THE QUALITY SYSTEM REGULATIONS

SUBPART G - PRODUCTION AND PROCESS CONTROLS

820.70- PRODUCTION AND PROCESS CONTROLS
820.72- INSPECTION, MEASURING, AND TEST EQUIPMENT
820.75- PROCESS VALIDATION
820.184- DEVICE HISTORY RECORD [SUBPART M]

21 CFR 820.70
Production and Process Controls

The purpose for the production and process control subsystem is to manufacture products that meet specifications. Developing processes that are adequate to produce devices that meet specifications, validating (or fully verifying the results) of those processes are all steps that help assure the result will be devices that meet specifications.

Source: QSIT Manual

21 CFR 820.70
Production and Process Controls

- General (820.70(a))
- Production and Process Changes (820.70(b))
- Environmental control (820.70(c))
- Personnel (820.70(d))
- Contamination control (820.70(e))
- Buildings (820.70(f))
- Equipment (820.70(g))
- Manufacturing Material (820.70(h))
- Automated processes (820.70(i))

- ISO 13485:2016 Section 7.5.1 and 7.5.2 (820.70(e))

Consider: 820.30; 820.40; 820.50; 820.184; 820.250

21 CFR 820.70
Production and Process Controls

(a) *General.*

Each manufacturer shall develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications. Where deviations from device specifications could occur as a result of the manufacturing process, the manufacturer shall establish and maintain process control procedures that describe any process controls necessary to ensure conformance to specifications.

21 CFR 820.70
Production and Process Controls

Continuation of 820.70(a)

Where process controls are needed they shall include:

(1) Documented instructions, standard operating procedures (SOP's), and methods that define and control the manner of production;

(2) Monitoring and control of process parameters and component and device characteristics during production;

(3) Compliance with specified reference standards or codes;

(4) The approval of processes and process equipment; and

(5) Criteria for workmanship which shall be expressed in documented standards or by means of identified and approved representative samples.

21 CFR 820.70
Production and Process Controls

820.70(b) Production and process changes.

Each manufacturer shall establish and maintain procedures for changes to a specification, method, process, or procedure. Such changes shall be verified or where appropriate validated according to 820.75, before implementation and these activities shall be documented. Changes shall be approved in accordance with 820.40.

Consider: 820.30; 820.50

21 CFR 820.70
Production and Process Controls

820.70(c) Environmental control.

Where environmental conditions could reasonably be expected to have an adverse effect on product quality, the manufacturer shall establish and maintain procedures to adequately control these environmental conditions. Environmental control system(s) shall be periodically inspected to verify that the system, including necessary equipment, is adequate and functioning properly. These activities shall be documented and reviewed.

21 CFR 820.70
Production and Process Controls

820.70(d) Personnel.

Each manufacturer shall establish and maintain requirements for the health, cleanliness, personal practices, and clothing of personnel if contact between such personnel and product or environment could reasonably be expected to have an adverse effect on product quality. The manufacturer shall ensure that maintenance and other personnel who are required to work temporarily under special environmental conditions are appropriately trained or supervised by a trained individual.

Consider: 820.25

21 CFR 820.70
Production and Process Controls

820.70(e) Contamination control.

Each manufacturer shall establish and maintain procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality.

820.70(f) Buildings.

Buildings shall be of suitable design and contain sufficient space to perform necessary operations, prevent mix ups, and assure orderly handling.

Consider: 820.30; 820.140; 820.150; 820.160; 820.170

21 CFR 820.70
Production and Process Controls

820.70(g)Equipment.

Each manufacturer shall ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use.

- *(1)Maintenance schedule. Each manufacturer shall establish and maintain schedules for the adjustment, cleaning, and other maintenance of equipment to ensure that manufacturing specifications are met. Maintenance activities, including the date and individual(s) performing the maintenance activities, shall be documented.*
- *(2)Inspection. Each manufacturer shall conduct periodic inspections in accordance with established procedures to ensure adherence to applicable equipment maintenance schedules. The inspections, including the date and individual(s) conducting the inspections, shall be documented.*
- *(3)Adjustment. Each manufacturer shall ensure that any inherent limitations or allowable tolerances are visibly posted on or near equipment requiring periodic adjustments or are readily available to personnel performing these adjustments.*

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Production and Process Controls

820.70(h) Manufacturing material.

Where a manufacturing material could reasonably be expected to have an adverse effect on product quality, the manufacturer shall establish and maintain procedures for the use and removal of such manufacturing material to ensure that it is removed or limited to an amount that does not adversely affect the device's quality. The removal or reduction of such manufacturing material shall be documented.

820.70(i) Automated processes.

When computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities and results shall be documented.

Consider: 820.30; 820.50; 820.80; 820.86; 820.90

21 CFR 820.70
Production and Process Controls

Warning Letter Examples:

Failure to establish and maintain adequate process control procedures to ensure the device conforms to its specifications, as required by 21 CFR 820.70(a).

For example: There were no work instructions for the manual assembly production of the XXX system including the XXX system. Additionally, your workers performed their assembly work based on unapproved drawings without any instructions. The drawings do not include any instructions on how to assemble the systems, or in what order.

Failure to establish and maintain procedures to control environmental conditions, as required by 21 CFR 820.70(c). For example:

A) Your firm did not establish electrostatic discharge (ESD) procedures or performed any maintenance on the ESD protective mats located in the production area were ESD sensitive components such as printed circuit board assemblies were handled.

B) Your firm did not monitor or control the temperature in the production areas where phantoms, which are affected by temperature variations according to the user guides, were used for routine testing activities. Additionally, discrepancies in the temperature readings of the phantoms for (b)(4) test area and for software testing ((b)(4), respectively) were observed. Your firm's user manuals for the (b)(4) phantom and Doppler Flow phantoms both contain the following statement: "….(b)(4)." No documentation was available for review to determine if utilizing the phantoms at conditions higher than room temperature would adversely affect the testing results.

21 CFR 820.72 Inspection, Measuring and Test Equipment

(a) *Control of inspection, measuring, and test equipment.*

Each manufacturer shall ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes and is capable of producing valid results. Each manufacturer shall establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained. The procedures shall include provisions for handling, preservation, and storage of equipment, so that its accuracy and fitness for use are maintained. These activities shall be documented.

ISO 13485:2016 Section 7.5.1 and 7.6

Consider: 820.30; 820.80; 820.86; 820.90

21 CFR 820.72 Inspection, Measuring and Test Equipment

820.72(b) Calibration.

Calibration procedures shall include specific directions and limits for accuracy and precision. When accuracy and precision limits are not met, there shall be provisions for remedial action to reestablish the limits and to evaluate whether there was any adverse effect on the device's quality. These activities shall be documented.

Consider: 820.30; 820.80; 820.86; 820.90

21 CFR 820.72
Inspection, Measuring and Test Equipment

820.72(b)(1)Calibration standards.

Calibration standards used for inspection, measuring, and test equipment shall be traceable to national or international standards. If national or international standards are not practical or available, the manufacturer shall use an independent reproducible standard. If no applicable standard exists, the manufacturer shall establish and maintain an in-house standard.

820.72(b)(2)Calibration records.

The equipment identification, calibration dates, the individual performing each calibration, and the next calibration date shall be documented. These records shall be displayed on or near each piece of equipment or shall be readily available to the personnel using such equipment and to the individuals responsible for calibrating the equipment.

Consider: 820.30;
820.180

21 CFR 820.72
Inspection, Measuring and Test Equipment

Warning Letter Examples:

Failure to establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained, as required by 21 CFR 820.72(a). Specifically:

I. Your pH Meters, used for testing of your products, reportedly require **(b)(4)** calibration by an outside calibration laboratory; however, this requirement is not documented in your Calibration Program procedure (SOP #XXX) and there is no requirement to ensure this **(b)(4)** calibration is performed as required. For example, the last three **(b)(4)** calibrations for the pH Meter with Serial #**(b)(4)** show that the meter was calibrated on **(b)(4)**, no record of any outside calibration was available for **(b)(4)**, and it was only calibrated by the outside calibration laboratory 25 months later on **(b)(4)**.

II. The Calibration Program procedure fails to require that the standards used for inspection, measuring, and test equipment are traceable to National or International standards, as specified by 21 CFR 820.72(b)(1). For example, the Weighing Scale Calibration Logs do not demonstrate that the standards used (calibration weights) are traceable to a National or International standard. **(b)(4)** calibration is performed on **(b)(4)** scales used for weighing raw materials for manufacturing. Additionally, the Scale Calibration Logs do not include a tolerance range or the actual weight measurements obtained to clearly demonstrate that the scales met specifications.

Calibration Considerations

- Meet the requirements of ISO 17025 “General Requirements for the Confidence of Testing and Calibration Laboratories” for your calibration program.
- Have an accurate list of all equipment and status.
- Ensure all equipment is calibrated on time.
- Trend calibration failures and include in management review.
- Ensure program is periodically audited.

21 CFR 820.75
Process Validation

(a) Where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures. The validation activities and results, including the date and signature of the individual(s) approving the validation and where appropriate the major equipment validated, shall be documented.

(b) Each manufacturer shall establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met.

21 CFR 820.75
Process Validation

(b)(1) Each manufacturer shall ensure that validated processes are performed by qualified individual(s).

(b)(2) For validated processes, the monitoring and control methods and data, the date performed, and, where appropriate, the individual(s) performing the process or the major equipment used shall be documented.

(c) When changes or process deviations occur, the manufacturer shall review and evaluate the process and perform revalidation where appropriate. These activities shall be documented.

Consider: 820.30; 820.80; 820.86; 820.90

21 CFR 820.75
Process Validation Guidance

Global Harmonization Task Force

- Quality Management Systems - Process Validation Guidance (SG3, Edition 2- January 2004)

The following model may be useful in determining whether or not a process should be validated:

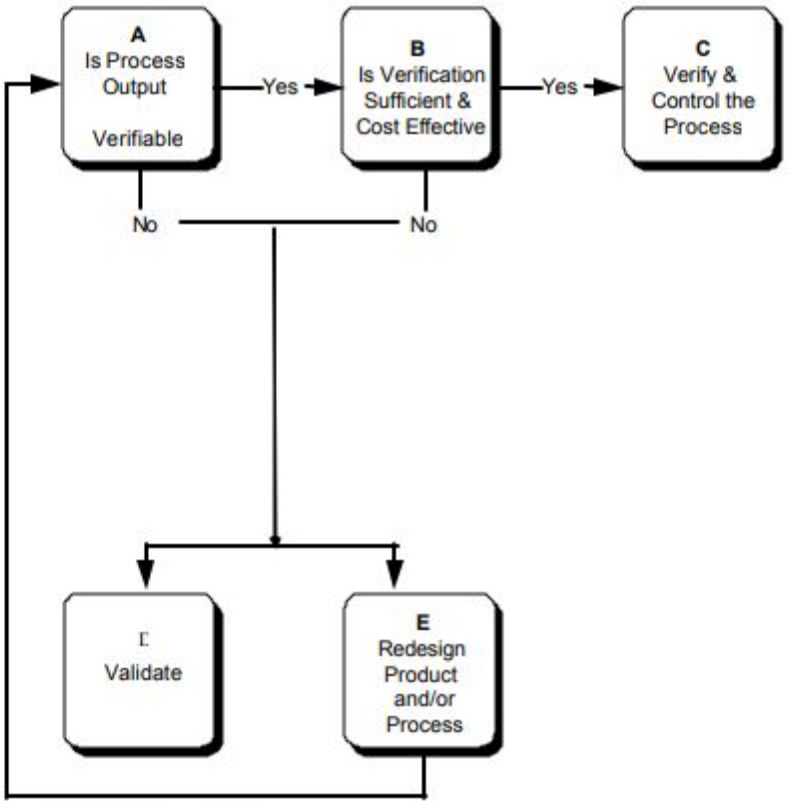

Figure 1: Process validation decision tree

http://www.imdrf.org/docs/ghtf/final/sg3/technical-docs/ghtf-sg3-n99-10-2004-qms-process-guidance-04010.pdf

Reference: GHTF- Quality Management Systems

GHTF Process Validation Guidance (SG3, Edition 2- January 2004)

Examples:

(1) Processes which should be validated:

Sterilization processes · Clean room ambient conditions · Aseptic filling processes · Sterile packaging sealing processes · Lyophilization process · Heat treating processes · Plating processes · Plastic injection molding processes

(2) Processes which may be satisfactorily covered by verification:

Manual cutting processes · Testing for color, turbidity, total pH for solutions · Visual inspection of printed circuit boards · Manufacturing and testing of wiring harnesses

(3) Processes which may be verifiable, but for business purposes, validation can be chosen:

Certain cleaning processes · Certain human assembly processes · Numerical control cutting processes · Certain filling processes

Linkage to 820.30(e) (Design Review)

Examples of processes for which Verification is potentially appropriate:

- Manual cutting processes
- Testing for color, turbidity, total pH for solutions
- Manufacturing & testing of wire harnesses
- Visual inspection
- printed circuit boards

Examples of processes for which Validation is appropriate:

- Sterilization
- Clean room ambient conditions
- Aseptic Filling
- Sterile Packaging
- Heat treating
- Injection molding

21 CFR 820.75
Process Validation

820.3(z)(1) Process validation means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

GHTF provides a similar definition in section 2.4: Process validation: establishing by objective evidence that a process consistently produces a result or product meeting its predetermined requirements.

Additional References: ISO 13485:2016 Section 7.5.6 and 7.5.7

21 CFR 820.75
Process Validation

Per FDA Guide to Inspections of Medical Device Manufacturers:

- Generally, process validation is a pre-production activity. Prospective validation includes considerations made before a new product is introduced, or when there is a manufacturing process change which may affect the product's characteristics.
- The validation program must be planned and documented, and the validation results must be documented and maintained.

Reference: GHTF The Process Validation Protocol

GHTF, section 2.5 Process validation protocol:
a document stating how validation will be conducted, including
test parameters, product characteristics, manufacturing equipment, and decision points on what constitutes acceptable test results.

Section 5.2 Protocol development-Detailed protocols for performing validations are essential to ensure that the process is adequately validated. Process validation protocols should include the following elements**(not an exhaustive list)** :

- Identification of the process to be validated
- Identification of device(s) to be manufactured using this process
- Objective and measurable criteria for a successful validation
- Relevant specifications that relate to the product, components, manufacturing materials, etc.
- Any special controls or conditions to be placed on preceding processes during the validation
- Process parameters to be monitored, and methods for controlling and monitoring
- Product characteristics to be monitored and method for monitoring
- Definition of what constitutes non-conformance for both measurable and subjective criteria
- Statistical methods for data collection and analysis
- Criteria for revalidation

Process Validation

When talking about Process Validation, there are typically three stages:

1. Installation Qualification (IQ)
   - *Is it installed properly?*
2. Operational Qualification (OQ)
   - *Establishing the control / action levels.*
3. Performance Qualification (PQ)
   - *Does the equipment consistently demonstrate the process will consistently produce acceptable product under normal operating conditions?*

Consider: 820.30; 820.180

Process Validation
Installation Qualification (IQ)

Establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification and that the recommendations of the supplier of the equipment are suitably considered.

– *GHTF Guidance, Section 2.1*

Process Validation
Installation Qualification (IQ)

Potential installation qualification considerations:

- Equipment design features (i.e. materials of construction cleanability, etc.)
- Installation conditions (wiring, utilities, functionality, etc.)
- Calibration, preventative maintenance, cleaning schedules
- Safety features
- Supplier documentation, prints, drawings and manuals
- Software documentation
- Spare parts list
- Environmental conditions (such as clean room requirements, temperature, humidity)

Process Validation
Operational Qualification (OQ)

Establishing by objective evidence process control limits and action levels which result in product that meets all predetermined requirements.

– *GHTF Guidance, Section 2.2*

Process Validation
Operational Qualification (OQ)

Potential OQ considerations include (but are not limited to):

- Process control limits (time, temperature, pressure, line speed, setup conditions, etc.)
- Software parameters
- Process operating procedures
- Process change control
- Short term stability and capability of the process, (latitude studies or control charts)
- Potential failure modes, action levels and worst-case conditions (Failure Mode and Effects Analysis, Fault Tree Analysis)
- The use of statistically valid techniques such as screening experiments to establish key process parameters and statistically

GHTF Guidance, Section 5.4

Process Validation:
Performance Qualification (PQ)

Establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.

GHTF Guidance, Section 2.3

Potential Performance Qualification considerations include:

- Actual product and process parameters and procedures established in OQ
- Acceptability of the product
- Assurance of process capability as established in OQ
- Process repeatability, long term process stability

Process Validation:
Performance Qualification (PQ)

One of the outputs of OQ and PQ is the development of attributes for continuous monitoring and maintenance. Process and product data should also be analyzed to identify any variation due to controllable causes. Depending on the nature of the process and its sensitivity, controllable causes of variation may include:

- *Temperature*
- *Humidity*
- *Environmental contaminants*
- *Light*
- *Human factors (training, ergonomic factors, stress, etc.)*
- *Variability of materials*
- *Wear and tear of equipment*

GHTF Guidance, Section 5.5

Process Validation: Final Report

At the conclusion of validation activities, a final report should be prepared. This report should

- summarize and reference all protocols and results
- derive conclusions regarding the validation status of the process.
- The final report should be reviewed and approved by the validation team and appropriate management.

GHTF Guidance, Section 5.6

Process Validation
Revalidation

The need for revalidation should be evaluated and documented. This evaluation should include historical results from quality indicators, product changes, process changes, changes in external requirements (regulations or standards) and other such circumstances.

Revalidation may be necessary under such conditions as:

- *change(s) in the actual process that may affect quality or its validation status*
- *negative trend(s) in quality indicators*
- *change(s) in the product design which affects the process*
- *transfer of processes from one facility to another*
- *change of the application of the process*

GHTF Guidance, Section 6.4

21 CFR 820.75
Process Validation

Warning Letter Examples:

Failure to ensure that when the results of a process cannot be fully verified by subsequent inspection and test that the process shall be validated with a high degree of assurance and approved according to established procedure, as required by 21 CFR 820.75(a).

For example, your firm's process validations under **(b)(4)** which include: **(b)(4)** Validation dated January 1, 2017, **(b)(4)** Validation dated January 5, 2017, **(b)(4)** dated June 1, 2017, and **(b)(4)** dated January 2, 2017 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.

Furthermore, the procedures for **(b)(4)** and **(b)(4)** include specifications for processing parameters, and batch sizes outside the scope of the validation performed.

21 CFR 820.184
Device History Record

Each manufacturer shall maintain device history records (DHR's). Each manufacturer shall establish and maintain procedures to ensure that DHR's for each batch, lot, or unit are maintained to demonstrate that the device is manufactured in accordance with the DMR and the requirements of this part.

Consider: 820.30; 820.80; 820.86; 820.90; 820.120; 830.130; 820.170; 820.181; 820.200

21 CFR 820.184
Device History Record

- *The DHR shall include, or refer to the location of, the following information:*
  (a) The dates of manufacture;
  (b) The quantity manufactured;
  (c) The quantity released for distribution;
  (d) The acceptance records which demonstrate the device is manufactured in accordance with the DMR;
  (e) The primary identification label and labeling used for each production unit; and
  (f) Any unique device identifier (UDI) or universal product code (UPC), and any other device identification(s) and control number(s) used.

ISO 13485:2016 Section 7.5.1

21 CFR 820.184
Device History Record

Warning Letter Examples:

Failure to demonstrate that the device was manufactured in accordance with the device master record, pursuant to 21 CFR 820.184.

For example, **(b)(4)**, XXX, explains the **(b)(4)** and **(b)(4)**. However, **(b)(4)** for XXX implants and XXY implants are not documented in Device History Records (DHR). Examples of DHRs which fail to include this testing includes: XXXX-JB1, XXXX-JH1, XXXX-RW1, XXXX-BW1, XXXX-BG1, XXXX-KK1, XXXX-GL1, XXXX-MB1, and XXXX-HM1.

QUESTIONS?