Inspection and Audit

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Topics

- Warning Letters
- Data Analysis
- §820.75 Process Validation
- Questions

Warning Letters

The Context

- Process Validation, §820.75, has a high Warning Letter citation rate.
- Overall (2008 to 2019), almost 40% of Warning Letters that cite QSR also cite Process Validation
- In the same period, about 70% of the Warning Letters that cite QSR also cite CA&PA, the most frequently cited section of QSR

Learning from Warning Letters

- The Warning Letter excerpts give you an opportunity to learn from the mistakes of others.
  - The full text is available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters
- For each Warning Letter excerpt ask yourself two questions
- Could this happen in my QMS?
  - If No, explain why not in a brief paragraph
- If it were to happen, would my internal quality audit program find it?
  - If yes, write a short paragraph explaining how that includes the particular audit as well as the particular checklist item or interview question

Warning Letter Role

- When FDA finds that a manufacturer has significantly violated FDA regulations, FDA notifies the manufacturer, usually in the form of a Warning Letter

- The Warning Letter identifies the violation, such as poor manufacturing practices, problems with claims for what a product can do, or incorrect directions for use.

- The letter also makes clear that the company must correct the problem and provides directions and a timeframe for the company to inform FDA of its plans for correction.
  - FDA then checks to ensure that the company's corrections are adequate.

Source: UCM278624

Directions and Time Frame

- Please notify this office in writing within fifteen business days from the date you receive this letter of the specific steps your firm has taken to correct the noted violations, as well as an explanation of how your firm plans to prevent these violations, or similar violations, from occurring again.

- Include documentation of the corrections and/or corrective actions (which must address systemic problems) that your firm has taken. If your firm's planned corrections and/or corrective actions will occur over time, please include a timetable for implementation of those activities. If corrections and/or corrective actions cannot be completed within fifteen business days, state the reason for the delay and the time within which these activities will be completed. Your firm's response should be comprehensive and address all violations included in this Warning Letter.

Source: TFI Biosciences, Inc. 3/6/19

Consequences

- Failure to promptly correct these violations may result in regulatory action being initiated by the FDA without further notice. These actions include, but are not limited to, seizure, injunction, and civil money penalties.

- Also, federal agencies may be advised of the issuance of Warning Letters about devices so that they may take this information into account when considering the award of contracts.

- Additionally, premarket approval applications for Class III devices to which the Quality System regulation violations are reasonably related will not be approved until the violations have been corrected.

- Requests for Certificates to Foreign Governments will not be granted until the violations related to the subject devices have been corrected.

Source: TFI Biosciences, Inc. 3/6/19

Warning Letter Close-Out

- FDA may issue a Warning Letter close-out letter ("close-out letter") once the Agency has completed an evaluation of corrective actions undertaken by a firm in response to a Warning Letter. A close-out letter may issue when, based on FDA's evaluation, the firm has taken corrective action to address the violations contained in the Warning Letter. This procedure applies to Warning Letters issued on or after September 1, 2009.

- A close-out letter will not be issued based on representations that some action will or has been taken. The corrective actions must actually have been made and verified by FDA. Usually, the standard for verifying that corrections have been implemented will be a follow-up inspection.

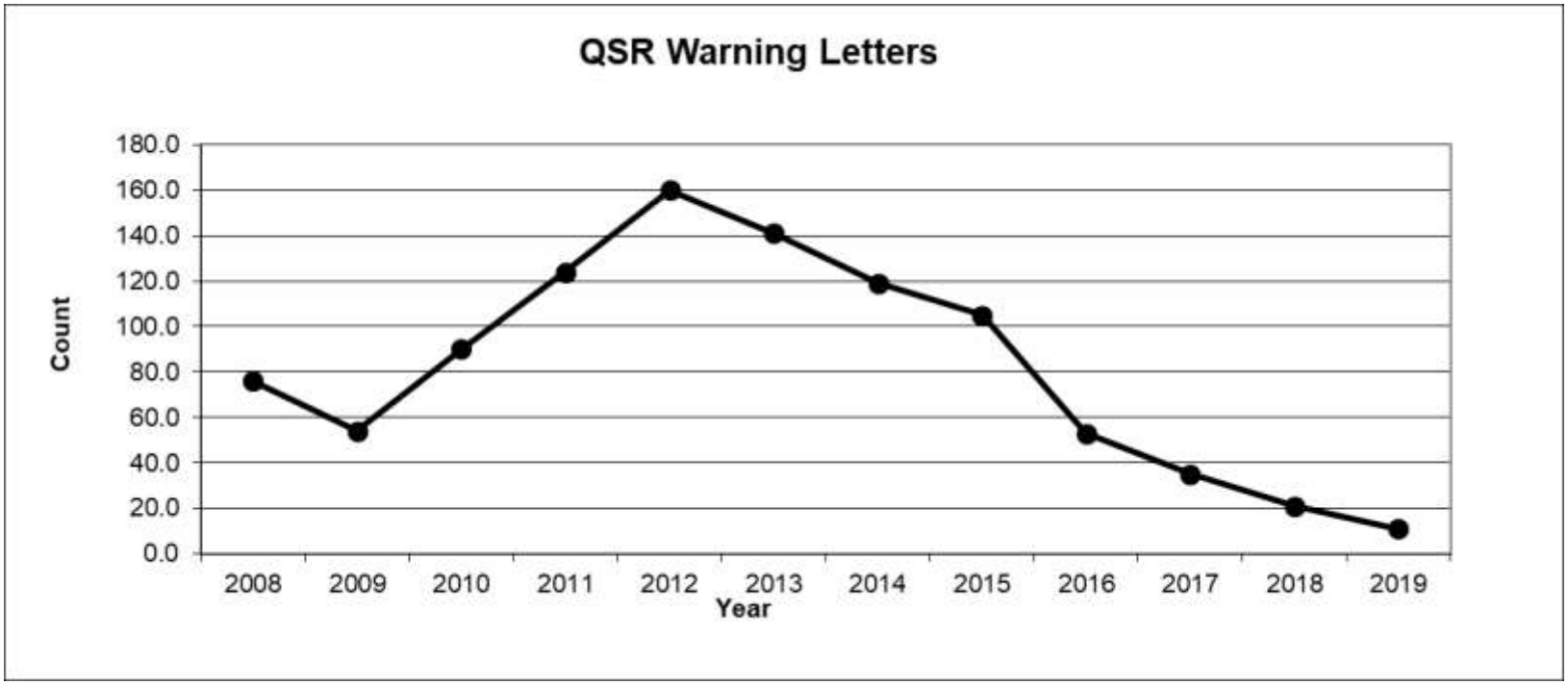
Source: UCM278624

Data Analysis

Scope

- The data analysis uses a database of Warning Letters that Ombu Enterprises, LLC maintains
- It includes all device Warning Letters from 2008
  - This is about 1,325 Warning Letters
- Ombu classifies each Warning Letter using a variety of attributes as shown on the next slide
- While Part 820, the Quality System Regulation is the primary source of Warning Letters, other parts are important to a device manufacturer's QMS.

QSR Warning Letters



Source

- The top two sources of Warning Letters are:

- Inspection 87.8%
- Website 9.1%

- The remaining sources have very small counts
  - Billboard appears one time

Countries

- The top ten countries are:
  - FDA counts Puerto Rico separately

USA	69.93%
China	5.35%
Germany	3.92%
Canada	3.01%
UK	2.11%
Italy	1.51%
Taiwan	1.36%
Japan	1.36%
Puerto Rico	0.83%
France	0.83%

Outside Expert Consultant

- 31 Warning Letters include the use of an outside expert

- We are requesting that you submit to this office on the schedule below, certification by an outside expert consultant that he/she has conducted an audit of your establishment's manufacturing and quality assurance systems relative to the requirements of the device QS regulation (21 CFR Part 820).
- You should also submit a copy of the consultant's report, and certification by your establishment's Chief Executive Officer (if other than yourself) that he or she has reviewed the consultant's report and that your establishment has initiated or completed all corrections called for in the report.
- The initial certifications of audit and corrections and subsequent certifications of updated audits and corrections (if required) should be submitted to this office by the following dates: [redacted]

Detention

- 103 Warning Letters include detention

- Given the serious nature of the violations of the Act, devices manufactured by your firm are subject to refusal of admission under section 801(a) of the Act, 21 U.S.C. §381(a), in that they appear to be adulterated. As a result, FDA is taking steps to refuse entry of these devices into the United States, known as "detention without physical examination", until these violations are corrected. In order to remove the devices from detention, your firm should provide a written response to this Warning Letter as described below and correct the violations described in this letter. We will notify you regarding the adequacy of your firm's responses and the need to re-inspect your firm's facility to verify that the appropriate corrections and/or corrective actions have been made.

Detention – Counties

- The list below includes countries with 3 or more detentions:

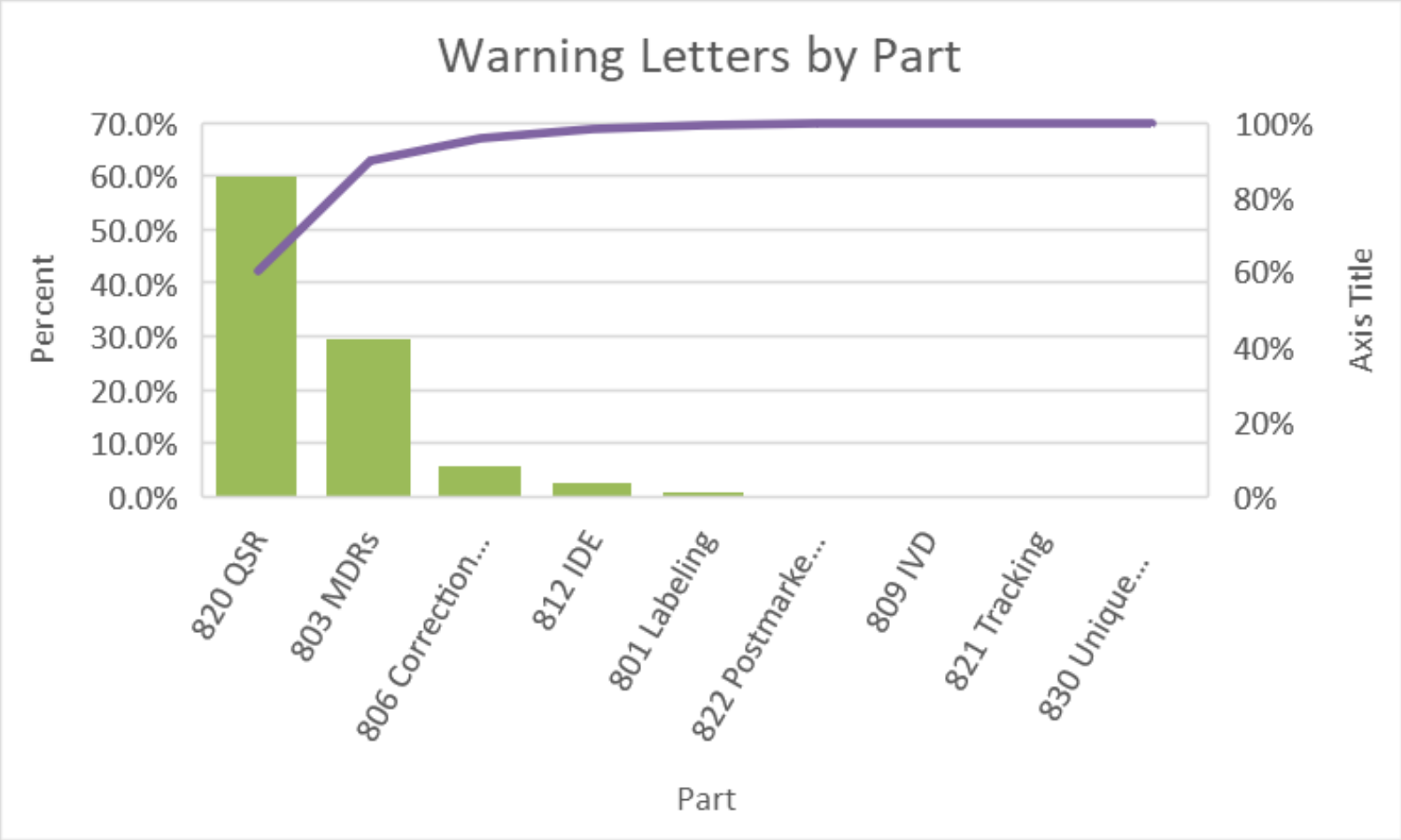
Country	WLs	Det	Percent
Australia	4	3	75.0%
Canada	40	9	22.5%
China	71	22	31.0%
Germany	52	9	17.3%
Italy	20	5	25.0%
Taiwan	18	3	16.7%
UK	28	11	39.3%

Parts

- Warning Letters often cite multiple parts of the regulations.

- The percentages below are for Warning Letters that cite any section of the part.
  - For example, a Warning Letter that cites five sections of Part 820 would be counted one time in this list.
- 801 Labeling 1.0%
- 803 MDRs 29.6%
- 806 Corrections & Removals 6.0%
- 809 IVD 0.1%
- 812 IDE 2.6%
- 820 QSR 60.2%
- 821 Tracking 0.1%
- 822 Postmarket Surveillance 0.3%
- 830 Unique Device Identification 0.1%

Parts


Warning Letters by Part
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
Percent
100%
80%
60%
40%
20%
0%
Axis Title
820 QSR
803 MDRs
806 Correction...
812 IDE
801 Labeling
822 Postmarke...
809 IVD
821 Tracking
830 Unique...
Part

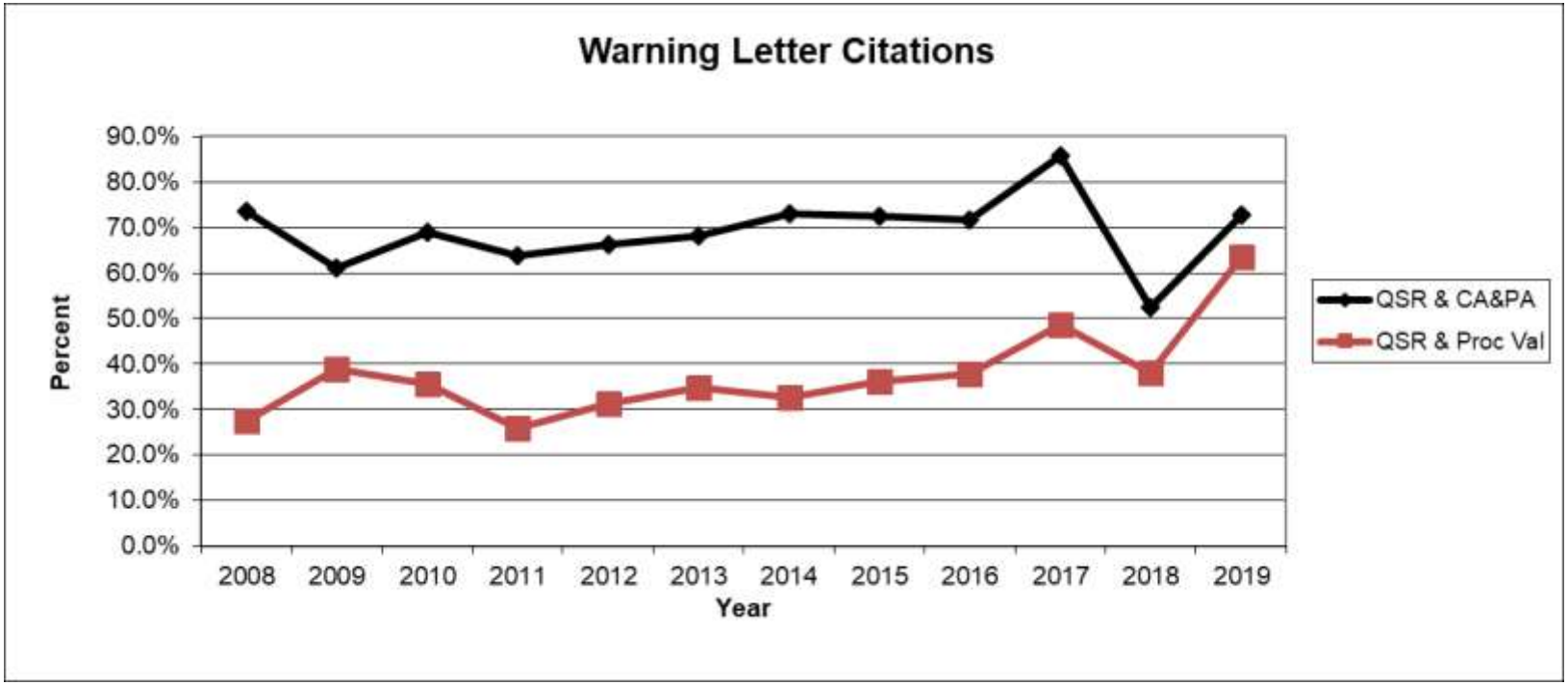
QSR Sections

- The top ten cited QSR sections are:

820.100	CA & PA	69.0%	Top Five
820.198	Complaints	59.9%	
820.30	Design Controls	54.6%	
820.80	Acceptance Activities	36.4%	
820.50	Purchasing Controls	35.1%	
820.75	Process Validation	33.8%	Next Five
820.70	P & PC	31.7%	
820.90	Nonconforming Product	28.5%	
820.22	Quality Audit	28.2%	
820.184	DHR	27.1%	

§820.75 Process Validation

Historical View



Expectations

- Validate a process when the output is not fully verified
  - Processes where the verification test is destructive
  - Processes where the verification test employs a sampling plan

- Process validation provides a high degree of assurance that the process output, the product, is conforming
  - The process capability index, $C_{pk} \geq 1.33$

- Process validation determines the process input parameters that ensure only conforming output

- A qualified operator monitors, adjusts, when necessary, and records the process inputs

QSIT

- Process: Production and Process Controls
- Objective #4: If the results of the process reviewed cannot be fully verified, confirm that the process was validated by reviewing the validation study.

- Points to cover:
  - If the process can be fully validated, the Investigator moves to the next objective
  - If the process requires process validation, review the protocol and report
  - Verify that there is objective evidence that the process will consistently generate a product or result meeting its predetermined specifications

QSIT

- Process: Production and Process Controls
- Objective #6 Verify that personnel have been appropriately qualified to implement validated processes or appropriately trained to implement processes which yield results that can be fully verified.

- Points to cover:
  - For validated processes create training and qualification for process operators
    - Be sure to cover all shifts
  - Ensure that validated process operators are aware of any device defects that may occur as a result of improper performance
  - Ensure that inspectors or testers are aware of any defects or errors they may encounter

MDSAP

- Process: Production and Service Controls
- Task #7 Determine if the selected processes and sub-processes have been reviewed, including any outsourced processes, to determine if validation of these processes is required

- Points to Consider:
  - During planning determine which production processes require validation and which processes can be verified

  - Document the decision and its rationale in the process plan

MDSAP

- Process: Production and Service Controls
- Task #8 Verify that the selected processes has been validated according to documented procedures if the result of the process cannot be fully verified or can be verified, but is not. Confirm that the validation demonstrates the ability of the processes to consistently achieve the planned result. In the event changes have occurred to a previously validated process, confirm that the process was reviewed and evaluated, and re-validation was performed where appropriate.

- Points to Consider:
  - Establish by objective evidence that a process consistently produces a result or product that meets predetermined specifications

MDSAP

- Process: Production and Service Controls
- Task #11 Verify that the processes used in production and service are appropriately controlled, monitored, operated within specified limits, and documented in the product realization records. In addition, verify that risk control measures identified by the manufacturer for production processes are implemented, monitored, and evaluated.

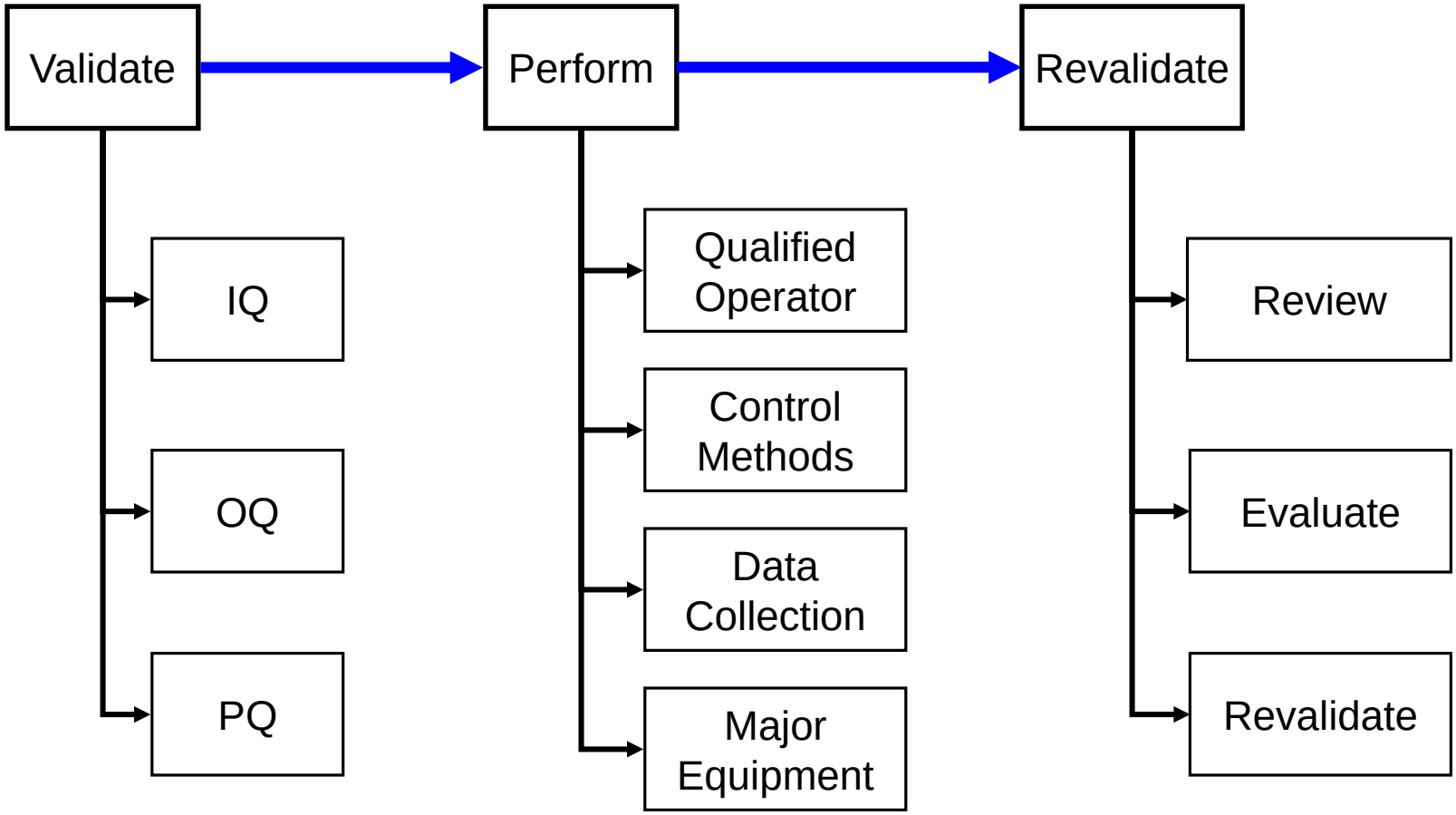
- Points to Consider:
  - Control and monitor validated processes
  - Document the monitoring of validated process input parameters and the controls to keep them within the established limits

MDSAP

- Process: Production and Service Controls
- Task #12 Verify that personnel are competent to implement and maintain the processes in accordance with the requirements identified by the organization.

- Points to Consider:
  - Establish competence requirements the people who operate a validated process
  - Create records to demonstrate the operator's competence

Process Validation Phases



Common Problems

- Problem: Failure to validate a process
- Phase: Validation

- Countermeasure
  - Draw a process map of the production process
  - Include each verification step (see §820.80(c) In-process acceptance activities)
  - For each verification, document the quantity verified such as: 100%, c=0 sampling plan with 1.0 index value, or 0.0%
  - For each verification, document CTQs verified such as:
  - 100% of CTQs for each piece in the sample
  - If the verification step is not 100% CTQs and 100% pieces, then validate the process

Warning Letter
Cardiomed Supplies, Inc.
September 21, 2018

- Failure to validate a process under §820.75(a)

- Your firm performed validation activities, as documented in the 'Doboy Hospital Sealer Validation and Inspection Report'. However, your firm did not establish a procedure to dictate how those activities would be performed, including test methods, process parameters, and acceptance criteria.

Warning Letter
TOADS, LLC
February 22, 2013

- Failure to establish contractor requirements under §820.50(a)
- Specifically, your firm has not ensured that your contract manufacturer has validated the process using the [redacted] to manufacture the Orthodontic Temporary Anatomical Anchor Device Systems (TAADS) distributed by your firm.
- According to your Supplier Agreement, dated 10/7/09, it is your contract manufacture's responsibility to complete "production process validations where verification [is] not possible".
- Your device history records for product numbers 270102, 270104, 270106, and 270108 document the final inspection and sometimes in-process inspections of each lot. During these inspections, verification of all characteristics for each TAAD is only completed on the first device of each lot.

Common Problems

- Problem: Failure to identify the relevant process input parameters
- Phase: Validation

- Countermeasure
  - Use a fishbone diagram to help identify the input parameters
  - Identify the relevant input parameters using a screening experiment
  - Use team judgement to help determine the relevant input parameters
  - Include all the relevant input parameters in the validation protocol

Common Problems

- Problem: Failure to define the validation sample size or to use the defined sample size
- Phase: Validation

- Countermeasure
  - Following §820.250(a) identify the statistical techniques for verifying the acceptability of process capability and product characteristics
  - Document the specific application of the statistical technique in the process validation protocol
  - Implement the approved protocol and create the associated quality records

Sample Size

- The process validation can produce two types of data – attributes and variables
- Attributes are usually pass/fail data. The value of the output is measured and converted to pass/fail
  - The conversion “throws away” information, causing a larger sample size
- If the CTQ is a variable, then use the data directly
  - This results in smaller sample sizes
  - Use the data to calculate C_{pk} at each point in the validation
- There are many software packages that can help plan and manage the data

Common Problems

- Problem: Failure to perform the validation protocol at the worst case conditions
- Phase: Validation

- Countermeasure
  - After identifying the relevant input parameters, consider the spec limits for each one
  - The validation protocol demonstrates that the process works satisfactorily at all worst case conditions
  - Satisfactory means a $C_{pk} \geq 1.33$

Warning Letter
Gulf Medical Fiberoptics, Inc.
July 27, 2011

- Failure to validate a process under §820.75(a) – Inadequate OQ

- Your validation study for your process to manufacture optical fibers … did not include complete analysis of the Furnace Temperature process variable in order to demonstrate the effect it may have on finished product quality. The OQ portion of the protocol did not analyze temperatures above 1800° F, and records covering the PQ portion of the protocol did not demonstrate inclusion of operating temperatures above 1804° F, although you listed 1810 - 1775° F as the acceptable range for the Furnace Temperature processing variable.

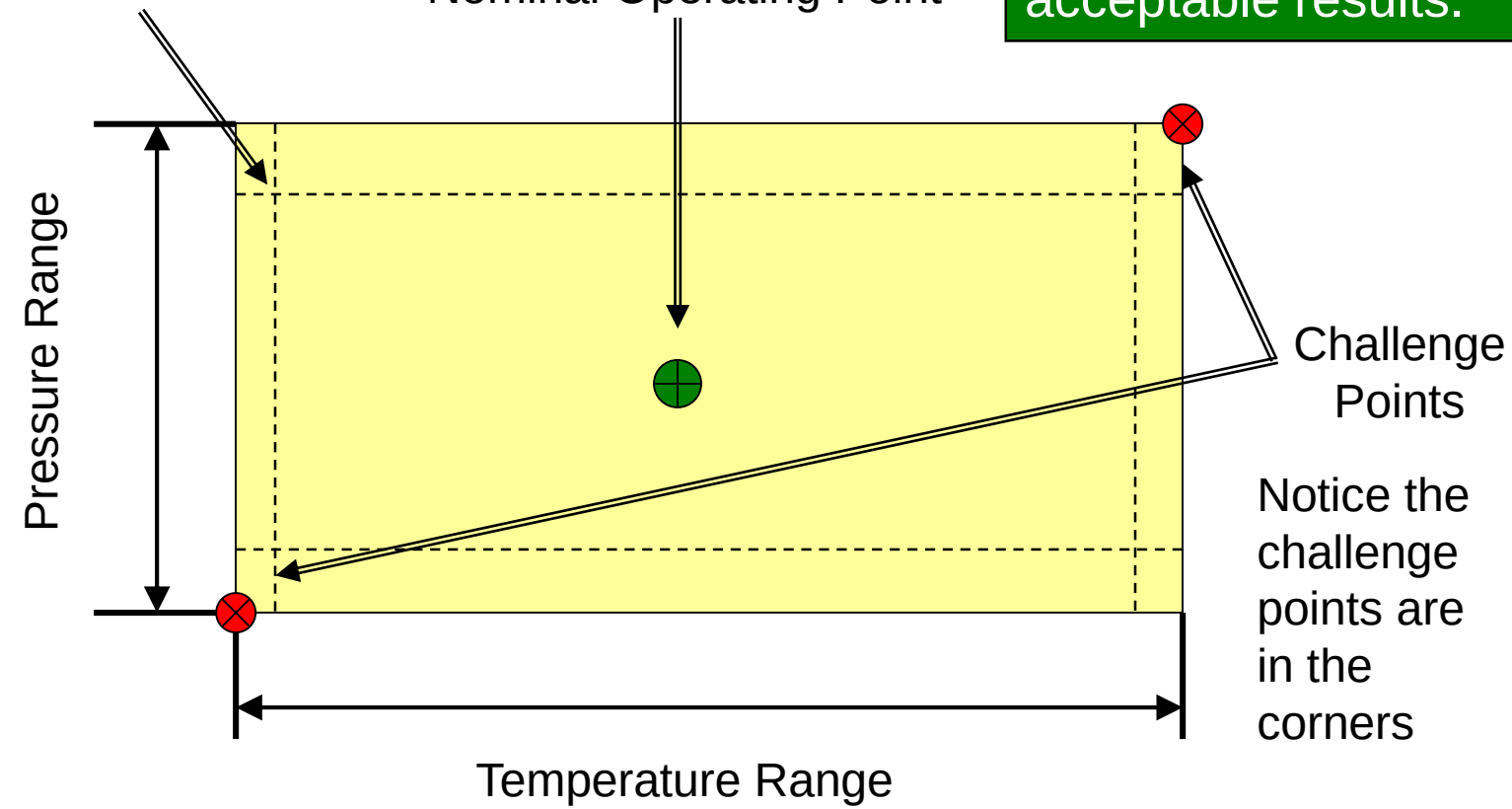
Warning Letter
GPC Medical Limited
October 20, 2017

- Failure to validate a process under §820.75(a)

- For example, your firm's process validations … are inadequate. These validations do not include:
  - final operational parameters of the equipment being validated,
  - justification of product selection (*e.g.,* most challenging to clean),
  - sampling acceptance criterion, or
  - verification of cleaning effectiveness.

Operating Points

Any point inside the box should produce acceptable results.



Notice the challenge points are in the corners

Common Problems

- Problem: Failure to consider variations in raw materials, components, and equipment
- Phase: Validation

- Countermeasure
  - Typically raw materials and components have a specification range
  - Consider the effects of an unstable supplier process – the values are across the specification range
  - Validate the process at the worst case conditions (near the upper and lower spec limits) for the raw material
  - Apply the same considerations to the components and to the production equipment

Common Problems

- Problem: Failure to consider failures during validation
- Phase: Validation

- Countermeasure
  - Validation demonstrates the ability to produce conforming product at the worst case conditions
  - A failure suggests that either the worst case conditions do not produce conforming material or that there is another input parameter that is affecting the output

Warning Letter
Facet Technologies, LLC
May 19, 2011

- §820.75(a) – Validate a process
- Your firm's mold validation and housing press validation for the OneTouch Delica Lancing Device/Aurora had process capability (C_{pk}) out-of-specifications that were not investigated or evaluated. Examples of this deficiency, as documented by our investigator, include, but are not limited to, the following observations.
  - Device components, such as the bottom housing, top housing, and depth dial, had C_{pk} values that were out-of-specification during Operational Qualification (OQ) and were not evaluated according to protocol prior to proceeding to Process Qualification (PQ).
  - Also, your firm's current Mold Qualification protocol has not been updated to correspond with critical-to-quality dimension acceptance criteria changes.
  - Additionally, your firm did not have evidence of deviations where front and back height process capabilities were not realized during validation.

Common Problems

- Problem: Failure to create procedures for monitoring and control of input process parameters
- Rationale: Perform

- Countermeasure
  - As part of the procedure for operating the validated process, define the input parameter action limits
  - Ensure the procedure includes the measurement method, the measurement frequency, and the adjustment criteria (action limits)
  - Create a data sheet to record the input parameters and whether they were adjusted
  - Ensure the DHR review includes a check that the data sheet is complete and correct

Warning Letter
American Contract Systems
November 6, 2018015

- Failure to monitor and control of process parameters – §820.75(b).

- Your firm does not have any procedures for the monitoring and control of critical process parameters such as: bag vacuum level; grams of [redacted] delivered; plastic bag serial number; plastic bag size; seal wattage; evaporation temperature; or [redacted] PSI, during routine sterilization operations.

Warning Letter
Cincinnati Sub-Zero Products, Inc.
July 13, 2010

- §820.75(b) – Run a validated process

- For example, your Process Instruction P-001, Rev. O describes that, for the Cold Therapy Packaging Process, three empty pouches should be inspected per visual standard GT-509, and that every twenty-fifth pouch should be sealed empty and held for inspection. However, the investigator noticed during the inspection that your operator did not use visual standard GT-509 to perform inspections. In addition, the investigator did not witness the segregation or inspection of every twenty-fifth pouch, and no documented evidence including Form 0156 could support the inspection of every twenty-fifth pouch per Process Instruction P-001 and Quality Instructions for Cold Therapy/ Heat Therapy Pads Q-001, Rev. W.

Common Problems

- Problem: Failure to re-validate after a specification or standard change
- Phase: Revalidate

- Countermeasure
  - Establish a procedure for revalidation
    - Process validation doesn't expire, it is not calibration
  - If the process implements a standard, such as an ISO standard, then a new or revised standard could affect the current validation
  - If there is a design change to a specification, it could affect the process validation
  - Evaluate each change for its affect on the process
  - If warranted by the evaluation results, revalidate the process
    - The revalidation may be partial. For example, a specification change may not require another Installation Qualification
  - Document the evaluation criteria and the decision

Warning Letter
MAPA GmbH
December 31, 2013

- Failure to perform revalidation when changes occur – §820.75(c).

- For example, a review of your firm's process validation reports for dipping machines used for manufacturing latex condoms, revealed that since 2011 your firm has been using new parameters for the dipping machines and running production batches in accordance with ISO 4704 standards. Your firm's initial process validation was conducted using different parameters and in accordance with the European standard (EN 600). However, your firm has not revalidated the dipping process for the new production parameters.

Warning Letter
Superstat Corporation
August 5, 2011

- §820.75(c) –Deviations and changes

- For example, in 2005 your firm changed the packaging of its Modified Collagen Hemostatic Sponge (Superstat) from inner trays/outer trays with lids to interior/exterior [redacted]. The effects of the sterilization process for this product on this packaging change were not evaluated to determine if sterilization process revalidation was necessary to ensure the new package design would continue to consistently produce a product. (*e.g.,* finished device, packaging material) or result (*e.g.,* Sterility Assurance Level) meeting predetermined specifications after sterilization.

Common Problems

- Problem: Failure to re-validate after the process produces non-conforming product
- Phase: Revalidate

- Countermeasure
  - For non-conforming product, §820.90, the evaluation should determine if the nonconformance is controlled by a validated process
  - If so, evaluate the process to determine the source of the problem
  - Determine the extent of the re-validation to ensure the process operates correctly

Warning Letter
Thermedx, LLC
April 8, 2015

- Failure to validate a process under §820.75(a) – Inadequate PQ
- Your PQ validation studies for the welding process (used to manufacture the cartridge) were conducted using a set of fixed values for the variables during the welding process. You have deviated from these "fixed" values 5 times since the validation studies with no documented rationale of acceptance or possible ramifications for deviating from the process.
- According to your Mechanical Engineering of Tech Service, complaints 13-0067, 14-0021, and 14-0057 are possibly attributed to the welding process.

QUESTIONS