Guidance for Industry

Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Drug Listing

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner

December 2008
Electronic Submission

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This is one in a series of guidance documents intended to assist persons making regulatory submissions to FDA in electronic format. This guidance is designed to assist manufacturers with electronic submissions of drug establishment registration and drug listing information. The guidance and accompanying technical documents explain:

- The statutory requirement to submit electronically drug establishment registration and drug listing information;
- How to create a Structured Product Labeling (SPL)[2] file for submitting drug establishment registration and drug listing information to FDA through the Electronic Submissions Gateway (ESG) using defined code sets and codes, i.e., a language recognized by the computer system; and
- On June 1, 2009, FDA will no longer accept registration and listing information in paper format unless a waiver is granted.

FDA intends to update these documents regularly to reflect the evolving technology and user experience.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

[1] The Office of Critical Path Programs, Office of the Commissioner, Food and Drug Administration prepared this guidance document in cooperation with the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center for Veterinary Medicine.

[2] SPL standard is a Health Level Seven, Inc. standard for the exchange of product information using extensible markup language (XML).

Requirements for drug establishment registration and drug listing are set forth in section 510 of the Federal Food, Drug, and Cosmetic Act (the Act) and section 351 of the Public Health Service Act (the PHS Act), and 21 CFR Part 207.[3] Fundamental to FDA's mission to protect the public health is the collection of this information, which is used for important activities such as postmarket surveillance for serious adverse drug reactions, inspection of drug manufacturing and processing facilities, and monitoring of drug products imported into the United States. Comprehensive, accurate, and up-to-date information is critical to conducting these activities with efficiency and effectiveness.

Section 510 of the Act and 21 CFR part 207, subject to certain limited exceptions, require establishment owners and operators (registrants) upon first engaging in the manufacture, preparation, propagation, compounding, or processing of drugs, (including human drugs, veterinary drugs, and biological drug products[4]) to register their establishments and submit listing information for all drugs and biological drug products in commercial distribution. Registrants are also required to submit updates to registration information for their establishments annually on or before December 31.[5] At the time of registration, registrants must also submit required listing information.[6] Additionally, registrants are required to update listing information in June and December of each year to include information for drugs and biological drug products that have not been previously listed.[7] Certain changes to information for previously listed drugs and biological drug products must also be submitted every June and December.[8]

Changes in the Act, resulting from the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85) (FDAAA),[9] require that drug establishment registration and drug listing information be submitted electronically unless a waiver is granted. Before FDAAA was enacted, section 510(p) of the Act expressly provided that drug establishment registration information be submitted electronically, based on a finding that electronic receipt was feasible, and section 510(j) of the Act stipulated 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.

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[3] This guidance document does not apply to establishment registration and product listing information required solely under 21 CFR part 607 (Blood and Blood Products), 21 CFR 807(Devices), and 21 CFR part 1271 (Human Cells, Tissues, and Cellular and Tissue-Based Products).

[4] Under section 351(j) of the PHS Act, the Act and regulations promulgated under the Act apply to biological drug products except that new Drug Applications (NDAs) are not required for products licensed under section 351(a) of the PHS Act.

[5] Section 510(b)(1) of the Act.

[6] Section 510(j)(1) of the Act.

[7] Section 510(j)(2)(A) of the Act.

[8] Section 510(j)(2) of the Act.

[9] Signed into law on September 27, 2007.

Paper-based drug establishment registration and drug listing information have, until now, been submitted 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).[10] Moving from a paper-based format to an electronic system will improve the timeliness and accuracy of the submissions. FDA is providing a transition period until June 1, 2009, to enable industry to begin submitting drug establishment registration and drug listing information electronically.

FDA is adopting the use of extensible markup language (XML) files in a standard SPL format for the exchange of drug establishment registration and drug listing information (including labeling as specified under 21 CFR 207.25). The automated submission process functions most efficiently and effectively when this information is provided in a standardized format with defined code sets and codes. This guidance and accompanying technical documents describe how to make these submissions using the SPL format, which FDA can process, review, and archive.[11] Information in a properly created and complete SPL file can be processed in minutes and allows for greater precision and accuracy through the use of coded data fields rather than just electronic text. Timely and accurate information will enhance FDA's efforts to help ensure the integrity of the drug supply and protect public health.

Technical specifications are provided in the following technical documents, which can be found on the FDA Data Standards Council website: *http://www.fda.gov/oc/datacouncil/spl.html* and are discussed in section IV:

- *Structured Product Labeling Implementation Guide for FDA Drug Establishment Registration and Drug Listing*
- *Step-by-Step Instructions for Creating Structured Product labeling (SPL) Files for Drug Establishment Registration and Drug Listing*
- *Structured Product Labeling Validation Procedures for Drug Establishment Registration and Drug Listing*

FDA issued a proposed rule that would amend 21 CFR part 207 to require electronic submission of drug establishment registration and drug listing information, among other provisions such as certain changes to the National Drug Code system and requiring the appropriate NDC on the drug label (71 FR 51276, August 29, 2006). FDA is considering comments submitted on the proposed rule and intends to revise, reissue, or revoke this guidance document as appropriate to make it consistent with the final rule, when the rule is issued.

III. DRUG ESTABLISHMENT REGISTRATION AND DRUG LISTING INFORMATION FOR ELECTRONIC SUBMISSION

[10] These forms are currently available at *http://www.fda.gov/opacom/morechoices/fdaforms/default.html*.

[11] When we are ready to receive a particular submission type in electronic format only, we generally identify the specific type of document that FDA can adequately process, review, and archive. This information can be found in the public docket 92S-0251 at *regulations.gov*. (21 CFR part 11) See also *Guidance for Industry: Part 11, Electronic Records; Electronic Signatures -- Scope and Application* (August 2003).

The following information should be submitted to FDA in the SPL file format using the defined code sets and codes as described in section IV of this document.

A. Drug Establishment Registration

1. Who must register and when?

The owner or operator of an establishment entering into the manufacture, preparation, propagation, compounding, or processing (which includes, among other things, repackaging and relabeling) of a drug or drugs[12] and not exempt under section 510(g) of the Act or subpart B of 21 CFR part 207, must register the establishment with FDA within 5 days after beginning the operation (21 CFR 207.21(a)). Alternatively, if the establishment has not previously entered into such an operation, the owner or operator must register within 5 days after submitting a drug application, biological license application, or medicated feed mill license application. Owners or operators must renew their registration information annually (21 CFR 207.21(a)).

Foreign establishments that engage in the manufacture, preparation, propagation, compounding, or processing (which includes, among other things, repackaging and relabeling) of a drug that is imported or offered for import into the United States (and that are not exempt) must upon first engaging in such activity immediately register and register annually thereafter (see section 510(i) of the Act and 21 CFR 207.40).

Amendments to drug establishment registration must be submitted in accordance with 21 CFR 207.26.

2. What information is required for drug establishment registration?

Under 21 CFR 207.25, drug establishment registration information has historically been submitted on Form FDA 2656. Section 510 of the Act and 21 CFR Part 207 set forth the registration information required to be submitted by domestic and foreign drug establishments (see sections 510(b), (c), (d), and (i) of the Act and 21 CFR 207.22(a), 207.25(a), 207.26, and 207.40).

Under 21 CFR 207.40(c), foreign registrants must provide certain additional information specific to their establishments. For example:

- The name, address, and phone number of the foreign registrant's United States agent, and
- Under section 510(i)(1)(A) of the Act, the name of each importer that is known to the establishment (this means each U.S. company or individual in the United States that is an owner, consignee, or recipient, of the foreign establishment's drug, that is imported into the United States. An importer does not include the consumer or patient who ultimately purchases, receives, or is administered the drug, unless the foreign establishment ships the drug directly to the consumer or patient.); and the name of each person who imports or offers for import (this means the name of each agent, broker, or other entity, other than a carrier, that the foreign drug establishment uses to facilitate the import of their drug into the United States).

[12] Means both human, including biological drug products, and animal drugs.

To facilitate correspondence between registrants and FDA, foreign registrants should submit the email address for the U.S. agent, and the telephone number(s) and email address for the importer and person who imports or offers for import described in section III.A.2 of this document.

Section 510(p) of the Act, as amended by FDAAA, now requires drug establishment registrations to be submitted electronically unless a waiver is granted. Therefore, the information previously submitted using Form FDA 2656 and the information required under 21 CFR 207.40(c) is now submitted electronically using SPL files with coded data fields.

Failure to register in accordance with section 510 of the Act is a prohibited act under section 301(p) of the Act. Failure to comply with section 510 of the Act renders drugs misbranded under section 502(o) of the Act.

3. What additional information is recommended?

Registrants have also voluntarily submitted additional drug establishment registration information on Form FDA 2656. For electronic submission, registrants are encouraged to also submit the following information in their SPL file:

- Official contact's name, mailing address, telephone number(s), and email address;
- Each registered establishment's telephone number(s); and
- The type of operation(s) performed at each registered establishment.

B. Drug Listing

1. Who must list and when?

Registrants, which do not include those exempt under 21 CFR 207.10, must submit the initial listing information for all drugs[13] in commercial distribution at the time of their initial registration of their establishment(s) (21 CFR 207.21(a)).

Although FDA does not accept drug establishment registration information from private label distributors, private label distributors may request their own NDC Labeler Code and elect to submit drug listing information to FDA (21 CFR 207.20(b)). In such instances, at the time of submitting or updating drug listing information, private label distributors must certify to the registered establishment(s) that manufactured, prepared, propagated, compounded or processed (which includes, among other things, repackaging and relabeling) the listed drug(s) that the drug listing submission was made (21 CFR 207.20(b)). The certification to the registered establishment by the private label distributor may be satisfied using paper forms.

Registrants (and, if applicable, private label distributors) must update their drug listing information, and include drugs that have been introduced for commercial distribution and have not previously been listed.[14] Any updates must be submitted every June and December.[15]

[13] Includes combination products and their constituents (see 21 CFR part 3).

[14] Section 510(j)(2) of the Act.

[15] Section 510(j)(2) of the Act.

306However, registrants (and, if applicable, private label distributors) are encouraged to submit
307updates through the registration and listing system more frequently as a change occurs, including
308updates to labeling required to be submitted. (21 CFR 207.21(b), 207.22(b), 207.25, and 207.30)
309
310 *2. What information is required for drug listing?*
311
312Under 21 CFR 207.25, listing information has historically been submitted on Forms FDA 2657
313and FDA 2658. Section 510 of the Act and 21 CFR Part 207 set forth the drug listing
314information required to be submitted by domestic and foreign drug establishments (see section
315510(j) of the Act and 21 CFR 207.25(b) and (c), 207.30, 207.31, and 207.40). However, if the
316carton and container labels required under 21 CFR 207.25(b) and 207.40 are submitted with a
317marketing[16] application, it is not necessary to resubmit the carton and container labels when
318listing a human prescription drug.
319
320Section 510(p) of the Act, as amended by FDAAA, now requires drug listing, including updates,
321to be submitted electronically unless a waiver is granted. Therefore, the information previously
322submitted using Form FDA 2657 and FDA 2658 is now submitted electronically using SPL files
323with coded data fields.
324
325Registrants and private label distributors can consult the National Drug Code Directory for all
326drug products listed with FDA. The registrant and private label distributor must provide
327complete and accurate information to be listed in the directory. If the drug product does not
328appear in the directory, FDA will not consider the drug product listed. This directory is available
329at the Data Standards Council website.
330
331 *3. What additional information is recommended?*
332
333 a. Additional information on Form FDA 2657
334
335Registrants and, if applicable, private label distributors have also voluntarily submitted
336additional drug listing information on Form FDA 2657 and Form FDA 2658. For electronic
337submission, registrants are encouraged to submit the following information in their SPL file:

338 • Name of establishment(s) manufacturing or processing the listed drug and the type of
339 operation(s) performed;
340 • DEA schedule;
341 • Route(s) of administration;
342 • Inactive ingredients and strength or amount;
343 • Marketing information (e.g., category, start/stop date);
344 • Information related to the application or OTC monograph citation number (e.g., type and
345 year of approval); and
346 • Package size and type.
347

74
75[16] New Drug Application (NDA), Biologics License Application (BLA), Abbreviated New Drug Application
76(ANDA), New Animal Drug Application (NADA), and Abbreviated New Animal Drug Application (ANADA).

b. Manufacturer's Information for Voluntary Reporting of Adverse Drug Reactions

In providing the labeling as specified under 21 CFR 207.25, FDA recommends for manufacturers with a Web site for voluntary reporting of adverse drug reactions that the registrant provide the manufacturer's telephone number and URL address that appears on the label (21 CFR 201.57(a)(11)).

c. Site-specific D-U-N-S® Number[17]

FDA recommends that the D-U-N-S® Number (as described in section V.B.2 of this document) should be submitted for each site-specific entity (e.g., the registrant, establishments, U.S. agent, importer). Submitting the site-specific D-U-N-S® Number for an entity would provide by reference to the number certain business information for that entity, e.g., trade names used by the entity, addresses, additional ownership information, such as the name of each partner or the name of each corporate officer and director, and the state of incorporation otherwise required for drug establishment registration.

d. NDC Product Code for a Source Drug Repacked or Relabeled

Repackers and relabelers may submit the NDC Product Code for the source drug that is repacked or relabeled to reference previously submitted manufacturing establishment information.

e. Reference Drug

In rare situations, the strength of the drug is based on a reference drug. In such cases, the registrant (and, if applicable, private label distributor) are encouraged to include the reference drug used as a basis for the strength of the listed drug to avoid confusion.

g. Distinctive Characteristics of Certain Listed Drugs

Registrants are encouraged to provide the following characteristics for the listed drug, when applicable. Registrants have previously provided these characteristics voluntarily as helpful information to the public for the safe and effective use of their products.

- Flavor

When applicable, the registrants (and, if applicable, private label distributor) may provide the flavor as a unique distinguishing characteristic of the listed drug. (Registrants have previously provided this information on Form FDA 2657 as an ingredient.)

- Color

[17] D-U-N-S® Numbers are proprietary to and controlled by Dun & Bradstreet (D&B). D&B grants a customer a non-exclusive, perpetual, limited license to use D-U-N-S® Numbers solely for identification purposes and only for the customer's internal business use. Where practicable, the customer will refer to the number as a "D-U-N-S® Number" and state that D-U-N-S is a registered trademark of D&B.

For liquid dosage forms, the registrant (and, if applicable, private label distributor) may provide the color as a unique distinguishing characteristic. This may be useful when the color of a solution is confused for contamination or a change in color may indicate contamination.

- Image

For solid oral dosage forms, the registrant (and, if applicable, private label distributor) may submit an image of the actual dosage form. This information is helpful to the consumer in determining the correctly dispensed drug. The registrant should obtain instructions on obtaining the image and the proper format in the SPL file by following the instructions for technical assistance in section V.D of this document.

h. Confidentiality Flag

Registrants (and, if applicable, private label distributor) may identify an inactive ingredient or the registrant's business relationship with an establishment that they view as confidential when submitting registration and listing information. Pursuant to a Freedom of Information Act request or on our own initiative, FDA will ultimately make determinations as to whether drug establishment registration and drug listing information can be disclosed to the public pursuant to the Trade Secrets Act, the Freedom of Information Act, and other applicable law (e.g., section 510(f) of the Act and 21 CFR 207.37).

IV. CREATING THE DRUG ESTABLISHMENT REGISTRATION AND DRUG LISTING FILE FOR ELECTRONIC SUBMISSION

A. Structured Product Labeling

SPL is the standard that is used for the exchange of drug establishment registration and drug listing information and is based on the Health Level Seven (HL7) version 3 Reference Information Model (RIM) and the Clinical Document Architecture (CDA).

FDA is using SPL release 4 (SPLr4) for electronic submissions of drug establishment registration and drug listing information. The technical details on using SPLr4 for registration and listing are available in the document *Structured Product Labeling Implementation Guide for FDA Drug Establishment Registration and Drug Listing* (SPL Implementation Guide).

FDA has been accepting SPL files for certain product information since 2004, and vendors have provided solutions for creating SPL files ranging from basic software tools to comprehensive information management systems. Additionally, FDA has collaborated with GlobalSubmit on software to create SPL files based on XForms technology. Information on using the XForms is available in the document *Step-by-Step Instructions for Creating Structured Product Labeling (SPL) Files for Drug Establishment Registration and Drug Listing*.

These documents are on the FDA Data Standards Council website.

B. Code Sets and Codes

As previously described, code sets and codes are used as a language that is recognized by a computer system. FDA has been working with a number of organizations to develop and maintain such code sets and codes used for submitting drug establishment registration and drug listing information electronically. Although many code sets and codes are already available at 21 CFR 207.3 and the Data Standards Council website, FDA is continuously updating these codes sets and adding additional codes. Information on the organizations that maintain the code sets for submitting drug establishment registration and drug listing information electronically and how to obtain the code sets and codes used for electronic drug registration and listing follows.

1. Unique Identifiers (UNII)

UNII is the defined code FDA uses for ingredients. FDA along with United States Pharmacopeia (USP) maintains the UNII using the FDA Substance Registration System. These names and identifiers are accessible through USP website at *http://www.usp.org* and publications, the Data Standards Council website and the NCI Thesaurus website at *http://evs.nci.nih.gov*. Additional ingredient identifiers may be requested through FDA by sending a request to *spl@fda.hhs.gov*. In submitting your request, identify in the subject line of the email the Center responsible for regulating the listed drug, i.e., Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, or the Center for Veterinary Medicine.

2. Data Universal Numbering System (D-U-N-S®) Number

Dun & Bradstreet assigns and maintains a database of the D-U-N-S® Numbers, which serve as unique identifiers (code) of business entities. Upon application, each business entity (e.g., registrant, establishment, importer, US agent) is assigned a distinct site-specific 9-digit D-U-N-S® Number. If the D-U-N-S® Number for a location has not been assigned, a business may obtain one for no cost directly from Dun & Bradstreet (*http://www.dnb.com*).

3. Other code sets

FDA collaborates with the National Cancer Institute Enterprise Vocabulary Services (NCI EVS) to maintain code sets for dosage form, routes of administration, package types, DEA schedule, product color, product shape, flavors, business operations, marketing categories and equivalence codes. These code sets are located in the NCI Thesaurus and may be accessed through the NCI EVS website at *http://evs.nci.nih.gov* and the Data Standards Council website. Additional code sets and codes for use in registration and listing may be requested though FDA by sending a request to *spl@fda.hhs.gov*.

The Regenstrief Institute[18] maintains a number of different code sets used in electronic drug establishment registration and drug listing including: document types, section headings, and units of measure. These code sets are located in the Logical Observation Identifiers Names and Codes

[18] The Regenstrief Institute is an internationally recognized informatics and healthcare research organization.

(LOINC) and Unified Codes for Units of Measure (UCUM) systems. Both of these terminologies are available at *http://www.regenstrief.org* and at other locations. Additional code sets and codes may be requested through FDA by sending a request to *spl@fda.hhs.gov* following the instructions in section IV.D of this document.

C. Submission and FDA Validation of Electronic Drug Establishment Registration and Drug Listing Information

The SPL file should be created following the technical specifications in the SPL Implementation Guide and other information found in this document. Other resources for creating the SPL file, including a link to a user-friendly software tool (XForms), are also available.[19] Once the SPL file is created, it can then be submitted (uploaded) by following the instructions for the FDA Electronic Submissions Gateway (ESG), including digital certification.[20]

FDA uses a computer system for processing the SPL files using controlled code sets and codes. The computer system automatically checks the SPL files for certain errors, mistakes and omissions prior to entering the information into FDA systems. FDA will work with companies to help correct identified problems in order to complete the registration and listing process. Information on the details used in checking SPL files for electronic drug establishment registration and drug listing are in the document *FDA's Structured Product Labeling Validation Procedures for Electronic Drug Establishment Registration and Drug Listing*.[21] This document is on the Data Standards Council website.

D. Technical Assistance

For technical problems or questions, or technical assistance with creating SPL files, send an email to *spl@fda.hhs.gov*. In submitting a request, identify in the subject line of the email the Center responsible for regulating the listed drug, i.e., Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, or Center for Veterinary Medicine.

V. IMPLEMENTATION

During the transition period, i.e., until June 1, 2009, FDA intends to continue to accept paper forms. During the transition period, the registrant should submit the drug establishment registration and drug listing information either electronically or using the Forms FDA 2656, FDA 2657, and FDA 2658, but not both.

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[19] See *http://www.fda.gov/oc/datacouncil/spl.html* for additional resources, terminology, and data standards regarding the SPL files. See *http://www.fda.gov/oc/datacouncil/xforms.html* for information on the user-friendly software tool.

[20] See *http://www.fda.gov/esg/default.htm* for information on other resources and using the FDA ESG.

[21] This document is used by FDA and describes FDA's computer instructions for automating the validation of submitted SPL files containing registration and listing information.

VI. WAIVER REQUEST

Under section 510(p) of the Act, registrations and listings (including the submission of updated information) must be submitted electronically unless FDA grants a waiver of such requirement because use of electronic means is not reasonable for the person requesting such waiver. FDA does not anticipate many instances in which electronic submission of registration and listing information will not be reasonable for the person requesting the waiver. If you are granted a waiver, you will be instructed as to how to submit the registration and listing information.

To apply for a waiver, submit a written request with a complete explanation of why you cannot submit your registration and listing information electronically to:

SPL Coordinator
U.S. Food and Drug Administration (HF-18)
5600 Fishers Lane
Rockville, MD 20857-0001

Phone: 1-888-463-6332

115

542/home/ec2-user/sec/disk/omb/icr/201203-0910-007/doc/31372401
543
544Revised: McKeever 10/15/08
545Comments: Levin, Smith 10/18/08
546Revised: McKeever 10/20/08
547Comments: Behrman 10/28/08
548Edited: Falvey 10/29/08
549Comments: CDER, CBER, CVM 1/21/08
550