

HOT TOPICS CURRENTLY IN FOCUS BY THE US-FDA



Bridge Associates International LLC

*"Partners for Quality and Manufacturing Excellence"*TM

Roy T. Cherris - Managing Partner

INTRODUCTION: DATA ?

Why is Data Important?

- Data is as important as the research and products we produce
- Everything we do in the regulated industry is supported by the appropriate data
- The data creates the trust required to discover, develop, commercialize, and distribute medicines successfully

Regulatory authorities have highlighted a continuing concern:

- Number of GMP Warning Letters that have a major focus on Data Integrity has increased significantly since calendar year 2010
 - 2 in 2010 to 10 in 2014
 - 17% of Warning Letters in 2014
 - 30% of Warning Letters in 2015
 - Failures were predominant in almost all API Warning Letters in 2015

INTRODUCTION: DATA ?

The past six years have brought increased concern and level of regulatory attention to issues surrounding:

- Supplier quality management
- Access controls to electronic systems
- Backing up of data
- Audit trail reviews

The primary deficiencies relating to data integrity found by the FDA in 2015 were:

- Failure to include complete data (211.194(a))
- Audit trail, data control, and sharing password (211.68(b))

Regulators always assume non-compliance or faulty data is intentional and not accidental.

FDA is continuously searching for systems and industry to assure “Transparency”

REGULATORY AND COMPLIANCE HOT TOPICS FROM 2015-2016

- FDASIA - Food and Drug Administration Safety and Innovation Act
- Data Integrity
- Quality Metrics
- Quality Culture
- Trends over recent years
- Current 483 Citations
- Current Medical Device Citations
- Warning Letters

FDA'S FDASIA TITLE VII DIRECTIVE

Introduced in 2012, Food and Drug Administration Safety and Innovation Act Title VII: What it Does...

Increases FDA's ability to:

- Collect and analyze data to enable risk-informed decision-making
- Advance risk-based approach to facility oversight
 - part of broader shift towards more strategic, risk-based approach to regulation and enforcement
- Partner with foreign regulatory authorities to leverage resources through information-sharing and recognition of foreign inspections
- Drive safety and quality throughout the supply chain through strengthened tools

FDA'S TITLE VII DIRECTIVE

Collect and Analyze Data to Enable Risk-Informed Decision-Making

701 & 702 Registration of foreign and domestic facilities - U.S. and foreign drug establishments must provide Unique Facility Identifier (UFI) so FDA knows where establishments are located

703 Identification of drug excipient information with product listing - Listing for a drug is to include name, address, and UFI for manufacturers of excipients used in that drug

704 Electronic registration and listing system - Ensure our drug registration and listing databases contain accurate, complete information and can interface with other relevant agency databases

713 Standards for admission of imported drugs - Shift burden of proof at the border and require importer to show compliance

714 Registration of commercial importers - Require commercial importers to register with FDA
Prescribe “good importer practices”

715 Notification - Require manufacturers, importers, distributors to notify FDA when drugs threaten serious injury/death or are lost/stolen/counterfeit

FDA'S TITLE VII DIRECTIVE

Advance Risk-Based Approaches to Facility Oversight

705 Risk-based inspection frequency

- Eliminates minimum inspection frequency requirement for domestic drug establishments
- Requires FDA to target both domestic and foreign inspections on the basis of risk
- Every two years as an average frequency will still be the norm until the Title VII program matures

706 Records for inspection

- Allows FDA to request and obtain records – electronically or in physical form – in advance or in lieu of an inspection

Partner with Foreign Regulatory Authorities

710 Exchange of information

- Allows FDA, under certain conditions, to exchange information with peer regulators globally

712 Recognition of foreign government inspections

- Allows FDA to recognize foreign inspections
- Foreign inspection results can be used to facilitate risk-based inspection, as evidence of compliance with cGMPs and import standards, and for any other “appropriate” purposes

FDA'S TITLE VII DIRECTIVE

Drive Safety and Quality Through Strengthened Tools

707 Delaying, denying, limiting or refusing inspection - Makes adulterated any drug that has been manufactured, processed, packed or held in a facility that has stymied FDA inspection

708 Destruction - Addresses problem of illegal products at international mail facilities

- With due process, allows FDA to destroy drugs refused entry into the U.S.

709 Administrative detention -Allows FDA to administratively detain drugs

- Already had this authority for tobacco, food, and devices

711 Enhancing safety and quality - Requires manufacturers to adopt quality management systems as part of cGMP

716 & 717 Enhanced penalties for counterfeiting and intentional adulteration

718 Extraterritorial jurisdiction - Intended to ensure that FDA can enforce FD&C Act outside the U.S

DATA INTEGRITY INITIATIVE

Data Integrity is the current Primary Concern and increased focus for FDA and Regulatory agencies worldwide:

- Data integrity is a prerequisite for the regulated healthcare industry as decisions and assumptions on product quality and compliance with the applicable regulatory requirements are made based on scientifically sound data.
- Drug and medical device manufacturers or service providers, healthcare organizations, regulators and other users (patients and healthcare professionals) rely on data provided to support the product's use.
- Breaches in data integrity can have negative consequences and may lead to patient injury, or even death.

It has become increasing more difficult to detect Data Integrity breaches:

- Previously in the past data integrity was relatively easy to prove using forensic methods in hardcopy, the advent of computerized systems has brought with it a different level of complexity.
- Identifying whether there could have been undocumented or even malicious changes to electronic data or records requires time, additional tools and expertise.
- It is much easier to change electronic data and records than it is to change a paper or other physical record, therefore there is a much higher possibility of fraudulent data changes .

The regulatory authorities have put much emphasis on data integrity in recent years, because they uncovered serious cases of data integrity breaches.

DATA INTEGRITY INITIATIVE

“Guilty until proven innocent” Was the classic approach

- Historical approaches based on technical justification and scientific rationale were not fully adequate
- Emphasis now is on providing evidence that the analytical results are not fraudulent
- Data integrity is the assurance that data records are accurate, complete, intact and maintained within their original context, including their relationship to other data records.
- This definition applies to data recorded in electronic and paper formats or a hybrid of both. **Which is it?**

Data Integrity key to:

- Reliable and trustworthy records
- Records that will withstand scrutiny during regulatory inspections
- According to FDA, which uses the acronym **ALCOA**, data needs to be “attributable, legible, contemporaneous, original, and accurate.”
 - **Attributable:** Who performed an action and when? If a record is changed, who did it and why? Link to the source data. Who did it? Secure, source data, meta-data, audit trails, final reported data
 - **Legible Data:** Must be recorded permanently in a durable medium and be readable. Permanently recorded?
 - **Contemporaneous:** The data should be recorded at the time the work is performed and date / time stamps should follow in order Was it done in “real time”?
 - **Original:** Is the information the original record or a certified true copy? Is it original or true copy?
 - **Accurate:** No errors or editing performed without documented amendments. Is it accurate?

DATA INTEGRITY INITIATIVE

FDA inspects for electronic data integrity during the pre- and post market product approval process using concepts of 21 CFR Part 11 commonly referred to as the “data integrity regulation.”

Four goals listed by FDA during assessments:

- Historical Form 483 inspectional observations (case studies) are used as “tests” during the assessment
- Assess the firm’s comprehension or continuing misinterpretations of Part 11 security
- Determine how firms are ensuring the integrity of electronic records.
- Extend scrutiny of raw and processed data
 - Human generated (performance qualification), checks for procedure & training effectiveness, is double-check needed, evaluate bias or falsified data (example: visual inspection test sets and bias)
 - Equipment generated (functional qualification), does equipment perform as designed and have a maintenance cycle
 - Computerized system (software validation), independent from the integrated equipment performance

Note: The current regulatory guidance regarding the qualification of analytical instrumentation and validation focuses on the instrument with little emphasis on computerized system validation. In contrast, the Good Automated Manufacturing Practice (GAMP) Good Practice Guide for Validation of Laboratory Computerized Systems from the International Society for Pharmaceutical Engineering (ISPE) looks exclusively at the computerized system. This guidance essentially ignores instrument qualification. The major problem and practical reality are that a computerized system cannot be validated without qualifying the analytical instrument, and vice versa.

This concern has been incorporated as General Chapter <1058> within the United States Pharmacopoeia (USP).

QUALITY METRICS DIRECTIVES

2015 Draft Guidance entitled “Request for Quality Metrics.”

- The Draft Guidance formally presents FDA’s current thinking and intentions regarding the collection and use of quality metrics
- This broad new initiative that will see the collection and review of potentially large groups of new information that was previously difficult for FDA to collect and assess systematically.
- FDA intends to use these data to make risk-based decisions when assigning facility inspections and to identify potential drug shortage issues earlier so that issues can be corrected before a shortage happens.

In the draft guidance, FDA defines quality metrics to include:

- Lot acceptance rate
- Product quality complaint rate
- Invalidated out-of-specification (OOS) rate
- Annual Product Review (APR) or Product Quality Review (PQR) on-time rate

QUALITY METRICS DIRECTIVES

In order to calculate these metrics, FDA will be asking manufacturers to provide:

- Number of lots attempted
- Number of lots pending disposition for more than 30 days
- Number of lots released
- Number of OOS results
- Number of lots rejected due to OOS
- Number of release and stability tests conducted
- Number of OOS results that are invalidated due to laboratory error
- Number of product quality complaints
- Number of APRs and PQRs required
- Number of APRs and PQRs completed within 30 days of due date

QUALITY CULTURE INITIATIVES

QA & QI Culture -They are not the same!!!

- Quality Assurance Culture:
 - Reactive - Works on problems after they occur
 - Focused on regulatory requirements
 - Led by management
 - Addressed - One point or problem at a time
- Quality Improvement Culture: Builds on the traditional QA foundation
 - Proactive – works on processes before problems occur
 - Self-determined on best practice
 - Led by staff
 - Continuous evolution and refinement
 - Exceeds expectations
- In order to establish a culture of quality, you must first decide what quality in your organization will look like and communicate that vision to others
- The structure and process for quality improvement should be visible and easily understood by everyone in the organization
- Buy-in and support at all levels is essential to successfully establishing a culture of Quality
- ISPE is studying the elements of establishing a sound quality culture; Reports are out for Phase 1, Phase 2

QUALITY CULTURE INITIATIVES

Step 1- Clearly communicate your Quality Improvement plan and efforts throughout the organization

- Create a Quality Improvement Program Description Document
 - Give an overview of Quality at the organization
 - Describe the structure for managing quality throughout the organization
 - Establish roles and responsibilities for all levels of staff in relationship to Quality Improvement efforts.
 - List and describe the organization's QI efforts
 - Establish QI goals for the organization

Step 2 – Train staff

- Introduction to Quality Improvement for all employees
- Incorporate QI into existing trainings, tell them **WHY** the process steps or data it is important
- Conduct orientation sessions to orient staff to the QI Plan
- Provide advanced QI training to prepare staff to conduct quality improvement projects

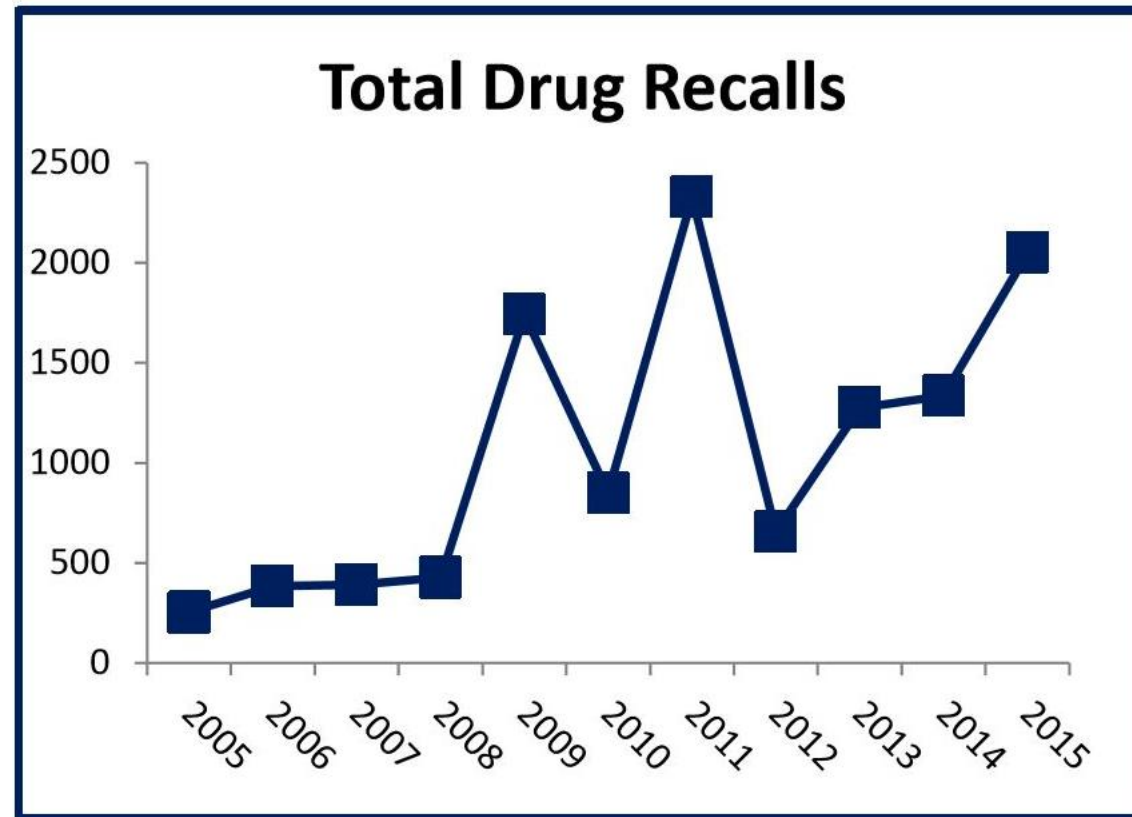
Step 3 - Provide Support

- Technical Assistance
- I:I Consultation
- Presentations at program-level meetings

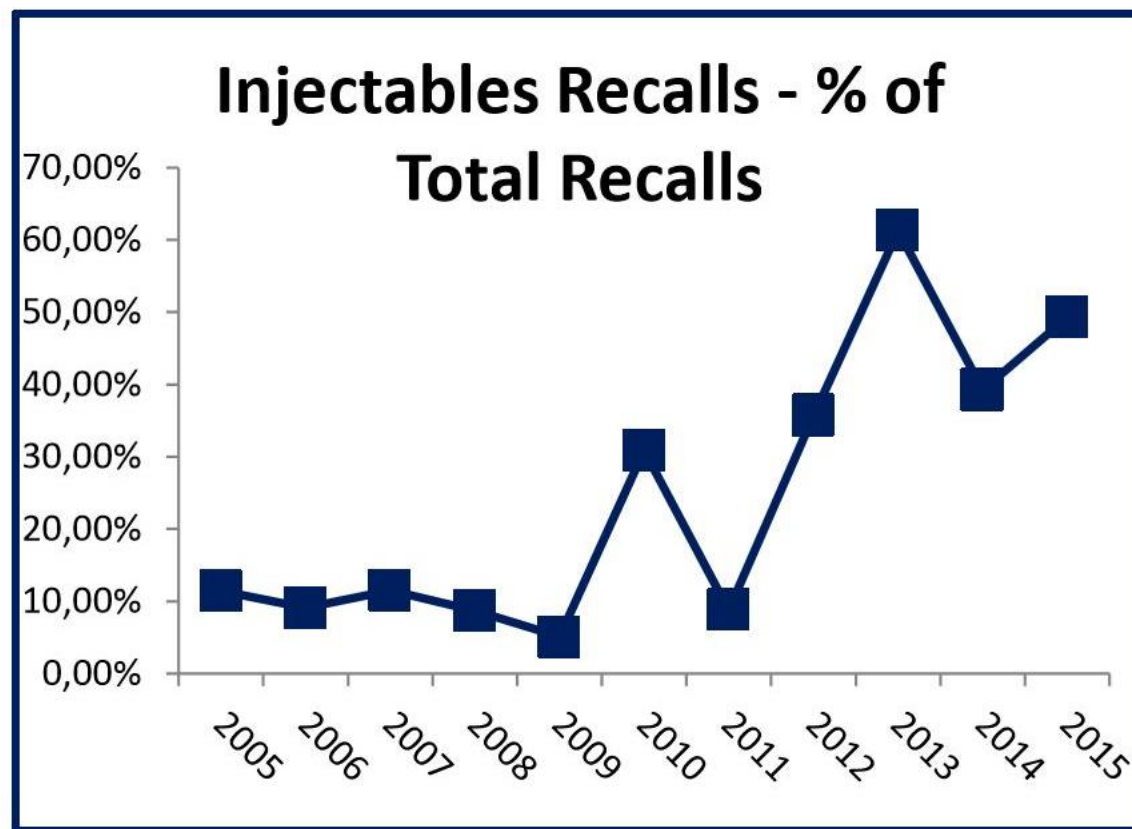


Recent Trends in FDA actions

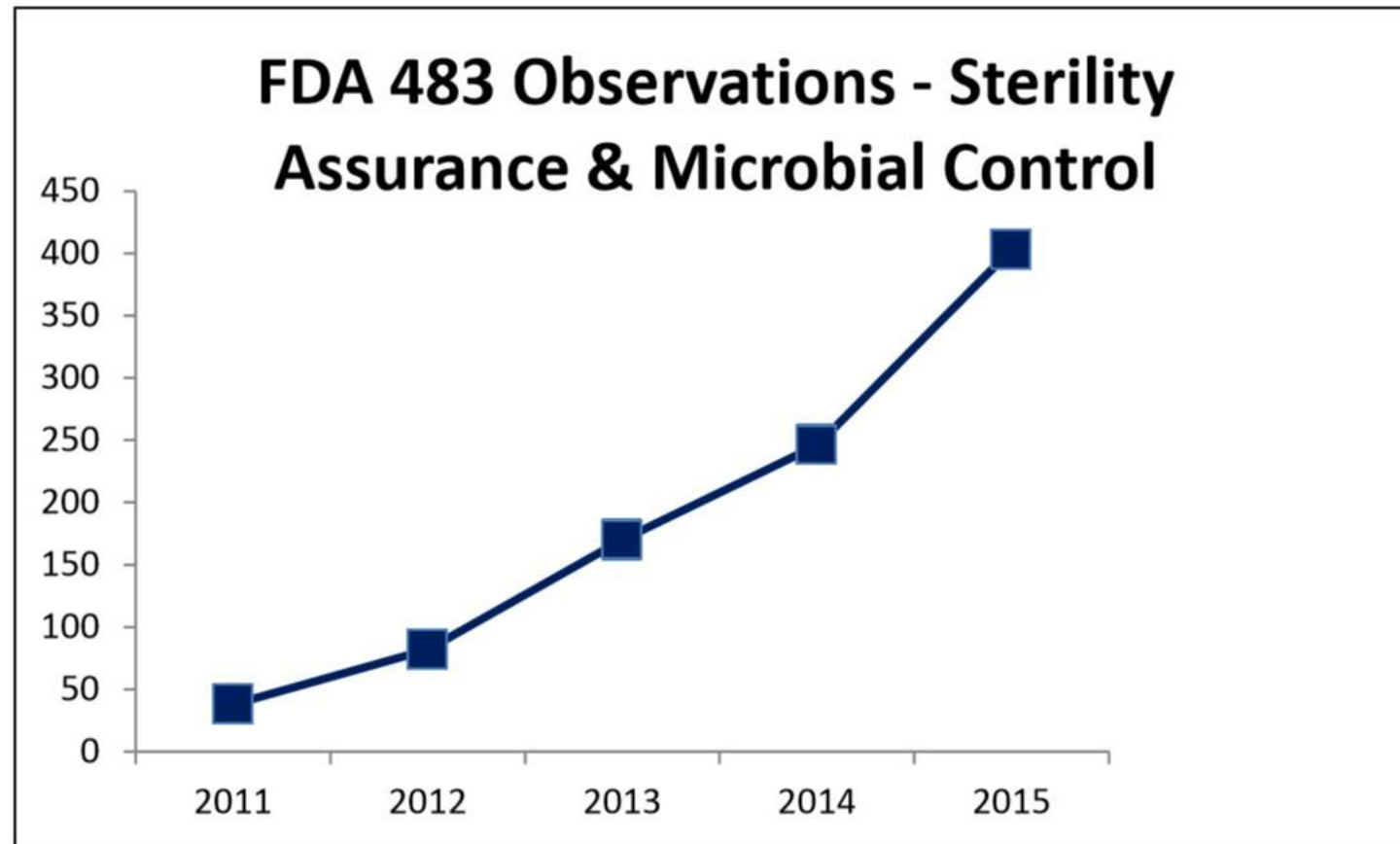
RECENT TRENDS IN FDA ACTIONS



RECENT TRENDS IN FDA ACTIONS



RECENT TRENDS IN FDA ACTIONS



TOP 10 FDA – 483 CITATION THEMES

| Cited Clause | Frequency | Short Description |
|--------------------------|-----------|--------------------------------------------------------|
| 21 CFR 211.192 | 250 | Extent of discrepancy, failure investigations |
| | | Investigations of discrepancies, failures |
| | | No written record of investigation |
| | | Quality control unit review of records |
| | | Written record of investigation incomplete |
| 21 CFR 211.22(d) | 160 | Procedures not in writing, fully followed |
| 21 CFR 211.113(b) | 157 | Procedures for sterile drug products |
| | | Validation lacking for sterile drug products |
| 21 CFR 211.160(b) | 130 | Scientifically sound laboratory controls |
| 21 CFR 211.100(a) | 123 | Absence of Written Procedures |
| | | Approval and review of procedures |
| | | Changes to Procedures Not Reviewed, Approved |
| 21 CFR 211.25(a) | 106 | GMP Training Frequency |
| | | Training, Education, Experience overall |
| | | Training--operations, GMPs, written procedures |
| 21 CFR 211.166(a) | 92 | Lack of written stability program |
| | | Results not used for expiration dates, storage cond. |
| | | Written program not followed |
| 21 CFR 211.42(c)(10)(iv) | 83 | Environmental Monitoring System |
| 21 CFR 211.110(a) | 82 | Control procedures fail to include the following |
| | | Control procedures to monitor and validate performance |
| | | Written in-process control procedures |
| 21 CFR 211.165(a) | 80 | Testing and release for distribution |

TOP 10 FDA – 483 CITATION THEMES

Number 1 - 21 CFR 211.192 - Investigations of discrepancies, failures

- Investigations of [an unexplained discrepancy] [a failure of a batch or any of its components to meet any of its specifications] did not extend to [other batches of the same drug product] [other drug products that may have been associated with the specific ***
- There is a failure to thoroughly review [any unexplained discrepancy] [the failure of a batch or any of its components to meet any of its specifications] whether or not the batch has been already distributed. Specifically, ***
- Written records are not [always] made of investigations into [unexplained discrepancies] [the failure of a batch or any of its components to meet specifications]. Specifically, ***
- Drug product production and control records, are not [reviewed] [approved] by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Specifically, ***
- Written records of investigations into [unexplained discrepancies] [the failure of a batch or any of its components to meet specifications] do not [always] include the conclusions and follow-up. Specifically, ***

TOP 10 FDA – 483 CITATION THEMES

- **Number 2 - 21 CFR 211.22(d) - Procedures not in writing or not fully followed**
 - The responsibilities and procedures applicable to the quality control unit are not [in writing] or [fully followed]. Specifically, ***
- **Number 3 - 21 CFR 211.113(b) –Procedures and Validation for sterile drug products**
 - Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not [established] [written] [followed]. Specifically, ***
 - Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include [adequate] validation of the sterilization process. Specifically, ***
 - Visual Inspection, Particulate and Physical Defect controls.

TOP 10 FDA – 483 CITATION THEMES

- **Number 4 - 21 CFR 211.160(b)- Scientifically sound laboratory controls**
 - Laboratory controls do not include the establishment of scientifically sound and appropriate [specifications] [standards] [sampling plans] [test procedures] designed to assure that [components] [drug product containers] [closures] [in-process materials]
- **Number 5 - 21 CFR 211.100(a)–Absence of Written Procedures; Approval and review of procedures; Changes to Procedures Not Reviewed or Approved**
 - There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Specifically, ***
 - Written procedures are not [drafted, reviewed and approved by the appropriate organizational units] [reviewed and approved by the quality control unit]. Specifically, ***
 - Changes to written procedures are not [drafted, reviewed and approved by the appropriate organizational unit] [reviewed and approved by the quality control unit]. Specifically, ***

TOP 10 FDA – 483 CITATION THEMES

- **Number 6 - 21 CFR 211.25(a) – GMP Training Frequency; Training , Education , Experience overall; Training--operations, GMPs, written procedures**
 - GMP training is not conducted [on a continuing basis] [with sufficient frequency] to assure that employees remain familiar with CGMP requirements applicable to them. Specifically, ***
 - Employees engaged in the [manufacture] [processing] [packing] [holding] of a drug product lack the [education] [training] [experience] required to perform their assigned functions. Specifically, ***
 - Employees are not given training in [the particular operations they perform as part of their function] [current good manufacturing practices] [written procedures required by current good manufacturing practice regulations]. Specifically, ***
- **Number 7 - 21 CFR 211.166(a) – Lack of written stability program; Results not used for expiration dates, storage conditions; Written program is not followed**
 - There is no written testing program designed to assess the stability characteristics of drug products. Specifically, ***
 - Results of stability testing are not used in determining [appropriate storage conditions] [expiration dates]. Specifically, ***
 - The written stability testing program is not followed. Specifically, ***

TOP 10 FDA – 483 CITATION THEMES

- **Number 8 - 21 CFR 211.42(c)(10)(iv) – Environmental Monitoring System**
 - Aseptic processing areas are deficient regarding the system for monitoring environmental conditions. Specifically,***
- **Number 9 - 21 CFR 211.110(a) – Control procedures fail to include the following; Control procedures to monitor and validate performance; Written in-process control procedures**
 - Control procedures fail to include [tablet or capsule weight variation] [disintegration time] [adequacy of mixing to assure uniformity and homogeneity] [dissolution time and rate] [clarity, completeness or pH of solutions]. Specifically,***
 - Control procedures are not established which [monitor the output] [validate the performance] of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Specifically***
 - Written procedures are not [established] [followed] that describe the [in-process controls] [tests] [examinations] to be conducted on appropriate samples of in-process materials of each batch. Specifically,***

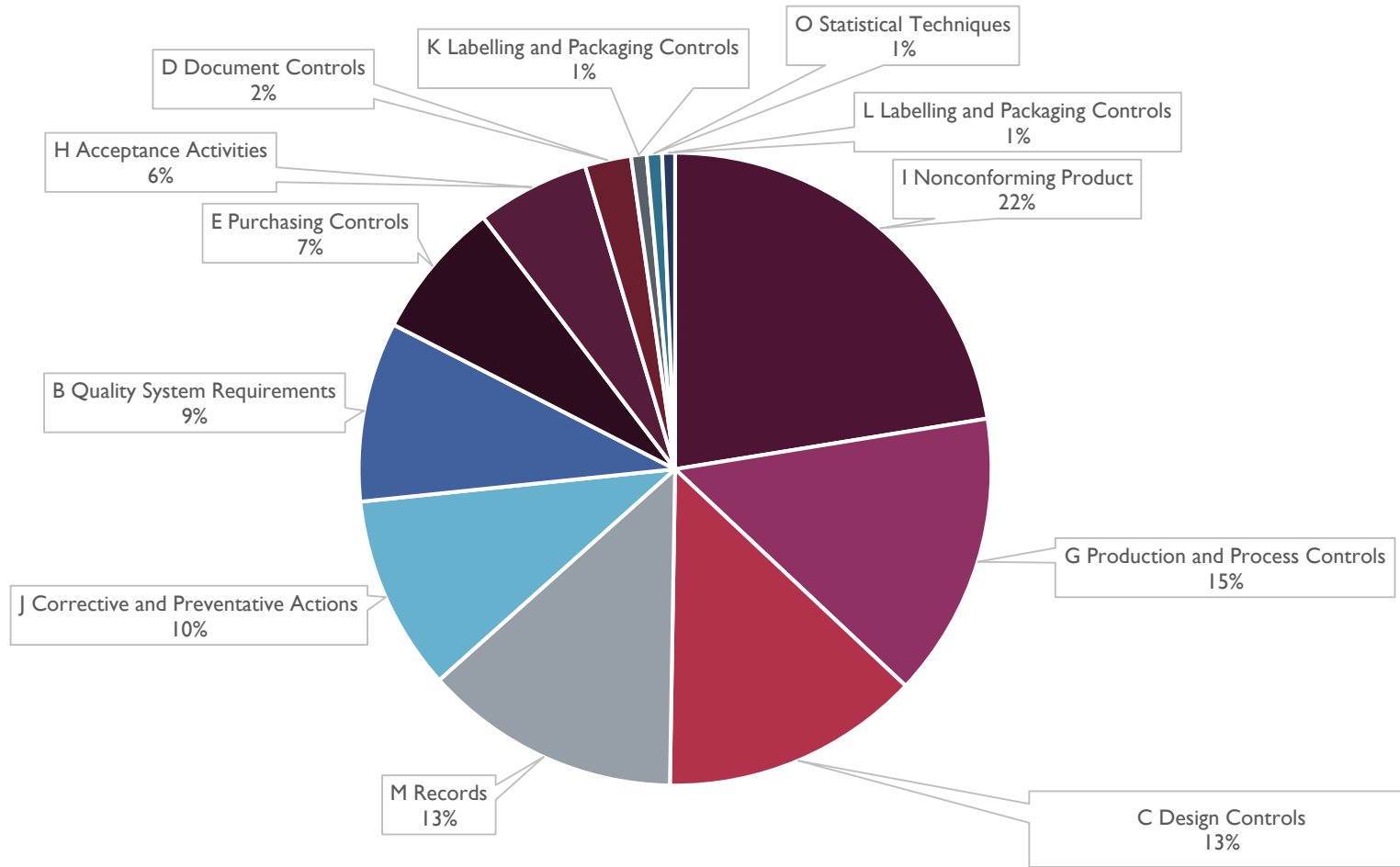
TOP 10 FDA – 483 CITATION THEMES

Number 10 - 21 CFR 211.165(a) - Testing and release for distribution

- Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the [final specifications] [identity and strength of each active ingredient] prior to release. Specifically,***
- Particulate Matter inspection and life-cycle controls
 - Inspection personnel not qualified using a consistent and sensitive method
 - Monitoring and trending of defects not performed
 - Components that are pre-processed (final cleaning) by the supplier are not adequately evaluated as to acceptance criteria and supplier control practices.

FDA – MEDICAL DEVICES

2015 - 21CFR820 Warning Letter Citations for Medical Devices



FDA – MEDICAL DEVICES

| 21 CFR 820 - Subpart | No of citations |
|---------------------------------------|-----------------|
| I Nonconforming Product | 171 |
| G Production and Process Controls | 111 |
| C Design Controls | 101 |
| M Records | 100 |
| J Corrective and Preventative Actions | 76 |
| B Quality System Requirements | 70 |
| E Purchasing Controls | 54 |
| H Acceptance Activities | 44 |
| D Document Controls | 18 |
| K Labelling and Packaging Controls | 6 |
| O Statistical Techniques | 6 |
| L Labelling and Packaging Controls | 5 |
| A General Provisions | |
| F Identification and Traceability | |
| N Servicing | |
| Grand Total | 762 |

TOP 10 FDA – MEDICAL DEVICE CITATION THEMES

Number 1 – 820 - J Corrective and Preventative Actions:100(a) – CAPA procedures, records & validation, Investigating all sources of quality data

- CAPA procedure does not require analysis of all sources of quality data, including complaints for recurrent failures, device service/repair data etc.
- CAPA actions do not adequately investigate root cause of the nonconformity
- Criteria to determine whether corrective action is necessary not established

Number 2– 820 - M Records:198(a)- Complaint management procedure, investigation & records, Contractor qualification

- Failure to adequately record and evaluate complaints from all sources (returned products, service calls etc.)
- Failure to establish procedure for evaluation of complaints to determine whether an investigation is necessary.
- Failure to maintain complaint records that include all required data elements (date of complaint, complainant contact information, date of investigation, and all communications to complainant etc.

TOP 10 FDA – MEDICAL DEVICE CITATION THEMES

Number 3 – 820 - G Production and Process Controls:75(a) Process & Equipment validation, validation records, Statistical rationale

- Failure to validate a complete range of process parameters.
- Lack of valid statistical rationale for validation sampling plan and acceptance criteria.
- Failure to assess the need for revalidation of critical processes

Number 4– 820 - B Quality System Requirements:22 - Quality audit procedure, Auditor independence & training, Audit records

- Failure to conduct scheduled internal quality system audits.
- Failure to ensure that individuals who conduct quality audits do not have direct responsibility for the matters being audited.
- Failure to establish and maintain adequate quality audit procedures

TOP 10 FDA – MEDICAL DEVICE CITATION THEMES

Number 5 – 820 - E Purchasing Controls:50 - Supplier qualification, Supplier quality agreement, Material evaluation criteria, Purchasing document records

- Agreements with software design contractors do not contain a provision that contractors agree to notify of changes in the product code or service so that parent firm may determine potential impact on quality of the product provided.
- Failure to adequately conduct and maintain records of supplier audits.

Number 6– 820 - I Non-conforming product:90(a) - Investigation of nonconformance, Nonconforming product or rework activities records, Disposition of nonconforming product records, Failure to follow established procedures

- Failure to establish procedures that require documented evaluation/investigation of suppliers of nonconforming materials.
- Failure to record all non-conformance and rework incidences and activities.
- Releasing products that failed established acceptance criteria without adequate non-conformity review and justification.

TOP 10 FDA – MEDICAL DEVICE CITATION THEMES

Number 7 – 820 - M Records:184 - Device History Record (DHR), In process & Finished product acceptance records,

- Failure to establish a written procedure to maintain a device history record (DHR).
- Failure to include in process and finished product acceptance records in device history record (DHR).
- Failure to the devices to meet specifications in the device history record (DHR)

Number 8– 820 - C Design Controls:30(g) - Design change validation, Process validation, Acceptance criteria, Risk analysis, Statistical rationale

- Failure to maintain an approved protocol that listed accepted criteria to demonstrate the finished products meeting approved criteria.
- Failure to follow approved design validation protocols and failure to record adequate justifications of deviations.
- Failure to document the design validation protocol and raw data in the Design History File (DHF).

TOP 10 FDA – MEDICAL DEVICE CITATION THEMES

Number 9 – 820 - C Design Controls:30(i) - Design change validation, Design change control, Design change records

- Failure to establish a written design change procedure.
- Failure to engage a formal change control for design changes.
- Failure to document, verify or validate, review, and approve design changes before implementation.

Number 10 – 820 - M Records:181 - Failure to maintain adequate device master record (DMR)

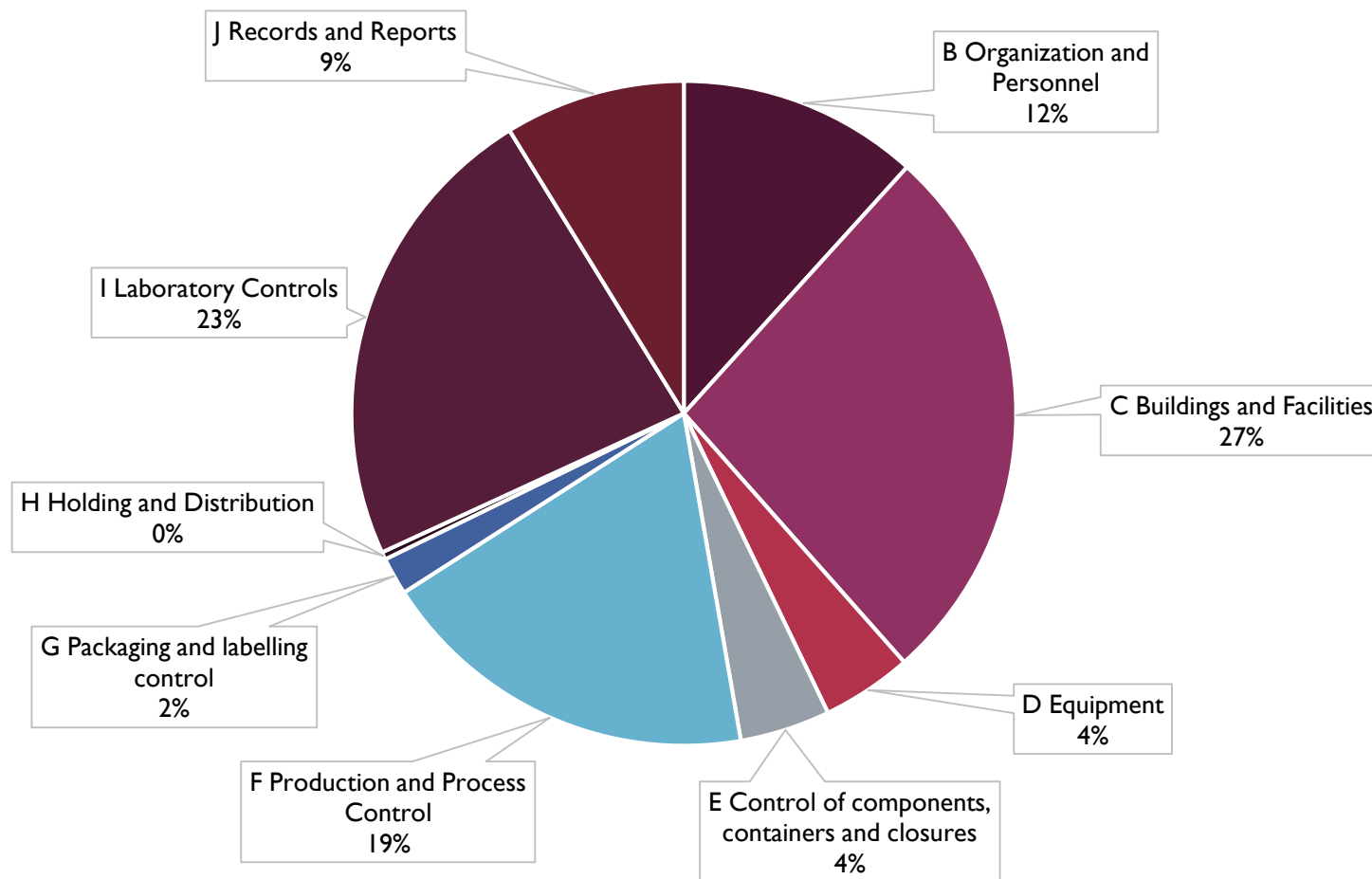
- 1. Failure to maintain a complete DMR that references all device specifications, production process specifications, quality assurance procedures and specifications, and packaging and labeling specifications.
- 2. Failure to maintain device master records (DMRs) that include, or refer to the location of, device specifications including appropriate drawings, composition, formulation, component specifications, and software specifications.

FDA – WARNING LETTER DEMOGRAPHICS

| FDA Warning Letters for Finished Pharmaceuticals and APIs - 2014-2015 | | | |
|-----------------------------------------------------------------------|------|------|-------|
| - | Year | | |
| Country | 2014 | 2015 | Total |
| Australia | 1 | | 1 |
| Canada | | 5 | 5 |
| China | 6 | 8 | 14 |
| Czech Republic | | 1 | 1 |
| Germany | 1 | 3 | 4 |
| Hong Kong | 1 | 1 | 2 |
| India | 7 | 12 | 19 |
| Ireland | 1 | | 1 |
| Italy | 1 | 3 | 4 |
| New Zealand | | 1 | 1 |
| Portugal | 1 | | 1 |
| Thailand | | 1 | 1 |
| USA | 23 | 84 | 107 |
| Total | 42 | 119 | 161 |

FDA – WARNING LETTERS

2014 and 2015 FDA Warning Letters - Finished Pharmaceuticals



TOP 10 FDA – 21 CFR 211 -WARNING LETTER CITATIONS THEMES

Number 1 – 211:42(c)(10) - Environmental Monitoring System (EMS)

- Inadequate EMS system in place to monitor aseptic processing areas
- Inadequate scientific studies/data to establish cross-contamination prevention
- Inadequate justification for sampling plans (location, frequency, method) for EMS

Number 2 – 211:166(a)- Stability Testing

- Failure to conduct finished product stability testing for all APIs in the product
- Un-validated stability test methods

Number 3 – 211:42(c)(10)(v) - Cleaning Validation

- Failure to sanitize/sterilize all equipment before being transported into the controlled environment
- Failure to use appropriate sterilization agents e.g. sporicidal disinfectants as indicated by monitoring or routine rotation
- Particulate matter reduction not included in cleaning validation

TOP 10 FDA – 21 CFR 211-WARNING LETTER CITATIONS THEMES

Number 4 – 211:28(a) - Gowning

- Not replacing gowns at the required frequency
- Use of non-sterile gowns in aseptic processing areas
- Exposed skin

Number 5 – 211:167(a)- Finished product testing

- Inadequate sterility testing on finished products, containers or closures

Number 6 – 211:113(b) – Micro-contamination

- Inadequate scientific data to establish that aseptic process hoods provide protect from lower quality surrounding air
- Use of non-sterile cleaning wipes
- Inadequate/lack of dynamic airflow studies in controlled environments

Number 7 – 211:165(a) - Finished product testing

- Failure to test all APIs in the finished product testing at the time of batch release
- **Failure to monitor API for particulate matter in a sterile suspension**

TOP 10 FDA – 21 CFR 211-WARNING LETTER CITATIONS THEMES

Number 8 – 211:22(d) - Documentation

- Failure to document procedures and roles and responsibilities applicable Quality Control Unit (QCU)
- Failure to follow written procedures

Number 9 – 211:68(b)- Access control

- Passwords to computer systems/database shared between multiple operators
- Audit trail features disabled in key data collection software
- Data files deleted without alternative record or justification

Number 10 – 211:194(a) – Data Integrity

- Incomplete batch documentation
- Falsification of data on batch documentation
- Data/test results deemed to be "trial" data and eliminated from released batch documentation without adequate justification
- Relevant data pages torn off from laboratory logs and found in trash bags

HOT TOPICS CONCLUSIONS

The FDA and world regulatory bodies are increasing the “tools” that can assure pharmaceutical R&D, Clinical Trials, Manufacturing, Testing/Release and Distribution Practices are, **by design**, made to be more robust and transparent to evaluation.

The Hot Topics take away is to design all systems to demonstrate very clearly the basic elements of Procedural Control, Monitoring, Data Integrity, Data Security and Quality Decisions in order to foster confidence and co-operation with regulators yielding an effective and consistent supply of medications to patients.

Get your Ducks in a Row!!

