

Supporting Statement

Reporting Requirements

Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients -- OMB Control No. 0910-0392

A. Justification

1. Circumstances of Information Collection

FDA regulations require pediatric studies of certain new drugs and biological products to ensure that those products that are likely to be commonly used in children or that represent a meaningful therapeutic benefit over existing treatments contain adequate pediatric labeling for the approved indications at the time of, or soon after, approval. (These regulations were issued in the Federal Register of December 2, 1998 (63 FR 66632)). Many new drugs and biological products represent treatments that are the best available treatment for children, but most of them have not been adequately tested in the pediatric population. As a result, product labeling frequently fails to provide directions for safe and effective use in pediatric patients. The regulations are intended to increase the number of new drugs and biological products, with clinically significant use in children, that carry adequate labeling for use in that subpopulation. Specifically, the regulations are intended to address the following concerns: (1) Avoidable adverse drug reactions in children -- drug reactions that occur because of the use of inadvertent drug overdoses or other drug administration problems that could have been avoided with better information on appropriate pediatric use; and (2) undertreatment of children with a potentially safe and effective drug because the physician either prescribed an inadequate dosage or regimen, prescribed a less effective drug, or did not prescribe a drug, due to the physician's uncertainty about whether the drug or the dose was safe and effective in children.

The regulations contain the following reporting requirements that are subject to the PRA:

21 CFR 201.23(a) - Manufacturers of marketed drug products submit an application containing data adequate to assess whether the drug product is safe and effective in pediatric populations; applicants develop a pediatric formulation for FDA approval.

21 CFR 201.23(c) -- Applicants request a full or partial waiver of § 201.23(a).

21 CFR 312.47(b)(1)(iv) -- Sponsors submit background information on the sponsor's plan for Phase 3, including plans for pediatric studies, including a time line for protocol finalization, enrollment, completion, and data analysis, or

information to support any planned request for waiver or deferral of pediatric studies.

21 CFR 312.47(b)(2) -- Sponsors submit information on the status of needed or ongoing pediatric studies.

21 CFR 314.50(d)(7) -- Applicants submit a pediatric use section, describing the investigation of the drug for use in pediatric populations.

21 CFR 314.55(a) -- Applications contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in pediatric subpopulations and to support dosing and administration.

21 CFR 314.55(b) -- Applicants request a deferred submission of some or all assessments of safety and effectiveness required under § 314.55(a).

21 CFR 314.55(c) -- Applicants request a full or partial waiver of the requirements under § 314.55(a).

21 CFR 314.81(b)(2)(i) -- Applicant's annual report includes a brief summary of whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population have been initiated.

21 CFR 314.81(b)(2)(vi)(c) -- Applicant's annual report includes an analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information.

21 CFR 314.81(b)(2)(vii) -- Applicant's annual report includes a status report containing a statement indicating whether postmarketing clinical studies in pediatric populations were required by FDA under § 201.23, and if so, the status of these studies.

21 CFR 601.27(a) -- Applications for new biological products contain data that are adequate to assess the safety and effectiveness of the biological product for the claimed indications in pediatric subpopulations, and to support dosing and administration information.

21 CFR 601.27(b) -- Applicants request a deferred submission of some or all assessments of safety and effectiveness required under § 601.27(a).

21 CFR 601.27(c) -- Applicants request a full or partial waiver of the requirements under § 601.27(a).

21 CFR 601.28(a) -- Sponsors submit to FDA a brief summary stating whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated.

21 CFR 601.28(b) -- Sponsors submit to FDA an analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information.

21 CFR 601.28(c) -- Sponsors submit to FDA a statement on the current status of any postmarketing studies in the pediatric

population performed by, or on behalf of, the applicant.

2. Purpose and Use of Information

FDA requires pediatric studies of certain new drugs and biological products to ensure that those products that are likely to be commonly used in children or that represent a meaningful therapeutic benefit over existing treatments contain adequate pediatric labeling for the approved indications at the time of, or soon after, approval. The purpose of these reporting requirements is to address the lack of adequate pediatric labeling of drugs and biological products by requiring the submission of evidence on pediatric safety and effectiveness for products with clinically significant use in children.

3. Use of Improved Information Technology

Electronic Regulatory Submissions for Archive. The Food and Drug Administration Modernization Act of 1997 (FDAMA) and the Prescription Drug User Fee Act (PDUFA) II reauthorization mandate that the agency develop and update its information management infrastructure to allow, by fiscal year 2002, the paperless receipt and processing of investigational new drug applications and new drug applications, as defined in PDUFA, and related submissions. Moving an information-intensive activity, such as drug regulatory review, from a paper-based to an electronic environment will provide a number of benefits. This is true simply from the perspective of generating, handling, and storing the huge volumes of paper commonly associated with applications.

In general, these paper applications (often containing hundreds of volumes) are submitted with several copies, a process that can take several days longer than preparation of a corresponding electronic submission, which the agency can easily reproduce. Preparation of applications in electronic format results in direct cost savings related to materials, supplies, and paper handling logistics (i.e., labor, facilities). However, this is expected to be only a small portion of the potential savings. The most substantial burden reduction may not be in information recording, reporting, and record-keeping, but in the flexibility, efficiency, speed, and ease of filing required information that will result in cost savings to regulated industry, as well as FDA.

In September 1997, FDA published the Guidance for Industry on Archiving Submissions in Electronic Format X NDAs. This guidance provided for the receipt and archive of electronic Case Report Forms (CRF) and Case Report Tabulations (CRT) without an accompanying paper copy. In FY 1998, FDA established an Electronic Document Room (EDR) to manage the receipt and handling

of all electronic submissions. In January 1999, FDA published the Guidance for Industry on AProviding Regulatory Submissions in Electronic Format X NDAs≅. This guidance document covers the full NDA and is not limited to CRTs and CRFs.

FDA has received 264 NDAs with electronic components since January 1999. Of these 89 were new submissions. In the same period the agency has also received 273 supplements with electronic components of which 170 were new supplements. As of the end of August 2000, the agency's EDR was comprised of three groups of NDAs: those that consisted of items 11 and/or 12 only (109 or 42.4%); those that consisted of various items with or without items 11 and 12 (105 or 40.9%); and those consisting of nearly all 19 possible NDA data items (43 or 16.7%). A total of 197 (76.7%) of NDAs with electronic components had items 11 and/or 12 submitted in an electronic format.

Secure E-Mail. During a drug's development cycle, communications between agency review divisions and the company developing the drug is sensitive and proprietary. Prior to using secure E-mail, agency methods of Asecure≅ communication included U.S. mail, courier, telephone, and facsimile. These methods, some of which are not entirely secure, can be inefficient or time consuming, and can significantly contribute to the overall length of time involved in the drug review process. The widespread use of E-mail across the Internet offers a more efficient and scaleable means of information exchange. However, security risks of communicating over the Internet are well known. The information technology industry is answering security concerns by developing new standards of cryptographic techniques, E-mail formats, authentication algorithms, and other related aspects of secure communications. In 1998, the agency conducted a formal requirements study for secure E-mail which led to the selection of Worldtalk Corporation's WorldSecure Server as the base pilot platform. The agency completed a pilot, the final system design and implemented the production system in October 1999. The system is used across the Center for Drug Evaluation and Research to communicate with over 15 companies and more than 150 individuals in those companies. The system also provides virus scanning and extensive E-mail filtering capabilities.

ICH M2. The International Conference on Harmonisation (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use was formed to minimize waste in the discovery, development, regulation, manufacture, marketing, and use of human therapeutic products worldwide. The regulatory authorities of Europe, Japan, and the United States joined with their respective

pharmaceutical trade associations in an agreement to take action on harmonization by participating in the ICH.

The ICH Multi-disciplinary Group 2 (M2) Expert Working Group (EWG) was established to determine electronic standards and provide solutions to facilitate international electronic communication in the three ICR regions. The first effort of the M2 EWG was to establish a series of recommendations that would form the basis for standardized electronic communication in each of the three regions. These recommendations included physical media formats, secure communications, and structured data formats. Building on these standards, the EWG completed a detailed specification for the secure, electronic transmission of individual case safety reports (adverse event reports). The specification is being used to format and transmit electronic adverse event reports directly from a company's database to the FDA Adverse Event Reporting System (AERS).

The production of a specification for an electronic common technical document (CTD) was the next major effort assigned to the M2 EWG. The ICH Steering committee agreed in March 1999 that this effort should be undertaken by the M2 EWG in cooperation with the subject matter expert working groups for each section of the CTD. The CTD working groups are charged with harmonizing the format and content of the application documents for new product applications. The resulting ICH guidances, when implemented, will change the content and format of NDA submissions to the FDA. The M2 EWG is working with the CTD Step 2 documents to define the functionality to be included in the electronic submission for CTD submissions.

4. Efforts to Identify Duplication

This reporting is the only practical means available to FDA to ensure that new drugs and biological products with clinically significant use in children carry adequate labeling for use in that subpopulation.

5. Involvement of Small Entities

As explained in the "Analysis of Impacts" section of the final rule (December 2, 1998 (63 FR 66632)), FDA concluded that the rule does not have a significant economic impact on a substantial number of small entities.

6. Consequences if Information Collected Less Frequently

FDA would be unable to ensure that new drugs and biological products with clinically significant use in children carry adequate labeling for use in that subpopulation.

7. Consistencies with Guidelines in 5 CFR 1320.5(d)(2)

Data collection for applications is consistent with all the requirements of section 1320.6.

8. Consultations Outside the Agency

In the Federal Register of October 16, 1992, FDA proposed to revise the "Pediatric Use" subsection of the prescription drug labeling regulations to allow a broader basis for the inclusion of information about use of a drug in the pediatric population. The proposal, which was finalized in the Federal Register of December 13, 1994, allowed pediatric claims based not only on adequate and well-controlled studies in the pediatric population but also, in some cases, on such trials in adults. The regulation described other data needed when pediatric claims are based on trials in adults, and indicated specific labeling language and the location of various kinds of information. FDA issued this rulemaking because most prescription drugs lack adequate information about their use in pediatric populations and, thus, practitioners are reluctant to prescribe certain drugs for pediatric patients or may prescribe them inappropriately, choosing dosages that are arbitrarily based on the child's age, body weight, or body surface area without specific information as to whether this is appropriate. FDA received comments on the proposed rule from prescription drug manufacturers, prescribers, professional societies, organizations with special interests in the pediatric population, and the lay public.

FDA proposed the requirements that are the subject of this information collection in the Federal Register of August 15, 1997, because, as explained in the preamble to the proposal, there had not been a substantial increase in the number of drugs and biological products for which there is adequate pediatric use information. FDA received 54 written comments on the proposed rule from pediatricians, professional societies, parents, members of the pharmaceutical industry, organizations devoted to specific diseases, and patient groups. FDA also held a day-long public hearing on October 27, 1997, at which recognized experts in the field, members of the pharmaceutical industry, and other

interested parties were given an opportunity to discuss the issues raised by the proposed rule. All of these comments, as well as FDA's responses, were discussed in the "Comments on the Proposed Rule" section of the final rule (December 2, 1998 (63 FR 66632)).

In the Federal Register of September 27, 2001 (66 FR 49389), requesting OMB extension of its approval of the information collection, FDA requested comments on the collection of information. FDA received one comment on the September 27, 2001, notice. The comment stated, generally, that FDA underestimated the resources required to satisfy the collection of information, and requested that the agency provide a more detailed discussion of the assumptions and methodology used to develop the estimates.

First, the comment stated that the burden to comply with the information collection requirements in § 201.23(a) "would involve hundreds of hours of development time and a variety of scientific specialities" if a sponsor would have to submit a supplemental application or a new drug application (NDA) for a pediatric formulation. The comment said that even if the burden for submitting a pediatric application is included under the other estimates in the Federal Register notice, the burden for § 201.23(a) (which "would be limited to the sponsor's opportunity for a written response and a meeting which may include an advisory committee meeting") would still be greater than the 48 hours per response estimated by FDA.

Second, the comment stated that FDA's estimate for compliance with the information collection requirements in §§ 314.55(a) and 601.27(a) is low "because the collection, analysis, and reporting of data adequate to support pediatric use of a new drug or biological product involves extensive resources of a multi-disciplinary team to plan and execute the necessary clinical development program."

Third, the comment questioned why FDA's estimate for the number of annual responses in § 314.50(d)(7) is not equal to the estimate for the number of annual responses in § 314.55(a), since "§ 314.50(d)(7) requires the pediatric section of an application to include 'information submitted under § 314.55.'"

Fourth, the comment questioned why FDA did not provide a burden estimate for §§ 314.50(d)(3) (human pharmacokinetics and bioavailability section of an application) and 314.50(d)(5) (clinical data section of an application).

Fifth, the comment stated that FDA's estimate of 100 respondents for §§ 314.81(b)(2)(i), 314.81(b)(2)(vi)(c), and 314.81(b)(2)(vii) is low, and that "FDA might expect approximately 3000 responses annually" (not including responses from holders of approved biological license applications) because

there are approximately 3000 NDAs included in the Approved Drug Products With Therapeutic Equivalence Evaluations.

FDA responded to the comment as follows:

Concerning the comments on the adequacy of FDA's burden estimates for §§ 201.23(a) and 314.55(a) (and 601.27(a)), the agency agrees that the collection and analysis of data adequate to support pediatric use and to develop a pediatric formulation would be more burdensome than the estimates provided in the September 27, 2001, notice. The September 27, 2001, notice and this notice, however, are part of the process to request that OMB extend approval for the collection of information described in the final rule entitled "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biologicals Products in Pediatric Patients," published in the Federal Register of December 2, 1998 (63 FR 66632 at 66659) (the final rule). In the final rule (63 FR 66632 at 66660), FDA also estimated the costs associated with conducting and analyzing efficacy studies, PK studies, and new dosage form development. These industry costs total approximately \$80 million annually. The analysis of the economic impact of the regulation is required under Executive Order 12866, the Regulatory Flexibility Act, and the Unfunded Mandates Reform Act. The added burden cited by the comment for §§ 201.23(a) and 314.55(a) (and 601.27(a)) has been estimated by FDA in the economic analysis. Only the burden associated with compiling and reporting to FDA information already obtained is the subject of this notice and the September 27, 2001, notice. FDA published for public comment its initial estimate of this collection of information in the Federal Register of August 15, 1997 (62 FR 43900 at 43909). In the final rule, FDA discussed the comments on the burden estimates and revised the estimate for §§ 201.23(a) and 314.55(a) (and 601.27(a)) from 16 hours to 48 hours. Thus, FDA believes that the collection of information estimate together with the cost estimate made in the analysis of the economic impact of the regulation provide an adequate assessment of the industry burden resulting from §§ 201.23(a) and 314.55(a) (and 601.27(a)).

As a result of the comment that number of annual responses in § 314.50(d)(7) should be equal to the number of annual responses in § 314.55(a), FDA has reconsidered its analysis of the collection of information resulting from these sections of the regulation. Under § 314.50(d)(7), applicants must submit as part of an application and supplement to an approved application a "pediatric use section." This section must describe the investigation of the drug for use in pediatric populations, including an integrated summary of the information that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications,

a reference to the full descriptions of such studies provided under §§ 314.50(d)(3) and (d)(5), and information required to be submitted under § 314.55. Under § 314.55(a), applications must contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. FDA has determined that, for purposes of this collection of information analysis, the requirement to submit pediatric use information would more appropriately come under § 314.50(d)(7). Section 314.55(a) is the requirement to obtain pediatric use information for reporting to FDA under § 314.50(d)(7). Thus, FDA is including the reference to § 314.55(a) in the same entry as § 314.50(d)(7) in Table 1 of this document. As a result of more recent data, FDA has revised its estimate of the number of responses and respondents under § 314.50(d)(7). Based on the number of submissions to FDA of the required assessments of pediatric safety and effectiveness during 2001, FDA estimates that approximately 59 applicants will submit approximately 78 assessments annually.

Concerning the comment that FDA did not provide a burden estimate for §§ 314.50(d)(3) and (d)(5), this notice and the September 27, 2001, notice are part of the process to request that OMB extend approval for the collection of information described in the final rule. The final rule did not amend §§ 314.50(d)(3) and (d)(5) and, therefore, these sections were not included in the collection of information analysis in the final rule. The information collection under §§ 314.50(d)(3) and (d)(5), as well as other provisions under 21 CFR 314, are already approved by OMB until November 30, 2004, under OMB Control Number 0910-0001.

The comment also stated that FDA's estimate of 100 respondents for §§ 314.81(b)(2)(i), 314.81(b)(2)(vi)(c), and 314.81(b)(2)(vii) is low, and that over 3000 responses should be expected annually. Under these sections, applicants must submit in their annual report a brief summary of whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population have been initiated, an analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information, and a status report containing a statement indicating whether postmarketing clinical studies in pediatric populations were required by FDA under § 201.23, and if so, the status of these studies. Thus, only the annual reports for those approved applications that contain or will contain pediatric use information would be covered by these sections. As a result of

more recent data, FDA has revised its estimates of the number of responses and respondents for these sections. Based on the number of currently approved applications that contain pediatric use information and the number of additional applications containing pediatric use information that FDA expects will be approved, FDA estimates approximately 119 applicants will submit approximately 158 annual reports under § 314.81(b)(2)(i), approximately 119 applicants will submit approximately 158 annual reports under § 314.81(b)(2)(vi)(c), and approximately 6 applicants will submit approximately 6 annual reports under § 314.81(b)(2)(vii).

As a result of more recent data for the number of requests for deferrals and waivers received in 2001, FDA has also revised the estimates for §§ 314.55(b) and (c).

9. Remuneration of Respondents

FDA has not provided and has no intention to provide any payment or gift to respondents under these requirements.

10. Assurance of Confidentiality

Confidentiality of the information submitted under these reporting requirements is protected under 21 CFR 314.430 and 601.51.

11. Questions of a Sensitive Nature

There are no questions of a sensitive nature.

12. Estimates of Annualized Hour Burden

FDA estimates that the PRA burden to comply with the regulations will be as follows:

Table 1 -- Estimated Annual Reporting Burden

<u>21 CFR Section</u>	<u>Number of Respondents</u>	<u>Number of Responses Per Respondent</u>	<u>Total Annual Responses</u>	<u>Hours Per Response</u>	<u>Total Hours</u>
201.23(a)	2	1	2	48	96
201.23(c)	0	0	0	0	0
312.47(b)(1)(iv)	103	1.2	122	16	1,952
312.47(b)(2)	102	1.3	130	16	2,080
314.50(d)(7); 314.55(a)	59	1.3	78	50	3,900
314.55(b)	60	1.3	80	24	1,920
314.55(c)	79	1.3	105	8	840
314.81(b)(2)(i)	119	1.3	158	8	1,264
314.81(b)(2)(vi)(c)	119	1.3	158	24	3,792
314.81(b)(2)(vii)	6	1	6	1.5	9
601.27(a)	2	1	3	48	144
601.27(b)	5	1	5	24	120
601.27(c)	3	1	4	8	32
601.37(a)	69	1	69	8	552
601.37(b)	69	1	69	24	1,656
601.37(c)	69	1	69	1.5	104
TOTAL					18,461

13. Estimates of Annualized Cost Burden to Respondents

The cost for submitting the applications and requests required under the final rule is based on the following wage rates: Upper management at \$56.00 per hour; middle management at \$36.55 per hour; and clerical assistance at \$18.28 per hour. Assuming that 25% of the total burden hours is expended by upper management, 50% by middle management, and 25% by clerical assistance, the total cost burden to respondents would be \$ **680,273.54** (258,496.00 + 337,374.77 + 84,366.77).

14. Estimates of Annualized Cost Burden to the Government

FDA estimates that it would take application reviewers an average of approximately 50 hours to review each additional application and request required under 21 CFR 201.23, 312.47(b)(1)(iv), 312.47(b)(2), 314.50(d)(7), 314.55(a), 314.55(b), 314.55(c), and 601.27(a), (b), and (c), and an average of approximately 4 hours to review each additional annual report section required under 21 CFR 314.81(b)(2)(i), (b)(2)(vi)(c), and (b)(2)(vii), and 21 CFR 601.37(a), (b), and (c). Based on an average hourly cost of \$50.00 per hour for this level of reviewer (including overhead expenses and clerical and administrative support), the total cost to FDA would be **\$1,428,300.00** (529 submissions x 50 hours x \$50 = \$1,322,500.00; 529 submissions x 4 hours x \$50 = \$105,800.00).

15. Changes in Burden

The change in burden is the result of new data on the number of submissions.

16. Time Schedule, Publication, and Analysis Plans

FDA does not intend to publish tabulated results of the information collection requirements that would be imposed by these requirements.

17. Displaying of OMB Approval Date

There are no forms associated with this collection.

18. Exceptions to the Certification Statement - Item 19

There are no exceptions to the "Certification for Paperwork

Reduction Act Submissions" for this collection. This collection complies with 5 CFR 1320.9.

praped.ss.doc 1/23/02