COMPARISON OF THE QUALITY SYSTEM REQUIREMENTS OF CODE OF FEDERAL REGULATIONS PART 820 AND INTERNATIONAL STANDARD ISO 13485

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ABSTRACT

This paper compares the quality system requirements of the Code of Federal Regulations 21 CFR part 820 with the quality system requirements of the International Standard ISO 13485. The medical devices industry that distributes product in the domestic (United States of America) market and in the international (European countries) market shall comply with the regulations (CFR 820 and ISO 13485:2003) and the harmonization of both requirements in one quality system is the ideal process to avoid the missing of any of the requirements. This comparison will help to understand the international and the domestic quality system requirements and the quality system maintenance. A guideline was developed for a sterile medical devices industry to implement a single quality system which includes international and the domestic quality system requirements without the missing of any of the requirements.

INTRODUCTION

The code of federal regulation 21 CFR part 820 is applicable to any finished device manufactured, imported, or offered for import in domestic market (any state of the United States (USA), the District of Columbia or the Commonwealth of PR). The international standard ISO 13485: 2003 is a volunteer alternative and used by the medical devices industries to achieve regulatory compliance for import in the international market (European countries such as Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland and the United Kingdom, in addition other countries such as Australia, Japan and Canada). The conformance to ISO 13485: 2003 does not constitute conformity with the national or regional regulatory requirements; therefore, the company is responsible to comply with the regulatory requirements.

Most of medical device industries sell their products in the international market. One of the concerns that the medical device industries have at the time they decide to move to the international market is how they will harmonize a quality system that complies with the code of federal regulation CFR 820 and the international organizational for standardization ISO 13485:2003 without compromise the product quality and complies with the regulatory requirements. The purpose of this investigation is how the medical devices industry can develop a quality system with the integration of the CFR 820 regulations and the ISO 13485:2003 requirements. This harmonization will provide a single quality system which complies with the domestic and international requirements.

BACKGROUND

Code of Federal Regulations (CFR Title 21 Part 820) Quality System Regulation (QSR) and Medical Devices – Quality Management Systems-Requirements for regulatory purposes (ISO 13485:2003) have differences and similarities in their quality system requirements for the medical devices. Code of Federal Regulations Title 21

(CFR) Part 820 QSR is the standard used by the United States of America (USA), Food & Drug Administration (FDA) to verify the compliance in the quality system regulations of the medical devices industry in the domestic market. This standard is published every year. (21 CFR 820 published on April 2008 will be used for the comparison). The modern manufacturing organization complexity led the development of the quality management systems. Global quality standards began in the late 1980's. The purpose of the standards was to provide internationally recognized set of quality management standards for all industries but the medical device industries need special consideration regarding quality management standards. Therefore, ISO 13485 edition 1996 was issued. ISO 13485:2003 is the standard used for medical devices in the international market. Today, certification of a quality management system to ISO 13485 in many case are mandatory for medical devices companies. According with the ISO Survey 2006 [1] about 8,000 certificates for ISO 13485 had been issued in 67 countries by the end of 2006.

To understand the topic, the quality system concepts will be defined. Medical devices is defined by ISO 13485:2003 as any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for diagnosis, prevention, monitoring, treatment or alleviation of disease, diagnosis, monitoring, treatment, alleviation of or compensation for an injury, investigation, replacement, modification, or support of the anatomy or of a physiological process, supporting or sustaining life, control of conception, disinfection of medical devices, providing information for medical purposes by means of in vitro examination of specimens derived from the human body, and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means. Quality is defined in different ways. Quality means a high degree of excellence. According with ISO 9000 [2], quality is the degree to which a set of inherent characteristics fulfill requirements. For Philip B. Crosby in Quality is Free [3], quality is the conformance to requirements. Taguchi [4] defines quality as uniformity around a target value and the loss a product imposes on society after it is shipped American Society for Quality [5] stated in its glossary that for Joseph M. Juran, quality is "Fitness for use." The glossary of American Society for Quality (ASQ) [5] defines quality as: "a subjective term for which each person has his or her own definition. In technical usage, quality can have two meanings: a. the characteristics of a product or service that bear on its ability to satisfy stated or implied needs; b. a product or service free of deficiencies." System is defined as a set of interacting or interdependent entities, real or abstract, forming an integrated whole. According with ISO 9000 [2], system is a set of interrelated or interacting elements. As per International Standard (ISO) Catalogue [6], the management system refers to what the organization does to manage its processes, or activities, so that its products or services meet the objectives it has set itself, such as: satisfying the customer's quality requirements, complying with regulations, or meeting environmental objectives. The quality system is defined by the CFR 21 part 820 [6] as the organizational structure, responsibilities, procedures, process, and resources for implementing quality management. For ISO 13485 [8] Medical Devices – Quality Management Systems- Requirements for regulatory purposes, specifies requirements for a quality management system that can be used by an organization for the design and development, production, installation and servicing of medical devices, and the design, development, and provision of related services. Also, it can be used by internal and external parties, including certification bodies, to assess the organization's ability to meet customer and regulatory requirements.

Not much information is found related to the comparison of quality system requirements of the 21 CFR 820 regulations and the ISO 13485:2003. A comparison chart was done with the FDA CFR 820 QSR edition 1996 and ISO 13485:1996. This comparison chart is found in the FDA Center for Devices and Radiological Health (CDRH). The major source of information which includes a comparison of the 21 CFR 820 regulations and the ISO 13485:2003 was the articles but a book was found that includes this comparison. The major methodology of comparison used was the comparison charts.

The article titled Implementing ISO 13485:2003 wrote by Basler & Pizinger [9] contrasted the QSR 820 and ISO 9001:1994. The authors wrote an article related to the implementation of the ISO 13485:2003 in which no section by section review was done of the ISO 13485:2003 but mentioned some differences and similarities between QSR 820 and ISO 13485:2003. One of the differences they mentioned is that ISO 13485:2003 is more detailed or prescriptive that the FDA QSR 820. Also QSR does not address the customer focus. One concern that FDA has is that the manufacturers meet the regulatory requirements. One similar approach from the ISO 13485:2003 and the QSR 820 is that both allow functions that are not performed by an organization to be excluded. According with Basler & Pizinger [9] ISO 13485:2003 and ISO 9001:2000 have differences such as quality management system and customer focus. ISO 13485:2003 helps to comply with the regulatory requirements because include the outputs of the management reviews as per Basler & Pizinger [9]. Implementation of the ISO 13485:2003 approach was summarized by Basler & Pizinger [9]. The steps to implement the ISO 13485:2003 are: gap analysis, selection of a consultant, plan development and plan implementation. They performed a chart with multiples standards to help of the implementation of one quality system that complies with multiple quality systems standards. According with the authors, this implementation needs strategic planning. As per Basler & Pizinger [9], compliance with a variety of quality systems including the QSR 820 and ISO 13484:2003 is very achievable and desirable.

Gallifa & Partner LLC [10] wrote a paper titled The new ISO 13485:2003 which introduces the ISO 13485:2003 and compared in details with the QSR 820 and ISO 9001:2000. Implementation of the standard ISO 13485 in few Swiss organizations was described. History of the standards creation was done and the issuance of a dedicated standard for medical devices (ISO 13485). According with Gallifa & Partner LLC [10] FDA participated in the revision of ISO 13485:2003 as part of the Global Harmonization Task Force (GHTF). GHTF represents countries that are home to world's major medical devices manufacturers. Gallifa & Partner LLC [10] stated as they know there is not an official comparison between FDA QSR 820 and ISO 13485:2003. The transition of the ISO 13485 in Europe was explained. Gallifa & Partner LLC [10] issued and structural approach. According to Gallifa & Partner LLC [10], it is necessary to understand the comparison the following approach. See Figure 1 below.

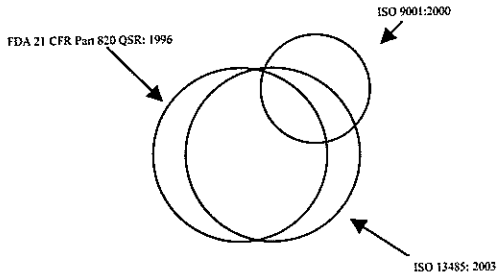

Figure 1: *Structural Approach*

The set of regulations were classified in three categorizes:

- Characteristics or requirements found in the FDA CFR 820 but not in ISO 13485:2003
- Characteristics or requirements found in the ISO 13485:2003 but not in CFR 820
- Characteristics or requirements found in the CFR 820 and in ISO 13485:2003.

820.20 Management Responsibility	5 Management Responsibility 6.2 Human resources	Standard and QSR include the management requirements. The standard is focused on meeting customer requirements in addition to meeting regulatory requirements. The QSR is focused on meeting those regulatory requirements that have as their objective the design, manufacture, distribution, and support of safe and effective medical devices. Standard requires the improvement as needed to keep the effectiveness of the quality management system and its processes.
820.20 (c) Management review	5.6 Management review	The intention of regulation and standard is to improve the quality system.
820.20 (d) Quality planning	5.4.2 Quality management system planning	The standard provides examples of the quality planning.
820.20 (e) Quality system procedure	4 Quality Management System 4.2 Documentation requirements	Standard and regulation require a documented quality system.
820.22 Quality Audit	8.2.2 Internal Audit	Standard and regulation have the same requirements for quality audits. Both require corrective action from observations.
820.25 Personnel	6.2 Human Resources	Same requirements for standard and regulation for trainings and personnel provision. Standard requires the evaluation of the effectiveness of the actions taken related to training.
820.30 Design Controls	7.3 Design and Development	Standard applies design controls to all medical devices and the regulation applies to medical devices classes II, II and class I automated with computer software & the devices listed in the section 820.30(a)(2)(ii). Standard and regulation contain the requirements for design outputs. Regulation indicates the risk analysis during the design validation process and standard calls during the product realization. Standard requires the creation of documentation and the regulation requires a design history file. Regulation does not require the evaluation of the effect of the changes on product already delivered. There is no specific section to design transfer in the standard only a note in the section 7.3.1. For the design validation process, the regulation has a number of requirements that the standard does not have. The closest the QSR gets to determining customer requirements related to the product in 820.30(c) design inputs. The customer requirements referred to in clause 7.2 of ISO 13485:2003 refer to those requirements associated with getting the product to the customer. This includes items associated with order handling. These are not focuses of the QSR.
820.40 Document controls	4.2.3 Control of documents	Standard requires retention time period for the obsolete documents.
820.50 Purchasing controls	7.4 Purchasing	Same requirements for standard and regulation for purchasing. Regulation requires that the supplier notify any change in the service or product.
820.60 Identification	7.5.3.1 Identification	Regulation does not explicitly require that device return to manufacturer for service or repair should be identified as well the standard requires.
820.65 Traceability	7.5.3.2 Traceability	Standard requires traceability for all kind of medical devices.
820.70 Production and Process Controls	7.5 Production and Service Provision	Regulation and standard provide details of control or the types of process to be controlled. Standard does not address the production & process changes in a specific section.
820.70 (c) Environmental control	6.4 Work environment	Standard requires the control of the product to avoid contamination with other product, manufacturing process or personnel as well as the QSR.
820.70 (d) Personnel	6.2 Human resources 6.2.1 General 6.2.2 Competence, awareness and training	Same requirements of standard and regulation for human resources.
820.70 (e) Contamination control	6.4 Work environment	Standard requires the control of the product to avoid contamination with other product, manufacturing process or personnel as well as the QSR.
820.70 (f) Buildings 820.70 (g) Equipment 820.70 (h) Manufacturing material	6.3 Infrastructure	Same requirements for standard and regulation for infrastructure. The regulation requires the creation of maintenance schedules, inspections, adjustment of equipment and has specific requirements related to manufacturing materials.

820.70 (i) Automated processes	7.5.2 Validation of processes for production and service provision	Same requirements of standard and regulation for software validation.
820.72 Inspection, measuring, and test equipment	7.6 Control of monitoring and measuring devices	QSR focus on the process calibration of the equipment and the standard provides guidance to control of monitoring and measuring devices. Also, the regulation does not have a section for measurement, analysis and improvement.
820.75 Process Validation	7.5.2 Validation of processes for production and service provision 7.5.2.1 General requirements	There are no specific requirements related to process validation of sterilization processes in the QSR. Regulation requires documentation of validation activities.
820.80 Receiving, in-process, and finished device acceptance	7.4.3 Verification of purchased product 8.2.4 Monitoring and measurement of product	The QSR is more detailed and stricter.
820.86 Acceptance Status	7.5.3 Identification and traceability 7.5.3.3 Status Identification	The QSR is stricter with the record of acceptance status.
820.90 Nonconforming Product	8.3 Control of Nonconforming Product	The QSR is more detailed in the documentation of the nonconforming product. Standard considers when a product is already released and rework activities.
820.100 Corrective and Preventive Action	8.5 Improvement 8.5.1 General 8.5.2 Corrective Action 8.5.3 Preventive Action	The QSR is stricter. The standard has a separate subsection for the preventive action. Regulation requires the verification or validation of the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device.
820.120 Device Labeling 820.130 Device Packaging	7.3.2 Design and development inputs 7.5.1 Control of production and service provision 7.5.1.1 General Requirements 7.5.5 Preservation of product	QSR contains many strict requirements related to label control and the handling, storage, packaging, preservation, and distribution of product not specifically called out in the standard. The QSR does not specifically address the issue of care to exercised over customer property when it is being held or processed by the organization as standard does under the subclause 7.5.4 Customer property.
820.140 Handling 820.150 Storage 820.160 Distribution 820.170 Installation	7.2 Customer-related processes 7.2.1 Determination of requirements related to the product 7.2.2 Review of requirements related to the product 7.5.1 Control of production and service provision 7.5.1.1 General requirements 7.5.5 Preservation of product 7.5.1.2.2 Installation activities	QSR contains many strict requirements related to label control and the handling, storage, packaging, preservation, and distribution of product not specifically called out in the standard.
820.180 General Requirements	4.2.4 Control of Records	Same requirements of standard and regulation for control records. QSR requires communication with FDA.
820.181 Device Master record 820.184 Device history record	7.3.3 Design and development outputs 7.3.7 Control of design and development changes 7.5.1 Control of production and service provision 7.5.1.1 General requirements	The standard does not have the requirement for DMR and DHR as a Quality System Record as the regulation does it. It requires the individual documents and records that would be contained within those files.
820.186 Quality System record	4 Quality management system 4.1 General requirements 4.2 Documentation requirements 4.2.1 General	Regulation requires a Quality System Record as separate file that contains the required documents. The standard does not require this separate file.
820.198 Complaint Files	7.2.3 Customer communication 8.2 Monitoring and measurement 8.2.1 Feedback 8.5 Improvement 8.5.1 General	QSR contains strict requirements regarding the handling of complaints. These requirements are not included in detail in the standard.
820.200 Servicing	7.5.1.2.3 Servicing activities	Standard and regulation requirements for servicing are similar.

820.250 Statistical Techniques	8 Measurement, analysis and improvement 8.1 General 8.2.3 Monitoring and measurement of processes 8.2.4 Monitoring and measurement of product	Regulation is more detail in the monitoring and measurement of processes. There is not a specific section in the regulation related to the analysis of data but it is found in different sections of the regulation.

ISO 13485: 2003 practically contains the same requirements that the 21 CFR Part 820 (QSR). Some requirements are included in detail in the standard and others are in the QSR. One of the differences is that the CFR part 820 does not have the requirement for a Quality Manual. The manual would be helpful in explaining the nature and extent of the quality management system. It would also be useful in the training of personnel with regard to the quality management system of the organization and their place within that system. The Quality Manual could be used as the repository of some of the individual quality management system documentation required by the Quality System Regulation (e.g., the organizational structure and interrelationships, the highest level procedures in a small organization dealing with items like document control, records keeping, and training). Also, the standard is focused on meeting customer requirements in addition to meeting regulatory requirements. The QSR is focused on meeting those regulatory requirements. Standard applies design controls to all medical devices and the regulation applies to medical devices classes II, II and class I automated with computer software & the devices listed in the section 820.30(a)(2)(ii).

In other hand, the QSR contains stricter requirements regarding the handling of complaints and other user input that would be useful in conducting corrective or preventive action. These requirements are not included in detail in ISO 13485:2003, but compliance with the requirements set out in the QSR would satisfy the requirements of ISO 13485:2003.

A guideline was created for a medical devices company with sterile products that wants to certify as ISO 13485. This guideline contains both requirements of ISO 13485:2003 and the regulation 21 CFR Part 820 (QSR). Refer to Table 2 for an example (only includes some of the documents).

Table 2: *Example of the Guideline of Harmonized Quality System for Sterile Medical Devices Company*

Document Number	21 CFR 820 Section	ISO 13485
SMD-002	Quality Management System	
	820.5 Quality System 820.180 General Requirements 820.20 (e) Quality system procedures 820.40 Document controls 820.186 Quality System record 820.22 Quality Audit 820.30 (j) Design History File (DHF) 820.181 Device Master Record 820.184 Device History Record 820.198 Complaint Files 820.200 Servicing 820.250 Statistical Techniques	4 Quality Management System 4.1 General Requirements 4.2.1 General 4.2 Documentation requirements 4.2.2 Quality Manual 4.2.3 Control of documents 4.2.4 Control of Records

SMD-003	Management Responsibility	
	820.20 Management Responsibility Quality policy Quality planning Quality system procedures Organization Responsibility and authority Management representative Organization Management review 820.30 Design Controls 820.5 Quality System	5 Management Responsibility 5.1 Management commitment 5.3 Quality policy 5.2 Customer Focus 5.4 Planning 5.4.1 Quality objectives 5.4.2 Quality management system planning 5.5 Responsibility, authority and communication 5.5.1 Responsibility and authority 5.5.2 Management representative 5.5.3 Internal communication 5.6 Management review
SMD-005	Product Realization	
	820.5 Quality System 820.30 (b) Design and Development Planning	7.0 Product Realization 7.1 Planning of product realization 7.2 Customer related process
SMD-006	Design Controls	
	820.30 Design Controls	7.3 Design & Development
SMD-008	Production and Services	
	820.70 Production and Process Control 820.140 Handling 820.150 Storage 820.160 Distribution 820.170 Installation 820.200 Servicing 820.75 Process Validation 820.30 (h) Design Transfer 820.60 Identification 820.66 Traceability 820.80 (e) Acceptance Records 820.86 Acceptance Status 820.120 Device Labeling 820.130 Device Packaging 820.140 Handling 820.150 Storage 820.160 Distribution 820.170 Installation 820.72 Inspection, Measuring & Test Equipment	7.5.1 Control of production and service provision 7.5.2 Validation of processes for production and service provision 7.5.1.2.4 Particular Requirements for Sterile Devices 7.5.3 Identification and Traceability 7.5.3.3 Status Identification 7.5.4 Customer Property 7.5.5 Preservation of product 7.6 Control of Monitoring, Measuring & Test Equipment
SMD-009	Measurement, Analysis & Improvement	
	820.250 Statistical Techniques 820.198 Complaint Files 820.22 Quality Audit 820.70 Production & Process Control 820.250 Statistical Techniques 820.80 Receiving, In-process & Finish Device 820.90 Nonconforming Product 820.250 Statistical Techniques 820.20 Management Responsibility 820.20 (c) Management Review 820.198 Complaints Files 820.100 Corrective and Preventive Action	8.1 General 8.2 Monitoring & Measurement 8.2.1 Feedback 8.2.2 Internal Audit 8.2.3 Monitoring & Measurement of Processes 8.2.4 Monitoring & Measurement of Product 8.2.4.1 General Requirements 8.3 Control of Nonconforming Product 8.4 Analysis of Data 8.5 Improvement 8.5.1 General 8.5.2 Corrective Action 8.5.3 Preventive Action

CONCLUSION

Medical devices industry can develop a quality system with the integration of the 21 CFR 820 regulations and the ISO 13485:2003 requirements. This research facilitates the development of a single quality system which includes international and the domestic quality system requirements without the missing of any of the requirements. This harmonization provides a single quality system which complies with the 21 CFR 820 regulations and the ISO 13485:2003 requirements. The

implementation of the standard with the implementation of the quality system under the regulation, it is an alternative to achieve the regulatory requirements. The obtained quality system will be a robust system that avoids the missing of the regulations or international requirements when you integrate the ISO 13485: 2003 requirements in the QSR based in the regulation 21 CFR part 820. Continuous monitoring and effectiveness verification of the quality system must be maintained to ensure the compliance of those requirements.

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