Manufacturing and Quality System Regulation (QSR)

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What is the QSR?

- Authorized by Section 520(f) of the Federal Food, Drug, and Cosmetic Act (FDCA)
- One of the "General Controls" of the FDCA
- Set of Regulations (21 C.F.R. Part 820) that governs:
  - The methods used in and
  - The facilities and controls used for
  - The design, manufacture, packaging, labeling, storage, installation, and servicing of finished devices intended for human use
- First Revision, Effective July 21, 1978
- Second Revision, Effective June 1, 1997
- "QMSR" Proposal (March 2022)

What is the QSR?

- **Applies** to **finished device manufacturers** who intend to commercially distribute medical devices
  - **Finished Device**: 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. See 21 CFR 820.3(l).
- Does **not** apply to:
  - Component / Material Suppliers
  - Design Consultants
  - Distributors

What is the QSR?

- Emphasizes quality system, not just a quality department
- Flexible
  - Regulation does not prescribe in detail how a manufacturer must produce a specific device
  - QMS should be commensurate with:
    - Risk presented by the device
    - Complexity of device and manufacturing processes
    - Size and complexity of organization
- Requires Company Judgment
  - Regulation provides framework for the manufacturer to develop a QMS consistent with its operation and compliant with FDA regulations

The principles of the QSR could be applied to ANY business that supplies a product or service to a customer

Why follow the QSR?

- FDA Enforcement
- Business Reasons
  - Recalls are expensive
  - Repairs/refunds are expensive
  - Poor yields, inefficient processes, are expensive
  - Enforcement actions can have a negative impact on your company in the marketplace and on Wall Street
- Other Good Reasons
  - Compliance Promotes Good Relationship with FDA, and vice-versa
  - Failure to comply could result in harm to patients (the patient could be you or someone you know!)

QSR: Brief Overview of the Regulation

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QSR Overview

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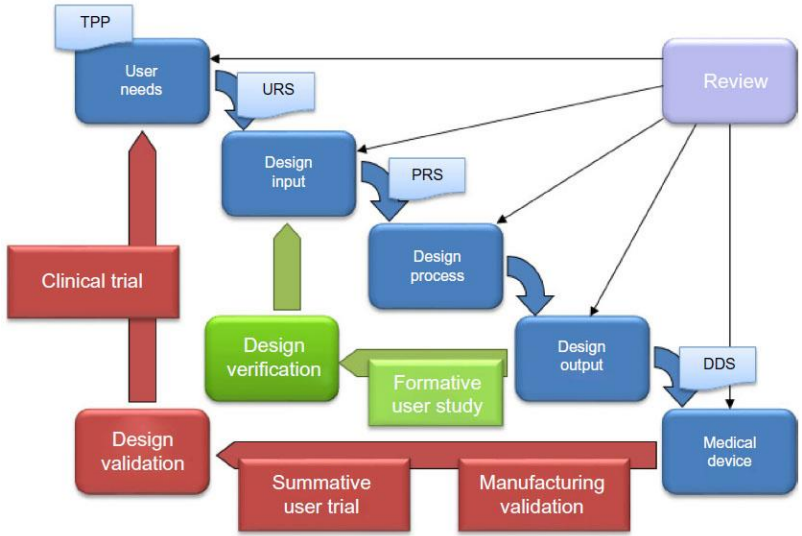
Elements of the QSR

- **Management Controls** (21 CFR §§ 820.20 820.22, 820.25)
  - Quality Policy
  - Management Representative
  - Management Review
  - Quality System Procedures
  - Quality Audits
  - Personnel Training and Awareness of Device Defects

Elements of the QSR

- **Design Controls** (21 CFR § 820.30)
  - Design and Development Planning
  - Design Input
  - Design Output
  - Design Review
  - Design Verification
  - Design Validation
  - Design Transfer
  - Design Changes
  - Design History File



Elements of the QSR

- Common Pitfalls
  - Entering design controls during “prototype” / feasibility stage
  - Design inputs are in conflict or ambiguous
  - Failure to document design outputs
  - Failure to use objective, measureable acceptance criteria in design testing
  - Failure to conduct testing (design verification and validation testing)
  - Failed test results
  - Unable to transfer design to manufacturing

Elements of the QSR

- **Production and Process Controls** (21 CFR §§ 820.70, 820.72, and 820.75)
  - Production and Process Changes
  - Environmental Control
  - Personnel
  - Contamination Control
  - Buildings
  - Equipment
  - Manufacturing Material
  - Automated Processes
  - Inspection, measuring and test equipment
  - Process validation
- **Nonconforming Product** (21 CFR § 820.90)

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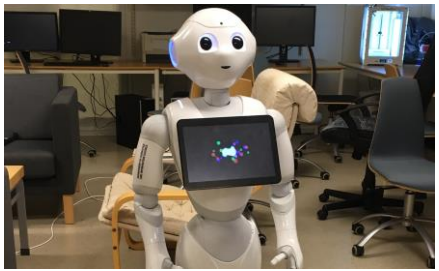
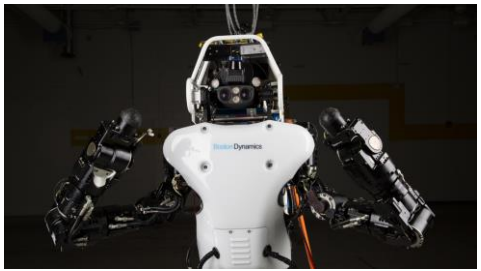
Elements of the QSR

- Production and Process Controls apply to:
  - All production steps and manufacturing areas
  - Includes areas and equipment shared between production and R&D
  - From receiving dock to customer site
  - Focuses on conditions, practices, operations, and handling that, if not controlled, could negatively affect device safety and effectiveness





Elements of the QSR

- Common Pitfalls
  - Production and Process Changes
    - "Small" changes introduced by "helpful" employees
    - Processes grouped together without assessing impact
    - Sequence and timing changes
    - Undocumented deviations
  - Environmental Control
    - Temperature requirements not met
    - Cleanliness not maintained
    - Staff follow "common practices," rather than documented processes
    - Gowning requirements
      - Protect the product and/or protect the employee?
      - Inconsistent application

Elements of the QSR

- Common Pitfalls
  - Equipment
    - Calibration and user standardization not conducted
    - Set-up not verified or documented
    - Incomplete change-over from previous production activity
  - Manufacturing Material
    - New material – “Everyone knows that olive oil works better than machine oil.”
    - New supplier - “It’s the same stuff, just from a different source.”
  - Inspection, Measuring and Test Equipment
    - Use of the wrong tool for the right job
    - Calibration or standardization not verified

Elements of the QSR

- Common Pitfalls
  - Process Validation
    - Lack of meaningful limits
    - Specifications not based on critical parameters
    - Performance not assessed at both extremes
    - Failure to calibrate equipment/instruments uses in validation testing
    - Failure to follow current SOPs
    - Failure to establish protocols that meet FDA's expectations (batch sizes, no. of runs, etc.)
    - Failure to explain deviations
    - Failure to investigate nonconformities
    - Failure to approve protocol in advance of conducting validation study

Elements of the QSR

- **Acceptance Activities** (21 CFR §§ 820.80 and 820.86)
  - Receiving, in-process, and finished device acceptance
  - Acceptance status

Elements of the QSR

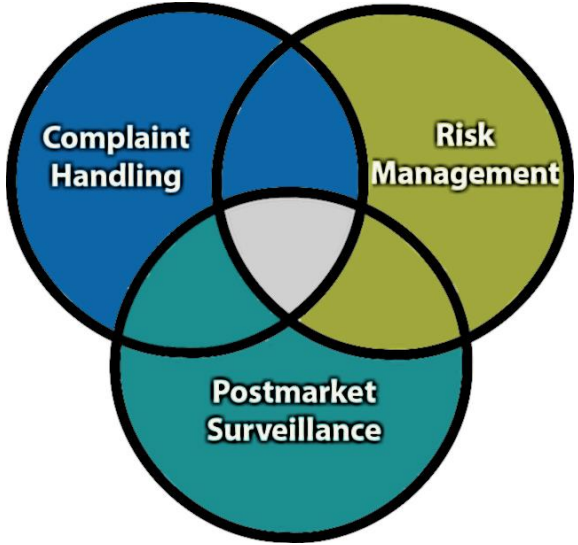
Acceptance Activity Hypothetical

- It's the end of the month and your supervisor reminds you that production levels have dropped. She says that there will be "no excuses" for not meeting the production quotas. After rushing back from your meeting with your supervisor, you begin a subassembly process which requires you to use components that have been released from the stock room to various bins near your work station. One of the pouches containing key components to make the subassembly is not marked "Released" and is not accompanied by paper work indicating that the parts have been accepted by Incoming Inspection/Receiving. You visually examine the parts and determine that they look okay to use.

Was this the proper action to take?

Elements of the QSR

- **Corrective and Preventive Action** (21 CFR § 820.100)
  - Initiate
  - Investigate
  - Root Cause Analysis
  - Corrective / Preventive Action
  - Verify Effectiveness
- **Complaint Handling** (21 CFR § 820.198)
  - Document
  - Evaluate (e.g., MDR)
  - Investigate
  - Escalate to CAPA
  - Close



Elements of the QSR

- **Document Controls** (21 CFR § 820.40)
  - Document Approval and Distribution
  - Document Changes
  - Must consider the regulatory implications of changes
    - Is FDA approval of the change required?
    - What needs to be done to verify or validate the change?
    - Does the change need to go through your design control system?

- **Records** (21 CFR §§ 820.180, 820.181, 820.184, and 820.186)
  - Device Master Record
  - Device History Record
  - Quality System Record

Elements of the QSR

Change Control Hypothetical

- You are in charge of performing one of the final tests on a subassembly to verify that it functions properly. After completing the test, you notice that the specification drawing with tolerances for acceptance is Revision B; however, you remember working from Revision C the day before and you cannot remember what are the differences between the documents.

- Then, while comparing the two drawings, you notice that the dimensional tolerances are very different (the new device is much thinner), and you don't remember how or why this design change was implemented.

What should you do about these observations?

Meeting FDA's Expectations

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Interpreting the QSR

- Preamble to Final Rule
- FDA's QSR Manual
- Quality System Inspection Technique Manual
- K. Trautman, *The FDA and Worldwide Quality System Requirements Guidebook for Medical Devices* (1997)
- Trade Press/Conferences
- Warning Letters Issued to Competitors
- Industry Standards
- Common Sense

What Does FDA Expect?

- Commitment to quality that starts with management and permeates throughout your company
  - "Company culture" that is quality-minded
  - Staff should call "time out" if SOPs do not reflect their actual practices

- Written procedures and work instructions that
  - Cover every QSR provision applicable to your company
  - Reflect your company's practices

What Does FDA Expect?

- Records showing that you followed your own procedures
  - Document What You Do
  - Do What You Document
- Consistent (Daily) compliance
- Responsiveness to problems
  - Closure of open items (close the loops)
  - Verification of the effectiveness of corrective actions;
  - Linked systems

Third Parties in Manufacturing and Quality Operations

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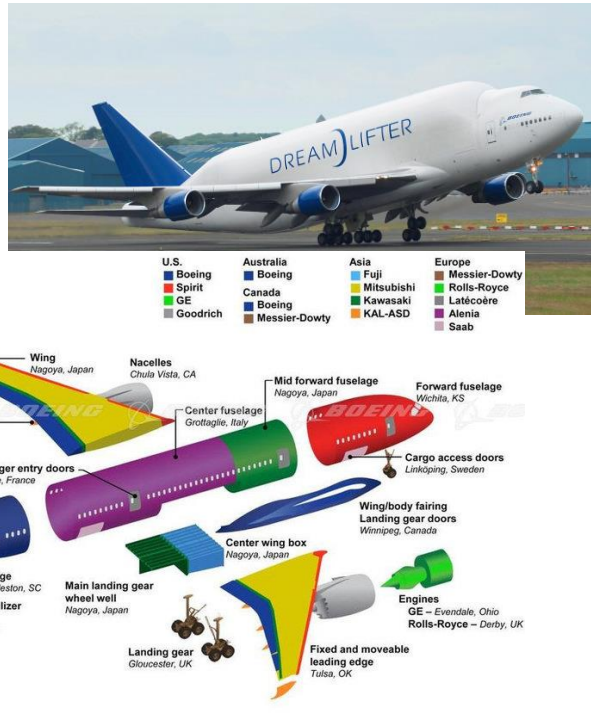
Global Supply Chain

- With globalization, finished device manufacturers rely on third-party entities to manufacture components and materials.
  - Finished Devices
  - Critical Materials / Components
  - Non-critical Materials / Components
  - Services

- **Purchasing Controls** (21 CFR § 820.50)
  - Evaluation of Suppliers, Contractors and Consultants
  - Purchasing Data



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Examples of Third-Party Entities

- **Contract Manufacturer**: Manufactures a finished device to another establishment's specifications.

- **Contract Sterilizer**: Provides a sterilization service for another establishment's devices.

- **Specification Developer**: Develops specifications for a device that is distributed under the establishment's own name but performs no manufacturing. This includes establishments that, in addition to developing specifications, also arrange for the manufacturing of devices labeled with another establishment’s name by a contract manufacturer.

FDA Expectations

- FDA's View:
  - Finished device manufacturer has ultimate responsibility for ensuring that device meets specifications.
  - Qualify and monitor suppliers in accordance with Purchasing Controls process and procedure (21 C.F.R. § 820.50).
  - Incoming acceptance of received goods to verify that components and materials meet requirements (21 C.F.R. § 820.80).

Quality Agreement

- **Quality Agreement**: Legal document that defines both specific *quality* parameters for a project AND which party is responsible for the execution of those parameters.

- When do you need a Quality Agreement?
  - Relying on supplier to perform regulatory requirements of QSR.
  - Control supplier so that finished device manufacturer meets regulatory requirements of QSR.

ISO, MDSAP, and the Proposed “QMSR”

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What is ISO 13485?

- International consensus standard for manufacturing medical devices.
- Used by jurisdictions to demonstrate that a company has established an appropriate quality system for manufacturing medical devices.
- Similar but ***not*** equivalent to the QSR

MDSAP and FDA Inspections

- **Medical Device Single Audit Program** allows an MDSAP recognized Auditing Organization (third party) to conduct a single regulatory audit of a medical device manufacturer that satisfies the relevant requirements of the regulatory authorities participating in the program
  - Organized around ISO 13485
- FDA accepts MDSAP audit reports as a substitute for routine Agency inspections
- FDA can still conduct directed inspections

What's the "QMSR"?

- QSR = Quality Management System Regulation ("QMSR")
- Incorporates "by reference" ISO 13485:2016
  - *Note that ISO 13485:2016 is only available by purchase*
- Guts the rest of the QSR, and leaves provisions not covered by ISO 13485:2016
  - Retains exclusion of certain Class I devices from design control requirements
  - Retains QSR packaging and labeling requirements
  - Complaint handling requirements for MDRs
- Corresponding changes to Combination Product regulation, 21 C.F.R. Part 4
- FDA will be issuing a new "inspection" guide
  - Certificate of Conformity to ISO 13485:2016 ≠ replacement of FDA inspection
- Provides a one (1) year implementation period

Does ISO 13485:2016 = QSR?

Yes, but there are differences

- Terminology Swap
  - Management with Executive Responsibility = Top Management
  - Design History File (DHF) = Design and Development Files
  - Device History Record (DHR) = *No Corresponding Term, but Production Records Required*
  - Device Master Record (DMR) = *Medical Device File?*
  - Process Validation = Validation of Processes
- Planning of "Product Realization"
- Idea that "Customer" includes suppliers
- Specific validation requirement for sterilization processes
- Specific process monitoring requirements
- "Preservation of Product"

Does ISO 13485:2016 = QSR?

Yes, but there are differences

- Do not need an independent reviewer to sit on design review
- Specific inclusion of Risk Management in quality management system
- Complaint specifically includes “electronic” information and information learned through servicing
- Additional flexibility to not investigate complaints
- Specific time expectation for implementing corrective action (“undue delay”)
- Specific requirements on preventative action

Biography

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Dennis C. Gucciardo counsels domestic and global medical device manufacturers to help ensure they are operating in compliance with the myriad of US Food and Drug Administration (FDA) regulations, requirements, and expectations. He works with companies—from small startups to large multinational corporations—throughout the product life-cycle on how to bring novel technologies to market, maintain compliance, and avoid FDA enforcement actions.

Dennis helps companies bring medical devices to market, including navigating the premarket process, establishing a quality system, and complying with postmarket requirements. Recently, in response to the coronavirus (COVID-19) global pandemic, Dennis assists companies (traditional medical device manufacturers and new market entrants) with navigating FDA enforcement policies and the Emergency Use Authorization (EUA) process for quickly bringing products to market.

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