Glisland® Training Series:

Quality System Regulation

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GMP & cGMP vs. QSR

1. GMP – Good Manufacturing Practice
2. cGMP – Current Good Manufacturing Practice
3. QSR – Quality System Regulation

   "Current good manufacturing practice (CGMP) requirements are set forth in this quality system regulation. "

   "The failure to comply with any applicable provision in this part renders a device adulterated under section 501(h) of the act. Such a device, as well as any person responsible for the failure to comply, is subject to regulatory action."

Device Related Laws

1. Federal Food, Drug & Cosmetic Act of 1938
2. Medical Device Amendments Act of 1976
3. Safe Medical Devices Act of 1990
4. Medical Device Amendments of 1992
5. FDA Export Reform and Enhancement Act of 1996
6. FDA Modernization Act of 1997
7. Medical Device User Fee and Modernization Act of 2002
8. FDA Amendments Act of 2007

FDA Quality System Regulation

1. In 1976, cGMP for medical devices: 520(f) of FD&C Act (21 U.S.C.. 360j(f))
2. Codified in 21 CFR Part 820, effective December 1978
3. Focused on production process in 1978 cGMP
4. Added design control provision in 1990 amended by *SMDA* (*Safe Medical Device Acts*)
   a) Added section 803 (21 U.S.C 383)
   b) Revised 1978 cGMP and harmonized with EU standard
   c) Rename cGMP for medical device to QSR
   d) Design Control effective June 1, 1998
5. The new QSR applies to the entire life cycle of a device

21 CFR Part 820 Components

1. General Provisions
2. Quality System Requirements
3. Design Controls
4. Document Controls
5. Purchasing Controls
6. Identification and Traceability
7. Production and Process Controls
8. Acceptance Activities
9. Nonconforming Product
10. Corrective and Preventive Action
11. Labeling and Packaging Control
12. Handling, Storage, Distribution, and Installation
13. Records
14. Servicing
15. Statistical Techniques

Subpart A - General Provisions

1. **Scope (§ 820.1)**
   a) From design, manufacture, packaging, labeling, storage, installation, to servicing
   b) Finished devices intended for human use
   c) Some Class I devices
   d) Device HTC/Ps
   e) Made in US or imported
   f) "where appropriate"
2. **Definitions (§ 820.3)**
3. **Quality system (§ 820.5)**
   a) Organizational structure, responsibilities, procedures, processes, and resources for implementing quality management
   b) Establish and maintain

Subpart B - Quality System Requirements

1. **Management responsibility (§ 820.20)**
   a) Quality policy and objectives
   b) Adequate organizational structure
   c) Management review
   d) Quality planning
   e) Quality system procedures
2. **Quality audit (§ 820.22)**
   a) Procedures, CAPA, review, documentation
3. **Personnel (§ 820.25)**
   a) Sufficient and qualified
   b) Training

Subpart C - Design Controls

a) Any class III, class II, and some class I (820.(a)(2))
b) Design and development planning: establish, review, update, approve
c) Design input: SOPs, requirements, review and approval
d) Design output: SOPs, acceptance criteria, review and approval
e) Design review: SOPs, representatives
f) Design verification: design output <-> design input
g) Design validation: production units <-> intended use
h) Design transfer: SOPs
i) Design changes: review and approval before change
j) Design history file: for each type of device

Subpart D - Document Controls

Establish and maintain procedures to control **all documents** that are required by this part:

a) Document approval and distribution
   - Review and approval prior to issuance
   - Available at all locations necessary
   - Remove obsolete documents promptly

b) Document changes
   - Original review and approval
   - Timely communication of changes
   - Change records

Subpart E - Purchasing Controls

Establish and maintain procedures to ensure that **all purchased** or otherwise received product and services **conform to specified requirements:**

a) Evaluation of suppliers, contractors, and consultants
   - Set requirements
   - Evaluate ability to meet the requirements
   - Controls
   - Records

b) Purchase data
   - Specification
   - Agreements
   - Approval according to 820.40

Subpart F – Identification and Traceability

1. **Identification (§ 820.60)**

   Identify product during all stages of receipt, production, distribution, and installation to prevent mixups.

2. **Traceability (§ 820.65)**
   - Surgical implants
   - Life support or sustain devices
   - Control number
   - Corrective action procedures
   - DHR (Device History Record)

Subpart G – Production and Process Controls

1. **Production and process controls (§ 820.70)**
   a) Develop, conduct, control, and monitor production processes
   b) Production and process change control (validate/verify/approve)
   c) Environmental control (e.g. air conditioning)
   d) Personnel: health, cleanliness, personal practice, clothing, training
   e) Contamination control
   f) Buildings: sufficient space, prevent mixups
   g) Equipment: Validation, maintenance
   h) Control of manufacturing materials
   i) Automated processes: software validation

Subpart G – Production and Process Controls

2. **Inspection, measuring, and test equipment (§ 820.72)**
   a) Qualification (DQ/IQ/OQ/PQ)
   b) Calibration
3. **Process validation (§ 820.75)**
   a) Required for a process cannot be fully verified
   b) Monitor and control validated processes
   c) Revalidate when changes or deviations occur

Subpart H - Acceptance Activities

1. **Receiving, in-process, and finished device acceptance (§ 820.80)**
   a) SOPs for Inspections, tests, verification
   b) Incoming product control
   c) In-process product control
   d) Finished device control
   e) Acceptance records in DHR
2. **Acceptance status (§ 820.86)**
   a) Establish acceptance criteria
   b) Identify conformance or nonconformance status (e.g. Passed, Failed)

Subpart I – Nonconforming Products

a) Control of nonconforming product
   - Procedures
   - Evaluation
   - Investigation
   - Notification
   - Documentation

b) Nonconformity review and disposition
   - Procedures that define responsibility and authority
   - Procedure for rework and reevaluation
   - Document in DHR

Subpart J – Corrective and Preventive Action

a) CAPA procedures:
   - Analyzing
   - Investigating
   - Identifying the action(s)
   - Verifying or validating CAPA
   - Implementing and recording changes
   - Communicating
   - Management review

b) Documenting CAPA activities

Subpart K – Labeling and Packaging Controls

1. **Device labeling Control**
   a) Label integrity
   b) Labeling inspection
   c) Labeling storage
   d) Labeling operations
   e) Control number
2. **Device packaging**
   a) Appropriate container design
   b) Prevention of alteration or damage during processing, storage, handling, and distribution

Subpart L - Handling, Storage, Distribution, and Installations

1. **Handling**
   a) Ensure that mixups, damage, deterioration, contamination, or other adverse effects to product do not occur during handling
2. **Storage**
   a) Prevent mixups, damage, deterioration, contamination
   b) Ensure that no obsolete, rejected, or deteriorated product is used or distributed
   c) Receipt and dispatch procedures
3. **Distribution**
   a) Distribution control
   b) Distribution records
4. **Installation**
   a) Provide instruction for installation and inspection/test
   b) Document installation and inspection/test results

Subpart M - Records

1. **General requirements**
   - Location: accessible, readily available for review and copying by FDA inspector(s)
   - Be legible, minimize deterioration, prevent loss
   - Confidential record may be marked as confidential
   - Retention time: expected life of the device, but not less than 2 years of the date of commercial release
   - Exceptions: management review, quality audit, and supplier audit reports are internal

Subpart - Records

2. **Device master record (DMR)**
   a) Device specifications
   b) Production process specifications
   c) Quality assurance procedures and specifications
   d) Packaging and labeling specifications
   e) Installation, maintenance, and servicing procedures and methods

Subpart - Records

3. **Device history record (DHR)**
   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 device identification(s) and control number(s) used.

Subpart - Records

4. **Quality system record (QSR)**
   - Quality policy
   - Responsibility and authority
   - Resources
   - Management representative
   - Management review
   - Quality planning
   - Quality system procedures

Subpart - Records

5. **Complaint files**
   a) SOPs for receiving, reviewing and evaluating complaints timely by a formally designated unit
   b) Investigation of the complaints
   c) Complaints involving the possible failure of a device, labeling, or packaging
   d) Part 803 Medical Device Reporting events
   e) Investigation records by formally designated unit
   f) Access of investigation records

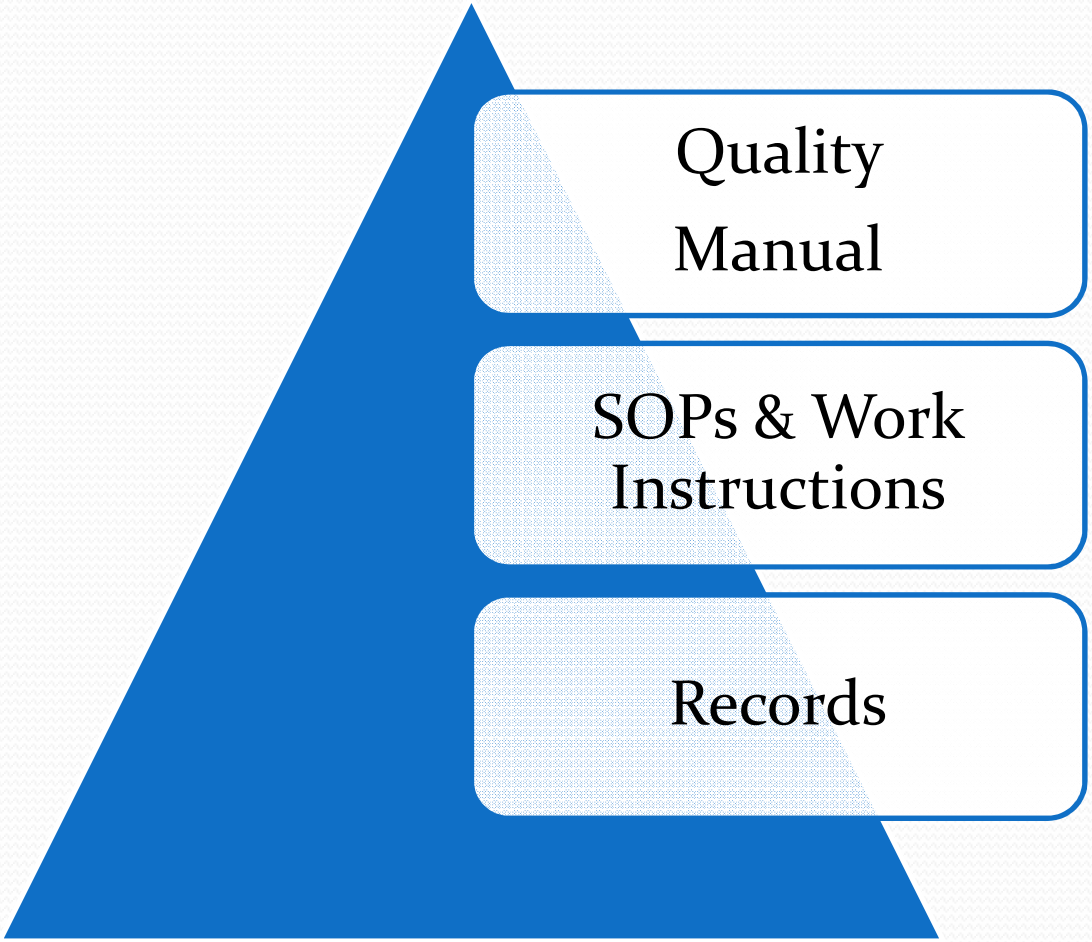
Subpart N - Servicing

a) Instructions and procedures for required servicing
b) Analysis of service reports
c) Handling a service report representing part 803 event
d) Documenting service reports

Subpart O - Statistical Techniques

a) SOPs for identifying valid required statistical techniques
b) Review and document sampling plans

QS Documentation Pyramid



FDA Enforcement Actions

- Establishment registration and product listing
- Marketing clearance/approval
- Reports
- Inspections
- Notice of Violations (FDA-483, Warning Letters…)
- Recalls
- Civil money penalties
- Seizure
- Injunction
- Prosecution

References

- *Fundamentals of US Regulatory Affairs*, 5th Edition, RAPS, 2007
- *Milestones in U.S. Food and Drug Law History,* http://www.fda.gov/opacom/backgrounders/miles.html
- Significant Amendments to the FD&C Act, http://www.fda.gov/opacom/laws/
- 21 CFR Part 820, http://www.gpoaccess.gov/nara/index.html
- *FDA Regulatory Procedure Manual 2007,* http://www.fda.gov/ora/compliance_ref/rpm/
- FDA Guidance Documents: http://www.fda.gov/cder/guidance/index.htm