SUPPORTING STATEMENT

Applications for FDA Approval to Market a New Drug

21 CFR Part 314 - OMB Control Number 0910-0001

A. Justification

1. Circumstances of Information Collection

Under Section 505(a) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(a)), a new drug may not be commercially marketed in the United States, imported, or exported from the United States, unless an approval of an application filed with FDA pursuant to sections 505(b) or (j) is effective with respect to such drug. Sections 505(b) and (j) require a sponsor to submit to FDA a New Drug Application (NDA), containing among other things, full reports of investigations that show whether or not the drug is safe and effective for use, a full list of articles used as components in the drug, a full description of manufacturing methods, samples of the drugs required, specimens of the labeling proposed to be used, and certain patent information as applicable. Under the Act, it is the sponsor's responsibility to provide the information needed by FDA to make a scientific and technical determination that the product is safe and effective.

This information collection approval request is for all information requirements imposed on sponsors by the regulations under 21 CFR 314, who apply for approval of a new drug application in order to market or to continue to market a drug.

The following sections in 21 CFR 314 set forth the specific format and content requirements for NDAs.

21 CFR 314.50(a): An application form (Form FDA 356h) must be submitted that includes basic introductory information about the drug as well as a

	checklist of enclosures. (Section 314.50(a) is already approved by OMB under 0910-0338 and is not included in the hour burden estimates in the chart below).
21 CFR 341.50(b)	Requires that an index must be submitted with the archival copy of the application and that it must reference certain sections of the application.
21 CFR 314.50(c)	A summary of the application must be submitted that presents a good general synopsis of all the technical sections and other information in the application.
21 CFR 314.50(d)	Requires that the NDA contain the following technical sections about the new drug: Chemistry, manufacturing, and controls; non-clinical pharmacology and toxicology; human pharmacokinetics and bioavailability; microbiology; clinical data; and statistical section.
21 CFR 314.50(e)	The applicant must submit samples of the drug if requested by FDA. In addition, the archival copy of the application must include copies of the label and all labeling for the drug.
21 CFR 314.50(f)	Requires that case report forms and tabulations must be submitted with the archival copy.

21 CFR 314.50(h)	Patent information as described under § 314.53 must be submitted with the application. (Section 314.50(h) is already approved by OMB under 0910-0305 and is not included in the hour burden estimates in the chart below).
21 CFR 314.50(i)	Requires that patent certification information must be submitted in 505(b)(2) applications for patents claiming the drug, drug product, method of use, or method of manufacturing. (Section 314.50(i) is already approved by OMB under 0910-0305 and is not included in the hour burden estimates in the chart below).
21 CFR 314.50(j)	Applicants that request a period of marketing exclusivity must submit certain information with the application. (Section 314.50(j) is already approved by OMB under 0910-0305 and is not included in the hour burden estimates in the chart below).
21 CFR 314.50(k)	Requires that an archival, review, and field copy of the application must be submitted.
21 CFR 314.52	Requires that notice of certification of invalidity or noninfringement of a patent to patent holders and NDA holders must be sent by 505(b)(2) applicants and must follow certain content and notification procedures. (Section 314.52 is already approved by OMB

	under 0910-0305 and is not included in the hour burden estimates in the chart below).
21 CFR 314.54	Sets forth the content requirements for applications filed under § 505(b)(2).
21 CFR 314.60	Sets forth reporting requirements for sponsors who amend an unapproved application.
21 CFR 314.65	States that the sponsor must notify FDA when withdrawing an unapproved application.
21 CFR 314.70 and 314.71	Requires that supplements must be submitted to FDA for certain changes to an approved application.
21 CFR 314.72	Requires sponsors to report to FDA any transfer of ownership of an application.
21 CFR 314.80(c)(1)and (c)(2)	Sets forth requirements for expedited adverse drug experience postmarketing reports and followup reports, as well as for periodic adverse drug experience postmarketing reports (Form FDA 3500A). (Sections 314.80(c)(1) and (c)(2) are already approved by OMB under 0910-0230 and 0910-0291 and are not included in the hour burden estimates in the chart below).
21 CFR 314.80(c)(i)(iii) and	Establishes recordkeeping requirements for reports of postmarketing adverse drug

314.80(i)	experiences. (Sections 314.80(c)(1)(iii) and 314.80(i) are already approved by OMB under 0910-0230 and 0910-0291 and are not included in the hour burden estimates in the chart below).
21 CFR 314.81(b)(1)	Field alert reports must be submitted to FDA (Form FDA 3331).
21 CFR 314.81(b)(2)	Annual reports must be submitted to FDA (Form FDA 2252).
21 CFR 314.81(b)(3)(i)	Drug advertisements and promotional labeling must be submitted to FDA (Form FDA 2253). (Section 314.81(b)(3)(i) is already approved by OMB in "Transmittal of Advertisements & Promotional Labeling for Drugs & Biologics For Human Use," which published in 62 FR 55408, and is not included in the hour burden estimates in the chart below).
21 CFR 314.81(b)(3)(iii)	Sets forth reporting requirements for sponsors who withdraw an approved drug product from sale. (Section 314.81(b)(3)(iii) is already approved by OMB under 0910-0045 and is not included in the hour burden estimates in the chart below).
21 CFR 314.90	Sets forth requirements for sponsors who request waivers from FDA for compliance with §§ 314.50 through 314.81. (The information collection hour burden estimate for NDA

	waiver requests is included in the chart below under estimates for §§ 314.50, 314.60, 314.70 and 314.71).
21 CFR 314.93	Sets forth requirements for submitting a suitability petition in accordance with 21 CFR 10.20 and 10.30. (Section 314.93 is already approved by OMB under 0910-0183 and is not included in the hour burden estimates in the chart below).

The following sections in 21 CFR 314 set forth requirements when submitting an Abbreviated New Drug Application (ANDA).

21 CFR 314.94(a) and (d)	An ANDA must contain the following information: Application form; table of contents; basis for ANDA submission; conditions of use; active ingredients; route of administration, dosage form, and strength; bioequivalence; labeling; chemistry, manufacturing, and controls; samples; patent certification.
21 CFR 314.95	Requires that notice of certification of invalidity or noninfringement of a patent to patent holders and NDA holders must be sent by ANDA applicants. (Section 314.95 is already approved by OMB under 0910-0305 and is not included in the hour burden estimates in the chart below).
21 CFR 314.96	Sets forth requirements for amendments to an

	unapproved application.
21 CFR 314.97	Sets forth requirements for submitting supplements to an approved ANDA for changes that require FDA approval.
21 CFR 314.98(a)	Sets forth postmarketing adverse drug experience reporting and recordkeeping requirements. (Section 314.98(a) is already approved by OMB under 0910-0230 and 0910-0291 and is not included in the hour burden estimates in the chart below).
21 CFR 314.98(c)	Requires other postmarketing reports: Field alert reports (Form FDA 3331), annual reports (Form FDA 2252), and advertisements and promotional labeling (Form FDA 2253) (The information collection hour burden estimate for field alert reports is included in the chart below under § 314.81(b)(1); the estimate for advertisements and promotional labeling is included under §314.81(b)(3)(i)).
21 CFR 314.99(a)	Sponsors must comply with certain reporting requirements for withdrawing an unapproved ANDA and for a change in ownership of an ANDA.
21 CFR 314.99(b)	Sets forth requirements for sponsors who request waivers from FDA for compliance with §§ 314.92 through 314.99. (The information collection hour burden estimate for ANDA

	waiver requests is included in the chart below under estimates for §§ 314.94(a)(d), 314.96, and 314.97).
21 CFR 314.101(a)	If FDA refuses to file an application, the applicant may request an informal conference with FDA and request that the application be filed over protest.
21 CFR 314.107 (c)(4)	Requires notice to FDA by ANDA or 505(b)(2) application holders of any legal action concerning patent infringement. (Section 314.107(c)(4) is already approved by OMB under 0910-0305 and is not included in the hour burden estimates in the chart below).
21 CFR 314.107(e) (2)(iv)	An applicant must submit a copy of the entry of the order or judgement to FDA within 10 working days of a final judgement. (Section 314.107(e)(2)(iv) is already approved by OMB under 0910-0305 and is not included in the hour burden estimates in the chart below).
21 CFR 314.107(f)	ANDA or 505(b)(2) applicants must notify FDA of the filing of any legal action filed within 45 days of receipt of the notice of certification. A patent owner may also notify FDA of the filing of any legal action for patent infringement. The patent owner or approved application holder who is an exclusive patent licensee must submit to FDA a waiver that waives the opportunity to file

	a legal action for patent infringement. (Section 314.107(f) is already approved by OMB under 0910-0305 and is not included in the hour burden estimates in the chart below).
21 CFR 314.110(a)(3) and (4)	After receipt of an FDA approvable letter, an applicant may request an opportunity for a hearing on the question of whether there are grounds for denying approval of the application. (Section 314.110(a)(3) and (4) is included under the Parts 10 through 16 hearing regulations, in accordance with § 314.201, and is not included in the hour burden estimates in the chart below).
21 CFR 314.110(a)(5)	After receipt of an approvable letter, an applicant may notify FDA that it agrees to an extension of the review period so that it can determine whether to respond further.
21 CFR 314.110(b)	After receipt of an approvable letter, an ANDA applicant may request an opportunity for a hearing on the question of whether there are grounds for denying approval of the application. (Section 314.110(b) is included under the Parts 10 through 16 hearing regulations, in accordance with § 314.201, and is not included in the hour burden estimates in the chart below).

21 CFR 314.120 (a)(3)	After receipt of a not approvable letter, an applicant may request an opportunity for a hearing on the question of whether there are grounds for denying approval of the application. (Section 314.120(a)(3) is included under the Parts 10 through 16 hearing regulations, in accordance with § 314.201, and is not included in the hour burden estimates in the chart below).
21 CFR 314.120 (a)(5)	After receipt of a not approvable letter, an applicant may notify FDA that it agrees to an extension of the review period so that it can determine whether to respond further.
21 CFR 314.122(a)	States that an ANDA or a suitability petition that relies on a listed drug that has been voluntarily withdrawn from sale must be accompanied by a petition seeking a determination whether the drug was withdrawn for safety or effectiveness reasons. (Section 314.122(a) is already approved by OMB under 0910-0183 and is not included in the hour burden estimates in the chart below).
21 CFR 314.122(d)	Sets forth requirements for relisting petitions for unlisted discontinued products. (Section 314.122(d) is already approved by OMB under 0910-0183 and is not included in the hour burden estimates in the chart below).

21 CFR 314.126(c)	Sets forth requirements for a petition to waive criteria for adequate and well-controlled studies. (Section 314.126(c) is already approved by OMB under 0910-0183 and is not included in the hour burden estimates in the chart below).
21 CFR 314.151(a) and (b)	Sets forth requirements for the withdrawal of approval of an ANDA and the applicant's opportunity for a hearing and submission of comments. (Section 314.151(a) and (b) is included under the Parts 10 through 16 hearing regulations, in accordance with § 314.201, and is not included in the hour burden estimates in the chart below).
21 CFR 314.151(c)	Sets forth the requirements for withdrawal of approval of an ANDA and the applicant's opportunity to submit written objections and participate in a limited oral hearing. (Section 314.151(c) is included under the Parts 10 through 16 hearing regulations, in accordance with § 314.201, and is not included in the hour burden estimates in the chart below).
21 CFR 314.152(b)	Sets forth the requirements for suspension of an ANDA when the listed drug is voluntarily withdrawn for safety and effectiveness reasons, and the applicant's opportunity to present comments and participate in a limited oral hearing. (Section 314.152(b) is

	included under the Parts 10 through 16 hearing regulations, in accordance with § 314.201, and is not included in the hour burden estimates in the chart below).
21 CFR 314.161(b) and (e)	Sets forth the requirements for submitting petition to determine whether a listed drug was voluntarily withdrawn from sale for safety or effectiveness reasons. (Section 314.161(b) and (e) is already approved by OMB under 0910-0183 and is not included in the hour burden estimates in the chart below).
21 CFR 314.200(c), (d), and (e)	Applicants or others subject to a notice of opportunity for a hearing who wish to participate in a hearing must file a written notice of participation and request for a hearing as well as the studies, data, and so forth, relied on. Other interested persons may also submit comments on the notice. This section also sets forth the content and format requirements for the applicants' submission in response to notice of opportunity for hearing. (Section 314.200(c), (d), and (e) is included under the Parts 10 through 16 hearing regulations, in accordance with § 314.201, and is not included in the hour burden estimates in the chart below).
21 CFR 314.200(f)	Participants in a hearing may make a motion to the presiding officer for the inclusion of

	certain issues in the hearing. (Section 314.200(f) is included under the Parts 10 through 16 hearing regulations, in accordance with § 314.201, and is not included in the hour burden estimates in the chart below).
21 CFR 314.200(g)	A person may respond to a proposed order from FDA denying a request for a hearing by providing sufficient data, information, and analysis to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing. (Section 314.200(g) is included under the Parts 10 through 16 hearing regulations, in accordance with § 314.201, and is not included in the hour burden estimates in the chart below).
21 CFR 314.420	States that an applicant may submit to FDA a drug master file in support of an application, in accordance with certain content and format requirements.
21 CFR 314.430	States that data and information in an application are disclosable under certain conditions, unless the applicant shows that extraordinary circumstances exist. (Section 314.430 is included under the Parts 10 through 16 hearing regulations, in accordance with § 314.201, and is not included in the hour burden estimates in the chart below).
21 CFR 314.530	If FDA withdraws approval of a drug approved

(c) and (e)	under the accelerated approval procedures, the applicant has the opportunity to request a hearing and submit data and information. (Section 314.530(c) and (e) is included under the Parts 10 through 16 hearing regulations, in accordance with § 314.201, and is not included in the hour burden estimates in the chart below).
21 CFR 314.530(f)	An applicant must first submit a petition for stay of action before requesting an order from a court for a stay of action pending review. (Section 314.530(f) is already approved by OMB under 0910-0194 and is not included in the hour burden estimates in the chart below).
21 CFR 314.550	Applicants must submit all promotional materials to FDA for consideration during the preapproval review period. (Section 314.550 is already approved by OMB in "Transmittal of Advertisements & Promotional Labeling for Drugs & Biologics For Human Use," which published in 62 FR 55408, and is not included in the hour burden estimates in the chart below).

2. <u>Purpose and Use of Information</u>

Section 505 of the Act requires that a new drug may not be marketed unless the manufacturer provides FDA with scientific

evidence that the drug is both safe and effective. The regulations at 21 CFR Part 314 provide the means through which pharmaceutical manufacturers can obtain FDA approval of a drug product marketing application, and the means through which FDA can assure the safety and effectiveness of marketed drug products. Without the information provided by industry on the drug products they seek to market, FDA would not be able to assure the safety and effectiveness of marketed drug products.

3. Use of Improved Information Technology

In the mid-1980's, FDA began working with pharmaceutical sponsors to develop Computer-Assisted New Drug Applications (CANDA). CANDAs were designed to provide information (text, data, image) electronically to facilitate the review of applications. These efforts yielded valuable information but were limited because for each new drug review division sponsors tended to develop different hardware and software approaches. A reviewer might be confronted with an array of hardware, software, and review tools to conduct a review that differed between sponsors and applications. Also, CANDAs were never approved as a substitute for the archival copy, so firms were still required to submit copies.

One solution to limitations of CANDAs was an approach whereby staff responsible for a particular review discipline (eg, chemistry, clinical) worked directly with pharmaceutical sponsors to develop a consistent approach that would be applicable to all sponsors and to all review divisions. Focus on this approach has evolved into the Electronic Regulatory Submission and Review (ERSR) Program. This new initiative is intended to ensure both the electronic availability of information and the means to manipulate this information electronically to yield a review.

ERSR has been made possible by other developments. The harmonization of FDA Form 356h has ensured that NDAs, ANDAs, and Biological License Applications would contain comparable information in the same sections of the submission. The promulgation of the "Electronic Records; Electronic Signatures" final rule allowed FDA to accept electronic submissions without an accompanying paper archival copy because electronic records are equivalent to paper records and electronic signatures are equivalent to hand-written signatures provided the requirements of 21 CFR Part 11 are met and the document has been identified in the agency's public docket as being acceptable for filing. The Guidance for Industry on "Archiving Submissions in Electronic Format - NDAs" provides for the receipt and archival of electronic report forms and tabulations. Another Guidance for Industry entitled "Providing Regulatory Submissions in Electronic Format - NDAs" is currently under development.

ERSR is made up of a variety of projects that are in different stages of development and implementation. These projects are categorized into 3 areas: First, "Electronic Submissions" includes standards-related projects to define the format and content of regulatory submissions; written guidance for industry to follow in preparing electronic submissions; an Electronic Document Room project to accommodate the receipt, archive, and storage of electronic transmissions; an Electronic Gateway project to provide an agency-level central point for receipt of secure electronic transmissions and routing to the Centers; and scientific databases that include structured databases, reference guides, and analytical tools used by reviewers. Second, "Corporate Databases, Documentbases and Applications" includes projects under the Electronic Document Management System and the Management Information System. Third, other electronic initiatives including technical infrastructure,

technical support, and training.

ERSR will impact the underlying business processes related to regulatory submissions and reviews. Document rooms will handle electronic media rather than paper copies. Reviewers will review submissions online and generate their review documents online. Reviewers will conduct data analysis using structured databases, which combine data extracted from the submission under review as well as historical data from earlier submissions. Industry sponsors and manufacturers will experience reduced paper costs and manpower to compile paper submissions and better access to application status information through electronic mail.

4. Efforts to Identify Duplication

The information collection required as a result of 21 CFR 314 does not duplicate any other information collection.

5. Involvement of Small Entities

Although new drug development is typically an activity completed by large multinational drug firms, the information collection required under 21 CFR 314 applies to small as well as large companies submitting marketing applications. However, under the Regulatory Flexibility Act, FDA regularly analyzes regulatory options that would minimize any significant impact on small entities. FDA also assists small businesses in complying with regulatory requirements.

6. Consequences If Information Collected Less Frequently

Part 314 establishes a reporting frequency that is dictated by the need to focus on potential problems concerning the safety

and effectiveness of human drugs. Less frequent data collection would hinder early detection of such threats to the public health.

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

Sections of 21 CFR 314 require reporting in less than 30 days. These are postmarketing reports and expedited notification to FDA is necessary in order for the agency to determine as soon as possible whether a threat to the public health exists that warrants immediate regulatory action.

More than an original and 2 copies of a submission is required (e.g., four copies of draft labeling or 12 copies of final printed labeling) in order to permit concurrent (and, consequently, quicker) review of the application.

Although applicants are required to submit proprietary, trade secret, and other confidential information, this information is protected under FDA regulations and the Act (see number 10 below).

The specific format and content requirements for application submissions is necessary to ensure complete submissions (and reduce the need for time-consuming resubmissions) and to assist FDA in efficient reviews.

8. Consultation Outside the Agency

FDA has had numerous ongoing consultations with the pharmaceutical industry, related associations, and the general public concerning the approval and review of marketed new drugs. In addition to several rulemaking documents on sections of 21 CFR Part 314 that have provided an opportunity for industry and general public comment, FDA has participated in conferences and

workshops sponsored by, among many others, the Food and Drug Law Institute, the Drug Information Association, the Pharmaceutical Research and Manufacturers of America, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, and by FDA.

On May 8, 1998, (63 FR 29229),in the notice proposing reinstatement of Applications for FDA Approval to Market a New Drug, the FDA invited comments on the collection of information specifically : (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, (2) the accuracy of FDA's est used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents including through the use of automated collection techniques, when appropriate, and other forms of information technology. No comments were received regarding this information collection.

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 under 21 CFR part 20. The unauthorized use or disclosure of trade secrets required in applications is specifically prohibited under Section 310(j) of the Act.

11. Questions of a Sensitive Nature

There are no questions of a sensitive nature.

12. Estimates of Annualized Hour Burden

Based on information provided by the pharmaceutical industry for the number of "hours per response," and based on submissions collected and data tabulated by FDA for the "number of respondents," the "number of responses per respondent," and the number of "total annual responses," FDA estimates the burden of this collection of information as follows:

Estimated Annual Reporting Burden

21 CFR Section; [Form Number]	Number of Respondents	Number of Responses Per Respondent	Total Annual Responses	Hours Per Response	Total Hours
314.50 (b), (c), (d), (e), (f), and (k)	83	1.49	124	1600	161,200
314.54	4	1.25	5	300	1,500
314.60	144	16.89	2432	80	194,560
314.65	18	1.28	23	2	46
314.70 and 314.71	418	5.33	2229	300	668,700
314.72	59	2.17	128	2	256
314.81(b)(1) [3331]	140	5	700	48	33,600
314.81(b)(2) [2252]	269	9.06	2438	40	97,520
314.94(a) and (d)	117	3.96	464	480	222,720
314.96	315	12.43	3915	80	313,200
314.97	152	19.74	3000	80	240,000
314.98(c) [2252]	265	17.17	4551	40	182,040
314.99(a)	46	13.04	600	2	1,200
314.110(a)(5)	55	1.13	62	8	496
314.120(a)(5)	26	1.12	29	8	232

314.420	450	1.11	500	8	4,000
Total					2,121,270

[Footnote: There are no capital costs or operating and maintenance costs associated with this collection of information]

13. Estimates of Annualized Cost Burden to Respondents

FDA's Economics Staff estimates an average industry wage rate of $50.00 per hour for preparing and submitting the information collection requirements under 21 CFR 314. This figure is an average of the following wage rates (based on the percentage of time required for each type of employee): Upper management at $70.00 per hour; middle management at $35.00 per hour; and clerical assistance at $23.00 per hour. Using the averaged wage rate of $50.00 per hour, and multiplied times the total hour burden estimated above, the total cost burden to respondents is $107,923,500.

14. Estimates of Annualized Cost Burden to the Government

Based on data obtained for the fourth quarter of 1997 from the Center for Drug Evaluation and Research's Human Resource Allocation Report, approximately 1,327.19 FTEs are devoted to "new drug evaluation," "generic drug evaluation," and "postmarketing surveillance and epidemiology." If each FTE equals approximately $100,000.00, the total cost burden to the Federal Government would be $132,719,000.

Please note that this estimate is high for the following reasons: The total number of FTEs above includes those hours for reviewing Investigational New Drug Applications (INDs) as well as for NDAs. The information collection burden for INDs is estimated under

OMB No. 0910-0014. The renewal application for 0910-0014 will be submitted to OMB during the next year, and at that time the number of FTEs for IND review will be separated out from the above total, and a correction will be made to this supporting statement. In addition, at that time the number of FTEs for 0910-0001 will be adjusted to reflect other overlapping FTE estimates from other OMB-approved packages, for example, OMB No. 0910-0230 (adverse drug experience reporting).

15. Changes in Burden

The decrease in burden hours from the last OMB approval is a result of new data derived directly from associates of the pharmaceutical industry on hours per response. In previous years this information was obtained from contractor estimates provided to FDA concerning these reporting requirements.

16. Time Schedule, Publication and Analysis Plans

FDA does not intend to publish tabulated results of these information collection requirements.

17. Exemption for Display of Expiration Date

All forms associated with this collection will bear the OMB approval date.

18. Certifications

There are no exceptions to the certification statement identified in Item 19, " Certification for Paperwork Reduction Act Submission," of OMB Form 83-I.