# Regulation of Drug Manufacturing

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Sidley Austin LLP



# **Establishment Registration**and Drug Listing

#### **Establishment Registration and Listing**

- Must register any "establishment in any State engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs." 21 U.S.C. § 360(b)
- Registration must also include "a list of all drugs
  ... (with each drug ... in each list listed by its
  established name (as defined in section 352(e)
  of this title) and by any proprietary name) which
  are being manufactured, prepared, propagated,
  compounded, or processed ... for commercial
  distribution," 21 U.S.C. § 360(j)

- As a policy matter, the information is intended to provide FDA with the location of drug establishments and information regarding the drugs manufactured at these establishments
- FDA also relies on this information for:
  - Inspections
  - Post-market surveillance
  - Recalls
  - Drug quality reports
  - Adverse event reports
  - Drug import and export
- Failure to comply with these requirements is a prohibited act under FDCA Section 301(p) [21 U.S.C. § 331(p)]

# **Adulteration and Misbranding**

#### **Adulteration**

- Insanitary Conditions. 21 USC 351(a)(2)(A).
  - If drug has been prepared, packed, or held under insanitary . . .
     whereby it may have been rendered injurious to health.
- Not Manufactured in Compliance with Current Good Manufacturing Practice (GMP). 21 USC 351(a)(2)(B).
  - Statutory cGMP and cGMP regulations
- Inferior Strength, Purity, or Quality.
  - Compendial Drugs. 21 USC 351(b).
  - Non-Compendial Drugs. 21 USC 351(c).
- Refusal or delay of inspection. 21 USC 351(j).
  - Limiting or refusing access to facility or records
  - Delaying production of records
  - Records in foreign language with no translation

#### **Current Good Manufacturing Practice (cGMP) for Drugs**

- The purpose of cGMP is to prevent drug product defects by rigorously controlling the manner of production.
  - Includes quality oversight over their suppliers
  - FDA has explicit authority to enforce requirements related to supply chain management
- If manufacturing processes are not compliant, the product is legally deemed to be adulterated
  - Product quality cannot be adequately ensured only by inspecting and testing a finished product because finished-product testing cannot detect all defects.
  - Quality must be built into a product with processes that are well-controlled during design and manufacturing.
- Manufacturers are required to establish and follow quality systems that control each step of the manufacturing process.
  - The goal is to ensure that manufacturing processes consistently produce products that meet predetermined specifications.

#### cGMP Regulations - 21 CFR Part 211

- Quality control unit
- Qualifications of personnel
- Building construction
- Receipt and testing of raw materials
  - Identity testing
- Production controls
  - Process validation
  - Testing of in-process material

- Laboratory controls
  - Method validation
  - Stability testing
- Packaging and labeling of finished products
- Recordkeeping and reporting requirements
  - Master production records
  - Batch production records

#### **Flexibility of cGMP Regulations**

- Conceptual and sometimes difficult to pin down. Descriptive rather than prescriptive.
   General rather than specific. Regulates the manner of accomplishing something. For example:
  - Personnel shall have education, training, and experience to enable them to perform their assigned functions.
  - Each lot of components, drug product containers, and closures shall be sampled, tested, or examined as appropriate.
  - Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures to assure that drug products conform to appropriate standards of identity, strength, quality, and purity.
  - Manufacturing and control processes shall be validated.

### Misbranding

- False or Misleading Labeling. 21 USC 352(a).
  - Labeling may mislead by suggesting that a particular product is safe, when in fact relying on it may be dangerous.
  - United States v. Milstein, 401 F.3d 53, 59-60 (2d Cir. 2005) (label falsely represented that the product was sterile)
- Inadequate Directions for Use. 21 USC 352(f)(1).
  - Backdoor new drug charge. No adequate directions for an Rx drug.
- Dangerous to Health when Used as Labeled. 21 USC 352(j).
  - United States v. Abbott Labs., 505 F.2d 565, 572 (4th Cir. 1974)
     (intravenous solutions contaminated with bacteria were dangerous to health when used as labeled)

# **FDA Inspections**

#### **FDA's Inspectional Authority**

- FDA has broad authority to inspect manufacturing facilities and cGMP records for prescription drugs and nonprescription (OTC) drugs intended for human use. 21 USC 374(a)(1).
  - Primary focus of FDA inspections is on determining whether a firm is in compliance with cGMP
  - Largely a record-review exercise
  - Request cGMP records prior to inspection
  - Refusal is prohibited act (criminal) and per se adulteration of drugs
- Extends to "all things", including "records, files, papers, processes, controls, and facilities" bearing on an establishment's compliance with cGMP
- A cGMP violation does not require evidence that a product does not conform to its specifications, or any evidence of injuries from its use to be legally sufficient.
  - A drug manufactured in violation of cGMP is adulterated "regardless of whether the drug is actually shown to be deficient in some respect." *United States v. Bel-Mar Laboratories, Inc.*, 284 F. Supp. 875, 881-83 (E.D.N.Y. 1968)

### **Examples of What FDA Investigators Review**

- Procedures
- Production, cleaning, and maintenance records
- Validation protocols and reports
- Product Development Reports & Summary
- Annual Product Reports/Annual Product Reviews
- Biological Product Deviation Reports (BPDRs) / Field Alert Reports (FARs)
- Change Controls
- Deviations, non-conformances, OOS results, stability failures, complaints
- Investigations and CAPAs
- Test data generated in Quality Control (QC) Laboratory (Data Integrity)
- cGMP training

### **FDA's Inspectional Authority - Limits**

- BUT FDA's inspectional authority does not extend to:
  - Financial data,
  - Sales data other than shipment data,
  - Pricing data,
  - Personnel data (other than data as to qualification of technical and professional personnel performing functions subject to the FDCA), and
  - Research data (other than data relating to 21 USC 355(i) (investigational new drug), 355(k) (postmarket studies), or 355(j) (ANDA))
- Thus, FDA does not have the authority to inspect every document within a company's possession

#### **FDA's Inspectional Authority - Limits**

- Additionally, an FDA inspection must be at reasonable times and within reasonable limits and in a reasonable manner. See 21 USC 374(a)(1).
  - This generally means that FDA cannot arrive for an inspection well outside of normal business hours and demand entry.
- Similarly, an FDA inspection must "be commenced and completed with reasonable promptness." Id.

#### **FDA Foreign Inspections**

- FDA's authority to inspect foreign facilities and review records does not come from FDA's primary inspection authority, 21 USC 374, but from the agency's ability to exercise enforcement over imported products, 21 USC 381, and commitments made by the sponsors of applications
- Therefore, during foreign inspections, FDA generally concentrates on records pertaining to products that are to be imported into the U.S. or on products that are seeking U.S. approval
  - But FDA investigators do also look to non-U.S. product to find cGMP violations
- 21 USC 351(j): Prohibition against delaying, limiting, or refusing inspection
  - Refusal of foreign inspection grounds for FDA to place facility on Import Alert
  - Import Alert 66-79, "Detention Without Physical Examination of Drugs From Foreign Establishments Refusing FDA Inspection."
- 21 USC 311: Extraterritorial jurisdiction

#### **Logistics of FDA Inspections**

- FDA inspections start with the issuance of a Form FDA 482, Notice of Inspection
  - Recites FDA's inspectional authority
  - Identifies the responsible individual
  - Not issued for international (OUS) inspections
- FDA inspections conclude with the issuance of a Form FDA 483, List of Inspectional Observations
  - Issued to firm management at the conclusion of an inspection when an investigator(s) has observed any conditions that in their judgment may constitute violations of the FDCA
  - Observations should be clear, specific, and significant
  - Not a final determination by FDA that cGMP violations exist
- Companies have 15 business days to respond to a Form FDA 483
  - Opportunity to explain findings, provide context, and, if needed, correct the record
  - Present corrective and preventative actions (CAPAs) to address observations

## Form FDA 482 Notice of Inspection

	ATIONS OPERATIONS MANUAL 2021				EXH				
OF	RM FDA 482 NOTICE OF INSPECTION								
		1. DISTRICT OFFICE ADDRESS 8	PHONE NO	).	,				
	DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	1431 Harbor Bay Parkway Alameda, CA 94502 (510)337-6700							
_	2. NAME AND TITLE OF INDIVIDUAL	3 DATE			-				
	Helen E. Castro, President		0	07/28/13					
	4. FIRM NAME			7:30	-				
то	ABC Bread Company			7:30	a.m.				
	6. NUMBER AND STREET 579 Main Street	3		50.50					
	7. CITY AND STATE & ZIP CODE	1-0	HONE NO. 8	p.m.					
	Richmond, CA 94805		0.1	(510) 123-45					
	otice of Inspection is hereby given pursuant to Section S.C. 374(a)11 and/or Part F or G. Title III of the Public Health			nd Cosmetic	cs Act [21				
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1	National Ombudsman's Office that receives comments from sr	nall businesses about Federal ag	ency enfon	cement actio	ns. If you				
ŀ	wish to comment on the enforcement actions of FDA, CALL (88	8) 734-3247. The website address	s is www.st	a.gov/ombud	dsman.				
	FDA has an Office of the Ombudsmen that can directly assist small business with complaints or disputes about actions of the FDA That office can be reached by calling (301) 796-8530 or by email at ombuds@cc.fda.gov.								
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F	For industry information, go to www.fda.gov/oc/industry.								
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#### FDA Form 483s

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    has observed any conditions that in their judgment may constitute violations of the FDCA
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- Companies have 15 business days to respond to a Form FDA 483
  - Opportunity to explain findings, provide context, and if needed, correct the record
  - Present corrective and preventative actions (CAPAs) to address observations
  - Chance to address agency concerns in advance of site classification

### Form FDA 483 List of Inspectional Observations

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DISTRICT ADDRESS AND P	ONE NUMBE	R	TOOD AND DAG	AJ ALMERICA I	DATESHOP INSPECTION				
Detroit District Off	fice				2/18-3/5/2021, 3/16/2021				
300 River Place, S	uite 5900				FEI MARKER				
Detroit, MI 48207	313-393	-8100			1819470				
Kenneth A. Whitel			Operations						
FRUNAVE				STREET ADDRESS	JORES				
Eli Lilly and Comp				1555 S. Hard					
Indianapoli:		46205		TYPE ESTABLISHM					
Indianapolis	3, 114	40203		Sterile Human Drug Manufacturer					
OBSERVATI	ON 2								
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The observations of objectionable conditions and practices listed on the front of this form are recorted:

- 1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
- To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employed making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, devoice, or cosmetic in such establishment (f) consists in whole or in part of any fifthirty, putting, or decomposed substance, or (2) has been prepared, packed, whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."

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#### **Search Warrants**

- Administrative Search Warrant
  - FDA does not routinely request warrants for administrative inspections
  - Used to gather information at domestic facilities when inspection is refused
  - Preemptive inspection where history of refusal
  - For drug products, FDA typically relies on adulteration provision, 21 USC 351(j) to prevent refusals
- Criminal Search Warrant
  - OCI responsible for working with U.S. Attorney's Office/Department of Justice
  - Obtained under Federal Rules of Criminal Procedure 41 upon showing of probable cause

#### **Photographs and Recordings**

- FDA considers photographs and recordings to be "an integral part of an FDA inspection because they present an objective and contemporaneous representation of facility conditions."
  - Impeding photography may be considered limiting an inspection, causing products to be adulterated
  - May be denied if there is a reasonable explanation, e.g., photography would negatively impact product quality

#### **Affidavits and Declarations**

- FDA inspectional authority allows review of documents, does not require creation of documents, making declarations, or swearing affidavits
  - Refusal does not render product adulterated and FDA cannot seek an administrative warrant
- FDA may request an affidavit to document material facts, such as movement of goods or events effecting condition
  - FDA typically prepares affidavit and has affiant read, correct, and sign
  - If individual refuses to read, FDA will read it
  - If individual refuses to sign, FDA will document refusal
- Affidavits and declarations during inspections are statements and if false, may lead to prosecution under 18 U.S.C. 1001

## **Types of Inspections**

- Surveillance Inspection
- For Cause Inspections
- Pre-Approval/Pre-License Inspections
- Post-Approval Inspections

#### **Pre-License and Pre-Approval Inspections**

- Additionally encompasses a review of:
  - All relevant data submitted with BLA or supplement
  - Verification of manufacturing history contained in submission
  - Observation of processes, manufacturing, and testing compared against submission
  - Review of product process, controls, analytical testing, and process validation
  - Review of facility and process changes not covered in submission with a bearing on product or manufacturing
  - Review of product development data
  - Out of specification batches/lots for completeness of investigation
  - Stability data and specification verification
  - New manufacturing areas, equipment, or utilities
  - Verification of raw material and component testing
  - Verification of product's incorporation into quality system
  - Shipping validation for drug substance and drug product
  - Procedures for reporting of Biological Product Deviation Reports and Adverse Experience Reports

#### **Classification and Closeout of Inspections**

- Inspectional Classifications:
  - Official Action Indicated (OAI)
  - Voluntary Action Indicated (VAI)
  - No Action Indicated (NAI)
- Consequence of OAI inspection may include:
  - Untitled/Warning Letter
  - Regulatory Meeting
  - Administrative Detention/Seizure/Injunction
  - Import Alert
  - Recalls
  - Complete Response Letters/Application Withdrawals
  - Criminal Prosecution
- Establishment Inspection Report released once inspection deemed closed
  - FMD-145 Letter
  - Closed when agency decides against enforcement or enforcement action complete

#### **COVID-19 and FDA Inspections**

- Covid-19 had significant impact on FDA inspections
  - Suspension of on-site inspections except mission critical inspections
  - Pre-announced inspections
- Alternative evaluation tools
  - Remote regulatory assessments
  - Mutual Recognition Agreements
  - Requests for records in lieu of inspection
- FDA is now performing routine inspections, including unannounced inspections domestically and in most foreign countries