



ASTM D10-F02 Workshop

FDA Regulatory Perspective

Patrick Weixel

FDA

Center for Devices and Radiological Health



FDA Regulatory Perspective

Focus of talk:

Use of Standards

Auditing Packaging Process

Deficiencies observed during device inspections

FDA's Involvement with Standards



21st Century Cures requirements:

- Requires CDRH to be involved in standards recognition and transparency of regulatory decisions.
- Improve the number of standards recognized from outside stakeholder requests
- Train all employees involved with premarket review
- Update guidance demonstrating principles for recognizing and withdrawing standards
- Firms can reference recognized standards in a Declaration of Conformity, which can satisfy a premarket submission requirement



Using Standards in Premarket Submissions

Premarket Notifications – 510(k) Submissions

Premarket Use of Standards - Devices

Firms use standards in their premarket submissions in order to :

- State conformance with recognized consensus standards. Stating conformance to a standard is strictly voluntary. Device firms are not mandated to comply with a standard once FDA has recognized a standard
- Recognition of consensus standards helps to streamline premarket submissions of devices to be marketed in the United States
- Recognition of standards minimizes data needed in premarket submissions

Medical Device Industry Use of Standards

- When a device manufacturer decides to recognize a standard to meet a premarket requirement, they must provide a declaration of conformance for the standard
- Must maintain data to demonstrate conformance
- This data may be requested by FDA at any time (typically during inspections)
- Failure to demonstrate or falsify conformance to a standard is a prohibited act. Devices will be considered misbranded



Auditing the Packaging Processes

Quality System requirements evaluated



FDA Inspection of the Sterilization/Packaging Process

- Evaluate Procedures – Ensure procedures meet FDA requirements and provide adequate instructions to complete the task
- Personnel – Adequate resources. Experienced and trained personnel
- Procedures are being implemented. Sterilization/Packaging records and Microbiology results maintained and reviewed
- When a non-conformances could occur during manufacturing, making sure process controls are implemented. Process control procedures
- Equipment is calibrated (sealing equipment, timers) and routine maintenance is identified for equipment



FDA Inspection of the Sterilization/Packaging Process

- Confirm sterilization and packaging process has been validated
- Review sterilization/packaging data from routine processed lots/batches to ensure they were sterilized within the validated parameters
- Appropriate records are maintained, reviewed and approved before releasing product
- Adequate controls established for nonconforming product
- Purchasing/Supplier controls – i.e. written agreement with contract sterilizer



FDA inspection of the Packaging Process

- FDA inspections of sterilization and packaging for medical devices often focuses on the process validation - 21 Code of Federal Regulation (CFR) 820.75
- Packaging can be evaluated throughout the Quality System regulation:

21 CFR 820.20 – Management Responsibility

- Ensure personnel involved in sterilization and packaging are adequately trained, ensure QS requirements are effectively established and maintained, conducting and documenting management reviews.



FDA inspection of the Packaging Process

21 CFR 820.22 – Quality Audit

- Ensuring packaging process is being reviewed during quality audits. If a contract packager is used, ensure they are adequately evaluated and complying with the QS regulation

21 CFR 820.25 – Personnel

- Training is documented. Personnel aware of device defects which may occur from improper job performance. Personnel that perform verification or validation – need to be made aware of defects or errors that may be encountered from their job function.

FDA inspection of the Packaging Process

21 CFR 820.30 – Design Controls

- Is packaging considered part of the design project?
- Design output definition includes...packaging and labeling.
- Packaging compatible with the sterilization process. Testing to verify shelf life date.

21 CFR 820.50 – Purchasing Controls

- Evaluate packaging suppliers or contractors and their ability to meet specified (quality) requirements.
- Define the type and extent of control to be exercised
- Maintain purchasing data that describe the specified requirements and maintain list of acceptable suppliers



FDA inspection of the Packaging Process

21 CFR 820.70 – Production and Process Controls

- Where deviations from a device specification could occur from manufacturing process, the manufacture shall establish process control procedures.

- b. Production and process changes
- c. Environmental Controls
- d. Personnel
- e. Contamination Control
- f. Buildings
- g. Equipment (i.e. sealer)
- h. manufacturing material
- i. automated process

21 CFR 820.72 – Inspection, Measuring and test equipment

- Control of inspection, measuring and test equipment; capable of producing valid results;
- Calibration - Calibration standards; Calibration records.



21 CFR 820.75 – Process Validation

- Packaging process has been validated according to procedures and specified parameters.
- Validation activities and results. Documentation of major equipment used. Conducted by qualified personnel.

21 CFR 820.130 – Device Packaging

- Designed and constructed to protect the device during processing, storage, handling, and distribution
- Validation of Sterile Packaging process is often inspected. Packaging issues are the reason for most recalls due to lack of sterility assurance



21 CFR 820.80 – Acceptance Activities – Receiving, In-process, and Finished device acceptance

- Incoming inspection of packaging material, In-process testing of sealing equipment, finished packaging acceptance activities

21 CFR 820.90 – Nonconforming Product

- Establish controls for product that do not meet specified requirements. (i.e. validated sealing parameters not used)

FDA inspection of the Packaging Process

- **21 CFR 820.100 – Corrective and Preventive Action**

1. Analyze sources of quality data	5. Implement changes to procedures
2. Investigate nonconformity cause	6. Disseminate information
3. Identify corrective/preventive action	7. Submit information for management review
4. Verify/Validate effectiveness of action	

- **Examples when corrective action may be needed:**
Out of box failures, complaints of compromised seals



FDA inspection of the Packagin Process

- 21 CFR 820.140 – Handling
 - Ensure mix-up, damage, deterioration, contamination to product do not occur during handling
- 21 CFR 820.150 – Storage
 - Control of storage areas and stock rooms for product to prevent mix-ups, damage, deterioration, or contamination. Ensure obsolete, rejected or deteriorated product is not used or distributed

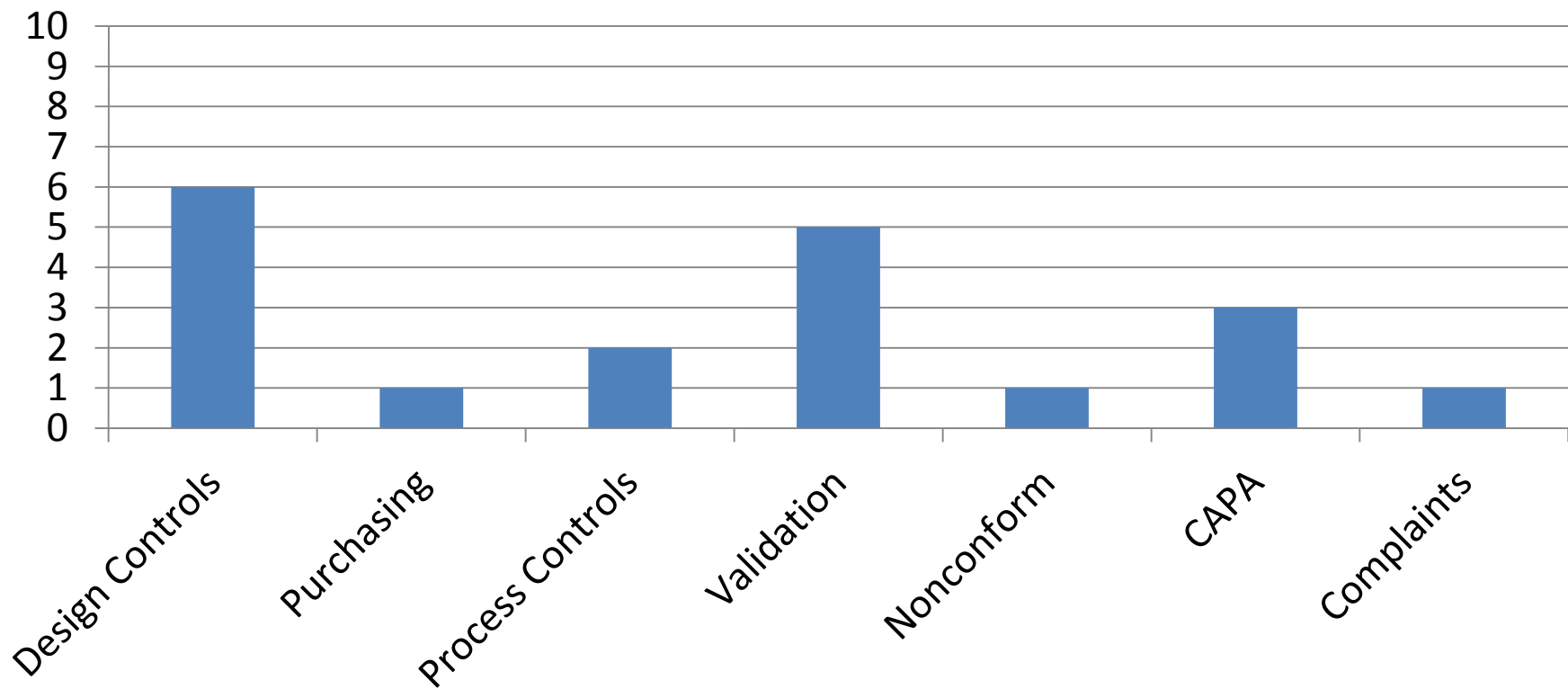


2016 Inspectional Observations

- 137 Inspections – Sterilization was audited
- Gamma – 46 inspections
- Ebeam – 6 inspections
- Ethylene Oxide - 81 Inspections
- Moist Heat – 17 inspections
- Gas Plasma - 5

2016 Packaging Observations

■ # of Observations



Packaging Observations

21 CFR 820.30 – Design Controls

- 3 observations - Shelf life stability testing not done
- Pouch design change and no verification or validation completed.
- Design input requirements for pouch seal strength were not available
- Changed to smaller sterile barrier system & no test results for peel test and seal strength

Packaging Observations

21 CFR 820.50 – Purchasing (Supplier) Controls

- Quality requirement for contract sterilizer were not maintained

21 CFR 820.70 – Production & Process Controls

- Sealers in cleanroom are capable of producing contaminants
- No maximum sealing parameter was established for the blister tray

Packaging Observation

21 CFR 820.75 – Process Validation

- Validation did not take into account manufacturing challenges per SOP requirements. No documentation that sealing machine met specifications
- Sealer not validated for temperature range used in manufacturing
- Validation did not cover all packaging configurations. Heat Sealer not qualified, transportation and shelf life not done

Packaging Observations

Process Validation continued

- Pouch Sealing process not validated
- Did not qualify if packaging equipment was properly installed for a manufacturing site change

21 CFR 820.90 – Nonconforming Product

- Packages sealed outside of the validated parameters and products released

Packaging Observations

21 CFR 820.100 – Corrective & Preventive Action

- 34 deviations w/ debris in packaging not properly documented. No statistical analysis
- No investigation of hair in tray
- Compromised seals and no root cause was determined. Due to compromised seals, a new pouch was implemented with verification/validation not being completed

Packaging Observations

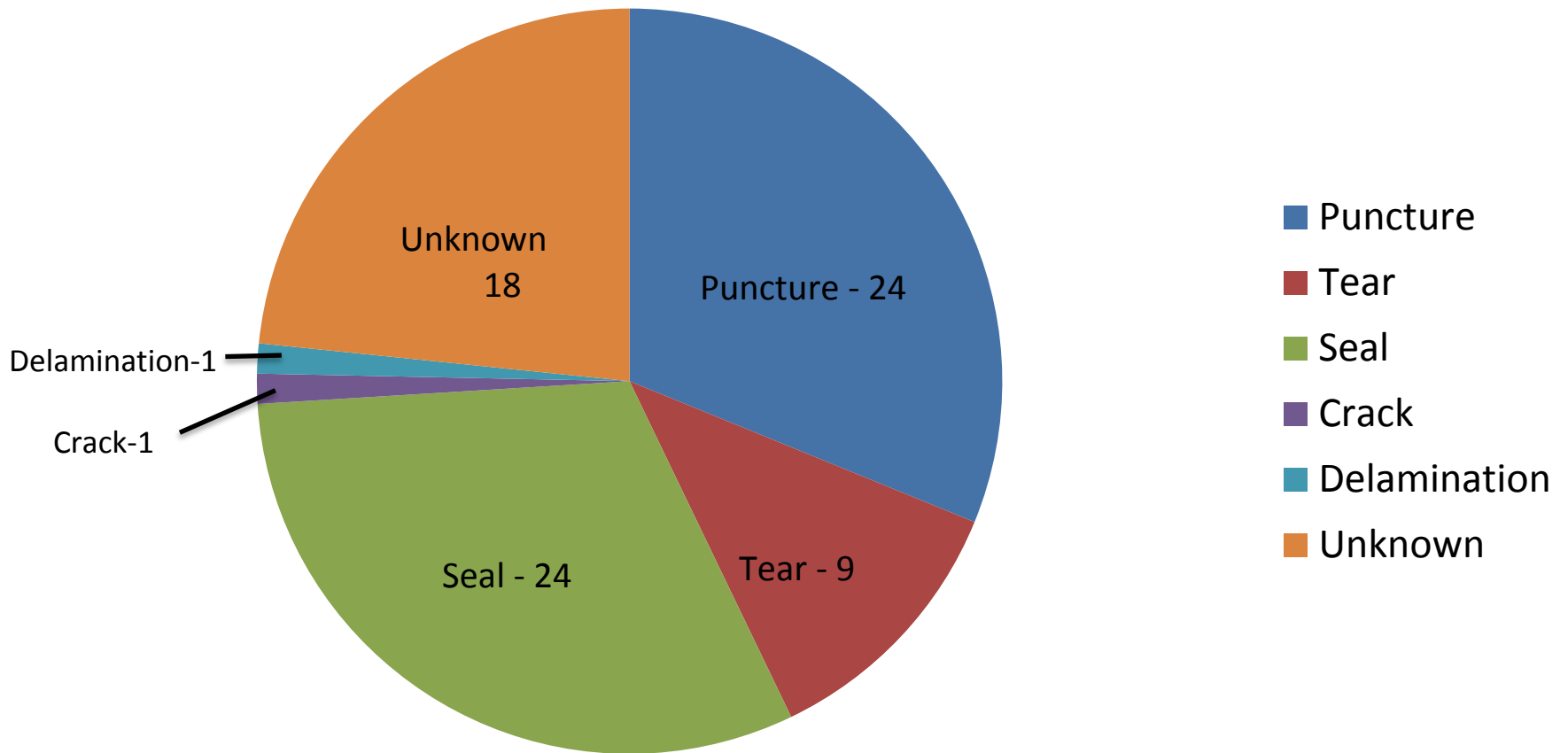
21 CFR 820.198 – Complaint Files

- Inadequate investigation of device packaging with foreign material in pouch

Packaging Recalls

Calendar year of 2016

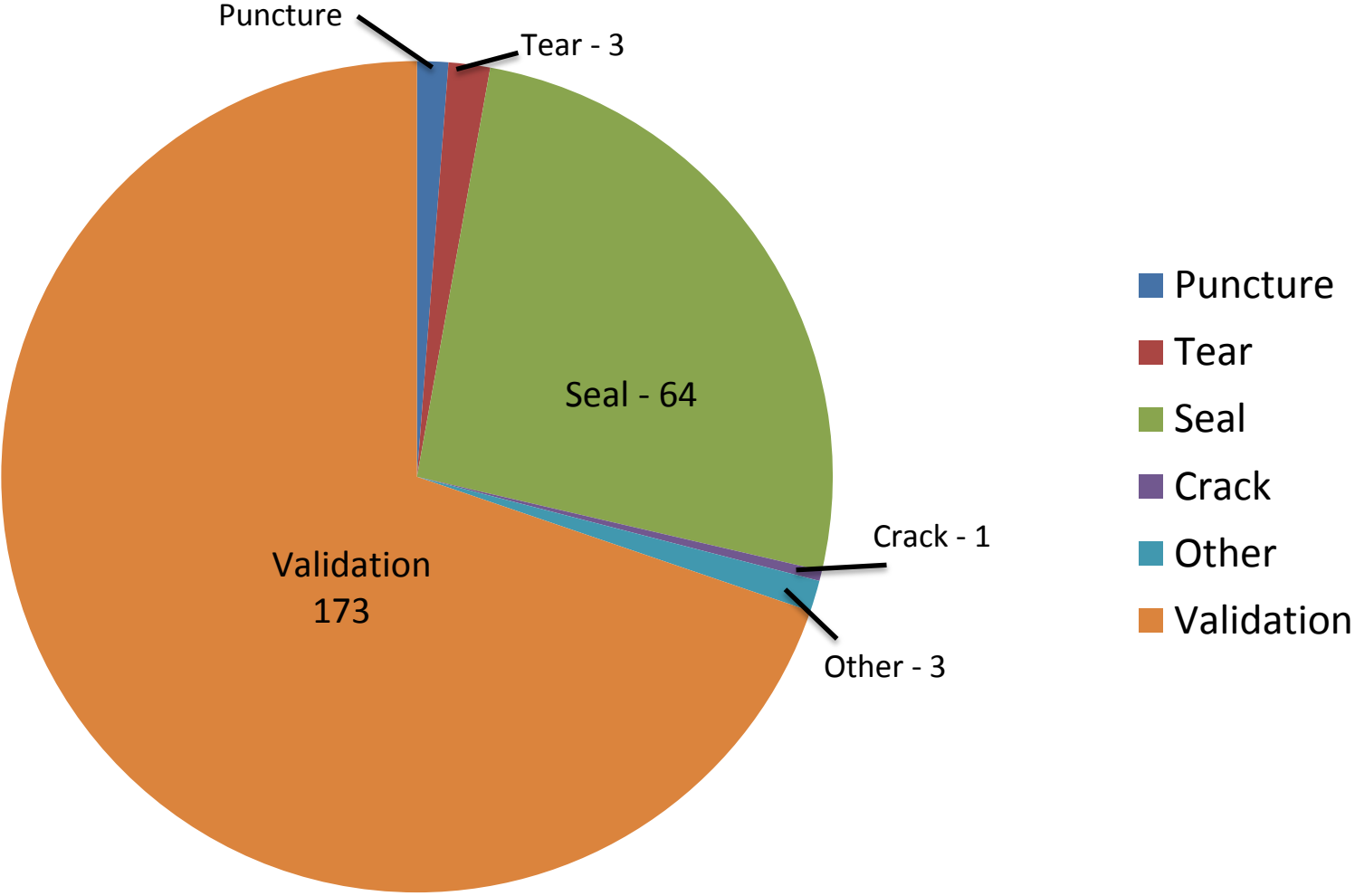
Design Recalls



Causes of Design Recalls

- Inadequate design - device punctures pouch
- Packaging System design requires folding pouch
- Device protective coverings came off punctured sterile barrier system
- Unknown recalls – seal integrity may be reduced

Production-Process Control Recalls



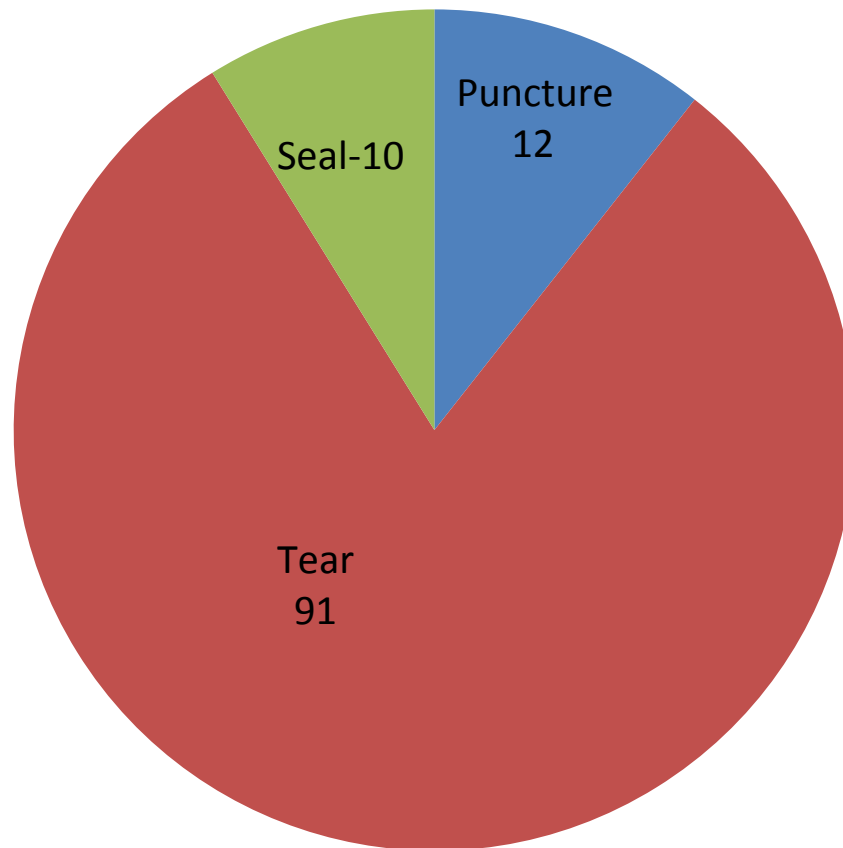
Causes of PPC recalls




- Variation in SBS material thickness – heat transfer
- Wrong sealing bar installed – heat transfer
- Debris on sealer
- Conveyor used to transport pouch punctured the pouch
- Forming of tray/pouch – too thin – when device placed in SBS punctures/cracks SBS.

Causes of PPC Recalls

- Incorrect temperature probe used on sealer
- Worst case product not used
- Maintenance of equipment did not control or assess variations of the equipment
- Aging &/or transportation testing not available
- Equipment was not calibrated
- Splicing of packaging material

Supplier Recalls

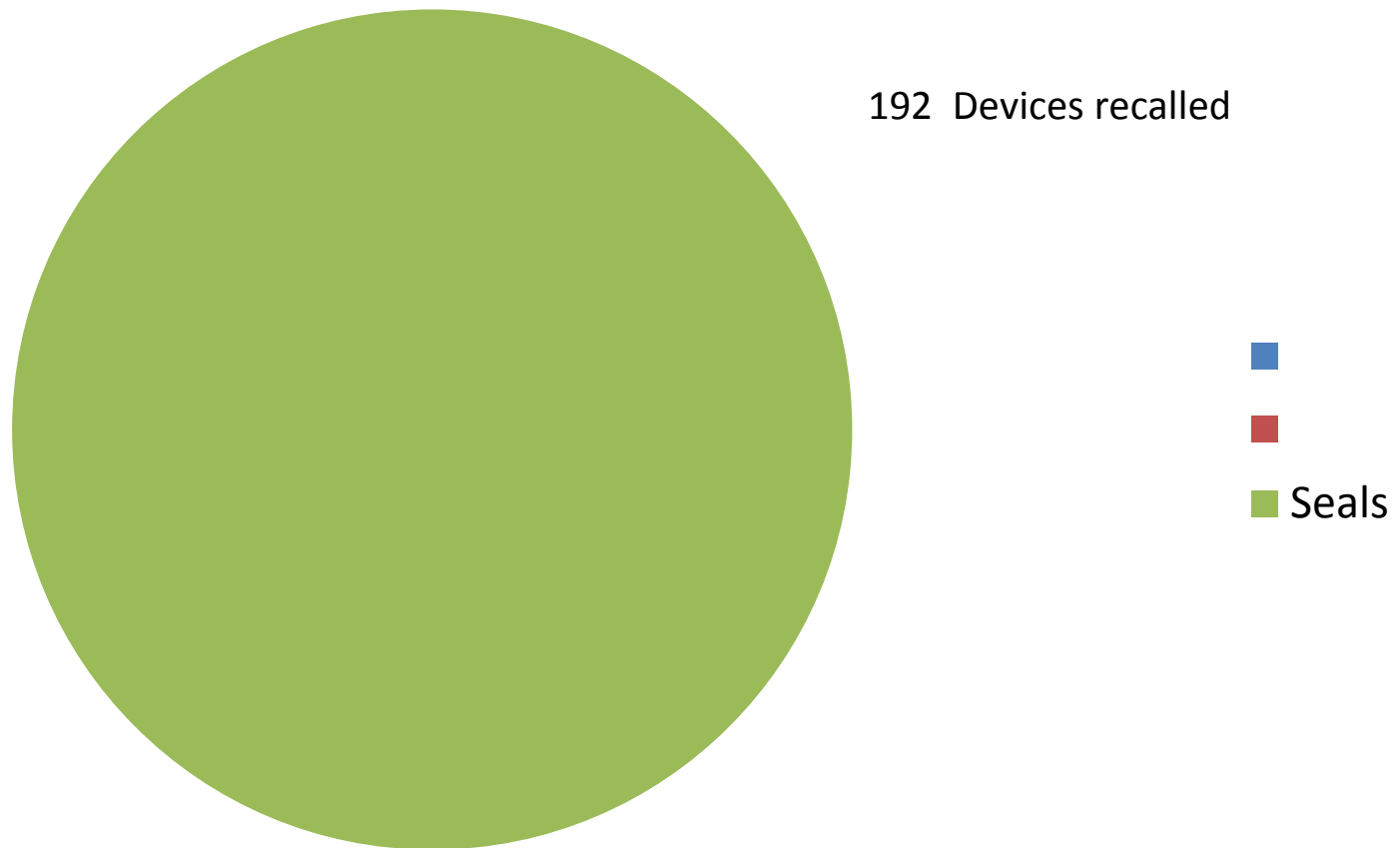


-  Puncture
-  Tear
-  Seal

Causes of Supplier Recalls

- Seal process deficient
- Seal opens under extreme shipping conditions
- SBS material had tears/cuts

Recalls due to Employee Errors



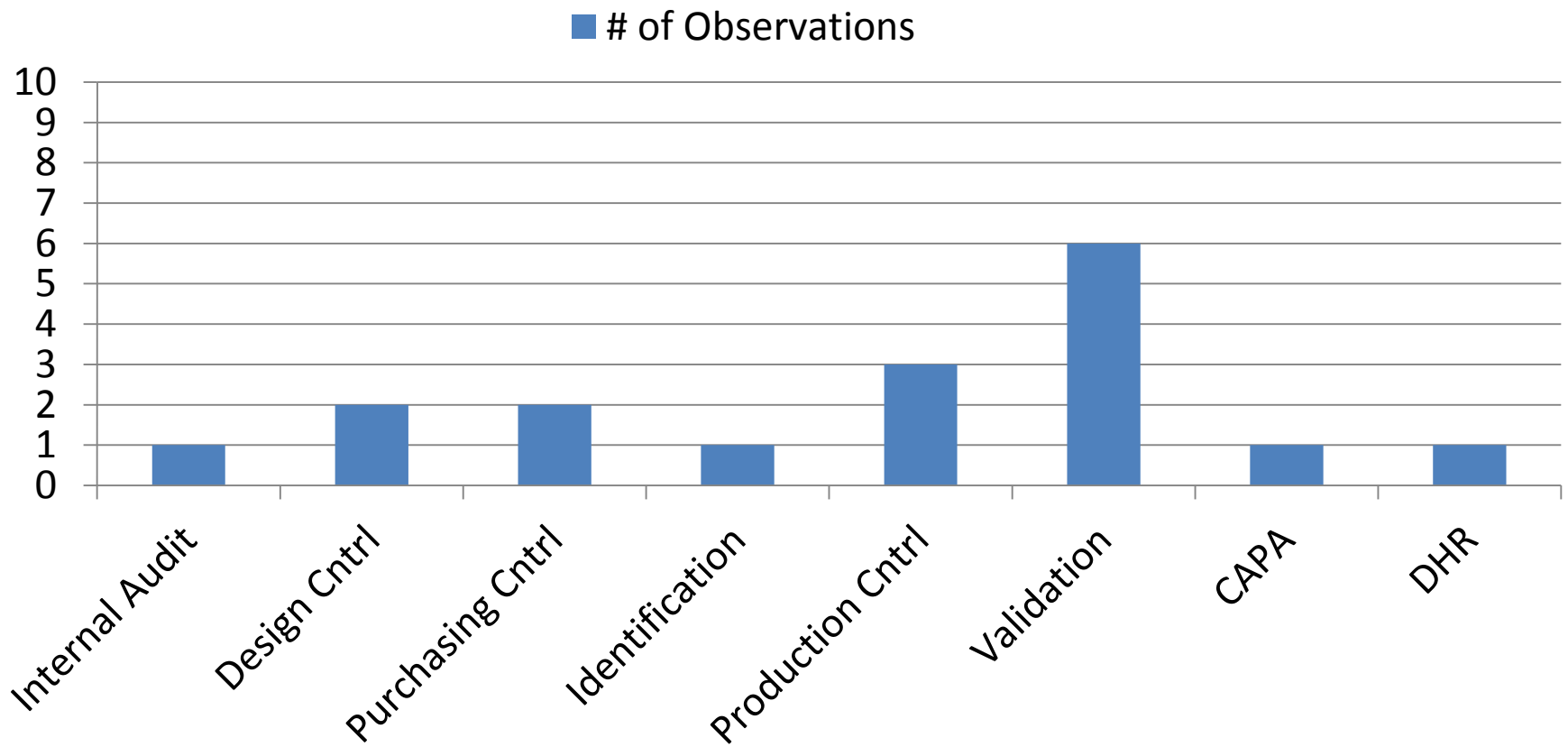
Causes of Employee Errors

- Employee technique may not have allowed for the proper seal to form
- Sealing and visual inspections not conducted
- Mixing sealed and unsealed product
- Misaligned incomplete seals
- Sealer switch not turned did not monitor equipment properly
- Product in sealing area

Labeling Recalls

- 86 device recalls due to mislabeled product or wrong product in package
- 17 device recalls due to wrong IFUs
- 5 device recalls due to wrong expiration date

2016 Radiation Observation



2016 Radiation Observations

21 CFR 820.22 – Internal Audits

- No Internal audits from 2013 – 2105

21 CFR 820.30 – Design Controls

- Package configuration changed (larger box & 9 more devices per box)
- Increased dose 10 kGy and package design change. No assessment on need to revalidate



Radiation Observations

21 CFR 820.50 – Purchasing Controls

- Did not reevaluate contract sterilizer annually as required by SOP
- No requirement to have supplier/contractor to notify manufacturer of changes to product or services that could impact the device.



Radiation Observations

21 CFR 820.60 – Identification

- Identification sticker showing product was sterilized was not on the product

21 CFR 820.70 – Production & Process Controls

- No monitoring of laminar flow hoods used for bioburden testing
- Environmental monitoring not documented; Not conducted at scheduled frequencies

21 CFR 820.75 – Process Validation

- Oven used in accelerated aging was not fully qualified. Temp. readout not documented. Temperature probe calibration not available
- Bioburden sample size not defined. Two bioburden test methods used, but no instructions on when each method is to be used. Bioburden action limit exceeded, no investigation

Radiation Observations

21 CFR 820.75 – Process Validation

- No rationale available for redefining product families. Simulated product used but lack rationale how all devices are represented
- No data available to ensure maximum dose of 40 kGy will not impact product
- Changed sterilization dose from 15 kGy to 17.5 kGy. No assessment on need for revalidation

Radiation Observations

21 CFR 820.75 – Process Validation

- Dose established in 2011, First dose audit done in 2013.

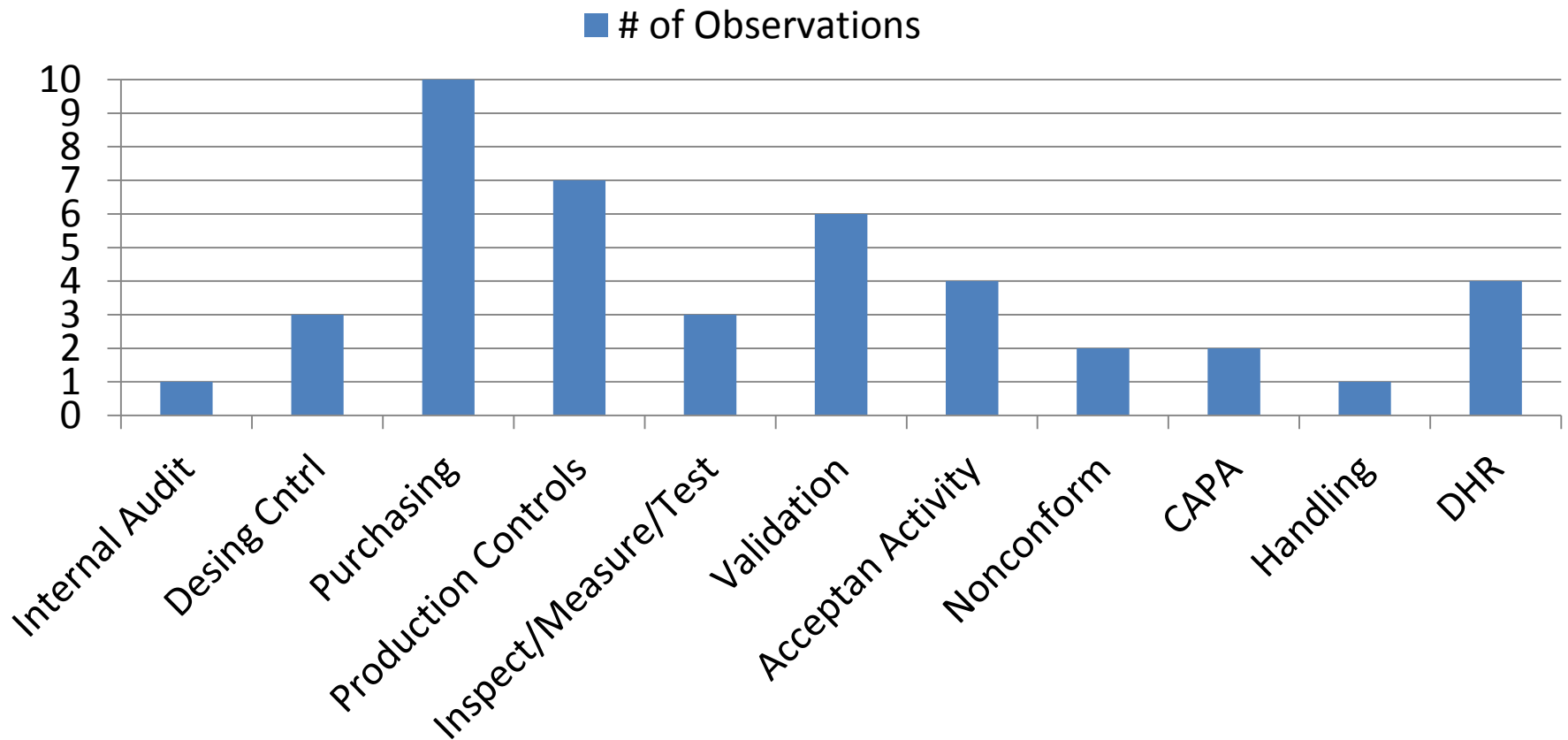
21 CFR 820.100 – CAPA

- 2 year real time shelf life testing done at 12 months and 30 months. Failed at 30 months. No investigation conducted

21 CFR 820.184

- No sterile batch information. Sterilization record location not maintained

2016 Ethylene Oxide Observations



Ethylene Oxide Observations

21 CFR 820.22 - Internal Audits

- Last internal quality audit conducted in 2014

21 CFR 820.30 – Design Controls

- No design control procedure. No assurance sterilization is part of the design
- No documentation of Lot #'s used in the sterilization study; test results dated prior the 2x sterilization cycle was conducted

Ethylene Oxide Observations

21 CFR 820.30 – Design Controls continued

- Did not validate the reprocessing and sterilization cycle per the IFU requirements

21 CFR 820.50 – Purchasing (Supplier) Controls

- 4 observations – Contract sterilizer not evaluated/supplier audits not conducted
- 2 observations – No written agreement w/ contract sterilizer (see also 21 CFR 801.150(e))
- No assurance contract manufacturer's sterilization process was validated

Ethylene Oxide Observations

Purchasing Controls continued

- No records maintained to ensure contract manufacturer provides a sterile component. Non-sterile components were received
- Biological Indicator not identified as a critical supplier
- Assessment of contract sterilizer survey used if sterilizing site “passes” FDA audit. Survey lacks Quality Control questions

Ethylene Oxide Observations

21 CFR 820.70 - Production and Process Controls

- Bioburden sampling not done at defined intervals
- EO sterilizer software not validated for its intended use
- Did not identify product as “quarantined” while awaiting BI test results (per firm’s SOPs)
- Equipment used to heat gas, was below the validated temperature

Ethylene Oxide Observations



Production & Process Controls continued

- Did not document repairs conducted on EO chamber. No unscheduled maintenance instructions
- EO containers stored in direct sunlight
- 4 of 5 cycles had precondition and exposure deviations and product was released

Ethylene Oxide Observations

- 21 CFR 820.72 – Inspection/Measurement/Test Equipment
- Thermocouples out of specification (OOS) – Calibration SOP does not require any investigation or potential customer notification when measuring equipment is OOS
- No assessment of impact to product when pressure controller was out of calibration
- 2 heat sealers – Calibration record does not identify which sealer was calibrated

Ethylene Oxide Observations



21 CFR 820.75 – Process Validation

- 2 observations – No documentation to show Internal and External Process Challenge Device (EPCD) is a greater challenge & no justification for location of EPCD
- Three, ½ cycles not done per customer requirements
- Partial cycle validation study resulted in over 50% of the BIs as positive for growth & results accepted

Ethylene Oxide Observations

Process Validation observations continued

- Requalification study and biological indicator was not put in the worst case location
- 2014 Validation study was not done per specifications:
- Routine aeration time less than validation time parameter
- Aeration temperature unknown; 9 instead of 21 temperature sensors used; maximum and minimum cycle documentation not available

Ethylene Oxide Observations



21 CFR 820.80 – Acceptance Activities

- Sterilization & Packaging acceptance reports do not require person performing the review and date of review to be documented
- 2 observations - No requirement to have sterilization records reviewed prior to release of product or review was documented
- 5 records revealed positive BI and product was released

Ethylene Oxide Observations

21 CFR 820.90 - Nonconforming Product

- No investigation conducted for 4 sterilization loads that had positive biological indicators
- No investigation for sterilization cycles that had nonconformance; Nonconformance report was not complete for low pressure during the dwell phase

Ethylene Oxide Observations



21 CFR 820.100 – Corrective Action Preventive Action

- Decrease in the cycle temperature and humidity and no verification/validation conducted for the corrective action
- Problem with new EO cycle and no corrective action was implemented

Ethylene Oxide Observations

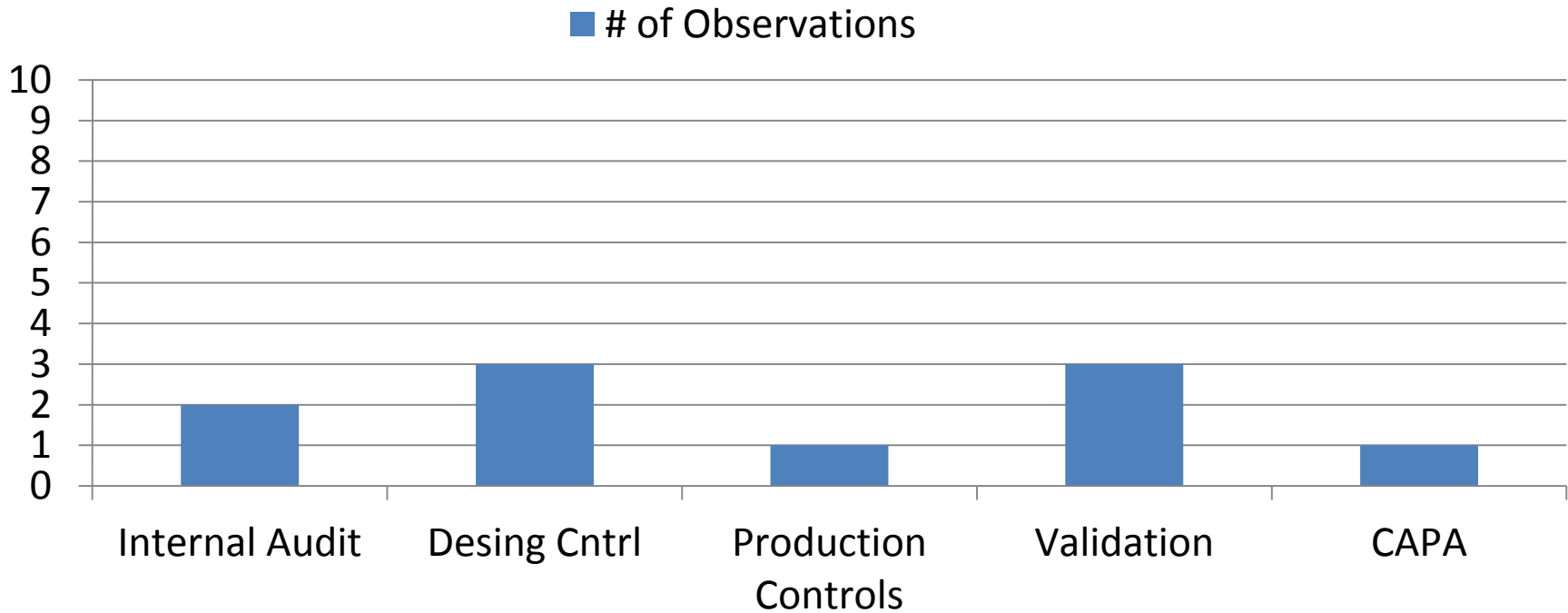
21 CFR 820.140 – Handling

- Device in bag tossed to sealing operator. Primary and Secondary pouch sealing done at same location and both are placed in same bin

21 CFR 820.184 – Device History Record

- DHR EO Exposure time exceeded
- DHR revealed multiple sterilization failures
- No documentation of the sterilization cycle used
- 10 lots released prior to receiving the BI results

2016 Moist Heat Observations



Moist Heat Observations

21 CFR 82.22 – Quality Audits

- Last audit conducted was 2 years ago
- No documentation that QS audit was done

21 CFR 820.30 – Design Controls

- No risk analysis conducted for leaking probes after sterilization
- 2 observations – Validation parameters do not match moist heat cycle in labeling instructions

Moist Heat Observations



21 CFR 820.70 – Production & Process Controls

- New software used to control the sterilizer has not been validated for its intended use

21 CFR 820.75

- Worst case challenge was not conducted during Operational Qualification
- Biological Indicators used once a week to monitor sterilization cycles
- No cleaning validation of reusable devices

Moist Heat Observations

21 CFR 820.100 – Corrective & Preventive Action

- Leakage was known to occur after moist heat cycles and no corrective action taken

FDA References

1. CDRH - Medical Devices Information –
<http://www.fda.gov/MedicalDevices/>
2. Medical Device Databases
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm>
3. Quality System regulation information
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/default.htm>
4. CDRH Learn - <http://www.fda.gov/Training/CDRHLearn/default.htm>
5. CDER Drug Information <http://www.fda.gov/Drugs/default.htm>
6. Office of Regulatory Affairs (ORA) – Inspection Information
<https://www.fda.gov/aboutfda/centersoffices/officeofglobalregulatoryoperationsandpolicy/ora/default.htm>



THANK YOU!

Patrick Weixel
Deputy Division Director
FDA/CDRH

Office of In Vitro Diagnostics and Radiological Health
Division of Radiological Health

Phone: 301.796.5537
Patrick.Weixel@FDA.HHS.GOV