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Packaging Trends Leading to Increased 483's

Accolades

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Agenda

- Code of Federal Regulations
- Observations (483's) and Recall Data
- Testing to mitigate these trends

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Packaging Regulations

21 CFR 820.130 Device Packaging

"Each manufacturer shall ensure that device packaging and shipping containers are designed and constructed to protect the device from alteration or damage during processing, storage, handling, and distribution"

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Packaging Regulations

21 CFR 820.75 Validation

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

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Packaging Regulations

21 CFR 820.70 Production/Process Controls

"Develop, conduct, control and monitor production processes to ensure that a device conforms to its specifications "

- Validation activities and results must be documented.
- Conducted by qualified personnel.

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Packaging Regulations

21 CFR 820.30 Design

– "Each manufacturer shall establish and maintain procedures for validating the device design.."

21 CFR 820.72 Inspection, Measuring and Test Equipment

- Equipment is suitable for intended purpose, capable and traceable

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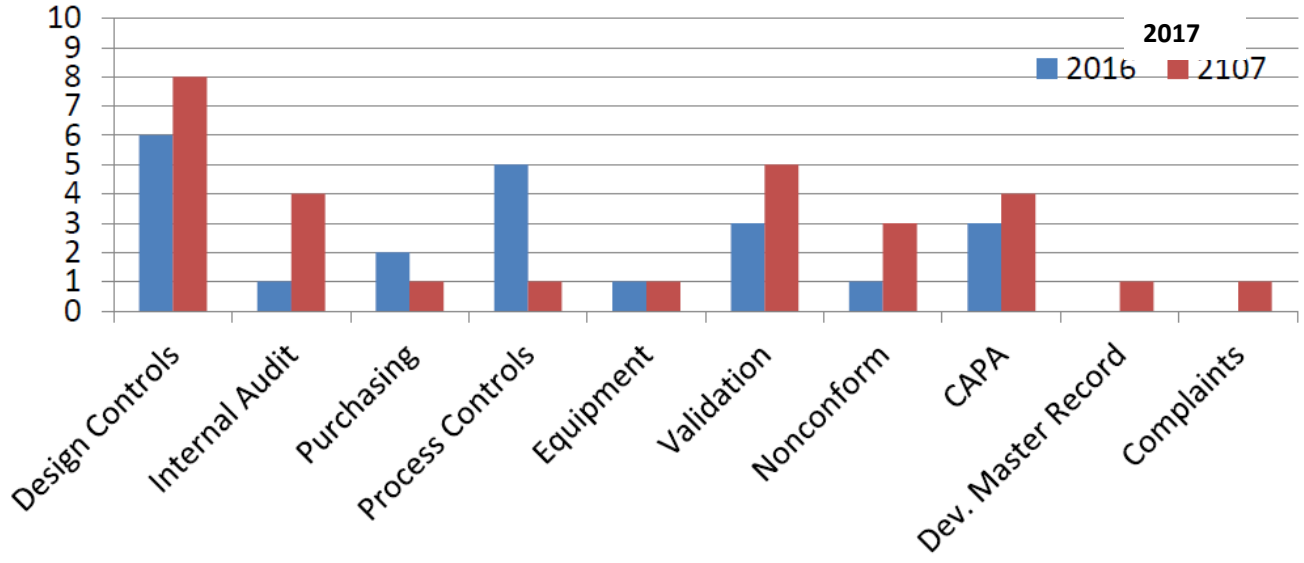
2016 vs 2017
Packaging Observations



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DESIGN

Configuration Changes

- Package configuration changed (larger box & 9 more devices per box)
- Pouch design change and no verification or validation completed.
- Changed to smaller sterile barrier system & no test results for seal strength

Sterilization Changes

- Increased dose 10 kGy and package design change. No assessment on need to revalidate

Shelf Life Changes

- Two (2) year real time shelf life testing done at 12 months and 30 months. Failed at 30 months. No investigation conducted
- Shelf life stability testing not done
- Increased shelf life, did not conduct testing
- Shelf life testing done by supplier. Did not match device manufacturer's equipment or SBS pouch size
- Expired product re-sterilized given another two-year shelf life

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PROCESS VALIDATION

Equipment

- No documentation that sealing machine met specifications
- Sealer not validated for temperature range used in manufacturing
- Did not qualify if packaging equipment was properly installed for a manufacturing site change
- Higher temps used in PQ vs. OQ temperature range

Package Seal

- Pouch sealing process not validated
- Validation did not cover all packaging configurations
- PQ did not include large and small packages

Burst test not documented for sealing validation

Multiple runs not conducted; no rationale for sample size

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PRODUCTION/PROCESS CONTROLS

Oven used in accelerated aging was not fully qualified

Sealers in cleanroom are capable of producing contaminants

Blister tray - No maximum sealing parameter

No procedure for monitoring sealing parameters

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SUPPLIER

No evidence supplier validated packaging process

CONTROL OF INSPECT, MEASURE, TEST EQUIPMENT

Adequate instructions for maintenance of sealing machine were not established

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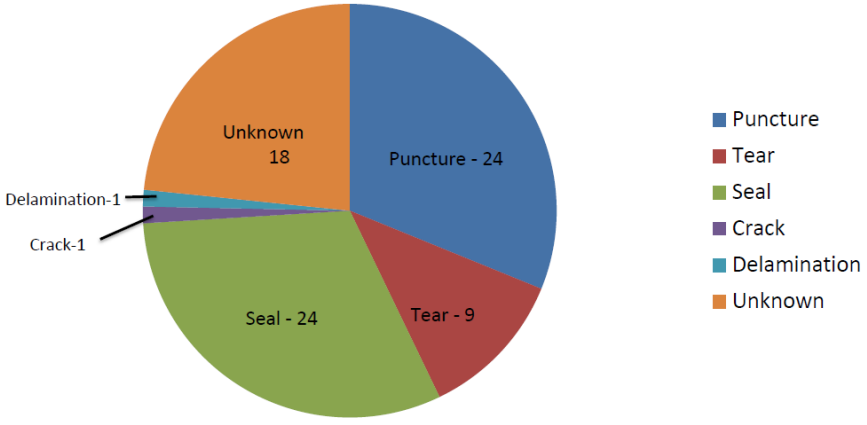
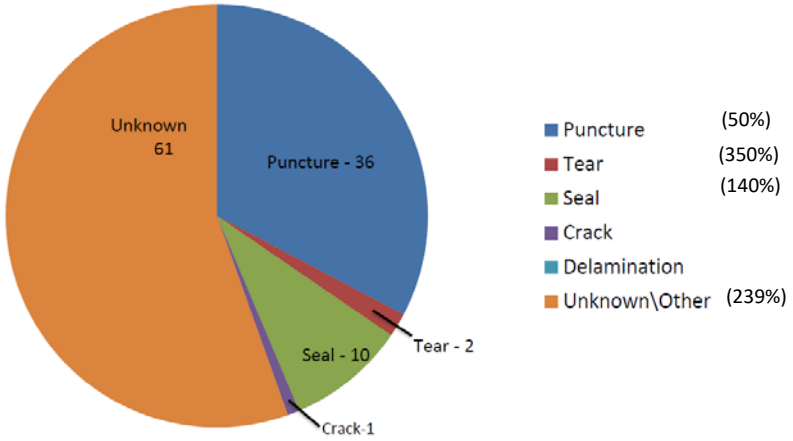
2016 Design Recalls



2017 Design Recalls



Unknown recalls – seal integrity may be reduced

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DESIGN RECALLS

Inadequate design –

- Device punctures pouch
- Device cracks blister package in same spot
- Device rubs against pouch-causes abrasion
- Cap not sized properly –may not seal properly
- Device moves during shipping puncturing SBS
- Device protective coverings came off punctured sterile barrier system

Packaging System design requires folding pouch

Failed distribution and simulation testing

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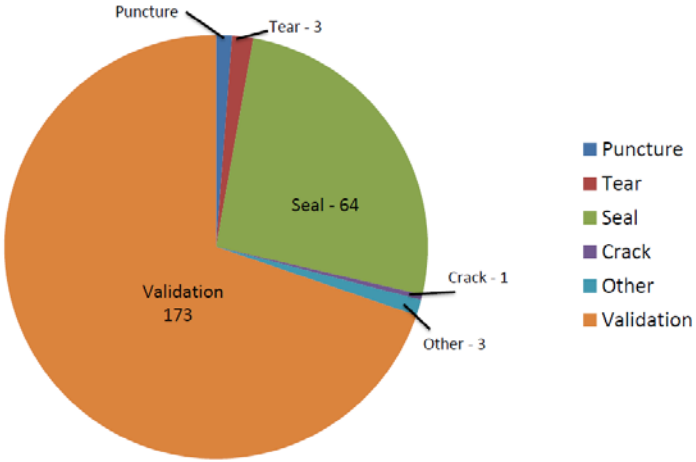
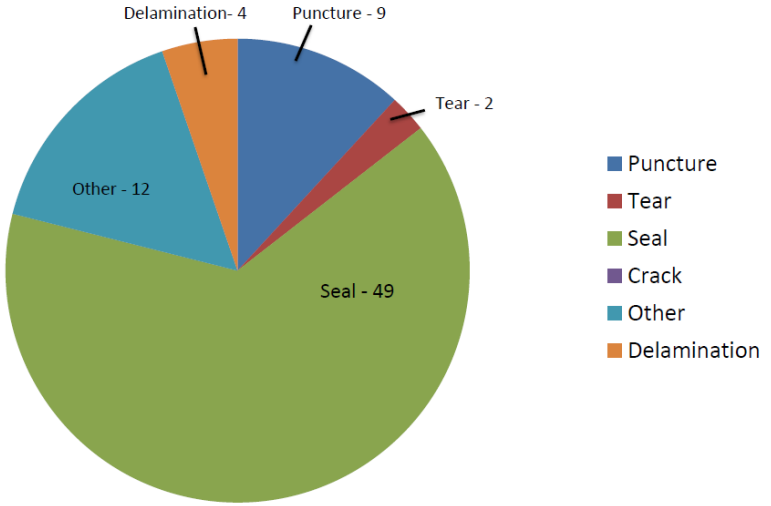
2016 Production-Process Control Recalls (245)



2017 Production-Process Control Recalls (76)



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Equipment

Wrong sealing bar installed –heat transfer
Debris on sealer
Conveyor used to transport pouch punctured the pouch
Maintenance of equipment did not control or assess variations of the equipment
Equipment was not calibrated
Seal bar too small; improper alignment of SBS
Maintenance of equipment; Loose wires, worn components – caused uneven heating
Minimum sealing temperature not met

PRODUCTION PROCESS CONTROL RECALLS

Material

Variation in SBS material thickness –heat transfer
Forming of tray/pouch –too thin, when device placed in SBS punctures/cracks.
Incorrect temperature probe used on sealer
All required products not placed in SBS
Splicing of packaging material

Testing

Worst case product not used
Aging &/or transportation testing not available
Poor SOPs –labeling of component results in compromising the sterile barrier;
Inner pouch contacts seal of outer pouch; not packaged per specifications
Inadequate training; Verification testing not performed

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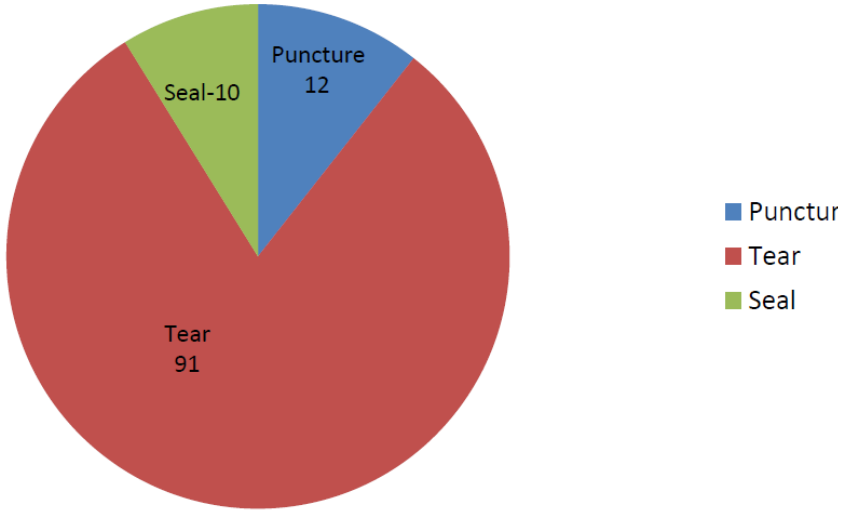
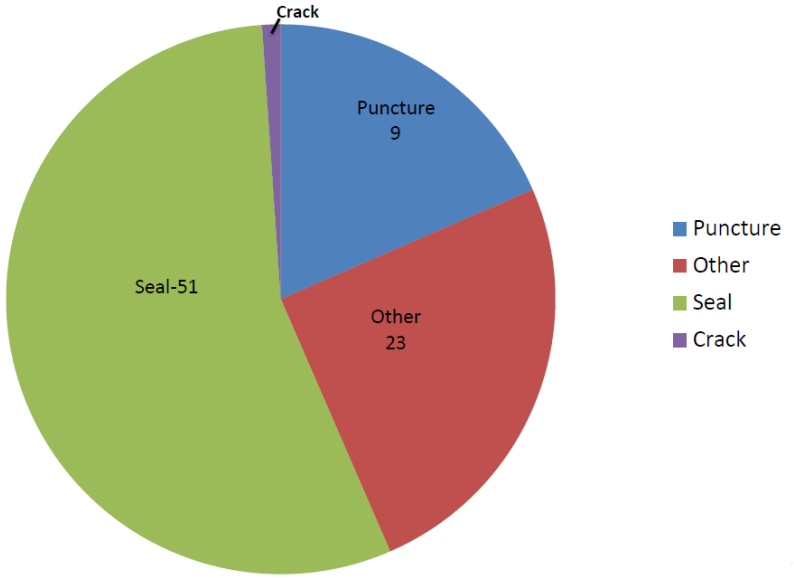
2016- Supplier Recalls



2017- Supplier Recalls



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SUPPLIER RECALLS

Sealing process deficient
Seal opens under extreme shipping conditions
SBS material had tears/cuts
SBS may puncture during shipping
Worn sealing plate
Packaging change was not properly validated.
Incomplete seals

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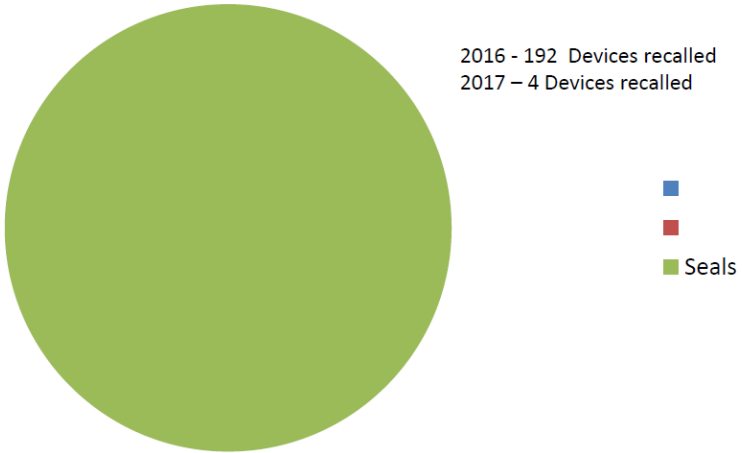
Recalls due to Employee Errors



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

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How can we change these trends?

- Design
- Processes
- Validation

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Device Packaging

Evaluated through all intended processes

- ✓ Sterilization
- ✓ Handling
- ✓ Distribution
- ✓ Storage
- ✓ Use by date

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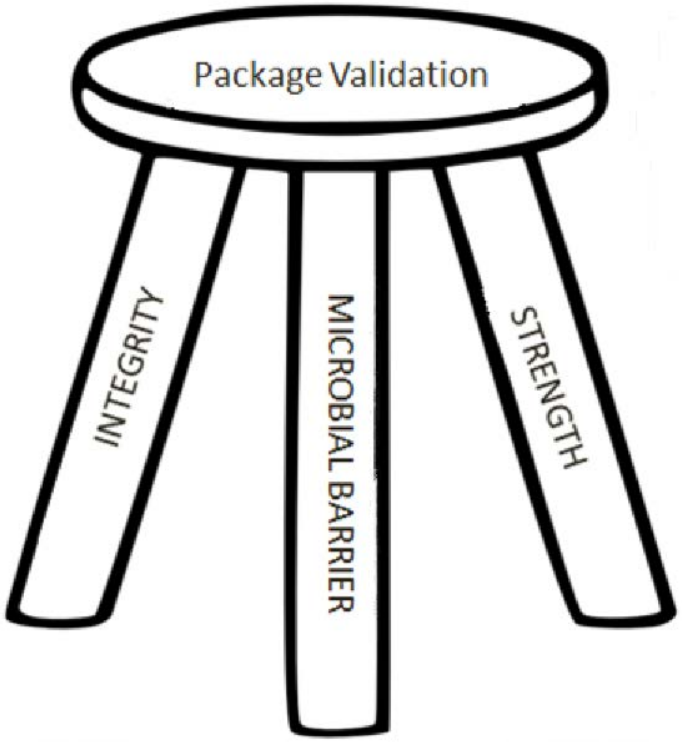
Basic Packaging Validation Plan

- You must demonstrate
  - Overall effectiveness of the packaging system
  - The sterile barrier system (SBS) effectiveness using 3 properties
  - Through the expected use by date



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Worst Case

"When similar medical devices use the same packaging system, a rationale for establishing similarities and identifying the worst case shall be documented." – ISO 11607

- Medical Device (heavy, light, sharp)
- Material (porous, nonporous)
- Sterilization (single, multiple)
- Distribution, storage, handling

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ISO 11607

Package Test Methods

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Test Method Key Points

- Any test method used needs to be validated for use in your facility and/or with your equipment:
  - Repeatability – variation within a lab
  - Reproducibility – variation from lab to lab
  - Sensitivity – measure of the limits of the test method
- Precision and bias statements that can be found in the standards can help assess any variability found in validation results.
- Some test methods are actually processes that prepare materials for evaluation by test methods.

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Visual Inspection - ASTM F1886

Visual Inspection is a process of methodically and purposefully examining a package for a specific range of defects and recording observations.

- ✓ Packages are checked for a list of common defects
- ✓ Analysts should be properly trained
- ✓ There should be adequate lighting
- ✓ Inspections should take 1-5 minutes a sample
- ✓ Observations are documented with writing and pictures

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Unsealed Areas

Example of open seal

Package misalignment

Equipment malfunction

Defects within the material or foreign body in the seal

Seal rupture

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Nonhomogeneous or Undersealed

Nonhomogeneous seals can occur with improper sealing parameters. For example: insufficient heat, pressure, or too short of dwell time.

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Failure issues

Over sealed as a result of too high temperatures causing melting/bending of materials and voids in the seals.

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Seal Peel Test - ASTM F88

Determines the strength of the seal at a specific place on the package

Measure a one inch segment of the package along one of the seals • Cut the package so that there are 3 inches of material on each side of the seal	2 Seals • Manufacturer's • MDM Seal • Testing both seals makes for easy acceptance criteria!	Porous or Non-porous Seal test only

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Dye Migration Test - ASTM F1929 Porous/ASTM F3039 Nonporous

Determines the integrity of the package seal

Involves injecting dye into the package

- Placing the weight of the solution against each portion of the seal for a specific length of time
- Dye migrating through the seal is a failure

Seal only test

Porous and Non-porous

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Accelerated Aging

Accelerated Aging - ASTM F1980

Purpose/Theory		
Demonstrate the package is not affected by aging to the expected shelf life	Does **not** replace real time aging	Based on the observations of Arrhenius

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Accelerated Aging

Q_{10} = 2; 25ºC ambient

ºF	ºC	1yr	2 yrs	3 yrs	4 yrs	5 yrs
77.0	25.0	52.0	104.0	156.0	208.0	260.0
86.0	30.0	36.8	73.5	110.3	147.1	183.9
95.0	35.0	26.0	48.5	72.8	97.0	121.3
104.0	40.0	18.4	36.8	55.2	73.5	91.9
113.0	45.0	13.0	26.0	39.0	52.0	65.0
122.0	50.0	9.2	18.4	27.6	36.8	46.0
131.0	55.0	6.5	13.0	19.5	26.0	32.5
140.0	60.0	4.6	9.2	13.8	18.4	23.0
149.0	65.0	3.3	6.5	9.8	13.0	16.3

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Accelerated Aging

Justify test conditions and duration	With or Without Product
• Ambient temperature • FDA recommends 25°C • Aging temperature • Relative humidity • < 10-15°C T_g for all polymers–*Caution!*	• The presence of a device can stress a package and affect performance. Use of simulants is not uncommon.

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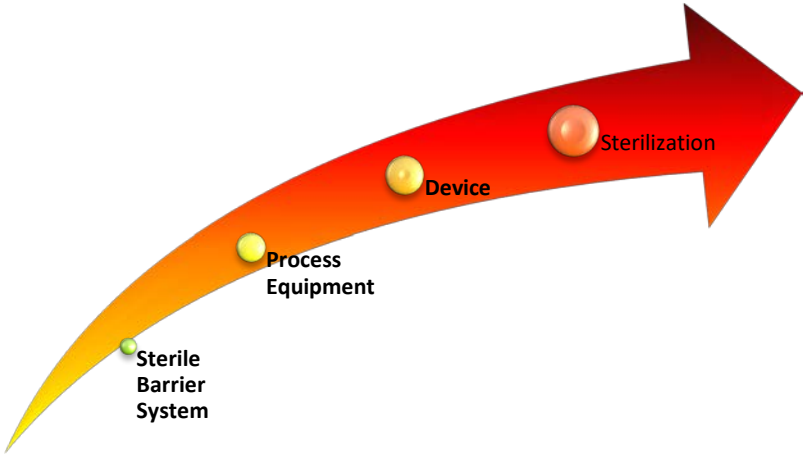
Re-validation

Changes to:



Re-validation

- Some changes are so minor that revalidation is not required – but a record of the justification for not revalidating is required
- Periodically a review should take place to determine if many small changes in total now require revalidation

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How can we change these trends?

- Design – ensuring that the packaging system is designed right from the start
- Processes – ensuring that the processes (equipment, tests, etc) are qualified
- Validation – ensure validation testing is performed according to the standards.

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Questions - B**ooth #3135**

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