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

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

The proposed rule would also require these applicants to submit an IPSR 7.5 years and 12.5 years after U.S. approval of the supplement. These applicants would be required to submit PSUR's and IPSR's to FDA even if the pediatric use supplement or original application was approved prior to January 1, 1998. FDA is proposing this action to harmonize acquisition of new safety information regarding pediatric populations for timely review by the agency.

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

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

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

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

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

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

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

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

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

III.F. Reporting Format

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

III.F.1. Forms versus Narrative Format

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Companies may license the latest version of MedDRA ~~3.3~~ 5.1 by contacting TRW in Reston, VA, toll free number 877-258-8280 (703-345-7799 in Washington, DC area), FAX 703-345-7755, e-mail subscrib@meddramsso.com, Internet at www.meddramsso.com. Updated versions of MedDRA will be provided to subscribers as part of the annual licensing fee.

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

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

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If FDA finds that this requirement is economically burdensome for a small company, the agency intends to grant the company a waiver. A large company may also be granted a waiver if, for instance, it only markets a single product that generates a few safety reports a year. FDA intends to grant all reasonable waiver requests. This determination will be made on a case-by-case basis.

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

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

III.F.4. Contact Person

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

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

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

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

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

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

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

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

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

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

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

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

FDA would consider "appropriate identifying information" to include:

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

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

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

III.F.6. Other Revisions

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

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

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

III.G. Patient Privacy

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

III.H. Recordkeeping

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

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

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

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

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

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

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

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

Proposed § 314.98(a) would also state that applicants holding an approved ANDA would determine the type of postmarketing periodic safety report that would be required to be submitted to FDA (i.e., TPSR, PSUR, or IPSR) based on the U.S. approval date of the application for the innovator NDA product. If the innovator NDA product (even if no longer on the market) was approved for marketing before January 1, 1998, applicants holding an approved ANDA for the drug product would have the option of submitting either TPSR's or PSUR's and IPSR's to FDA. In these cases, an applicant holding an approved ANDA may choose to submit TPSR's to FDA even though other applicants with approved applications for the drug product submit PSUR's and IPSR's. If the innovator NDA product was approved for marketing on or after January 1, 1998, applicants holding an approved ANDA for the drug product would be required to submit PSUR's and IPSR's to FDA.

Proposed § 314.98(a) also provides that applicants holding an approved ANDA would determine the frequency of submission for postmarketing periodic safety reports based on the U.S. approval

date of the application for the innovator NDA product. For example, if the innovator NDA product is the first human drug product containing the drug substance approved in the world and the application is approved for marketing on June 15, 1980, applicants of the innovator NDA product and all ANDA products with the same drug product would either submit a TPSR or PSUR to FDA every 5 years based on the U.S. approval date of the innovator NDA product (e.g., data lock point of June 15, 2000, June 15, 2005). In this case, an applicant with an ANDA approved on January 1, 1999, would have a data lock point of June 15, 2000, even though the reporting period for the drug product is less than 5 years; the next reporting period for the drug product would cover a 5-year period (i.e., June 16, 2000 through June 15, 2005). If the first human drug product containing the drug substance was approved for marketing in Europe on February 1, 1980, and the same drug product was approved in the United States on June 15, 1980, applicants of this drug product and all ANDA products with the same drug product would either submit a TPSR or PSUR to FDA with a 5-year frequency based on the U.S. approval date and with a date lock point based on the European approval date (e.g., February 1, 2000, February 1, 2005).

All applicants holding an approved NDA or ANDA would be required to submit postmarketing individual case safety reports--semiannual submissions to FDA every 6 months (see section III.E.4

in this document). Thus, even though the agency would not be receiving TPSR's, PSUR's, and IPSR's for drug products with approved ANDA's frequently after approval of the product, FDA would receive in a timely manner individual case safety reports for the product (i.e., expedited reports, individual case safety reports--semiannual submission) that would identify any potential problems associated with the formulation of the product. It is not necessary to receive TPSR's, PSUR's, or IPSR's for drugs with approved ANDA's more frequently because the innovator NDA product has been evaluated for a number of years.

III.J. Postmarketing Approved New Drug Application (NDA) and Biologics License Application (BLA) Annual Reports

Current § 314.81(b)(2) requires applicants of marketed drug products subject to an NDA to submit an annual report to FDA within 60 days of the anniversary date of U.S. approval of the application. This annual report must contain a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product and a description of actions the applicant has taken or intends to take as a result of new information, such as submitting a labeling supplement, adding a warning to the labeling, or initiating a new study (§ 314.81(b)(2)(i)). This summary section must also contain, in accordance with the 1998 pediatric final rule, a statement of whether labeling supplements for pediatric

use were submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population were initiated. The 1998 pediatric final rule also requires that the summary section include, where possible, an estimate of the patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents), including dosage form. The annual report also must contain a section on nonclinical laboratory studies that includes copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (e.g., mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the ingredients in the drug product (§ 314.81(b)(2)(v)). The applicant must submit a copy of a published report if requested by FDA. The annual report also must contain a section on clinical data that includes, among other data, published clinical trials on safety of the drug (or abstracts of them) and reports of clinical experience pertinent to safety (for example, epidemiological studies or analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the applicant (§ 314.81(b)(2)(vi)). The clinical data section also must contain, in accordance with the 1998 pediatric final rule, an analysis of available safety and efficacy data in the pediatric population, changes proposed in the labeling based on

this information, and an assessment of data needed to ensure appropriate labeling for the pediatric population.

Current § 601.37 requires, in accordance with the 1998 pediatric final rule, applicants of licensed biological products to submit an annual report to FDA within 60 days of the anniversary date of U.S. approval of the application. This annual report must contain, among other information, a brief summary stating whether labeling supplements for pediatric use were submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population were initiated (§ 601.37(a)). This summary section also must contain, where possible, an estimate of the patient exposure to the product, with special reference to the pediatric population (neonates, infants, children, and adolescents), including dosage form. The annual report also must contain a section on clinical data that includes an analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information (§ 601.37(b)). This clinical data section also must contain an assessment of data needed to ensure appropriate labeling for the pediatric population.

As noted in section I of this document, FDA received comments on the October 1994 proposal that noted that the proposed amendments to the agency's postmarketing safety

reporting requirements would duplicate certain information required in postmarketing approved NDA annual reports. In light of these comments, FDA is proposing to revoke the requirement for safety-related information in postmarketing approved NDA and BLA annual reports to eliminate duplicative reporting.

FDA is proposing to remove the requirement in § 314.81(b)(2)(i) to report safety information or safety-related labeling changes in the summary section of approved NDA annual reports. FDA is also proposing to remove the requirement in §§ 314.81(b)(2)(i) and 601.37(a) to submit an estimate of patient exposure to the drug product with special reference to the pediatric population. FDA is also proposing to remove the requirement in § 314.81(b)(2)(v) to include the section on nonclinical laboratory studies in approved NDA annual reports. FDA is also proposing to remove the requirement in §§ 314.81(b)(2)(vi) and 601.37(b) to submit safety-related information in the clinical data section of approved NDA and BLA annual reports. FDA is proposing these changes because this safety-related information for a drug or licensed biological product would be provided to the agency in postmarketing safety reports (i.e., expedited reports, TPSR's, PSUR's, IPSR's, individual case safety reports--semiannual submissions). For example, proposed §§ 314.80(c)(2)(ii) and 600.80(c)(2)(ii) would require postmarketing expedited reports for certain information

that would be sufficient, based on appropriate medical judgment, to consider changes in product administration (e.g., any significant unanticipated safety finding or data in the aggregate from an in vitro, animal, epidemiological, or clinical study, whether or not conducted under an IND, that suggests a significant human risk such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease). Under proposed §§ 314.80(c)(3)(ii)(E), 314.80(c)(3)(iii)(E), 600.80(c)(3)(ii)(E), and 600.80(c)(3)(iii)(E), PSUR's and IPSR's would contain a section on worldwide patient exposure that includes, when possible, data broken down by gender and age (especially pediatric versus adult). Under proposed §§ 314.80(c)(3)(ii)(G), 314.80(c)(3)(iii)(F), 600.80(c)(3)(ii)(G) and 600.80(c)(3)(iii)(F) PSUR's and IPSR's would include a section on safety studies that would contain a discussion of nonclinical, clinical, and epidemiological studies that contain important safety information. This safety studies section would include all applicant-sponsored studies newly analyzed during the reporting period; new studies specifically planned, initiated, or continuing during the reporting period; and published safety studies in the scientific and medical literature.

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

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

FDA's existing in vivo bioavailability and bioequivalence study regulations, under § 320.31(a), require submission of an IND, as prescribed under part 312, for certain studies in humans (i.e., studies that involve a new chemical entity, a radioactively labeled drug product, or a cytotoxic drug product). Section 320.31(b) requires an IND for certain studies in humans using a drug product that contains an already approved, non-new chemical entity (i.e., a single-dose study where either the maximum single or total daily dose exceeds that specified in the approved labeling for the drug product, a multiple-dose study where either the single or total daily dose exceeds that specified in the approved labeling of the drug product, a multiple-dose study on a controlled release product on which no single-dose study has been completed). Section 320.31(d) exempts

all other in vivo bioavailability and bioequivalence studies in humans from the requirements of part 312 if certain conditions are satisfied (i.e., samples of any test article and reference standard are reserved by the person conducting the study and released to FDA upon request, studies are conducted in compliance with the requirements for institutional review set forth in 21 CFR part 56 and informed consent set forth in 21 CFR part 50).

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

The act provides authority to FDA to require safety reports for human bioavailability and bioequivalence studies that are not

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

subject to an IND. Section 505(i) of the act provides broad authority for FDA to issue regulations governing the clinical investigation of new drugs to protect the rights, safety, and welfare of human subjects and otherwise to protect the public health. In addition, section 701 of the act (21 U.S.C. 371) provides that the agency has authority to issue regulations for the efficient enforcement of the act.

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

significant human risk, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of a lack of efficacy with a drug or biological product used in treating a life-threatening or serious disease. In addition, under proposed § 312.32(c)(2), a telephone or facsimile transmission safety report must be submitted within 7 calendar days to FDA for any unexpected fatal or life-threatening SADR.

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

reports, as required under proposed § 312.32(c)(1)(i) for IND safety reports.

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

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

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

Under proposed § 312.32(c)(4), a sponsor of a clinical study under an IND for a drug marketed in the United States is only required to submit IND safety reports to FDA (review division that has responsibility for the IND) for SADR's that occur during

the clinical study itself, whether from domestic or foreign study sites of the IND. Proposed § 312.32(c)(4) would apply to human bioavailability and bioequivalence studies that are the subject of proposed § 320.31(d). In these cases, the reference listed drug would be the marketed drug and persons conducting human bioequivalence and bioavailability studies that are not subject to an IND would only be required to submit safety reports to FDA from their studies.

III.L. Proposed Implementation Scheme

FDA proposes that any final rule that may issue regarding the proposal to require that SADR's in individual case safety reports be coded using MedDRA become effective 1 year after its date of publication in the FEDERAL REGISTER. FDA proposes that any final rule that may issue based on all other proposals become effective 180 days after its date of publication in the FEDERAL REGISTER.

IV. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

V. Analysis of Impacts

V.A. Background and Summary

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

select the least costly, most cost-effective, or least burdensome alternative that achieves the objective of the rule.

The following analysis, in conjunction with the remainder of this document, demonstrates that this proposed rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866 and in the other two statutes. The proposed rule would amend current safety reporting requirements for human drug and biological products. Based on the analysis below, as summarized in table 11, FDA projects that the annual benefits would exceed the costs if this proposed rule resulted in a 2 percent reduction in hospital-related SADR's. The agency believes that a reduction in hospital related SADR's of at least 2 percent is a reasonable and likely outcome of this rule. The agency has determined that the proposed rule is an economically significant rule as described in the Executive Order. As required by the Regulatory Flexibility Act, the agency's Initial Regulatory Flexibility Analysis is included in this section. Because the rule may impose a mandate on the private sector that will result in a 1-year expenditure of $110 million or more (the current inflation adjusted threshold), FDA has conducted a cost-benefit analysis according to the Unfunded Mandates Reform Act. The relationship of this proposed rule with other agency rulemaking is described in the background section (e.g.,

reproposal of postmarketing periodic safety reporting requirements) (see section I of this document).

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

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

The proposed rule would also amend FDA's regulation on postmarketing annual reports for human drugs and licensed biological products to revoke the requirement for submission of safety-related information. The agency would also require the submission of expedited safety reports for certain bioavailability and bioequivalence studies that are exempt from submission of an IND.

The summary of the costs and benefits of this proposed rule are presented in table 11. The total one-time costs of $144.2

million are primarily for adopting MedDRA and include planning for implementation of the MedDRA requirements, purchasing materials, and converting existing systems to the new dictionary. Firms would also incur annual operating costs of about $106.6 million for complying with the revised safety reporting and recordkeeping requirements and $28.5 million for maintaining the new MedDRA system. Total annualized costs are $155.6 million (assuming a 10-year regulatory period and a 7 percent discount rate). A 10-year regulatory period for annualizing the costs and benefits of this proposed rule was selected as a reasonable time frame to adjust for investments, returns and savings given the potential for unforseen advances in both medical and information technology. In addition, by the fourth year savings and costs remain constant.

The expected health benefits of the rule would result from the improved timeliness and quality of the safety reports and analyses. Submission of more complete safety information would reduce the number and duration of hospitalizations due to SADR's. If the proposed rule reduced the incidence of SADR-related hospitalizations by 2 percent, these annual savings could be $368.5 million (see table 11). In addition, industry will experience economic benefits due to the more efficient allocation of resources permitted by the international harmonization of the safety reporting requirements. The annualized present value of

a 1 percent reduction in hospital related events would save $184 million annually; a 3 percent reduction would save $553 million annually

these savings is $28.5 million assuming a 7 percent discount over 10 years (see table 11). The agency believes this represents only a partial estimate of future industry savings.

Table 11.--Summary of the Costs and Benefits ($ million)

Benefits Assuming a 2 Percent Reduction in Hospital Related SADR's	Annual
Reducing hospital costs	368.5
More efficient use of resources	28.5[1]
Total benefits	397.0

Costs	One-Time	Annual	Annualized
Safety Reporting and Recordkeeping:			
Expedited reports (Except medication errors)	-	29.0	29.0
Expedited reports - medication errors	-	68.0	68.0
Periodic/other reports	-	9.6	9.6
Implementing MedDRA	144.2	28.5	49.0
Total	144.2	135.1	155.6

[1]This is the annualized present value of the estimated savings assuming a 7 percent discount over 10 years.

V.B. Market Failure

The host of international requirements and procedures that currently govern safety reporting for drugs and biologics creates substantial economic inefficiencies for firms. Manufacturers of drug and biological products operating in global markets must meet the regulatory safety reporting requirements of each country in which the product is marketed. In many cases, these safety reporting requirements, in particular submission timeframes for SADR reports, vary substantially among countries. Thus, drug and

biologics manufacturers must devote considerable resources to reformatting the data and information pertaining to each SADR according to specific national requirements. Also, because the timing of report submissions is typically determined by product approval dates for each country, manufacturers must submit reports to different countries at different intervals. Such activities impose substantial costs on both industry and regulatory authorities. Moreover, product safety can be compromised due to the difficulty of analyzing SADR reports based on the inconsistent use of terms derived from multiple dictionaries.

Despite the general recognition that manufacturers could realize substantial gains if safety reporting and terminologies were standardized globally, companies currently have limited incentives to invest capital and resources in standardized reporting systems (e.g., MedDRA) unless the standards are required by regulation. This shortfall in industry incentives occurs because the economic gains of harmonization cannot be attained by individual firms acting alone. Although most regulatory authorities have agreed in principal to implement international standardized reporting procedures, formal procedures have not yet been established. A few companies have voluntarily invested in the standardized process, but in the absence of global standards, these firms are uncertain of potential gains. FDA believes that the proposed rule is a necessary step toward achieving the

desired international standardization and its corresponding economic and health benefits.

V.C. Benefits

The benefits of the proposed rule would result both from the public health gains attributable to the improved scope, uniformity, and quality of information and analyses submitted in safety reports and the economic savings attributable to the more efficient use of industry and regulatory resources.

V.C.1. Expanded Safety Information

New drug approval decisions are based on safety and testing information derived from clinical trials that typically include several thousands of patients. However, the number of individuals tested in preapproval trials is not sufficiently large to reliably detect rare, serious SADR's. Patient exposure can quickly grow from thousands to millions after product launch. Thus, especially in the first few years after product launch, postmarketing surveillance is a critical component of the overall continuing review and assessment of drug safety (Ref. 1). Recent studies have identified common factors associated with increased risks of SADR's. These factors include subpopulations who differ from the clinical trial participants, e.g., the elderly, patients taking multiple medications or medications that require therapeutic monitoring, and patients with concurrent comorbidities (Refs. 2 through 5). The proposed rule would

Pg 213 (a)

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OMB

Industry would benefit from FDA action to reduce uncertainties associated with investments in harmonization and from the ability to more efficiently allocate resources associated with safety reporting. Society would benefit from the improved quality of adverse event information that is a critical component to reducing health care costs associated with avoidable SADR's. More timely and improved information on SADR's is needed to ensure the safe use of products and to monitor early warnings and unexpected

risks associated with drugs, drug-drug interactions, drug-food interactions, and risks to certain patient populations.

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This proposed rule would require improved factual and analytic data underlying safety reporting and analysis, provide for more timely safety information for certain serious SADR's, and would require a common medical dictionary, MedDRA.

The timely identification of SADR's is critical to managing risk information and to the safe prescribing and use of new drugs. Accurate and timely risk information is especially significant in the early months after product launch to develop appropriate prescribing and use behaviors as health care practitioners and consumers are learning about the product safety and use. Newly approved product use can quickly grow from a few thousand patients (the population in clinical trials) to many thousands or millions. Rare but serious SADR's are detected only after exposure to very large patient populations. Forty percent of SADR reports are for drugs approved within the last 3 years. Compounding this need for timely serious SADR information, U.S. patients are increasingly the first in the world to have access to new medications (49 percent of new drugs were first approved in the U.S. between 1996 and 1998, compared with 31 percent in 1991-1995).

More timely and improved factual information would also enhance the identification of other important factors associated with the risks of SADR's. These factors include subpopulations that may differ from clinical trial participants, patients taking multiple medications or medications that require therapeutic monitoring, and patients with concurrent comorbidities.

This rule would require affected entities to complete either a minimum or full set of data in safety reports, reflecting levels of risk. That is, more detail is required for higher risk events and reduced reporting for lower risk events. This rule would also

next p. 213

(c)

OMB

require the use of MedDRA, a medical dictionary developed by the ICH, in coding SADR terms. MedDRA will provide a uniform, consistent and specific presentation of medical terms. By eliminating the use of multiple dictionaries, MedDRA would facilitate the retrieval, presentation, and summarization of SADR data and enhance the global communication and acceptance of safety information and reports. The use of a single dictionary will substantially upgrade the quality of safety analysis by incorporating uniformity of terms. MedDRA will aid in more expeditious and broader international drug use comparisons within a class, and prescribing and use decisions. Providing more complete information and more timely safety assessments would enhance the ability of the manufacturers to more quickly identify, monitor and communicate the potential risks and benefits of marketed drugs and biologics.

It is well recognized that drug safety information is a critical element in the risk management of marketed drugs and biologics. In addition, the medical literature provides substantial documentation of avoidable hospitalizations associated with SADR's. Improving the quality and timeliness of safety information and accelerating the communication of risk information will enable health care practitioners and consumers to take appropriate corrective actions (in the case of medication errors) and to make more informed decisions about treatments. Moreover, the management of risk information is an essential component of risk-based decisions that determine the continued marketing or withdrawal of effective products with newly identified serious SADR's. We discuss benefits more fully below and show that a small reduction in the number of hospitalizations due to SADR's (as low as 0.85 percent), due to improved prescribing and use decisions, would result in the annual benefits outweighing the total costs.

require companies to collect proactively more complete safety information, improving the factual and analytical data underlying the safety analyses. This expanded risk information would enable health care practitioners and consumers to take appropriate corrective actions (in cases of avoidable medication errors) and to make more informed decisions about treatments.

V.C.2. Improved Uniformity and Quality of Safety Information

For years, numerous health care organizations, teaching hospitals, health care professionals, and educators have recognized the importance to public health of monitoring SADR's. Substantial evidence demonstrates that effective monitoring and analyzing of SADR's facilitate the identification of trends and warning signals that result in improved medication use and patient care (Refs. 6 through 10). Yet, the current drug and biologics safety reporting system, encompassing raw material suppliers, manufacturers, health care providers, and consumers, is fragmented with respect to its oversight and lacks common reporting procedures and tools for evaluating SADR's. For example, FDA oversees mandatory safety reporting by manufacturers of drug and biological products and voluntary reporting from health care providers and consumers. Health care facilities, on the other hand, may be subject to safety reporting oversight by individual state regulatory programs, although not all states have oversight systems. The Joint Commission on Accreditation of

Health Care Organizations (JCAHO), which accredits health care facilities, has had standards for establishing SADR reporting systems for hospitalized patients for many years. Hospitals may establish their own systems independently and almost all conform to the JCAHO standards (Ref. 11). Despite growing evidence that avoidable SADR's and serious SADR's are important public health problems and widespread acknowledgment that monitoring SADR's provides public health benefits, FDA continues to receive reports of only a small percentage of the serious and avoidable SADR's that occur in health care facilities (Ref. 12). This proposed rule would improve safety reporting by drug and biologics manufacturers, which may serve to provide a national framework for improved data collection and analysis of safety reports from a variety of sources.

The proposed rule would also require the use of MedDRA, a single, medical terminology developed by ICH that can be used for the coding of SADR terms. MedDRA is a broad-based dictionary, developed for international use, that combines both SADR and morbidity terminology to provide a uniform, consistent, and specific presentation of medical terms. By eliminating the use of multiple dictionaries, MedDRA would facilitate the retrieval, presentation, and summarization of SADR data and enhance the global communication and acceptance of safety information and reports. In addition, the use of a single comprehensive medical

dictionary by drug safety reporters and reviewers would substantially upgrade the quality of safety analysis by incorporating uniformity of terms. Standardizing the terms and improving the quality of the roughly 250,000 safety reports submitted annually to FDA would lead to better and more timely safety assessments and to improved communication of risk information. The widespread use and acceptance of standardized SADR information by regulators would ultimately enhance drug comparisons within a class and drug prescribing and use decisions.

V.C.3. Potential Savings From Reduced SADR-Related Hospitalizations

Improved timeliness and analysis of SADR data would lead to a better understanding and a more rapid communication of the risks of SADR's. By providing such improvements, the proposed rule would reduce the incidence of SADR's. An agency estimate of the potential economic benefits of the rule is presented below and reflects the value of the expected hospital cost savings and the avoided lost wages that might result from reduced numbers of SADR's.

V.C.3.a. Reduced rate of SADR-related hospitalizations. Numerous studies have documented drug-related hospitalizations (60 FR 44182 at 44232, August 24, 1995). A comprehensive review of 36 articles focused specifically on SADR's as the primary

cause of hospitalization. This study counted the number of reactions attributed to unintended consequences of drug therapy, excluding admissions due to overdose, intentional poisoning, attempted suicides, drug abuse, or intoxication. The percentage of hospitalizations due to SADR's ranged from 0.2 to 22 percent, with a mean of 5.5 percent. FDA adjusted this figure to 5 percent to remove over-the-counter drugs (Ref. 13). Based on 27.8 million hospital admissions reported in 1997, excluding obstetrical admissions (Ref. 14), the agency estimates the annual number of SADR-related hospitalizations at about 1.4 million (5 percent x 27.8 million). Applying an estimated cost of $9,177 for an average hospital stay (Ref. 15) implies total annual SADR-related hospital admission costs of about $12 billion ($9,177 x 1.4 million).

If the improved reporting and analyses of SADR's led to the avoidance of only 2 percent of these hospitalizations, the economic savings would amount to $252.2 million annually.

V.C.3.b. Reduced rate of in-hospital SADR's. Bates et al. conducted a random sample of nonobstetrical admissions to two large tertiary care hospitals in Massachusetts over a 6-month period (Ref. 16). His prospective investigation of SADR's included interviews with medical staff and daily reviews of all medical charts. He estimated the incidence of all SADR's, including medical errors, at 6.5 percent with an average increase

Absent available data, the agency assumes the costs associated with SADR-related hospitalizations are similar to the average cost of a hospital stay, but requests comments and supporting data on this assumption. Therefore,

OMB

in hospital costs of $2,595 per case. Extrapolating these findings, FDA estimated the annual number of in-hospital SADR's at 1.8 million and the total additional hospital cost at $4.7 billion annually. If this proposed rule led to a 2 percent reduction, the economic benefits would be $93.6 million annually.

In a comprehensive review of studies that estimated the incidence of SADR's and/or the magnitude of hospital costs due to SADR's, the U.S. General Accounting Office cited substantial variation in estimates (Ref. 17). These differences may be due to inconsistent definitions of SADR's, different study methodologies (active prospective investigation versus retrospective review of patient records), representativeness of the samples, and particular methods used to extrapolate study findings to a national level. For example, Lazarou et al. and Classen et al. estimated the incidence of serious SADR's using the World Health Organization definition of SADR and excluding other factors such as poisonings, intentional overdoses, and therapeutic failure (Refs. 18 and 19). These two studies had findings similar to Bates et al. On the other hand, Thomas et al. reviewed randomly selected hospital discharge records in two states and found a lower incidence of "drug injury". However, he used a particularly restrictive definition of SADR, one that resulted in prolonged hospitalization or disability at discharge (Ref. 20). Despite the uncertainties of estimating the incidence

and cost of hospital related SADR's, FDA believes that the $4.7 billion estimate for in hospital SADR's derived above provides a plausible estimate of the hospitalization costs of SADR's.

V.C.3.c. Indirect benefits of reducing the hospital costs of SADR's. The indirect benefits of reduced drug-related illnesses are derived from estimates of the costs of missed work or reduced productivity. Several studies on SADR-related hospital admissions stratified findings by patient age. Roughly 58 percent of SADR admissions were for patients aged 20 to 59. The remaining 42 percent were for patients under 20 years (less than 10 percent) and over 59 years old (Refs. 21 through 23). To calculate productivity losses, the agency assumed 56 hours per admission for patients aged 20 to 59 years (40 hours of lost work per hospitalization plus 16 additional hours for recovery and followup doctor visits) (1) and 14 hours for the remaining groups (to account for lost volunteer time or for time away from work for the care givers of dependent patients). The wage rates used are the average hourly production workers earnings of $15.96 for patients aged 20 to 59 ($12.28 plus 30 percent for benefits), and $12.28 for the remaining patients or their care givers (Ref. 14). The estimated value of this lost productivity is $812 million.

To estimate similar indirect benefits for in-hospital SADR's, the agency assumed the same distribution of patient ages. Related productivity losses are assumed to be 16 and 6 additional

(1) *The agency used 40 hours to estimate work productivity losses. This estimate is consistent with current hospital discharge data and with the length of stay for drug-related hospitalizations (Ref. 21).*

hours respectively, for patients aged 20 to 59, and for the remaining groups. The estimated value of this lost productivity is $323 million.

A 2 percent reduction in costs of SADR-related hospitalizations and prolonged hospitalizations would yield indirect benefit savings of $22.7 million. These estimates may somewhat overstate the value of lost productivity for the 20 to 59 age group because all patients are assumed to be employed. On the other hand, indirect benefits for the remaining age groups are understated because many of these patients are in the workforce and for those who are not, data are inadequate to measure their contribution to society.

V.C.3.d. Sum of SADR-related costs. Summing these estimates, the total annual direct and indirect benefits of reducing avoidable SADR-related hospitalizations and longer hospital stays by 2 percent would lead to economic benefits of $368.5 million per year. Varying the assumption of a 2 percent reduction in hospital costs with a 1, 3, and 5 percent reduction, would yield annual benefits of $184 million, $553 million, and $921 million, respectively. INSERT ~~Under any of these scenarios the SADR-related hospital savings of this rule would outweigh the costs over 10 years.~~ With a 2 percent or greater reduction, the annual benefits would outweigh the costs beginning in the first year. Nonetheless, the agency seeks comment on ~~this assumption.~~ our estimates of expected reductions in hospital-related costs, including the potential for reducing the incidence and length of stay of hospital-related SADR's.

p. 220(a)

OMB

A reduction of only 0.85 percent in the hospital costs associated with SADR's would be needed to outweigh the annualized industry costs of $155 million. Furthermore, under any of these scenarios, the total SADR-related hospital savings would outweigh the costs of this rule.

In contrast to focusing only on hospital costs of SADR's, one study estimated the direct costs of drug-related morbidity and mortality for the ambulatory population at $76.6 billion annually, with the largest component $47.4 billion for drug-related hospitalizations (Ref. 24). The remaining cost components included: $14.4 billion for long-term care, $7.5 billion for physician visits, $5.3 billion for emergency department visits, and $1.9 billion for additional prescriptions. Again, assuming a 2 percent reduction, savings are approximately $948 million annually.

V.C.4. Cost Savings and More Efficient Use of Resources

The proposed rule is intended to complement and formalize international efforts by industry representatives and major international regulatory bodies to achieve a more uniform and global approach to safety reporting. The content, analyses, and timing of SADR report submissions would closely align with international initiatives and recommendations. To the extent that U.S. requirements become harmonized within a global context, companies that compete internationally would benefit from this proposed rule. Multiple international due dates for safety report submissions and reformatting of the same information to meet different regulatory requirements represent opportunity costs that could be allocated elsewhere. Companies would accrue savings through a substantial reduction or elimination of the

reformatting of postmarketing periodic safety report information to meet varying international requirements and by synchronizing report frequencies and due dates internationally. Thus, as the international community harmonizes, companies would achieve efficiencies, eliminate duplicative processes, and reallocate those resources more efficiently.

The agency contracted with the Eastern Research Group, Inc. (ERG), an economics consulting firm, to estimate the potential benefits that would accrue to drug and biologics companies in the long run, as international harmonization efforts align and generate cost savings. These savings include more efficient regulatory safety reporting, more efficient sharing of safety information, and a common medical terminology. ERG estimated the following specific categories of benefits: More efficient management of drug safety data, more efficient intercompany agreements, and international harmonization of the postmarketing periodic safety report format (i.e., use of PSUR format). ERG applied estimates of savings by category and firm size to the number of affected firms within each affected industry. The methodologies and procedures for deriving these estimates are fully presented in ERG's final report (Ref. 25).

V.C.4.a. Savings related to maintaining and building data bases of SADR's and intercompany transfers of drug safety data.

Drug and biologics companies maintain safety data bases of all domestic and foreign SADR's involving their products. The management of these data bases can be quite complex depending on the individual circumstances of manufacturing and marketing. Companies may have foreign subsidiaries, domestic and foreign manufacturing sites, and varied licensing agreements with other companies for marketing products. Foreign subsidiaries and licensees generally submit SADR reports to U.S. companies by fax. U.S. companies then reenter the reports into their own databases. Use of standardized safety report formats and content internationally will lend itself to electronic transmission of safety information. In these cases, intercompany and intracompany sharing of safety information will be substantially facilitated. ERG estimated these benefits at $3.1 million annually.

V.C.4.b. Savings related to greater ease in entering into intercompany agreements. As requirements for drug and biologics safety reporting become harmonized, drug and biologics companies will find it easier to coordinate safety reporting efforts when entering into various agreements with other manufacturers or sales organizations. In the current organizational structure of the industry, companies are frequently negotiating licensing agreements, mergers, joint ventures, and other contractual matters with other companies. For these arrangements, companies

must develop, share, and merge drug safety reports from around the world. At present, negotiation of drug safety data sharing is often complicated by reporting formats and requirements that differ between regions. ERG estimated the potential savings that would accrue from simplified negotiation of licensing agreements due to standardized reporting formats and requirements at $4.2 million annually.

V.C.4.c. Savings related to eventual international harmonization to the PSUR format. ERG estimated the potential savings to industry of preparing a single PSUR that would be accepted by regulatory authorities internationally on the same date. Currently, companies are faced with many inconsistent requirements and must meet the individual requirements and timeframes of each country. ERG estimated these savings at $24.3 million annually.

V.C.4.d. Potential savings in clinical trial management. Some companies noted that they would convert medical terms from clinical trials to MedDRA whether or not it was required by FDA. Assuming that this transition will gradually apply to future clinical trials, a single medical terminology, internationally developed, accepted, and applied, would allow companies to more easily transmit, integrate, and analyze clinical trial data from global sites. Subsequent reductions in time and resources would contribute to reduced costs during drug development. Based on

input from industry, ERG developed a narrow focus of savings associated with clinical trial data management valued at $7.2 million annually.

V.C.4.e. Leveraging specialized knowledge. This proposed rule also provides the groundwork for establishing focused centers of technical information on drug safety. Global companies and regulatory agencies will have the opportunity to create economies of expertise by concentrating specialized knowledge of global drug use and product risks and benefits in centralized locations. To the extent that safety information is better managed, understood, and shared with interested parties, substantial benefits will accrue. Neither ERG nor FDA could quantify these benefits.

V.C.4.f. Total benefits. ERG estimated the total industry savings from more efficient use of resources to be $38.8 million annually. This estimate, however, accounts for only a modest portion of the potential benefits of the broader set of initiatives that enhance electronic submissions and global harmonization of safety reporting. Table 12 summarizes the estimated annual benefits of this proposed rule. The agency recognizes, however, that the industry savings component will not be fully realized until safety reporting requirements are harmonized internationally. The agency believes that these benefits could be achieved in a relatively short period after

this rule becomes final. The agency is ready to accept PSUR formats and the use of MedDRA for coding of individual case safety reports at the present time (see draft guidance of 2000). In addition, the European Union and Japan currently accept PSUR formats and the use of MedDRA.

Table 12.--Summary of the Annual Benefits

Savings Category	$ Million (annually)
Public health benefits for a 2 percent reduction in SADR-related hospital costs:	
Reduced SADR-related hospital admissions	252.2
Reduced in-hospital SADR's	93.6
Indirect benefits from reduced hospitalizations	22.7
Total hospital-related savings	368.5
Expanded safety information on product approvals	Not estimated
Improved risk communication and product selection	Not estimated
Future Industry Savings:	
Efficiencies in database maintenance	3.1
Facilitation of PSUR submissions	24.3
Facilitation of intercompany negotiations	4.2
Clinical trial management	7.2
Total Industry Savings	38.8[1]
Economies of Managing Drug Expertise	Not estimated

[1]Assuming 1/3 of these savings begin in year 2 ($11.6 million), 2/3 in year 3 ($23.3 million), and $38.8 million in years 4 through 10, the annualized present value is $28.5 million, discounted at 7 percent over 10 years. The 10-year time horizon allows a reasonable projection of current information given the unforseen progress and impacts of medical and computer technology.

V.D. Costs of Compliance

This section presents the estimated compliance costs of the proposed requirements. As explained below, the proposed rule

clarifies and expands existing requirements for submitting premarketing expedited reports, postmarketing expedited initial and followup reports, and postmarketing periodic safety reports to FDA. Drug and biologics manufacturers would be required to use direct verbal contact to collect information sufficient to determine the nature, severity, and outcome of SADR's and to evaluate and describe the safety profile or changes in the safety profile of marketed drugs. The proposed regulation also specifies criteria for reporting individual case safety reports and designates data elements that must be completed as a condition for initial and followup reporting. Each SADR in a postmarketing individual case safety report for human drugs and biologics must be coded using the appropriate "preferred term" in the latest version of MedDRA. The proposal also requires a physician to review the postmarketing expedited and periodic safety reports. The proposed rule would codify the data elements, analyses, and report format of the required postmarketing periodic safety report submissions and harmonize many of these requirements with ICH initiatives. Applicants holding an approved marketing application would be required to submit semiannual individual case safety reports and more detailed postmarketing periodic safety reports that contain cumulative and comprehensive data, analyses, tabulations, summaries, and other information. The proposed rule also includes revisions to IND safety reporting requirements and bioavailability and bioequivalence study requirements.

V.D.1. Costs of New Recordkeeping and Reporting Requirements

V.D.1.a. Number of reports. In 1998, manufacturers and applicants of human drug and biological products submitted approximately 230,000 individual case safety reports of SADR's to FDA. Data from about 130,000 of these individual case safety reports in the agency's Adverse Event Reporting System (AERS) were analyzed to estimate the annual number of future SADR reports expected to be included as revised expedited and new semiannual submissions. However, not enough data exists to predict the number of new expedited reports the agency may expect each year. For this analysis, estimates of new expedited reports for human drugs and biological products were based on counts of similar reports received by the agency during 1998. The estimated number of expedited reports for blood products is derived from published studies (Refs. 26 and 27).

The agency does not know how many TPSR's, and PSUR's and IPSR's would be submitted annually, because applicants with pre-1998 drug approvals can submit either format. In addition, applicants with ANDA's approved on or after January 1, 1998, may choose to submit a TPSR rather than a PSUR or IPSR if the innovator NDA was approved before January 1, 1998. Despite this uncertainty, this analysis estimates the number of new filings of postmarketing periodic safety reports based on average counts of pre- and post-1998 drug approvals.

The number of affected reports for prescription drugs marketed for human use without an approved application, IND safety reports, bioavailability/bioequivalence safety reports, and other reports were projected from counts of similar reports received by FDA. Estimates

for the total number of reports affected by the proposed rule are shown in table 13.

Table 13.--Number of Affected Reports by Regulatory Status

Type of Report	Drugs Marketed Without an Approved Application	NDA/ANDA	Biologics	Blood Products	IND	Bioavailability and Bioequivalence	Total
Expedited Serious and unexpected SADR's	350	50,000	3,000	0	0	0	53,350
Always expedited report	50	1,500	100	0	0	0	1,650
Unexpected SADR with unknown outcome	46	912	25	0	0	0	983
Information sufficient to consider product administration changes	5	300	4	0	0	0	309
Medication errors	1,000	100,000	10,000	0	0	0	111,000
30-day followup	340	43,000	3,000	0	0	0	46,340
Serious SAR's - blood products	0	0	0	7,000	0	0	7,000
IND Safety Information sufficient to consider product administration changes	0	0	0	0	600	0	600
Bioavailability/ bioequivalence safety report	0	0	0	0	0	200	200

Table 13.--Number of Affected Reports by Regulatory Status (Continued)

Type of Report	Drugs Marketed Without an Approved Application	NDA/ANDA	Biologics	Blood Products	IND	Bioavailability and Bioequivalence	Total
Periodic							
TPSR	0	1,400	35	0	0	0	1,435
PSUR	0	2,500	35	0	0	0	2,535
ISUR	0	350	3	0	0	0	353
Individual case safety reports--semiannual submission	0	4,726	480	0	0	0	5,206
Other							
Reports to manufacturer or applicant	4	4,548	100	0	0	0	4,652
Submit safety records to FDA upon request	2	15	4	0	0	0	21
Annual reports	0	2,363	69	0	0	0	2,432

V.D.1.b. New time burden. The proposed rule requires manufacturers and applicants to use active query to acquire the outcome (i.e., whether an SADR is serious or nonserious) and required data set for any spontaneously reported individual case safety report that they receive pertaining to their marketed human drug or biological product. Furthermore, the proposed rule requires that every individual case safety report submitted to the agency be assigned an appropriate MedDRA code. Although individual case safety reports are currently submitted for most SADR's, depending on the type of SADR, the proposed rule may impose an additional burden on health professional personnel if active query is not already used routinely by a manufacturer or applicant. Regulatory affairs personnel working with the health professional may spend additional time assigning the MedDRA code and documenting the active query.

V.D.1.b.i. Expedited reports. The nature of the SADR (i.e., whether the SADR is expected or unexpected) and whether the outcome is known (i.e., SADR is serious or nonserious) will determine the data needed and when and if an individual case safety report should be submitted to FDA. At present, individual case safety reports of SADR's that are both serious and unexpected are submitted as 15-day alert reports.

The proposed rule adds conditions for determining expedited reports (e.g., minimum data set required). In addition, it specifies that an expedited report for an individual case safety report must contain a full data set, including MedDRA codes, and that supporting documentation such as hospital discharge records, autopsy reports, or

The agency seeks comment on the reasonableness of the estimates of the time burden and the type of employee anticipated to fulfill the new requirements detailed below.

death certificates must be submitted, if available. This aspect of the proposal may impose a new burden estimated at 1 hour each for health professionals and regulatory affairs personnel (see table 14).

The proposal defines new criteria for determining when expedited reports should be submitted. Certain medically significant SADR's as listed in the proposal, whether unexpected or expected, and all domestic reports of actual and potential medication errors would be required to be submitted to FDA in an expedited manner. Furthermore, when the outcome of a spontaneous, unexpected SADR cannot be determined, an expedited report must be submitted to the agency. In these circumstances, manufacturers and applicants are assumed to allocate from 16 to 24 hours more time for health professionals and regulatory affairs and clerical personnel to prepare and submit these new reports. Table 14 lists the additional hours each type of employee may spend complying with these new requirements.

In addition to individual case safety reports, manufacturers and applicants may receive safety information from domestic or foreign studies that is judged to be sufficient to consider a change in product administration. In this case, the proposed rule requires that a narrative report of these findings be submitted to the agency as an expedited report. Preparing and submitting this new report may take up to 8 hours of time from health professionals and regulatory affairs and clerical personnel as shown in table 14.

V.D.1.b.ii. Followup reports. The proposed rule establishes timeframes and data elements required for submission of expedited individual case safety reports. If required data elements were not

submitted with the initial filing of an expedited report of a serious SADR or a medication error report, then the applicant must continue to use active query to obtain the additional information. This information must be submitted to FDA in a followup report within 30 calendar days of the previous filing. If the full data set is still not obtainable, the 30-day followup report must include all safety information obtained, highlighting new information and stating the reasons for the inability to obtain complete information. The agency estimates that 8 additional hours, as shown in table 14, are needed for these followup reports.

Applicants must also submit any new safety information to FDA for any other expedited or followup report within 15 days of receipt of the new information. This provision is currently required; therefore, no additional hours are allocated to this provision.

V.D.1.b.iii. Blood products. Collection and transfusing facilities are currently required to investigate, prepare, and maintain written reports of complaints of SAR's arising as a result of blood collection or transfusion. Furthermore, if a fatality occurs as a complication of blood collection or transfusion, facilities must notify FDA as soon as possible and follow up with a written report within 7 calendar days after the fatality occurs. The proposed rule will require that all written reports submitted to the agency use the individual case safety report format. This change in reporting format is not expected to increase the time needed to prepare and submit reports of fatalities. In addition, the proposed rule will require that any serious nonfatal SAR related to collection or transfusion of

blood and blood components be submitted as a expedited report within 45 calendar days. As shown in table 14, blood facilities may spend up to 16 hours more preparing and submitting each of these expedited reports.

V.D.1.b.iv. IND and bioavailability/bioequivalence safety reports. Sponsors of an IND are currently required to submit written and telephone safety reports. The proposed rule will add some conditions for reporting and require that reportable SADR's include the minimum data set. Sponsors of IND's will be required to submit written safety reports to FDA and all participating investigators of: (1) Any SADR that, based on the opinion of either the sponsor or investigator, is both serious and unexpected and (2) any information that might materially influence the benefit-risk assessment of an investigational drug or that would be sufficient to consider a change in either product administration or in the overall conduct of a clinical investigation. The agency is also expanding the current requirement for telephone and facsimile transmission of safety reports of unexpected death or life-threatening SADR's to include those that meet these criteria based on the opinion of either the sponsor or investigator. In addition, the agency is making minor changes to align current IND safety reporting requirements with the proposed changes to postmarketing safety reporting.

The agency anticipates that very few investigator-initiated reports would be submitted under the proposed rule. Because the number of new reports (i.e., approximately 10 per year) would represent less than 0.2 percent of all individual IND safety reports submitted to the agency in a year, no additional burden is estimated.

NOTE! There are NO pages 237 → 245

However, up to 4 hours may be needed for sponsors to accommodate the new requirements for written safety reports for information sufficient to consider a change in product administration (see table 14).

In addition, the agency would require submission of expedited safety reports for certain bioavailability and bioequivalence studies that are exempt from submission of an IND. The agency estimates 14 hours per report are needed to comply (see table 14).

V.D.1.b.v. Semiannual submissions of postmarketing individual case safety reports. The current regulations require that postmarketing individual case safety reports from domestic marketing experience for serious expected adverse drug experiences, nonserious unexpected adverse drug experiences, and nonserious expected adverse drug experiences be submitted to the agency in postmarketing periodic safety reports. Under the proposed rule, most individual case safety reports not submitted to FDA as an expedited report would be submitted as a separate report twice a year. All reports of actual or potential medication errors, whether or not an SADR occurs, would be submitted as expedited reports and not submitted semiannually. Individual case safety reports of nonserious SADR's that are expected or listed would no longer be submitted to the agency. Exceptions, for vaccines, would be reports of nonserious, expected SAR's and expected SAR's with an unknown outcome, which would be submitted semiannually. Nevertheless, applicants would be expected to maintain these reports and include them in tabular summaries provided in the postmarketing periodic safety reports (e.g., PSUR's).

Whereas the current postmarketing periodic safety reporting regulations do not apply to foreign reports of SADR's, the proposed rule would require that foreign individual case safety reports of serious and expected or listed SADR'S be submitted

semiannually. The agency is unable to predict how many foreign reports may be submitted. For the purpose of this analysis, therefore, the number of nonserious and expected or listed individual case safety reports is assumed to be equal to the number of serious and expected or listed foreign reports, and the overall number of individual case safety reports submitted in a year would remain unchanged.

Although the number of individual case safety reports submitted annually as a postmarketing periodic safety report is expected to remain stable, the timing of these submissions may change. Reports will be submitted less frequently (semiannually rather than quarterly) for products that have been on the market for less than 3 years and more frequently (semiannually rather than annually) for products that have been on the market for more than 3 years. Furthermore, additional time may be needed for an active query to obtain a full data set for reports of serious and expected or listed SADR'S and a minimum data set for all SADR'S. Based on reports to AERS in 1998, the agency estimates that, on average, approximately 35 individual case safety reports may be submitted semiannually for each drug product. Regulatory affairs personnel and health professionals might spend up to 10 additional hours each to obtain and process information for each semiannual submission (see table 14).

Table 14.--Estimated New Burden for Expedited and Semiannual Reports

Type of Report	New or Revised	New Burden (hours)			
		Health Professional	Regulatory Affairs	Clerical	Total
Expedited Serious and unexpected SADR	Revised	1	1	0	2
Always expedited report	New	2	12	2	16
Unexpected SADR with unknown outcome	New	3	18	3	24
Information sufficient to consider product administration changes.	New	3	3	2	8
Medication errors	New	2	12	2	16
30-day followup	New	3	4	1	8
Serious SAR's - blood products	Revised	2	12	2	16
IND Safety Information sufficient to consider product administration changes	Revised	1	2	1	4
Bioavailability/ bioequivalence safety report	New	1	11	2	14
Individual case safety reports-- semiannual submission	Revised	10	10	0	20

V.D.1.b.vi. Postmarketing periodic safety reports (TPSR, PSUR, and IPSR). Current agency regulations require applicants to submit postmarketing periodic safety reports at specified intervals. Each periodic safety report must contain a narrative summary and analysis of adverse drug experiences received since the last periodic report. The proposed regulation would require applicants to provide more thorough review and analysis of the safety profile for certain drugs.

For all applications approved on or after January 1, 1998, these reports would be in the PSUR format (with some variation) that is currently accepted by other regulatory authorities. These applications would be submitted semiannually for 2 years after the U.S. approval date, annually for the next 3 years, and every 5 years thereafter. In contrast to current regulations, postmarketing periodic safety reports would have to contain a more comprehensive analysis of the product's safety record. Specifically, applicants would be required to submit, as described in chart 1, summary tabulations of SADR's (i.e., all SADR terms and counts of occurrences) received since the last periodic report categorized by body system or standard organ system classification scheme.

Chart 1--Required Summary Tabluations of SADR's for PSUR's

Source	Outcome
Spontaneous submissions from health care professionals	All serious and nonserious
Studies or individual patient IND's	All serious
Scientific literature	All serious; all nonserious unlisted
Regulatory authorities	All serious
Other (e.g. poison control centers, epidemiological data bases)	All serious

In addition, applicants would have to submit cumulative summary tabulations for SADR's that are both serious and unlisted. Applicants would be required to include a discussion of these data including the medical significance or mechanism.

Applicants would be required to submit a discussion of safety information from applicant-sponsored studies (either planned or initiated) and published safety studies and abstracts. Furthermore, applicants would be required to include a discussion of certain lack of efficacy reports and important new information received after the data lock point. In addition to analysis of individual case safety reports and studies, applicants would be required to submit a comprehensive analysis of other safety

information specified in the proposal, such as increased frequencies of listed SADR's, specific populations, and drug interactions.

Applicants would also be required to provide other relevant safety and baseline information as specified in the proposal. This information would include worldwide marketing status, changes to the CCSI, actions taken for safety reasons, and worldwide patient exposure. Appendices would include additional safety information as specified in the proposal including information related to the current (or proposed changes) in the U.S. labeling and safe use of the product, summary tabulations of spontaneous individual case safety reports from individuals other than a health care professional, summary tabulations of individual case safety reports of SADR's with unknown outcome and medication errors, summary tabulations of SADR's from class action lawsuits, U.S. patient exposure, assessments of lack of efficacy reports and new information on resistance to antimicrobial drug products. In addition, the name and telephone number of the licensed physicians responsible for the content and medical interpretation of the information in the PSUR and the addresses where all safety reports and other safety related records are maintained would be included.

The proposal also requires IPSR's for approvals on or after January 1, 1998. While following a similar format as the PSUR,

the IPSR is less comprehensive than the PSUR (i.e., does not require submission of summary tabulation information). This report would be submitted 7.5 and 12.5 years after the U.S. approval date.

Under the proposed regulation, TPSR's would be required for applications approved before January 1, 1998. Although less comprehensive than the PSUR, the TPSR would have to contain product safety information, including summary tabulations and a narrative summary and analysis of individual case safety reports, and a history of safety-related actions taken during the reporting period. The timing for these report submissions would be at 5, 7.5, 10, 12.5, and 15 years after U.S. approval of the product and then every 5 years thereafter. Applicants would have the option to file using the PSUR and IPSR formats.

The additional times required to complete the proposed changes to postmarketing periodic safety report submissions are shown in table 15. The agency estimates that the new burdens would be 16 hours for TPSR's, 40 hours for PSUR's, and 30 hours for IPSR's. These times represent estimates of the average time per report, recognizing that preparation times for each postmarketing periodic safety reports may take as little as a day for products with few or no SADR's or as much as several months for other products that are more complex or associated with many SADR'S. Based on reports received by the agency, a few products

account for the majority of the reports of SADR'S. For example, 1998 AERS data showed that approximately 75 percent of the postmarketing periodic safety reports for drug products included 10 or fewer individual case safety reports, accounting for only about 5 percent of all of those reports submitted with postmarketing periodic safety reports. The other 25 percent of postmarketing periodic safety reports included the remaining 95 percent of individual case safety reports submitted in 1998.

Table 15.--Estimated New Burden for Periodic Safety Reports and Other Reports

Type of Report	New or Revised	New Burden (hours)			
		Health Professional	Regulatory Affairs	Clerical	Total
Periodic TPSR - application approved before 1/1/95	Revised	3	9	4	16
PSUR - application approved on or after 1/1/95	New	8	24	8	40
IPSR - application approved on or after 1/1/95	New	6	18	6	30
Other Reports of nonserious SADR's and certain medication errors to manufacturer or applicant	New	0	1	0	1
Submit safety records to FDA upon request	New	0	4	4	8
Annual reports	Revised	(3)[1]	(7.5)	(3)	(14)

[1]Values in parentheses represent an estimate of the decrease in burden.

V.D.1.b.vii. Other reports. Currently, persons submitting postmarketing safety reports may elect to submit reports of serious adverse drug experiences to the manufacturer or applicant rather than submitting serious unexpected adverse drug experiences directly to FDA. The proposed rule would require submission of all safety reports (i.e., serious and nonserious SADR's and medication errors) to the manufacturer or applicant within 5 calendar days of initial receipt of the information. Contractors may need to allocate up to 1 additional hour to prepare and submit each report of a nonserious SADR or medication error that does not result in an SADR (see table 15).

Persons maintaining records of SADR's may be asked to submit any or all records to FDA within 5 calendar days. The agency estimates that 21 such requests for SADR records would be made in a given year. This new reporting requirement may take regulatory affairs and clerical personnel up to 4 hours each to fulfill each request (see table 15).

FDA will no longer require that applicants subject to an NDA or BLA submit certain safety related information with annual reports. This reduction in reporting requirements will decrease the burden on these applicants. To prepare and submit each annual report, applicants may save an estimated 13.5 hours annually (see table 15).

V.D.1.c. Annual cost of the reporting and recordkeeping provisions. Hourly compensation estimates for personnel implicated in the proposed changes to safety reports are shown in table 16. The additional cost of the proposed changes for each type of affected report and the total annual cost of the proposed rule are summarized in table 17.

However, because the annual costs depend on the actual number and type of reports submitted to FDA, these costs are uncertain and may fluctuate from year to year. For example, if there are 50 percent fewer reports than estimated, annual costs would be approximately $52.2 million instead of $106.6 million. If the number of reports submitted is 50 percent more than shown in table 17, the annual costs would be about $159.9 million. The agency seeks comments on the reasonableness of its estimates of number of reports, burden hours, and costs.

Table 16.--Hourly Compensation

Health Practitioner[1]	Regulatory Affairs[2,3]	Clerical[2]
$67.31	$36.92	$17.39

[1]Hourly compensation derived from the annual salary range for clinical research physicians in the pharmaceutical industry from http://careers.yahoo.com. Hourly compensation includes benefits equal to 40 percent of hourly wage.

[2]U.S. Department of Labor, BLS, "Employer Costs for Employee Compensation, Table 12," March 1999.

[3]Includes biostatisticians.

Table 17.--Total Annual Cost of New Reporting Burden

Type of Report	Number of Affected Reports	Per Report Cost of New Burden	Annual Cost ($ mil)
Expedited Serious and unexpected SADR's	53,350	$104.23	$5.6
Always expedited reports	1,650	$612.44	$1.0
Unexpected SADR with unknown outcome	983	$918.65	$0.9
Information sufficient to consider product administration changes	309	$347.46	$0.1
Medication errors	111,000	$612.44	$68.0
30-day followup	46,340	$366.99	$17.0
Serious SAR's - blood products	7,000	$612.44	$4.3
IND Safety Information sufficient to consider product administration changes	600	$158.54	$0.1
Bioavailability/bioequivalence safety report	200	$508.21	$0.1
Periodic TPSR	1,435	$603.76	$0.9
PSUR	2,535	$1,563.66	$4.0
IPSR	353	$1,172.75	$0.4
Individual case safety reports--semiannual submission.	5,206	$1,042.28	$5.4
Other Reports of nonserious SADR's and certain medication errors to manufacturer or applicant	4,652	$36.92	$0.2
Submit safety records to FDA upon request	21	$217.24	$0.0
Annual reports	2,432	($530.99)[1]	($1.3)
Total Annual Cost of New Reporting Burden			$106.60

[1] Values in parentheses represent an estimate of cost savings.

V.D.2. Costs of MedDRA

FDA contracted with ERG to estimate the industry cost of using MedDRA terms to code individual case safety reports. In the fall of 1999, ERG and FDA staff visited three drug companies and conducted telephone interviews with several more companies and industry consultants. The purpose of the interviews was to collect information to assist in estimating the major cost components of implementing MedDRA. ERG's complete report is on file with the hearing clerk (Ref. 25).

Companies were asked to describe costs incurred or projected based on company experiences. Companies identified major cost elements that include one-time implementation costs such as planning and coordination of the conversion, converting existing data and information systems, and training. Recurring costs include MedDRA subscription and maintenance costs.

ERG applied estimates of cost by category and firm size to the number of affected firms within each industry. Estimates of affected drug and biologic product manufacturers are derived by applying data from 1998 FDA Adverse Drug Event Reports and Vaccine Adverse Event Reports to aggregate firm data from the Small Business Administration, Census of Manufactures and the National Science Foundation. Estimates of affected blood facilities are derived from the FDA Center for Biologics Evaluation and Research database of licensed and/or registered

establishments, the National Blood Data Research Center and the Census Bureau.

Limitations on ERG cost estimation include the complexities associated with firms' abilities to separate incremental costs from factors that substantially influence expenditures, such as integrating operations of one or more newly merged corporations, isolating U.S. corporate polices and operations from global corporate policies and operations, and reaching consensus on the extent and timing of the conversion of historical SADR's and data.

V.D.2.a. One-time costs

V.D.2.a.i. Planning and coordination. Companies will need to allocate time to plan and coordinate the conversion of MedDRA across their affected operations. Planning costs are affected by the extent of decentralization of coding and pharmacovigilance work within the corporate structure. Managers for drug and biologics firms are expected to spend from 240 hours for very small firms to 1,400 hours for very large firms (greater than 750 or 500 employees respectively for drug and biologics firms) for planning and coordination. Costs per company ranged from $10,800 to $64,500 for drug and biologics firms. In contrast to drug and biologics firms, blood facilities have a limited range of products, do not need to convert legacy data, and typically operate only in the United States. Therefore, ERG judged that

compliance costs for blood facilities would be 4 to 5 percent of equivalent-sized drug and biologics firms. Estimated costs per firm range from $450 to $2,260 for very small and very large firms, respectively.

V.D.2.a.ii. Development of information technology support structure. Companies reported that information technology (IT) personnel will need to modify existing database systems to:

- Accommodate adding a new medical dictionary,
- Allow for MedDRA's complex hierarchical structure and wider field widths,
- Reconcile the comparability of existing dictionaries with MedDRA (in the short term),
- Integrate a web browser, and
- Install or modify an autoencoder system.

IT personnel are estimated to need from 720 hours for very small firms to 1,920 hours for very large firms to develop and validate computer data systems that will accommodate MedDRA. Costs are estimated to range from $25,850 to $68,900 for drug and biologics firms. No costs were forecast for blood facilities.

V.D.2.a.iii. Purchase or development of an autoencoder. Companies reported that they currently use an existing database such as COSTART or WHOART and supplement these dictionaries with their own medical vocabulary. Autoencoders assist with the automated conversion of existing medical terms to MedDRA.

Companies may purchase autoencoders, adapt existing in-house versions, or use outside contractors. Converting existing terms to MedDRA is estimated to cost from $20,000 to $100,000 for drug and biologics firms. Costs are not applicable to blood facilities.

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V.D.2.a.iv. Conversion of legacy safety data. ~~Companies reported that they will convert virtually all of their SADR data into MedDRA terms even if it is not required by FDA.~~ Some companies reported that they would convert virtually all of their legacy data into MedDRA terms even though it is not required by this proposal. Some companies maintain that this conversion includes information from clinical trials. Nonetheless, some companies may not convert their legacy drug safety data into MedDRA or may convert only some of their products, based on criteria associated with experience and history of the drug. ERG estimated that 75 percent of companies would incur conversion costs to allow for the range of company responses. The number of terms that are converted automatically (with autoencoders) or manually will affect conversion costs. Estimated costs per company for converting existing legacy data range from about $16,500 (for converting 15,000 terms) for very small firms to $275,000 (for converting roughly 250,000 terms) for very large drug firms. Costs for biologics firms of corresponding size range from $3,300 (for 3,000 terms) to $55,000 (for about 50,000 terms). Costs are not applicable to blood facilities.

V.D.2.a.v. Training of personnel. Companies reported that staff most likely to receive MedDRA training include medical coders, biostatisticians, and pharmacovigilance, IT, and regulatory affairs personnel. In addition to formal training, medical data coders will require several months of experience before they become proficient with coding in MedDRA. Training costs are dependent on the number of employees that must be trained in MedDRA and the level of training needed for their relevant duties. Training costs were estimated to range from $9,300 to $330,300 for very small to very large drug manufacturers and from $9,300 to $90,600 for biologics firms of corresponding size. ERG estimated training costs from $1,300 to $4,300 for very small to very large blood facilities.

V.D.2.a.vi. Revision of standard operating procedures (SOP's). Companies will revise a substantial group of SOP's in implementing MedDRA. Affected procedures include dictionary/coding, IT, and drug safety/pharmacovigilance. Drug and biologics firms are expected to need from 130 to 1,300 hours for very small to very large firms to revise their SOP's for MedDRA, with costs ranging from $5,900 to $59,200. ERG allocated 8 to 50 hours for developing or revising SOP's for blood facilities. Per firm costs for SOP's are estimated to range from $370 to $2,260 for very small to very large blood facilities.

V.D.2.b. Recurring costs

V.D.2.b.i. MedDRA core subscription. Companies must pay subscription costs on an annual basis to the MedDRA MSSO. Core subscription costs vary with the size of the company and with the level of services. Estimates of costs range from $5,000 to $40,000 for drug and biologics firms. ERG judged that blood facilities would incur only modest annual costs associated with MedDRA subscription and updates because of the limited range of terminology describing medical outcomes. ERG assumed that blood facilities would either work through industry associations to negotiate lower per firm subscription costs or, alternatively, contract with contract research organizations to obtain the necessary MedDRA codes.

V.D.2.b.ii. MedDRA versions and quarterly updates. Currently the MSSO intends to provide quarterly updates as well as periodic new versions of MedDRA. Companies did not have a sufficient history with incorporating MedDRA changes to estimate the costs of updates. Cost components would include senior level reviews of each update, communicating the changes to affected personnel, and IT support to upload and reconcile new versions. Costs are estimated to range from $5,700 to $43,000 for drug and biologics firms. No costs were assigned to blood facilities.

V.D.2.b.iii. Maintenance of existing dictionaries. Companies reported that they may need to maintain their existing dictionaries for an indeterminate time. Conditions that could

influence whether and for how long a company would need to maintain its existing dictionaries are: (1) The company uses different dictionaries for its postmarketing safety and clinical study data bases; (2) the company has products in late-stage clinical trials; and (3) the company has marketed products near the end of their useful life. ERG estimates the maintenance costs for existing dictionaries are expected to range from $4,300 to $136,400 annually for drug manufacturers and from $4,300 to $43,400 annually for biologics manufacturers. No costs were assigned to blood facilities.

Table 18 presents the estimated costs to industry of implementing MedDRA for each cost category.

Table 18.--Total Compliance Costs of MedDRA by Cost Category

Drugs and Biologics	Total Cost[1] ($ million)	Percent of Total[1]
First-Time Costs Planning and coordination	16.3	9
Purchase or development of auto-encoder	20.5	12
Personnel training	46.0	27
Development of IT structure	14.7	9
Legacy safety data conversion	31.9	18
Revision of SOP's	14.8	9
Total First-time	144.2	83
Recurring Costs Annual MedDRA core subscription	6.6	4
MedDRA versioning	6.9	4
Maintenance of additional medical dictionary	15.0	9
Total recurring	28.5	16
Total first year costs (First-time + recurring)	172.8	100

[1]Totals may not add due to rounding.

V.E. Small Business Analysis

The following analysis along with other sections of this preamble constitute the agency's regulatory flexibility analysis as required under the Regulatory Flexibility Act.

V.E.1. Need for and Objectives of the Rule

A primary objective of this proposed rule is the harmonization of FDA's safety reporting requirements with international initiatives. The proposed rule would also improve the quality of information contained in postmarketing safety reports for marketed human drug and biological products. By providing more complete information for individual case safety reports, the revised reports would enhance the ability of manufacturers, applicants, and the agency to identify, monitor, and communicate the risks and benefits of marketed drug and biological products. Monitoring these risks and benefits is especially critical for recently approved products introduced to large and diverse patient populations following market approval.

V.E.2. Description and Estimate of Small Entities

The proposed rule applies to manufacturers, applicants, and contractors of drug and biological products, and persons involved in blood collection and transfusion. The Small Business Administration (SBA) defines a small business in Standard Industrial Classification (SIC) 2834 (or North American Industry Classification System (NAICS) code 325412) as one employing fewer

than 750 employees and in SIC 2836 (or NAICS code 325414) as one employing fewer than 500 employees. According to 1996 U.S. Bureau of the Census statistics, almost 90 percent of the firms under these SIC codes are considered small businesses. A review of 1998 AERS data, which contain postmarketing 15-day and periodic safety reports from manufacturers and applicants of marketed drug and biological products, found that about 200 firms submitted at least one individual case safety report for a trade name product and that the majority of these firms were considered large under the SBA definitions. However, the number of firms submitting reports vary from year to year. Therefore, using the 1998 AERS data, estimates of the percentages of reporting firms by size were distributed to the number of firms in each SIC, suggesting that about 230 drug and 72 biologics firms would be affected by the proposed rule, of which 190, or about 60 percent, would be considered small.

FDA estimates that about 3,200 blood facilities would be affected by the proposed regulation. Approximately 3,000 are hospitals with blood collection and/or compatibility testing operations, classified in SIC 8062 (or NAICS code 62211), and 200 are blood banks or non-hospital blood and plasmapheresis centers, classified in SIC 8099 (or NAICS code 621991). The SBA defines businesses in SIC 8062 and 8099 with annual revenues of $25 million and $7.5 million or less, respectively, as small. ERG

estimated the number of small businesses affected in SIC's 8062 and 8099 at 1,786 and 188, respectively. This is approximately 60 and 94 percent of the blood facilities in SIC's 8062 and 8099, respectively, that will be implementing the MedDRA requirements.

V.E.3. Projected Reporting, Recordkeeping, and Other Compliance Requirements

V.E.3.a. Reporting and recordkeeping requirements. The proposed rule may impose an additional burden on manufacturers of human drug products for which SADR's are reported. In any year, SADR's may be reported for about half of the products marketed in the United States. AERS data from 1998 suggest that small firms manufactured less than 12 percent of the products for which SADR's were reported. Moreover, during this same year, only about 2 percent of the postmarketing 15-day alert reports submitted to the agency were from small firms. Nevertheless, the proposed changes to the postmarketing safety reporting requirements may impose a substantial burden on a significant number of small firms, especially small startup firms with only one product on the market. The extent of the impact will depend on the time that has elapsed since the drug was approved and the number and types of individual case safety reports received in a reporting period.

To illustrate the impact of the safety reporting and recordkeeping requirements of the proposed rule, table 19 shows the hypothetical first-year burden for a drug approved 6 months

prior to the effective date of the final rule. Under this scenario, the first-year burden incurred for a newly approved product might be as much as $19,600, assuming 26 expedited and 6 followup reports, two semiannual reports, and two PSUR's had been submitted.

Table 19.--Hypothetical First-Year Reporting and Recordkeeping Burden for Newly Approved Drug Product

	Expedited (serious, unexpected SADR)	Expedited (medication errors)	Expedited (unexpected SADR with unknown outcome)	Always Expedited Report	30-Day Follow-up	Individual Case Safety Report--Semi-annual Submission	PSUR	Total
Per report new burden[1]	$104	$612	$919	$612	$367	$1,042	$1,564	
Number of reports	8	16	1	1	6	2	2	36
Totals[2]	$834	$9,799	$919	$612	$2,202	$2,084	$3,128	$19,578

[1]Only whole dollar values are shown.

[2]Values rounded to the nearest whole number.

V.E.3.b. Implementing MedDRA. Implementing MedDRA would impose additional significant one-time and recurring costs on drug and biological product manufacturers. Costs would vary among individual firms depending on circumstances, including the number of products manufactured, the frequency of SADR's, and the extent of legacy data converted. Table 20 displays ERG's estimates per firm of revenues, annualized compliance costs and costs as a percent of revenues. Costs for small entities are 0.15 percent and 0.28 percent of revenues for drug and biological product manufacturers, respectively. Similarly, average compliance costs for small entities are 0.01 percent and 0.03 percent of revenue for SIC's 8062 and 8099, respectively.

Table 20.--Compliance Costs as a Percent of Estimated Revenues for Small Entities

Industry Classification	Number of Employees	Number of Affected Firms	Per Firm Estimated Revenues ($000)	Per Firm Annualized Compliance Costs ($000)	Compliance Cost as a Percent of Estimated Revenues
SIC 2834 Pharmaceutical preparations	< 750	146	44,265	66.9	0.15
SIC 2836 Biological products	< 500	44	15,752	44.4	0.28
SIC 8062 General medical and surgical hospitals	< 500	1,786	13,366	0.6	0.01
SIC 8099 Blood banks (Health and allied services, NEC)	< 500	188	1,320	0.3	0.03

The reporting, coding, and analysis of SADR's are standard procedures that manufacturers routinely conduct under current regulations. No additional professional skills would be necessary to comply with this rule. However, current safety reviewers, analysts, and IT personnel would need training to implement MedDRA.

V.E.4. Alternatives and Steps to Minimize the Impact on Small Entities

The major objectives of this proposed rule are to harmonize FDA's safety reporting requirements with international initiatives and to improve the quality of safety reports. With these objectives in mind, the agency considered alternatives to this proposed rule.

V.E.4.a. Do nothing. The agency considered but rejected the option of not proposing this rule. The proposed rule would align FDA's safety report terms, formats and requirements for human drugs and biological products with the recommendations of ICH. With regard to use of a medical dictionary for safety reporting purposes, at the present time, major problems exist with comparing safety data globally because multiple medical dictionaries are being used internationally for coding of SADR's (see section III.F.2 of this document). In this rule, the agency proposes to require the use of MedDRA, the medical dictionary developed by ICH. FDA believes that "to do nothing" would be

inconsistent with the agency's efforts to harmonize safety reporting with international initiatives.

Another objective of this proposed rule is to improve the quality of safety reports. In this preamble, the agency cited a substantial number of studies that estimate the number of SADR's that have resulted in a hospitalization or that occur in a hospital and the hospital costs related to SADR's. Safety reports that are complete are critical and necessary to reduce SADR's, medication errors, and hospital costs. This proposed rule would improve the agency's ability to monitor the safety of human drugs and biological products. In light of this information, "to do nothing" would be inconsistent with the agency's mission of protecting public health.

V.E.4.b. Waivers for economic hardship. The agency recognizes that requiring individual case safety reports to be coded using MedDRA will likely impose significant costs on some small firms (see section III.F.2 of this document). One alternative would be to consider the option of allowing companies to request a waiver from MedDRA coding, based on economic hardship. The agency is seeking comment on ways to reduce economic hardships of implementing MedDRA while maintaining adequate procedures to monitor and assess the safety of products.

V.E.4.c. Small business outreach, training, and assistance. The agency has received both written and verbal input from

p. 276(a)

Page 276, Insert C after V.E.4.a.

V.E.4.b. Do not require a medical dictionary. The agency considered but rejected the alternative of not requiring the use of MedDRA terms in individual case safety reports. MedDRA is an integral part of the postmarket safety reporting system that was developed jointly with international stakeholders. Requiring MedDRA terms in safety reports will enhance the analysis of drug safety information. Moreover, MedDRA is a medical dictionary designed to translate terms in multiple languages, thus aiding in more expeditious and broader international drug use comparisons and analysis. Not requiring MedDRA would compromise the agency objective of improving drug safety reporting and analysis. In addition, continued use of multiple medical dictionaries to code SADR's will perpetuate the major problems with comparing safety data globally that currently exist.

V.E.4.c. Do not require medication errors as expedited reports. The agency considered but rejected the alternative of not requiring medication errors as expedited reports. Requiring expedited reports of medication errors would allow the agency to review critical information and take appropriate and more timely action on SADR's that are preventable. Not requiring expedited reports of medication errors would ignore a key step in reducing medical errors.

V.E.4.d. Do not require blood establishments to submit reports for all serious SADR's associated with blood collection and transfusion. The agency considered but rejected the alternative of not requiring blood establishments to submit reports for all serious SADR's associated with blood collection and transfusion, in addition to the current requirement to submit reports of fatalities. Because these establishments are currently required to conduct investigations and prepare and maintain reports of serious SADR's, this proposal would impose minimal costs. However, only some serious SADR's must be reported in a timely manner. The agency believes it is critical that we receive all such reports. This would improve the agency's ability to take appropriate action to protect the blood supply more consistently, to enhance donor safety and to ensure the safety, purity and potency of blood and blood components for administration to patients.

V.E.4.e. Do not require certain bioavailability and bioequivalence reports as expedited reports. The agency considered but rejected the alternative of not requiring expedited

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reports of SADR's for bioavailability and bioequivalence studies not subject to an IND. This requirement would allow the agency quicker access to information and would facilitate appropriate action to protect those enrolled in clinical trials.

interested parties, including small businesses, on the recommendations of ICH regarding safety reporting for human drugs and biological products (e.g., the ICH E2A guidance, the ICH E2C guidance, and ICH M1). These public comments addressed published draft versions of the ICH guidances as well as numerous agency presentations at public workshops and forums (e.g., sponsored by the Drug Information Association (DIA) or the Pharmaceutical Education and Research Institute (PERI)). The agency has considered these comments in development of this proposed rule.

Once this proposed rule is finalized, the agency will provide the public with an overview of the provisions in the rule at workshops and forums (e.g., DIA meetings, PERI workshops). All firms, including small firms, would have an opportunity to attend these presentations.

Firms can access AERS-related information on the Internet at www.fda.gov/cder/aers/index.htm. The AERS site includes a "Reporting Regulations and Guidances" page that provides a summary of the rulemaking (proposed rules, final rules) and guidances regarding the agency's safety reporting requirements for human drugs and biological products. This site is updated as changes to the safety reporting requirements are made.

V.F. Unfunded Mandates Reform Act of 1995

On the basis of the preceding discussion, under the Unfunded Mandates Reform Act, FDA concludes that if only 2 percent of the