REGISTRATION OF PRODUCERS OF DRUGS AND LISTING OF DRUGS IN COMMERCIAL DISTRIBUTION

OMB #0910-0045

SUPPORTING STATEMENT

A. Justification

1. Circumstances Making the Collection of Information Necessary

Under section 510 of the Federal Food, Drug, and Cosmetic Act (the act), (21 U.S.C. 360), FDA is authorized to establish a system for registration of producers of drugs and for listing of drugs in commercial distribution. To implement Section 510 of the act, FDA issued part 207 (21 CFR part 207).[1] Under current 21 CFR 207.20, manufacturers, repackers, and relabelers that engage in the manufacture, preparation, propagation, compounding, or processing of human or veterinary drugs and biological products, including bulk drug substances and bulk drug substances for prescription compounding, and drug premixes as well as finished dosage forms, whether prescription or over-the-counter, are required to register their establishment. In addition, manufacturers, repackers, and relabelers are required to submit a listing of every drug or biological product in commercial distribution. Owners or operators of establishments that distribute under their own label or trade name a drug product manufactured by a registered establishment are not required either to register or list. However, distributors

1 This document addresses the information collection in current part 207. In the Federal Register of August 29, 2006 (71 FR 51276), FDA proposed to revise part 207. The proposed revisions would reorganize, consolidate, clarify, and modify current regulations concerning who must register establishments and list, and describes when and how to register and list and what information must be submitted for registration and listing. In addition, the proposal would make certain changes to the National Drug Code (NDC) system and would require the appropriate NDC number to appear on the labels for drugs subject to the listing requirements. The proposed regulations generally also require the electronic submission of all registration and most listing information. The August 29, 2006, proposed rule requested comments on the information collection for revised part 207. When the proposal is finalized, the information collection for revised part 207 will replace the information collection in this document.

may elect to submit drug listing information in lieu of the registered establishment that manufactures the drug product. Foreign drug establishments must also comply with the establishment registration and product listing requirements if they import or offer for import their products into the United States.

Under current § 207.21, establishments, both domestic and foreign, must register with FDA within 5 days after beginning the manufacture of drugs or biologicals, or within 5 days after the submission of a drug application or biological license application. In addition, establishments must register annually. Changes in individual ownership, corporate or partnership structure, location, or drug-handling activity must be submitted as amendments to registration under current § 207.26 within 5 days of such changes. Under § 207.20(b), private label distributors may request their own labeler code and elect to submit drug listing information to FDA. In such instances, at the time of submitting or updating drug listing information, private label distributors must certify to the registered establishment that manufactured, prepared, propagated, compounded or processed (which includes, among other things, repackaging and relabeling) the listed drug that the drug listing submission was made. Establishments must, within 5 days of beginning the manufacture of drugs or biologicals, submit to FDA a listing for every drug or biological product in commercial distribution at that time. Private label distributors may elect to submit to FDA a listing of every drug product they place in commercial distribution. Registered establishments must submit to FDA drug product listing for those private label distributors who do not elect to submit listing information.

Under § 207.25, product listing information submitted to FDA by domestic and foreign manufacturers must, depending on the type of product being listed, include any

new drug application number or biological establishment license number, copies of current labeling and a sampling of advertisements, a quantitative listing of the active ingredient for each drug or biological product not subject to an approved application or license, the National Drug Code number, and any drug imprinting information.

In addition to the product listing information required, FDA may also require, under § 207.31, a copy of all advertisements and a quantitative listing of all ingredients for each listed drug or biological product not subject to an approved application or license; the basis for a determination, by the establishment, that a listed drug or biological product is not subject to marketing or licensing approval requirements; and a list of certain drugs or biological products containing a particular ingredient. FDA may also request, but not require, the submission of a qualitative listing of the inactive ingredients for all listed drugs or biological products, and a quantitative listing of the active ingredients for all listed drugs or biological products subject to an approved application or license.

Under § 207.30, establishments must update their product listing information every June and December or, at the discretion of the establishment, when any change occurs. These updates must include the following information: (1) A listing of all drug or biological products introduced for commercial distribution that have not been included in any previously submitted list; (2) all drug or biological products formerly listed for which commercial distribution has been discontinued; (3) all drug or biological products for which a notice of discontinuance was submitted and for which commercial distribution has been resumed; and (4) any material change in any information previously

submitted. No update is required if no changes have occurred since the previously submitted list.

In certain cases, if it is unreasonable to expect a person to submit registration and listing information electronically, FDA may grant a waiver from the electronic format requirement.

Historically, drug establishment registration and drug listing information has been submitted in paper form using Form FDA 2656 (Registration of Drug Establishment/Labeler Code Assignment), Form FDA 2657 (Drug Product Listing), and Form FDA 2658 (Registered Establishments' Report of Private Label Distributors). Changes in the Federal Food, Drug, and Cosmetic Act (the Act), resulting from enactment of the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85) (FDAAA)[2] require that drug establishment registration and drug listing information be submitted electronically unless a waiver is granted. Before the enactment of FDAAA, section 510(p) of the Act expressly provided for electronic submission of drug establishment registration information upon a finding that electronic receipt was feasible, and section 510(j) of the Act provided that drug listing information be submitted in the form and manner prescribed by FDA. Section 224 of FDAAA, which amends section 510(p) of the Act, now expressly requires electronic drug listing in addition to drug establishment registration.

2. Purpose and Use of the Information Collection

The information obtained from establishment registration is used by FDA and other government agencies to keep an accurate and current list of all human and animal

2 Signed into law on September 27, 2007.

drug manufacturers, repackers, relabelers and other drug processors located in this country and of foreign establishments whose drugs are imported or offered for import into the United States. This list is used by FDA for inspectional purposes as required by the Act. In addition, the data is used by the public and private sector as a listing of the names and locations of drug firms.

The information obtained from listing is used, through assignment of the National Drug Code numbers, for third party reimbursement payment in Medicare and Medicaid as well as other health care insurance firms. Use of the assigned NDC numbers on insurance reimbursement forms is essential for payment. The NDC numbers also help industry, retailers, wholesalers and so on, as well as large government purchasing agencies such as the Defense Department, to maintain an accurate list of drug products for inventory purposes. The data obtained from listing is also used by FDA to determine which products containing certain drug ingredients may be found to be unsafe or not effective. In addition, the data is used to produce a National Drug Code Directory to meet demands of the drug and health care industry for a complete list of prescription drugs marketed in the United States. The listing information is also used for the assessment of certain user fees.

If the collection of this information were not conducted, there would be no third-party reimbursement for drugs. Also, many systems which rely on drug inventories would be hindered as well as FDA's efforts to regulate the drug industry. Concerning the drug imprint information, poison control centers use imprinted drug codes to help identify drug products in overdose emergencies. Consumers and health professionals use imprinted drug codes to recognize whether a different manufacturer's product has been

dispensed or whether a prescription has been incorrectly filled. Imprinting can also aid in the prevention of emergencies caused by tampering. It can also assist law enforcement, regulatory, and other public officials to trace counterfeit and defective drug products.

3. Use of Improved Information Technology and Burden Reduction

The information collected during drug establishment registration and drug listing is fundamental to FDA's mission to protect the public health, including surveillance for serious adverse drug reactions, inspection of facilities used for drug manufacturing and processing, and monitoring drug products imported into the United States. Comprehensive, accurate, and up-to-date information is important for conducting these activities with efficiency and effectiveness. Electronic drug establishment registration and drug listing using a computerized system would lead to significant improvements in the timeliness and accuracy of the information received compared with a paper-based system. This automated process can function most efficiently and effectively when the information is provided in a standardized format using defined terminology.

4. Efforts to Identify Duplication and Use of Similar Information

Although several systems do exist in FDA that have related data, they exist for different uses. This information is not already submitted to the agency, and thus, there is no duplicate reporting.

5. Impact on Small Businesses or Other Small Entities

Data collection may include small businesses. FDA has established a Division of Small Manufacturers Assistance to provide workshops, onsite evaluations, and other technical assistance to small manufacturers. Each FDA Field Office has small business representatives which help small businesses fill out forms, discuss regulatory requirements, and provide clarification to firm registration and drug listing matters.

6. Consequences of Collecting the Information Less Frequently

Information on the registration of drug firms and the listing of drug products cannot be collected less frequently. FDA believes that in order to fulfill its statutorily mandated responsibility under Section 510 of the Act, the agency needs to keep its listing current with changes in the industry.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

None of the collection requirements are inconsistent with 5 CFR 1320.5(d)(2).

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

In the FEDERAL REGISTER of July 11, 2008 (73 FR 39964), FDA published a 60-day notice requesting public comment on the information collection provisions. Nineteen comments were received of which four remarked on the information collection.

(Comment 1) On the topic whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have a practical utility, one comment agreed that the proposed collection

of information is necessary for us to perform its functions and is consistent with the provisions of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85). The comment continued to say that the information is also necessary to support the transition from paper format to electronic format, and that the additional information requested by us is logical and reasonable and is not an undue burden.

(Response) We appreciate the support and concurrence of the comment.

(Comment 2) On the topic whether the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used, one comment stated that we underestimated the effort to prepare, review, approve, implement and maintain internal standard operation procedures (SOPs) for electronic submission of drug establishment registration and drug listing information because of the following reason. Particularly for most large companies, drug establishment registration and drug listing information (currently submitted in paper format under 21 CFR 207.22) and content of labeling (currently submitted in electronic format under 21 CFR 314. 50(l)(1)(i)) are handled by completely different functional experts and/or departments in the companies. To coordinate these processes, additional time is needed to define new procedures and interactions that cross functional departments and possibly international groups. Therefore, large companies will expend more than 40 hours to prepare, review, approve, implement and maintain SOPs.

Another comment asserts that the hours per response in Table 1 are underestimated if the estimate accounts for the time required to become familiar with the Structured Product Labeling (SPL) standard.

(Response) In estimating hours per record (Table 2), we considered the various sizes of entities affected and proposed an average number of hours per activity. For example, the estimated 40 hours per record are based on smaller entities requiring approximately 20 hours per record and larger entities requiring approximately 60 hours per record. Therefore, because the comment did not provide a revised estimate, we are maintaining an estimate of 40 hours per record, which is consistent with preparing SOPs for paper format submissions and also includes coordination efforts.

Regarding the comment on underestimating the hours per response in Table 1, the software designed to create the SPL files, the step-by-step instructions in the technical guides, and our technical assistance email address are provided by us for the purpose of minimizing the need to learn the SPL standard before submitting information electronically.

(Comment 3) On the topic of ways to minimize the burden of the collection on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology, one comment encouraged us to continue the availability of Xforms at no cost for industry to use as a software tool for the creation of SPL. The comment also requested that we continue this practice as technology evolves and provide support for this tool.

(Response) We appreciate the encouragement of the comment and will consider the request to continue the practice and provide support as technology evolves.

(Comment 4) Two comments did not agree with our statement that there are no capital or operating and maintenance costs associated with the collection of information. The comments explained that some companies may choose alternative tools to the Xform

software or work with external conversion providers, which may involve the purchase and maintenance of software plus the use of internal information technology personnel for installation, configuration and maintenance. These comments further stated that these costs are significant and need to be considered in the overall cost for industry to comply with the electronic submission requirement.

(Response) As the comments stated, companies may choose to use alternative tools or work with external conversion providers. We do not disagree. However, we have made every effort to eliminate costs to industry to comply with the statutory requirement to electronically submit drug establishment registration and drug listing information.

We also received comments that were specifically related to the technical documents referenced in the draft guidance. Although these comments are not directly related to the draft guidance document that contains the information collection, we will consider the comments when reviewing the technical documents for revision.

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 this provision.

10. Assurance of Confidentiality Provided to Respondents

Confidentiality of drug listing information is safeguarded by 21 CFR 207.37.

11. Justification for Sensitive Questions

This information collection does not contain questions pertaining to sex, behavior, attitude, religious beliefs, or any other matters that are commonly considered private or sensitive in nature.

12. Estimates of Annualized Burden Hours and Costs

The information collection requirements of the Drug Listing and Establishment Registration regulations have been grouped according to the information collection areas of the regulations. The estimates are based upon registration and listing data collected and compiled in FDA's Office of Compliance.

FDA estimates the annual information collection burden for part 207 as follows:

Table 1.—Estimated Annual Reporting Burden					
Activity	**Number of Respondents**	**Number of Responses Per Respondent**	**Total Annual Responses**	**Hours Per Responses**	**Total Hours**
(1) – *Registration of Drug Establishment* (New registrations, including new labeler codes for private label distributors)	39	14.72	574	4.50	2,583
(2) – *Annual Update of Drug Establishment* (Update of registration information)	3,256	2.99	9735	4.50	43,808
(3) – *Drug Product Listing* (New drug listings)	1,567	6.57	10,295	4.50	46,328
(4) – *Registered Establishments' Report of Private Label Distributors* (New listings for private label distributor drugs)	146	10.06	1,469	4.50	6,611
(5) – (June and December updates of all listing information)	1,677	11.21	18,799	4.50	84,596
(6) Waiver requests	1	1	1	1	1
Total					183,927

Table 2. – Estimated Annual Recordkeeping Burden[1]					
Activity	No. of Recordkeepers	Annual Frequency per	Total Annual Records	Hours per Record	Total Hours

		Recordkeeping			
One-time preparation of SOP	3,295	1	3,295	40	131,800
SOP maintenance	3,295	1	3,295	1	3,295
Total					135,095

13. Estimates of Other Annualized Cost Burden to Respondents and Record Keepers

Based on an industry hourly wage average cost of $50 per hour, the annual cost is as follows:

Total burden hours of 319,020 (183,925 + 135,095) @ $50 per hour equals $ 15,951,000.

There are no capital costs or operating and maintenance costs associated with the transition from paper to electronic submissions. To create an SPL file and submit it to FDA, a registrant would need the following tools: A computer, appropriate software, access to the Internet, knowledge of terminology and standards, and access to FDA's Electronic Submission Gateway (ESG).

Registrants (and most individuals) have computers and Internet access available for their use. If a business does not have an available computer or access to the Internet, free use of computers and Internet are usually available at public facilities, e.g., a community library; or they may request a waiver from submitting the information electronically.

Software is necessary to create a “document.” The SPL file or “document” may be created internally by a business with experience with SPL, or a business may use a user-friendly software (XForms)[3] available at no cost for industry use. In addition to the

3 See *http://www.fda.gov/oc/datacouncil/xforms.html*.

software, FDA also provides technical assistance, and other resources, terminology, and data standards regarding SPL files.[4]

Once the SPL file is created, the registrant would upload the file through the ESG. A digital certificate is needed to use the ESG. The digital certificate binds together the owner's name and a pair of electronic keys (a public key and a private key) that can be used to encrypt and sign documents. However, a small fee of up to $20.00 is charged for the digital certificate and the registrant may need to renew the certificate not less than annually. FDA is not calculating this small fee as cost of doing business because it is less than or equal to the biannual courier costs the registrant incurs for paper submissions.

14. Annualized Cost to the Government

FDA currently devotes approximately 30 FTEs to maintaining the registration and listing database for human and veterinary drugs and biologics. If each FTE equals approximately $250,000, the total cost to the government is approximately $7,500,000.

15. Explanation for Program Changes or Adjustments

The increase in burden is for the collection of any information not currently submitted using the FDA Forms, to create and upload the SPL file, and to prepare and maintain SOPs for submitting drug establishment registration and drug listing information electronically. FDA anticipates that the hours per response in table 1 will decrease over time due to the flexibility of submitting information for registering multiple establishments or listing multiple drugs in one SPL file instead of submitting individual FDA Forms, and increasing familiarity with the use of

4 See *http://www.fda.gov/oc/datacouncil/spl.html*.

the standards and terminology for creating the SPL file. FDA also anticipates that the hours per record in table 2 will decrease significantly once the SOPs are initially prepared, reviewed, and implemented.

16. Plans for Tabulation and Publication and Project Time Schedule

No comprehensive tabulation of the data is planned or anticipated.

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

The FDA Forms involved in this collection will display the OMB expiration date.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

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