Post-Approval Inspections

CDER Small Business - Regulatory Education for Industry (REdI)  
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The presentation will summarize what to expect from an FDA inspection of your manufacturing facility. You will learn about the different kinds of inspections FDA performs, the standards by which your facility will be assessed (e.g., the Current Good Manufacturing Practices (CGMPs) regulations), and what happens when deviations are uncovered. The top 5 drug quality violations will be revealed with insight given on how to make sure your facility is not committing them.
Agenda

• Drug Law: Basic Elements +
• FDA inspection types and techniques
  – main types of inspections post-approval
  – possible outcomes
• Hosting an inspection
  – before, during, and after
  – dos and don’ts
• Top 5 Quality Problem Areas

• Questions
What is a drug?

The term “drug” means\(^1\) …

A) An article *recognized* in the US Pharmacopeia (USP) or Homeopathic Pharmacopeia of the US (HPUS) or National Formulary (NF).

B) Articles *intended* for use in the *diagnosis, cure, mitigation, treatment, or prevention* of disease in man or other animal.

C) Articles *(other than food) intended* to affect the structure or function of the body of man or other animal.

D) Articles *intended* for use as a *component* of any article specified in A, B, or C.

\(^1\) As defined in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act
‘Marketing’ Status

- IND (clinical trial materials)
- NDA (new drug) or BLA (biologic) or ANDA (generic)
  - Rx and OTC
- OTC Monograph (e.g., toothpaste w/ fluoride, antiperspirant, aspirin)
- Unapproved drug
- Homeopathic
- Medical gas (certificate or A/NDA)
Legal Bases for CGMP

Section 501(a)(2)(B):

“A drug... shall be deemed to be adulterated if 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 Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.”
Legal Bases for CGMP

FDASIA 2012 amendment to section 501:

CGMP “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.”
“Current” in CGMP...

• Any practice can be “CGMP”
  – dynamic; flexible enough to accommodate innovation
  – need not be prevalent
  – both “feasible and valuable” in assuring quality

• Who decides?
  – collaborative; notice/comment process; courts

• Based on what?
  – risk; cost/benefit; response to problems
CGMP Regulations for Finished Pharmaceuticals – Brief History

- **1962**: Authorizing legislation passed
- **1963**: Initial version; several minor changes followed
- **1978**: Major revision; most remains in current version
- **1979 – 2008**: Many revisions, incl. tamper-evident packaging, label control, reserve samples
- **Pending revisions?**: address “oversight” and “safety of raw materials” added by FDASIA in 2012?
CGMPs in manufacturing, processing, packing, or holding of drugs; General

• 210.1 – **Minimum standard for methods** used in, and **facilities or controls** to be used for the manufacture, processing, packing or holding of a drug to ensure that such drug meets **requirements of the act** as to safety, and has the identity and strength and meets the quality and purity it purports

• 210.2 – INDs: Phases II & III; only guidance for Phase I

• Definitions
CGMP for *Finished Pharmaceuticals*

21 CFR Part 211

- **Subpart A** - General Provisions
- **Subpart B** - Organization and Personnel
- **Subpart C** - Buildings and Facilities
- **Subpart D** - Equipment
- **Subpart E** - Control of Components and Drug Product Containers and Closures
- **Subpart F** - Production and Process Controls
- **Subpart G** - Packaging and Labeling Controls
- **Subpart H** - Holding and Distribution
- **Subpart I** - Laboratory Controls
- **Subpart J** - Records and Reports
- **Subpart K** - Returned and Salvaged Drug Products
Subpart A - General Provisions

- **Minimum standards** for human and animal finished pharmaceuticals

- **Biologics** – applicable; also 21 CFR Part 600+
Subpart B - Organization and Personnel

• Quality unit: Responsible for… almost everything
• Operators are to be trained and in sufficient number for the work
• Operators must not contaminate the process/product: wear appropriate clothing, refrain from activities when ill, wash their hands
Subpart C - Buildings and Facilities

- Designed to facilitate cleaning and maintenance
- Be big enough and have separation to prevent mix-ups and cross contamination
- For aseptic processes: have smooth walls and ceiling, temperature and humidity controls, HEPA filtration and under positive pressure air, environmental monitoring, cleaning and disinfection processes
- **PENICILLIN** will be in a **separate facility** with **SEPARATE HVAC**
Subpart C - Buildings and Facilities

• Adequate controls for air pressure, microbial, dust, humidity and temperature for manufacture, processing, packing or holding
• Recirculation – beware of risk for cross contamination
• Lights, potable water supply, drains have air break or mechanism to prevent back-siphonage
• Keep the place clean and keep it maintained
Subpart D - Equipment

• Appropriate equipment for intended use that isn't reactive, additive, or absorptive so as to alter safety, identity, strength, quality or purity

• Keep it clean and sanitized appropriate to prevent contamination of the product

• Keep it maintained and identified
Subpart D - Equipment

• Electronic equipment: calibrated, inspected to ensure proper performance.
  – Changes made by authorized person
  – See electronic signatures in 21 CFR 11
    • Guidance for Industry, *Part 11, Electronic Records; Electronic Signatures - Scope and Application*:

• Filters: not fiber releasing; no asbestos filters
Subpart E - Control of Components and Drug Product Containers and Closures

- Components, containers and closures are handled to prevent contamination, stored off the floor, appropriately identified as to status (quarantined, approved, rejected)
- Examined upon receipt, stored under quarantine until released
- Each lot of component is withheld from use until sampled (a representative sample), tested and released by quality
- Sampled and examined as described
Subpart E - Control of Components and Drug Product Containers and Closures

• At least one test to determine identity
• Tested to ensure meets specifications or accepted with a CoA from a manufacturer that has been established (historic use, testing, audits) as a reliable source
• Checked for contamination or filth, and for micro as appropriate
• First-in, first-out
• Containers and closures should be appropriate to preserve quality and not harm the product
Subpart F - Production and Process Controls

- Written procedures “designed to assure” that drug products meet established specifications
  – are followed and documented at the time of performance; deviations justified
- Formulated to not less than 100% LS
- Components identified, examined by a 2nd person before added
Subpart F - Production and Process Controls

• Yields checked
• Equipment status identified
• In-process checks
• Hold times
• Reprocessing – allowed, but controlled and quality approved
• Prevent objectionable microorganisms (sterile or non-sterile)
Subpart G - Packaging and Labeling Controls

- Finished product examined and retains pulled
- Tamper evident packaging (for OTC products)
- Expiration dating – shall bear and be supported by stability
  - Exemption for homeopathic, allergenic extracts, INDs, certain OTCs
Subpart H - Holding and Distribution

• Controls for
  – Proper storage (temperature and humidity) to protect: identity, strength, quality, purity.
  – Keep separated until released

• First-in, first-out

• System to facilitate recall
Subpart I - Laboratory Controls

• Establish “scientifically sound” specifications, standards, sampling plans, test procedure
• Calibrate instruments
• Test each batch of drug product with validated test methods
• Stability program
  – Exceptions: homeopathic; allergenic extracts
Subpart I - Laboratory Controls

• Special tests
  • Sterility and pyrogen tested, if relevant
  • Ophthalmic ointments tested for foreign/abrasive particles
  • Controlled release products checked for rate of release (i.e., multipoint dissolution)

• Keep/check reserve samples
• Test non-penicillin products for penicillin when *reasonable possibility* of cross-contamination
Subpart J - Records and Reports

- Keep records for production, distribution and make available for inspection
- Conduct *at least annual* review of each drug product for changes (look at batch records, complaints, recalls and investigations)
- Tell management (in writing) if there is a problem (*e.g.*, complaints or returns)
- Keep a log for the use and cleaning of equipment
- Keep component, container, closure, and labeling records
Subpart J - Records and Reports

- Keep and control master production records (*full signature* and secondary check)
- Master record has the name strength and description, the name and weight of the active, complete list of components
- Batch production records for each batch is an accurate reproduction of the master record.
- Document significant steps in the manufacture, processing, packing, and holding
  - dates, people, equipment, weights, in-process results, inspections, yields, labeling, and investigations
  - include any changes, with appropriate justification
Subpart J - Records and Reports

• Production records to be reviewed/approved by quality control unit (before released or distributed) with all discrepancies investigated

• Laboratory data for how it was tested (all methods sampling, weights, calculations, and comparison to standards)

• Distribution records with lot numbers

• Complaint procedures and investigations when necessary
Subpart K - Returned and Salvaged Drug Products

• Returned goods are controlled. If in doubt, returned product shall be destroyed unless tests, examination, and investigation can prove identity, strength, quality, or purity.

• Salvage (product subject to storage extremes, humidity, fumes, pressure, age or radiation, fires, accidents) only if tests and inspection show it has identity, strength, quality, purity.
Which facilities routinely get inspected?

- dosage form ✓
- active pharmaceutical ingredient ✓
- excipient ?
- clinical trial material ?
- “biotech” (e.g., MaB; therapeutic proteins) ✓
- medical gas processors and transfillers ✓
- contract packagers/labelers ✓
- contract sterilizers ✓
- contract laboratories ✓
- ‘export-only’ involved in any of above ✓
The visit of the inspectors shall be unannounced.

It shall be the duty of the inspectors to call first upon the head of the establishment or member of the firm, stating the object of their visit.

The proprietor of the establishment being inspected shall extend every facility to the inspectors to aid them in their work. The inspectors shall be permitted to examine all portions of the premises, appliances, methods, stables, barns, warehouses, records, and, if requested by the inspectors, shall be shown the methods employed in actual operation.

The inspectors are authorized, when they consider it necessary, to interrogate the proprietor, members of the firm, and employees of the establishment under oath.
2013 General Inspection Protocol

• Arrive unannounced

• Ask for the most responsible person
  – show credentials (i.e., special photo ID)
  – issue a written “Notice of Inspection” (FDA 482)
  – briefly state objective of the inspection

• Conduct inspection (facility/records/people)
  – issue written “Inspectional Observations” (FDA 483) when warranted
  – collect samples, as needed (FDA 484)
  – take affidavits, as needed
Post-Approval Inspections

• Surveillance (Routine) CGMP Inspections
  – comprehensive; risk-based frequency
• For-Cause (Compliance) Inspections
  – directed; usually very specific purpose
    • f/u past violations
    • f/u on complaint, informant allegation
• “Post-Approval”
  – product specific soon after approval
Human Drug CGMP Compliance Programs

- **7356.002**: Drug Manufacturing Inspections
- **7356.002A**: Sterile Drug Process Inspections
- **7356.002B**: Drug Repackagers & Relabelers
- **7356.002C**: Radiopharmaceuticals
- **7356.002E**: Medical Gases
- **7356.002F**: API Process Inspection
- **7356.002M**: Inspections of Licensed Biological Therapeutic Drug Products
- **7356.002P**: Positron Emission Tomography
- **7356.843**: Post-Approval Inspections
- **7346.832**: Pre-approval Inspections (A-NDA/BLA)
What is covered during a routine, CGMP inspection?
Goals of Routine CGMP Inspections: 7356.002

✓ **Determine compliance** with CGMP requirements; provide evidence for action as necessary

✓ **Support application** approval decisions

✓ Provide **feedback to firms** to improve their compliance; and,

✓ **Aid FDA** in determining the adequacy of CGMP requirements, regulatory policy, and guidance
Systems-based

1. **Quality System**
2. Facilities and Equipment System
3. Materials System
4. Production System
5. Packaging and Labeling System
6. Laboratory Control System
How is a System covered?

- Sufficiently detailed, with specific examples to determine state of control for every profile class
  - profile class = categorization of different processing conditions & product types
  - related to requirements (CGMPs)
- If System is in control, all profiles covered by system are deemed in control
- Unique profile class material/process under a system selected at discretion of Investigator
Inspection Rigor

2 basic approaches

1. Full Inspection Option
   • Quality System + NLT 3 other systems

2. Abbreviated Inspection Option
   • Quality System + NMT 2 other systems
Inspection Rigor

- **Full Inspection When:**
  - initial establishment inspection
  - previous inspection findings warrant; violative history
  - significant changes since last inspection

- **Abbreviated Inspection Permitted If:**
  - good history
  - no major changes to operations
  - no pattern of recalls and problems
Why a ‘Systems’ Approach?

• Reinforces proactive compliance & reduces reliance on FDA as QA

• Extrapolation: judgment made on all products based on Systems & products actually inspected

• Potentially decreased time to inspect, overall
What is covered during a for-cause inspection?

whatever causes the need for the inspection
What is covered during a “post-approval” inspection?
“Post-Approval” Inspection

- Product-specific; soon following application approval
- Assigned/requested; carefully selected
- Covers aspects of Quality...
  1. not ready during application review period, and
  2. more critical to assure quality
- Including:
  - process validation
  - component supplier qualification
  - stability
Manufacturer’s Role: Before

- Register facility and list all drugs
- If associated with an application
  - keep DMF current; aligned with application role
  - be ready to justify any changes since approval
- Know and follow the quality regulations and guidance
- Be confident in your staff and your operation
  - cultivate honesty and integrity
  - be able to explain why you do what you do
Manufacturer’s Role: During

- Allow access to all areas of manufacturing
  - facility, equipment, materials, records, people

- Answer questions
  - don’t answer if unsure; check

- Provide all info requested
  - clarify request if unclear
  - indicate how long it will take
  - can redact financial info
Manufacturer’s Role: After

- Inspectional Observations not issued
  - expect a copy of FDA inspection report
  - reinspection from 2 – 4 years depending on facility

- Inspectional Observations issued
  - the 483 is for you; ask questions if unclear
  - inform investigator of any incorrect statements
  - if citation isn’t scientifically valid, explain why
  - and…
Manufacturer’s Role: After (continued)

Got a 483?

*Do…*

- correct ASAP if you agree
- assess hazard w/ marketed batches
- respond in writing **within 15 days**
- be very specific with what and when
- attach copies
- explain why an observation isn’t significant or is incorrect
Manufacturer’s Role: After (continued)

Got a 483?

*Don’t* …

- make excuses
- promise what you can’t deliver
- ignore the bigger picture
- be afraid to disagree
Enforcement of Quality Standards (CGMPs)

1. Inspection findings are reviewed in District
   – written warning of violations
   – withhold/withdrawal marketing approval
   – seizure/injunction/criminal prosecution

2. FDA CDER Office of Compliance reviews recommendation + firm’s response to 483
   – accept or reject or alter action
   – shortage evaluation
   – advisory/administrative actions taken (warnings, import alerts, application withhold)

3. FDA/OCC reviews seizure/injunction/prosecution

4. DOJ + FDA/OCC litigates
Top 5 Quality (CGMP) Problem Areas
<most associated with regulatory action>

1. Investigating & correcting discrepancies or defects (211.192)
2. Micro controls for sterile & non-sterile (211.113)
3. Stability program (211.166(a))
4. Process design & qualification (validation) (211.100(a))
5. Establishing & following sound tests & sampling plans (211.160)
Recent and Emerging Drug Quality Policies

• Inspection programs recently revised (*Compliance Program Guidance Manuals*)
  – 7356.002A – Aseptic Processing; 7356.002P – PET Drugs

• Enforcement policies (*Compliance Policy Guides*)
  – Parametric Release - Terminally Moist Heat Sterilized Products
  – Interference with Compendial Tests

• Guidance for Industry
  – Non-Penicillin Beta-Lactam Drugs: A CGMP Framework for Preventing Cross-Contamination (final)
  – Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality (final)
  – Contract Manufacturing Arrangements for Drugs: Quality Agreements (*finalize soon*)
Protecting Consumers, Promoting Public Health

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