Understanding FDA's Quality System Regulation

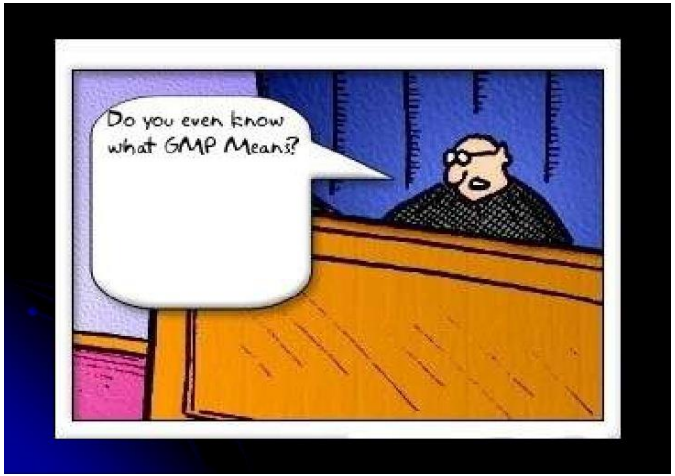
Elaine H. Tseng
King & Spalding
etseng@kslaw.com

FDLI

Agenda

- QSR Fundamentals
  - Background, purpose and scope
- QSR Elements
  - Key components of the QSR
- QSR noncompliance
  - Implications and strategies

QSR Fundamentals



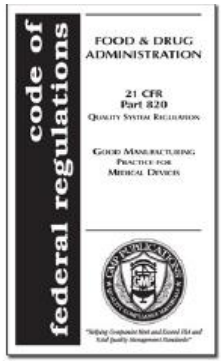
Authority

- "[FDA] may … prescribe regulations requiring that … a device conform[s] to current good manufacturing practice, as prescribed in such regulations, to assure that the device will be safe and effective and otherwise in compliance with this chapter."

21 U.S.C. § 360j(f)(1)(A)

Purpose

- The QSR represents FDA's current good manufacturing practice (cGMP) requirements for medical devices.
    - Addresses device design, manufacture, packaging, labeling, storage, installation, and servicing
    - Ensures devices consistently meet applicable specifications and requirements
    - QSR/cGMP violations may exist even if device specifications are met.



See 21 C.F.R. Part 820.

Purpose (cont'd)

- To achieve the QSR's fundamental purpose:

  "Each manufacturer shall establish and maintain a quality system that is appropriate for the specific medical device(s) designed or manufactured, and that meets the requirements of this part." (21 C.F.R. § 820.5)

- "Establish" means define, document, and implement. (21 C.F.R. § 820.3(k))

- "Quality system" means the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

21 C.F.R. § 820.3(v)

Scope

- QSR applies to "finished devices"
  - Excludes "components" (but compliance "encouraged" [21 C.F.R. § 820.1(a)])
  - Includes 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" [21 C.F.R. § 820.3(l)]

  e.g., blood tubing, diagnostic x-ray components

Scope (cont'd)

- Certain devices are exempt from QSR per classification regulations (see 21 C.F.R. §§ 862-892).
  - Exemption does not extend to QSR requirements for complaint files or records.
- QSR authorizes exemptions or variances to be sought (see 21 C.F.R. § 820.1(e)).

Scope (cont'd)

- QSR applies to "manufacturers"

"*Manufacturer* means any person who designs, manufactures, fabricates, assembles, or processes a finished device. Manufacturer includes but is not limited to those who perform the functions of contract sterilization, installation, relabeling, remanufacturing, repacking, or specification development, and initial distributors of foreign entities performing these functions." (21 C.F.R. 820.3(o)) (emphasis added)

Scope (cont'd)

- QSR is not presently applied to third-party servicers
  - "FDA is not including the terms "servicer" or "refurbisher," as they relate to entities outside the control of the original equipment manufacturer, in this final regulation, even though it believes that persons who perform such functions meet the definition of manufacturer."

QSR Preamble

Approach

- QSR reflects an "umbrella" approach
  - Not detailed/prescriptive for any specific device
  - Sets forth a general framework - manufacturers must "fill in the details that are appropriate to a given device according to the current state-of-the art manufacturing for that specific device." [QSR Preamble]
  - Each quality system is to be commensurate with the risk and complexity of the device and the firm's operations [QSR Preamble]
  - "[T]he regulations … have the virtue of generality and the vice of imprecision." *United States v. Utah Medical Products, Inc.*, 404 F. Supp. 2d 1315, 1323 (D. Utah 2005)

Approach (cont'd)

- QSR reflects general alignment with international requirements, in particular ISO 13485:2016
- FDA has announced intent to "harmonize and modernize" the QSR by "supplant[ing]" certain existing requirements "with the specifications of…ISO 13485:2016"
  - Goal is "to reduce compliance and recordkeeping burdens"
  - Proposed rule anticipated

QSR Elements

Provisions of the QSR

PART 820—QUALITY SYSTEM REGULATION

Subpart A—General Provisions

Sec.
820.1 Scope.
820.3 Definitions.
820.5 Quality system.

Subpart B—Quality System Requirements

820.20 Management responsibility.
820.22 Quality audit.
820.25 Personnel.

Subpart C—Design Controls

820.30 Design controls.

Subpart D—Document Controls

820.40 Document controls.

Subpart E—Purchasing Controls

820.50 Purchasing controls.

Subpart F—Identification and Traceability

820.60 Identification.
820.65 Traceability.

Subpart G—Production and Process Controls

820.70 Production and process controls.
820.72 Inspection, measuring, and test equipment.
820.75 Process validation.

Subpart H—Acceptance Activities

820.80 Receiving, in-process, and finished device acceptance.
820.86 Acceptance status.

Subpart I—Nonconforming Product

820.90 Nonconforming product.

Subpart J—Corrective and Preventive Action

820.100 Corrective and preventive action.

Subpart K—Labeling and Packaging Control

820.120 Device labeling.
820.130 Device packaging.

Subpart L—Handling, Storage, Distribution, and Installation

820.140 Handling.
820.150 Storage.
820.160 Distribution.
820.170 Installation.

Subpart M—Records

820.180 General requirements.
820.181 Device master record.
820.184 Device history record.
820.186 Quality system record.
820.198 Complaint files.

Subpart N—Servicing

820.200 Servicing.

Subpart O—Statistical Techniques

820.250 Statistical techniques.

Quality System Sub-Systems

Management Controls Sub-System

- 21 C.F.R. § 820.20 Management Responsibility
- 21 C.F.R. § 820.22 Quality Audits
- 21 C.F.R. § 820.25 Training

Management Controls Sub-System

- Purpose: ensure an adequate and effective quality system is established (defined, documented, and implemented).
- "Management with executive responsibility" (MWER) must:
  - Establish quality policy
  - Ensure quality planning and quality system procedures
  - Provide adequate organizational structure and resources
  - Monitor and make adjustments to the QS as needed
- Linked to other sub-systems: major nonconformances in other sub-systems may signal inadequacy of management controls.

21 C.F.R. § 820.20

Management Controls – Quality Policy

- MWER must:
  - Establish its policy and objectives for, and commitment to, quality.
  - Ensure that the quality policy is understood, implemented, and maintained at all levels of the organization.

21 C.F.R. § 820.20(a)

Management Controls – Quality Plan

- MWER must ensure establishment of a quality plan defining the quality practices, resources, and activities necessary for the requirements for quality to be met.

21 C.F.R. § 820.20(d)

Management Controls – Adequate Organization

- An adequate organizational structure is one that provides
    - appropriately defined responsibilities, authorities, and interrelation of personnel, and
    - adequate resources

  for the management, performance, and assessment of work affecting quality.

  21 C.F.R. § 820.20(b)(1) and (2)

Management Controls - Personnel

- Ensure sufficient personnel with necessary education, background, training, and experience.
  - Procedures must identify training needs and specify how and when training will be accomplished.
  - Training must include making personnel aware of device defects that may result from improper job performance.

21 C.F.R. § 820.25

Management Controls – Management Representative

- MWER must appoint a management representative who is
  - A member of management
  - Responsible for ensuring effective establishment and maintenance of quality system requirements and reporting on quality system performance to MWER.

21 C.F.R. § 820.20(b)(3)

Management Controls – Management Review

- MWER must review the suitability and effectiveness of the quality system
  - At defined intervals
  - With sufficient frequency
  - According to established procedures
- Dates and results to be documented but not reviewed in FDA inspections

21 C.F.R. §§ 820.20(c), 820.180(c)

Management Controls - Quality Audits

- Periodic internal audits required to “determine the effectiveness of the quality system.”
  - To be conducted by individuals not having direct responsibility for areas audited.
  - Perform corrective action(s).
  - Document audit results for management review. Reports not reviewed during FDA inspections.

21 C.F.R. §§ 820.22, 820.180(c)

Design Controls Sub-System

- 21 C.F.R. § 820.30 Design Controls
- 21 C.F.R. § 820.70(b) Production and Process Changes
- 21 C.F.R. § 820.181 Device Master Record
- 21 C.F.R. § 820.250 Statistical Techniques

Design Controls Sub-System

- Purpose: control design process to ensure devices meet user needs, intended uses, and specified requirements
  - Historically, many recalls linked to design issues
  - Establish design and development plans
    - Include interfaces with different groups that provide input to design and development process

21 C.F.R. § 820.30

Design Controls Sub-System

- Define and document design inputs and outputs
  - Design inputs – physical and performance requirements
  - Design outputs – results of design efforts
- Conduct design reviews
  - At appropriate design stages, evaluate adequacy of design requirements and capability of design to meet requirements

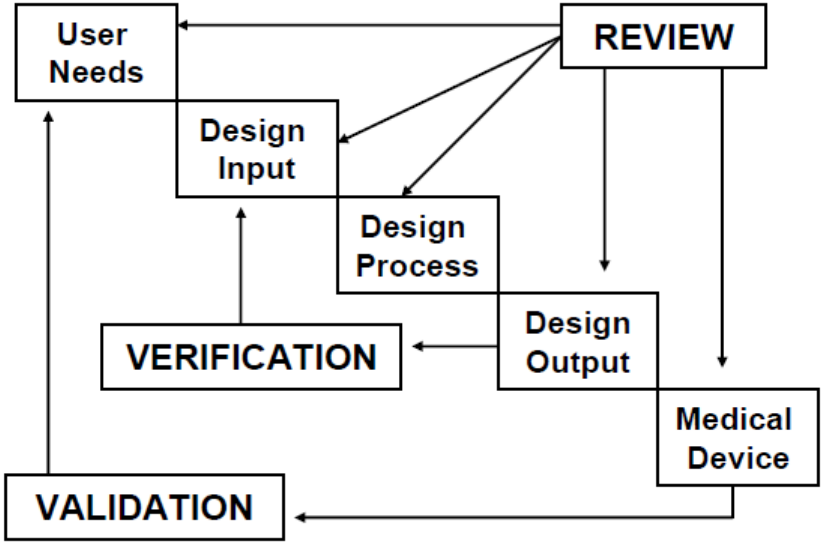
21 C.F.R. § 820.30

Design Controls Sub-System

- Verify design outputs align with design inputs (design verification) *Did I build the device right?*
- Validate approved design meets user needs and intended uses (design validation) *Did I build the right device?*
- Correctly transfer design to production specifications
- Document, validate/verify, review, approve design changes prior to implementation

21 C.F.R. § 820.30

Design Controls Process



Corrective and Preventive Actions (CAPA) Sub-System

- 21 C.F.R. § 820.100 CAPA
- 21 C.F.R. § 820.90 Nonconforming Product
- 21 C.F.R. § 820.198 Complaints
- 21 C.F.R. § 820.200 Servicing
- 21 C.F.R. § 820.250 Statistical Techniques

Corrective and Preventive Actions (CAPA) Sub-System

- Purpose: collect and analyze information to identify actual and potential product and quality problems, investigate causes, and take appropriate and effective corrective and/or preventive action. Includes
  - Ensuring review of appropriate data sources
  - Identifying nonconformances, other quality issues, and root cause(s)
  - Identifying and implementing corrections, corrective actions, and preventive actions
  - Verifying or validating effectiveness of actions
  - Communicating information to the appropriate people
  - Providing information for management review

21 C.F.R. §§ 820.100, 820.250, 820.90

CAPA Data Sources

Internal Data Sources

- Quality audits
- Service records
- Nonconforming product (scrap, rework)
- Test/inspection data
- Process control data
- Device History Records
- Training records

External Data Sources

- Complaints and adverse event reports (MDRs)
- Returned product
- Supplier control data
- Data regarding similar marketed devices
- Legal claims

Correction vs. Corrective Action vs. Preventive Action

- **“Correction”** refers to repair, rework, or adjustment and relates to the disposition of an existing nonconformity
- **“Corrective action”** refers to eliminating the cause(s) of an existing nonconformity
- **“Preventive action”** refers to eliminating the cause(s) of potential nonconforming product and other quality problems

Complaint Handling

- Manufacturers must
  - Maintain complaint files
  - Designate a formal complaint handling unit
  - Establish and maintain procedures to receive, review, and evaluate complaints.

21 C.F.R. § 820.198

- "Complaint" means "any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device after it is released for distribution."

Complaint Handling (cont'd)

- Procedures must ensure that
  - All complaints are processed in a uniform and timely manner, including oral complaints
  - Complaints are evaluated to determine if they require a Medical Device Report (MDR)
  - Complaints are evaluated to determine if they require investigation
  - If no investigation is made, the reason and person responsible for the decision must be documented.

Production and Process Controls Sub-System

- 21 C.F.R. § 820.50 Purchasing controls
- 21 C.F.R. § 820.60 Identification
- 21 C.F.R. § 820.65 Traceability
- 21 C.F.R. § 820.70 Production and process controls
- 21 C.F.R. § 820.72 Inspection, measuring, and test equipment
- 21 C.F.R. § 820.80 Process validation
- 21 C.F.R. § 820.80 Receiving, in-process, and finished device acceptance
- 21 C.F.R. § 820.86 Acceptance status
- 21 C.F.R. § 820.120 Device labeling
- 21 C.F.R. § 820.140 Handling
- 21 C.F.R. § 820.150 Storage
- 21 C.F.R. § 820.160 Distribution
- 21 C.F.R. § 820.170 Installation

Production and Process Controls Sub-System

- Purpose: develop, conduct, control, and monitor production processes to ensure each device conforms to its specifications. Includes establishing
  - Process controls for manufacturing processes
  - Procedures to control changes to specifications, methods, processes, or procedures
  - Requirements for health, cleanliness, and personnel practices
  - Requirements for purchasing controls (suppliers)
  - Requirements for product acceptance

21 C.F.R. §§ 820.50, 820.70, 820.72, 820.75, 820.80, 820.86

Purchasing Controls

- Must establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements
  - Define requirements to be met by suppliers, contractors, and consultants
  - Evaluate and select based on ability to meet specified requirements
  - Define controls to be exercised over suppliers
  - Maintain records of acceptable suppliers
  - Implement quality agreements where possible.

21 C.F.R. § 820.50

Purchasing Controls

- Suppliers subject to purchasing controls include
  - External suppliers
  - Internal suppliers, if not part of same quality system and internal audit program.

Material Controls Sub-System

- 21 C.F.R. § 820.50 Purchasing controls
- 21 C.F.R. § 820.60 Identification
- 21 C.F.R. § 820.65 Traceability
- 21 C.F.R. § 820.80 Receiving, in-process, and finished device acceptance
- 21 C.F.R. § 820.86 Acceptance status
- 21 C.F.R. § 820.120 Device labeling
- 21 C.F.R. § 820.130 Device packaging
- 21 C.F.R. § 820.140 Handling
- 21 C.F.R. § 820.150 Storage

Material Controls Sub-System

- Purpose: ensure appropriate controls for use and removal of manufacturing materials that could reasonably be expected to have an adverse effect on product quality. Includes
  - Assuring identification and traceability
  - Requirements for acceptance
  - Controls for labeling and packaging
  - Ensuring proper handling and storage

21 C.F.R. §§ 820.50, 820.60, 820.65, 820.80, 820.86, 820.120, 820.130, 820.140, 820.150

Equipment and Facility Controls Sub-System

- 21 C.F.R. § 820.70 Production and process controls
- 21 C.F.R. § 820.72 Inspection, measuring, and test equipment

Equipment and Facility Controls Sub-System

- Purpose: ensure devices are not adversely affected by the manufacturing environment, buildings, or equipment
  - Requirements to use facilities of suitable size and design, control the environment, and implement contamination controls
  - Ensure equipment and instruments are appropriately installed, maintained, adjusted, and calibrated.

21 C.F.R. §§ 820.70, 820.72

Records, Documents, and Change Controls Sub-System

- 21 C.F.R. § 820.40 Document controls
- 21 C.F.R. § 820.180 General requirements
- 21 C.F.R. § 820.181 Device master record
- 21 C.F.R. § 820.184 Device history record
- 21 C.F.R. § 820.186 Quality system record

Records, Documents, and Change Controls Sub-System

- Purpose: ensure all necessary quality system records are maintained and only current documents are used
  - Ensure changes are reviewed, approved, and incorporated into documents
  - Ensure documents are maintained for required length of time and available for inspection as appropriate.

21 C.F.R. §§ 820.40, 820.180, 820.181, 820.184, 820.186

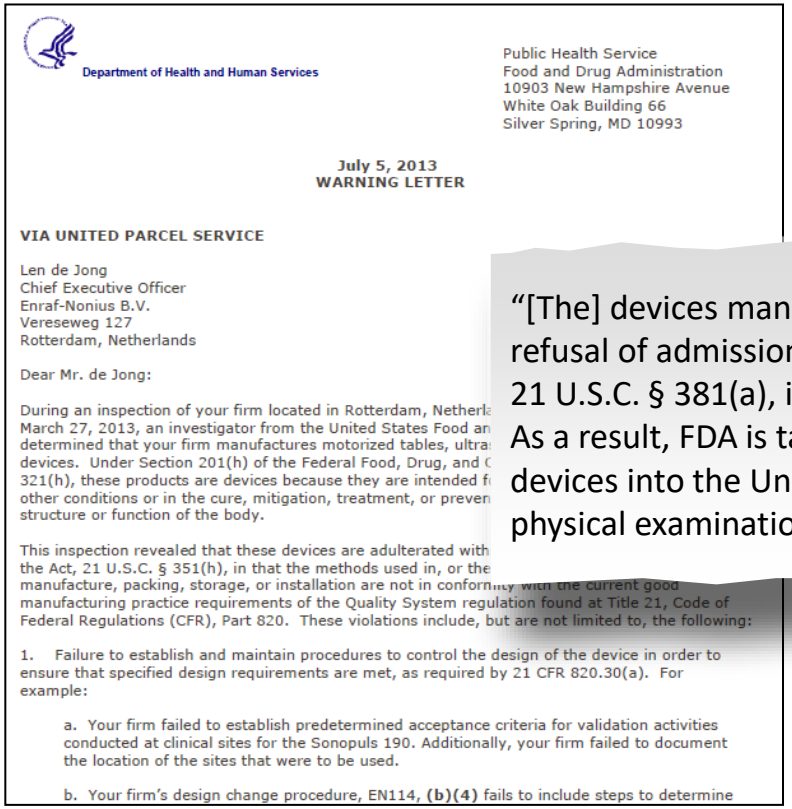
QSR Noncompliance: Practical Impacts

Regulatory and Legal Ramifications

FDA Warning Letters

- Typical first step in event of significant cGMP/QSR noncompliance
  - Usually preceded by a negative inspection (Form FDA-483)
  - Usually state that PMA reviews may be held and export certificates denied pending remediation, and federal agencies notified for purposes of awarding government contracts
  - Sometimes impose additional measures

Import Refusal



Department of Health and Human Services

Public Health Service
Food and Drug Administration
10903 New Hampshire Avenue
White Oak Building 66
Silver Spring, MD 10993

July 5, 2013
WARNING LETTER

VIA UNITED PARCEL SERVICE

Len de Jong
Chief Executive Officer
Enraf-Nonius B.V.
Vereseweg 127
Rotterdam, Netherlands

Dear Mr. de Jong:

During an inspection of your firm located in Rotterdam, Netherl
March 27, 2013, an investigator from the United States Food an
determined that your firm manufactures motorized tables, ultra
devices. Under Section 201(h) of the Federal Food, Drug, and C
321(h), these products are devices because they are intended f
other conditions or in the cure, mitigation, treatment, or preven
structure or function of the body.

This inspection revealed that these devices are adulterated with
the Act, 21 U.S.C. § 351(h), in that the methods used in, or the
manufacture, packing, storage, or installation are not in conform
manufacturing practice requirements of the Quality System regulation found at Title 21, Code of
Federal Regulations (CFR), Part 820. These violations include, but are not limited to, the following:

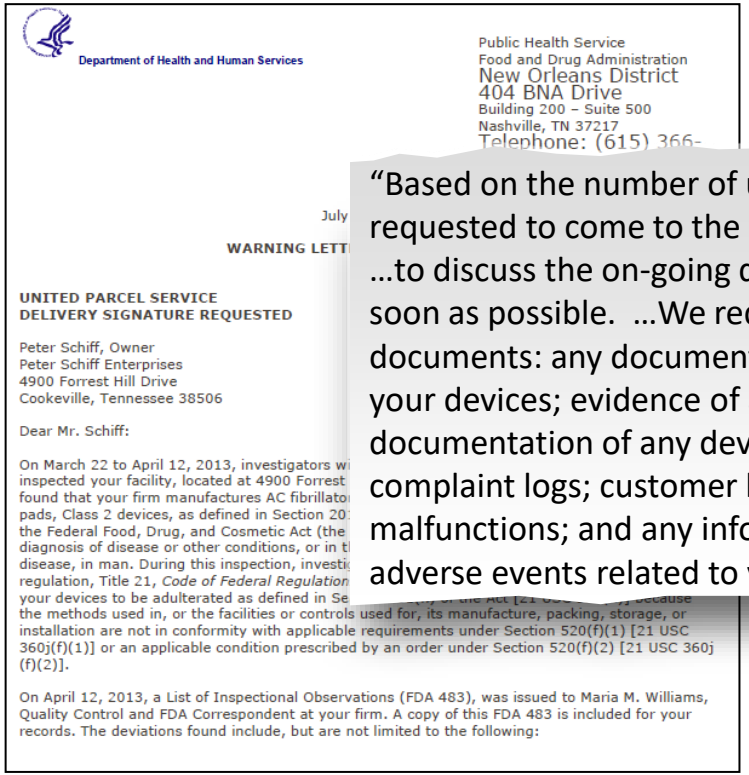
1. Failure to establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met, as required by 21 CFR 820.30(a). For example:

   a. Your firm failed to establish predetermined acceptance criteria for validation activities conducted at clinical sites for the Sonopuls 190. Additionally, your firm failed to document the location of the sites that were to be used.

   b. Your firm's design change procedure, EN114, **(b)(4)** fails to include steps to determine

"[The] devices manufactured by your firm are subject to refusal of admission under section 801(a) of the Act, 21 U.S.C. § 381(a), in that they appear to be adulterated. As a result, FDA is taking steps to refuse entry of these devices into the United States, known as "detention without physical examination," until these violations are corrected."

Regulatory Meeting



Department of Health and Human Services

Public Health Service
Food and Drug Administration
New Orleans District
404 BNA Drive
Building 200 – Suite 500
Nashville, TN 37217
Telephone: (615) 366-

July

WARNING LETT

UNITED PARCEL SERVICE
DELIVERY SIGNATURE REQUESTED

Peter Schiff, Owner
Peter Schiff Enterprises
4900 Forrest Hill Drive
Cookeville, Tennessee 38506

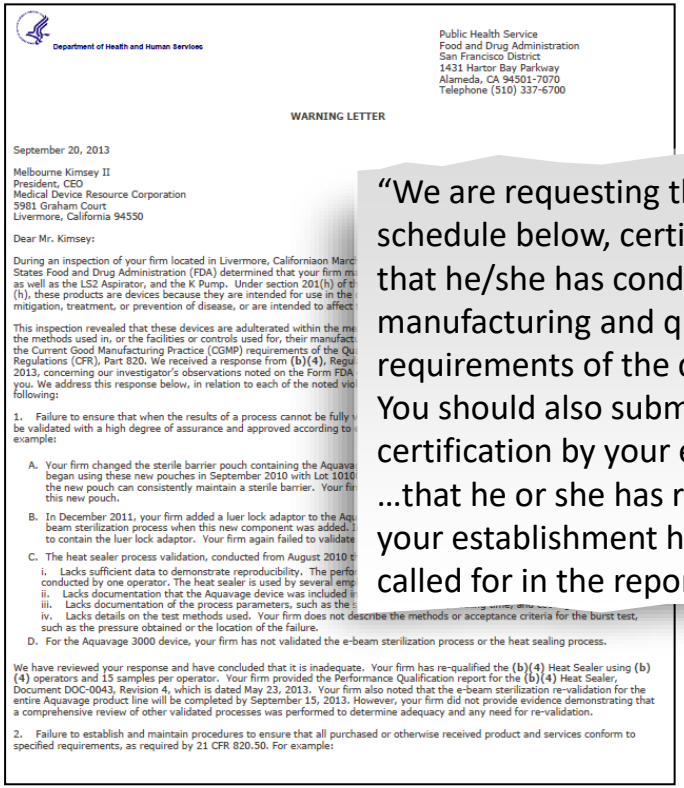
Dear Mr. Schiff:

On March 22 to April 12, 2013, investigators wi
inspected your facility, located at 4900 Forrest
found that your firm manufactures AC fibrillato
pads, Class 2 devices, as defined in Section 20
the Federal Food, Drug, and Cosmetic Act (the
diagnosis of disease or other conditions, or in t
disease, in man. During this inspection, investi
regulation, Title 21, *Code of Federal Regulation*
your devices to be adulterated as defined in Se
the methods used in, or the facilities or controls used for, its manufacture, packing, storage, or
installation are not in conformity with applicable requirements under Section 520(f)(1) [21 USC
360j(f)(1)] or an applicable condition prescribed by an order under Section 520(f)(2) [21 USC 360j
(f)(2)].

On April 12, 2013, a List of Inspectional Observations (FDA 483), was issued to Maria M. Williams, Quality Control and FDA Correspondent at your firm. A copy of this FDA 483 is included for your records. The deviations found include, but are not limited to the following:

"Based on the number of unresolved deviations…you are requested to come to the FDA New Orleans District Office …to discuss the on-going quality deviations at your firm as soon as possible. …We request you bring the following documents: any document pertaining to any defect with your devices; evidence of any devices not meeting specifications; documentation of any device problems; all complaints and complaint logs; customer lists; documentation of any device malfunctions; and any information and documentation of any adverse events related to your devices.

Third Party Review and Certification



Department of Health and Human Services

Public Health Service
Food and Drug Administration
San Francisco District
1431 Harbor Bay Parkway
Alameda, CA 94501-7070
Telephone (510) 337-6700

WARNING LETTER

September 20, 2013

Melbourne Kimsey II
President, CEO
Medical Device Resource Corporation
5981 Graham Court
Livermore, California 94550

Dear Mr. Kimsey:

During an inspection of your firm located in Livermore, Californiaon Marc
States Food and Drug Administration (FDA) determined that your firm m
as well as the LS2 Aspirator, and the K Pump. Under section 201(h) of t
(h), these products are devices because they are intended for use in the
mitigation, treatment, or prevention of disease, or are intended to affect

This inspection revealed that these devices are adulterated within the me
the methods used in, or the facilities or controls used for, their manufact
the Current Good Manufacturing Practice (CGMP) requirements of the Qu
Regulations (CFR), Part 820. We received a response from (b)(4), Regu
2013, concerning our investigator's observations noted on the Form FDA
you. We address this response below, in relation to each of the noted vio
following:

1. Failure to ensure that when the results of a process cannot be fully
be validated with a high degree of assurance and approved according to
example:

A. Your firm changed the sterile barrier pouch containing the Aquava
began using these new pouches in September 2010 with Lot 1010
the new pouch can consistently maintain a sterile barrier. Your fir
this new pouch.

B. In December 2011, your firm added a luer lock adaptor to the Aqu
beam sterilization process when this new component was added.
to contain the luer lock adaptor. Your firm again failed to validate

C. The heat sealer process validation, conducted from August 2010 t
i. Lacks sufficient data to demonstrate reproducibility. The perfo
conducted by one operator. The heat sealer is used by several emp
ii. Lacks documentation that the Aquavage device was included i
iii. Lacks documentation of the process parameters, such as the
iv. Lacks details on the test methods used. Your firm does not describe the methods or acceptance criteria for the burst test, such as the pressure obtained or the location of the failure.

D. For the Aquavage 3000 device, your firm has not validated the e-beam sterilization process or the heat sealing process.

We have reviewed your response and have concluded that it is inadequate. Your firm has re-qualified the (b)(4) Heat Sealer using (b)(4) operators and 15 samples per operator. Your firm provided the Performance Qualification report for the (b)(4) Heat Sealer, Document DOC-0043, Revision 4, which is dated May 23, 2013. Your firm also noted that the e-beam sterilization re-validation for the entire Aquavage product line will be completed by September 15, 2013. However, your firm did not provide evidence demonstrating that a comprehensive review of other validated processes was performed to determine adequacy and any need for re-validation.

2. Failure to establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements, as required by 21 CFR 820.50. For example:

"We are requesting that you submit to this office on the schedule below, certification by an outside expert consultant that he/she has conducted an audit of your establishment's manufacturing and quality assurance systems relative to the requirements of the device QS regulation (21 CFR, Part 820). You should also submit a copy of the consultant's report, and certification by your establishment's Chief Executive Officer …that he or she has reviewed the consultant's report and that your establishment has initiated or completed all corrections called for in the report."

What You Can Do

- Understand current industry standards, best practices, and compliance trends
- Get a reality check
- Don’t skimp on FDA-483 responses

What You Can Do: Prioritize FDA-483 Follow-up and Responses

- **FDA may decide "to not issue a Warning Letter because adequate corrective action has been taken, or …is being taken or has been promised...."**

(FDA Regulatory Procedures Manual, ch. 4-1-3)

When a firm is in the process of correcting the violations or has made a written promise to take prompt corrective action, a district or center should consider the following factors when determining whether or not to issue a Warning Letter:

d. The overall adequacy of the firm's corrective action and whether the corrective action addresses the specific violations, related violations, related products or facilities, and contains provisions for monitoring and review to ensure effectiveness and prevent recurrence;

e. Whether documentation of the corrective action was provided to enable the agency to undertake an informed evaluation;

f. Whether the timeframe for the corrective action is appropriate and whether actual progress has been made in accordance with the timeframe; and,

g. Whether the corrective action taken ensures sustained compliance with the law or regulations

Selected References

- Quality System Regulation; Final Rule – Preamble (61 Fed. Reg. 52601-52662) (Oct. 7, 1996)

  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/ucm230127.htm
- Guide to Inspections of Quality Systems; Quality System Inspection Technique [QSIT]

  http://www.fda.gov/downloads/iceci/inspections/ucm142981.pdf
- FDA, Quality System Information for Certain Premarket Application Reviews: Guidance for Industry and FDA Staff

  http://www.fda.gov/cdrh/comp/guidance/1140.pdf
- FDA Compliance Program 7382.845, Inspection of Medical Device Manufacturers

  http://www.fda.gov/ora/cpgm/default.htm#devices

Questions? Thank you

Elaine H. Tseng
Partner
FDA & Life Sciences

etseng@kslaw.com
+1 415 318 1240