Establishment Registration and Listing for Human Drugs

人用药品企业注册和产品列表

Highlighting Recent Amendments to 21 CFR Part 207

侧重最近对21篇207部分的修订

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Overview 内容介绍

Topics we'll cover in this presentation include:

本次发言涵盖的内容包括：

- Basic background on drug registration & listing **药品注册和列表的背景**
- Things that are new in the amended regulations
- 修订后法规中的新内容
- How does electronic submission work? 如何进行电子提交？
- Compliance deadlines for the new requirements
- 必须符合新要求的截止日期
- Topics of special interest: 某些主题的内容
  - Private Label Distributors (PLDs) 贴标分销商
  - Unique Facility Identifiers (UFIs) 唯一企业识别码
  - "No changes" certifications "无变更"证明
  - NDCs on drug labels 药品标签上的NDC

Basic background on drug registration & listing:
药品注册和列表背景介绍

What is drug establishment registration and what does it involve?
什么是药品企业注册，药品企业注册涉及什么内容？

- Statutory obligation dating back to 1962
- 1962年的法规要求
- What triggers the establishment registration obligation?
- 企业注册责任是如何产生的？
- Who is exempt from drug establishment registration?
- 谁可以被豁免而不进行药品企业注册？
- What information is submitted to FDA to register a drug establishment?
- 注册药品企业需要向FDA提交什么信息？
- How often does the information get updated or renewed?
- 信息更新的频率如何？
  - Annual registration 年度注册
  - Updates when information changes 如有信息变更进行的更新
- Who is exempt from drug establishment registration?
- 谁可以被豁免而不进行药品企业注册？
- How does establishment registration apply to foreign drug establishments?
- 企业注册如何适用于美国境外药品企业？

"Importers" and Foreign Establishment Registration
"进口商"和美国境外企业注册

Note the distinction: 请注意区别：

- *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.
- *进口商*是指美国境外企业的药品，或含有新兽药的动物饲料被进口到美国时，产品入境时位于美国境内的该产品的所有人、收货人。
- *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.
- 进口或计划进口的人是指将某一药品从美国境外国家发货或运往美国的该药品的所有人或出口商，包括通过国际邮寄方式或其他私营邮寄业务将药品发往美国的人，但不包括只负责运输该药品的承运方。

- 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.
- 注册时，美国境外企业需要列出每个已知的工厂所生产、再包装、重新贴标或返工的药品的进口商，以及每个出口或计划出口该药品到美国的人。

What is drug listing and what does it involve?
什么是药品列表（备案），包括什么信息？

- Statutory obligation dating back to 1973
- 法定责任始于1973年
- What triggers the drug listing obligation? 什么促使了药品列表责任的产生？
- What information is submitted to FDA to list a drug?
- 药品列表（备案）时需要提交给FDA什么信息？
- How often does the information get updated or renewed?
- 信息更新的频率如何？
  - June and December listing updates 6月和12月列表更新
  - Updates when information changes 有信息变更时的更新
- Who is exempt from drug listing? 谁可以被豁免不进行药品列表？
- How does the listing obligation apply to foreign drug establishments?
- 药品列表的责任如何适用于国外药厂？
- How does FDA use the information?
- FDA如何使用这些信息？

Basic background on drug registration & listing
药品注册和列表背景介绍

National Drug Code (NDC) 国家药品代码

- The NDC is a unique number assigned to drug products
- NDC是分配给药品的一个唯一编码
- Three segments identify: 包括三个部分，界定不同的信息：
  - The company **12345**-6789-0 (the Labeler code) 厂家号（贴标商号）
  - The product 12345-**6789**-0 (formulation, dosage form, physical form)
  - 产品号（配方、剂型、外观形状）
  - The package 12345-6789-**0** (size and type of package)
  - 包装型号（包装的尺寸和类型）
- Two main configurations: 两种主要的数字组合格式
  - 5-4-1 *example 例如: 12345-6789-0*
  - 5-3-2 *example 例如: 12345-678-90*
- FDA assigns the labeler code, Firm assigns the rest.
- 厂家号由FDA提供，其他号码由厂家提供
  - All numeric 编码全部为数字
  - 10 digits total (will expand to 11 digits when 10-digit combinations are exhausted)
  - 共10位数字（当10位数的组合全部被使用后将扩增到11位数）

Basic background on drug registration & listing
药品注册和列表背景介绍

National Drug Code (NDC) 国家药品代码

- Changes to a listed drug that require a new NDC
- 列表药品如有以下变更将需要新的NDC代码
  - New strength or new active ingredient 新规格或新活性成分
  - New Dosage form 新的剂型
  - Any change in physical appearance (size, shape, color, scoring, imprint, etc.)
  - 外观的任何变化（大小、形状、颜色、刻痕、压印，等）
  - Changes to inactive ingredients do not require a new NDC
  - 对非活性成分的改变不需要新的NDC编码
    - Unless it affects one of the above attributes
    - 除非它影响以上任何性状

- NDCs should not appear on the labels of non-drug products
- 非药品产品标签上不应该有NDC编码

Public availability of drug establishment registration and listing information
药品企业注册和药品列表信息公开

- Establishment registration information is generally available to the public
- 企业注册信息一般是对外公开的
- Drug listing information is generally available to the public with certain exceptions 药品列表信息一般也是对外公开的，几种情况除外：
  - information submitted as the basis upon which a registrant has determined that a particular drug is not subject to premarket approval
  - 作为注册人决定某一药品不需要进行上市前审批的依据而提交的信息
  - inactive ingredients that are confidential 保密的非活性成分
  - information that reveals certain business relationships 显示某些商业关系的信息
- NDC Directory
- NDC 目录
- Drug Establishments Current Registration Site (DECRS)
- FDA药品企业注册信息网页

What's new? 有哪些新内容？

Things that are new in the amended regulations include:

修订后的法规里的新内容包括：

- Required electronic submission of drug establishment and listing information
- 要求电子提交药品企业注册和列表信息
- Unique Facility Identifiers (UFIs) 唯一企业识别码
- "No changes" certifications for drug listing information
- 药品列表信息"无变更"的证明
- Identification of inactive ingredients in listed drugs
- 列表药品非活性成分说明

How does electronic submission work?
如何进行电子提交？

- 2009 Guidance for Industry: *Providing Regulatory Submissions in Electronic Format – Drug Establishment Registration and Drug Listing*
- 2009年行业指南：*以电子格式提交申请–药品企业注册和药品列表*
  - Designates Structured Product Labeling (SPL) as the format for submissions
  - 指定结构化产品标识(SPL)为提交需要采用的格式
  - Paper forms are no longer accepted, even for updates and discontinuances of existing product listings
  - 不再接受纸质申请，包括信息更新和现有产品列表的终止
- What is Structured Product Labeling (SPL)? 什么是结构化产品标识(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)
  - 结构化产品标识(SPL) 是HL7卫生信息交换标准所批准的文件标记标准，SPL被FDA采用作为交换产品和企业信息的机制。SPL文件使用可扩展标记语言(XML)
  - SPL files feature standardized terminology and codes, allowing for faster and more efficient automated validation of files
  - SPL文件的特点是标准化的术语和编码，以便能对文件进行更快更高效的自动验证

How does electronic submission work?
如何进行电子提交？

- Creating and submitting SPL files 创立和提交SPL文件
  - 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).
  - 可使用任何SPL创作工具/软件来创立文件。一旦建立，XML文件及所附jpg文件必须适当压缩到一个文件夹，并通过电子提交系统(ESG)上传给FDA
    - If any particular SPL tool does not offer submit capabilities, an ESG WebTrader account is required to upload submissions.
    - 如果某个SPL工具没有设置提交功能，则需使用ESG WebTrader帐户进行上传提交
  - FDA offers two such authoring tools:
  - FDA提供两种创作工具：
    - ***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.
    - ***XForm*** 可创建几乎任何FDA接受的SPL文件类型，但仍需要使用ESG WebTrader帐户提交文件
    - ***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.
    - ***CDER Direct*** 可以不使用WebTrader帐户提交文件，但只限于注册和列表相关SPL文件

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.

如果使用第三方工具创建文件，需确保其遵循最新的SPL提纲标准、编码组和207数据成分。

How does electronic submission work?
如何进行电子提交？

- Three basic types of files: 三种基本的文件类型

  - ***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)
  - ***贴标商号SPL：***[文件类型：NDC 贴标商号表格、NDC贴标商号停用表格]用来申请NDC贴标商号，并保留贴标商号对应的企业和联系方式数据。在更新注册期间也被用来证实在当前年度内对产品列表没有进行更改或更新（见后面幻灯片“相关主题的内容”）
  - ***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).
  - ***企业注册SPL：***[文件类型：企业注册、企业取消注册、无变更通知、停业通知]用来提交企业首次注册，以及后续对注册的更新。如果在年度注册更新期间(10月1日 – 12月31日)提交，更新的企业注册SPL可被用来满足年度重新注册的要求。
  - ***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)
  - ***产品列表SPL：***[很多文件类型，包括但不限于：人用处方药标签、人用OTC药品标签、大宗原料成分、需进一步加工的药品]用来提交首次产品列表及更新产品列表数据和标签。当前年度内不需要更新的产品列表必须证明没有进行变更（见“相关主题的内容”）

Compliance deadlines for the new requirements
符合新要求的截止期限

- Effective Date = November 29, 2016
- 生效日期：2016年11月29日

- Registrants should continue to submit electronically under part 207.
- 注册人应继续按207部分要求通过电子方式提交

- 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.
- 大约到2018年年底，FDA计划清除过去以纸质提交并还未转至电子提交的药品注册和列表信息

Compliance deadlines for the new requirements
符合新要求的截止期限

Regarding establishment registration: 关于药品企业注册

- 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.
- 注册人必须根据207部分修订后的子部分B部分要求，提交并更新企业注册信息，且必须在本终版规定生效一年后注册信息提交或更新的截止日期之前完成。如果生效日期在10月1日和12月31日之间，则注册人必须在下一个10-12月年度审核和更新阶段之前或期间提交修订后的子部分B部分要求的信息。
- 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.
- 然而，终版规定生效之后，注册人还必须遵守新的§ 207.29(a)（某些企业注册信息发生变更后的加快更新）部分的要求。

Compliance deadlines for the new requirements
符合新要求的截止期限

Regarding drug listing information: 关于药品列表信息：

- 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].
- 注册人必须根据207部分修订后的子部分D部分要求，提交并更新药品列表信息（包括提交207部分C子部分所要求格式的NDC代码），且必须在本终版规定生效一年后（即2017年12月）列表信息提交或更新的截止日期之前完成。

Additional Topics 其他内容

- Unique Facility Identifiers (UFIs) 唯一企业代码
  - 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.
  - 现行指南：药品企业注册的唯一企业代码系统规定将邓白氏号码作为提交注册和列表时要求使用的唯一企业代码

- *FDA Establishment Identifiers (FEI)*
- *FDA工厂代码*
  - *The FEI is a number assigned by FDA upon initial registration and is used in certain submissions and communications with FDA.*
  - *FEI号是企业首次注册时FDA为其分配的编码，FEI号在提交某些申请时和与FDA的沟通中会用到*

Additional Topics 其他内容

- Private Label Distributors (PLDs)贴标分销商
  - 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.
  - 2016年版的21篇207部分继续之前的要求，即贴标分销商的产品列表责任最终由已注册的生产企业来承担。但是，贴标分销商仍然可以作为注册企业的代理提交自己的产品列表。
  - 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.
  - 不管谁提交贴标分销商的产品列表数据，注册的生产企业仍必须也在他自己NDC项下提交产品列表。
    - These manufacturer listings should employ one of the MANUFACTURED EXCLUSIVELY FOR PRIVATE LABEL DISTRIBUTOR marketing categories.
    - 这些生产企业的产品列表应该选“只为贴标分销商生产”的选项。
    - Listings under these categories are not published. 在这些项下的产品列表将不会被公开。
    - 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.
    - 如果生产企业为多个贴标经销商生产同一个产品，则只需用生产企业自己的贴标商号码用一个NDC将产品列一次即可。然而，每个贴标经销商需要用自己的NDC号将其贴标的产品进行产品列表。

Additional Topics其他内容

- Blanket “No Changes” Certifications to Product Listings
- 产品列表“无变更”证明
  - 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.
  - 重新注册时，注册人必须确认所有当前年度未更新的产品列表没有对数据或标签的变更
  - Requiring a separate submission for each SPL would be burdensome, particularly for larger firms.
  - 每个SPL文件都单独进行一次提交太麻烦了，尤其对大的公司来说
  - 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.
  - 注册人可以通过提交一次更新的贴标商号SPL文件证明NDC是某一共同贴标商号的所有无变更的产品列表
    - Review all data on the Labeler Code SPL file, including contact information, and ensure it is correct.
    - 核实贴标商号SPL文件中的所有数据，包括联系方式信息，确保信息是正确的。
    - Receipt of a Labeler Code SPL during the annual reregistration period will satisfy the certification requirement.
    - 在年度重新注册期间提交贴标商号SPL文件将满足证明的要求。

NDCs on Drug Labels 药品标签上的NDC编码

- FDA's bar code regulation (21 CFR 201.25) has long required NDCs in bar codes on the labels of human drug products.
- FDA的条形码法规(21 CFR 201.25) 一直要求人用药品标签上需要有NDC号的条形码。

- Additionally, 21 CFR 201.2 currently states that NDCs are "requested but not required" to appear on all drug labels.
- 另外， 21 CFR 201.2 部分目前的规定是要求所有药品标签上有NDC编码，但不是必须的。

- 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.
- 2006年修订207部分的草案包括要求每个列表药品的标签上都要有可辨识的NDC编码，以及定义合适的NDC编码的条款。草案的这些部分还没有最终发布。

- 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.
- 2013年《药品供应链安全法案》现要求药品生产企业和再包装企业在人用的某些处方药包装上贴上或印上"产品代码"。"产品代码"需要人肉眼可辨识，并可机读，且包括NDC编码。

21 CFR part 207 vs. 607 vs. 1271
21篇207部分跟607部分和1271部分相比较

- This presentation has focused on registration and listing for human drugs under 21 CFR part 207.
- 本次发言主要涵盖21篇207部分的人用药品注册和列表
- See appropriate regulations for different product types:
- 不同产品类型的相关法规如下：
  - Part 207: human and animal drugs, including human drugs regulated under a biologics license application (BLA)
  - 207部分：人用药品、兽药，包括生物制品许可申请(BLA)项下的人用药品
  - Part 607: blood and blood products
  - 607部分：血液和血制品
  - Part 1271: human cells, tissues, and cellular and tissue-based products (HCT/Ps)
  - 1271部分：人体细胞、组织和细胞组织衍生产品(HCT/Ps)

Contact information 联系方式

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  - edrls@fda.hhs.gov
  - www.fda.gov/edrls
- SPL Helpdesk 咨询
  - spl@fda.hhs.gov
  - http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
- CDER Direct Helpdesk 咨询
  - cderdirect@fda.hhs.gov
  - https://direct.fda.gov
- Electronic Systems Gateway Helpdesk 电子提交系统咨询
  - ESGHelpDesk@fda.hhs.gov
  - http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm2005551.htm


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