Guidance for Industry

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

DRAFT GUIDANCE

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Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*. Submit electronic comments to http://www.regulations.gov.

For questions regarding this draft document contact Lonnie Smith, 301-594-0011.

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

July 2008
Electronic Submission

Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry

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

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U.S. Department of Health and Human Services
Food and Drug Administration
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July 2008
Electronic Submission

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Guidance for Industry[1]
Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Drug Listing

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 explains how to participate in a voluntary Pilot Program that has been designed to assist manufacturers with transitioning from paper-based to electronic submissions of drug establishment registration and drug listing information and to test the performance of FDA's electronic system for this type of submission. The guidance, along with accompanying technical documents, explains what registration and listing information (including labeling) to submit and describes how to submit the information electronically in Structured Product Labeling (SPL) files, using a defined terminology. FDA intends to update regularly guidance documents on electronic submissions to reflect the evolving nature of the technology and the experience using this technology.

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

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

[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.

Act (the PHS Act), and 21 CFR Part 207.[2] Drug establishment registration and drug listing information is currently 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).[3]

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 the current paper-based system. This automated process can function most efficiently and effectively when the information is provided in a standardized format using defined terminology.

Section 510 of the Act and 21 CFR part 207, subject to certain limited exceptions, require owners and operators of establishments (registrants) upon first engaging in the manufacture, preparation, propagation, compounding, or processing of drugs, (including human drugs, veterinary drugs, and biological drug products) to register their establishments and submit listing information for all drugs and biological drug products in commercial distribution. Registrants are also required to submit, on or before December 31 of each year, updates to registration information for their establishments.[4] Registrants must, at the time of annual registration, also submit required listing information.[5] 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.[6] Certain changes to information for previously listed drugs and biological drug products must also be submitted in June and December of each year.[7]

Under section 351(j) of the PHS Act, the Act and regulations promulgated under the Act apply to biological drug products.

Changes in the Act, resulting from enactment of the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85) (FDAAA),[8] require that drug establishment registration and

[2] This guidance document does not apply to establishment registration and product listing information required solely under 21 CFR part 607, 21 CFR 807, and 21 CFR part 1271.

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

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

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

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

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

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

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. FDA intends to exercise enforcement discretion and does not intend to take action to enforce this electronic submission requirement, but rather intends to pilot voluntary electronic submission during a transition period as discussed below.

Efforts are under way at FDA to transition from a paper-based to an electronic submission environment, making it possible for FDA to begin to receive drug establishment registration and drug listing information electronically. FDA is creating the voluntary Pilot Program to assist manufacturers to transition from paper-based to electronic submissions and to assist the Agency in testing the performance of its systems for processing electronic submissions.[9] This guidance and accompanying technical documents lay out the procedures for those wishing to participate in the Pilot Program. Any persons subject to the provisions in section 510 of the Act and 21 part 207 may participate in this Pilot Program.[10] FDA intends to only accept electronic drug establishment registration and drug listing information beginning June 1, 2009 (unless a waiver is granted.)

As another part of the transitioning effort, 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 still in the process of considering comments submitted on the proposed rule and intends to revise, reissue, or revoke this guidance document as appropriate for consistency with the final rule, when issued.

III. VOLUNTARY PILOT PROGRAM AND TRANSITION

FDA is launching a Pilot Program that enables industry to begin voluntarily submitting drug establishment registration and drug listing information in electronic format. This guidance document describes how to transition from submitting drug establishment registration and drug listing information on paper forms to submitting the information using the SPL format, an electronic format that FDA can process, review, and archive. FDA is adopting the use of

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[9] When we are ready to receive a particular submission type in electronic format only, we generally identify it in the public docket 92S-0251. Under 21 CFR part 11, you then have the option of providing that submission type in electronic format in a manner that FDA can adequately process, review, and archive. See also *Guidance for Industry: Part 11, Electronic Records; Electronic Signatures -- Scope and Application* (August 2003).

[10] See footnote 2.

extensible markup language (XML) files in a standard Structured Product Labeling (SPL)[11] format as the standard format for the exchange of drug establishment registration and drug listing information. Information in a properly created and complete SPL file can be processed in minutes. In addition, the use of SPL with defined terminology allows for more precise and accurate registration and listing information. Timely and accurate information will enhance FDA's efforts to help ensure the integrity of the drug supply and protect the public health.

This guidance, and accompanying technical documents, describes how to electronically create and submit SPL files using a defined terminology for drug establishment registration and drug listing information (including labeling as specified under 21 CFR 207.25). Technical specifications are provided in the following technical documents:

- *Structured Product Labeling Implementation Guide for FDA Drug Establishment Registration and Drug Listing*
- *Instructions for Using Electronic Drug Establishment Registration and Drug Listing XForms*
- *FDA's Structured Product Labeling Validation Procedures for Electronic Drug Establishment Registration and Drug Listing*

These documents are on the FDA Website at *http://www.fda.gov/oc/datacouncil/spl.html* and are discussed in section V of this document.

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

The following information in this section should be submitted to FDA in the SPL file format as described in section V 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

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

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

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?

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). Such drug establishment information includes, for example, the name and address of each drug establishment, all trade names used by the establishment, the kind of ownership or operation (i.e., individually owned, partnership or corporation), and the name of the owner or operator. Under 21 CFR 207.40(c), foreign registrants must provide certain additional information specific to their establishments. For example, a foreign registrant must submit the name, address, and phone number of its 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). Section 510(p) of the Act, as amended by FDAAA, now requires drug establishment registrations to be submitted electronically unless a waiver is granted.

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.

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 IV.A.2 of this document.

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)).

Because 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)).

Registrants (and, if applicable, private label distributors) must update their drug listing information, and include drugs that have subsequently been introduced for commercial distribution and, therefore, have not previously been listed.[14] Any updates must be submitted every June and December.[15] However, registrants (and, if applicable, private label distributors) are encouraged to submit updates through the registration and listing system more frequently as a change occurs, including updates to labeling required to be submitted. (21 CFR 207.21(b), 207.22(b), 207.25, and 207.30)

2. What information is required?

Listing information has historically been submitted on Form FDA 2657. Section 510 of the Act and 21 CFR Part 207 set forth the drug listing information required to be submitted by domestic and foreign drug establishments (see section 510(j) of the Act and 21 CFR 207.25(b) and (c), 207.30, 207.31, and 207.40). Such drug listing information includes, for example, the listed drug's established name and proprietary name, application number (if any), and the NDC number. Labels, labeling, and/or advertisements are also required to be submitted as specified in section 510(j) of the Act and 21 CFR 207.25(b) and 207.40. Section 510(p) of the Act, as amended by FDAAA, now requires drug listing, including updates, to be submitted electronically unless a waiver is granted.

3. What additional information is recommended?

a. Additional information on Form FDA 2657

Registrants and, if applicable, private label distributors have also voluntarily submitted additional drug listing information on Form FDA 2657 and Form FDA 2658. For electronic submission, registrants are encouraged to submit the following information in their SPL file:

- Name of establishment(s) manufacturing or processing the listed drug and the type of operation(s) performed;

[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.

- DEA schedule;
- Route(s) of administration;
- Inactive ingredients and strength or amount;
- Marketing information (e.g., category, start/stop date);
- Information related to the application or OTC monograph citation number (e.g., type and year of approval); and
- Package size and type.

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[16]

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.

[16] 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.

- 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

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).

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

A. Structured Product Labeling

Structured Product Labeling (SPL) is the standard that will be 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). The SPL file used for information exchange is written in XML.

FDA intends to use 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 *Instructions for Using Electronic Drug Establishment Registration and Drug Listing XForms*.

These documents are on the FDA web site at: *http://www.fda.gov/oc/datacouncil/spl.html*.

B. Terminology

FDA has been working with a number of organizations to develop and maintain terminology used for submitting drug establishment registration and drug listing information electronically. Although many terms and codes are already available, FDA is continuously updating this terminology and adding additional codes. Information on the organizations that maintain the terminology for submitting drug establishment registration and drug listing information electronically and how to obtain the terms and codes used for electronic drug registration and listing follows.

1. Unique Ingredient Identifiers (UNII)

UNII is the defined terminology 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 Web site at *http://www.usp.org* and publications, the FDA Web site at *http://www.fda.gov/oc/datacouncil* and the NCI Thesaurus Web site 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 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 terminology

FDA collaborates with the National Cancer Institute Enterprise Vocabulary Services (NCI EVS) to maintain terminology for dosage form, routes of administration, package types, DEA schedule, product color, product shape, flavors, business operations, marketing categories and equivalence codes. These terminologies are located in the NCI Thesaurus and may be accessed

through the NCI EVS Web site at *http://evs.nci.nih.gov* and FDA web site at *http://www.fda.gov/oc/datacouncil/spl.html*. Additional terms 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[17] maintains a number of different terminologies used in electronic drug establishment registration and drug listing including: document types, section headings, and units of measure. These terminologies are located in the Logical Observation Identifiers Names and Codes (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 terms and codes may be requested through FDA by sending a request to *spl@fda.hhs.gov*.

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.[18] 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.[19]

FDA uses a computer system for processing the SPL files using controlled terminology. 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*.[20] This document is on the FDA web site at: *http://www.fda.gov/oc/datacouncil/spl.html*.

D. Technical Assistance

For technical problems or questions, or technical assistance with creating SPL files, send an email to *spl@fda.hhs.gov*.

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

[18] 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.

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

[20] 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. IMPLEMENTATION

As previously discussed, FDA intends to transition its paper-based drug establishment registration and drug listing to an electronic process. During the transition period, FDA intends to continue to accept paper forms.[21] However, beginning June 1, 2009, FDA plans to complete the voluntary Pilot Program and, unless a waiver is granted, expects to receive all drug establishment registration and drug listing information in electronic format[22] only.

FDA envisions few instances in which electronic submission of registration and listing information will not be reasonable and, thus, does not anticipate the need to grant many waivers.[23]

[21] During the voluntary Pilot Program, 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.

[22] Section 510(p) of the Act.

[23] Section 510(p) of the Act.