

Approaches to GMP inspection

CDER Small Business - Regulatory Education for Industry (REdI)

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Overview

- Pre-Approval Inspection (PAI)
- Risk-Base GMP Inspection
 - Routine
 - Post-Approval
 - Trends
- Product Recall

Framework from Pharmaceutical Quality for the 21st Century Initiative

The Guiding Principles:

- Strong public health protection
- Risk-based orientation
- Science-based policies and standards
- Integrated quality systems orientation
- International cooperation

The Desired State: A Mutual Goal of Industry, Society, and the Regulators

A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight.

Janet Woodcock, M.D.

The Pre-Approval Inspection Program

The Food, Drug, and Cosmetic Act provides that FDA may approve an NDA or an ANDA only if the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and testing of the drug are found adequate to ensure and preserve its identity, strength, quality, and purity.

§§ 505(d) and 505(j)(4)(A) (21 U.S.C. §§ 355(d)(3) and 355(j)(4)(A))

When to Perform a PAI: Priority Inspection Criteria

An inspection will be initiated:

1. The first time an establishment is named in an Application submitted to FDA, including those that have never been inspected and those that have only been inspected for non-Application drugs;
2. For the first Application filed by applicant (for coverage of finished dosage manufacturing and testing);
3. For the first ANDA filed for an approved drug (specific coverage of finished dosage manufacturing and testing);

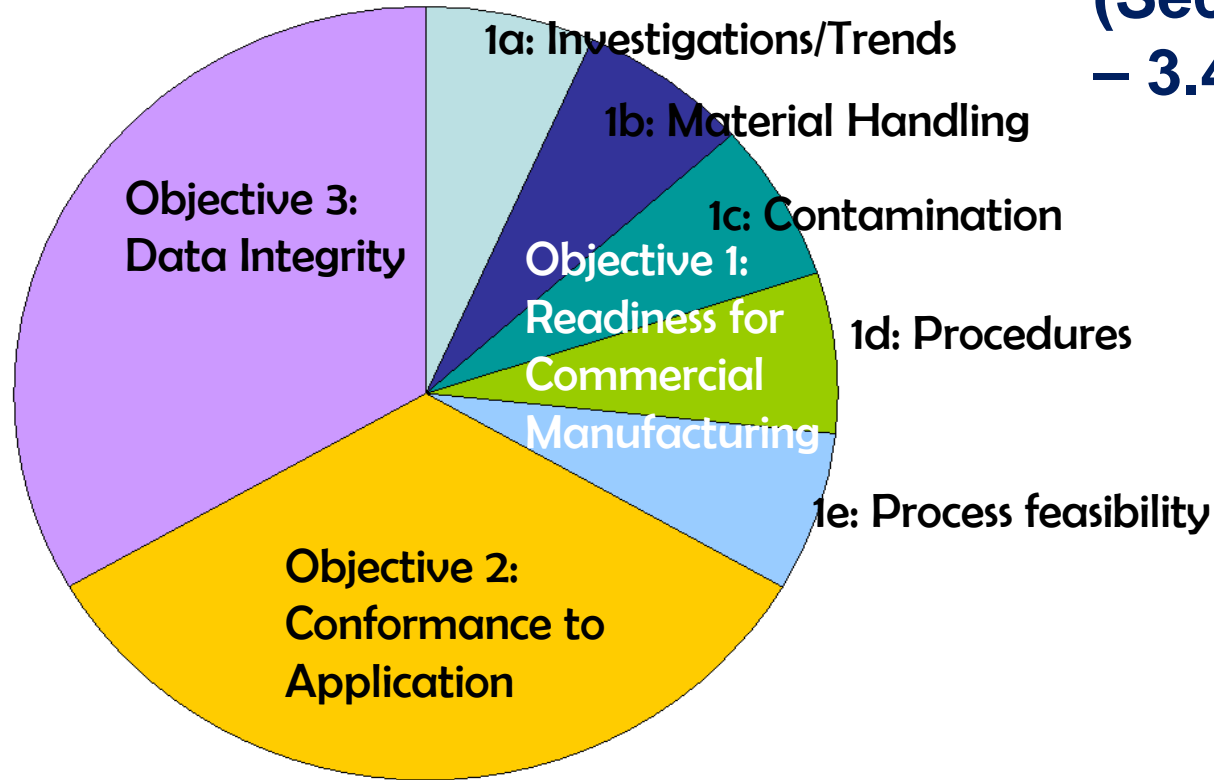
When to Perform a PAI: Priority Inspection Criteria

4. When the finished product contains a **New Molecular Entity** (NME) (does not apply to supplements);
5. When the finished product content assay has a **narrow range** (e.g., 95-105% labeled strength for narrow therapeutic index drugs) or drug is expected to require **titrated dosing** (does not apply to supplements);
6. Finished product or API is manufactured by a ***substantially different manufacturing process*** or dosage form than previously covered at the establishment;

When to Perform a PAI: Priority Inspection Criteria

7. API derivation is high risk (e.g., API is derived from animal tissues) or the intended use has significantly changed (e.g., API previously used in non-sterile product is now intended for a sterile drug product);
8. Numerous application submissions or certain site/process/product changes that are expected to pose significant challenge to the state of control of the facility or process; and
9. Profile class status of Application product or API is “unacceptable” or not updated via a site inspection within the past 2 years (3 years for control laboratories and 4 years for packaging and labeling), for original applications or significant pre-approval CMC supplements.

PAI Objectives (Sections 3.3 – 3.4 CPGM)



Principal reasons for a PAI withhold recommendation

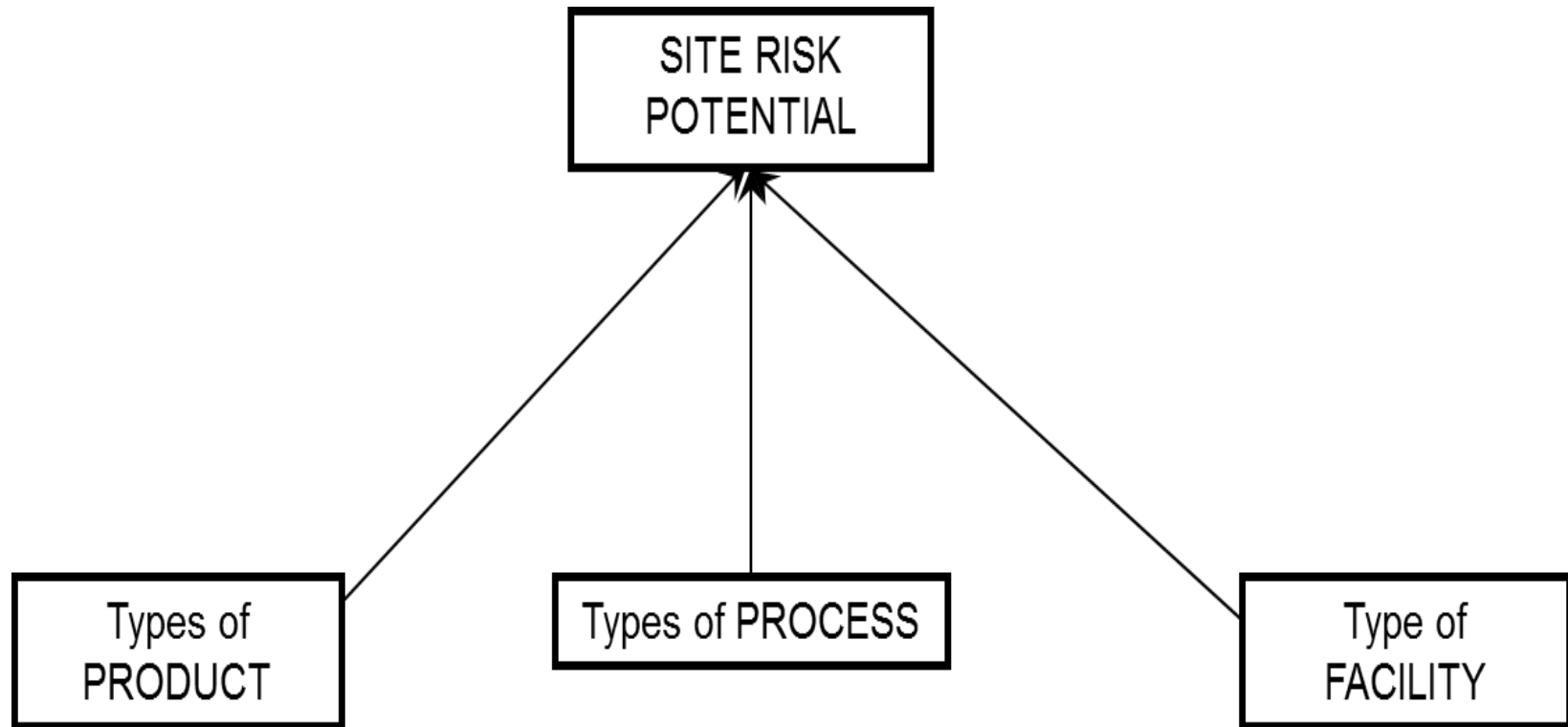
- Pending enforcement action/previous deviations persist
- Firm not ready/drug not made here/facility withdrawn
- Insufficient development data/ production/process controls
- Inadequate lab controls
- Inadequate QA functions

*Data source: Establishment Evaluation System (EES), withhold recommendations



Risk-based Approach

Risk-Based framework for prioritizing sites for GMP inspection



Risk-base goals of GMP

- Ensure that FDA resources are used effectively and efficiently to address the most significant public health risks.
- Risk in the context of pharmaceutical quality :
 - Depends on the potential harm associated with the loss of pharmaceutical quality

ICH q9/q10

- **Quality:** Degree to which a set of inherent characteristics of a product, system or process fulfils *requirements*
- **Requirements:** *Needs or expectations* that are stated, generally implied or obligatory by the *patients or their surrogates* (e.g. health care professionals, regulators and legislators)
- **Combining key terms:** *Risk to quality* is the probability/severity that a drug will fail to meet the needs/expectations of the patients and their surrogates

Needs and Expectations of Patients/Surrogates

- For *drug quality*, what are the needs/expectations of patients/ surrogates?
 - Clinical performance
 - Availability

Clinical Performance

- Drug performs as described in the approved labeling
- Delivers the relevant *attributes* of the drug in the clinical database on which the FDA approval decision was based
- *What are these attributes* that can serve as surrogates for clinical performance?

Clinical Performance Surrogates

- A product's clinical performance surrogates are its established quality attributes, including:
 - Identity/potency
 - Purity
 - Strength
 - Bioavailability/delivery (e.g., dissolution)
 - Labeling/packaging
 - Physical performance/appearance (including aspects that influence adherence and acceptability)

Identify Predicted/Known Hazards to Quality

Attributes: Risk Factors

- Risks to pharmaceutical quality can be identified based on the **probability** and **severity** of adverse impact on these quality attributes
 - Explicitly include factors that mitigate probability/severity of adverse effects or factors that have a positive impact
 - The ability to **detect** a drug product with compromised quality attributes would reduce the probability of harm

Risk Ranking Model: Product Factors

- What are the intrinsic properties of products such that deficiencies in quality, if any, would have more adverse public health impact than others?
 - sterile
 - Rx
 - non-medical gas
- Recall data identifies products or dosage forms associated with frequent and/or serious recalls



Inspections: *What's next?*

Which facilities routinely get inspected?

- dosage formulation
- active pharmaceutical ingredient (API)
- “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.*

2014 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

1. 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 when:
 - 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

Expectation of Manufacturer's Role: Before Inspection

- 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

Expectation of Manufacturer's Role: During Inspection

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

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

- Provide all information requested
 - clarify request if unclear
 - indicate how long it will take
 - can redact financial info

Expectation of Manufacturer's Role: After Inspection

- Inspectional Observations **not** issued
 - expect a copy of FDA inspection report
 - re-inspection 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 Inspection (continued)

Got a 483?

Do...

- correct ASAP if you agree
- assess hazard w / marketed batches
- respond in writing **within 15 days**
 - not mandatory to respond
 - later better than never
 - if timely, will be considered in deciding outcome

Manufacturer's Role: After Inspection (continued)

Got a 483?

Do...

- be very specific with what and when
- attach copies to respond
- demonstrate management awareness and support, including financial commitment to corrections
- explain why an observation isn't significant or is incorrect

Manufacturer's Role: After Inspection (continued)

Got a 483?

Do...

- get outside assistance if needed
- address each deficiency separately
- describe cause if known; if not, explain how you will determine
- address impact on other countries

Manufacturer's Role: After Inspection (continued)

Got a 483?

Don't...

- promise what you can't deliver
- let problems go unaddressed
- ignore the bigger picture
 - other products, other operations, foundational failure to assure Q
- 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

Case Study: Inadequate Process Validation (Oct. 2012)

For example, your firm has not established scientific evidence that your manufacturing processes are capable of consistently manufacturing quality products... your firm changed the manufacturing process of **(b)(4)** (Lot #**(b)(4)**) without the quality unit's approval. An additional inactive ingredient, "**(b)(4)**," was added without change control (e.g., additional studies to determine its impact on product quality).

Case Study: Component Controls

(March 2013)

For example... your firm failed to subject the water used as a component to routine microbiological testing. .. and you failed to validate the water system to ensure consistent water quality for drug production and implement procedures for maintaining or monitoring the quality of the water produced. You can determine the frequency of water testing based upon the intended use of the product and other considerations.

Case Study: Facility Maintenance

(March 2013)

For example... investigator observed condensate leaking into a bucket that was secured to the ceiling over the production area, and peeling paint on the floors, walls and support beams in the production area.

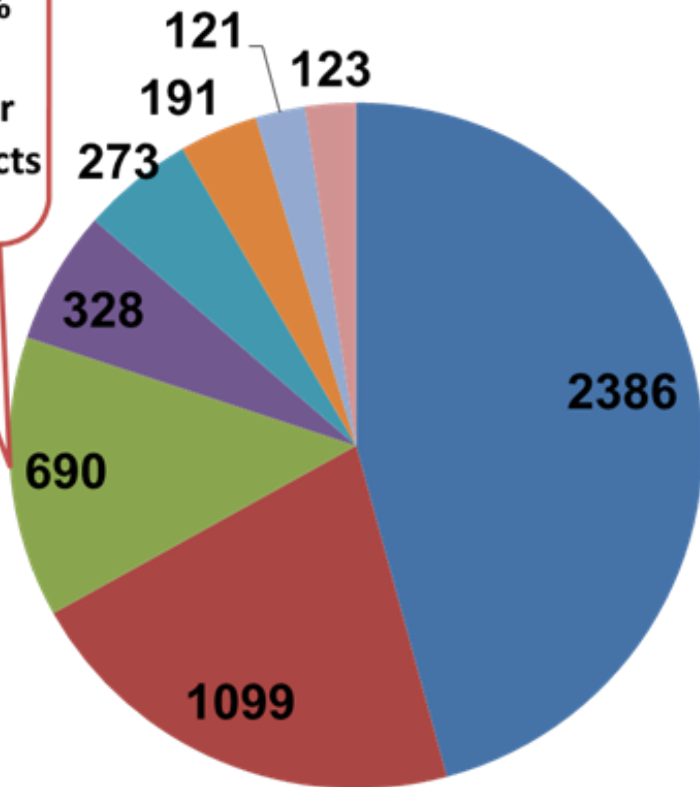


FDA Form 483 data

INSPECTIONAL TRENDS

Number of FDA Form 483's issued in FY 2013

Around 13% of issued 483's are for drug products



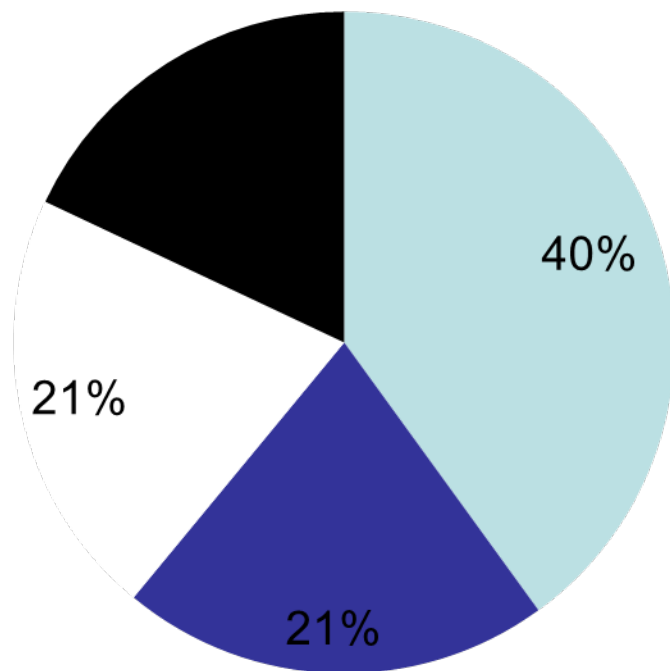
By commodity

- Food
- Devices
- Drugs
- Veterinary Medicine
- Bioresearch monitoring
- Biologics
- Human tissue
- Other

- <http://www.fda.gov/ICECI/EnforcementActions/ucm381526.htm#drugs> for FY 2013

Interpretation of Observations

Top citations over the past 4.5 years

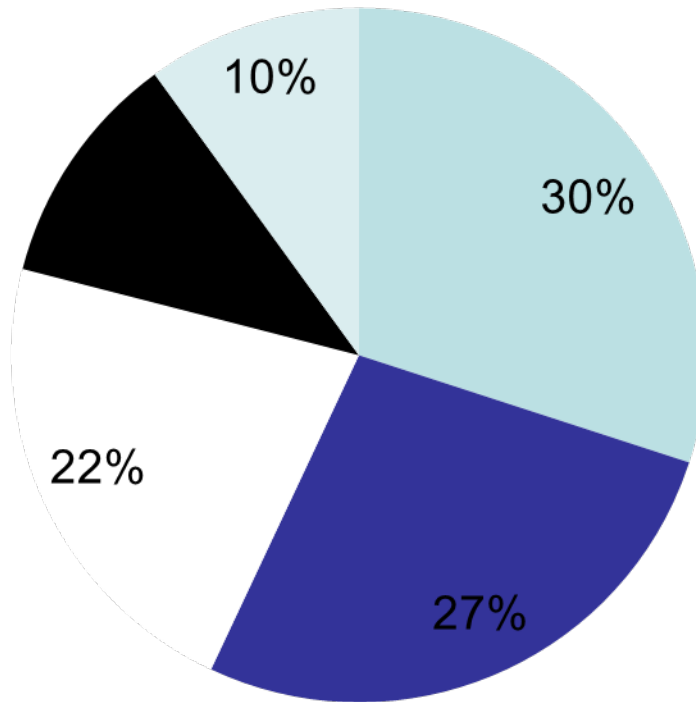


“System” Categories

- Quality
- Laboratory
- Process
- Equipment

Quality

of the 40%



Quality Unit

Investiagtions

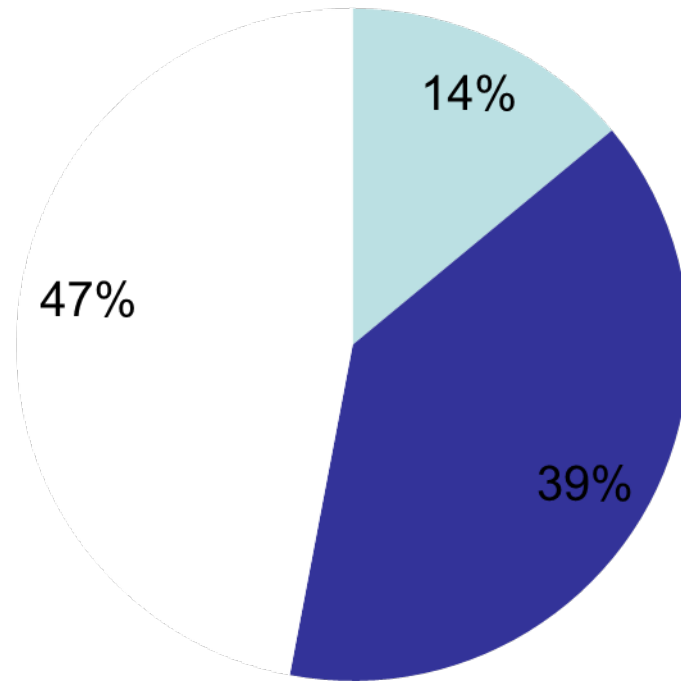
Training

Complaint

Annual Reporting

Laboratory

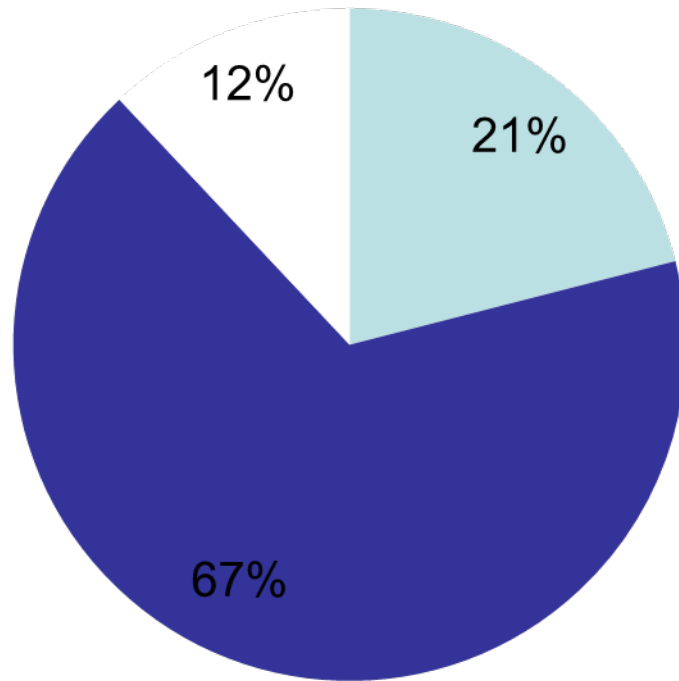
of the 21%



- Stability
- Testing
- Methods

Process

of the 21%



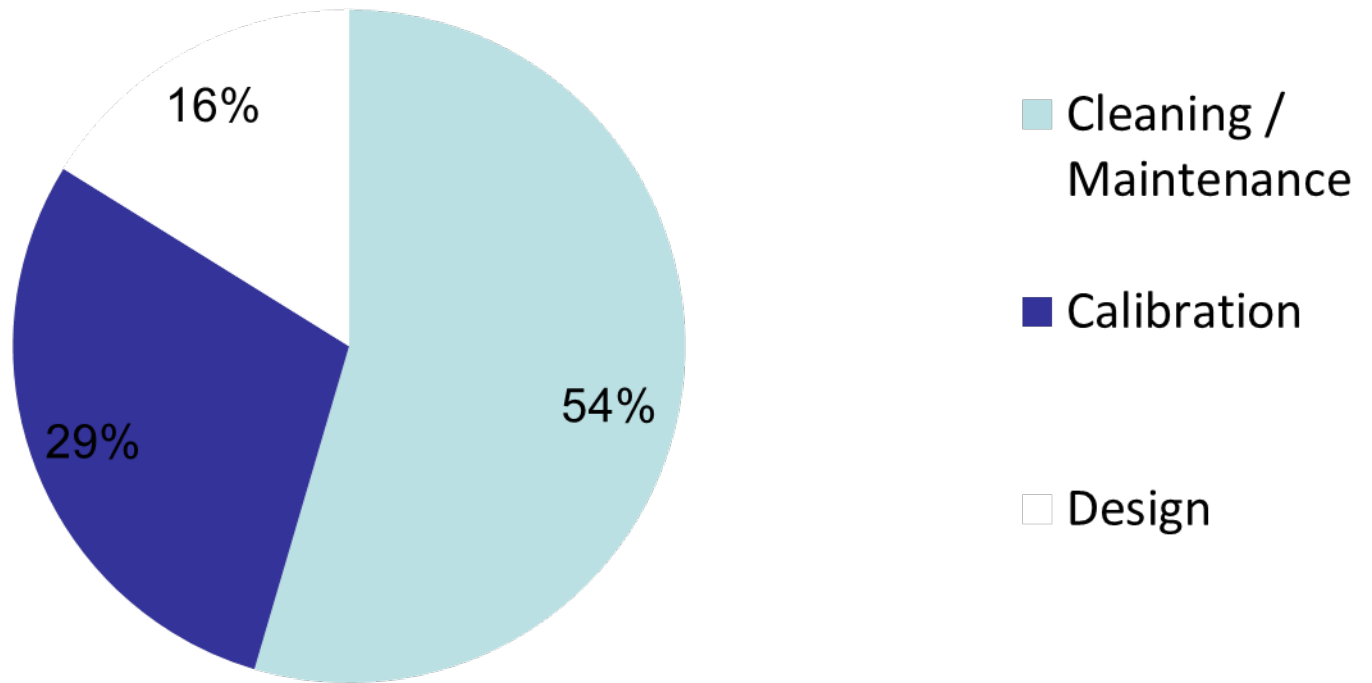
- Process Validation
- Process Controls
- Sterility Assurance

Interpretation of Turbo EIR observations between 09/01/09 and 3/31/13 as of 4/1/14

Equipment

Interpretation of Turbo EIR observations between 9/01/09 and 3/31/13 as of 4/1/14

of the 18%



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)

Definition: recall

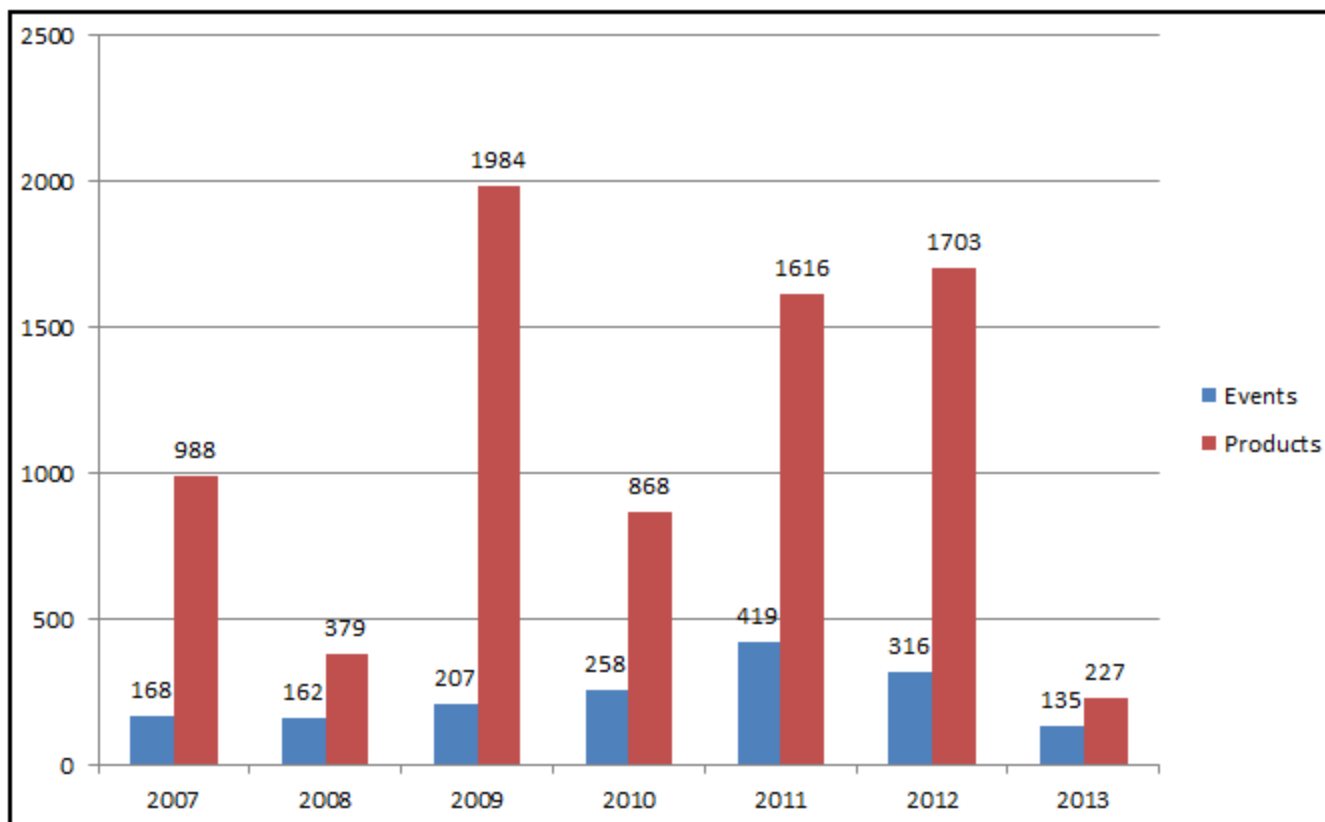
- 21 Code of Federal regulations, Section 7.3(g)
- A firm's removal or correction of a marketed product that the Food and Drug Administration considers to be in violation of the laws it administers and against which the agency would initiate legal action, i.e., seizure.

Recall Classification

- **Class I** – a situation where there's a reasonable probability that the use of, or exposure to, a violative product **will cause serious adverse health consequences or death.**
- **Class II** – a situation where the use of, or exposure to, a violative product **may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.**
- **Class III** – a situation where the use of, or exposure to, a violative **product is *not* likely to cause adverse health consequences.**

Total Event vs Product Recalls FY 2007 - 2013* (Updated 4/1/13)

Data from office of drug security, integrity & recall



Recall data continued

Note:

- **FY2007:** 168 Events and 988 Products. One contract packaging site caused packaging mix-ups accounting for approximately 670 product recalls.
- **FY2008:** 162 Events and 379 Products.

Recall data continued

- **FY2009:** 207 Events and 1984 Products. One contract manufacturer accounted for 1335 product recalls resulting in various CGMP violations discovered during an inspection. Also, one tablet manufacturer recalled 190 Rx products.
- **FY2010:** 258 Events and 868 Products.
- **FY2011:** 419 Events and 1616 Products. Single firm recalls more than 800 products resulting from Penicillin cross-contamination. Also, one firm recalls 114 products for microbial contamination of non-sterile products.

Recall data continued

- **FY2012:** 316 Events and 1703 Products. Two firms with over 850 products for Penicillin cross-contamination and bacterial contamination in alcohol pads.
- **FY2013*:** 135 Events and 227 Products. Second quarter data only.

Fiscal Year FY2013 (Updated 6/1/13)

Type	Class 1	Class 2	Class 3	Total
Recall Events*	29	106	64	199
Product Recalls	43	362	93	498



Top CDER Reasons for Recall by Event

Reasons for Recall	Total # of Events
Lack of Assurance of Sterility	21
Marketed Without an Approved NDA/ANDA	16
Impurities/Degradation Products	15
Subpotent (Single Ingredient Drug)	13
Presence of Foreign Substances(s)	12

Acknowledgements

- **Brian Hasselbalch**
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- **Tamara Ely**

We must use time wisely and forever realize
that the time is always ripe to do right.

~ NELSON MANDELA

For More cGMP information

Pre-Approval Inspection Compliance Program Guidance Manual
(7346.832)

<http://wcms.fda.gov/FDAgov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnsweronCurrentGoodManufacturingPracticescGMPforDrugs/UCM071871.pdf>

CGMP Subject Contacts

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

Questions and Answers

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124740.htm>