Introduction to Drug Law and Regulation: Regulation of Drug Manufacturing

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FDLI

Drug Manufacturing

- Applies to both small molecule (traditional) drugs, large molecule (biologic) drugs
- Applies to Active Pharmaceutical Ingredients (API) at the level of the statute, but only to finished drug products at the level of the regulations
- “Manufacturing” should be thought of as inclusive of all GMP-governed activities, not just hands-on product contact

Adulteration

- Includes:
  - Contamination: 21 USC §351(a)(1)
  - Insanitary conditions: 21 USC §351(a)(2)(A)
  - Failure to comply with GMP: 21 USC §351(a)(2)(B)
  - Failure to meet one of its specifications: 21 USC §351(b) for Compendial (USP) drugs or 21 USC §351(c) for drugs under NDA
  - Miscellaneous other adulteration provisions

GMP

- 21 USC 351(a)(2)(B): "A drug…shall be deemed to be adulterated…if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess"
- Added to the FDCA via the Kefauver-Harris amendments in 1962
- First GMP regulation promulgated June 20, 1963 as 21 CFR 133 (*see Federal Register* Thursday, June 20, 1963 at p. 6385

And by the way….

- The FDA Safety and Innovation Act of 2012 added the following to 21 USC 351(a)(2)(B):
- “Section 501 (21 U.S.C. 351) is amended by adding at the end the following flush text: "For purposes of paragraph (a)(2)(B), the term 'current good manufacturing practice' includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.“
- Intent was to strengthen control of the supply chain by manufacturers

Drug GMP Regulations

- 21 CFR 210: Mostly scope and definitions; applies to both API and finished drug products
- 21 CFR 211: Applies to both human and veterinary finished drug products and also biologic drugs, including investigational drug products and placebos; limited exemption for Phase 1 investigational drugs
- 21 CFR 212: Specialized GMP for Positron Emission Tomography (PET) drugs
- 21 CFR 225 and 226: Medicated animal feeds and premixes for medicated feeds
- 21 CFR 606 and 640: Human blood and blood components for transfusion
  - Where there is conflict or ambiguity, the more specific requirement supersedes the more general

API and Phase 1 Drugs

- No binding regulation for API; statutory GMP requirement still applies
  - Guideline ICH Q7 is accepted world wide as the “GMP” for API though not a regulation in the US
- Another guideline covers most Phase 1 drugs unless already marketed or in Phase 2 or 3 simultaneously (rare exceptions); statutory requirement still applies

Interplay between adulteration provisions and GMP

- GMP violations can and do lead to:
  - Contamination (microorganisms, chemical, foreign matter, etc.)
  - Insanitary conditions
  - Failure to meet specifications
  - Even misbranding, if the wrong label is applied (mislabeling) which is both a GMP violation and a form of misbranding

Meaning of "CGMP"

- Acronym taken directly from the statute
- CGMP, cGMP and just GMP are used interchangeably; all mean the same thing
- "Although the practices must be 'current' in the industry, they need not be widely prevalent. Congress did not require that a majority or any other percentage of manufacturers already be following the proposed mandated practices, as long as it was a current good manufacturing practice in the industry, i.e., that it had been shown to be both feasible and valuable in assuring drug quality." - Reply to public comment, *Federal Register*, Vol. 43, No. 190, Friday, Sept. 29, 1978, comment #17

“Current, Good”…??

- Terms “current” and “good” were challenged by a claimant in a 1973 seizure action brought by FDA as unconstitutionally vague and overly broad;
- 7th Circuit disagreed on appeal, *see United States v. An Article Of Drug Consisting Of 1 Drum Of 104,000 Tablets, More Or Less, Labeled In Part: (Drum) "Name White Quadrisect…”* 484 F.2d 748
- Terms have not been challenged since

Structure of the Regulations

- Huge topic; no time to cover in depth
- See cited regulations for details
- Generally speaking, regulations require control over facilities, equipment, materials, laboratory operations, packaging and labeling, distribution and shipment, and the number, health and qualifications of employees performing governed operations
- Regulations require that companies have written procedures and that they follow them; in this way, the generalities of the regulations can be made more specific to a given site, product, process, etc.

The Role of Written Procedures in GMP

- 21 CFR 211.100(b) says: "Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified."
- IMPORTANT - Note this says "written procedures", which includes SOPs, Work Instructions, Job Aids, or whatever else you choose to call them! It is not true that if you do not call something an SOP you don't have to follow it!
- By writing SOPs, companies are writing a document that becomes legally enforceable by the FDA, so SOPs are very important documents in GMP compliance.
- You can't change the GMP regulations, but you can change your SOPs if they are not working well for you.

FDA Inspections

- FDA enforces GMP (and most everything else) through inspections
- FDCA, 21 USC §374(a) imparts both general authority to "enter and inspect" as well as certain specific authority for drug manufacturing sites
- Most of the authority derives from the Factory Inspection Amendments of 1953, with some later amendments

Reasons for Inspections

- Routine periodic surveillance
- For cause
  - Follow up prior violative inspection
  - Consumer complaints
  - Whistleblowers
  - Competitor complaints
  - Company is conducting a recall
  - Filing of field alert under 21 CFR 314.81/314.98
  - Any of several other for cause reasons

Types of Inspections

- General GMP inspection
- Pre-approval or Pre-license (biologic) inspection
- Industry survey (more surveillance than compliance)
- Any of a number of other reasons

GMP vs PAI

- In addition to GMP compliance, a PAI evaluates:
  - Readiness for commercial manufacturing (which includes GMP compliance)
  - Ability to conform to CMC commitments
  - Application data integrity

Warrantless Search?

- Yep.
  - Pharmaceutical industry is a "closely regulated" industry "long subject to close supervision and inspection," *see* Colonnade Catering Corp. v. United States, 397 U. S. 72, 397 U. S. 74, 397 U. S. 77
- Allowable with certain limitations and controls…
  - Display credentials (identification)
  - Issue a Notice of Inspection to the “owner, operator or agent in charge” (this varies a lot in practice)
  - Reasonable time, reasonable limits, reasonable manner
  - Reasonable time = Whenever FDA-regulated activities are taking place at the site

In Scope for an FDA Inspection

- “[a]ll pertinent equipment, finished and unfinished materials, containers, and labeling therein…” and also…
- “[I]n the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, …are manufactured, processed, packed, or held, the 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, …which are adulterated or misbranded within the meaning of this chapter, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this chapter, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this chapter.”

Out of Scope for an FDA Drug Manufacturing Inspection

- "[N]o 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 qualification of technical and professional personnel performing functions subject to this chapter), and research data (other than data relating to new drugs, antibiotic drugs, …subject to reporting and inspection under regulations lawfully issued …"

OK So what about…

- Things not specifically cited?
  - Generally, discretionary on the part of the inspected location. Most people will cooperate with any reasonable ask which does not clearly fall within an exempted category.
- Photographs
  - Controversial and long-battled area. FDA takes the position that photographs are sometimes necessary to a "reasonable" inspection and are thus permitted by the "reasonable manner" rule. Industry has often objected, sometimes loudly, and this area has been a battleground for ages.
  - Best approach is to permit limited photography with the company taking duplicate photos at the same time. Many companies follow this approach; FDA is accustomed to it and will ordinarily agree.
  - FDA can and sometimes does pursue an administrative inspection warrant to compel photography in the face of a refusal.

Administrative Inspection Warrants

- These are quite rare
- Not a search warrant
- Court order affirming FDA's statutory authority
- Does not change FDA's statutory authority, but may be somewhat more specific, such as compelling photography
- A Deputy US Marshall normally accompanies FDA on service of the warrant and may arrest anyone who persists in refusal

Avoid Refusals!

- If an FDA Investigator asks “Are you refusing me permission to…”?
  - Don’t say yes unless you are empowered to speak on behalf of the company
  - Involve counsel in the decision to refuse
  - Best to say no, not refusing, but first need to confer with senior leadership and counsel
  - Refusal is a prohibited act [21 USC (f) or (e), depending] but criminal charges virtually never brought
  - Refusing, obstructing, delaying or limiting an inspection can result in product made at the site being deemed adulterated, 21 USC 331(j) as amended by FDASIA in 2012

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OREGON

WARRANT FOR INSPECTION UNDER THE

FEDERAL FOOD, DRUG, AND COSMETIC ACT

To James C. Henry or any other authorized United States Food and Drug Investigator:

Application having been made by James C. Henry, United States Food and Drug Investigator, for a Warrant for Inspection of the establishment described as:

Priority Products, Inc.
2300 SE Belmont and
2230 SE Morrison
Portland, Oregon 97214

Pursuant to the Federal Food, Drug, and Cosmetic Act 21 U.S.C. 374, you are authorized to enter the above-described premises at reasonable times during ordinary business hours, and to inspect in a reasonable manner and to a reasonable extent, the establishment and all pertinent equipment, finished and unfinished materials, containers and labeling therein. Samples may be collected and photographs taken.

FORM FDA 470 (3/83) PREVIOUS EDITION IS OBSOLETE

A return shall be made to this Court within 10 days following completion of the inspection.

Dated: _____

_____

United States Magistrate

Foreign Inspections

- FDA routinely conducts ex-US inspections
- FDCA inspection authority does not apply but adulteration and misbranding provisions do
- General procedure is the same as domestic, except that the Notice of Inspection is not issued
- Unannounced inspections are rare, situation is complicated since the mandatory entry authority does not apply, but FDA has managed to do unannounced inspections with cooperation from local authorities
- For further details see https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/field-management-directives/foreign-inspection-program

Import Detention and Refusal

- Upon offer for entry into US Commerce, FDA may detain, examine, test and/or refuse entry of products subject to its jurisdiction, *see* 21 USC §381 et. seq.
- The standard is an "appearance" of a violation; very low bar to cross
- FDA works in cooperation with DHS/Customs to effect detention and refusal, see https://www.fda.gov/industry/import-program-food-and-drug-administration-fda for details

Inspection Classification

- After the inspection a comprehensive narrative report (the Establishment Inspection Report or “EIR”) is written and reviewed
- The EIR is classified as:
  - No Action Indicated (NAI),
  - Voluntary Action Indicated (VAI), or
  - Official Action Indicated (OAI)

Classification Meaning

- NAI: usually no 483 issued, if so, observations are minor in nature and few in number
- VAI: relatively minor observations but need prompt voluntary attention; no escalation by FDA
- OAI: some formal escalated response, most often a Warning Letter, will follow; pending market applications will be put on hold; more serious sanctions such as seizure, injunction or prosecution may result, but these are relatively rare cases
- For biologics, license suspension or revocation are options

“Decisional Letters”

- For drug GMP inspections only (not PAIs), FDA sends out so-called “decisional letters” communicating the classification status, goal is to send the letter within 90 days of inspection closure
- NAI letter: https://www.fda.gov/media/113096/download
- VAI letter: https://www.fda.gov/media/113124/download
- OAI letter: https://www.fda.gov/media/113121/download

What is an FDA-483?

- Report issued to an inspected company at the conclusion of an inspection which lists the observations made by the FDA employee(s) conducting the inspection which in their opinion may, after subsequent review within FDA, be deemed to be violations
- It is NOT a final agency determination of noncompliance
- It IS a serious matter which requires priority attention
- Section 704(b) of the FDCA states in part: "Upon completion of any … 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 judgment, indicate that any …product … 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."

What about other kinds of observations?

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.

Reverse side of the 483 reveals twofold purpose of the form.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC374(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 the health. A copy of such report shall be sent promptly to the Secretary."

The Written 483 Response

- **In the *Federal Register* of August 11, 2009 FDA posted its policy regarding timeliness of the written response to a 483.**

- **Key point:**
- **If you want your response to be considered by FDA as part of their overall decision whether to issue a Warning Letter, you must get your written response to the agency within 15 business days.**

- **The law does not require that you respond to a 483 at all, either orally or in writing. But everyone does, almost without exception, and if you do not, it will be seen as very anomalous and quite negative.**

The Written 483 Response

An effective outline for response to each item…

1. In response to this observation, we are taking the following actions: [list what you are doing]

2. We believe this approach is reasonable because [state]:
   a) Your assessment of the reason(s) why the observation occurred; "root cause"
   b) Your assessment of the impact on product quality
   c) Your assessment of the scope of impact (other batches, other products) and how you determined the scope

3. We will complete these actions by [date]

4. We will take the following steps to ensure these actions had the intended effect [list; generally, this will be audit or monitoring]

What is a "Remote Interactive Evaluation"?

- In the US FDA context, a Remote Interactive Evaluation (RIE) is NOT an "inspection"!
- Why not?
  - FDA's lawful inspection authority was primarily written into the Food, Drug and Cosmetic Act (FDCA) in 1953 (with one exception)
  - The law is based on the assumption that an "inspection" is an in-person event; authority conferred upon FDA by law is designed for that context
  - There are several requirements FDA must comply with to do an inspection lawfully
  - If FDA does not do those things, the evidence gathered during an inspection is tainted and could be suppressed in the event of inspection related litigation
  - For these reasons and some others, FDA chooses not to use the term "remote inspection" or anything like that to refer to assessments conducted remotely

Why are Remote Interactive Evaluations needed?

- The COVID-19 pandemic has made it difficult, at times impossible, to conduct traditional inspections:
  - The virus presents an exposure risk to FDA employees
  - The presence of an FDA representative on site could present a risk to company employees
  - Many companies are in partial or complete shutdown, or have strictly limited operations
  - Many FDA offices are also shut down with employees operating from remote locations
  - Many companies have prohibitions or limitations on visitors; while these ordinarily would not apply to regulators, FDA seeks to cooperate and minimize risk to all concerned to the best of their ability and consistent with public health protection
  - The need for FDA to continue to advance its mission of consumer protection and evaluation of new products for approval continues
  - Remote assessments help to temporarily bridge the gap between the ongoing need and the limitations

Are Remote Interactive Evaluations mandatory or voluntary?

- Strictly speaking, they are voluntary; FDA cannot force anyone to allow them
- Not agreeing to one may have adverse consequences, including delays or denials of product application approvals
- In one specific respect there is a mandatory element:
  - For drug manufacturing sites, FDA has authority under Section 704(a)(4) of the FDCA to demand that records be produced and provided to the agency "…in advance of or in lieu of an inspection…"; in other words, such a request is NOT an inspection
  - These requests are sent to the company on form FDA-4003; when the company complies with the request, a receipt is sent on form FDA-4003a
  - Failure to submit records requested under section 704(a) may cause the company's product(s) to be deemed adulterated within the meaning of section 501(j) of the FDCA
    - For a non-US location, this can result in import detention or refusal of entry into the United States
  - The entire 704(a)(4) process is described in FDA "Staff Manual Guide" (SMG) 9004.1
    - You can get a PDF copy here: https://www.fda.gov/media/124338/download

How do Remote Interactive Evaluations differ from inspections?

Inspections

- On site
- In the US, form FDA-482[1] is issued
- Form FDA-483 issued for observations
- When the file is closed, courtesy copy of the full report (EIR) is sent to the company

Remote interactive evaluations

- Off site
- No FDA-482 is issued
- Observations are reported orally (no 483)
- A report (not called an EIR) is prepared, but is not routinely sent
  - Copy can be requested through FOIA

[1]Form FDA-482 is the Notice of Inspection; not used outside the United States, only for domestic inspections

Key References

- Compliance Programs: *See* *https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-compliance-programs*
- ICH "Q" Guidelines*: http://ich.org NB ICH Q7, Q8, Q9, Q10, Q11, Q12*
- *Guidance for Industry: Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency*, FDA, April, 2022 available on line at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/remote-interactive-evaluations-drug-manufacturing-and-bioresearch-monitoring-facilities-during-covid
- FDA "Staff Manual Guide" (SMG) 9004.1 https://www.fda.gov/media/124338/download (FDA's procedure for records demands and responses by industry)
- Updated "Resiliency Roadmap for FDA Inspectional Oversight" https://www.fda.gov/media/148197/download
- *Guidance for Industry: Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency - Questions and Answers*, FDA, April 2020, https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-frequently-asked-questions

Thank You!!


thank you
danke
謝謝
ngiyabonga
teşekkür ederim
спасибо
dank je
gracias
tapadh leat
bedankt
dziękuje
hvala
mauruuru
machchakkeram
go raibh maith agat
obrigado
sukriya
kop khun krap
arigalò
dakujem
terima kasih
grazie
merci
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мерси