(2)(iii) would require manufacturers and applicants to submit a report to FDA for each SADR that is unexpected and for which the determination of an outcome is unattainable (i.e., SADR with unknown outcome) within 45 calendar days after initial receipt by the manufacturer or applicant of the minimum data set for an unexpected SADR. Expedited reports of unexpected SADR's with an unknown outcome are a new type of safety report. Based

on data concerning the number of unexpected SADR reports with an unknown outcome currently received by the agency, FDA estimates that approximately 46 expedited reports of an unexpected SADR with an unknown outcome will be submitted annually under proposed § 310.305(c)(2)(iii); approximately 912 reports will be submitted annually under proposed § 314.80(c)(2)(iii); and approximately 25 reports will be submitted annually under proposed § 600.80(c)(2)(iii). FDA estimates that approximately 10 manufacturers under proposed § 310.305(c)(2)(iii) will submit these expedited reports; approximately 109 applicants under proposed § 314.80(c)(2)(iii) will submit these expedited reports; and approximately 12 applicants under proposed § 600.80(c)(2)(iii) will submit these expedited reports. Based on the agency's familiarity with the content of expedited reports for serious and unexpected SADR's, FDA estimates that it will take an average of 24 hours for manufacturers and applicants to prepare and submit an expedited report for an unexpected SADR with an unknown outcome to FDA. Preparation of expedited reports for unexpected SADR's with an unknown outcome would include gathering information (proposed §§ 310.305(b) and (c)(1), 314.80(b) and (c)(1), and 600.80(b) and (c)(1)), providing attachments, if applicable (proposed §§ 310.305(c)(2)(ix) and (c)(2)(x), 314.80(c)(2)(ix), and 600.80(c)(2)(ix)), and formatting information (proposed §§ 310.305(c)(2)(xii), (d), and

(e), 314.80(c)(2)(xi), (c)(4), and (e), and 600.80(c)(2)(xi), (c)(4), and (e)).

Proposed §§ 310.305(c)(2)(iv), 314.80(c)(2)(iv), and 600.80(c)(2)(iv) would require manufacturers and applicants to submit to FDA each SADR, received or otherwise obtained, whether foreign or domestic, that is the subject of an always expedited report. Certain medically significant SADR's (e.g., ventricular fibrillation, liver necrosis, confirmed or suspected transmission of an infectious agent by a marketed drug or biological product) which may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject would be subject to an always expedited report. These SADR's would be submitted to FDA whether unexpected or expected and whether or not the SADR leads to a serious outcome. Always expedited reports would be submitted to the agency within 15 calendar days after initial receipt by the manufacturer or applicant of the minimum data set for the report. Always expedited reports are a new type of safety report. Based on data concerning the number of safety reports currently received by the agency for the SADR's specified under proposed §§ 310.305(c)(2)(iv), 314.80(c)(2)(iv), and 600.80(c)(2)(iv), FDA estimates that approximately 50 always expedited reports will be submitted annually under proposed § 310.305(c)(2)(iv); approximately 1,500 reports will be submitted annually under

proposed § 314.80(c)(2)(iv); and approximately 100 reports will be submitted annually under proposed § 600.80(c)(2)(iv). FDA estimates that approximately 10 manufacturers under proposed § 310.305(c)(2)(iv) will submit these expedited reports; approximately 100 applicants under proposed § 314.80(c)(2)(iv) will submit these expedited reports; and approximately 10 applicants under proposed § 600.80(c)(2)(iv) will submit these expedited reports. Based on the agency's familiarity with the content of expedited reports for serious and unexpected SADR's, FDA estimates that it will take an average of 16 hours for manufacturers and applicants to prepare and submit an always expedited report to the agency. Preparation of always expedited reports would include gathering information (proposed §§ 310.305(b) and (c)(1), 314.80(b) and (c)(1), and 600.80(b) and (c)(1)), providing attachments, if applicable (proposed §§ 310.305(c)(2)(ix) and (c)(2)(x), 314.80(c)(2)(ix), and 600.80(c)(2)(ix)), and formatting information (proposed §§ 310.305(c)(2)(xii), (d), and (e), 314.80(c)(2)(xi), (c)(4), and (e), and 600.80(c)(2)(xi), (c)(4), and (e)).

Proposed §§ 310.305(c)(2)(v), 314.80(c)(2)(v), and 600.80(c)(2)(v) would require manufacturers and applicants to submit all domestic reports of medication errors, whether actual or potential. Expedited reports of medication errors are a new type of safety report. Based on data concerning the number of

domestic reports of medication errors voluntarily submitted to the agency, FDA estimates that approximately 1,000 reports of medication errors will be submitted annually under proposed § 310.305(c)(2)(v); approximately 100,000 reports will be submitted annually under proposed § 314.80(c)(2)(v); and approximately 10,000 reports will be submitted annually under proposed § 600.80(c)(2)(v). FDA estimates that approximately 10 manufacturers under proposed § 310.305(c)(2)(v) will submit these expedited reports; approximately 150 applicants under proposed § 314.80(c)(2)(v) will submit these expedited reports; and approximately 30 applicants under proposed § 600.80(c)(2)(v) will submit these expedited reports. Based on the agency's familiarity with the content of expedited reports for serious and unexpected SADR's, FDA estimates that it will take an average of 16 hours for manufacturers and applicants to prepare and submit an expedited report of a medication error to the agency. Preparation of medication error reports would include gathering information (proposed §§ 310.305(b) and (c)(1), 314.80(b) and (c)(1), and 600.80(b) and (c)(1)), providing attachments, if applicable (proposed §§ 310.305(c)(2)(ix) and (c)(2)(x), 314.80(c)(2)(ix), and 600.80(c)(2)(ix)), and formatting information (proposed §§ 310.305(c)(2)(xii), (d), and (e), 314.80(c)(2)(xi), (c)(4), and (e), and 600.80(c)(2)(xi), (c)(4), and (e)).

Proposed §§ 310.305(c)(2)(vi), 314.80(c)(2)(vi), and 600.80(c)(2)(vi) would require manufacturers and applicants to submit a 30-day followup report to FDA for any expedited report under proposed §§ 310.305(c)(2)(i),(c)(2)(iv),(c)(2)(v), 314.80(c)(2)(i), (c)(2)(iv), (c)(2)(v), 600.80(c)(2)(i), (c)(2)(iv), and (c)(2)(v) that does not contain a full data set. These 30-day followup reports would be submitted within 30 calendar days after submission of the expedited report. Thirty-day followup reports are a new type of safety report. Based on data concerning the number of followup reports received by the agency, FDA estimates that approximately 340 30-day followup reports will be submitted annually under proposed § 310.305(c)(2)(vi); approximately 43,000 30-day followup reports will be submitted annually under proposed § 314.80(c)(2)(vi); and approximately 3,000 30-day followup reports will be submitted annually under proposed § 600.80(c)(2)(vi). FDA estimates that approximately 7 manufacturers under proposed § 310.305(c)(2)(vi) will submit 30-day follow up reports; approximately 140 applicants under proposed § 314.80(c)(2)(vi) will submit 30-day follow up reports; and approximately 69 applicants under proposed § 600.80(c)(2)(vi) will submit 30-day followup reports. Based on the agency's familiarity with the content of followup reports for serious and unexpected SADR's, FDA estimates that it will take an average of 8 hours for manufacturers and applicants to prepare

and submit a 30-day follow up report to the agency. Preparation of 30-day follow up reports would include gathering information (proposed §§ 310.305(b) and (c)(1), 314.80(b) and (c)(1), and 600.80(b) and (c)(1)), providing attachments, if applicable (proposed §§ 310.305(c)(2)(ix) and (c)(2)(x), 314.80(c)(2)(ix), and 600.80(c)(2)(ix)), and formatting information (proposed §§ 310.305(c)(2)(xii), (d), and (e), 314.80(c)(2)(xi), (c)(4), and (e), and 600.80(c)(2)(xi), (c)(4), and (e)).

Proposed §§ 310.305(c)(2)(vii), 314.80(c)(2)(vii), and 600.80(c)(2)(vii) would require manufacturers and applicants to submit a 15-day followup report to FDA concerning any new information, received or otherwise obtained, after any initial expedited report or any followup report, except for expedited reports which are subject to the 30-day followup reporting requirement under proposed §§ 310.305(c)(2)(vi), 314.80(c)(2)(vi), and 600.80(c)(2)(vi). Proposed §§ 310.305(b)(2), 314.80(b)(2), and 600.80(b)(2) would also require manufacturers and applicants to submit 15-day followup reports to FDA with any new information concerning an individual case safety report forwarded to the manufacturer or applicant by FDA. Proposed §§ 310.305(c)(2)(viii)(A), 314.80(c)(2)(viii)(A), and 600.80(c)(2)(viii)(A) would also require manufacturers and applicants to submit to FDA as 15-day followup reports any documents required under these paragraphs that become available

after submission of an expedited report. These 15-day followup reports would be submitted within 15 calendar days of initial receipt of the new information by the manufacturer or applicant. Based on data concerning the number of followup reports currently received by the agency, FDA estimates that approximately 55 15-day followup reports will be submitted annually under proposed § 310.305(b)(2), (c)(2)(vii), and (c)(2)(viii)(A); approximately 10,000 15-day followup reports will be submitted annually under proposed § 314.80(b)(2), (c)(2)(vii), and (c)(2)(viii)(A); and approximately 1,000 15-day followup reports will be submitted annually under proposed § 600.80(b)(2), (c)(2)(vii), and (c)(2)(viii)(A). FDA estimates that approximately 10 manufacturers under proposed § 310.305 will submit 15-day followup reports; approximately 184 applicants under proposed § 314.80 will submit 15-day followup reports; and approximately 69 applicants under proposed § 600.80 will submit 15-day followup reports. Based on the agency's familiarity with the content of followup reports for serious and unexpected SADR's, FDA estimates that it will take an average of 4 hours for manufacturers and applicants to prepare and submit a 15-day followup report to FDA. Preparation of 15-day followup reports would include gathering information (proposed §§ 310.305(b) and (c)(1), 314.80(b) and (c)(1), and 600.80(b) and (c)(1)), providing attachments, if applicable (proposed §§ 310.305(c)(2)(ix) and (c)(2)(x),

314.80(c)(2)(ix), and 600.80(c)(2)(ix)), and formatting information (proposed §§ 310.305(c)(2)(xii), (d), and (e), 314.80(c)(2)(xi), (c)(4), and (e), and 600.80(c)(2)(xi), (c)(4), and (e)).

Proposed §§ 310.305(c)(2)(xi), 314.80(c)(2)(x), and 600.80(c)(2)(x) would require contractors and shared manufacturers to submit safety reports of any SADR's or medication errors for the product to the manufacturer (proposed §§ 310.305(c)(2)(xi)) or applicant (proposed §§ 314.80(c)(2)(x) and 600.80(c)(2)(x)) within 5 calendar days of its receipt by the contractor or shared manufacturer. Based on information included in individual case safety reports currently submitted to the agency, FDA estimates that approximately 10 safety reports will be submitted to manufacturers annually under proposed § 310.305(c)(2)(xi); approximately 11,370 safety reports will be submitted to applicants annually under proposed § 314.80(c)(2)(x); and approximately 250 safety reports will be submitted to applicants annually under proposed § 600.80(c)(2)(x). FDA estimates that approximately 5 contractors under proposed § 310.305 will submit safety reports to the manufacturer; approximately 100 contractors under proposed § 314.80 will submit safety reports to the applicant; and approximately 20 contractors and shared manufacturers under proposed § 600.80 will submit safety reports to the applicant.

Based on the agency's familiarity with the content of individual case safety reports, FDA estimates that it will take an average of 2 hours for contractors and shared manufacturers to prepare and submit a safety report to a manufacturer or applicant.

Proposed § 312.32(c)(1)(i) would require sponsors to notify FDA and all participating investigators in a written IND safety report of any SADR, based on the opinion of the investigator or sponsor, that is both serious and unexpected, as soon as possible, but in no case later than 15 calendar days after receipt by the sponsor of the minimum data set for the serious, unexpected SADR. The sponsor would identify all safety reports previously filed with the IND concerning a similar SADR and would analyze the significance of the SADR in light of previous, similar reports. Based on data concerning the number of written IND safety reports currently received by the agency, FDA estimates that approximately 4,860 written IND safety reports of serious and unexpected SADR's will be submitted annually under proposed § 312.32(c)(1)(i) for human drugs, and approximately 2,980 written IND safety reports will be submitted annually under proposed § 312.32(c)(1)(i) for human biological products. FDA estimates that approximately 457 sponsors will submit written IND safety reports for human drugs, and approximately 602 sponsors will submit written IND safety reports for human biological products. Based on the agency's familiarity with the content of

written IND safety reports for serious and unexpected SADR's, FDA estimates that it will take an average of 16 hours for sponsors to prepare and submit one of these reports to FDA. Preparation of a written IND safety report for a serious and unexpected SADR would include gathering information (proposed § 312.32(b)) and formatting information (proposed § 312.32(c)(1)(iii)).

Proposed § 312.32(c)(1)(ii) would require sponsors to notify FDA and all participating investigators in a written IND safety report of information, based on appropriate medical judgment, that might materially influence the benefit-risk assessment of an investigational drug, or would be sufficient to consider changes in either product administration or in the overall conduct of a clinical investigation (e.g., any significant unanticipated safety finding or data in the aggregate from an in vitro, animal, epidemiological, or clinical study, whether or not conducted under an IND, that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease). This information would be submitted as soon as possible, but in no case later than 15 calendar days after determination by the sponsor that the information qualifies for expedited reporting. Based on information contained in written IND safety reports that the

agency has received in the past, FDA estimates that approximately 300 written IND safety reports concerning information that might materially influence the benefit-risk assessment of an investigational drug, or that would be sufficient to consider changes in either product administration or in the overall conduct of a clinical investigation will be submitted annually under proposed § 312.32(c)(1)(ii) for human drugs, and approximately 300 reports will be submitted annually under proposed § 312.32(c)(1)(ii) for human biological products. FDA estimates that approximately 100 sponsors will submit these written IND safety reports for human drugs, and approximately 100 sponsors will submit these reports for human biological products. Based on the agency's familiarity with the content of written IND safety reports, FDA estimates that it will take an average of 8 hours for sponsors to prepare and submit this type of written IND safety report to FDA. Preparation of these written IND safety reports would include gathering information (proposed § 312.32(b)) and formatting information (proposed § 312.32(c)(1)(iii)).

Proposed § 312.32(c)(2) would require sponsors to notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening SADR based on the opinion of the investigator or sponsor as soon as possible but in no case later than 7 calendar days after receipt by the sponsor of the minimum

data set for an unexpected fatal or life-threatening SADR. Based on data concerning the number of telephone IND safety reports currently received by the agency, FDA estimates that approximately 490 telephone and facsimile IND safety reports will be submitted annually under proposed § 312.32(c)(2) for human drugs, and approximately 290 reports will be submitted annually under proposed § 312.32(c)(2) for human biological products. FDA estimates that approximately 135 sponsors will submit these reports for human drugs, and approximately 180 sponsors will submit these reports for human biological products. Based on the agency's familiarity with telephone and facsimile IND safety reports, FDA estimates that it will take an average of 4 hours for sponsors to prepare and submit one of these reports to FDA. Preparation of a telephone or facsimile IND safety report would include gathering information (proposed § 312.32(b)).

Proposed § 312.64(b) would require an investigator to notify the sponsor of any serious SADR immediately and any other SADR promptly unless the protocol or investigator's brochure specifies a different timetable for reporting the SADR. Based on data concerning the number of sponsors currently conducting clinical investigations under an IND and the number of written IND safety reports currently received by the agency, FDA estimates that approximately 100,000 investigator safety reports will be submitted to sponsors annually under proposed § 312.64(b) for

human drugs, and approximately 60,000 investigator safety reports will be submitted to sponsors annually under proposed § 312.64(b) for human biological products. FDA estimates that approximately 10,000 investigators will submit safety reports to sponsors for human drugs, and approximately 6,000 investigators will submit safety reports to sponsors for human biological products. Based on the agency's familiarity with the content of IND safety reports, FDA estimates that it will take an average of 2 hours for an investigator to prepare and submit one of these reports to the sponsor.

Proposed § 320.31(d)(3) would require persons conducting human bioavailability and bioequivalence studies that are not subject to an IND to submit to FDA written safety reports as prescribed under proposed § 312.32(c)(1) and telephone and facsimile safety reports as prescribed under proposed § 312.32(c)(2). These persons would submit these safety reports 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 would be forwarded to the new drug review division that has responsibility for that drug; safety reports for the investigational drug product would be forwarded to the Director, Division of Bioequivalence, Office of Generic Drugs). These persons would be required to identify all safety reports previously filed for the bioavailability or

bioequivalence study concerning a similar SADR, and analyze the SADR in light of previous similar reports, as required under proposed § 312.32(c)(1)(i). Written, telephone, and facsimile safety reports for bioavailability and bioequivalence studies not subject to an IND are a new type of safety report. Based on data concerning voluntary reporting to the agency of safety information for these bioavailability and bioequivalence studies, FDA estimates that approximately 200 safety reports will be submitted annually under proposed § 320.31(d)(3). FDA estimates that approximately 10 sponsors will submit these safety reports. Based on the agency's familiarity with the content of IND safety reports, FDA estimates that it will take an average of 14 hours for sponsors to prepare and submit a safety report to FDA.

Proposed § 606.170(b) would require blood establishments to notify FDA in a written report of any serious SAR, except a fatality, within 45 calendar days after determination of a serious SAR. These written reports would be submitted to FDA using the reporting format provided in proposed § 600.80(c)(4). Based on data from the scientific literature and reports voluntarily received by the agency, FDA estimates that approximately 7,000 written reports will be submitted annually under proposed § 606.170(b). FDA estimates that approximately 3,062 blood establishments will submit these written reports. Based on the agency's familiarity with the content of expedited

reports for serious and unexpected SADR's, FDA estimates that it will take an average of 16 hours to prepare and submit each of these written reports to FDA.

Proposed § 606.170(c) would require blood establishments to notify FDA by telephone, facsimile, express mail, or electronically transmitted mail as soon as possible of an SAR that results in a fatality. Proposed § 606.170(c) would also require these facilities to submit a written report to FDA within 7 calendar days after the fatality. The written reports would be submitted using the reporting format provided in proposed § 600.80(c)(4). Based on data concerning the number of reports for fatalities associated with blood collection and transfusion currently received by the agency, FDA estimates that approximately 75 reports will be submitted annually under proposed § 606.170(c). FDA estimates that approximately 75 blood establishments will submit these reports. Based on the agency's familiarity with the content of written reports for a fatality, FDA estimates that it will take an average of 20 hours to prepare and submit each of these reports to FDA.

VI.B. Periodic Safety Reports

Proposed §§ 314.80(c)(3)(i) and 600.80(c)(3)(i) would require persons holding an application (i.e., NDA, ANDA, BLA) approved before January 1, 1995, to submit a TPSR every 5 years after U.S. approval of the application. These persons would also be

required to submit a TPSR at 7.5 and 12.5 years after U.S. approval of the application. Based on data concerning postmarketing periodic safety reports currently received by the agency, FDA estimates that approximately 1,400 TPSR's will be submitted annually under proposed § 314.80(c)(3)(i); approximately 35 TPSR's will be submitted annually under proposed § 600.80(c)(3)(i). FDA estimates that approximately 80 applicants under proposed § 314.80(c)(3)(i) will submit TPSR's, and approximately 20 applicants under proposed § 600.80(c)(3)(i) will submit TPSR's. Based on the agency's familiarity with the content of postmarketing periodic safety reports, FDA estimates that it will take an average of 20 hours for applicants to prepare and submit a TPSR to FDA. Preparation of a TPSR would include gathering information (proposed §§ 314.80(b) and 600.80(b)), and providing attachments (proposed §§ 314.80(c)(3) and 600.80(c)(3)).

Proposed §§ 314.80(c)(3)(ii) and 600.80(c)(3)(ii) would require persons holding an application (i.e., NDA, ANDA, BLA) approved on or after January 1, 1998[8], to submit a PSUR to FDA according to the following schedule: Semiannually for 2 years after U.S. approval of the application, annually for the next 3 years, and then every 5 years thereafter. Proposed §§ 314.80(c)(3)(i) and 600.80(c)(3)(i) would permit persons holding an application (i.e., NDA, ANDA, BLA) approved before

January 1, 1998, to submit a PSUR, in lieu of a TPSR, every 5 years after U.S. approval of the application. Proposed §§ 314.80(c)(3)(iv) and 600.80(c)(3)(iv) would require persons holding an approved supplement to an approved application for use of the human drug or biological product in the pediatric population to submit a PSUR (even if the supplement or application was approved prior to January 1, 1998) to FDA 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. Based on data concerning postmarketing periodic safety reports currently received by the agency, FDA estimates that approximately 2,500 PSUR's will be submitted annually under proposed § 314.80(c)(3)(i), (c)(3)(ii), and (c)(3)(iv), and approximately 35 PSUR's will be submitted annually under proposed § 600.80(c)(3)(i), (c)(3)(ii), and (c)(3)(iv). FDA estimates that approximately 200 applicants under proposed § 314.80(c)(3) will submit PSUR's, and approximately 20 applicants under proposed § 600.80(c)(3) will submit PSUR's. Based on the agency's familiarity with the content of PSUR's voluntarily submitted to the agency, FDA estimates that it will take an average of 40 hours for applicants to prepare and submit a PSUR to the agency. Preparation of a PSUR would include gathering

information (proposed §§ 314.80(b) and 600.80(b)) and providing attachments (proposed §§ 314.80(c)(3) and 600.80(c)(3)).

Proposed §§ 314.80(c)(3)(iii) and 600.80(c)(3)(iii) would require persons holding an application (i.e., NDA, ANDA, BLA) approved on or after January 1, 1998, to submit an IPSR to FDA 7.5 years and 12.5 years after U.S. approval of the application. Proposed §§ 314.80(c)(3)(i) and 600.80(c)(3)(i) would permit persons holding an application (i.e., NDA, ANDA, BLA) approved before January 1, 1998, to submit an IPSR at 7.5 and 12.5 years after U.S. approval of the application. Proposed §§ 314.80(c)(3)(iv) and 600.80(c)(3)(iv) would require persons holding an approved supplement to an approved application for use of the human drug or biological product in the pediatric population to submit an IPSR (even if the supplement or application was approved prior to January 1, 1998) to FDA at 7.5 and 12.5 years after U.S. approval of the supplement. Based on data concerning postmarketing periodic safety reports currently received by the agency, FDA estimates that approximately 350 IPSR's will be submitted annually under proposed § 314.80(c)(3)(i), (c)(3)(iii), and (c)(3)(iv), and approximately 3 IPSR's will be submitted annually under proposed § 600.80(c)(3)(i), (c)(3)(iii), and (c)(3)(iv). FDA estimates that approximately 40 applicants under proposed § 314.80(c)(3) will submit IPSR's, and approximately 3 applicants under proposed

§ 600.80(c)(3) will submit IPSR's. Based on the agency's familiarity with the content of PSUR's voluntarily submitted to the agency, FDA estimates that it will take an average of 30 hours for applicants to prepare and submit an IPSR to FDA. Preparation of an IPSR would include gathering information (proposed §§ 314.80(b) and 600.80(b)) and providing attachments (proposed §§ 314.80(c)(3) and 600.80(c)(3)).

Proposed §§ 314.80(c)(3)(v) and 600.80(c)(3)(v) would require persons holding an application (i.e., NDA, ANDA, BLA) to submit to FDA every 6 months after U.S. approval of the application a report that consists of individual case safety reports (i.e., FDA Form 3500A's, VAERS forms for vaccines, CIOMS I forms, if desired, for foreign SADR's) for certain spontaneously reported SADR's for marketed human drug and biological products. Applicants that submit TPSR's to FDA would submit a report consisting of individual case safety reports for each spontaneously reported serious, expected SADR, whether domestic or foreign, and each spontaneously reported nonserious, unexpected SADR occurring in the United States during the reporting period. Reports for vaccines would include a VAERS form for each spontaneously reported nonserious, expected SAR and each expected SAR with unknown outcome occurring in the United States during the reporting period. Applicants that submit PSUR's or IPSR's to FDA would submit a report consisting of

individual case safety reports for each spontaneously reported serious, listed SADR, whether domestic or foreign, and each spontaneously reported nonserious, unlisted SADR occurring in the United States during the reporting period. Reports for vaccines would include a VAERS form for each spontaneously reported nonserious, listed SAR and each listed SAR with unknown outcome occurring in the United States during the reporting period. If a full data set is not available for a report of a serious SADR, the reason(s) for the lack of such information would be provided. Based on data concerning postmarketing periodic safety reports currently received by the agency, FDA estimates that approximately 4,726 of these reports will be submitted annually under proposed § 314.80(c)(3)(v), and approximately 480 of these reports will be submitted annually under proposed § 600.80(c)(3)(v). FDA estimates that approximately 285 applicants under proposed § 314.80(c)(3) will submit these reports, and approximately 69 applicants under proposed § 600.80(c)(3) will submit reports. Based on the agency's familiarity with the content of postmarketing periodic safety reports, FDA estimates that it will take an average of 120 hours for applicants to prepare and submit a report under proposed §§ 314.80(c)(3)(v) and 600.80(c)(3)(v) to the agency. Preparation of a report under proposed §§ 314.80(c)(3)(v) and 600.80(c)(3)(v) would include gathering information (proposed

§§ 314.80(b) and (c)(1), and 600.80(b) and (c)(1)), providing attachments, if applicable (proposed §§ 314.80(c)(2)(ix) and (c)(3), and 600.80(c)(2)(ix) and (c)(3)), and formatting information (proposed §§ 314.80(c)(4) and (e), and 600.80(c)(4) and (e)).

VI.C. Other Reports

Proposed §§ 310.305(f)(1), 314.80(f), and 600.80(f) would require manufacturers, applicants, contractors, and shared manufacturers to submit to FDA, when appropriate, any or all records required to be maintained by these persons. These records would be required to be submitted within 5 calendar days after receipt of the request by the person. Records of all safety information pertaining to the person's 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 would be included, as well as records required to be maintained under proposed § 310.305 (§ 310.305(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(xi)(C)), proposed § 314.80 (§ 314.80(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(x)(C)), and proposed § 600.80 (§ 600.80(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(x)(C)). Submission of SADR records to FDA represents a new reporting

requirement. Based on the agency's requests for voluntary submission of safety records, FDA estimates that approximately 2 requests for submission of records will be fulfilled annually under proposed § 310.305(f)(1), approximately 15 requests for submission of records will be fulfilled annually under proposed § 314.80(f), and approximately 4 requests for submission of records will be fulfilled annually under proposed § 600.80(f). FDA estimates that approximately 2 manufacturers and contractors under proposed § 310.305 will submit these records, approximately 15 applicants and contractors under proposed § 314.80 will submit these records, and approximately 4 applicants, contractors and shared manufacturers under proposed § 600.80 will submit these records. Based on the volume of safety information voluntarily submitted to FDA in response to an agency request for such information, FDA estimates that it will take an average of 8 hours for manufacturers, applicants, contractors, and shared manufacturers to fulfill each request for submission of records to the agency.

Proposed § 314.81(b)(2) would require applicants of marketed drug products subject to an NDA to submit an annual report to FDA within 60 days of the anniversary date of U.S. approval of the application. This report would contain summary information; distribution data; chemistry, manufacturing, and controls changes; clinical data; and a status report of any

postmarketing studies performed by, or on behalf of, the applicant. Based on data concerning the number of approved NDA annual reports received by the agency, FDA estimates that approximately 2,363 reports will be submitted under proposed § 314.81(b)(2). FDA estimates that approximately 286 applicants will submit these reports. Based on the agency's familiarity with the content of approved NDA annual reports, FDA estimates that it will take an average of 35.5 hours for applicants to prepare and submit one of these annual reports to FDA.

Proposed § 601.37 would require applicants of licensed biological products to submit an annual report of postmarketing pediatric studies to FDA within 60 days of the anniversary date of approval of the application. This report would contain summary information, clinical data in the pediatric population, and a status report of any postmarketing studies in the pediatric population. Based on data concerning the number of approved BLA annual reports received by the agency, FDA estimates that approximately 69 reports will be submitted under proposed § 601.37. FDA estimates that approximately 69 applicants will submit these reports. Based on the agency's familiarity with the content of approved BLA annual reports, FDA estimates that it will take an average of 25 hours for applicants to prepare and submit an annual report to the agency.

VI.D. Recordkeeping

Proposed §§ 310.305(c)(2)(xi)(B), 314.80(c)(2)(x)(B), and 600.80(c)(2)(x)(B) would require that contracts between manufacturers and contractors (proposed § 310.305(c)(2)(xi)(B)) and applicants and contractors (proposed §§ 314.80(c)(2)(x)(B) and 600.80(c)(2)(x)(B)) specify the safety reporting responsibilities of the contractor. For purposes of this section, a record represents a contract. Based on information contained in individual case safety reports submitted to the agency in the past (i.e., report source), FDA estimates that approximately 4 records will be maintained annually under proposed § 310.305(c)(2)(xi)(B), approximately 480 records will be maintained annually under proposed § 314.80(c)(2)(x)(B), and approximately 2 records will be maintained annually under proposed § 600.80(c)(2)(x)(B). FDA estimates that approximately 2 manufacturers under proposed § 310.305 will maintain these records, approximately 160 applicants under proposed § 314.80 will maintain these records, and approximately 2 applicants under proposed § 600.80 will maintain these records. Based on the agency's familiarity with recordkeeping processes, FDA estimates that it will take an average of 1 hour for manufacturers and applicants to maintain each record annually under proposed §§ 310.305(c)(2)(xi)(B), 314.80(c)(2)(x)(B), and 600.80(c)(2)(x)(B).

Proposed §§ 310.305(f), 314.80(f), and 600.80(f) would require manufacturers, applicants, contractors, and shared manufacturers to maintain for a period of 10 years records of all safety information, 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. These persons would also be required to retain for a period of 10 years any records required to be maintained under proposed § 310.305 (§ 310.305(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(xi)(C)), proposed § 314.80 (§ 314.80(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(x)(C)), and proposed § 600.80 (§ 600.80(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(x)(C)). For the purposes of this section, a record includes any and all documentation regarding an individual SADR or medication error. Based on data concerning the number of SADR's currently reported to the agency, FDA estimates that approximately 500 records will be maintained annually under proposed § 310.305(f), approximately 220,000 records will be maintained annually under proposed § 314.80(f), and approximately 20,000 records will be maintained annually under proposed § 600.80(f). FDA estimates that approximately 25 manufacturers and contractors under proposed § 310.305 will maintain these records, approximately 700

applicants and contractors under proposed § 314.80 will maintain these records, and approximately 69 applicants, contractors, and shared manufacturers under proposed § 600.80 will maintain these records. Based on the agency's familiarity with recordkeeping processes, FDA estimates that it will take an average of 5 hours for manufacturers, applicants, contractors, and shared manufacturers to maintain each record annually under proposed §§ 310.305, 314.80, and 600.80.

Proposed §§ 310.305(g), 314.80(g), and 600.80(g) would require manufacturers, applicants, contractors, and shared manufacturers to maintain written procedures for the surveillance, receipt, evaluation, and reporting of safety information to FDA. Based on the number of persons subject to the postmarketing safety reporting regulations, FDA estimates that approximately 25 records will be maintained annually under proposed § 310.305(g), approximately 700 records will be maintained annually under proposed § 314.80(g), and approximately 69 records will be maintained annually under proposed § 600.80(g). FDA estimates that approximately 25 manufacturers and contractors under proposed § 310.305 will maintain these records, approximately 700 applicants and contractors under proposed § 314.80 will maintain these records, and approximately 69 applicants, contractors, and shared manufacturers under proposed § 600.80 will maintain these records. Based on the

agency's familiarity with recordkeeping processes, FDA estimates that it will take an average of 1 hour for manufacturers, applicants, contractors, and shared manufacturers to maintain a record of the written procedures annually under proposed §§ 310.305(g), 314.80(g), and 600.80(g).

Proposed § 312.32(c) would require sponsors to maintain records for reports of SADR's that do not contain a minimum data set. This would include any information received or otherwise obtained for the SADR along with a record of their efforts to obtain a minimum data set for the report. For the purposes of this section, a record includes any and all documentation regarding an individual SADR. Maintaining records of SADR's that do not contain a minimum data set represents a new recordkeeping requirement. Based on information contained in IND safety reports, FDA estimates that approximately 200 records will be maintained annually under proposed § 312.32(c) for human drugs; approximately 240 records will be maintained annually under proposed § 312.32(c) for human biological products. FDA estimates that approximately 50 sponsors will maintain these records for human drugs and approximately 60 sponsors will maintain these records for human biological products. Based on the agency's familiarity with recordkeeping processes, FDA estimates that it will take an average of 1 hour for sponsors to maintain each record annually under proposed § 312.32(c).

Proposed § 606.170(a) would require blood collection and transfusing facilities to maintain records for complaints of SAR's regarding each unit of blood or blood product. These facilities must prepare a written report of the investigation of SAR's, including followup and conclusions. Based on data for records currently maintained by blood collection and transfusing facilities, FDA estimates that approximately 4,512 records will be maintained annually under proposed § 606.170(a). FDA estimates that approximately 376 facilities will maintain these records. Based on the agency's familiarity with recordkeeping processes, FDA estimates that it will take an average of 12 hours for facilities to maintain each record annually under proposed § 606.170(a).

Description of Respondents: Business or other for-profit organizations.

In compliance with section 3507(d) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted a copy of this proposed rule to OMB for its review and approval of these information collections. Interested persons are requested to send comments regarding this information collection, including suggestions for reducing this burden, to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA. Submit written comments on the information

collection by [insert date 30 days after date of publication in the FEDERAL REGISTER].

Table 21.--Estimated Annual Reporting Burden[1]

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours Per Response	Total Hours
310.305(c)(2)(i)[2]	14	25	350	16	5,600
310.305(c)(2)(ii)	5	1	5	8	40
310.305(c)(2)(iii)	10	4.6	46	24	1,104
310.305(c)(2)(iv)	10	5	50	16	800
310.305(c)(2)(v)	10	100	1,000	16	16,000
310.305(c)(2)(vi)	7	48.6	340	8	2,720
310.305(b)(2), (c)(2)(vii), and (c)(2)(viii)(A)	10	5.5	55	4	220
310.305(c)(2)(xi)	5	2	10	2	20
310.305(f)(1)	2	1	2	8	16

Table 21.--Estimated Annual Reporting Burden[1] (Continued)

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours Per Response	Total Hours
312.32(c)(1)(i)[3] -- human drugs	457	10.6	4,860	16	77,760
312.32(c)(1)(ii) -- human drugs	100	3	300	8	2,400
312.32(c)(2) -- human drugs	135	3.6	490	4	1,960
312.32(c)(1)(i) -- human biological products	602	4.9	2,980	16	47,680
312.32(c)(1)(ii) -- human biological products	100	3	300	8	2,400
312.32(c)(2) -- human biological products	180	1.6	290	4	1,160
312.64(b) -- human drugs	10,000	10	100,000	2	200,000
312.64(b) -- human biological products	6,000	10	60,000	2	120,000

Table 21.--Estimated Annual Reporting Burden[1] (Continued)

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours Per Response	Total Hours
314.80(c)(2)(i)[4]	282	177.3	50,000	16	800,000
314.80(c)(2)(ii)	50	6	300	8	2,400
314.80(c)(2)(iii)	109	8.4	912	24	21,888
314.80(c)(2)(iv)	100	15	1,500	16	24,000
314.80(c)(2)(v)	150	666.7	100,000	16	1,600,000
314.80(c)(2)(vi)	140	307.1	43,000	8	344,000
314.80(b)(2), (c)(2)(vii), and (c)(2)(viii)(A)	184	54.3	10,000	4	40,000
314.80(c)(2)(x)	100	113.7	11,370	2	22,740
314.80(c)(3)(i)	80	17.5	1,400	20	28,000
314.80(c)(3)(i), (c)(3)(ii), and (c)(3)(iv)	200	12.5	2,500	40	100,000
314.80(c)(3)(i), (c)(3)(iii), and (c)(3)(iv)	40	8.7	350	30	10,500
314.80(c)(3)(v)	285	16.6	4,726	120	567,120
314.80(f)	15	1	15	8	120
314.81(b)(2)	286	8.3	2,363	35.5	83,886

Table 21.--Estimated Annual Reporting Burden[1] (Continued)

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours Per Response	Total Hours
320.31(d)(3)	10	20	200	14	2,800
600.80(c)(2)(i)[5]	69	43.5	3,000	16	48,000
600.80(c)(2)(ii)	4	1	4	8	32
600.80(c)(2)(iii)	12	2.1	25	24	600
600.80(c)(2)(iv)	10	10	100	16	1,600
600.80(c)(2)(v)	30	333.3	10,000	16	160,000
600.80(c)(2)(vi)	69	43.5	3,000	8	24,000
600.80(b)(2), (c)(2)(vii), and (c)(2)(viii)(A)	69	14.5	1,000	4	4,000
600.80(c)(2)(x)	20	12.5	250	2	500
600.80(c)(3)(i)	20	1.8	35	20	700

Table 21.--Estimated Annual Reporting Burden[1] (Continued)

21 CFR Section	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours Per Response	Total Hours
600.80(c)(3)(i), (c)(3)(ii), and (c)(3)(iv)	20	1.8	35	40	1,400
600.80(c)(3)(i), (c)(3)(iii), and (c)(3)(iv)	3	1	3	30	90
600.80(c)(3)(v)	69	6.9	480	120	57,600
600.80(f)	4	1	4	8	32
601.37	69	1	69	25	1,725
606.170(b)	3,062	2.3	7,000	16	112,000
606.170(c)	75	1	75	20	1,500
Total	23,283	2,149.7	424,794	896.5	4,541,113

[1]There are no capital costs or operating and maintainence costs associated with this collection of information.

[2]The paragraphs of § 310.305 cited in the table include burdens associated with gathering information under § 310.305(b) and (c)(1), providing attachments, if applicable, under § 310.305(c)(2)(ix) and (c)(2)(x), and formatting information under § 310.305(c)(2)(xii), (d), and (e).

[3]The paragraphs of § 312.32 cited in the table include burdens associated with gathering information under § 312.32(b) and formatting information under § 312.32(c)(1)(iii).

[4]The paragraphs of § 314.80 cited in the table include burdens associated with gathering information under § 314.80(b) and (c)(1), providing attachments, if applicable, under § 314.80(c)(2)(ix) and (c)(3), and formatting information under § 314.80(c)(2)(xi), (c)(4), and (e).

[1] *The estimates provided in this table are not only attributed to the new proposed requirements in this rulemaking but also include burdens associated with our current safety reporting requirements.*

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[5]The paragraphs of § 600.80 cited in the table include burdens associated with gathering information under § 600.80(b) and (c)(1), providing attachments, if applicable, under § 600.80(c)(2)(ix) and (c)(3), and formatting information under § 600.80(c)(2)(xi), (c)(4), and (e).

Table 22.--Estimated Annual Recordkeeping Burden (1)

21 CFR Section	Number of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Record	Total Hours
310.305(c)(2)(xi)(B)	2	2	4	1	4
310.305(f)[2]	25	20	500	5	2,500
310.305(g)	25	1	25	1	25
312.32(c)--human drugs	50	4	200	1	200
312.32(c)--human biological products	60	4	240	1	240
314.80(c)(2)(x)(B)	160	3	480	1	480
314.80(f)[3]	700	314.3	220,000	5	1,100,000
314.80(g)	700	1	700	1	700
600.80(c)(2)(x)(B)	2	1	2	1	2
600.80(f)[4]	69	289.8	20,000	5	100,000
600.80(g)	69	1	69	1	69
606.170(a)	376	12	4,512	12	54,144
Total	2,238	653.1	246,732	35	1,258,364

2 Includes records required to be maintained under § 310.305(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A); and (c)(2)(xi)(C).

3 Includes records required to be maintained under § 314.80(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(x)(C).

4 Includes records required to be maintained under § 600.80(c)(1)(ii), (c)(1)(iii)(A), (c)(2)(ii), (c)(2)(viii)(A), and (c)(2)(x)(C).

[1] *The estimates provided in this table are not only attributed to the new proposed requirements in this rulemaking but also include burdens associated with our current safety reporting requirements. There are no capital costs or operating costs associated with this collection of information. There are maintenance costs of $2,025 annually per recordkeeper ($2,000 annually per recordkeeper for existing recordkeeping requirements (see 67 FR 47821) and $25 annually per recordkeeper*

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VII. Executive Order 13132: Federalism

Executive Order 13132 requires Federal agencies to carefully examine regulatory actions to determine if they would have a significant impact on federalism. Using the criteria and principles set forth in the Order, the agency has considered the impact of this proposed rule on the States, on their relationship with the Federal Government, and on the distribution of power and responsibilities among the various levels of government.

FDA is publishing this proposed rule to revise its regulations governing the format, content, and submission of safety reports to the agency for human drugs and biological products. The proposal would revise current regulations to implement definitions and reporting formats and standards recommended by ICH and CIOMS. The proposal would codify the agency's expectations for timely acquisition, evaluation, and submission of relevant safety information for marketed drugs and biological products. The proposal would require that postmarketing individual case safety reports of unexpected SADR's that cannot be classified as either serious or nonserious be submitted to the agency in an expedited manner. The proposal would also require that certain medically significant SADR's always be submitted to FDA in an expedited manner whether the SADR is unexpected or expected. The proposal would also require that all domestic reports of medication errors, whether actual or

potential, be submitted to FDA in an expedited manner. The proposal would clarify certain safety reporting requirements and make other minor revisions. The proposal would also amend the agency's postmarketing annual reports regulations for applicants of human drugs and licensed biological products to revise the content for these reports. The proposal would also amend the agency's bioavailability and bioequivalence study regulations for sponsors of human drugs to require expedited safety reports for certain studies which are exempt from submission of an IND. Because enforcement of these safety reporting requirements would be a Federal responsibility, there would be little, if any, impact on the States from this rule if finalized.

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 320

Drugs, Reporting and recordkeeping requirements.

21 CFR Part 600

Biologics, Reporting and recordkeeping requirements.

21 CFR Part 601

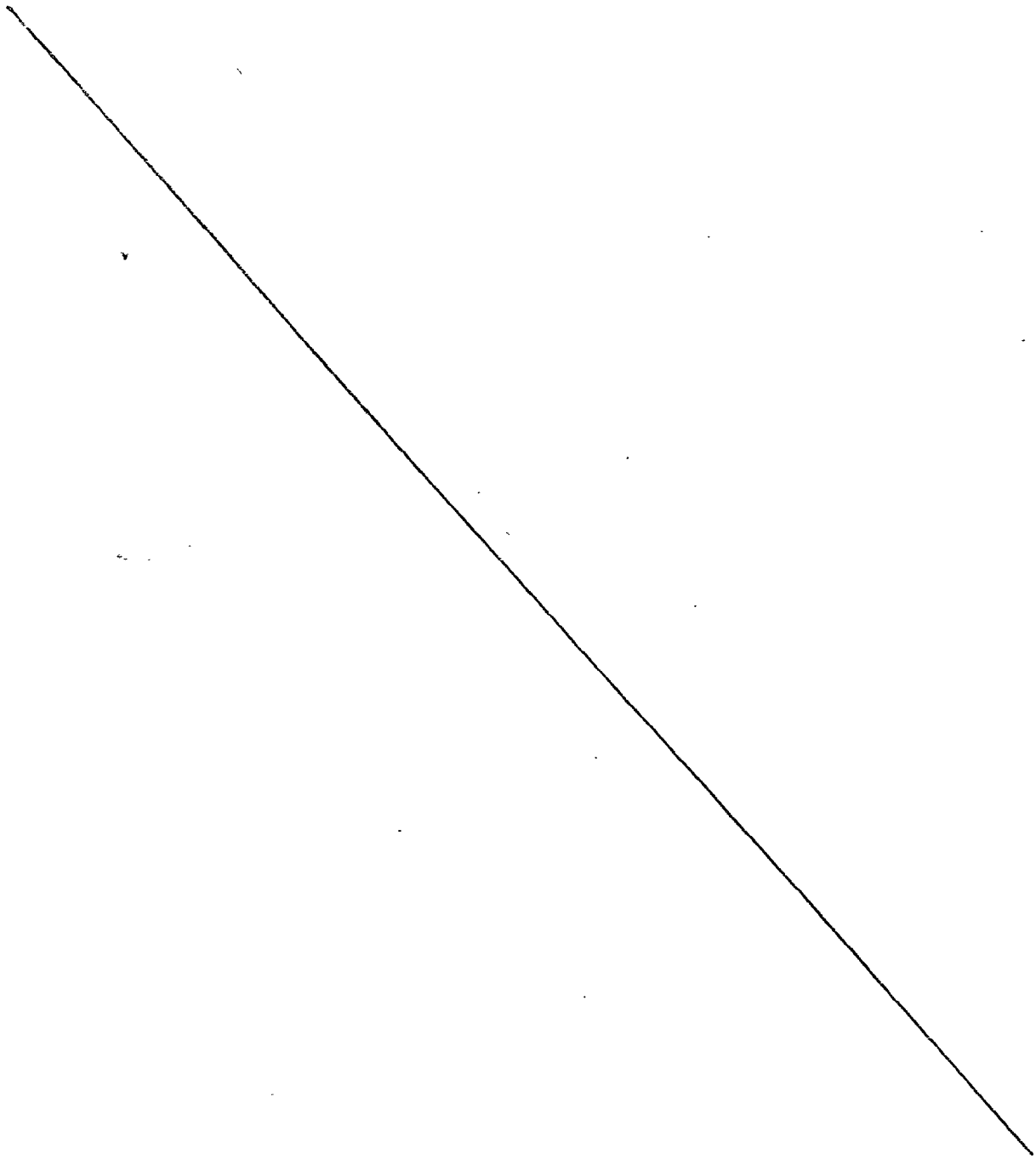
Administrative practice and procedure, Biologics, Confidential business information.

21 CFR Part 606

Blood, Labeling, Laboratories, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR

parts 310, 312, 314, 320, 600, 601, and 606 be amended as follows:



PART 310--NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b-360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b-263n.

2. Section 310.305 is revised to read as follows:

§ 310.305 Safety reporting and recordkeeping for manufacturers of prescription drugs marketed for human use without an approved application.

(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 drug reaction (SADR) or a medication error by a health care professional (e.g., physician, physician assistant, pharmacist, dentist, nurse, any individual with some form of health care training) representing the manufacturer. For SADRs, active query entails, at a minimum, a focused line of questioning designed to capture clinically relevant information associated with the drug product and the SADR, 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 SADR, nonserious SADR, or no SADR.

Contractor means any person (e.g., 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 manufacturer to manufacture, pack, sell, distribute, or develop the drug or to maintain, create, or submit records regarding SADR's or medication errors.

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 on a Council for International Organizations of Medical Sciences (CIOMS) I form for reports of foreign SADR's), including a concise medical narrative of the case (i.e., an accurate summary of the relevant data and information pertaining to an SADR or medication error).

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

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 drug product, and an SADR.

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

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.

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

Serious SADR means any SADR that results in any of the following outcomes: Death, a life-threatening SADR, 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 SADR 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 SADR or medication error. It does not include cases identified from information solicited by the 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 drug reaction (SADR) means a noxious and unintended response to any dose of a drug 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 SADR means any SADR that is not included in the current U.S. labeling for the drug 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 SADR that has not been previously observed (i.e., included in the U.S. labeling); it does not refer to an SADR that might be anticipated from the pharmacological properties of the drug product. SADR's that are mentioned in the U.S. labeling as occurring with a class of drugs but not specifically mentioned as occurring with the particular drug are considered unexpected.

(b) Review of safety information. (1) Each manufacturer of a prescription drug product marketed for human use without an approved application must promptly review all safety information pertaining to its product obtained or otherwise received by the manufacturer 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 manufacturers 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 manufacturer.

(2) Individual case safety reports that are forwarded to the manufacturer by FDA must not be resubmitted to the agency by the manufacturer; however, manufacturers must submit to FDA all followup information for these reports.

(c) Reporting requirements. The manufacturer must submit to FDA one copy of each expedited report (described under paragraphs (c)(2)(i) through (c)(2)(vii) of this section) pertaining to its drug product. Upon written notice, FDA may require, when appropriate, that the manufacturer submit reports under this section to FDA at times other than those stated.

(1) Determination of outcome, minimum data set, and full data set--(i)(A) Initial determinations. Upon initial receipt of an SADR report, the manufacturer must immediately determine, ~~using active query,~~ the outcome for the SADR (whether the SADR is serious or nonserious) and at least the minimum data set for the individual case safety report. For reports of actual medication errors that do not result in an SADR and potential medication

errors, the manufacturer 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 manufacturer 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 drug product caused the spontaneously reported event.

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

(ii) SADR's with unknown outcome. For an SADR with unknown outcome that cannot be immediately determined, the manufacturer must continue to use active query to attempt to determine the outcome of the SADR within 30 calendar days after initial receipt of the SADR report by the manufacturer. The manufacturer must maintain a record of its efforts to determine the outcome for an SADR with unknown outcome.

(iii)(A) Minimum data set for SADR reports. The manufacturer must not submit an individual case safety report for an SADR to FDA if the report does not contain a minimum data set; instead, the manufacturer must maintain records of any

information received or otherwise obtained for the SADR 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 SADR. For reports of actual medication errors that do not result in an SADR, 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 SADR). These reports must contain at least an identifiable patient, an identifiable reporter, and a suspect drug 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 SADR). These reports must contain at least an identifiable reporter and a suspect drug product.

(iv) Full data set. For reports of serious SADR'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 manufacturer must ~~use active query to obtain~~ submit a full data set. If a full data set ~~cannot be obtained~~ is not available for the report, the manufacturer must: use active query to obtain this information. If a full data set is not obtainable, after active query, the manufacturer 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 SADR's not initially reported by health care professional. For a serious SADR that was not initially reported to the manufacturer by a health care professional (e.g., report from a consumer), ~~active query must be used by~~ the manufacturer 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.

(2) Postmarketing "expedited reports"--(i) Serious and unexpected SADR. The manufacturer must report to FDA each SADR, 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 manufacturer of the minimum data set for the serious, unexpected SADR. If a full data set is not available for the serious and unexpected SADR report at the time of initial submission of the report to FDA, the manufacturer 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.

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.

(ii) Information sufficient to consider product administration changes. The manufacturer 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 manufacturer must submit this information to FDA, as soon as possible, but in no case later than 15 calendar days after determination by the manufacturer that the information qualifies for expedited reporting. Examples of such information include any significant unanticipated safety finding or data in the aggregate from an in vitro, animal, epidemiological, or clinical study, whether or not conducted under an 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 drug product used in treating a life-threatening or serious disease. The manufacturer 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 SADR with unknown outcome. The manufacturer must also report to FDA each SADR that is unexpected and for which the determination of an outcome is unattainable (i.e., SADR with unknown outcome) within 45 calendar days after initial receipt by the manufacturer of the minimum data set for

the unexpected SADR. The manufacturer must document in the expedited report the reason(s) for the inability to determine the outcome.

(iv) Always expedited report. (A) The manufacturer must also report to FDA each SADR, 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 manufacturer of the minimum data set for the report. The following medically significant SADR's, which may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject, 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 SADR that FDA determines to be the subject of an always expedited report (i.e., may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject).

(B) SADR's that are the subject of an always expedited report must be submitted to FDA whether unexpected or expected and whether or not the SADR 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 manufacturer 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 errors--(A) Actual medication error. The manufacturer must also submit to FDA each domestic report of an actual medication error, received or otherwise obtained, as soon as possible, but in no case later than 15 calendar days after

receipt by the manufacturer of the minimum data set for a report of an SADR or, if an SADR does not occur, the minimum information described under paragraph (c)(1)(iii)(B) of this section (i.e., identifiable patient, identifiable reporter, and suspect drug product).

(B) Potential medication error. The manufacturer 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 manufacturer of the minimum information described under paragraph (c)(1)(iii)(C) of this section (i.e., identifiable reporter and suspect drug 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 manufacturer 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 manufacturer 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

manufacturer. 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 manufacturer 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 manufacturer. 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 manufacturer must submit a copy of the autopsy report to FDA, if it is available. If an autopsy report is not available, the manufacturer must submit a death certificate to FDA. If an

autopsy report becomes available after the manufacturer has submitted a death certificate to the agency, the autopsy report must be submitted to FDA. If the patient was hospitalized, the manufacturer 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. Manufacturers 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) in this section) within 15 calendar days of initial receipt of the document by the manufacturer. 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 manufacturer 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 manufacturer.

(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 manufacturer. When appropriate, FDA may require a manufacturer 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) Attachments. Each expedited report must be accompanied by a copy of the current U.S. labeling for the drug product and a list of current addresses where all safety reports and other safety-related records for the drug product are maintained by manufacturers and contractors.

(xi) Submission of safety reports by contractors. (A) Contractors must submit to the manufacturer safety reports of any SADR's or medication errors for the manufacturer's drug product, obtained or otherwise received, within 5 calendar days of initial receipt of the report by the contractor. The contractor must submit a safety report for an SADR to the manufacturer even if the report does not contain a minimum data set. Upon receipt of the safety report from a contractor, the manufacturer must comply with the postmarketing safety reporting requirements of this section.

(B) A contract between the manufacturer and a contractor must specify the postmarketing safety reporting responsibilities

of the contractor. The manufacturer is responsible for ensuring that the contractors of its drug products comply with these postmarketing safety reporting responsibilities.

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

(1) A copy of each safety report;

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

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

(4) The name and address of the manufacturer.

(D) The recordkeeping, written procedures, and disclaimer provisions under paragraphs (f) through (h) of this section apply to contractors.

(xii) 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--§ 310.305--serious and unexpected SADR," "expedited report--§ 310.305--30-day followup report." Each type of report (e.g., serious and unexpected SADR 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 SADR, nonserious SADR, or no SADR occurred, e.g., "expedited report--§ 310.305--actual medication error--nonserious SADR," "expedited report--§ 310.305--potential medication error."

(d) Reporting format. (1)(i) Except as provided in paragraphs (d)(1)(ii), (d)(1)(iv), and (d)(5) of this section, the manufacturer must complete an FDA Form 3500A for each individual case safety report of an SADR. Reports based on information about individual cases or case series in the scientific literature must be submitted on an FDA Form 3500A(s).

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

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

(iv) 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.

(2) 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 manufacturer 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.

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

(4) 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).

(5) Instead of using FDA Form 3500A, the manufacturer 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.

(e) Patient privacy. The names and addresses of individual patients should not be included in reports under this section; instead, the manufacturer and its contractors should assign a unique code to each report, preferably not more than eight characters (i.e., numbers/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. (1) Each manufacturer 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. The manufacturer must also retain for a period of 10 years any records required to be maintained under this section. When appropriate, FDA may require a manufacturer to submit any or all of these records to the agency within 5 calendar days after receipt of the request.

(2) Manufacturers and packers may retain the records required in paragraph (f)(1) of this section as part of its complaint files maintained under § 211.198 of this chapter.

(3) Manufacturers must permit any authorized FDA employee, at all reasonable times, to have access to and copy and verify the records established and maintained under this section.

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

(h) Disclaimer. A report or information submitted by a manufacturer under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the manufacturer or by FDA, that the report or information constitutes an admission that the drug caused or contributed to an SADR. The manufacturer 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.

PART 312--INVESTIGATIONAL NEW DRUG APPLICATION

3. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 371; 42 U.S.C. 262.

4. Section 312.32 is amended by revising paragraphs (a), (b), the introductory text of paragraph (c), paragraphs (c)(1) and (c)(4), and the first sentence of paragraph (c)(2); in paragraph (d)(3) by removing the phrase "adverse drug experience" and by adding in its place the abbreviation "SADR" and by removing the phrase "such experience" and by adding in its place the phrase "such reaction"; and in paragraph (e) by removing the phrase "adverse experience" both times it appears and by adding in its place the abbreviation "SADR" to read as follows:

§ 312.32 IND safety reports.

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

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

Life-threatening suspected adverse drug reaction (SADR) means any SADR that, in the view of the investigator or sponsor, places the patient or subject at immediate risk of death from the SADR as it occurred. It does not include an SADR that, had it occurred in a more severe form, might have caused death.

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

Serious SADR means any SADR that results in any of the following outcomes: Death, a life-threatening SADR, 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 SADR 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.

Suspected adverse drug reaction (SADR) means a noxious and unintended response to any dose of a drug 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 SADR means any SADR, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only included cerebral vascular accidents. "Unexpected," as used in this definition, refers to an SADR that has not been previously observed (e.g., included in the investigator brochure); it does not refer to an SADR that might be anticipated from the pharmacological properties of the drug product. SADR's that are mentioned in the investigator's

brochure as occurring with a class of drugs but not specifically mentioned as occurring with the particular drug are considered unexpected.

(b) Review of safety information. The sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not been previously reported to FDA by the sponsor and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

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

(1) Written reports--(i) Serious and unexpected SADR. The sponsor must notify FDA and all participating investigators in a written IND safety report of any SADR that, based on the opinion of the investigator or sponsor, is both serious and unexpected, as soon as possible, but in no case later than 15 calendar days

after receipt by the sponsor of the minimum data set for the serious, unexpected SADR. The sponsor must identify all safety reports previously filed with the IND concerning a similar SADR, and must analyze the significance of the SADR in light of previous, similar reports.

(ii) Information sufficient to consider product administration changes. The sponsor must also notify FDA and all participating investigators in a written IND safety report of information that, based upon appropriate medical judgment, might materially influence the benefit-risk assessment of an investigational drug or that would be sufficient to consider changes in either product administration or in the overall conduct of a clinical investigation. The sponsor must submit this information to FDA and all participating investigators as soon as possible, but in no case later than 15 calendar days after the determination by the sponsor that the information qualifies for reporting under this paragraph. Examples of such information include any significant unanticipated safety finding or data in the aggregate from an in vitro, animal, epidemiological, or clinical study, whether or not conducted under an IND, that suggests a significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity or reports of a lack of efficacy with a drug product used in treating a life-threatening or serious disease.

(iii) Submission of written reports. Each written report may be submitted on an FDA Form 3500A or in a narrative format. Foreign SADR's may be submitted either on an FDA Form 3500A or, if preferred, on a Council for International Organizations of Medical Sciences (CIOMS) I form. 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. Each written notice must bear prominent identification of its contents, i.e., "IND safety report." Each written notification to FDA must be transmitted to the FDA review division that has responsibility for the review of the IND. If FDA determines that additional data are needed, the agency may require further data to be submitted.

(2) Telephone and facsimile transmission safety reports. The sponsor must also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening SADR based on the opinion of the investigator or sponsor as soon as possible but in no case later than 7 calendar days after receipt by the sponsor of the minimum data set for the unexpected fatal or life-threatening SADR. * * *

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(4) Investigations of marketed drugs. A sponsor of a clinical study under an IND for a drug marketed in the United States is only required to submit IND safety reports to FDA

(review division that has responsibility for the IND) for SADR's from the clinical study itself, whether from domestic or foreign study sites of the IND. The sponsor must also submit to FDA safety information from these clinical studies as prescribed by the postmarketing safety reporting requirements under §§ 310.305, 314.80, and 600.80 of this chapter.

* * * * *

5. Section 312.64 is amended by revising paragraph (b) to read as follows:

§ 312.64 Investigator reports.

* * * * *

(b) Safety reports. An investigator must report to the sponsor any serious SADR (as defined in § 312.32(a)) immediately and any other SADR (as defined in § 312.32(a)) promptly unless the protocol or investigator's brochure specifies a different timetable for reporting the SADR.

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PART 314--APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG

6. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 371, 374, 379e.

7. Section 314.80 is revised to read as follows:

§ 314.80 Postmarketing safety reporting and recordkeeping.

(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 drug reaction (SADR) or medication error by a health care professional (e.g., physician, physician assistant, pharmacist, dentist, nurse, any individual with some form of health care training) representing the applicant. For SADR's, active query entails, at a minimum, a focused line of questioning designed to capture clinically relevant information associated with the drug product and the SADR, 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 SADR, nonserious SADR, or no SADR.

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 drug substance. 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 drug substance. It is the reference information by which an SADR 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, packer or distributor whether its name appears on the label of the product; licensee; contract research organization) that has entered into a contract with the applicant to manufacture, pack, sell, distribute, or develop the drug or to maintain, create, or submit records regarding SADR'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 on a Council for International

Organizations of Medical Sciences (CIOMS) I form for reports of foreign SADR's), including a concise medical narrative of the case (i.e., an accurate summary of the relevant data and information pertaining to an SADR or medication error).

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

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

Listed SADR means an SADR 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 drug product, and an SADR.

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

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.

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

Serious SADR means any SADR that results in any of the following outcomes: Death, a life-threatening SADR, 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 SADR 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 SADR or medication error. It does not include cases identified from information solicited by the applicant 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 drug reaction (SADR) means a noxious and unintended response to any dose of a drug 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 SADR means any SADR that is not included in the current U.S. labeling for the drug 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 SADR that has not been previously observed (i.e., included in the U.S. labeling); it does not refer to an SADR that might be anticipated from the pharmacological properties of the drug product. SADR's that are mentioned in the U.S. labeling as occurring with a class of drugs but not specifically mentioned as occurring with the particular drug are considered unexpected.

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

(b) Review of safety information. (1) Each applicant having an approved application for a drug product under section 505(c) of the act 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 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. 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 one copy of 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 drug product. 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 for a human drug product covered by the report. 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 FDA 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 § 314.90.

(1) Determination of outcome, minimum data set, and full data set--(i)(A) Initial determinations. Upon initial receipt of an SADR report, the applicant must immediately determine ~~using active~~ query the outcome for the SADR (whether the SADR is serious or nonserious) and at least the minimum data set for the individual case safety report. For reports of actual medication errors that do not result in an SADR 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 determine the information immediately 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 drug product caused the spontaneously reported event.

(C) Clinical trials. For a clinical trial, the possibility that the drug product caused the SADR 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) SADR's with unknown outcome. For an SADR with unknown outcome that cannot be immediately determined, the applicant must

continue to use active query to attempt to determine the outcome of the SADR within 30 calendar days after initial receipt of the SADR report by the applicant. The applicant must maintain a record of its efforts to determine the outcome for an SADR with unknown outcome.

(iii)(A) Minimum data set for SADR reports. The applicant must not submit an individual case safety report for an SADR 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 SADR 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 SADR. For reports of actual medication errors that do not result in an SADR, 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 SADR). These reports must contain at least an identifiable patient, an identifiable reporter, and a suspect drug 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 SADR). These reports must

contain at least an identifiable reporter and a suspect drug product.

(iv) Full data set. For reports of serious SADR'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 ~~cannot be obtained~~ is not available for the report, 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 SADR's not initially reported by a health care professional. For a serious SADR 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 ~~to~~ must 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 SADR's. For reports of nonserious SADR's with a minimum data set, except for those resulting from a

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.

medication error, all safety information received or otherwise obtained by the applicant must be submitted to FDA even though information in addition to the minimum data set is not required to be acquired. Reports of nonserious SADR'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 SADR. The applicant must report to FDA each SADR, 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 SADR. If a full data set is not available for the serious and unexpected SADR at the time of initial submission of the expedited 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 from 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 drug 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 SADR with unknown outcome. The applicant must also report to FDA each SADR that is unexpected and for which the determination of an outcome is unattainable (i.e., SADR with unknown outcome) within 45 calendar days after initial receipt by the applicant of the minimum data set for the unexpected SADR. 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 SADR, 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 SADR'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 SADR that FDA determines to be the subject of an always expedited report (i.e., may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject).

(B) SADR's that are the subject of an always expedited report must be submitted to FDA whether unexpected or expected and whether the SADR leads to a serious outcome or not. 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 errors--(A) Actual medication error. The applicant must also submit to FDA each domestic report of an actual 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 SADR or, if an SADR does not occur, the minimum information described under paragraph (c)(1)(iii)(B) of this section (i.e., identifiable patient, identifiable reporter, and suspect drug 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 drug 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. (A) Contractors must submit to the applicant safety reports of any SADR's or medication errors for the applicant's drug product, obtained or otherwise received, within 5 calendar days of initial receipt of the report by the contractor. The contractor must submit a safety report for an SADR to the applicant even if the report does not contain a minimum data set. Upon receipt of the safety report from the contractor, 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 assuring that the contractors of its drug products comply with these postmarketing safety reporting responsibilities.

(C) The contractor 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;

(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 (i) of this section apply to contractors.

(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 SADR," "expedited report--30-day followup." Each type of report (e.g., serious and unexpected SADR 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 SADR, nonserious SADR, or no SADR occurred, e.g., "expedited report--actual medication error--nonserious SADR," "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 new drug application number(s) (i.e., NDA number(s)) for the human drug product(s) covered by the postmarketing periodic safety report. The international birth date for combination products is the

international birth date of the human drug product containing the drug substance most recently approved for marketing.

(i) Traditional periodic safety reports (TPSR's). An applicant holding an application for a human drug product approved under section 505(c) of the act before January 1, 1998, 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 TPSR, PSUR, or IPSR 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. Each TPSR must contain:

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

(1) A narrative summary and analysis of serious, expected SADR's and nonserious, unexpected SADR's occurring in the United States that were submitted to the applicant during the reporting period from all spontaneous sources (i.e., health care professionals and other individuals) (with an index consisting of a line listing of the applicant's manufacturer report number and SADR term(s));

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

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

(4) The applicants' 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 SADR terms and counts of occurrences) presented by body system or by standard organ system classification scheme for:

(1) All serious expected SADR's, nonserious unexpected SADR's, nonserious expected SADR's, and expected SADR's with