Overview of the FDA Quality System Regulation (QSR) for Medical Devices

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Background

- Published October 7, 1996
- Effective June 1, 1997, replacing the 1978 GMP regulation for medical devices
- Preamble to the 1997 regulation - VERY Important
- Provides framework of basic requirements for manufacturers to follow

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Bottom line …
It's your Quality System!

A manufacturer must develop a QS commensurate with:

- risk presented by the device
- complexity of device and manufacturing processes
- size and complexity of manufacturing facility

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FDA & Regulatory Strategies

Inspections

- Mandated by law, every 2 years for Class II and Class III device manufacturers.
- Required prior to PMA approvals and all 510(k) clearances of Class III devices.
- May be conducted for recalls, enforcement actions, complaints, significant MDRs, audits of clinical investigators, or as part of surveys.

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FDA & Regulatory Strategies

FDA Enforcement Authorities

- 483 deficiency observations
- Warning letter
- Order to repair, replace, or refund devices
- Notification to users or public
- PMA suspension/withdrawal
- Prohibition of import

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FDA & Regulatory Strategies

FDA Enforcement Authorities (continued)

- Device seizure
- Injunction/consent decree
- Criminal prosecution of company and/or responsible individuals
- Civil penalties

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FDA & Regulatory Strategies

Medical Device Recalls – 21 CFR Part 7 – Voluntary Recalls

- Class 1 – reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.
- Class II – may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.
- Class III – not likely to cause adverse health consequences.

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FDA Inspections

- Are conducted in both US and foreign countries
- To evaluate compliance with
  - Quality System regulation, Part 820
  - Medical Device Reporting, Part 803
  - Medical Device Tracking, Part 821
  - Corrections and Removals, Part 806
  - Registration and Listing, Part 807
  - Other regulations such as Part 11 Electronic Records and Signatures

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FDA Inspections

- Required for all foreign manufacturers selling in the U.S.
- U.S. firms usually are notified about 5 days in advance that an inspection will take place and what the investigator wants to cover.
- Foreign firms typically notified at least 2 months in advance.
- Firm has opportunity to make sure documents are readily available and key people will be present during inspection.

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Quality System Regulation

Scope

820.1 (d) Foreign manufacturers

- It will be assumed that the foreign manufacturer does not conform to the Quality System regulation and that the devices are adulterated if the manufacturer refuses to permit inspection.

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FDA Inspections

Based on inspection results, inspection will be designated as

- OAI – "Official Action Indicated,"
- VAI – "Voluntary Action Indicated," or
- NAI – "No Action Indicated"

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FDA Inspections

"Official action indicated" follow-up

- Warning letter
- Seizure of nonconforming product
- Injunction
- Civil penalties
- Etc.

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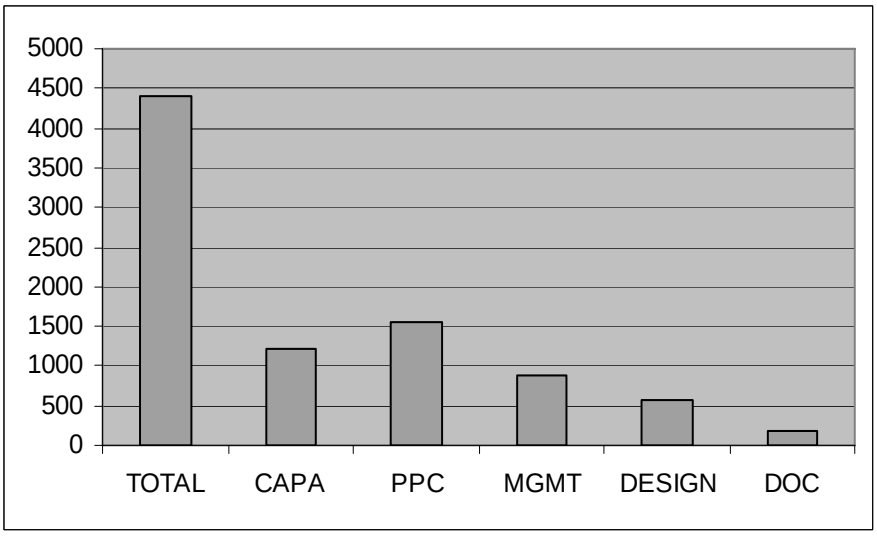
Number of Observations (n-4412) 1/1/2004 to 12/31/2004



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QSIT Overview

- Quality System Inspection Technique (QSIT) is based on a "top-down" inspection of a manufacturer's quality system.
- Start by looking at a firm's "systems" and procedures for addressing quality problems as opposed to "bottom-up" which starts by looking at one or more problems that may point to a failure in the quality system.

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QSIT Overview

System approach based on 7 subsystems

- Management Control
- Design Control
- Production and Process Control
- Corrective and Preventative Action
- Records, Documents, & Change Controls
- Facility and Equipment Control
- Material Control

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QSIT Overview

- The following diagram shows the interrelationship of these seven subsystems.
- QSIT focuses on four
  - Management Controls
  - Design Controls
  - Corrective and Preventive Action
  - Production and Process Control

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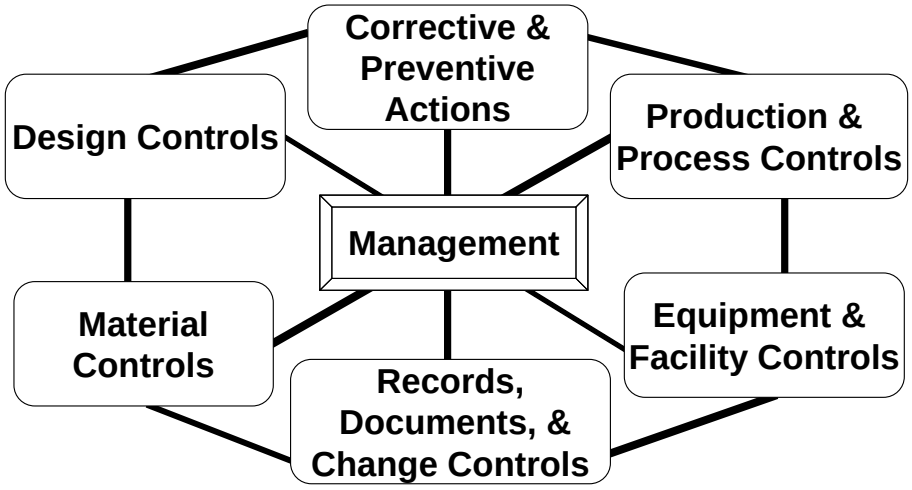
Relationship of Seven Subsystems



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Compliance Program 7382.845
Part III Inspectional

Inspection Level	Reason for Inspection	QSR System Inspected
1	Abbreviated	CAPA plus 1
2	Baseline	Four major subsystems
3	Compliance Follow-up	As directed by guidance

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Standard Warning Letter

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure that your manufacturing operations comply with all applicable requirements of the Act and FDA regulations.

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Standard Warning Letter

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

- …can deny export certification
- …also advise other federal agencies … so they may take this information into account when considering award of contract

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Warning Letter Response

We have reviewed your response and while your letter promises corrections to the observations listed on the form FDA 483, we must consider the response as inadequate because no evidence or documentation of corrections was provided with your response.

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Warning Letter with CAPA Cites 2004

- January – December 2004
- FDA issues 113 Warning Letters to medical device firms
- 89/113 or 79% contained cites for CAPA deficiencies

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Warning Letter with Design Control Cites 2004

- January – December 2004
- FDA issues 113 Warning Letters to medical device firms
- 57/113 or 50% contained cites for Design Control deficiencies

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Warning Letter with Process Validation Cites 2004

- 113 Warning Letters issued in 2004 to medical device manufacturers
- 33 contained citations for deviations on process validation
- 33 out of 113 letters = 29%

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Harmonization

When Part 820 was developed in 1996 it was harmonized with

- ISO 9001:1994 – Quality assurance in design, development, production, installation, and servicing.
- ANSI/AAMI/ISO 13485:1996 – Medical devices – particular requirements for the application of ISO 9001.
- ISO 8402:1994 – Quality management and quality assurance – vocabulary.

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ANSI/AAMI/ISO 13485:2003

- Has been revised and issued as a stand-alone quality system standard that specifies quality management system requirements for regulatory purposed for medical device manufacturers.
- It quotes extensively from ISO 9001:2000, but is independent of future revisions to ISO

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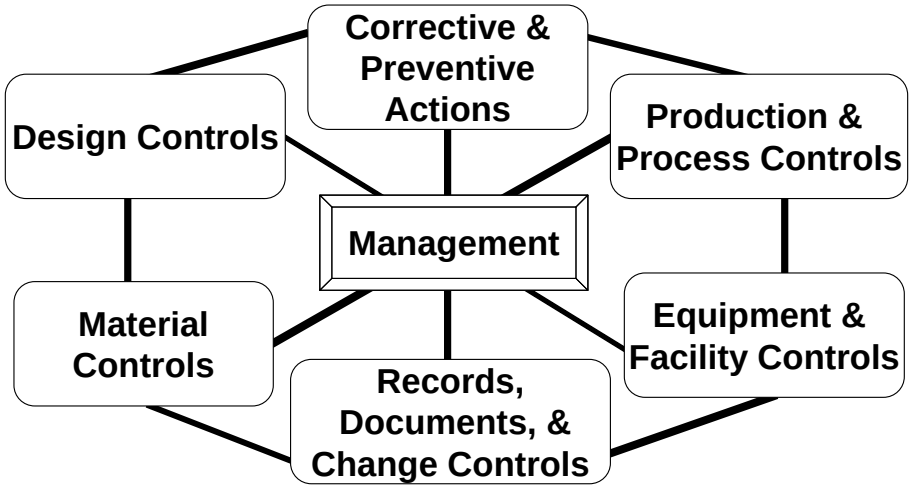
Quality System



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21 CFR Part 820

- 820.1 Scope
- 820.3 Definitions
- 820.20 Management Responsibility
- 820.30 Design Controls
- 820.40 Document Controls
- 820.50 Purchasing Controls
- 820.70 Production and Process Controls

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21 CFR Part 820

- 820.80 Acceptance activities
- 820.90 Nonconforming Product
- 820.100 Corrective and Preventive Action
- 820.181 Device Master Record
- 820.198 Complaints
- 820.250 Statistical techniques

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Management Controls

- Management with executive responsibility MUST:
  - Establish a Quality Policy
  - Establish adequate organization resources and structure
  - Conduct management review meetings on quality issues at defined intervals
  - Assign a member of top management as the Management Representative

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Management Representative

- Appointed and documented as the member of top management with authority and responsibility for:
  - Ensuring EFFECTIVE quality systems
  - Reporting on the performance of the quality system to top management and ensure these meetings are tied to the company's CAPA system

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Design Controls

Applicable to:

- Class II
- Class III
- Some Class I per 21CFR 820.30(a)

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Design Reviews

- Purpose

- Participants

- Timing

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Design Verification

Are the product specifications being met and can I prove it?

Did I make the device right?

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Design Validation

Is the product meeting user needs and intended uses for all specifications and can I prove it?

Did I make the right device?

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Design Validation vs. Process Validation

Design **Validation…**

Is the product meeting user needs and intended uses and can I prove it?

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Design Validation vs. Process Validation

Process Validation…

Does the process consistently produce a result or product meeting predetermined specifications and can I prove it?

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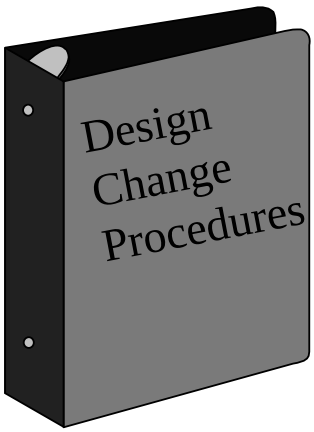
Define and Document Design Change Procedures



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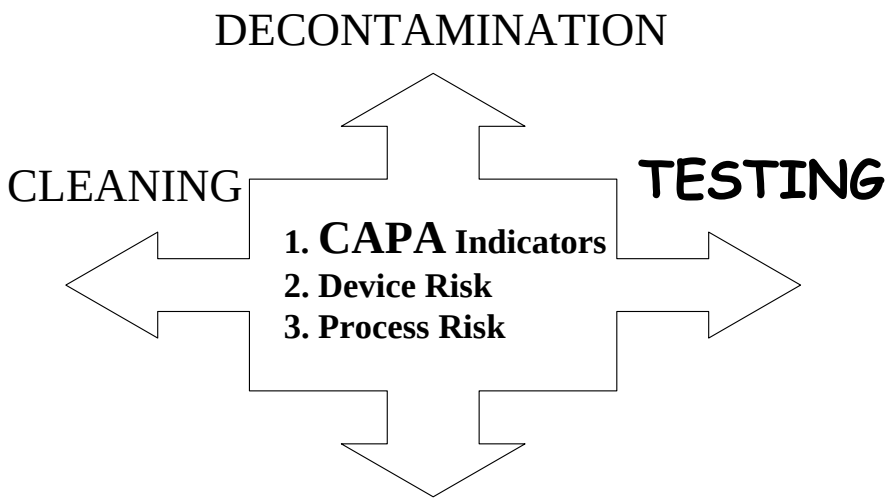
Production and Process Controls



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Plus...

- ✓ Purchasing
- ✓ Acceptance
- ✓ Buildings & Equip.
- ✓ Calibration
- ✓ Personnel
- ✓ Statistical Tech.'s
- ✓ Others

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Automated Processes

- Requirements
- Validation Protocol
- Validation Activities
- Validation Results
- Change Controls

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Is The Process Operating Within Specified Limits?

If NO, then review…

- Nonconforming Product Controls
- Resulting CAPA's
- Equipment Adj., Cal. & Maint.
- Validation (where required)

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Production and Process Controls

- Validate processes if results cannot be fully verified by subsequent inspection and test
- Validate software used in manufacturing and in the quality system
- Control and monitor manufacturing processes

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Purchasing Controls

- Ensures that all purchased or otherwise received product and services conform to specified requirements, including quality requirements
- Product is defined as broadly to include everything for manufacturing and delivering an item to the market

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Purchasing Controls

- Includes not only consultants but also any subcontractor or supplier
- Requires anyone performing a service or providing a product to be evaluated and the extent of control defined and to keep records of effectiveness including quality

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Purchasing Controls

- Extremely helpful in closing the loop holes with respect to so much being subcontracted out
- Places the ultimate responsibility on the finished product manufacturer versus on the FDA to try and regulate down the supplier chain

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Corrective and Preventive Action

- Collect and analyze data to identify nonconforming product and other quality problems
- Investigate cause
- Identify and implement corrective and preventive action

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Corrective and Preventive Action

- Verify or validate effectiveness
- Communicate information about quality problems to staff
- Forward information for management review

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Have the CAPA requirements been "established"?

- Defined
- Documented
- Implemented

§820.3(k)

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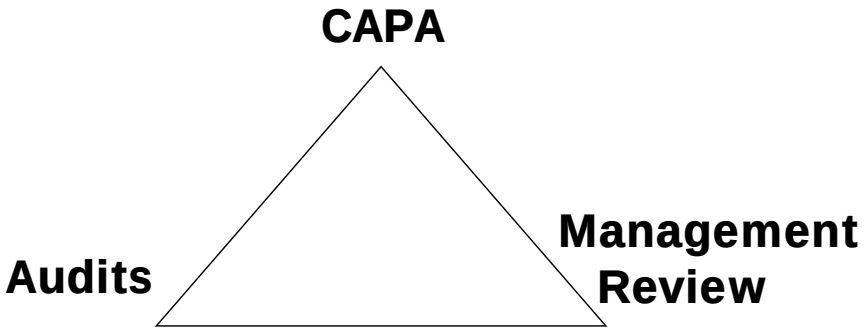
Staying informed …



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Correction vs. **Corrective Action**

"Correction" refers to repair, rework, or adjustment and relates to the disposition of an **existing** nonconformity

"Corrective action" relates to the elimination of the **causes** of an existing nonconformity

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"Healthy" CAPA subsystem procedures include provisions to ...

1. Identify and correct **existing** nonconforming product or other quality problems ("Correction");

2. Identify and eliminate the **causes** of existing nonconforming product and other quality problems ("Corrective Action"); and,

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“Healthy” CAPA subsystem procedures include provisions to ...

- 3. Identify and eliminate the causes of **potential** nonconforming product and other quality problems (“Preventive Action”)

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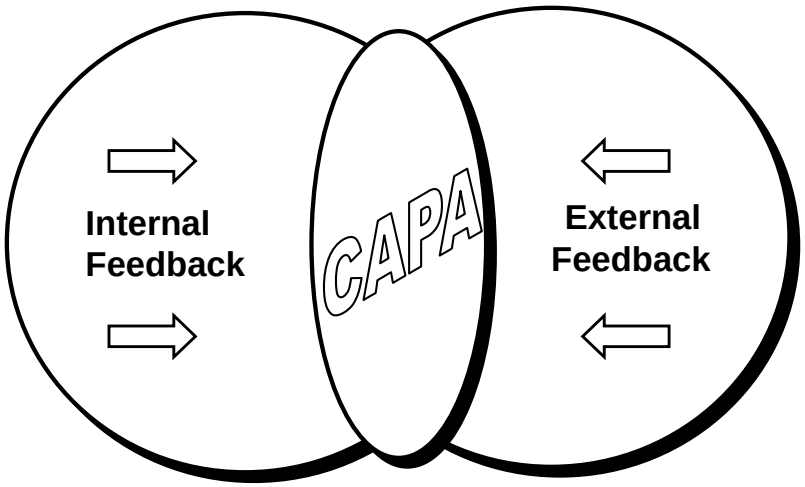
Quality Data Sources



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Internal Data Sources

- **Acceptance Activities (Inspection and Test Data)**
  - component, in-process and final test
  - scrap/yield

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Internal Data Sources

- **Nonconforming product**
  - scrap, rework, UAI
- **Process monitoring**
  - process control data, control charts, SPC

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Internal Data Sources

- **Equipment monitoring**
  - calibration, maintenance
- **Device History Records**
- **Change Control Records**

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Internal Data Sources

- **Internal Audits**
- **3rd Party Audits**
  - ISO
  - FDA
- **Supplier Audits**
- **Management Review Results**

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External Data Sources

- **Complaints & MDR's**
- **Servicing**
  - **warranty, non-warranty**
  - **field service reports**
  - **returns**
- **Recalls**
- **Legal Claims**

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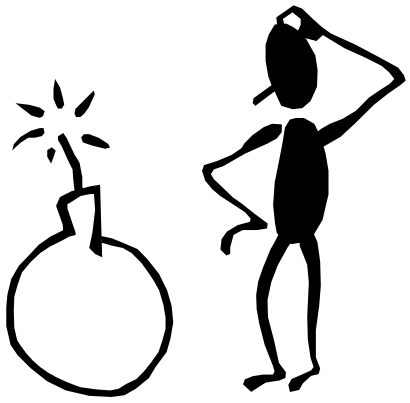
CAPA Program

- ***PRO*** active

  vs.
- ***RE*** active



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CAPA Program

- Identify data sources
- Document the problem
- Establish a priority system
  - consider impact / risks and select items with major impact
  - proceed to items with less impact

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CAPA Program

- Analyze the problem
  - root cause analysis
- Develop an action plan
  - consider impact and need for…
  - short term corrective action
  - long term corrective action

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CAPA Program

- Verification and Validation
  - analysis of data may lead to more than one solution, assure solution is appropriate
- Implementation
  - tracking for on-time completion

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CAPA Program

- **Documentation and follow-up**
  - corrective action effective
  - adverse effect on product
  - records
- **Communicate changes**
  - to those directly responsible
  - management review

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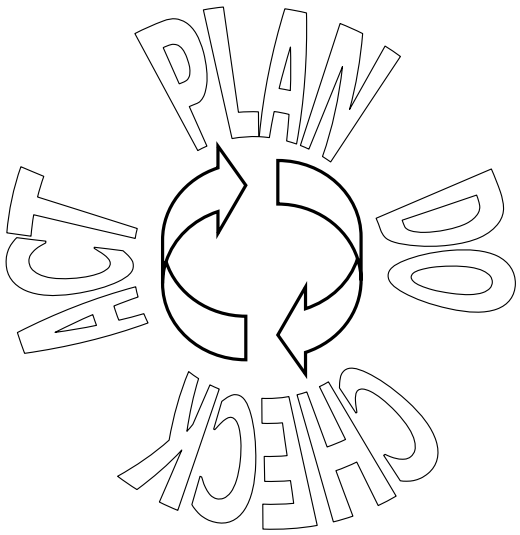
Close the loop...



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For Further Information

- General
  - www.fda.gov/cdrh/index.html
- Quality System Regulation and Preamble
  - www.fda.gov/cdrh/fr1007ap.pdf
- QSIT Guide
  - www.fda.gov/ora/inspect_ref/igs/qsit/qsitguide.pdf

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For Further Information

- Small Entity Guide
  - www.fda.gov/cdrh/dsma/gmpman.html

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Questions?

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Appendix
"Definitions"

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Federal Food, Drug and Cosmetic Act

SEC. 201.(321)

"device" means … an instrument, apparatus, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, party, or accessory, which is … intended for use in the diagnosis …cure, mitigation, treatment, or prevention of disease, in man or other animals, or … intended to affect …the body of man or other animals.

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Quality System Regulation

Definitions

820.3 (I) Finished Device

- Finished device means any device or accessory to any device that is suitable for use or capable of functioning, whether or not it is packaged, labeled, or sterilized.

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Quality System Regulation

Definitions

807.20 (a)(5) Accessories

- … accessories which are ready to be used for any intended health-related purpose and are packaged or labeled for commercial distribution for such health-related purpose, e.g. blood filters, hemodialysis tubing, or devices which of necessity must be further processed by a licensed practitioner or other qualified person to meet the needs of a particular patient, e.g. a manufacturer of ophthalmic lens blanks.

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Quality System Regulation

Definitions

820.3 (c) Component

- Component means any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device.

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Quality System Regulation

Scope

820.1 (a)(1) Applicability

- Does not apply to component manufacturers or manufacturers of human blood and blood components.

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Quality System Regulation

Scope

820.1 (a)(3) Applicability

- "Where appropriate"
  - Unless the manufacturer can document justification otherwise
  - If non-implementation could result in product not meeting requirements or the manufacturer is not able to take necessary corrective action

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Quality System Regulation

Definitions

820.3 (o) Manufacturer

- Manufacturer means any person who designs, manufacturers, fabricates, assembles, or processes a finished device. Manufacturer includes but is not limited to those who perform the functions of contract sterilization, installation, relabeling, remanufacturing, repacking, or specification development, and initial distributors of foreign entities performing these functions.

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Quality System Regulation

Definitions

820.3 (r) Product

- Product means components, manufacturing materials, in-process devices, finished devices, and returned devices.

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Quality System Regulation

Definitions

820.3 (s) Quality

- Quality means the totality of features and characteristics that bear on the ability of a device to satisfy fitness-for-use, including safety and performance.

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Quality System Regulation

Definitions

820.3 (w) Remanufacturer

- Remanufacturer means any person who processes, conditions, renovates, repackages, restores, or does any act to a finished device that significantly changes the finished device's performance or safety specifications, or intended use.

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