

Applications for FDA Approval to Market a New Drug - 21 CFR Part 314

0910-0001

SUPPORTING STATEMENT

**Terms of Clearance: None.**

**A. Justification**

1. Circumstances Making the Collection of Information Necessary

Under section 505(a) of the Federal Food, Drug, and Cosmetic Act (the FD&C 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 FD&C 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 approval request is for all information collection requirements imposed on applicants by the regulations under part 314 (21 CFR 314) who apply for approval of a new drug application (NDA) or abbreviated new drug application (ANDA) 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; statistical; and pediatric use sections.

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.

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 the application contain a financial certification or disclosure statement or both.

Section 314.50(l) requires that an archival, review, and field copy of the application be submitted, including the content of labeling and all labeling and labels.

Section 314.52 requires that any notice of certification of invalidity or non-infringement 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 FD&C 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), (g), (i), (j), (k) and (l)).

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).

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 the estimates for each section that is in subpart B of part 314.)

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 non-infringement 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 certain changes to the application.

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 the estimates for each

section that is in subpart C of part 314.)

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. (The information collection burden estimate for § 314.107(c) is included in table 1 of this document under the estimates for § 314.50 (a), (b), (c), (d), (e), (f), (g), (i), (j), (k) and (l)).

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. (The information collection burden estimate for § 314.107(e) applications is included in table 1 of this document under the estimates for § 314.50 (a), (b), (c), (d), (e), (f), (g), (i), (j), (k) and (l)).

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. (The information collection burden estimate for § 314.107(f) is included in table 1 of this document under the estimates for § 314.50 (a), (b), (c), (d), (e), (f), (g), (i), (j), (k) and (l)).

Section 314.110(b)(3) states that, after receipt of an FDA complete response 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(b)(3) are included under parts 10 through 16 (21 CFR parts 10 and 16) hearing regulations, in accordance with § 314.201, and are not included in the burden estimates in table 1 of this document.)

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 § 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 314.153(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 are 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 § 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 are 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 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(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 314.550 requires an applicant with a new drug product being considered for accelerated approval to submit copies of all promotional materials to the FDA during the preapproval and post-approval periods.

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), (k) and (l) 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.

The burden of this information collection is calculated in section 12.a. below.

## 2. Purpose and Use of the Information Collection

Section 505 of the FD&C 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 and Burden Reduction

FDA encourages the electronic submission of the information required under part 314, and has issued several guidance documents describing the process for submitting information to the Agency in electronic format. These guidance documents and others are available at FDA's web site <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

## 4. Efforts to Identify Duplication and Use of Similar Information

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

5. Impact on Small Businesses or Other 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 of Collecting the Information 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. Special Circumstances Relating to 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 FD&C 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. Comments in Response to the Federal Register Notice and Efforts to Consult 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. FDA also has participates 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.

In the Federal Register of March 24, 2014 (79 FR 16003), FDA published a notice requesting comment on this information collection. We received one comment. The comment requested clarification of the duties, responsibilities, and potential liabilities of the person denoted as the “Authorized U.S. Agent” in field 39 of Form FDA 356h. The comment also requested that the formatting for field 39 be revised to clarify “what exactly it is that the Authorized U.S. Agent is attesting to by its signature.”

*FDA response.* Neither the form nor the instructions are intended to capture the exact duties, responsibilities, and potential liabilities of the person identified in field 39. Rather, as the instructions indicate, field 39 is intended to capture a countersignature where one is required in accordance with 21 CFR 314.50(a)(5): “If the person signing the form in Field 38 does not reside

or have a place of business within the United States, the form must be countersigned in Field 39 by an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.”

9. Explanation of Any Payment or Gift to Respondents

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

10. Assurance of Confidentiality Provided to Respondents

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 FD&C Act.

11. Justification for Sensitive Questions

There are no questions of a sensitive nature.

12. Estimates of Annualized Burden Hours and Costs

12a. Annualized Hour Burden Estimate

FDA estimates the burden of this information collection as follows:

Table 1 - Estimated Annual Reporting Burden

21 CFR Section; [FDA Form Number]	No. of Respondents	No. of Responses Per Respondent	Total Annual Responses	Average Burden Per Response	Total Hours
314.50 (a), (b), (c), (d), (e), (f), (g), (i), (j), (k) and (l) [356h]	106	1.42	151	1,923	290,071
314.52	7	3	21	16	336
314.95	209	3	627	16	10,032

314.60	277	8.73	2,419	80	193,520
314.65	18	1.16	21	2	42
314.70 and 314.71	374	7.63	2,854	150	428,100
314.72	66	2.20	145	2	290
314.81(b)(1) [3331]	260	16.31	4,241	8	33,928
314.81(b)(2) [2252]	930	11.28	10,495	40	419,800
314.81(b)(3)(i) [2253]	520	87.43	45,461	2	90,922
314.94(a) and (d)	251	4.73	1,186	480	569,280
314.96	434	24.60	10,675	80	854,000
314.97	306	18.34	5,611	80	448,880
314.99(a)	219	3.01	659	2	1,318
314.101(a)	1	1	1	.50	.50
314.420	524	1.98	1,038	61	63,318
314.550	20	7	140	120	16,800
<b>Total</b>					<b>3,420,637.50</b>

There are no capital costs or operating and maintenance costs associated with this collection of information.

#### 12b. Annualized Cost Burden Estimate

FDA estimates an average pharmaceutical industry wage rate of \$75.00 per hour for preparing and submitting the information collection requirements under 21 CFR 314. Multiplied times the total hour burden estimated above, the total labor cost burden to respondents is \$256,547,812.50.

#### 12. Estimates of Other Total Annual Costs to Respondents and/or Recordkeepers/Capital Costs

There are no capital costs or operating and maintenance costs associated with this collection of information.

#### 14. Annualized Cost to the Federal Government

Approximately 835 FTEs are devoted annually to reviewing the submissions under 21 CFR 314. If each FTE equals approximately \$175,000 for these review activities, the total cost burden to the Federal Government would be approximately \$146,125,000.

15. Explanation for Program Changes or Adjustments

The burden for this information collection has decreased by 45,399.50 (from 3,466,037 to 3,420,637.50). The change in burden hours is a result of updated data on the number of submissions received by FDA.

16. Plans for Tabulation and Publication and Project Time Schedule

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

17. Reason(s) Display of OMB Expiration Date is Inappropriate

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

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.