SUPPORTING STATEMENT

Applications for FDA Approval to Market a New Drug - Part 314 (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 under section 505(b) or 505(j) of the act is effective with respect to such drug. Under the act, it is the sponsor's responsibility to provide the information needed by FDA to make a scientific and technical determination whether the product is safe and effective for use.

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

Section 314.50(a) requires that an application form (Form FDA 356h) be submitted that includes introductory information about the drug as well as a checklist of enclosures.

Section 314.50(b) requires that an index be submitted with the archival copy of the application and that it reference certain sections of the application.

Section 314.50(c) requires that a summary of the application be submitted that presents a good general synopsis of all the technical sections and other information in the application.

Section 314.50(d) requires that the NDA contain the following technical sections about the new drug: Chemistry, manufacturing, and controls; nonclinical pharmacology and toxicology; human pharmacokinetics and bioavailability; microbiology; clinical data; and statistical section.

Section 314.50(e) requires the applicant to 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.

Section 314.50(f) requires that case report forms and tabulations be submitted with the archival copy, *including tabulations of the data from each adequate and well-controlled study under §314.126*.

Section 314.50(h) requires that patent information, as described under § 314.53, be submitted with the application. (The burden hours for § 314.50(h) are already approved by OMB under OMB control number 0910-0513 and are not included in the burden estimates in table 1 of this document.)

Section 314.50(i) requires that patent certification information be submitted in section 505(b)(2) applications for patents claiming the drug, drug product, or method of use.

Section 314.50(j) requires that applicants that request a period of marketing exclusivity submit certain information with the application.

Section 314.50(k) requires that an archival, review, and field copy of the application be

submitted.

Section 314.52 requires that any notice of certification of invalidity or noninfringement of a patent to each patent owner and the NDA holder be sent by a section 505(b)(2) applicant that relies on a listed drug. A 505(b)(2) applicant is required to amend its application at the time notice is provided to include a statement certifying that the required notice has been provided. A 505(b)(2) applicant also is required to amend its application to document receipt of the required notice.

Section 314.54 sets forth the content requirements for applications filed under section 505(b)(2) of the act. (The information collection burden estimate for 505(b)(2) applications is included in table 1 of this document under the estimates for § 314.50 (a), (b), (c), (d), (e), (f), and (k)).

Section 314.60 sets forth reporting requirements for sponsors who amend an unapproved application.

Section 314.65 states that the sponsor must notify FDA when withdrawing an unapproved application.

Sections 314.70 and 314.71 require that supplements be submitted to FDA for certain changes to an approved application.

Section 314.72 requires sponsors to report to FDA any transfer of ownership of an application.

Section 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). (The burden hours for §§ 314.80(c)(1) and (c)(2) are already approved by OMB under OMB control numbers 0910-0230 and 0910-0291 and are not included in the burden estimates in table 1 of this document.)

Section 314.80(i) establishes recordkeeping requirements for reports of postmarketing adverse drug experiences. (The burden hours for § 314.80(i) are already approved by OMB under OMB control numbers 0910-0230 and 0910-0291 and are not included in the burden estimates in table 1 of this document.)

Section 314.81(b)(1) requires that field alert reports be submitted to FDA (Form FDA 3331).

Section 314.81(b)(2) requires that annual reports be submitted to FDA (Form FDA 2252).

Section 314.81(b)(3)(i) requires that drug advertisements and promotional labeling be submitted to FDA (Form FDA 2253). Form FDA 2253 has been revised by FDA as follows: On line 8, "Please check one or both" has been revised to read "Please check only one." In the instruction for line 8, the sentence "Consumer and professional pieces should be submitted separately" has been added.

Section 314.81(b)(3)(iii) sets forth reporting requirements for sponsors who withdraw an approved drug product from sale. (The burden hours for § 314.81(b)(3)(iii) are already approved by OMB under OMB control number 0910-0045 and are not included in the burden estimates in table 1 of this document.)

Section 314.90 sets forth requirements for sponsors who request waivers from FDA for compliance with §§ 314.50 through 314.81. (The information collection burden estimate for NDA waiver requests is included in table 1 of this document under estimates for §§ 314.50,

314.60, 314.70 and 314.71.)

Section 314.93 sets forth requirements for submitting a suitability petition in accordance with § 10.20 (21 CFR 10.20) and § 10.30. (The burden hours for § 314.93 are already approved by OMB under 0910-0183 and are not included in the burden estimates in table 1 of this document.)

Section 314.94(a) and (d) requires that an ANDA 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.

Section 314.95 requires that any notice of certification of invalidity or noninfringement of a patent to each patent owner and the NDA holder be sent by ANDA applicants.

Section 314.96 sets forth requirements for amendments to an unapproved ANDA.

Section 314.97 sets forth requirements for submitting supplements to an approved ANDA for changes that require FDA approval.

Section 314.98(a) sets forth postmarketing adverse drug experience reporting and recordkeeping requirements for ANDAs. (The burden hours for § 314.98(a) are already approved by OMB under OMB control numbers 0910-0230 and 0910-0291 and are not included in the burden estimates in table 1 of this document.)

Section 314.98(c) requires other postmarketing reports for ANDAs: Field alert reports (Form FDA 3331), annual reports (Form FDA 2252), and advertisements and promotional labeling (Form FDA 2253). (The information collection burden estimate for field alert reports is included in table 1 of this document under § 314.81(b)(1); the estimate for annual reports is included under § 314.81(b)(2); the estimate for advertisements and promotional labeling is included under § 314.81(b)(3)(i).)

Section 314.99(a) requires that sponsors comply with certain reporting requirements for withdrawing an unapproved ANDA and for a change in ownership of an ANDA.

Section 314.99(b) sets forth requirements for sponsors who request waivers from FDA for compliance with §§ 314.92 through 314.99. (The information collection burden estimate for ANDA waiver requests is included in table 1 of this document under estimates for § 314.94(a) and (d) and §§ 314.96 and 314.97.)

Section 314.101(a) states that 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.

Section 314.107(c) requires notice to FDA by the first applicant to submit a substantially complete ANDA containing a certification that a relevant patent is invalid, unenforceable, or will not be infringed of the date of first commercial marketing.

Section 314.107(e) requires that an applicant submit a copy of the entry of the order or judgment to FDA within 10 working days of a final judgment.

Section 314.107(f) requires that ANDA or section 505(b)(2) applicants notify FDA immediately 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. If the patent owner or approved application holder who is an exclusive patent licensee waives its opportunity to file a legal action for patent infringement within the 45-day period, the patent owner or approved application holder must submit to FDA a waiver in the specified format.

Section 314.110(a)(3) and (a)(4) states that, 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. (The burden hours for § 314.110(a)(3) and (a)(4) are included under parts 10 through 16 (21 CFR part 16) hearing regulations, in accordance with § 314.201, and are not included in the burden estimates in table 1 of this document.)

Section 314.110(a)(5) states that, 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.

Section 314.110(b) states that, 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. (The burden hours for § 314.110(b) are included under parts 10 through 16 hearing regulations, in accordance with Sec. 314.201, and are not included in the burden estimates in table 1 of this document.)

Section 314.120(a)(3) states that, 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. (The burden hours for § 314.120(a)(3) are included under parts 10 through 16 hearing regulations, in accordance with § 314.201, and are not included in the hour burden estimates in table 1 of this document.)

Section 314.120(a)(5) states that, 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.

Section 314.122(a) requires 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. (The burden hours for § 314.122(a) are already approved by OMB under OMB control number 0910-0183 and are not included in the burden estimates in table 1 of this document.)

Section 314.122(d) sets forth requirements for relisting petitions for unlisted discontinued products. (The burden hours for § 314.122(d) are already approved by OMB under OMB control number 0910-0183 and are not included in the burden estimates in table 1 of this document.)

Section 314.126(c) sets forth requirements for a petition to waive criteria for adequate and well-controlled studies. (The burden hours for § 314.126(c) are already approved by OMB under 0910-0183 and are not included in the burden estimates in table 1 of this document.)

Section 314.151(a) and (b) set forth requirements for the withdrawal of approval of an ANDA and the applicant's opportunity for a hearing and submission of comments. (The burden hours for § 314.151(a) and (b) are included under parts 10 through 16 hearing regulations, in accordance with Sec. 314.201, and are not included in the burden estimates in table 1 of this document.)

Section 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. (The burden hours for § 314.151(c) are included under parts 10 through 16 hearing regulations, in accordance with § 314.201, and are not included in the burden estimates in table 1 of this document.)

Section 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. (The burden hours for § 314.152(b) are included under parts 10 through 16 hearing regulations, in accordance with § 314.201, and is not included in the burden estimates in table 1 of this document.)

Section 314.161(b) and (e) sets forth the requirements for submitting a petition to determine whether a listed drug was voluntarily withdrawn from sale for safety or effectiveness reasons. (The burden hours for § 314.161(b) and (e) are already approved by OMB under OMB control number 0910-0183 and are not included in the burden estimates in table 1 of this document.)

Section 314.200(c), (d), and (e) requires that applicants or others subject to a notice of opportunity for a hearing who wish to participate in a hearing 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. (The burden hours for §§ 314.200(c), (d), and (e) are included under parts 10 through 16 hearing regulations, in accordance with § 314.201, and are not included in the burden estimates in table 1 of this document.)

Section 314.200(f) states that participants in a hearing may make a motion to the presiding officer for the inclusion of certain issues in the hearing. (The burden hours for § 314.200(f) are included under parts 10 through 16 hearing regulations, in accordance with Sec. 314.201, and are not included in the burden estimates in table 1 of this document.)

Section 314.200(g) states that a person who responds to a proposed order from FDA denying a request for a hearing provide sufficient data, information, and analysis to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing. (The burden hours for § 314.200(g) are included under parts 10 through 16 hearing regulations, in accordance with § 314.201, and is not included in the burden estimates in table 1 of this document.)

Section 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.

Section 314.430 states that data and information in an application are disclosable under certain conditions, unless the applicant shows that extraordinary circumstances exist. (The burden hours for § 314.430 is included under parts 10 through 16 hearing regulations, in accordance with § 314.201, and is not included in the burden estimates in table 1 of this document.)

Section 314.530(c) and (e) states that, if FDA withdraws approval of a drug approved under the accelerated approval procedures, the applicant has the opportunity to request a hearing and submit data and information. (The burden hours for § 314.530(c) and (e) are included under parts 10 through 16 hearing regulations, in accordance with § 314.201, and are not included in the burden estimates in table 1 of this document.)

Section 314.530(f) requires that an applicant first submit a petition for stay of action before requesting an order from a court for a stay of action pending review. (The burden hours for § 314.530(f) are already approved by OMB under 0910-0194 and are not included in the burden estimates in table 1 of this document.)

Section 314.610(b)(1) requires that applicants include a plan or approach to postmarketing study commitments in applications for approval of new drugs when human

efficacy studies are not ethical or feasible, and provide status reports of postmarketing study commitments. (The information collection burden estimate for § 314.610(b)(1) is included in table 1 of this document under the estimates for §§ 314.50 (a), (b), (c), (d), (e), (f), and (k) and 314.81(b)(2)).

Section 314.610(b)(3) requires that applicants propose labeling to be provided to patient recipients in applications for approval of new drugs when human efficacy studies are not ethical or feasible. (The information collection burden estimate for § 314.610(b)(3) is included in table 1 of this document under the estimates for § 314.50(e)).

Section 314.630 requires that applicants provide postmarketing safety reporting for applications for approval of new drugs when human efficacy studies are not ethical or feasible. (The burden hours for § 314.630 are already approved by OMB under OMB control numbers 0910-0230 and 0910-0291 and are not included in the burden estimates in table 1 of this document.)

Section 314.640 requires that applicants provide promotional materials for applications for approval of new drugs when human efficacy studies are not ethical or feasible. (The information collection burden estimate for § 314.640 is included in table 1 of this document under the estimates for § 314.81(b)(3)(i)).

Respondents to this collection of information are all persons who submit an application or abbreviated application or an amendment or supplement to FDA under part 314 to obtain approval of a new drug, and any person who owns an approved application or abbreviated application.

2. Purpose and Use of Information

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 Federal Register of December 11, 2003 (68 FR 69009), FDA published a final rule amending its regulations governing the

format in which certain labeling is required to be submitted for review with NDAs, certain biological license applications, ANDAs, supplements, and annual reports. The final rule requires that certain labeling content be submitted electronically in a form that FDA can process, review, and archive.

FDA has also issued the following guidance documents, among others, to explain the process for submitting information to the agency in electronic format:

- "Providing Regulatory Submissions in Electronic Format--NDAs" (January 28, 1999). This guidance provides information on how to submit a complete archival copy of an NDA in electronic format and applies to the submission of original NDAs as well as to the submission of supplements and amendments to NDAs. Among other things, the guidance provides recommendations on how to submit "labeling text"[1] in electronic format. "Labeling text" is the term used in the guidance to mean labeling required under 21 CFR 201.100(d)(3), including all text, tables, and figures required by or included under those sections. The guidance recommends that labeling text be submitted as a PDF file.

- "Providing Regulatory Submissions in Electronic Format--General Considerations" (January 28, 1999). This guidance includes a description of the types of electronic file formats that we are able to accept to process, review, and archive electronic regulatory submissions. The guidance also states that documents submitted in electronic format should, among other things, enable you to: (1) Easily view a clear and legible copy of the information; (2) print each document page by

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1 For clarity we now use the term "content of labeling" instead of "labeling text."

page, as it would have been provided in paper, while maintaining fonts, special orientations, table formats, and page numbers; and (3) copy text and images electronically into common word processing documents. To achieve these and other goals, the guidance recommends that all electronic regulatory submissions be submitted as PDF files.

- “Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format” (November 12, 1999). This guidance provides information to assist applicants in submitting documents in electronic format for review and archive purposes as part of a BLA, product license application (PLA), or establishment license application (ELA).

- "Providing Regulatory Submissions in Electronic Format-— Prescription Drug Advertising and Promotional Labeling" (January 31, 2001). This draft guidance discusses issues related to the electronic submission of advertising and promotional labeling materials for prescription drug and biological products.

- "Providing Regulatory Submissions in Electronic Format-— ANDAs" (June 27, 2002). This guidance discusses issues related to the electronic submission of ANDAs and supplements and amendments to those applications.

- "Providing Regulatory Submissions in Electronic Format-— Annual reports for NDAs and ANDAs" (August 2003). This draft guidance discusses issues related to the electronic submission of annual reports for NDAs and ANDAs.

- "Providing Regulatory Submissions in Electronic Format-— Postmarketing Periodic Adverse Drug Experience Reports" (June 2003). This guidance discusses general issues related to the electronic submission of postmarketing periodic adverse drug experience reports for NDAs, ANDAs, and BLAs.

• "Providing Regulatory Submissions in Electronic Format-—Human Pharmaceutical Product Applications and Related Submissions" (August, 2003). This draft guidance discusses issues related to the electronic submission of ANDAs, BLAs, INDs, NDAs, master files, advertising material, and promotional labeling.

• "Providing Regulatory Submissions in Electronic Format-—General Considerations" (October 2003). This draft guidance discusses general issues common to all types of electronic regulatory submissions.

• "Providing Regulatory Submissions in Electronic Format-—Content of Labeling" (February 2004). This draft guidance discusses issues related to the submission of the content of labeling in electronic format for marketing applications for human drug and biological products.

These guidance documents and others are available at FDA's web site http://www.fda.gov/cder/guidance/index.htm.

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 and are necessary 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 holds numerous ongoing public meetings, conferences, and the like 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.

In the Federal Register of _____,2008 (__ FR _____), FDA announced an opportunity for public comment on these information collection estimates. No comments were submitted that pertained to the information collection estimates in the _____,2008, notice.

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

Table 1 - 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 (a), (b), (c), (d), (e), (f), and (k)	85	1.41	120	1,917	230,040
314.50(i) and 314.94(a)(12)	96	9.61	923	2	1,846
314.50(j)	71	4.02	286	2	572
314.52 and 314.95	71	3.66	260	16	4,160
314.60	305	15.05	4,590	80	367,200
314.65	13	1.08	14	2	28
314.70 and 314.71	281	9.30	2,613	150	391,950
314.72	69	3.40	235	2	470
314.81(b)(1) [3331]	114	2.68	306	8	2,448
314.81(b)(2) [2252]	724	11.15	8,073	40	322,920
314.81(b)(3)(i) [2253]	390	61.39	23,942	2	47,884
314.94(a)(1)-(11) and (d)	110	7.21	793	480	380,640
314.96	300	28	8,400	80	672,000
314.97	215	20.66	4,442	80	355,360
314.99(a)	40	2.02	81	2	162
314.101(a)	1	1	1	.50	.50
314.107(c) -	56 25	4.1 3.92	230 98	.50 .50	115 49

314.107(e) - 314.107(f) -	56	4.1	230	.50	115
314.110(a)(5)	45	1.15	52	.50	26
314.120(a)(5)	10	1.20	12	.50	6
314.420	487	1.98	964	61	58,804
Total					**2,836,796.00**

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 estimates an average pharmaceutical industry loaded wage rate of $74.00 per hour for preparing and submitting the information collection requirements under 21 CFR 314. Multiplied times the total hour burden estimated above, the total cost burden to respondents is $209,922,867.

14. Estimates of Annualized Cost Burden to the Government

Based on CDER's human resource allocation data, approximately 835 FTEs are devoted annually to reviewing the submissions under 21 CFR 314. If each FTE equals approximately $230,000 for these review activities, the total cost burden to the Federal Government would be $192,050,000.

15. Changes in Burden

The change in burden hours is a result of updated data on the number of submissions received by FDA as a result of 21 CFR 314.

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 certifications required.

PAPERWORK REDUCTION ACT SUBMISSION