

Establishment Registration and Listing for Human Drugs

Highlighting Recent Amendments
to 21 CFR Part 207

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Overview

Topics we'll cover in this presentation include:

- Basic background on drug registration & listing
- Things that are new in the amended regulations
- How does electronic submission work?
- Compliance deadlines for the new requirements
- Topics of special interest:
 - Private Label Distributors (PLDs)
 - Unique Facility Identifiers (UFIs)
 - “No changes” certifications
 - NDCs on drug labels

Basic background on drug registration & listing:

What is drug establishment registration and what does it involve?

- Statutory obligation dating back to 1962
- What triggers the establishment registration obligation?
- Who is exempt from drug establishment registration?
- What information is submitted to FDA to register a drug establishment?
- How often does the information get updated or renewed?
 - Annual registration
 - Updates when information changes
- Who is exempt from drug establishment registration?
- How does establishment registration apply to foreign drug establishments?

“Importers” and Foreign Establishment Registration

Note the distinction:

- Importer means . . . a person in the United States that is an owner, consignee, or recipient, at the time of entry, of a foreign establishment's drug, or an animal feed bearing or containing a new animal drug, that is imported into the United States.
- Person who imports or offers for import means . . . the owner or exporter of a drug who consigns and ships a drug from a foreign country to the United States. This includes persons who send a drug to the United States by international mail or other private delivery service, but it does not include carriers who merely transport the drug.
- When registering, foreign establishments identify each *importer* of drugs manufactured, repacked, relabeled, or salvaged at the establishment that is known to the establishment along with each *person who imports or offers for import* such drugs into the U.S.

What is drug listing and what does it involve?

- Statutory obligation dating back to 1973
- What triggers the drug listing obligation?
- What information is submitted to FDA to list a drug?
- How often does the information get updated or renewed?
 - June and December listing updates
 - Updates when information changes
- Who is exempt from drug listing?
- How does the listing obligation apply to foreign drug establishments?
- How does FDA use the information?

Basic background on drug registration & listing

National Drug Code (NDC)

- The NDC is a unique number assigned to drug products
- Three segments identify:
 - The company **12345**-6789-0 (the Labeler code)
 - The product 12345-**6789**-0 (formulation, dosage form, physical form)
 - The package 12345-6789-**0** (size and type of package)
- Two main configurations:
 - 5-4-1 *example: 12345-6789-0*
 - 5-3-2 *example: 12345-678-90*
- FDA assigns the labeler code, Firm assigns the rest.
 - All numeric
 - 10 digits total (will expand to 11 digits when 10-digit combinations are exhausted)



Basic background on drug registration & listing

National Drug Code (NDC)

- Changes to a listed drug that require a new NDC
 - New strength or new active ingredient
 - New Dosage form
 - Any change in physical appearance (size, shape, color, scoring, imprint, etc.)
 - Changes to inactive ingredients do not require a new NDC
 - Unless it affects one of the above attributes
- NDCs should not appear on the labels of non-drug products



Public availability of drug establishment registration and listing information

- Establishment registration information is generally available to the public
- Drug listing information is generally available to the public with certain exceptions
 - information submitted as the basis upon which a registrant has determined that a particular drug is not subject to premarket approval
 - inactive ingredients that are confidential
 - information that reveals certain business relationships
- NDC Directory
- Drug Establishments Current Registration Site (DECRS)

What's new?

Things that are new in the amended regulations include:

- Required electronic submission of drug establishment and listing information
- Unique Facility Identifiers (UFIs)
- “No changes” certifications for drug listing information
- Identification of inactive ingredients in listed drugs

How does electronic submission work?

- 2009 Guidance for Industry: *Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Drug Listing*
 - Designates Structured Product Labeling (SPL) as the format for submissions
 - Paper forms are no longer accepted, even for updates and discontinuances of existing product listings
- What is Structured Product Labeling (SPL)?
 - Structured Product Labeling (SPL) is a document markup standard approved by Health Level Seven (HL7) and adopted by FDA as a mechanism for exchanging product and facility information. SPL files employ extensible markup language (XML)
 - SPL files feature standardized terminology and codes, allowing for faster and more efficient automated validation of files

How does electronic submission work?

- Creating and submitting SPL files
 - Any SPL authoring tool/software may be used to create files. Once created, the XML file and accompanying jpg files must be appropriately zipped into a folder and uploaded to FDA through the Electronic Systems Gateway (ESG).
 - If any particular SPL tool does not offer submit capabilities, an ESG WebTrader account is required to upload submissions.

 - FDA offers two such authoring tools:
 - **XForm** Offers the ability to create nearly any SPL document type the FDA accepts, but still requires the use of an ESG WebTrader account to submit files.
 - **CDER Direct** Features a capability to submit files without the need of a WebTrader account, but is limited to Registration and Listing related SPL files.

If using a third party tool to create files, make sure it follows the most up-to-date SPL Schema standards and code sets **and 207 data elements.**

How does electronic submission work?

- Three basic types of files:
 - **Labeler Code SPL:** [file types: NDC LABLER CODE FORM, NDC LABLER CODE INACTIVATION] Used to request an NDC Labeler code and maintain company and contact data associated with a particular labeler code. Also used during registration renewal to certify no changes to product listings not otherwise updated within the year. (See Topics of Special Interest later in this presentation)
 - **Establishment Registration SPL:** [file types: ESTABLISHMENT REGISTRATION, ESTABLISHMENT DEREGISTRATION, NO CHANGES NOTIFICATION, OUT OF BUSINESS NOTIFICATION] Used to submit initial registration for an establishment as well as updates to registration. An updated establishment registration SPL may be used to satisfy the annual reregistration requirement if it is submitted during the annual registration renewal period (Oct 1 – Dec 31).
 - **Product Listing SPL:** [many file types, including but not limited to: HUMAN PRESCRIPTION DRUG LABEL, HUMAN OTC DRUG LABEL, BULK INGREDIENT, DRUG FOR FURTHER PROCESSING] Used to submit initial product listings and update product listing data and labeling. Product listings that are not required to be updated within the year must be certified that no change has occurred. (See Topics of Special Interest)

Compliance deadlines for the new requirements

- Effective Date = November 29, 2016
- Registrants should continue to submit electronically under part 207.
- By approximately the end of 2018, FDA intends to purge drug registration and listing information submitted in the past on paper and not yet migrated to electronic submission.

Compliance deadlines for the new requirements

Regarding establishment registration:

- Registrants are required to submit and update establishment registration information in accordance with amended subpart B of part 207 no later than the time when registration information is due after the first anniversary of the effective date of this final rule. **If the effective date falls between October 1 and December 31, registrants must submit information required by amended subpart B no later than the next October through December annual review and update period.**
- However, registrants must comply with new § 207.29(a) (expedited updates when certain establishment registration information changes) upon the effective date of the final rule.

Compliance deadlines for the new requirements

Regarding drug listing information:

- Registrants are required to submit and update drug listing information in accordance with amended subpart D of part 207 (including the submission of NDCs that are formatted in accordance with subpart C of part 207) no later than the time when listing information is due after the first anniversary of the effective date of this final rule [i.e., in December 2017].

Additional Topics

- Unique Facility Identifiers (UFIs)
 - Current Guidance: *Specification of the Unique Facility Identifier (UFI) System for Drug Establishment Registration* establishes the DUNS number as the UFI required for Registration and Listing submissions.
- *FDA Establishment Identifiers (FEI)*
 - *The FEI is a number assigned by FDA upon initial registration and is used in certain submissions and communications with FDA.*

Additional Topics

- Private Label Distributors (PLDs)
 - The 2016 version of 21 CFR 207 continues the longstanding requirement that the ultimate responsibility for a PLD's product listing lies with the registered manufacturing establishment. However, a PLD may still choose to submit its own product listing, acting as an agent for the registered manufacturer.

 - Regardless of which party submits the PLD's listing data, the registered manufacturer is still obligated to list the product under its own NDC as well.
 - These manufacturer listings should employ one of the MANUFACTURED EXCLUSIVELY FOR PRIVATE LABEL DISTRIBUTOR marketing categories.
 - Listings under these categories are not published.
 - If a manufacturer makes an identical product for multiple PLDs, it need only list the product once under a single NDC with its own labeler code. However, we expect a unique NDC from each PLD for their version of the product.

Additional Topics

- Blanket “No Changes” Certifications to Product Listings
 - At the time of reregistration, a registrant must certify that all product listings **which were not updated** within the year have had no changes occur to the data or labeling.
 - Requiring a separate submission for each SPL would be burdensome, particularly for larger firms.
 - Instead, a registrant may certify all un-updated product listings with NDCs under a specific labeler code with a single updated **Labeler Code SPL** submission.
 - Review all data on the Labeler Code SPL file, including contact information, and ensure it is correct.
 - Receipt of a Labeler Code SPL during the annual reregistration period will satisfy the certification requirement.

NDCs on Drug Labels

- FDA's bar code regulation (21 CFR 201.25) has long required NDCs in bar codes on the labels of human drug products.
- Additionally, 21 CFR 201.2 currently states that NDCs are "requested but not required" to appear on all drug labels.
- The 2006 proposed rule to amend part 207 included a requirement that the NDC appear in human-readable form on the label of each listed drug and provisions that would have defined the appropriate NDC for that purpose. These aspects of the proposed rule were not finalized.
- The Drug Supply Chain Security Act (DSCSA) (2013) now requires drug manufacturers and repackagers to affix or imprint a "product identifier" on packages for certain prescription drugs for human use. The "product identifier" is in human and machine readable form and includes the NDC as one component.

21 CFR part 207 vs. 607 vs. 1271

- This presentation has focused on registration and listing for human drugs under 21 CFR part 207.
- See appropriate regulations for different product types:
 - Part 207: human and animal drugs, including human drugs regulated under a biologics license application (BLA)
 - Part 607: blood and blood products
 - Part 1271: human cells, tissues, and cellular and tissue-based products (HCT/Ps)



Contact information

- DRLS Helpdesk
 - edrls@fda.hhs.gov
 - www.fda.gov/edrls

- SPL Helpdesk
 - spl@fda.hhs.gov
 - <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

- CDER Direct Helpdesk
 - cderdirect@fda.hhs.gov
 - <https://direct.fda.gov>

- Electronic Systems Gateway Helpdesk
 - ESGHelpDesk@fda.hhs.gov
 - <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm2005551.htm>

