Manufacturing and Quality System (QS) Regulation

Food and Drug Law Institute

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Manufacturing and Quality System Regulation

- **History, Purpose, and Scope**
- **Regulatory Requirements for Device Manufacturing and Distribution**
- **Quality System and FDA Expectations**
  - Management controls
  - Quality audit and personnel
  - Design controls
  - Production and process controls
  - Complaint handling
  - Corrective and preventive action (CA/PA)
  - Records, documents and change control
  - Equipment and facilities controls
  - Materials controls
- **Third Parties in Manufacturing and Quality Operations**
  - Quality Agreements
  - Contract specification developers
  - Contract manufacturers, packagers, labelers
  - Component suppliers
- **Similarities/Differences between International Standards Organization (ISO) and Medical Device Single Audit Program (MDSAP)**

What is the Quality System Regulation?

- Authorized by Section 520(f) of the Federal Food, Drug, and Cosmetic (FD&C) Act
- Set of regulations (21 C.F.R. Part 820) that governs:
  - The design, manufacture, packaging, labeling, storage, installation, and servicing of finished devices intended for human use.
- First published in 1976, effective July 21, 1978
- Revised in 1996, effective June 1, 1997
- Proposed revision March 2022
  - “Quality Management System Regulations”
  - No definitive effectivity date

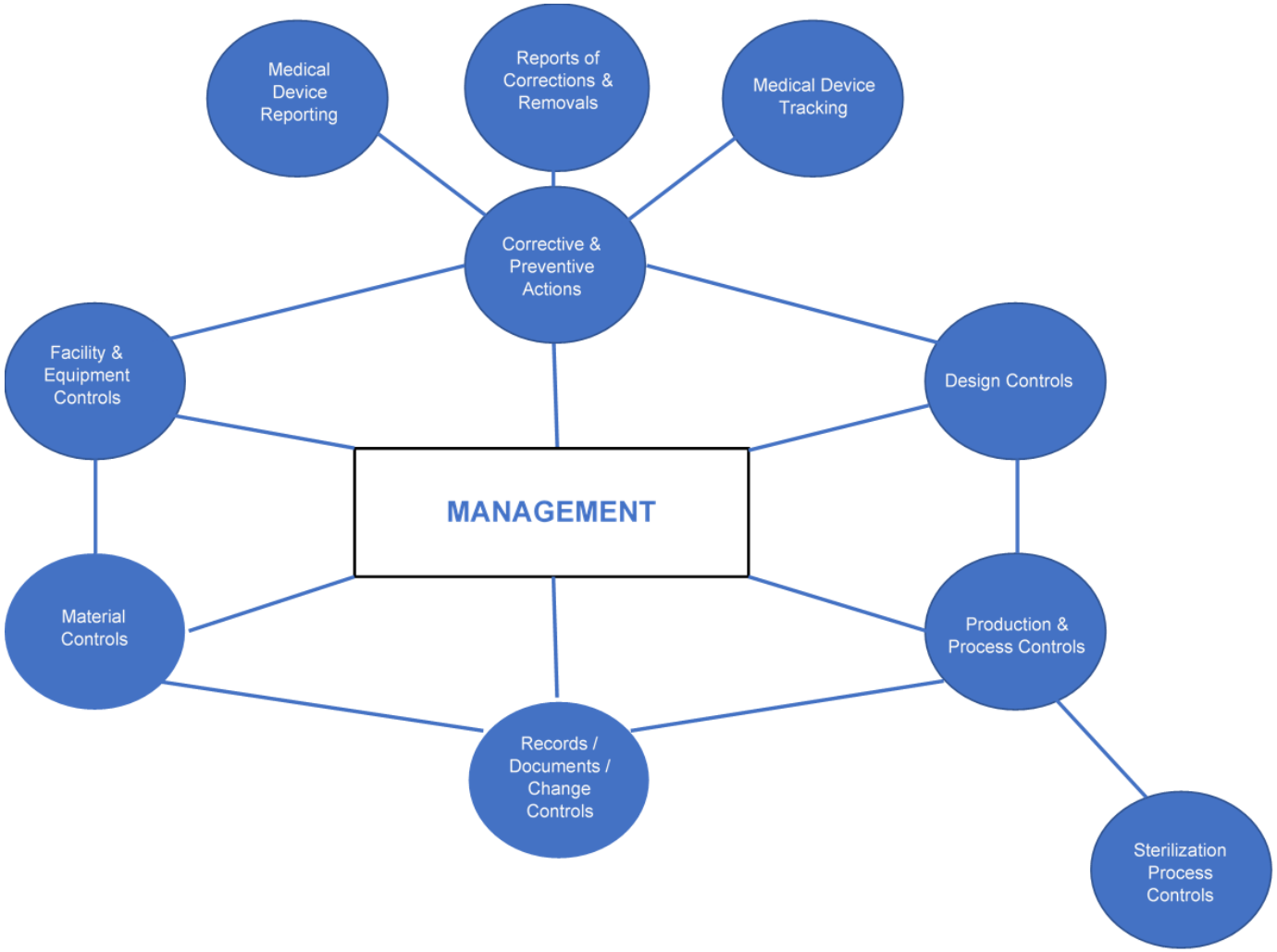
Some History…

- Safe Medical Device Act of 1990 amended section 520(f) of the Federal Food, Drug, and Cosmetic (FD&C) Act
  - This amendment provided FDA with the authority to add preproduction design controls to the regulation
    - This change was based on the fact that a significant proportion of all device recalls were attributed to poor product design.
  - Additionally, the Safe Medical Device Act added requirements to section 803
    - This change authorized the FDA to enter into agreements with foreign countries to facilitate commerce in devices
      - This encouraged mutual recognition of GMP regulations

Why implement a Quality Management System?

- Specific requirements to help manufacturers ensure their products consistently meet applicable customer and regulatory requirements and specifications
- Regulation does not prescribe in detail how a manufacturer must produce a specific device
- Regulation provides framework for the manufacturer to develop a Quality Management System (QMS) consistent with its operation and compliant with FDA regulations
  - QMS should be <u>appropriate</u> with:
    - Risk presented by the device
    - Complexity of device and manufacturing processes
    - Size and complexity of organization

Quality System Regulations (QSRegs) Overview

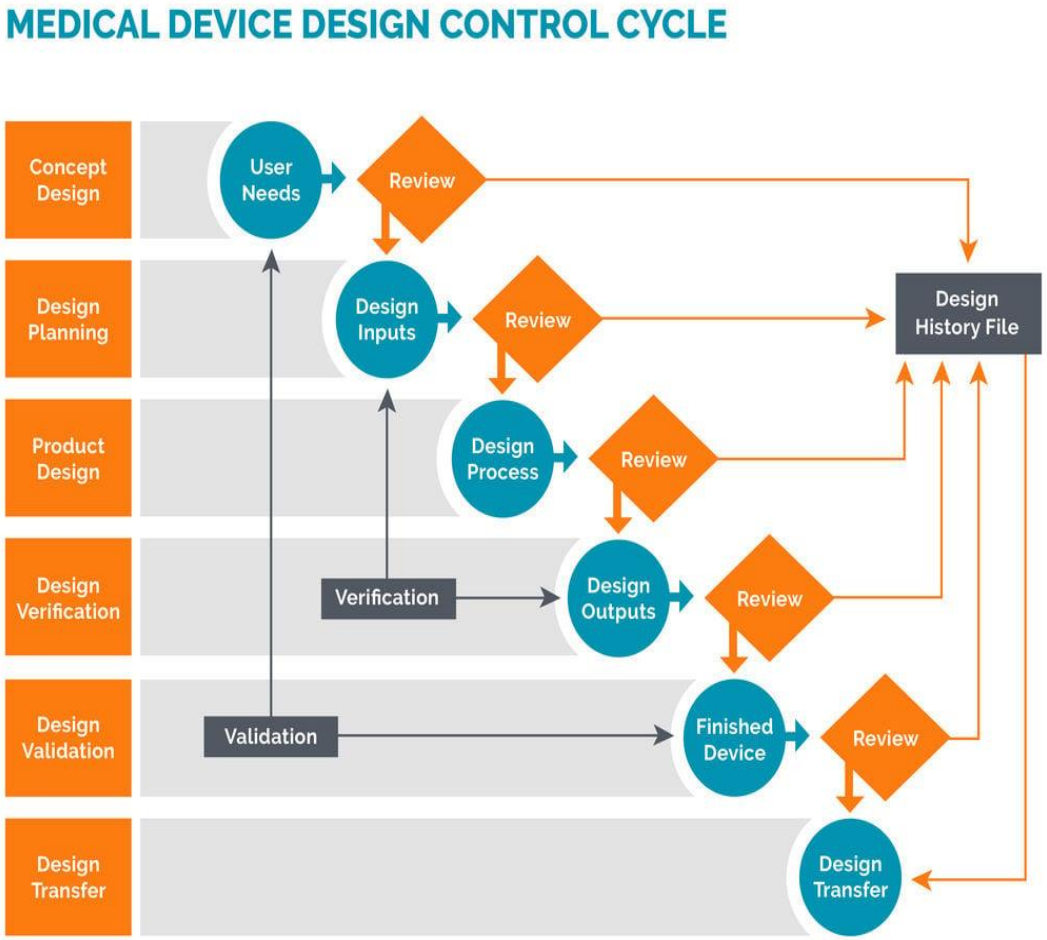


Elements of the QSRegs

- **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 QSRegs

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

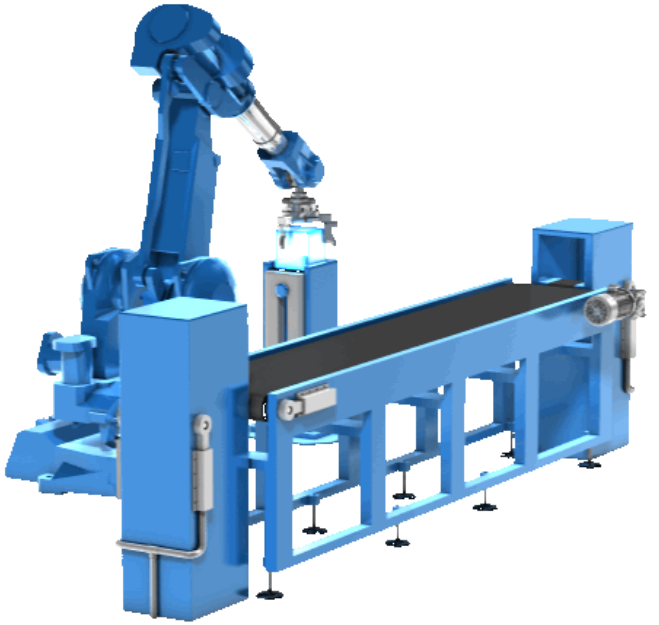


Elements of the QSRegs

- Common Pitfalls
  - Design Controls
    - 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 QSRegs

- **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)



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

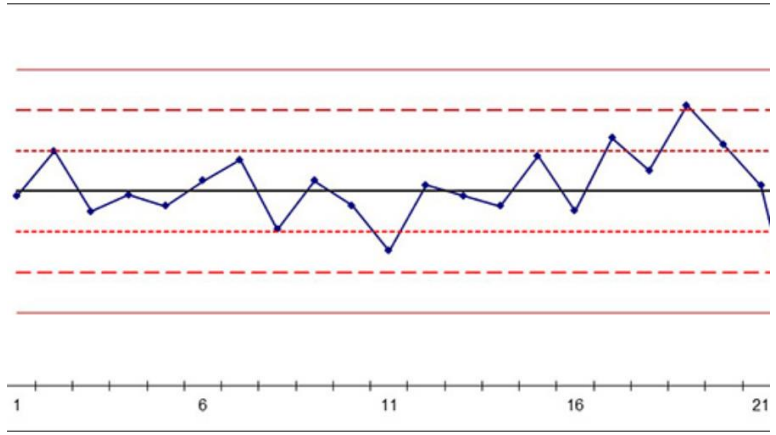
- Common Pitfalls
  - Production and Process Changes
    - "Small" uncontrolled changes introduced by "helpful" employees
    - Processes grouped together without assessing impact
    - Sequence and timing changes
    - Undocumented deviations
  - Environmental Control
    - Temperature requirements 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 – “Bleach is bleach regardless of the brand.”
  - New supplier - “It’s the same stuff, just from a different source.”
- Inspection, Measuring and Test Equipment
  - Use of the wrong tool for the 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 used 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 workstation. One of the pouches containing key components to make the subassembly is not marked "Released" and is not accompanied by paperwork 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 oversee 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 the differences are 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

Interpreting the QSRegulations

- Preamble to Final Rule
- FDA's QSRegulation Manual
- Quality System Inspection Technique Manual
- A. Daniel, E. Kimmelman, *The FDA and Worldwide Quality System Requirements Guidebook for Medical Devices, Second Edition* (2008)
- Trade Press/Conferences
- Warning Letters Issued to Competitors
- Industry Standards
- Common Sense

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What Does FDA Expect?

- Commitment to quality that starts with management
  - "Company culture" that is quality-minded
  - Employees should call "time out" if SOPs do not reflect their actual practices

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

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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

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

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 QSRegs.
  - Control supplier so that finished device manufacturer meets regulatory requirements of QSRegs.

ISO, MDSAP, and the Proposed "QMSR"

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 QSRegs

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"?

- QSRegs = 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 QSRegs, 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 = QSRegs?

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 = QSRegs?

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

Does ISO 13485:2016 = QSRegs?

TABLE 1—HIGH-LEVEL SUMMARY OF 21 CFR PART 820 PROPOSED RULE DIFFERENCES AND ADDITIONS		
Current part 820 [1]	**ISO 13485 requirements [1]**	**Proposed rule**
Subpart A—General Provisions	Clause 1. Scope, Clause 4. Quality Management System	Requirements substantively similar
Subpart B—QS Requirements	Clause 4. Quality Management System, Clause 5. Management Responsibility, Clause 6. Resource Management, Clause 8. Measurement, Analysis, and Improvement	Requirements substantively similar
Subpart C—Design Controls	Clause 7. Product Realization	Requirements substantively similar
Subpart D—Document Controls [2]	Clause 4. Quality Management System	Differences addressed in 820.35
Subpart E—Purchasing Controls	Clause 7. Product Realization	Requirements substantively similar
Subpart F—Identification and Traceability	Clause 7. Product Realization	Requirements substantively similar
Subpart G—Production and Process Controls	Clause 4. Quality Management System, Clause 6. Resource Management, Clause 7. Product Realization	Requirements substantively similar
Subpart H—Acceptance Activities	Clause 7. Product Realization, Clause 8. Measurement, Analysis, and Improvement	Requirements substantively similar
Subpart I—Nonconforming Product	Clause 8. Measurement, Analysis, and Improvement	Requirements substantively similar
Subpart J—Corrective and Preventive Action	Clause 8. Measurement, Analysis, and Improvement	Requirements substantively similar
Subpart K—Labeling and Packaging Control	Clause 7. Product Realization	Differences addressed in 820.45
Subpart L—Handling, Storage, Distribution, and Installation	Clause 7. Product Realization	Requirements substantively similar
Subpart M—Records	Clause 4. Quality Management System	Differences addressed in 820.35
Subpart N—Servicing	Clause 7. Product Realization	Differences addressed in 820.35
Subpart O—Statistical Techniques	Clause 7. Product Realization, Clause 8. Measurement, Analysis, and Improvement	Requirements substantively similar

[1] This table is not intended to be a requirement-by-requirement analysis, but a higher-level mapping of the totality of the subparts and clauses of the standard and the QS regulation for reference purposes only.

[2] It's important to note that while there are differences specifically identified in subpart D, document requirements exist in most subparts and clauses of the standard and the QS Regulation.

Biography

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Janet Book is a Principal Consultant for NSF, one of the world's leading consulting and service companies in medical technology. She has more than 35 years' experience in quality management systems, auditing and training for medical devices.

Prior to joining NSF, Janet has worked in a wide variety of industries, including blood banking, food processing, quality consulting, chemicals, pharmaceuticals and medical devices.

Janet has broad expertise in U.S., EU and other global regulations, as well as extensive training expertise in the fields of auditing, CAPA and root cause analysis.

She conducts audits, due diligence evaluations as well as capability assessments. Additionally, she has experience establishing audit programs, developing quality management systems, and developing and presenting quality-related training and seminars.

Janet holds a Master of Business Administration from Phoenix University, a Bachelor of Arts in Biology from Wittenberg University and a Certificate in Privacy Law and Cybersecurity from Seton Hall University.

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