THE REGULATORY PROCESS

A MANUFACTURER’S PERSPECTIVE

Medical Devices
Catheters, monitors, heart valves, etc
Cotton Swabs
Incontinence pads
Tongue depressors
Medical lasers
In-Vitro Diagnostics

- Atomic Absorption Spec
- Automated Urinalysis System
- Colony Counters
- Hematocrite Measuring Systems
- Home Pregnancy Test
- HPLC

Registration and Listing
21 CFR, 807

- Manufacturers must register each facility and update annually – now you have to pay
- List all devices
  - updated twice annually
- Notify before marketing
- Changes require 30 notice
  - Ownership
  - Establishment name
  - Official correspondent
  - Address

Registration (cont)

- Initiates or develops specifications
- Manufactures for commercial distribution a device
  Repackages or relabels a device
- Manufactures components or 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
New Process

- FURLS (electronic ER and DL)
- Difficult for foreign manufacturers
- Difficult for consultants
- Issues with certain browsers

Classification of Devices
21 CFR, 860

- Class I – Minimal potential for harm
  - Control by GMP (Bandages, stethoscope, toothbrush)
- Class II – Higher potential for harm
  - Control by performance standards (Ultrasound imaging, catheters)
- Class III – Life sustaining
  - Proof of safety and effectiveness (Heart valves, pacemakers)
- Request for classification - 513(g)
- Radiation and Laser Products
Panels
- Anesthesiology
- Cardiovascular
- Dental
- ENT
- GU
- General Hospital
- OB/GYN
- General and Plastic
- Neurology
- Ophthalmic
- Orthopedic
- Radiology
- Physical Medicine
- Pathology
- Hematology
- Clinical Toxicology
- Immunology
- Microbiology
- Clinical Chemistry

Approvals to Market
- Class I Exempt
- Premarket Notification (510K)
- Pre Market Approval
- Product Development Protocol
- Custom Device
- DeNovo

510(K)
- New Device
  - Substantial Equivalence to a predicate
- Change in intended use
- Changes and Modifications for existing device
  - submission required when change could affect safety or effectiveness (guidance available)
- 90 Day review time
Expedited Review

- Breakthrough technology
- No approved alternative therapy exists
- Significant advantages over existing technology
- Availability in the best interest of patients

510(K) Submission Elements

Traditional

- Name and address of applicant
- Facility registration number
- Classification of Device
- Description of subject device
- Intended use of subject device
- Description of predicate device
- Comparison of subject to predicate (intended use, materials, principle of operation, routes of admin, etc.)
- Results and conclusions of testing
- Label and directions for subject device
- Label and directions of predicate device
- Summary of safety and effectiveness

Required Elements

- Performance Data
- Biocompatibility – ISO 10993/G95-1
- Sterilization and Packaging
- Software
- Standards Forms
Labeling

21 CFR, 801

- Product Package
- Product Insert
- Instructions for Use
- Advertising- Brochures and Flyers
- Direct Mail Pieces
- Websites
- Dear Dr. Letters
- Verbal Representations

Labeling

- General content
  - Name and place of business
  - Role of the labeler
- Intended Use
  - Objective intent - label claims, advertising, oral statements
- Adequate Directions for Use
  - Describes how to safely obtain intended use
  - Device preparation, route of administration
  - Special conditions

Labeling

- Misleading Statements
- Prescription Devices
  - Caution statement
  - Indications, routes of admin, hazards, warnings and precautions
  - Date of latest revision
- Exemptions
  - Shipment of nonsterile product labeled sterile
  - Elements of written agreement
Unique identifier program

- Medical device identification
- Develop a system to identify medical devices
- Unique at all levels of packaging

Three parts to program

- Direct part marking with UDI
- Package labeling with UDI
- Data entry of UDI and attributes into UDI Database

Data Requirements

- Lab testing
- Animal testing
- Cadaver testing
- Human testing
DATA

- Device specific guidance's
- FDA Recognized Consensus Standards
- Also – European harmonized standards
- Other – ISO, ASTM, AAMI, etc

DATA – IMPORTANT

- Biocompatibility – on sterile finished device – through all its normal processes
- Shelf life/stability – on sterile finished device – accelerated aging and REAL TIME aging
- Packaging – sterile and aged also. Compare pre and post sterile data to set up process controls

Biocompatibility

- Strict adherence
- Not accepting literature reviews
- Testing done before 510(k) submitted
- Not accepting promissory notes
- Not accepting widely used materials without testing
Verification and Validation
Testing

Test Methods/Protocols/Acceptance Criteria
Test Reports
Shelf Life/Stability
Safety and Compatibility Testing Requirements
for Electrical Equipment

Software

- Level of Concern
- Software Description
  - Features controlled
  - Operational environment
- Device Hazard Analysis
- SRS
  - Hardware requirements
  - Programming language
  - Interface requirements
  - Software performance and functional requirements
- Architecture Design Chart

More Software

- Design Specification
- Traceability Analysis
  - Matrix which links requirements, design specification, hazards, and validation
- Development life cycle
- Validation, Verification and testing
  - Description of the verification activities at the unit, integration and system level
- Revision Level History
- Unresolved Anomalies (Bugs)
- Release Version Number
510(k)
Paradigm - Alternate approaches

- Traditional
- Abbreviated
- Special
- DeNovo

510(k)
Paradigm - Alternate approaches

Abbreviated - data to be completed
- mfg intends to market new class II device
- device subject to special controls, guidance, standards
- declaration of conformity to standards or summary/exception to special controls

Special - data to be completed
- modification of own device (does not affect intended use or scientific technology),
- declare conformity w/ design controls and summary of design control activities

DENOVO

- Alternative to PMA for lower risk devices
- Appropriateness is determined on a case by case basis and is always risk based
- Submit a 510(k) for a new device that would otherwise require a PMA application
- MAY enable the manufacturer to get to market sooner
**DENOVO**

- Discuss with FDA possibility of de novo application
- Submitted to the FDA as 510(k) application
- FDA reviews the 510(k) application
- 510(k) will result in an NSE (not substantially equivalent) letter (because of lack of predicate device).
- Within 30 days of receipt of the NSE letter, the sponsor sends a petition requesting classification of the new device.

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**DENOVO**

- New product code identified
- Final labeling reviewed
- Special Controls Guidance Document (SCGD) prepared with input from sponsor.

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**Denovo Application**

- Cover sheet identifying the submission as "Request for Evaluation of Automatic Class III Designation"
- 510(k) number on the NSE letter
- Statement of cross reference to the information in the 510(k)
Denovo Application
Classification request should include (cont.):
– Risk/benefit analysis
– Classification (mfg recommendation based on risk analysis)
– Discussion of proposed controls that would be needed to assure the safety and effectiveness of the device

Denovo – Special Controls
● Guidance Document
● Performance standards
● Device labeling
● Postmarket surveillance/data

DeNovo – Time Limits
● FDA has 60 days to:
  – Review the request,  
  – Evaluate the risk  
  – Identify applicable controls  
  – Write SCGD  
  – Classify the device  
  – Write the Approval Order,  
  – Write FR notice of availability of draft SCGD
DeNovo Final Action

- Signed Approval Order classifying the device (Class I, II, or III)
- New device can be marketed
- 30 days after final, Approval Order published in FR

510(k)

- Submit to FDA
- Submit for Third party review
- Responses
  - More data needed
  - SE
  - NSE - Need PMA or Reclassification (DeNovo route)
  - Exempt

Significant Changes

- Intended Use
- Design- control mechanism, operating principal, environmental specification, performance specification
- Materials
- Energy Source
- Manufacturing Process
Recent Roadblocks

- Use of old guidance documents
- Identical to predicate
- Intended use can only be exactly as stated in the regulation policy change
- Requiring sterilization validation protocols

More Roadblocks

- Re-usable devices cleaning protocols rather than citing standards
- Re-usable devices new organisms
- Topical ointments review of components as drugs

And More

- Requirements for new types of testing
  - New "thinking" at FDA resulting in new / more (nonpublished) requirements
  - Clinical data requirements – more and more for certain intended uses
PMA
21 CFR, 814

- Content and arrangement
  - Name and address of applicant
  - Table of contents
  - Summary section
    - Indications
    - Device description
    - Alternative clinical practices
    - Marketing history
    - Summary of studies
    - Conclusions from studies

PMA
(Content and arrangement cont)

- Complete device description
  - Functional components
  - Principles of operation
  - Device master record
- Technical Section
  - Nonclinical lab studies
  - Clinical studies
- Manufacturing section
- Bibliography
- Labeling
- Environmental assessment

PMA
(cont)

- Proof of safety and effectiveness - Clinical data
- Pre-approval GMP inspection
- PMA supplements
**PMA (cont)**

- Risk Based Classification
  - Escape automatic Class III - DeNovo
  - NSE --- Class I or II
- Classification Panels - Defined role
- Collaborative Review Process - 100 day meeting
- Use of Data by FDA - 6 years after PMA

**PDP**

- Plan to develop and test
- Guidance Document Available
- Not typically used

**IDE Regulation Significant Risk**

- (1) intended as implant and presents a potential for serious risk to the health, safety, or welfare;
- (2) use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare;
- (3) for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- (4) otherwise presents a potential for serious risk to a subject.
IDE Regulation
Non - significant risk

- Approval from IRB, Comply with portion of IDE regulation
- Label the product as investigational
- Obtain IRB approval, informed consent
- Monitor the study
- Maintain records
- Maintain reports

IDE Regulation

- Exemption from various regulations
- Overall intent - protection of patient rights - benefits outweigh risks

IDE Elements

- Description
- Prior studies
  - bench tests
  - biocompatibility tests
  - animal data
  - clinical data
- Manufacturing information
- Labeling
- IRB Certifications
Investigational Plan

- Study objective
- Clinical protocol
- Risk analysis
- Device description
- Monitoring procedures
- Case report forms
- Informed consent
- Investigator agreements

IDE

- Allow Protocol and Device Changes
- Early Collaboration - Binding Protocol
- Scope of Review - Reliance on Post Market Controls
- Humanitarian Use - Approval, Emergency Use
- Expanded Access
  - Emergency Use,
  - Individual or small group,
  - Treatment IDE (wider access - post study)

Custom Devices

21 CFR, 812.3

- Meets all of the following
  - Not generally available
  - Not commercially available in finished form
  - Not generally used by other physicians
  - Not offered through labeling or advertising
  - Intended for use for specific patient
- Physician may order custom devices for his patients on routine basis
- Device can only be provided to one physician only
ISO 14971:2007

- Harmonized in July 2002
- It is a framework for effective management by the manufacturer of the risks associated with the use of medical devices

Continued

- It specifies a procedure by which the manufacturer can identify the hazards associated with medical devices and their accessories, including IVD medical devices, estimate and evaluate the risks, control these risks and monitor the effectiveness of the control
- It applies to all stages of the life cycle
- It does not specify acceptable risk levels
- The method of checking compliance is shown
Implementation

- ISO 14971 is not mandatory although ISO 13485:2003 requires documented requirements for risk management throughout product realization.

Compliance

- Audits - checking a sample of
  - Risk management files
  - Personnel records
  - labels and IFUs
  - Post production feedback data and analysis
General Requirements

- Regulatory requirements
- Process
  - risk analysis
  - risk evaluation
  - risk control
  - post production information
- Usually incorporated into the design process

General Requirements

- Management responsibilities
- Risk management plan
- Risk management file
  - This can reference documents elsewhere in the quality system

Risk Analysis

- Risk analysis procedure
- Intended use/misuse and safety characteristics (see Annex A)
- Identification of hazards (see Annex B, C, D)
- Estimation of risk for each hazard (see Annex E, F)
Management Responsibilities

- Define Policy
- Ensure adequate resources
- Ensure assignment of trained personnel
- Periodically review

Policy

1. Establish set of rules that will be applied when evaluating individual and cumulative risks for all products.
2. Document the specific qualifications (training, education, etc.) of those who will apply the rules.
3. Confirm that personnel assigned to apply the rules are not directly involved in the design or development of the product being evaluated

Cumulative Risk

- Limit on the number of risks falling in the broadly acceptable and ALARP regions of the graphical analysis
- Broadly acceptable risks - argument can be made that such risks should not be considered in establishing the acceptability of cumulative risks.
Acceptable number of ALARP??

- Group of experts
  - backgrounds in device regulation, liability, engineering, medical practice, and other areas.
- Reviews the risk assessments, makes an acceptability determination, reach consensus on the acceptability of the overall residual risk.
- Although subjective - ensures appropriate evaluation performed using predetermined limits for overall risk, and that various perspectives are considered.

Adequate Resources

- Team approach
- Impartial Leader
- QA/RA/R&D/Operations/…

Trained Personnel

- Risk management
- Technical
- Clinical (use environment)
- Reliability
- Ethics
- Product History
Management Review

- Complaints
- Comparative rates of occurrence
- Effectiveness of control measures
- Application tools

Plan

- Scope:
- Allocation of Responsibilities
- Requirements for Review
- Criteria for acceptability

Risk Management - Steps

Step 1 - Risk Analysis
- Intended use
- Identification of Known hazards
- Estimation of Risk

Step 2 - Risk Evaluation
- The severity of the risk
- Technology – Benefit –
Risk Management - Steps

Step 3 - Risk Control

Option Analysis
- Inherent safety by design
- Protective measures in the device or manufacturing process
  Information for safety

- Implementation
- Residual Risk evaluation
- Risk / benefit analysis
- Completeness of risk evaluation
- Overall residual risk evaluation

Step 4 - Risk Management Report

Risk Analysis

- Early preliminary hazard analysis to establish the baseline hazards associated with a device
- List major components and operating requirements of the device and evaluating their potential hazards.
  - Components - raw materials and wastes, hardware, monitoring and control systems, human-device interfaces, services, and the operating environment.
  - Potential hazards - toxicity, flammability, and reactivity of raw materials and wastes; sensitivity to environmental factors such as temperature and humidity; mechanical or electronic hazards; and human factors associated with the operator-device interface, patient-device interface

Risk Evaluation

- Risk acceptability decisions
  - Early on - insufficient detail to evaluate hazard likelihood accurately
    - Comparisons with similar devices.
    - Goal - eliminate all high-severity hazards and reduce as many medium- and low-severity hazards as possible
  - Later - more detailed -
    - process and mechanical drawings available
    - basic process operations have been defined
    - The device and its operation can be reviewed by a number of analysis techniques
Estimations

- **Likelihood**
  - Similarity to other products
  - Prior experience
  - Reliability studies
  - Probability calculations

- **Severity**
  - Prior experience
  - Published literature

Index

- **Likelihood**
  - a numeric probability
  - or as remote, possible, likely, certain, etc.

- **Severity**
  - ranges from minor injury through severe injury to permanent injury or death

- **Likelihood and Severity combined to establish risk index**
  - Risk Index = Severity Index + Likelihood Index

Levels

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<th>Hazard-Severity</th>
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<td>Level</td>
<td>Definition</td>
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<tr>
<td>4</td>
<td>Death to the patient or operator</td>
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<tr>
<td>3</td>
<td>Serious injury or occupational illness (requiring medical intervention) to the patient or operator</td>
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<tr>
<td>2</td>
<td>Minor injury or occupational illness (not requiring medical intervention) to the patient or operator</td>
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<td>Negligible injury, occupational illness, or product damage/malfunction</td>
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<tr>
<td>Level</td>
<td>Description</td>
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<tr>
<td>4</td>
<td>Frequent - Likely to occur frequently</td>
</tr>
<tr>
<td>3</td>
<td>Probable – Expected to occur frequently</td>
</tr>
<tr>
<td>2</td>
<td>Occasional – Expected to occur several times</td>
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<tr>
<td>1</td>
<td>Remote - Unlikely but may occur in isolated cases, ie cannot be totally ruled out</td>
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Risk Acceptability

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<th>Probability</th>
<th>Negligible - 1</th>
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<td>Frequent - 3</td>
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Categories

- Unacceptable - unacceptable under any terms
- As low as reasonably practicable (ALARP) - may be acceptable if an evaluation shows that the resulting residual risk is justified because there are product benefits that offset it
- Broadly acceptable - low enough in severity, likelihood, or both to be roughly equivalent to the day-to-day risks encountered in ordinary life.
- Implicit - “zero risk” does not exist.
Based On
- Current technology
- Use of controls
- Ability to detect

Risk Control
- Risk reduction
- Option analysis
- Implementation of risk control measures
- Residual risk evaluation
- Risk/benefit analysis
- Other generated hazards
- Completeness of risk evaluation
- Overall residual risk evaluation
- Risk management report

Residual Risk
- Determine if acceptable using the criteria defined in the risk management plan.
- If unacceptable, gather and review data and literature on the medical benefits of the intended use/intended purpose to determine if they outweigh the overall residual risk.
- If evidence does not support the conclusion that the medical benefits outweigh the overall residual risk, then the risk remains unacceptable.
Control

- Eliminate problem by design
- Protection should it occur
- User information and training
- Evaluate change – new hazards?
- Risk - benefit

Risk Benefit Balance

- Intended Use
- Performance
- Risk associated with use
- Risk and benefit of clinical procedure
- Generally accepted state of the art

State of the Art

- Maude
- Product literature
- Complaints
- Reliability Studies
- Clinical studies
- Comparison studies
Report

- Device Overview
- Identification of Device Characteristics
- Hazards Analysis Record and tools
- Risk Evaluation
- Risk Control Measures
- Overall Residual Risk Evaluation
- Post-production Information
- Risk Management Report
- Trace matrix

Post Production Information

- Information shall be evaluated for
  - previously unrecognized hazards
  - risks not now acceptable
  - invalidation of original assessment
- Review of previous steps if required
- Design acceptable to user
- Change Controls – re-review impacts

Update Risk Analysis - When

- A change in a device’s design or intended use
- A change in the design
- Testing that uncovers an unanticipated product nonconformance to specifications
- Safety-related complaints or returned products
- Recalls
Post Market Requirements

- QSR Compliance
- ISO Compliance
- MDR
- Recall
- Post Market Surveillance
- Device Tracking

QSR QSIT Areas

- Breaks the Quality System Regulation into Subsystems
- Represents a top down review of a firm’s quality system
- QSIT Inspections are Quality System Focused

QSR QSIT Areas

- Management Responsibility
- Process Controls
- Design Controls
- Corrective Action
ISO 13485:2003

1. Scope
2. Normative references
3. Terms and definitions
4. Quality management system
5. Management responsibility
6. Resource management
7. Product (and/or service) realization
8. Measurement, analysis & improvement

FOCUS

- Focus on Regulatory – All relevant markets
- Focus on Process
- Focus on Customer
- Focus on QMS effectiveness

How to blend the requirements
ISO 13485:2003 & QSR & CMDR
Standard Operating Procedures Matrix
Clause 4 - Quality management system QSR Subpart A, B, D, M

4.1 General requirements
- establish document and maintain a QMS
- define and manage processes
- define the interaction of these processes
- maintain effectiveness of QMS
- control outsourced activities

4.2 General documentation requirements
- Documented policy, objective
- Device Files
- 4.2.3 Control of Documents –
  - Maintain Procedures
  - Review and approve
  - Available at point of use
  - Identify, review and approve changes
  - Master List
  - External Standards

4.2.4 Control of Records –
- Storage to prevent loss or damage
- Retention times established
- DMR
- DHR
Document Control System

- Justification - support with data
- Substantiation - rationale
- Regulatory Review - rationale

Change Control

- Review for affect on design controls (FDA QSR 820.30/ISO 4.4)
  - Validation - confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled
  - Verification - confirmation by examination and provision of objective evidence that specified requirements have been fulfilled
- Label review – labels, literature, advertising, web sites, videos, journal articles
  - Review claims, intended use, indications and contraindications

Device Changes

- Implementing and recording changes in methods or procedures
  - Change Control
  - Design Control
- Ensure that the information is disseminated to those responsible
  - Internal
  - External parties (i.e., OEM)
Change Control

- Device changes (FDA QSR 820.40/ISO 4.5)
  - Must be reviewed to determine the need for a new submission or notification to FDA, notified body, or other regulatory agency (UL, CSA)
  - Assessment checklist
  - FDA Guidance document

Clause 4 - Quality management system  QSR Subpart A, B, D, M

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Clause 5 - Management responsibility - QSR Part A, B, M

- **5.1 Management commitment** -
- Emphasis on Top management
  - must demonstrate commitment to development/improvement of the quality system
  - Communicate regulatory requirements
  - Quality Policy and Objectives Established and Communicated
  - Define Responsibilities and authority
  - Management review - documented
Clause 5 - Management responsibility - QSR Part A, B, M

5.2 Customer focus - Customer needs and expectations must be converted into requirements

5.3 Quality policy - Quality policy must include commitment to meeting requirements and maintain effectiveness of QMS, provide a framework for establishing/reviewing quality objectives; must be periodically reviewed for continuing suitability

5.4 Planning -

5.4.1 Objectives: establish measurable quality objectives at relevant functions and levels in the organization; and, identify and plan processes and resources required for the quality system and for achieving quality objectives

5.4.2 QMS Planning – Inputs – objectives, requirements and standards – Outputs – QM, gap analysis, action plans

5.5 Responsibility and Authority - management representative must promote awareness of customer and regulatory requirements throughout the organization;
- Defined, documented, communicated
- Establish inter-relationship of personnel
- Responsibility of PMS and vigilance
Clause 5 - Management responsibility

5.5 Internal Communications
- Internal communications regarding the system must be established
- Communicate effectiveness, process, improvements
- Variety of means (intranet, poster board, email)

5.6 Management review
- Input - changes and recommendations for improvement, process performance, regulatory requirements
- Outputs - improvements and resources
  - evaluate the need for changes to the quality system (including policy and objectives) by reviewing specified inputs (improvement opportunities) and reporting specified outputs (related management actions)

Clause 5 - Management responsibility - QSR Part A, B, M

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Clause 6 - Resource management QSR Part B, G, M

- **6.1 Provision of resources** - Provide adequate resources (human, equipment, facilities, etc)
- **6.2 Human resources** - Competence and evaluate effectiveness of training at defined intervals and ensure employees are aware of the importance of their activities and how they contribute to achieving quality objectives
  - Procedures to identify training needs
  - Provide appropriate training
  - Defect awareness
  - Records
- **6.3 Facilities/Infrastructure** - To achieve conformity to requirements
  - Documented procedure for maintenance

- **6.4 Work environment** - Manage environment to achieve product conformance
  - Contamination control
  - Environmental controls

Clause 6 - Resource management QSR Part B, G, M

- **6.1 Provision of Resources**
  - Training
  - Records supporting training in CMDR
  - QSR 201.20

- **6.3 Infrastructure**
  - System back up
  - Equipment Release
  - Preventive Maintenance

- **6.4 Work Environment**
  - Environmental controls
  - ESD Controls
Clause 7 - Product realization
QSR Part B, C

7.1 Planning of realization processes - Documented risk management - THROUGHOUT Product Realization. Take into account all clauses in section 7.

7.2 Customer-related processes

7.2.1 Determination of Requirements Related to Product
- Document customer expectations and define the processes for communicating with the customer
- Determine requirements not stated but necessary for specified/intended use
- All statutory and regulatory requirements

7.2.2 Review of requirements related to the product
- Requirements adequately defined
- Capability to perform the job
- Resolve differences
- Amendments
- Records

7.2.3 Customer Communication - proactive – open channels of communication – advisory notices
Clause 7.2 – Customer Process
QSR Part B, C

<table>
<thead>
<tr>
<th>Customer Related Processes</th>
<th>Risk Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determination of Requirements to the product</td>
<td>CMDR 28-43</td>
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<tr>
<td>Review of Requirements related to the product</td>
<td>32(4)(d)</td>
</tr>
<tr>
<td>Customer Communication</td>
<td>Class IV Licensing</td>
</tr>
</tbody>
</table>

Records to ensure only products supported by active Licenses are sold in Canada

Clause 7 - Product realization
QSR Part C

7.3 Design and/or development
- Outsourced processes, clinical evaluation, change process include an evaluation of the effects of changes on constituent parts
- Design and Development Planning
- Organization and Technical Interfaces
- Design Input
- Design Output
- Design Review

Design Controls
- Design and Development Planning
  - describe and define development activities and responsibilities, describe interfaces, reviewed and app.
- Design Input
  - performance, functional, descriptive, environmental, safety, QA, RA requirements defined, reviewed and recorded. Quantify where practicable.
- Design Output
  - Final technical documents
- Design Review
  - Formal documented reviews at various stages
Clause 7 - Product realization
QSR Part C

7.3 Design and/or development

- Verification
- Validation - CLINICAL EVALUATION
- Transfer
- Changes
- DHF

Design Controls (cont)

- Verification – confirmation that specified requirements have been fulfilled (does it meet its specs, output meets the input requirements). Results documented.
- Validation – establishing by objective evidence that device specs conform to user needs and intended use. (Does it do what the user wants). Results documented.
- Transfer – review and approval of specs and procedures, proving adequacy of spec and procedures. Pilot runs qualified through simulated use testing. Extent governed by risk of device.
- Changes – documentation of design changes before their implementation
- DHF – Records needed to demonstrate the design was developed in accordance with the QSR requirements.

Clause 7.3 – Design
QSR Part C

<table>
<thead>
<tr>
<th>7.3 Design &amp; Development</th>
<th>Design Controls</th>
<th>FMEA</th>
<th>Validations</th>
<th>Risk Management</th>
<th>Software controls</th>
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<td>Planning</td>
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<td>Outputs</td>
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<td>Controls</td>
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<td>Validation</td>
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<td>D&amp;D changes</td>
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</table>

CMDR 10-20 Safety and Effectiveness
12 Clinical Evaluations
21 Software Validation
21(6)(f), 21(4)(i) Class III and IV Device Safety
510(k) Clinical Evaluations
CMDR 27-23
CMDR 28-34
34(a) License Amendments
Clause 7 - Product realization  
QSR Part E

7.4 Purchasing
- Ensure product conforms to specified requirements
- Evaluation of Suppliers and subcontractors – selected on basis of ability
- Records of acceptable suppliers
- Establish criteria for re-evaluation of suppliers. Not just monitoring

7.4 Purchasing
- Purchasing Data
  - Data and requirements defined and approved. Where possible an agreement to notify the manufacturer of changes in the product or service
- Verification
  - Incoming inspection

Supplier Controls
- Materials
  - Raw Materials
  - Subassemblies
  - OEM
- Services
  - Repair
  - Calibration
  - Sterilization
  - Testing
- Consultants
Assessments

- On site Audit
- Self Assessment
- Past History
- Published Literature
- First article
- Product Qualification

Clause 7.4 - Purchasing
QSR Part E

<table>
<thead>
<tr>
<th>7.4 Purchasing</th>
<th>Supplier Qualification</th>
<th>9(1) and 9(2) Manufacturers Obligations</th>
<th>820.50</th>
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<td>- Purchasing Information</td>
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<td>- Verification of Purchased</td>
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<td>Product</td>
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</tbody>
</table>

Clause 7 - Product realization
QSR Part G, K, L, M, N

- 7.5 Production and service operations –
  - Identify and plan the processing steps
  - Instructions and Procedures
  - Monitoring of Processes
  - Compliance with Standards
  - Approval of process and equipment
  - Criteria for workmanship
  - Production and process changes
  - Environmental control
Clause 7 - Product realization  
QSR Part G, K, L, M, N

### 7.5 Service
- Analyze reports
- Documentation to include
  - name of device
  - control number
  - date of service
  - individual performing
  - service performed
  - test and inspection data

Service Reports (FDA QSR 820.200/ISO 4.19)
- Routine versus Non Routine
- Warranty versus non warranty
- Reprocessing or refurbishments
- To be reviewed for complaint reportability
- Use of trend analysis (or other statistical methodology) (FDA QSR 820.250/ISO 4.20)

### 7.5.2 Production and service operations – Validations
- Process validation
- Software validation
- Particular requirements for sterile products - Sterilization records and sterilization validation procedures
Clause 7 - Product realization
QSR Part F, H

7.5.3 Identification and traceability
- Identification – procedures where appropriate
- Traceability – unique identification if applicable
- Returned products distinguished
- Status Identification

---

Clause 7 - Product realization
QSR Part NA

7.5.4 Customer Property –
- Customer property includes intellectual property
  - Protect from damage
  - Maintain procedures for verification, storage and maintenance
  - Products unsuitable must be recorded and reported

---

Clause 7 - Product realization
QSR Part L

7.5.5 Preservation
- Procedures for preserving conformity of product during internal processing and delivery to intended destination
  - Establish, document and maintain procedures
  - Method to prevent damage or deterioration
  - Secure storage
  - Receipt and dispatch methods
  - Protect after final inspection
  - Packaging and labeling
### Clause 7 - Production
QSR Part F, G, H, K, L, M, N

<table>
<thead>
<tr>
<th>Control of Production</th>
<th>Calibration</th>
<th>ISO 7455</th>
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<tbody>
<tr>
<td>Control of Production</td>
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<tr>
<td>Installation &amp; Servicing</td>
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<td>Production &amp; Process Control</td>
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<td>Inventory controls</td>
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<td>Sterilization Processing</td>
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<td>Device History Record</td>
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<td>Label Controls</td>
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<td>Service Installation</td>
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<td>Validation of Processes for Production &amp; Service</td>
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<td>Validations SW Validation</td>
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<td>Identification &amp; Traceability ID &amp; Traceability Inspection/Test Status</td>
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<td>CMDR 21-23 Labeling requirements CMDR 52-56 Distribution Records CMDR 66-88 Implant registration 820.60, .65, .120 820.80, .184 820.86</td>
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<td>Customer Property NA</td>
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<td>Preservation of Product</td>
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<td>Handling, Storage, Packaging, Preservation &amp; Delivery Shipping Receiving</td>
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<tr>
<td>14 Characteristics and Performance not affected by storage or transport 820.72</td>
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</tr>
</tbody>
</table>

---

### Clause 7 - Product realization
QSR Part G

- **7.6 Control of measuring and monitoring devices**
  - Control calibrate and maintain
  - Identify accuracy and measurement
  - Procedures
  - Identify status
  - Standards traceable
  - Suitable environment
  - Records
  - Includes software

---

### Clause 7.6 - Calibration
QSR Part G

<table>
<thead>
<tr>
<th>Control of Monitoring &amp; Measuring Devices</th>
<th>Calibration</th>
<th>ISO 7455</th>
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</tbody>
</table>
Clause 8 - Measurement, analysis and improvement
QSR Part B, H, I, J, M, O

8.1 General

8.2 Measurement and monitoring

- 8.2.1 Feedback - measure and monitor if met customer requirements. Post market surveillance - early warning

- 8.2.2 Internal audits - process
  - Criteria, scope, frequency, and methods defined
  - Independent
  - Responsibilities for planning, conducting, reporting
  - Consider prior results
  - Schedule according to importance
  - Document results and communicate
  - Reviewed by management - timely corrective action

- 8.2.3 Monitoring and Measurement of Process - performance of processes used to manage the quality system
Clause 8.2 – Monitoring and Measurement
QSR Part B, H, I, J, M, O

8.2.4 Monitoring and Measurement of Product
- No release of product until planned arrangements are completed
- Verify according to quality plan
- Define criteria for acceptance - acceptance or rejection documented
- Perform in process and final inspections
- Records
Clause 8.3 – Non Conforming Materials
QSR Part H, I

8.3 Control of Non-Conforming Product
Non-Conforming Materials
Rework
820.90

Clause 8 - Measurement, analysis and improvement
QSR Part O

8.4 Analysis of data – Analyze data to determine quality system effectiveness and to provide information on customer feedback, process/product performance, and supplier performance – not just management review – How often, what data

Analysis and Trending

● Statistical techniques or other trend analysis (FDA QSR 820.250/ISO 4.20)
  – Excel
  – Access
  – SPC OR Control Charting
  – Statgraphics
  – Other statistical data base
● Management Review (FDA QSR 820.20/ISO 4.1)
What Data

- Customer Feedback - Complaints, Service reports, Shipping errors
- Conformity to product requirements such as non conformances, service levels and recalls
- Characteristics and trends of processes and products including opportunities for preventive action – first pass yield, Incoming, inprocess and final inspection results
- Supplier quality - MRB activity by supplier, Supplier CAPAs, Open MRB

Clause 8.4 – Analysis of Data
QSR Part O

Clause 8 - Measurement, analysis and improvement
QSR Part J

8.5 Improvement –
- Maintain continued suitability and effectiveness of the QMS
- Procedures for Recalls and advisory notices
- Procedures for complaints – include communications with outside organizations
- Procedures for adverse event reporting
Clause 8 - Measurement, analysis and improvement

8.5.2 Corrective Action

- Analyze and Investigate
- Identify preventions
- Verify and validating
- Implementing changes
- Disseminating information
- Management review

8.5.2 Preventive Action

- Identify problems before they occur
- Trend data
- Risk management provides input
- PMS may provide input

Clause 8.5 – Improvement
QSR Part J

<table>
<thead>
<tr>
<th>Action</th>
<th>GMP 215.55</th>
<th>GMP 215.65</th>
<th>CMDR 57-65</th>
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<td>57(a)</td>
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<td>57(a)</td>
</tr>
<tr>
<td>Customer Adverse Events</td>
<td>57(b)</td>
<td>57(b)</td>
<td>57(a)</td>
</tr>
<tr>
<td>Mandatory Problem Reporting</td>
<td>57(b)</td>
<td>57(b)</td>
<td>57(a)</td>
</tr>
</tbody>
</table>

Corrective Action

- Corrective & Preventive Action

Preventive Action

- Corrective & Preventive Action
Complaints

- Record
- Investigate
- Document
- Follow up
- Corrective Action

Complaint Handling

- Quality System Regulation Elements
  - Quality Records
  - Corrective and Preventative Action
  - Management Review
  - Servicing
  - Statistical Techniques
  - Design and Document Control (if device or system changes are made)

Sources

- Customers by letter, credit memo, returned goods form, or phone;
- Manufacturer's representative, or other employees;
- MedWatch voluntary reporting program;
- Service or repair request;
- Journal articles;
- FDA;
- Attorney;
- Health care professionals
Required Elements

- Document, review, evaluate, and file all complaints;
- Formally designate a unit or individual to perform these activities;
- Determine if an investigation is necessary;
- Record the reason (and individual) if no investigation is made;
- Assign responsibility for deciding when not to investigate; and,
- Determine if the complaint requires an MDR or vigilance report.

Steps

- Document
- Acknowledge - if desired
- Investigate - OBTAIN SAMPLES
- Corrective Action
- Reply - if desired
- Closure
- Trending

Complaint Form

- Customer Information
- Product Information
- Event Information - Was device in use
- MDR Information
- Investigation
- Corrective/Preventative Action
- Closure, Disposition and Review
Watch Outs

- Multiple complaints on a single report form
- Investigation and analysis that leads to information that now falls into MDR
- Wording
- Root cause and corrective action – findings that FDA frequently look for and are missing in investigations
- Response to customer – if any – may need to do this in some cases, esp if user error is the cause. May need marketing and/or legal review.
- Timeliness
- Trend analysis – FDA looks for this and action upon – i.e. management review

Other Sources of Complaint Information
- Reply cards and email information – these are sources of complaint information
- Also market intelligence data – sales questionnaires, customer responses, etc.
- Service Reports
- Trade Shows
- Sales Reps

Corrective and Preventative Action
- Analyze
- Investigate
- Identify preventions
- Verify and validating
- Implementing changes
- Disseminating information
- Management review
Corrective and Preventative Action

- Identify action needed to correct and prevent recurrence (FDA QSR 820.100/ISO 4.14)
- Verifying the corrective and preventative measures are effective
  - Corrective – Action taken to eliminate the causes of an existing non-conformity, defect or other undesirable situation in order to prevent recurrence.
  - Preventative – Action taken to eliminate the cause of a potential non-conformity, defect or other undesirable situation in order to prevent reoccurrence.

What Happened
Why did it happen (proximate cause)
Why did that happen (examine processes)
Why did that happen (underlying systems)

Determine Sequence of Events
Define Causal Factors
Analyze Each Causal Factor Root Cause
Analyze each root cause generic cause
Develop and evaluate actions
Report and Implement

4 Phases
- Phase I: Problem Identification
- Phase II: Investigation
- Phase III: Cause Analysis
- Phase IV: Solution Development
  - Communication
  - Management Review
Source of Evaluation

- Actual unit involved
- Another unit from same lot
- DHR Review
- Trends
- CAPAs

Types of Evaluations

- Visual
- Electrical
- Mechanical (dynamic or static)
- Chemical
- Software
- Optical
- Environmental

5 Ps

- **PARTS**  Any failed components
- **POSITION**  Where were things at the time of failure? What are the instrument’s settings? Position of parts?
- **PAPER**  Operating conditions prior to, during, and after the incident (temperatures, pressures, levels, etc.), equipment histories, operating procedures, manufacturing procedures and equipment specifications.
- **PEOPLE**  What did they see, hear, feel or smell prior to, during, and after the incident? Was anything unusual being done around the time of failure?
- **PARADIGMS**  What are the cultural norms of the organization? What do people accept as a way of doing business, such as communication between units or shifts?
Symptom vs Cause

- **Problem symptoms**
  - What people traditionally call problems are frequently only symptoms of problems. For example, the problem of decreased sales is really a symptom of whatever is causing sales to drop, which is the real problem. Defining a problem in terms of its symptoms obscures the real cause and leads to symptomatic solutions that fail to correct the basic condition.

- **Problem causes**
  - Problems are undesired results caused by structural relationships among system components. When these relationships are complex and hidden, traditional problem solving is not effective and another technique is needed. Root cause problem solving consists of discovering and correcting these structural relationships.

Differentiating between problem symptoms and problem causes

1. Identify the undesirable condition that needs to be corrected or the events associated with this condition.
2. Use the “multiple why” process to identify the causes underlying this undesirable condition.
3. Continue this “multiple why” process until a fundamental or root cause is apparent.

Resolutions

- Change in Procedures/Instructions
- Change in Acceptance Activities
- Customer Letters
- Recalls
- Training - formal meetings vs. informal
Consider

- Immediate Action
- Short Term Action
- Long Term Action
- Corrective Action
- Preventive Action

Tools


MDR

21 CFR, 803

- Reports of device related incidents
  - Death
  - Serious injury
  - Malfunction
- Malfunction - if likely to cause or contribute to death or injury if recurred
- Definition of likely shifted-
  - More probable than not
  - Remotely possible
MDR 21 CFR 803

- MDR Reportable Event: an event about which company or its employee has received or become aware of information that reasonably suggests that one of the marketed devices:
  - a. May have caused or contributed to a death or serious injury, or,
  - b. Has malfunctioned and that the device or a similar device would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur.

Definitions

- **Serious Injury** - an injury that is life threatening; or results in permanent impairment of a body function or permanent damage to a body structure; or necessitates medical or surgical intervention by a health care professional to preclude permanent impairment of a body function or permanent damage to a body structure.

- **Malfunction** - An event in which the product fails to meet any of its performance specifications or to otherwise perform as intended.

Malfunctions

- Chance of causing such an event is not remote
- Affects device in a catastrophic manner that may lead to death or injury
- Manufacturer takes or would be required to take action to prevent a health hazard as a result of the malfunction
- Malfunction of the same type has actually caused or contributed to a death or injury
- Causes the device to fail to perform its essential function and compromises the device's effectiveness
- Involves a long-term implant that would prevent the implant from performing its function
- Device is life-supporting or life-sustaining
Investigation of MDR Events

- Investigate whether the device failed to meet its specs
- Whether device was being used for treatment or diagnosis
- Relationship (if any) of the device to the reported event

Records

- Name of device
- Date complaint received
- Device control number or identification
- Name, address and phone number of complainant
- Nature and details of complaint
- Dates and results of investigation
- Any corrective action taken (EN– if none – why not)
- Any reply to complainant

Reporting Timeframes

- 5 days – remedial action
  - prevent an unreasonable risk of substantial harm to the public health
  - where FDA has specified that a 5-day report is needed
- 30 days – death, injury, malfunction
**Forms**

- Mandatory MEDWATCH
  - 30 day report
  - 5 day report
  - supplemental report
- Baseline Reporting
  - GONE

**MDR**

Not Required

- An event is not device related.
- Written justification for this conclusion.
- The device involved in the reportable event was not manufactured or distributed by company.
- Information supporting this finding shall be forwarded to the FDA under an explanatory cover letter so the correct manufacturer may be notified.

**Summary Reporting of MDRs**

- Goal: Reduce “noise” in the MDR system, improve the signal to noise ratio
  - Allow periodic submission of well-known, repetitive reports in line item format
  - Expect 38,000 summary reports in FY ‘99
  - 45 manufacturers participating
  - 52 exemptions
  - New system in place for January 2000
Exemption Requests

- Request for an exemption or variance should include an explanation of the impact of the device problem on the patient and why the requested reporting approval is more appropriate than the standard MDR reporting requirements.

Global Harmonization

- Europe
- Canada
- Japan
- Australia
- Other …

Global Harmonization

- Vigilance Reporting
  - Initial report to competent authorities
  - Final report to competent authorities
Global Harmonization

- Evaluation of the Manufacturers Reporting Guidance
- SG2 "Adverse event reporting guideline for decisions for manufacturers and their representatives"
- Evaluation of the Timeframes Needed by Manufacturers:
- Compilation of Globally recognized "Known and Well-defined" (well-characterized) Adverse Events or Incidents
- Establishment of Criteria for Generation of a Competent Authority (CA) Report (CAR)

Incident

Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.”

serious deterioration

- a) life-threatening illness
- b) permanent impairment of a body function or permanent damage to a body structure
- c) a condition necessitating medical or surgical intervention to prevent a) or b)
- d) indirect harm as a consequence of an incorrect diagnostic or IVD test results
**Timeframes**

- 5 Day – serious public health threat
- 10 days –
- 30 days –
  - Guidance document –
    - lists competent authorities
    - Other international agencies

**Trend Reporting**

- Increase in trend of:
  - already reportable incidents
  - incidents that are usually exempt from reporting
  - events that are usually not reportable

**Remedial Action**

- Recall
- Correction
- Removal
Definitions

- Recall - Removal or correction of a marketed product that FDA considers to be in violation. FDA would consider action.
- Withdrawal - Removal or correction of product which involves a minor violation. FDA would not consider action. (stock rotation, routine equipment adjustment or repair)
- Stock Recovery - Removal or correction of product not yet marketed or otherwise left firms control

Definitions

- Correction - Repair, modification, adjustment, relabeling, destruction or inspection without physical removal to some other location
- Removal - Physical removal of device from point of use for repair, modification, adjustment, inspection, relabeling, destruction
- Routine Servicing - Regularly scheduled maintenance including replacement of parts at the end of life expectancy

Risk to Health

- Reasonable probability that use of or exposure to the product will cause serious adverse health consequences or death
- Use of or exposure to product may cause temporary or medically reversible health consequences or on outcome where the probability of serious adverse health consequence is remote
Reporting

- Within 10 working days if initiated to
  - reduce risk to health or
  - remedy violation of the act caused by the device, unless
    - already submitted under MDR
    - exempt from reporting (market withdrawal, routine service, stock recovery)

Classification

- Class I - Report required
  - strong likelihood of risk to health
- Class II - Report required -
  - may cause temporary or medically reversible adverse health consequence
  - may present risk to health
- Class III - Report not required
  - not likely to cause adverse consequence

Important

- Recall Procedure
- Traceability
- Distribution Records
- Effectiveness checks
- 510 Impact (11/21/95 K95-1)
Reports

- Date
- Company information
- Product information and identification
- Event information
- Marketing status
- Adverse events
- Distribution information

Health Risk Assessment

- Risk Index
  - Likelihood
  - Probability
  - Severity

Likelihood

- Remote 0
- Rare 1
- Occasional 2
- Frequent 3
- Continuously occurring 4
### Probability
- Extremely unlikely: 0
- Unlikely but possible: 1
- Likely: 2
- Very Likely: 3
- Extremely Likely: 4

### Severity
- None (no adverse conseq): 0
- Limited (transient): 1
- Moderate (significant, temporary): 2
- Severe (serious, permanent): 3
- Life Threatening: 4

### Risk Index
- III - 0-3: None/negligible
- II - 4-6: Low
- II - 7-9: Moderate
- I - 10-12: High
Electronic Products

- Any manufactured or assembled product (or component, part, or accessory of such product) which, when in operation,
  - (i) contains or acts as part of an electronic circuit and
  - (ii) emits (or in the absence of effective shielding or other controls would emit) electronic product radiation.

Electronic Product Radiation

1) any ionizing or non-ionizing electromagnetic or particulate radiation, or
2) any sonic, infrasonic, or ultrasonic wave, which is emitted from an electronic product as the result of the operation of an electronic circuit in such product.

Medical Examples

- diagnostic x-ray or ultrasound imaging devices
- microwave or ultrasound diathermy devices
- microwave blood warmers or sterilizers
- laser coagulators
- ultrasound phacoemulsifiers
- x-ray or electron accelerators
- sunlamps
- ultraviolet dental curing devices
Non Medical

- microwave ovens
- televisions receivers and monitors (video displays)
- entertainment lasers
- industrial x-ray systems
- cordless and cellular telephones
- industrial RF sealers of plastics and laminates
- laser CD players

Reports

- Variance or Exemptions
- Accidental Radiation Occurrences
- Product Reports
- Annual Reports
- Notice of Defect or Noncompliance

Exporting 801 and 802

- US exporting requirements
  - Tier 1 and Tier 2 countries (written authorization or CFG)
- Class II and III – tier 1
  - Notification to FDA
  - Conditions
- Class III non tier 1
  - Submission of scientific data
  - Safety assessment by FDA
  - FDA issues a written permit
TIER I COUNTRY

- Australia
- Canada
- Israel
- Japan
- New Zealand
- Switzerland
- South Africa
- European Economic Area (EEA)

European Economic Area

- Austria Luxembourg
- Belgium Netherlands
- Denmark Portugal
- Germany Spain
- Greece Sweden
- Finland United Kingdom
- France Iceland
- Ireland Liechtenstein
- Italy Norway

Exports

- NO FDA authorization required (Conditions)
- Send FDA “simple notification” for 1st shipment.
- Exporter maintains records with foreign governments, copies of labeling and market authorization.
- FDA Certification?
Conditions for Export

- 1) Registration and listing with FDA;
- 2) Substantial compliance with GMP or ISO 9001;
- 3) Not “adulterated” - clean/sterile;
- 4) Not packed or held under unsanitary conditions; and
- 5) Does not contain any poisonous or deleterious substance.
- 6) Meets foreign purchaser’s specs.,
- 7) Not in conflict with importing country’s law,
- 8) Shipping package labeled for export,
- 9) NOT offered for sale in the U.S. (*),
- 10) Not an eminent hazard to health,
- 11) Labeled to meet the Tier 1 country’s specs.

Investigational Devices

- Export to Tier I country/FDA OK not needed,
- Compliance with U.S. investigational device exemption regulations (IDE) not necessary.
- FDA OK is needed for export to NON Tier I countries.

Europe and ROW
Registration and Dossiers
- Classifications
- Quality Systems
- Design Information
- Manufacturing Information
- Process validations
- Clinical data requirements
- Risk analysis
- Standards compliance
Inspections

- FDA Inspections are authorized by section 704(a) of the Food Drug and Cosmetic Act
- Types of Inspections
  - Pre-Approval
  - Routine GMP/Quality System
  - For Cause

Inspection Priorities

- Scheduling inspections considers health-hazard significance
  - Priority A
    - High-risk devices, Class III and Class II
  - Priority B
    - Class II and Class I
  - All others
    - As resources permit

Inspection Policy

- Establish a written policy
- Define roles and responsibilities
- Train personnel
Inspection Responsibilities

- Identify the person who will have principle responsibility for coordinating the inspection
  - communicates with top management
  - defines inspection strategy
  - identify backup person

Inspection Policy

- Document company policy for the following situations
  - photographic or other recording equipment
  - request for samples
  - affidavits
  - FDA communication with line employees

FDA Inspection Policy

- Handling of confidential or proprietary information
  - trade secrets
- Records not shown unless subpoenaed
  - personnel records
  - medical records
  - audit reports
Post-Inspectional Activity

A. Establishment Inspection Report

B. Response to FDA-483

C. Post-Inspectional correspondence

1. Copy of FDA-483 to top management if not available during closeout

2. NAI letter

3. VAI letter (combine with response to FDA-483 response letter)

4. FMD-145 (Copy of EIR if case closed)

Websites

- FDA.GOV
- GHTF.ORG
- Europa.eu.int
- New Approach.org
- Eucomed.be
- MHRA

THANK YOU