Regulation of Drug Manufacturing

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FDLI

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)]

FDA, Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers Guidance for Industry, (Oct. 2019);
Drugs Intended for Human Use That Are Improperly Listed Due to Lack of Annual Certification or Identification of a Manufacturing Establishment Not Duly Registered With the Food and Drug Administration; Action Dates, 84 Fed. Reg. 40417, 40417 (Aug. 14, 2019).

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.*

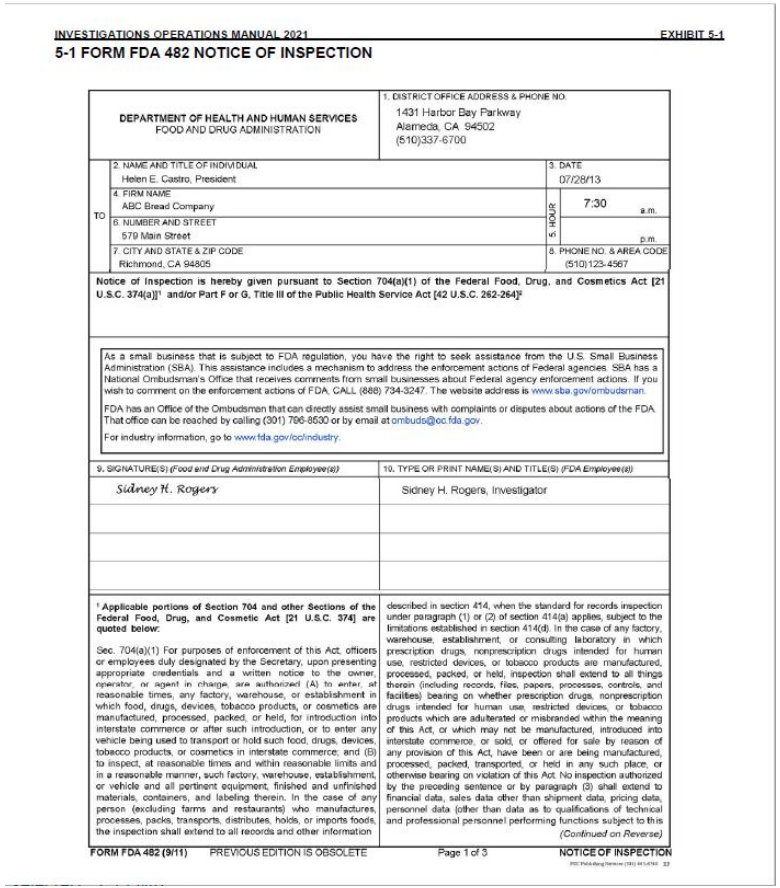
FDA Foreign Inspections

- 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



INVESTIGATIONS OPERATIONS MANUAL 2021 EXHIBIT 5-1

5-1 FORM FDA 482 NOTICE OF INSPECTION

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	1. DISTRICT OFFICE ADDRESS & PHONE NO. 1431 Harbor Bay Parkway Alameda, CA 94502 (510)337-6700
TO: 2. NAME AND TITLE OF INDIVIDUAL Helen E. Castro, President	3. DATE 07/28/13
4. FIRM NAME ABC Bread Company	5. HOUR 7:30 a.m. p.m.
6. NUMBER AND STREET 579 Main Street	
7. CITY AND STATE & ZIP CODE Richmond, CA 94805	8. PHONE NO. & AREA CODE (510)123-4567

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetics Act [21 U.S.C. 374(a)][1] and/or Part F or G, Title III of the Public Health Service Act [42 U.S.C. 262-264][2]

As a small business that is subject to FDA regulation, you have the right to seek assistance from the U.S. Small Business Administration (SBA). This assistance includes a mechanism to address the enforcement actions of Federal agencies. SBA has a National Ombudsman's Office that receives comments from small businesses about Federal agency enforcement actions. If you wish to comment on the enforcement actions of FDA, CALL (888) 734-3247. The website address is www.sba.gov/ombudsman.

FDA has an Office of the Ombudsman 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@oc.fda.gov.

For industry information, go to www.fda.gov/oc/industry.

9. SIGNATURE(S) *(Food and Drug Administration Employee(s))*	10. TYPE OR PRINT NAME(S) AND TITLE(S) *(FDA Employee(s))*
Sidney H. Rogers	Sidney H. Rogers, Investigator

[1] **Applicable portions of Section 704 and other Sections of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374] are quoted below:**

Sec. 704(a)(1) For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, tobacco products, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, tobacco products, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein. In the case of any person (excluding farms and restaurants) who manufactures, processes, packs, transports, distributes, holds, or imports foods, the inspection shall extend to all records and other information described in section 414, when the standard for records inspection under paragraph (1) or (2) of section 414(a) applies, subject to the limitations established in section 414(d). In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products are manufactured, processed, packed, or held, inspection shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products which are adulterated or misbranded within the meaning of this Act, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this Act, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this Act. No inspection authorized by the preceding sentence or by paragraph (3) shall extend to financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualifications of technical and professional personnel performing functions subject to this

(Continued on Reverse)

FDA Form 483s

- **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
  - Chance to address agency concerns in advance of site classification

Form FDA 483 List of Inspectional Observations

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Detroit District Office 300 River Place, Suite 5900 Detroit, MI 48207 313-393-8100	2/18-3/5/2021, 3/16/2021
	FEI NUMBER 1819470

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Kenneth A. Whitehead, Vice President IPM Operations

FIRM NAME	STREET ADDRESS
Eli Lilly and Company	1555 S. Harding St.
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Indianapolis, IN 46285	Sterile Human Drug Manufacturer

OBSERVATION 2
Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed.

Specifically,

A. Individual RAB (b) (4) on the aseptic vial line are not tracked. The firm stated the (b) (4) are replaced every (b) (6) while (b) (4) integrity testing is performed (b) (4) . Failures in (b) (4) integrity are not considered deviations and are not investigated. Numerous (b) (4) failures were found in the Deviation Observation log:

Observation #	Date	Line
TR 40209421	08 FEB 21	B103 Vial Filling
TR 40208503	06 FEB 21	B103 Vial Filling
TR 40192846	17 DEC 20	B103 PFS
TR 40188205	06 DEC 20	B103 Vial Filling
TR 40184073	20 NOV 20	B103 PFS
TR 40174573	23 OCT 20	B103 PFS
TR 40174245	21 OCT 20	B103 Vial Filling
TR 40167253	22 SEP 20	B103 PFS
TR 40164233	21 SEP 20	B103 Vial Filling
TR 40047970	12 JUL 19	B103 Vial Filling

(b) (4)

Due to the high rate of failed RABS (b) (4) Tests occurring since September 2020 on the PFS and the Vial Filling lines in B103, a trend report was initiated on 16 Dec 20. This trend is still awaiting investigation.

SEE REVERSE OF THIS PAGE	Robert Ham, Investigator Sandra Boyd, Investigator Muna Algharibeh, Investigator Rafeeq Habeeb, Investigator	RJH MA X RAH	3/16/2021

FORM FDA 483 (09/08) PREVIOUS EDITION OBSOLETE **INSPECTIONAL OBSERVATIONS** PAGE 4 OF 13 PAGES

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. 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 employee 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, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."

FORM FDA 483 (9/08)

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