Regulation of Drug Manufacturing

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Agenda

- Establishment Registration and Drug Listing
- Adulteration
- Misbranding
- Inspections
- cGMPs
- Responding to 483s
- Closing of Inspections

Establishment Registration

- Drug establishments must register with the FDA.

Establishment Registration and Drug Listing

- Who must register?
  - Domestic:
    - Manufacturers
    - Repackers
    - Relabelers
    - Salvagers
  - Foreign:
    - Manufacturers
    - Repackers
    - Relabelers
    - Salvgers

Establishment Registration and Drug Listing

- Private label distributors do not have to register with FDA
- Exemption entities:
  - Pharmacies
  - Hospitals, clinics, public health agencies
  - Practitioners
  - Manufacturers, repackers, relabelers, or salvagers who manufacture, repack, relabel, or salvage drugs solely for use in research, teaching, or chemical analysis and not for sale
  - Manufacturers, repackers, and relabelers of harmless inactive ingredients such as excipients, colorings, flavorings, emulsifiers, lubricants, preservatives, or solvents that become components of drugs
  - Outsourcing facilities

Establishment Registration and Drug Listing

- How to register:
  - Electronically
  - SPL format

What Information is Required?

- Name of the owner or operator of each establishment
- Each establishment's name, physical address, and telephone number(s);
- All name(s) of the establishment
- Registration number of each establishment, if previously assigned by FDA;
- A Unique Facility Identifier in accordance with the system specified under section 510 of the Federal Food, Drug, and Cosmetic Act.
- All types of operations performed at each establishment;
- Name, mailing address, telephone number, and email address of the official contact for the establishment; and
- For foreign establishments:
  - The name, mailing address, telephone number, and email address of US agent;
  - The name, mailing address, telephone number, and email address of each importer in the United States of drugs manufactured, repacked, relabeled, or salvaged at the establishment that is known to the establishment; and
  - The name, mailing address, telephone number, and email address of each person who imports or offers for import such drug to the United States.

When to Register

- Initial
  - Domestic establishment - no later than 5 calendar days after beginning to manufacture, repack, relabel, or salvage a drug or an animal feed bearing or containing a new animal drug at such establishment.
  - Foreign establishment - before a drug or an animal feed bearing or containing a new animal drug manufactured, repacked, relabeled, or salvaged at the establishment is imported or offered for import into the United States.
- Updates
  - No later than 30 calendar days for:
    - Closing or selling an establishment;
    - Changing an establishment's name or physical address; or
    - Changing the name, mailing address, telephone number, or email address of the official contact or the United States agent. A registrant, official contact, or United States agent may notify FDA about a change of information for the designated official contact or United States agent, but only a registrant is permitted to designate a new official contact or United States agent.
  - Annual review

What is an NDC?

- The NDC for a drug is a numeric code. Each finished drug product or unfinished drug subject to the listing requirements of this part must have a unique NDC to identify its labeler, product, and package size and type.

Who Must List?

- Each registrant must list each drug that it manufactures, repacks, relabels, or salvages for commercial distribution.
- Each domestic registrant must list each such drug regardless of whether the drug enters interstate commerce.

Timing of Listing

- No later than 3 calendar days of initial registration of establishment

What to List

- NDC
- Package type and volume
- Established and proprietary name
- Name and quantity of each active ingredient
- Inactives
- Dosage form
- Approval number
- Drug type
- Route of administration
- Certain labeling

What does registration and listing mean?

- Registration of an establishment or listing of a drug does not denote approval of the establishment, the drug, or other drugs of the establishment, nor does it mean that a product may be legally marketed. Any representation that creates an impression of official approval or that a drug is approved or is legally marketable because of registration or listing is misleading and constitutes misbranding.

What does registration and listing mean?

- FDA's acceptance of registration and listing information, inclusion of a drug in our database of drugs, or assignment of an NDC does not denote approval of the establishment or the drug or any other drugs of the establishment, nor does it mean that the drug may be legally marketed. Any representation that creates the impression that a drug is approved or is legally marketable because it appears in our database of drugs, has been assigned or displays an NDC, or the establishment has been assigned an establishment registration number or Unique Facility Identifier is misleading and constitutes misbranding.

What does registration and listing mean?

- Neither registration nor listing constitutes a determination by FDA that a product is a drug as defined by section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act. Registration or listing may, however, be evidence that a facility intends to or does manufacture, repack, relabel, distribute, or salvage drugs or that a product is intended to be a drug.

Contact Person/Agent

- Registrant must have an official contact.
- Registrants of foreign establishments must have a designated US agent.

FDA Certificates

- FDA does not issue certificates of registration

Prohibited Acts

- **21 U.S.C. §331. Prohibited acts**
  - The following acts and the causing thereof are prohibited:
    - (a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.
    - (b) The adulteration or misbranding of any food, drug, device, tobacco product, or cosmetic in interstate commerce.
    - (c) The receipt in interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.

Adulteration

Adulteration – Insanitary Conditions

- **21 U.S.C. §351. Adulterated drugs and devices**
  - A drug or device shall be deemed to be adulterated-
    - **(a) Poisonous, insanitary, etc., ingredients; adequate controls in manufacture**

Example of Violation

- **Insanitary Conditions Violations**
  - The inspector observed filthy conditions in your facility
  - Your water system is not adequate for its intended use.
    - The water system is a **(b)(4)** system, with no filters.
    - Many objectionable microorganisms can reside in **(b)(4)** (e.g., pathogenic gram-negative and spore-formers) making the water produced by the water system highly susceptible to microbial contamination.
  - Your water system also has uncovered in-process storage tanks that are accessible to pests and the environment. Furthermore, your in-process storage tanks are corroded and coated with an unknown residue. You also do not monitor the water for microbiological growth.
  - FDA collected and tested water samples from your water system. Our test results show high levels of microbiological growth as well as the presence of objectionable microorganisms such as Pseudomonas aeruginosa.
  - In your response, you stated that, “The tanks have a continuing purifying process,” but you did not provide any scientific data to support your claim. Your response is inadequate because it does not address the violation.

Adulteration - Departure from Compendial or Represented Standards

- **21 U.S.C. §351. Adulterated drugs and devices**
  - A drug or device shall be deemed to be adulterated-
    - **(b) Strength, quality, or purity differing from official compendium**

Adulteration - Departure from Compendial or Represented Standards

- Section 501(b) of the Food, Drug, and Cosmetic Act (the Act) deems an official drug (i.e., a drug purported to be or represented as a drug the name of which is recognized in an official compendium) to be adulterated if it fails to conform to compendial standards of quality, strength or purity

Regulatory Action

- In cases where there is a health hazard, the first choice of action should be recall.
- Then seizure. FDA CPG 420.100.

Example of Violation

- [The tablets are] outside of the USP acceptance criteria are adulterated within the meaning of section 501(b) of the FD&C Act, 21 U.S.C. 351(b), in that their strength, quality, or purity falls below the standards set forth in an official compendium recognized in the FD&C Act. FDA notified your customer of this violation in Warning Letter **(b)(4)**.
- Articles represented as a drug recognized in an official compendia must conform to the compendial standards for strength, quality, or purity. We acknowledge that you updated the **(b)(4)** tablets active ingredient assay specification.

Example of Violation

- FDA collected ten samples during the inspection, covering several different strengths of WP Thyroid and Nature-Throid. Six samples were found to be sub-potent for at least one of the two active ingredients.
- Thyroid Tablets outside of the USP acceptance criteria are adulterated within the meaning of 501(b) of the FD&C Act, 21 U.S.C. 351(b), in that their strength, quality, or purity falls below the standards set forth in an official compendium recognized in the FD&C Act.

Adulteration – Supplier Quality

- Problems with components of drugs can also render a drug adulterated

Misbranding

- **21 U.S.C. §352. Misbranded drugs and devices**
  - A drug or device shall be deemed to be misbranded-
    - **(a) False or misleading label**

Misbranding

- Part of the manufacturing process is labeling and label control

Example of Violation

- **False or Misleading Risk Presentation**
  - Promotional materials misbrand a drug if they are false or misleading with respect to risk. The determination of whether promotional materials are misleading includes, among other things, not only representations made or suggested in promotional materials, but also failure to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.
- **False or Misleading Claims about Efficacy**
  - Promotional materials misbrand a drug if they are false or misleading with respect to efficacy. The determination of whether promotional materials are misleading includes, among other things, not only representations made or suggested in promotional materials, but also failure to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.

Inspections

- FDA conducts inspections to determine compliance with FDA's laws and regulations

Inspection Process and Procedure

- Generally, an in-person visit
- Credentials and Notice of Inspection (Form 482)
- Review of processes and procedures
- Discussion
- Issuance of Form 483, if necessary

Search Warrants

- Administrative
- Criminal

Photographs and Recordings

- Can FDA engage in these practices during an inspection?

Affidavits

- FDA uses affidavits during inspections to memorialize information related to products reviewed during an inspection

Types of Inspections

- Routine
- For Cause
- Follow Up
- Pre-Approval Inspection (PAI)
- COVID-19

Routine Inspections

- Regular inspections
- Unannounced

For Cause Inspections

- Investigation of a specific problem
- Not great when this happens

Follow Up Inspections

- An inspection to follow-up on previously noted deficiencies or violations
- Verification of corrective action

Pre-Approval Inspections

- After a company applies to FDA to market a new product

Inspection Classifications

- No Action Indicated (NAI) which means no objectionable conditions or practices were found during the inspection (or the objectionable conditions found do not justify further regulatory action),
- Voluntary Action Indicated (VAI) which means objectionable conditions or practices were found but the agency is not prepared to take or recommend any administrative or regulatory action, or
- Official Action Indicated (OAI) which means regulatory and/or administrative actions will be recommended.

Inspections During COVID-19

- Inspections changed significantly during COVID
- Changes are ongoing
- Backlog

Remote Interactive Evaluations

- April 2021 guidance
- A remote interactive evaluation is not the same as an inspection
- No 483 will be issued
- FDA is not requesting requests from facilities

Current Good Manufacturing Practice (cGMP)

- Major part of drug manufacturing is compliance with cGMP requirements
- The regulations are a framework for how to operate

21 CFR Part 210

- Minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

21 CFR Part 211

- Current good manufacturing practice for finished pharmaceuticals
- Minimum requirements for preparation of drug products

High Level

- Personnel qualifications and responsibilities
- Building, facility, and equipment standards
- Control of drug components
- Production and process controls
- Packaging and Labeling Control
- Holding and distribution
- Laboratory controls
- Record and Reports

21 CFR 211.100(a)

- There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

21 CFR 211.160

- Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity.

Observation Examples

Citation Program Area	Cite Id	Reference Number	Short Description	Long Description	Frequency
Drugs	1105	21 CFR 211.22(d)	Procedures not in writing, fully followed	The responsibilities and procedures applicable to the quality control unit are not [in writing] [fully followed]. Specifically, ***	215

Drugs	2027	21 CFR 211.192	Investigations of discrepancies, failures	There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed. Specifically, ***	167

Drugs	3603	21 CFR 211.160(b)	Scientifically sound laboratory controls	Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials] [labeling] [drug products] conform to appropriate standards of identity, strength, quality and purity. Specifically, ***	145

Drugs	1361	21 CFR 211.100(a)	Absence of Written Procedures	There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Specifically, ***	108

Drugs	1213	21 CFR 211.67(a)	Cleaning / Sanitizing / Maintenance	Equipment and utensils are not [cleaned] [maintained] [sanitized] at appropriate intervals to prevent [malfunctions] [contamination] that would alter the safety, identity, strength, quality or purity of the drug product. Specifically, ***	99
Drugs	1883	21 CFR 211.165(a)	Testing and release for distribution	Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the [final specifications] [identity and strength of each active ingredient] prior to release. Specifically, ***	90
Drugs	3585	21 CFR 211.110(a)	Control procedures to monitor and validate performance	Control procedures are not established which [monitor the output] [validate the performance] of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Specifically, ***	81

- Don’t forget FDA guidance – cGMPs are continually being interpreted through guidance

- Look for trends in 483s and enforcement to determine where key cGMP and inspection pitfalls are

Responding to 483 Observations

- So, you survived the inspection, but you got a 483. Now what?
  - Make a plan
  - Act fast, but be thorough (and don’t panic)

- Written corrections need to be implemented
- Repeat observations are not good!

Closing an Inspection

- When an inspection is deemed closed, as Establishment Inspection Report is provided to the establishment

Establishment Inspection Report (EIR)

- An EIR is essentially a narrative of the inspection
- May contain observations that did not warrant being added to a 483

Import Alerts

- Detention Without Physical Examination (DWPE) for products in violation of FDA laws and regulations

Supply Chain Issues

- Supply chain is top of mind for FDA
- It was prior to COVID, but even more so now

What are the Concerns?

- Drug shortages
- Most API manufacturing does not occur in the US
  - API security
  - API manufacturing oversight

Questions?