



U.S. Food and Drug Administration

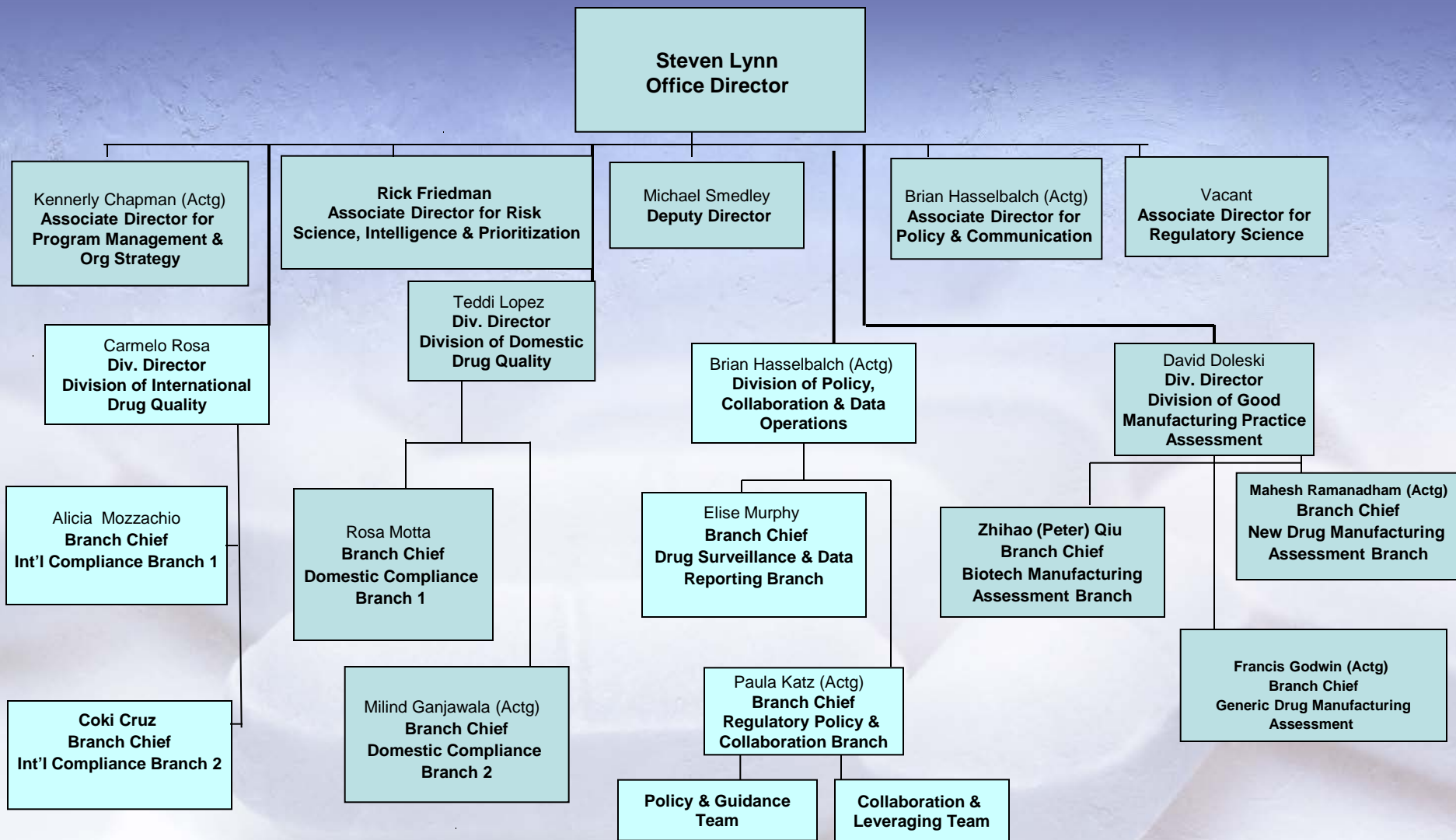
Generic Drug User Fee Amendments of 2012

Post-Approval & Surveillance Inspection Programs for Pharmaceutical Manufacturers

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Agenda

- Organizational Overview – Office of Manufacturing & Product Quality
- Roles and Responsibilities
- GDUFA and You (related to inspections)
- FDA Inspection Types and Techniques
- Hosting an Inspection
 - Before, during, and after
 - Dos and Don'ts



Office of Manufacturing and Product Quality

OMPQ Roles & Responsibilities

- Office of Manufacturing and Product Quality (OMPQ) reviews and approves CGMP regulatory actions based on scientific and technical merit
- OMPQ acts as a liaison between the field and Center offices to evaluate and coordinate product quality issues and to determine if regulatory action is necessary
- Participate in establishment inspections – both foreign and domestic

Generic Drug Program: Not just OGD

- Involves all of CDER
 - OGD is the interface for ANDA applicants to interact with the Generic Drug Program
- Other FDA units:
 - ORA (the field)
 - CDRH
 - Office of the Commissioner
 - Office of Chief Counsel



Key Aims of GDUFA

- **Safety** – Ensure that industry participants are held to high quality standards & are inspected biennially w/ foreign & domestic parity.
- **Access** – Expedite the availability of low cost, high quality generic drugs by bringing greater predictability to the review process.
- **Transparency** - Requiring the identification of facilities involved in the manufacture of generic drugs and improving FDA's communications and feedback with industry in order to expedite product access.

FDA Inspection Commitments:

- **Prioritize establishment inspections**
ANDAs that are otherwise approvable or eligible for tentative approval except for an outstanding inspection and establishments not inspected previously
- **Public Information: results and date of inspection**
Make inspection classification results and date of the last facility inspection available to the public and industry on FDA's website
- **Foreign inspections**
Study foreign government regulator inspections, report findings publicly, and develop a program to utilize foreign inspections classifications when and where appropriate

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 ✓

1903 General Inspection Protocol

- 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)

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm252671.htm>



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 Inspections

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

1. Full Inspection Option
 - Quality System + NLT 3 other systems
2. Abbreviated Inspection Option
 - Quality System + NLT 1 other system

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

“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 and FDA's risk model
- 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

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

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

Frequently-Observed Quality Problems and CGMP Violations

- Investigating & correcting discrepancies or defects (211.192)
- Micro controls for sterile & non-sterile (211.113)
- Stability program (211.166(a))
- Process design & qualification (validation) (211.100(a))
- Establishing & following sound tests & sampling plans (211.160)

Where to Get Help with CGMPs and Quality Issues

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductandTobacco/CDER/ucm096102.htm>

<http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm>

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