THE CERTIFIED BIOMEDICAL AUDITOR PRIMER

THERE CAN BE NO IMPROVEMENTS WHERE THERE ARE NO STANDARDS.

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Quality System Regulations

Quality System Regulations are presented in the following topic areas:

- **Quality System Regulation (QSR) Requirements (21 CFR 820)**
- **Post-market Surveillance (Guidance under Section 522 of FD&C Act)**

Quality System Regulation (QSR) Requirements (21 CFR 820)

Quality System Regulation (QSR) Requirements (21 CFR 820) are presented in the following key section areas:

- **Management Responsibility (20, 22, 25)**
- **Design Control System (30)**
- **Document (Part 40) and Record Control (180-186)**
- **Purchasing Controls and Acceptance Activities (50, 80, 86)**
- **Identification and Traceability (60, 65)**
- **Production and Process Controls (70, 72, 75)**
- **Nonconforming Product (90)**
- **Corrective and Preventive Action (CAPA) System (100)**
- **Product Handling, Storage, Distribution, and Installation (140-170)**
- **Servicing (200)**
- **Statistical Techniques (250)**

Additionally, General Provisions (1, 3, 5), Labeling and Packaging Control (120 and 130), and Complaint Files (198) will be discussed.

Often regulations overlap and must be understood together in order to avoid unacceptable gaps in a quality system. For example, 21 CFR 820.198 of the QSR establishes requirements for complaint files; this section must be understood and must also satisfy the requirements of 21 CFR 803, Medical Device Reports, 21 CFR 806, Reports of Removals and Corrections, 21 CFR 801, Labeling, where these apply to a complaint received.

21 CFR 820 (Continued)

As an example, if a firm received a complaint reading, "Just a quick email to thank you for your prompt service! A patient received a minor burn because the label on the device stated that the dial should be set to 'Medium' but when it was set to medium it performed at the 'High' level. We called your service department and they came and replaced the unit with another one that worked fine."

This statement initially may not sound like a serious complaint. Yet it must not only be investigated as a device failure (under 21 CFR 820.198) but it also must be reported as an MDR (under 21 CFR 803), and as part of CAPA activities (under 21 CFR 820.100) similar devices may be subject to report as a recall (under 21 CFR 806), and it could have a labeling issue (under 21 CFR 801).

The section below will outline the Quality System Regulation (QSR) requirements, describe them in more detail, then will describe related regulatory requirements flowing from the statutes, and more details of the regulations related to, but not part of, the QSR (21 CFR 820).

Device Classifications

The FD&C Act created three classifications for devices: Class I, II, and III. Volume 8 of Title 21, contains parts 800 to 1299, and some of these parts describe specific devices and their classification, while others, such as Parts 801, 803, 807, and 820, among others, describe other regulatory requirements.

- **Class I devices are subject only to general controls because they are simple, present fewer risks and any risks are of lower severity than other device classes, so that general controls, including where stated, specific exemptions from portions of the good manufacturing practices (GMPs), are considered adequate to provide assurance of safety and effectiveness.**

- **Class II devices are more complex, than Class I devices, are subject to general controls, and, because general controls do not provide reasonable assurance of the devices' safety and effectiveness, Class II devices may also be subject to specific performance standards, postmarket surveillance, various guidance documents, and are subject to premarket notification ("510(k) filings").**

- **Class III devices cannot be classified as Class I or Class II because general and special controls do not provide reasonable assurance of their safety and effectiveness, the device is to be used in supporting or sustaining human life, and the device presents a potential for unreasonable risk of illness, injury, or death. Class III devices are subject to premarket approval ("PMA" review process and approval).**

21 CFR 820 (Continued)

Device Classifications (Continued)

- **Predicate devices are devices which were legally marketed prior to May 28, 1976 which was the effective date of the Medical Device Amendment of 1976. Predicate devices are also used to clear a device that is similar in features to one cleared by a 510(k). These are the "me too devices" used to prove substantial equivalence for quick market entry.**

All Class I and Class II devices must have a predicate device identified for the regulatory approval process. All "new" devices, or devices without a predicate are designated as Class III devices. If such devices are cleared for sale, they may later be reclassified into Class I or Class II based on post market experience, including few adverse events.

The humble and well-known "tongue depressor" is in fact a medical device. Its full publication in the regulations is shown as:

[Code of Federal Regulations]
[Title 21, Volume 8]
[Revised as of April 1, 2012]
[CITE: 21CFR880.6230]

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H--MEDICAL DEVICES
PART 880 -- GENERAL HOSPITAL AND PERSONAL USE DEVICES

Subpart G--General Hospital and Personal Use Miscellaneous Devices

Sec. 880.6230 Tongue depressor.
(*a) Identificatio*n. A tongue depressor is a device intended to displace the tongue to facilitate examination of the surrounding organs and tissues.

***(b) Classification*. Class I (general controls). The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter, subject to the limitations in 880.9. If the device is not labeled or otherwise represented as sterile, it is also exempt from the current good manufacturing practice requirements of the quality system regulation in part 820 of this chapter, with the exception of 820.180, with respect to general requirements concerning records, and 820.198, with respect to complaint files.**

[45 FR 69682-69737, Oct. 21, 1980, as amended at 66 FR 38806, July 25, 2001]

A search for "tongue depressor" on http://www.fda.gov returns the reference above.

21 CFR 820 (Continued)

Device Classifications (Continued)

The location within the regulations, the place and date of publication in the Federal Register ("FR" pages published on October 21, 1980 and amended on July 25, 2001), and the description (identification) and classification of the device are stated. Furthermore, in this case, (unless sterility is claimed) the tongue depressor can be manufactured in a facility exempt from "…good manufacturing requirements of the quality system regulation in part 820 of this chapter with the exception…" noted.

Quality System Regulation (QSR)

The "Quality System Regulation" is often cited simply as "QSR", as "CGMP", or as "cGMP", and is set forth in the Federal Code of Federal Regulations (CFR) as "Title 21 Code of Federal Regulations, Part 820" ("21 CFR 820").

The subparts of this regulation followed the ISO 9001 (1987) standard in structure, in support of "harmonization," and though the content of subsequent versions (1994, 2000, 2008, 2012) continued to apply (with the exception of a requirement in ISO 9001 for "continual improvement" that is absent from QSR or the medical device specific ISO 9000 family standard, ISO 13485), the QSR subparts do not follow the 1994 and later clauses of the ISO standards.

The Federal Register published on Monday, October 7, 1996, the "Final Rule" describing how the QSR was developed, FDA's thinking and response to comments on the proposed regulations over the six years since SMDA was passed in 1990. This document, called "the preamble," is important to understand. It can be obtained as a PDF by searching within the FDA website at http://www.fda.gov for "preamble."

QSR, 21 CFR 820 is only a small (though critical) portion of the regulations that must be followed by medical device designers, manufacturers, distributors, and marketers.

21 CFR 820 (Continued)

Key subparts of CFR Title 21 Part 820 are shown as an outline in the table below.

Name	Citation	Comments
General Provisions	21 CFR 820.1	Scope
	21 CFR 820.3	Definitions
	21 CFR 820.5	Quality System
Quality System Requirements	21 CFR 820.20	Management Responsibility
	21 CFR 820.22	Quality Audit
	21 CFR 820.25	Personnel (includes training)
Design Controls	21 CFR 820.30	Design Controls – only one clause, but significant requirements; DHF included.
Document Controls	21 CFR 820.40	See "Part 11" discussion for electronic records
Purchasing Controls	21 CFR 820.50	Includes controls on selection and oversight of suppliers; supplier auditing also involves 21 CFR 820.22.
Identification and Traceability	21 CFR 820.60	Identification – Includes identification of devices, components and ties to DMR and DHR
	21 CFR 820.65	Traceability – includes requirements for individual unit or batch identification; not to be confused with "Device Tracking" requirements in 21 CFR 821.
Production and Process Controls ("P&PC")	21 CFR 820.70	Production and process controls, in general
	21 CFR 820.72	Inspection, Measuring and Test Equipment ("IMTE"); includes calibration.
	21 CFR 820.75	Process Validation
Acceptance Activities	21 CFR 820.80	Receiving, In-Process, and Finished Device acceptance; includes release of components, subassemblies and finished products.
	21 CFR 820.86	Acceptance status

Table 5.0 Key Subparts of 21 CFR 820

(FDA 21CFR820, 2012)[3]

21 CFR 820 (Continued)

Name	Citation	Comments
Nonconforming Product	21 CFR 820.90	Relates also to CAPA and complaints.
Corrective and Preventive Action ("CAPA")	21 CFR 820.100	CAPA is of especially critical importance as the heart of a quality system
Labeling and Packaging Control	21 CFR 820.120	Device Labeling – labeling is also covered under 21 CFR 801
	21 CFR 820.130	Device Packaging
Handling, Storage, Distribution and Installation	21 CFR 820.140	Handling
	21 CFR 820.150	Storage
	21 CFR 820.160	Distribution
	21 CFR 820.170	Installation (does not include servicing)
Records	21 CFR 820.180	General Requirements
	21 CFR 820.181	Device Master Record (DMR)
	21 CFR 820.184	Device History Record (DHR)
	21 CFR 820.186	Quality System Record (QSRc)
	21 CFR 820.198	Complaint Files (also related to a special category of complaints under 21 CFR 803)
Servicing	21 CFR 820.200	Servicing – intended for repairs, whether under warranty or not. Repairs ("corrections") in the field or returned to the manufacturer could also be regulated under the "Removals & Corrections" regulations in 21 CFR 806
Statistical Techniques	21 CFR 820.250	Requires rational basis for sampling, determinations of adequacy.

Table 5.0 Key Subparts of 21 CFR 820 (Continued)

Table 5.1, 1 above provides the outline of the sections of the QSR. Each subpart citation will be described on the following pages.

21 CFR 820.1 /820.3 / 820.5

General Provisions

This section includes scope and applicability (§820.1); definitions (§820.3); and a very brief, one sentence statement:

> **"§820.5 Quality system. 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."**

The definitions are important and sometimes subtle. They are listed below and reproduced in the Glossary. FDA attempted to harmonize these, where possible, but as noted in the *Preamble*, FDA did not believe the ISO standards, as written, were adequate to establish a quality system for medical devices.

Act means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-903, 52 Stat. 1040 et seq., as amended (21 U.S.C. 321-394)). All definitions in Section 201 of the act shall apply to the regulations in this [21 CFR 820] citation.

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.

Component means any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device.

Control number means any distinctive symbols, such as a distinctive combination of letters or numbers, or both, from which the history of the manufacturing, packaging, labeling, and distribution of a unit, lot, or batch of finished devices can be determined.

Design history file (DHF) means a compilation of records which describes the design history of a finished device.

Design input means the physical and performance requirements of a device that are used as a basis for device design.

Design output means the results of a design effort at each design phase and at the end of the total design effort. The finished design output is the basis for the device master record. The total finished design output consists of the device, its packaging and labeling, and the device master record.

21 CFR 820.1 /820.3 / 820.5 (Continued)

General Provisions (Continued)

Design review means a documented, comprehensive, systematic examination of a design to evaluate the adequacy of the design requirements, to evaluate the capability of the design to meet these requirements, and to identify problems.

Device history record (DHR) means a compilation of records containing the production history of a finished device.

Device master record (DMR) means a compilation of records containing the procedures and specifications for a finished device.

Establish means define, document (in writing or electronically), and implement.

Finished device means 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.

Lot or batch means one or more components or finished devices that consist of a single type, model, class, size, composition, or software version that are manufactured under essentially the same conditions and that are intended to have uniform characteristics and quality within specified limits.

Management with executive responsibility means those senior employees of a manufacturer who have the authority to establish or make changes to the manufacturer's quality policy and quality system.

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.

Manufacturing material means any material or substance used in or used to facilitate the manufacturing process, a concomitant constituent, or a byproduct constituent produced during the manufacturing process, which is present in or on the finished device as a residue or impurity not by design or intent of the manufacturer.

Nonconformity means the nonfulfillment of a specified requirement.

Product means components, manufacturing materials, in- process devices, finished devices, and returned devices.

21 CFR 820.1 / 820.3 / 820.5 (Continued)

General Provisions (Continued)

Quality means the totality of features and characteristics that bear on the ability of a device to satisfy fitness-for-use, including safety and performance.

Quality audit means a systematic, independent examination of a manufacturer's quality system that is performed at defined intervals and at sufficient frequency to determine whether both quality system activities and the results of such activities comply with quality system procedures, that these procedures are implemented effectively, and that they are suitable to achieve quality system objectives.

Quality policy means the overall intentions and direction of an organization with respect to quality, as established by management with executive responsibility.

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

Remanufacturer means any person who processes, conditions, renovates, repackages, restores, or does any other act to a finished device that significantly changes the finished device's performance or safety specifications, or intended use.

Rework means action taken on a nonconforming product so that it will fulfill the specified DMR requirements before it is released for distribution.

Specification means any requirement with which a product, process, service, or other activity must conform.

Validation means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.

Process validation means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

Design validation means establishing by objective evidence that device specifications conform with user needs and intended use(s).

Verification means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.