DEVELOPING A COMPREHENSIVE CGMP/QUALITY SYSTEM IMPLEMENTATION PLAN TO MEET FDA REGULATIONS FOR CLASS II MEDICAL DEVICES

by

NARAN PATEL

(Under the Direction of Paul Brooks)

ABSTRACT

According to United States Code of Federal Regulations (CFR) listed in 21 CFR Part 820, medical device manufacturers must establish and follow Quality Systems to ensure that their products consistently meet applicable requirements and specifications. If the FDA determines that a manufacturer repeatedly failed to correct the violations FDA outlined in the form 483 and is non-complaint with 21 CFR, a typical first step is issuance of a FDA Warning Letter, which communicates the Agency's position and provides an opportunity for the manufacturer to take prompt corrective action to prevent an FDA enforcement action. Using a qualitative action research methodology, this research was designed to identify and verify the most common causes of FDA warning letters issued to device companies and use these finding to design a standard "implementation plan" that start-up device companies could use to help guide their development of quality systems and prevent issuance of a warning letter. The research consisted of three distinct research phases. The first research phase was to analyze publically available FDA Warning Letters issued to 120 medical device companies from January 2008 through August 2010 in the area of Good Manufacturing Practices/Quality System Regulations to determine the most common violations that triggered FDA Warning Letters. From the analysis of these

Warning Letters, it was determined that violations were most numerous in three broad areas: (1) Design Control, (2) Corrective and Preventive Action and (3) Complaint files. The second research phase was to interview, experts in medical device industry to help attest to the findings in phase 1 and generate qualitative data reflecting expert views for the recurrence of violations in the areas of Design Control, CAPA and Complaint files. Data gathered through interviews were analyzed using the constant comparative method and common themes were identified. The third research phase was to use the analyses of the Warning Letters and the interview data (phases 1 and 2) to design a standard quality system implementation plan that could be used by a small start-up class II medical device company to help assure CFR compliance and avoid Warning Letter issuance.

INDEX WORDS: 21CFR820; ISO13485:2003; Design Controls; CAPA; Complaint Files; Medical Devices; Quality System Regulation.

DEVELOPMENT OF A COMPREHENSIVE CGMP/QUALITY SYSTEM FOR CLASS II BIOMEDICAL DEVICE MANUFACTURING FACILITY

by

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DEDICATION

This thesis is dedicated to Daxa and our children Dhara and Darpan for all their time and support.

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ABBREVIATIONS

FDA	Food and Drug Administration; also referred to as Agency
CDRH	Center for Devices and Radiological Health
ICH	The International Conference on Harmonization (ICH)
ISP	International Organization for Standardization (ISO)
cGMP	Current Good Manufacturing Practices (cGMP)
QS	Quality Systems
CFR	Code of Federal Regulations
QSR	Quality System Regulation
CAPA	Corrective and Preventive Action
SOP	Standard Operating Procedure
P&PC	Production and Process Controls
DSMA	Division of Small Manufacturers Assistance
RAPS	Regulatory Affairs Professional Society
ISO	International Organization for Standardization
MDR	Medical Device Reporting
TCON	Teleconference

1 CHAPTER- Overview

1.1. Introduction

FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States. The long legal odyssey towards implementing medical device regulations began with the Food and Drugs Act (FD&C Act) of 1906.[1] Medical devices were not included in the FD&C Act of 1906 as no one in those times could have envisioned how the increasing complexity of such technology would eventually necessitate regulations. Since then, technological advances have required the FDA to include regulations pertaining to medical devices.

Devices were first regulated by FDA in 1976 under the Medical Device Amendments (known as the Amendments). Prior to that time, devices were subject only to the adulteration and misbranding provisions of the FD&C Act.[2] The Amendments established medical device safety and effectiveness requirements and placed devices into three classifications- Class I, II, and class III- based upon their inherent risk and benefits. Each class imposes an increased level of risks and benefits. The following is a brief overview of medical device classes defined in this Amendment[3]:

Class I devices present a low risk of harm to the user and are subject to general controls that are sufficient to protect the user. Most are exempt from the regulatory process.

[1] http://coursesa.matrix.msu.edu/~hst203/documents/pure.html - accessed 09 November 2010
[2] Fundamentals of US Regulatory Affairs-Fifth Edition; pg 155
[3] http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/default.htm - accessed 09 November 2010

Examples: non-powered breast pumps, elastic bandages, tongue depressors, examination gloves, most hearing aids, arm slings, microbial analyzers, keratoscopes

Class II devices are more complicated and require special controls for labeling, guidance, tracking, design, performance standards, and postmarket monitoring. Most require Premarket Notification 510(k).

Examples: powered wheelchairs, CT scanners, contact lens care products, topical antimicrobial skin cleanser and wound moisturizing solutions, endolymphatic shunts

Class III devices usually sustain or support life, are implanted, or present potential unreasonable risk of illness or injury. They have the toughest regulatory controls. Most of these devices require Premarket Approval because general and special controls alone cannot reasonably assure their safety and effectiveness.

Examples: pacemakers, implanted weight loss devices, non-invasive glucose testing devices, medical imaging analyzers, cochlear implants, breast implants

The passing of the Safe Medical Device Act of 1990 (SMDA) strengthened the FDA's regulatory authority over the medical device industry. Specifically, the SMDA established Quality System requirements for device manufacturers.[4]

The SMDA of 1990 indicated that manufacturers must establish and follow quality systems to help ensure that their products consistently meet applicable requirements and specifications. The quality systems approach for FDA-regulated products (food, drugs, biologics, and devices) is known as current good manufacturing practices (CGMP's). The medical device CGMP

[4] http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHTransparency/ucm203018.htm - accessed 02 November 2010

regulations were identified as the Quality System Regulation (QSR). In June 1, 1997 the agency harmonized the quality system regulation in Code of Federal Regulations (CFR) section 21 Part 820 with the requirements for quality systems. The CFR contains the complete and official text of agency regulations. The CGMP requirements for devices are provided in 21 CFR Part 820 (Part 820), and are applicable to manufacturers, packagers, labelers, distributors, and analytical testing facilities. This Part 820 establishes basic requirements applicable to manufacturers of finished medical devices [5]

The QSR as defined in 21 CFR Part 820 apply regardless of the types of devices meaning they embraces the same "umbrella" approach as the CGMP regulation and must apply to many different types of devices. According to 21 CFR Part 820, manufacturers must establish and follow quality systems to help ensure that their products consistently meet applicable requirements and specifications. The regulations provide a framework as to what is required, (i.e. establishment of written procedures and policies, process controls, etc); The manufacturer, packager or labeler must define how compliance can be achieved.

1.2. Overview of Quality System Model and Analyses of Compliance Status

The FDA QSR for devices is depicted in Figure 1 and is presented in this paper from a Guide to Inspections of Quality Systems.[6] According to the Inspection of Medical Device Manufacturers-Manual 7382_845, although the Quality System regulation has seven subsystems, the following four subsystems are considered major subsystems and are the basic foundation of a firm's quality system: Management Controls, Design Controls, Corrective and Preventive Actions (CAPA), and Production and Process Controls (P&PC). The three remaining subsystems (Facilities and

[5] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820&showFR=1 – accessed 12 January 2011.
[6] http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm

Equipment Controls, Materials Controls and Document/Records/Change Controls) cut across a firm's quality system.[7] Though not depicted in figure 1, The Document/Records/Change Controls component of the quality system includes Device master record, Device history record, Quality system record, and Complaint files.

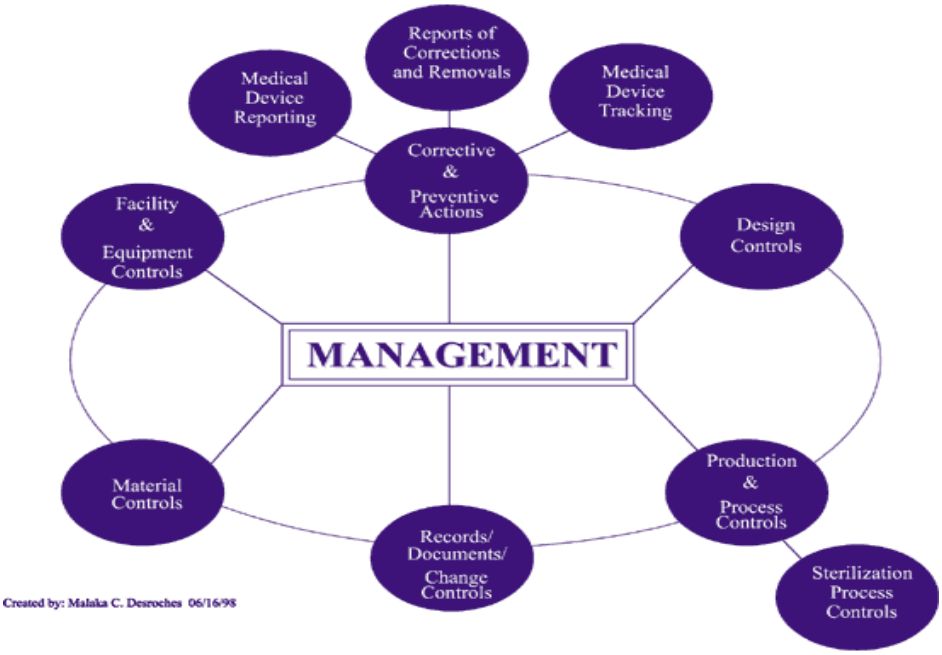


Figure 1.1: Seven subsystems with related satellite programs

For a successful inspection at a small start up Device Company, it is critical that the above mentioned Quality System is established that meets the 21 CFR 820 requirements. According to the FDA compliance program manual (7382.845) inspection level correlates with the type of inspection intended as mentioned in the table below. FDA determines which area of the quality system should be inspected to meet the need of each particular inspection. Based on the guide to

[7] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072753.htm - accessed 09 November 2010

inspections mentioned in the Manual 7382.845 the FDA would inspect CAPA, Production and Process Controls (P&PC) and/or Design Controls during any level of the inspection.[8]

Inspection Level	Type of Inspection	Guide to Inspections
1	Abbreviated	QSIT – Two subsystems; Corrective and Preventive Actions (CAPA) plus Production and Process Controls (P&PC) or Design Controls
2	Comprehensive	QSIT - The four major subsystems; Management Controls, Design Controls, CAPA and P&PC
3	Compliance Follow-up	As directed by inspectional guidance and elements of QSIT

In order to develop a focused implementation plan it was important to determine the current compliance status of medical device manufacturers and the areas of focus for the regulatory authorities.

Therefore, the researcher performed a preliminary risk assessment exercise by conducting a brief survey of Warning Letters that FDA issued to medical device manufacturers specifically for CGMP/QSR violations spanning six months from January to June in 2010. A Warning Letter is typically issued for significant regulatory violations that require prompt and adequate corrective actions[9]. The use of Warning Letters and the prior notice policy such as observations issued in the form 483, are based on the expectation that most individuals and firms will voluntarily comply with the law[10]. However, if a firm does not comply with the law, the FDA may seek use of its judicial tools (such as seizure, injunction, civil money penalties or

[8] Inspection of Medical Device Manufacturers- Compliance Program Manual 7382.845, Completion Date- 30 September 2004

[9] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090279.htm - accessed 12 February 2011.

[10] http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htm - accessed 08 November 2010.

prosecution). The intent for surveying the Warning Letters for this study was to assess and identify what type of violations the FDA identified and noted in Warning Letters. FDA issued Warning Letters to twenty eight device manufacturers during the first six months of year 2010. Each Warning Letter was reviewed and areas of concern grouped by appropriate quality systems. Based on the data collected through this initial risk assessment process it became evident that the highest number of violations affected the following areas of quality systems:[11]

1. Receiving, in-process, and finished device acceptance:

Failure to establish and maintain procedures describing inspection, testing, verification and acceptance of incoming product. Failure to describe procedures for acceptance/rejection of the material. Inadequate procedures for productions documents including handling of in-process materials as required by 21 CFR § 820.80.

2. Corrective and preventive action:

Failure to establish and maintain procedures for implementing corrective and preventive action (CAPA) as required by 21 CFR § 820.100(a).

3. Complaint files:

Failure to maintain complete complaint files and complete complaint handling procedures (21 C.F.R. § 820.198).

However, the preliminary assessment and resulting data came from a feasibility study analysis of only six months of Warning Letters. To more clearly examine and verify the preliminary findings, a further analysis was warranted and additional Warning Letters from last three years (January 2008 thru August 2010) were analyzed and used for the development of comprehensive quality system implementation plan to meet the FDA regulations. Using

[11] Thesis Plan- Developing a Comprehensive cGMP/Quality System Implementation Plan to Meet the FDA Regulations for Class II Medical Devices"- Date: 02 Aug 2010

methodological approaches described in "The concept of action learning- by Ortrun Zuber-Skerritt"[12] and by Bob Dick titled "Postgraduate programs using action research"[13] the researcher employed a similar qualitative action research methodology to gather additional information needed for the study

1.3. Research Methodology

According to the publication titled "The concept of action learning"- by Ortrun Zuber-Skerritt[14] action research typically involves learning from experience. This approach can be further elaborated via critical reflection—through discussion, trial and error, discovery, and learning from and with each other. As stated above, to get more concrete analyses of data the researcher analyzed Warning Letters from January 2008 through August 2010 and compiled the information in table form in Appendix 1 to identify any trends and the number of violations issued to the medical device companies. After compiling this information from Warning Letters, the investigator evaluated each violation by the CFR reference and categorized them by quality system, followed by subcategory within the quality system. Based on the review of Warning Letters it was evident that the FDA is focused on Design Controls, Corrective and Preventive Action, and Complaint files of the quality system. The Complaint Files is a part of quality system called Records/Documentation/Change Controls. The purpose of this research is to develop a comprehensive quality system implementation plan for a small start up company. Therefore, focus was given to identify the areas of frequent deficiencies within these three quality systems as well as to include the requirements pertaining to the facility and equipment system.

[12] http://emeraldinsight.com/0969-6474.htm
[13] http://www.emeraldinsight.com/0969-6474.htm
[14] http://emeraldinsight.com/0969-6474.htm

Furthermore, according to the article by Bob Dick titled "Postgraduate programs using action research"[15] the action research allows one to learn from experience.

A human research application DHHS Assurance No.: FWA00003901 was submitted to the Human Subjects Office at University of Georgia for Investigational Review Board approval. The human subject application also contained subsequent attachments for Investigational Review Board to approve were the Information Letter (Appendix 2), Interview Questions (Appendix 1) and Consent Form (Appendix 4). After the human subject application and supporting documents were approved the researcher contacted experts in the medical device industry and interviewed them to get more evidence and to clarify findings from the Warning Letter analysis. Interview questions were designed based on information from the trend analyses of Warning Letters. Each participant was interviewed for about 60 minutes and requested to answer the previously validated questions. Interviews were audio recorded and then used to carefully document the feedback from each expert. The experts' opinions were then summarized in a table using a comparative analysis approach (Table 4-1:, Table 4-2, and Table 4-3). Commonly identified gaps in certain areas by the participants were used as the basis for determining major concerns for violations. These gaps were then included in the implementation plan to ensure the gaps are addressed so small start up device companies could establish a robust quality system.

1.4. Hypothesis

It is industry knowledge that in the past, during the surveillance inspection, the Agency used to inspect records pertaining to a product specific system rather than the entire quality system, thus limiting the risk to that specific product. For example, during the surveillance inspection, the

[15] http://www.emeraldinsight.com/0969-6474.htm

Agency used the "bottom-up" approach, which focused on specific problems associated with one or more individual product.

In recent years, however, the Agency has adopted a risk based quality system approach when inspecting a manufacturing facility.[16] Because of this approach, manufacturers must ensure that all quality systems are in compliance at all times. Products are at risk if the quality system fails to meet regulatory requirements by not controlling the process of manufacture. It is important that manufacturers maintain the quality systems after they are established and implemented. The manufacturer should assure adequacy of the quality systems during periods of growth and process or product changes. This can be ensured by following the plan outlined in the last section of this thesis.

[16] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072753.htm#p3 – accessed 15 November 2010

2 CHAPTER - Quality Systems and Risk Assessment

2.1. Description of Quality Systems for Devices

Quality system regulations include requirements related to the methods used in and the facilities and controls used for: designing, purchasing, manufacturing, packaging, labeling, storing, installing and servicing of all types of medical devices in accordance with 21 CFR Part 820 and its description in the QSIT Manual[17]. The minimum requirements for the components listed below are further explained in the following chapters based on the findings from the review of Warning Letters and the information gathered from the interviews.

Each quality system is briefly described below per QSIT Manual:[18]

Corrective and Preventive Actions

The purpose of the corrective and preventive action subsystem is to collect information, analyze information, identify and investigate product and quality problems, and take appropriate and effective corrective and/or preventive actions to prevent their recurrence.

Design Controls

The purpose of the design control subsystem is to control the design process to assure that devices meet user needs, intended uses, and specified requirements. Attention to design and development planning, identifying design inputs, developing design outputs, verifying that design outputs meet design inputs, validating the design, controlling design changes, reviewing design results, transferring the design to production, and compiling a design history file help assure that resulting designs will meet user needs, intended uses and requirements.

[17]Guide to Inspections of Quality Systems http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm - accessed 15 November 2010

[18]Guide to Inspections of Quality Systems http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm - accessed 15 November 2010

Records/Documentation/Change Controls

This system covers activities and procedures that apply to: design; components, including software; labeling and packaging; device manufacturing processes; production equipment; manufacturing materials; and all associated documentation such as quality system procedures, standard operating procedures, quality acceptance procedures and data forms, and product-specific documentation. Change control should also be applied to any production aids such as labeled photographs and models or samples of assemblies and finished devices. Handling of product complaint files is also the part of this component.

Facility and Equipment Controls

Facility should be of suitable design and contain sufficient space to perform necessary operations, prevent mixups, and assure orderly handling. All equipments used in the manufacturing process must meet specified requirements and be appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use.

Management Responsibility

As can be seen in Figure 1: *Seven subsystems with related satellite programs* the Management component is depicted in the center of the quality system because executive management team shall appoint a member from among themselves who will have authority over and responsibility for:

- Ensuring that quality system requirements are effectively established and effectively maintained; and
- Reporting the performance of the quality system to executive management.

Material Controls

“Manufacturing material" is any material or substance used to facilitate the manufacturing process or used during the manufacturing process in the form of a concomitant constituent or byproduct constituent that is present in or on the finished device as a residue or impurity not by design or intent of the manufacturer. Examples of manufacturing materials include: cleaning agents, mold-release agents, lubricating oil, or other substances used to facilitate a manufacturing process which were not intended by the manufacturer to be included in the finished device.

Production and Process Controls

The purpose of the production and process control subsystem is to manufacture products that meet specifications. Developing processes that produce devices that meet specifications, validating (or fully verifying the results of) those processes, and monitoring and controlling the processes are all steps that help assure that the resultant devices will meet specifications.

Each of these components requires specific information about the product cycle from development to manufacturing and postmarketing activities. Each component is also interrelated as to manage the quality system that meets the quality system regulations. Therefore, complying with quality systems regulations is a complex regulatory process. This is further confirmed by the results from the researcher's literature review in trending violations issued in recent years of Warning Letters to the medical device companies.

2.2. Risk Assessment

Quality risk assessment process consists of the identification of problems and the analysis and evaluation of risks associated with exposure to those problems. Based on the preliminary analysis of Warning Letters described under Section 1.2 the risk of issuance of recurring violations of quality systems was evident. Therefore, in order to develop a robust quality system implementation plan it was necessary to identify the problem linked to quality system. It was prudent to evaluate the current trend in compliance status as well as the FDA's current focus during the quality system inspections. Based on the trend seen from the preliminary analysis of Warning Letters from first six months of 2010, the researcher expanded the review of Warning Letters to about last three years. Findings from the analysis of Warning Letters were used to determine specific questions to discuss with the experts in medical device companies. This action research methodology helped evaluate the risk and seek for remedies from the well experienced experts from the device industry. In summary this risk assessment was comprised of the following three steps:

1. Review of literature such as FDA periodic news for recent trend in the device industry from compliance perspective;
2. Comprehensive analysis of the FDA Warning Letters issued to medical device manufacturers from last three years to look for trends; and
3. Interviewing experts to determine best practices.

Data generated from the research methods were subsequently analyzed and used to develop a comprehensive cGMP/QS implementation plan to meet FDA regulations for class II devices.

During the literature review it was noted that medical device recalls have escalated in the last few years. For example, in a recent article from *The Silver Sheet*- May 2010 "*FDA Worried*

That Class I Recall Jump Reflects Industry Rush To Market" the FDA raised concerns due to a recent spike in recalls, questioning whether manufacturers are sacrificing quality to rush products to the market. The FDA is in the process of examining recall data to specify where recalls occur, the reason for recalls, and their classification criteria. However, manufacturers have the principal duty to ensure the quality and the integrity of their products. [19]

To understand this recall trend, the researcher hypothesized that FDA issued Warning Letters could be indicative of the factors involved. Individual Warning Letters from years 1996 to present are available on the FDA Web Site[20]. Therefore, the investigator decided to review historical data from January 2008 through August 2010 to determine current trends in the FDA's expectations, including a delineation of the quality systems focused on during inspection.

The objective of this study was to perform a qualitative methodological analysis of the relevant literature and review Warning Letters and information collected from interviews of industry experts to develop a suggested implementation plan for a small start-up biomedical device manufacturer.

The Warning Letters were accessed from the *FDA Web Home Page*[21] by clicking *Warning Letters* on the main page. Then on the Warning Letters page[22] the researcher selected a year and retrieved the Warning Letters specifically issued to the medical device company for CGMP/QSR/ Manufacture/Packing/Storage/ Installation/Adulterated. The researcher copied each violation listed in the Warning Letters from January 2008 through August 2010 and

[19]"The Silver Sheet" - May, 2010 - May, 2010
[20]Warning Letters available on FDA site- http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm - accessed 15 November 2010
[21]FDA Home Page: http://www.fda.gov/ - accessed on 15 November 2010
[22]Warning Letter page on the FDA web site: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm - accessed 15 November 2010

compiled the following information in a table form in Appendix 1. The table categories included:

- Date Warning Letter issued,
- Company names, and
- Specific violation(s).

After compilation of the information from Warning Letters, the investigator categorized each violation by CFR reference and grouped by number of violations per quality systems. Then calculated how many times the violations were issued to the each quality system (Appendix 1). The investigator further categorized the group of violations by subcategory within the quality system as below:

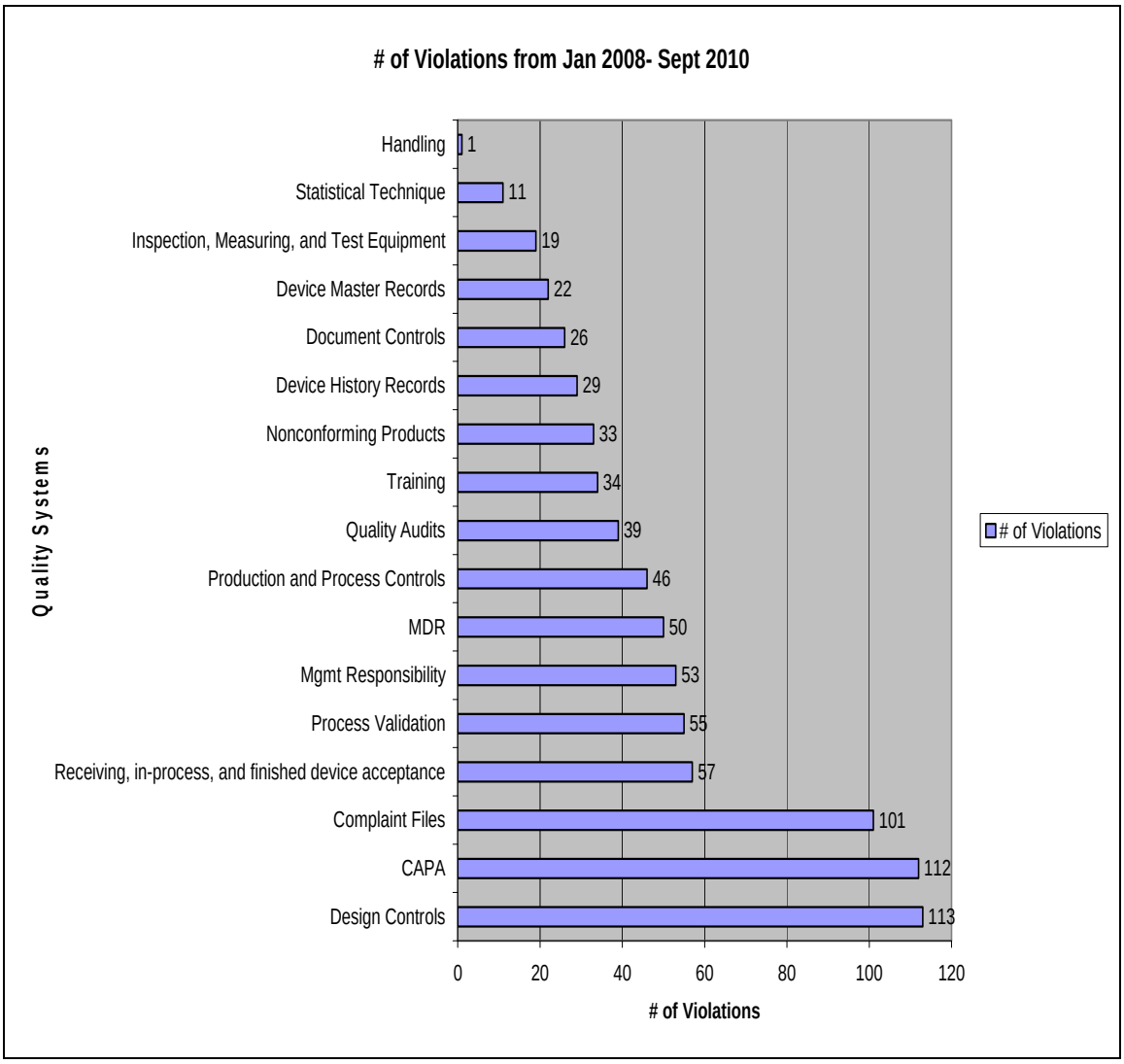
- Tabulated each violation by subcategory,
- Calculated how many time violations were issued to the same CFR reference, and
- Graphed the results using excel to show number of violations issued within each quality system.

Analysis of the FDA Warning Letters helped identify the most common problems with device manufacturing quality systems and the most prevalent violations. There were a total of 120 companies cited for violations by the FDA in the areas of CGMP/QSR/ Manufacture/ Packing/Storage/ Installation/Adulterated during the investigated period. Compilation of these violations and the information grouped by number of violations per quality system is provided in Table 2-1. The data sets in Table 2-1 were labeled as 'quality system', 'Number of Violations' and 'Percent'.

Table 2-1: 21CFR Part 820- Number of Violations from January 2008 thru August 2010

Quality Systems	# of Violations	%
Design Controls- 820.30	113	14
CAPA- 820.100	112	14
Complaint Files- 820.198	101	13
Receiving, in-process, and finished device acceptance- 820.80	57	7
Process Validation- 820.75	55	7
Management Responsibility- 820.20	53	7
Medical Device Reporting- 803	50	6
Production and Process Controls- 820.70	46	6
Quality Audits- 820.22	39	5
Personnel/Training- 820.25	34	4
Nonconforming Products- 820.90	33	4
Device History Records- 820.184	29	4
Document Controls- 820.40	26	3
Device Master Records- 820.181	22	3
Inspection, Measuring, and Test Equipment- 820.72	19	2
Statistical Technique- 820.250	11	1
Handling- 820.140	1	0
Total number of violations observed	801	100

To represent this compilation of data in a graphical presentation researcher created the following graphs using Microsoft Excel by entering the two sets of data in excel sheet from Table 2-1 above. In the Excel sheet selected the type of graph as bar graph. Under Chart Options tab entered Titles and labeled X and Y-axis, under Data Labels tab selected Value option to display number of violations per quality system.



Graph 2-1: 21 CFR Part 820- Number of violations from January 2008 thru August 2010

In summary, this comprehensive risk assessment exercise, to review two years worth of data, was conducted to identify quality systems the FDA tends to focus on during the inspection. From the review of Warning Letters it was observed that the maximum numbers of violations were associated with the following areas:

1. Design Controls;
2. Corrective and Preventive Action (CAPA); and
3. Complaint files (components of Records system per 21 CFR Part 820).

Findings from the comprehensive risk assessment is inconsistent with the information collected from preliminary assessment by reviewing six months worth of data, as explained in Chapter 1.2, The preliminary assessment showed maximum numbers of violations associated with top three areas as (1) Receiving, in-process, and finished device acceptance; (2) CAPA; and (3) Complaint files. Whereas, review of more than two years worth of data, showed top three maximum numbers of violations associated with the (1) Design Controls; (2) CAPA; and (3) Complaint files.

Other systems that had relatively higher number of violations were associated with Receiving, in-process, and finished device acceptance; Process Validation; Management Responsibility; Production and Process Controls; Employee Training; Change Control; and Documents Management. And the lowest numbers of violations were in the area of preventing mixups, damage, deterioration, contamination, or other adverse effects to product during handling.

According to the findings from the comprehensive review of the Warning Letters and as demonstrated in the Table 2-1, focus was given to identify the gaps in the area of the quality system. The summary of Warning Letters above suggests that the FDA will pay greater attention to Design Controls, Corrective and Preventive Action, and Complaint files or those companies have the most problems complying with design controls, which include activities from development through post-marketing design changes. Therefore, it was evident based on the findings, there were recurring violations affecting the medical device from development through post marketing.

With these data in mind, emphasis was given to these three systems during the research to understand the cause of recurring violations affecting these quality systems. In order to

determine the specific area that may be the reason for recurring violations within each of these three quality systems, the researcher tabulated each violation by subcategory in the specific quality system. The three graphs below demonstrate the areas within these quality systems that accounted for the majority of violations. Further analysis of each of these quality systems was performed with the intent of determining if there was any specific area that was inadequate in these three quality systems.

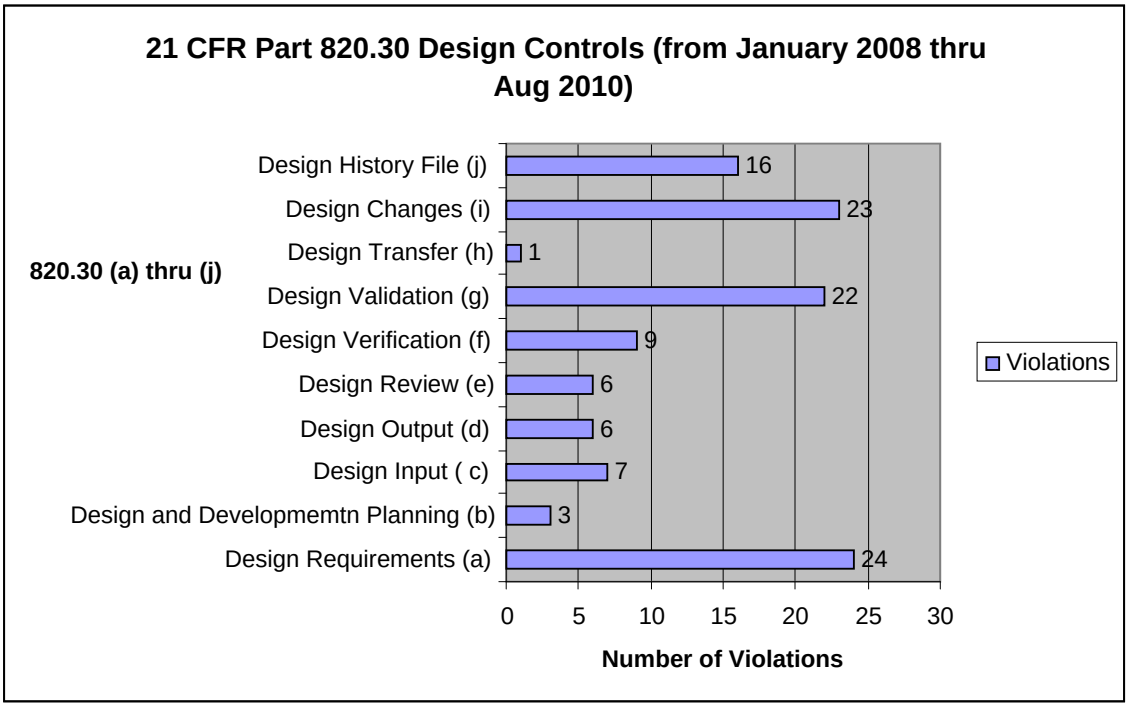
2.2.1 Design Controls

Design Control represented the quality system with the highest number of violations observed by the researcher during the two years worth of retroactive Warning Letter data. The investigator further categorized the group of violations associated with the Design Controls by subcategory within the 21 CFR 820.30(a) thru (j). Compilation of these violations and the information grouped by number of violations per subcategory is provided in Table 2-2. The data sets in Table 2-2 were labeled as subcategory of Design Controls- 820.30 (a) thru (j), Number of Violations, and Percent calculated using the total number of violations.

Table 2-2: Part 820.30 (Design Control) - Number of Violations per Subcategory

Design Controls- 820.30 (a) thru (j)	**# of Violations**	**%**
Design Requirements (a)	24	20
Design and Development Planning (b)	3	3
Design Input (c)	7	6
Design Output (d)	6	5
Design Review (e)	6	5
Design Verification (f)	9	8
Design Validation (g)	22	19
Design Transfer (h)	1	1
Design Changes (i)	23	20

Design History File (j)	16	13
Total number of violations	117	100



Graph 2-2: Part 820.30 Number of Violations per Subcategory

As reflected in Graph 2-2 the top three most violated Design Control subsections were 820.30(a)- device design requirements, 820.30 (i)- design changes, and 820.30(g)- design validation. These findings are important since they help determine the specific area FDA issued violations within the Design Control system. With knowledge gained from the review of Warning Letters and the quality system regulations from 21 CFR Part 820.30, the researcher outlined the potential problems below which may have contributed for highest number of violations issued to these three subcategories. Moreover, to increase validity of the Design Control retrospective review, the observations were further discussed with the experts in industry during the interviews and their opinions and recommendations have been provided in the Chapter 4.

Design Requirements [820.30(a)]

1. Failed to determine the user/patients requirements;
2. Failed to meet regulatory requirements and standards;
3. Failed to develop specifications for the device and the released device failed to meet specification;
4. Failed to establish procedure for the selection and evaluation of components and suppliers;
5. Failed to establish procedure for the development and approval of product labels and user instructions;
6. Failed to develop adequate in-process controls and specifications for manufacturing processes;
7. Failed to demonstrate safety and performance of prototype and final devices;
8. Lacked compatibility data with the environment and other devices;
9. Failed to specify manufacturing facilities and utilities necessary to manufacture the finished device;
10. Failed to develop and validate manufacturing processes;
11. Failed to train employees;
12. Failed to document the details of the device design and processes;
13. Lacked procedure identifying organizational responsibilities with respect to assuring quality during the design requirements and development phase;

Design Changes [820.30(i)]

The higher number of violations observed in this subcategory may be comprised of failure to follow two main administrative components handling design changes:

Document control—consists of design documents (e.g. drawings and other items of design input or output), and tracking their status and revision history.

Change control—covers deficiencies and corrective actions arising from verification and review of the design, and tracking their resolution prior to design transfer. More specifically design change violations included failure in the following areas:

1. Failed to maintain manufacturing and testing documents (e.g. manufacturing batch records, analytical procedures, packaging records, investigations, protocols, reports, etc) with specific identification in accordance with some logical scheme which links the documents to the product or component they described or depicted and illuminated the drawing hierarchy;
2. Failed to maintain a master list or index of documents such as device prototypes, device history files, components specifications, design requirements and specifications, approved manufacturing and analytical documents, etc;
3. Lacked approved procedure which govern entry of documents into the document control system;
4. Failed to maintain a history of document revisions and lack of procedure for removal and deletion of obsolete documents;
5. Failed to maintain procedure for the design problem reporting and review process;

6. Failed to follow procedure to accept, reject, or defer a change request and corrective and preventive actions; and
7. Lacked adequate procedure defining process for when to revise documents affected by a change order and updates of appropriate design documentation that accurately reflect the revised design.

Device Design [820.30(g)]

Higher number of violations observed in this subcategory may be comprised of failure in the follow areas:

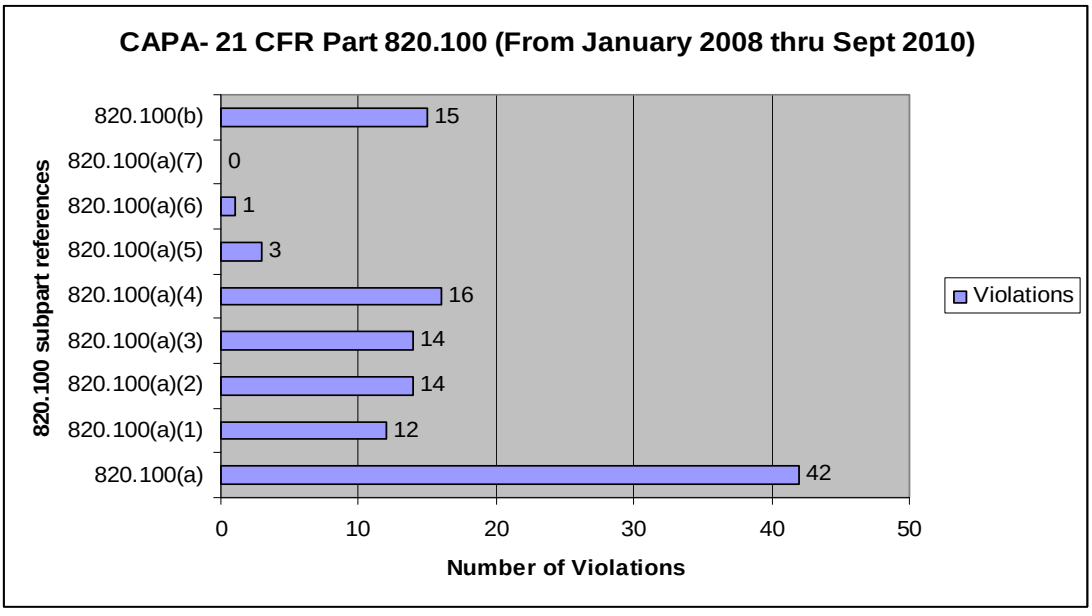
1. Failed to establish validation methods and acceptance criteria;
2. Lacked appropriate information in the validation plan and not reviewed for appropriateness, completeness, and failed to ensure that end user needs and intended uses are addressed;
3. Validation failed to address product packaging and labeling;
4. Validation failed to include simulation of the expected environmental conditions, such as temperature, humidity, shock and vibration, corrosive atmospheres, etc.

2.2.2 CAPA

CAPA had the second highest violations observed by the researcher during the two years worth of retroactive Warning Letter data. The investigator categorized the group of violations associated with the CAPA system by subcategory within the 21 CFR 820.100(a)(1) thru (7) and (b). Compilation of these violations and the information grouped by number of violations per subcategory is provided in Table 2-3. The data sets in Table 2-3 were labeled as subcategory of CAPA- 820.100(a) (1) thru (7) and (b), Number of Violations, and Percent calculated using the total number of violations.

Table 2-3: Part 820.100 (CAPA) - Number of Violations per Subcategory

CAPA- 820.100 (a) (1) thru (7) and (b)	# of Violations	%
820.100(a)- Establish and maintain procedures	42	36
820.100(a)(1) – Analyzing the quality problems	12	10
820.100(a)(2) – Investigating the cause of failure	14	12
820.100(a)(3) – Identifying the actions for CAPA	14	12
820.100(a)(4) – Verifying/validating the CAPA	16	14
820.100(a)(5) – Implementation of CAPA	3	3
820.100(a)(6) – CAPA related communication	1	1
820.100(a)(7) – Management review of CAPA	0	0
820.100(b) – CAPA related documentation	15	13
Total number of violations	117	100



Graph 2-3: Part 820.100 (CAPA) - Number of Violations per Subcategory

Table 2-3 above shows that subsection 820.100(a) had the most violations for not having establishment and maintain procedures for implementing Corrective and Preventive Actions. Other prominent CAPA violations were subsections 820.100(a)(4) and 820.100(b), which involved failure to verify, validate and document CAPA related activities to ensure that such action is effective and does not adversely affect the finished device.

The following list provides potential deficiencies for the companies within this quality system that may have caused the higher number of CAPA violations. These observations were further discussed with the experts in industry during the interviews and their opinions and recommendations are further described in Chapter 4.

1. Failed to establish methods and procedures to input product or quality problems into the CAPA subsystem.
2. Failed to establish and maintain procedures identifying product and quality problems that may require preventive action and failure to perform periodic review of historical records such as trending data, corrective actions, acceptance activities (component history records, process control records, finished device testing, etc.) and other quality system records for unfavorable trends.
3. Lacked procedures for conducting failure investigations and failed to include provisions for identifying the failure modes, determining the significance of the failure modes, the rationale for determining if a failure analysis should be conducted as part of the investigation, and the depth of the failure analysis. Failed to issue and close of deviation, proper documentation in change control system

4. Failed to establish a preventive action procedure that describes how to identify potential problems and root causes, assess possible consequences, and actions to be considered.

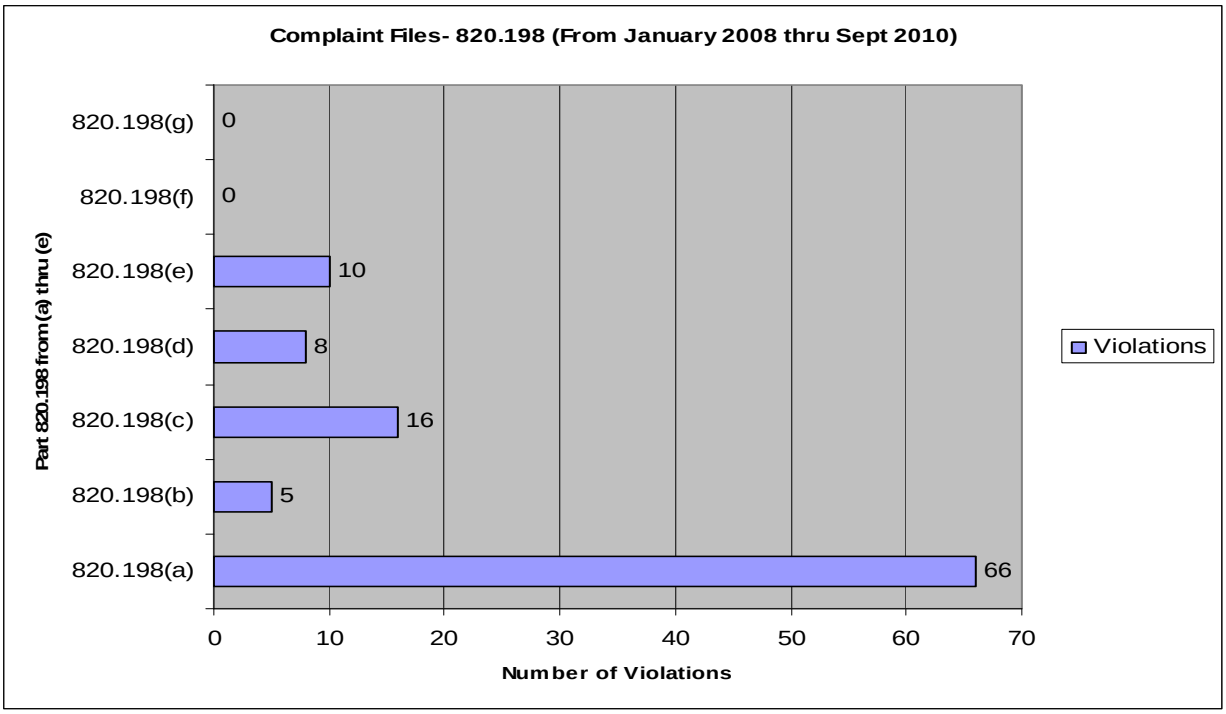
5. Failed to follow procedure for the implementation, evaluation and documentation of the preventative action, and processes to monitor the effectiveness of the action.

2.2.3 Complaint Files

The third highest number of violations FDA issued was with regards to the Complaint Files. Complaint files are a component of the quality system named Records/Documentation. The investigator categorized the group of violations associated with the Complaint files by subcategory within the 21 CFR 820.198(a) thru (f). Compilation of these violations and the information grouped by number of violations per subcategory is provided in Table 2-4. The data sets in Table 2-4 were labeled as subcategory of Complaint files- 820.198(a) thru (f), Number of Violations, and Percent.

Table 2-4: Part 820.198 (Complaint Files) - Number of Violations per Subcategory

Complaint Files- 820.198(a) thru (f)	# of Violations	%
820.198(a) – Procedure for handling and maintaining complaint files	66	63
820.198(b) – Procedure describing a need for investigation	5	5
820.198(c) – Handling of a complaints due to device failure	16	15
820.198(d) – Procedure for reporting of an event	8	8
820.198(e) – Maintenance of investigation records	10	10
820.198(f) – Accessibility of investigated complaints and the records	0	0
Total number of violations	105	100



Graph 2-4: Part 820.198 (Complaint files) - Number of Violations per Subcategory

Graph 2-4 demonstrates that the majority of the violations were for the subcategory of [820.198(a)] where manufacturers failed to maintain complaint files, failed to process complaints in a uniform and timely manner [820.198(a)(1)]; and failed to report complaints to the FDA per Medical Device Reporting requirements [820.198(a)(3)]. The following list provides potential deficiencies for the companies within this quality system that may have caused the higher number of Complaint files violations. FDA issuance of violations to these areas was further discussed with the participants during the interviews to learn how to mitigate this risk.

1. Failed to properly train personnel to adequately perform their duties and employees lacked proper education and training to process complaints;
2. Failed to log, record, categorize, file complaint records, and any relevant data.

3. Failed to establish a procedure that clearly describes handling of the complaints, reporting of events to the FDA, and defining categories for resolution and record-keeping;

4. Lacked effective complaint investigation procedure;

Graphical presentation of the findings above depicted the weak areas in each of the quality systems discussed above.

Based on these findings the researcher focused, while interviewing the experts in the device industry, on getting in depth perspective on these gaps such as why there were recurring violations in these three specific systems and how the resultant risk could be mitigated. In order to get experts' opinion on these findings of recurring violations, the researcher interviewed four experts, each of which had a very thorough understanding of quality systems. Prior to contacting prospective participants, the prospected participant researcher had approval from the Investigational Review Board to conduct the human participation research. The following section summarizes information gathered from each participant and their recommendations/ suggestions for each of these three quality systems.

3 CHAPTER - Research Methodology and IRB Process

3.1. Research Methodology

Researcher employed qualitative action research methodology and conducted structured interviews of carefully selected four experts in the device industry. Each participant had number of years experience in medical device company. Input from participants was important based on their experience with quality systems to develop a robust quality system implementation plan. Discussion of issue with the experts was an active way of learning from their experience. This methodology helped obtain experts' perspective how to mitigate the risk of recurring violations observed from data analysis. Each participant was interviewed approximately 60 minutes and the interviews were audio recorded for careful analysis for research purpose.

In order to systematically analyze information from interviews, researcher employed the constant comparative method as recommended for this type of research in the articles "Teaching the analysis of textual data: an experiential approach" by Phillip Burnard [23] and "Enthnographic Research and the Problem of Data Reduction" by Judith Preissle Goetz and Margaret D. LeCompte[24]. Researcher transcribed quotes of recommendations or opinions from each interview specific to the issues discussed about three quality systems and documented information in two columns identified as 'Participants' and 'Recommendations/Opinions.' All data relevant to each category (Design Control, CAPA, and Complaint files) were identified and examined using the constant comparison, in which each recommendation or opinion was checked or compared with all other data to determine common findings per categories or quality system.

[23] Teaching the analysis of textual data: an experiential approach by Phillip Burnard; Nurse Education Today (1996) 16, 278-281

[24] Enthnographic Research and the Problem of Data Reduction by Judith Preissle Goetz and Margaret D. LeCompte; Anthropology &Education Quarterly, Vol. 12, No. 1, Issues in Social Ethnography (Spring, 1981), pp. 51-70

3.2. IRB Process

A qualitative action research methodology was used to gather interview data from experts in the device industry. Action research methodology typically involves learning from experience using critical reflection—through discussion, trial and error, discovery, and learning from and with each other.[25] This action research methodology approach allowed the researcher to discuss findings from the risk assessment exercise described in Section 2.2 with the experts in the device industry. Interview questions were designed based on the findings from the analyses of Warning Letters and to reduce the variability in information obtained from the interviews, each interview question was field tested with either a co-worker of the researcher who was working within the healthcare industry, with someone who is familiar with the subject, or with fellow students who had conducted research before. The order and content of questions were kept the same for all participants.

3.3. Selection of Participants

Participants were carefully selected by following the strict IRB approved inclusion/exclusion criteria listed below:

List of inclusion criteria:

- Must have experience in the biomedical device industry
- Must have worked in the biomedical device industry and have minimum of two years experience in the relevant area
- Must have/had worked in quality assurance, regulatory affairs or validation department in the industry. Work experience information was collected based on the series of questions listed in Section 2 in this document.

[25] http://emeraldinsight.com/0969-6474.htm

- Must have access to e-mail and/or telephone

List of exclusion criteria:

- Regulatory Affairs professional and/or Quality Assurance experts with less than two years of experience in industry

One of the participants was a Vice President of a medical device company; where as the other three participants were at a Director level in the quality department at different companies. The purpose of interviewing experts in the field was to identify the concerns noted in the previous sections from the analyses of Warning Letters and ultimately to discuss recurring violations associated with three quality systems (Design controls, CAPA, and Complaint files). This interview process was to obtain opinions on the best practices and the measures that should be taken to prevent the recurrence of violations in these three quality systems. The researcher employed a qualitative action research methodology for the information gathered through interviews.

3.4. Qualitative questions based interview process

The participants were either phone interviewed or face-to-face (approximately 60 minutes) and asked the same questions to eliminate variability of information gathered from various participants. It was not feasible to interview all participants face-to-face due to their locations in terms of distance. However, the investigator did not experience any major difference between the phone or face-to-face interview process in terms of collecting the research related information. Prior to interview researcher provided a copy of graphs presented in Section 2 to each participant to focus discussion related to three quality systems. Data during the interview were captured by handwritten notes and/or audio recordings and analyzed through close scrutiny of notes and audio files. From the audio files some of their recommendations or opinions was

transcribed in a text and provided in Appendix 5. Based on analyses of the data, the researcher identified gaps associated with these three systems and captured the findings in the implementation plan.

Background of Participants:

Participants have been working in the healthcare industry and have experience in the medical device industry for a number of years, with the exception of one participant. This participant did not work for a medical device company but has many years of experience in establishing and maintaining quality systems in the pharmaceutical industry. The following outlines brief background information of each participant, identified as Participant 1 thru 4:

Table 3-1: Participants Background Information

Background Information	Participant ID			
	1	2	3	4
Number of years experience	25	~9 years	30+	23
Size of Company/ Industry	Mid size/ Pharmaceuticals	Large/ Medical device	Large and Small/ Pharma and Medical device	Mid and Small/ Pharma and Medical device
Experience establishing QS	Yes	No	Yes	Yes
Optimizing QS to meet FDA regulations	Yes	Yes	Yes	Yes
Interview Process	Face-to-Face	TCON	TCON	Face-to-Face

4 CHAPTER – Findings from Action research

4.1. Method of Data Analysis

The researcher employed qualitative action research methodology and applied it for the following research activities:

1. Performed comprehensive review and analysis of the FDA Warning Letters issued to medical device manufacturers, and
2. Conducted structured interviews of carefully selected four experts in the device industry.

From the analysis of these Warning Letters the Researcher identified major areas of concern such as Design Controls, CAPA and Complaint files. Within the Warning Letters the FDA also listed some examples for deficiencies with references to the 21CFR820 explaining reasons for issuing violations to the device companies. For example, in one of the Warning Letters issued to Swiss American Products, Inc. dated 18 September 2008, FDA stated:

"Failure to establish and maintain adequate procedures for validating the device design to ensure that the device conforms to user needs and intended uses; that acceptance criteria are established prior to performing validation activities; that design risk analysis is conducted and documented; that testing of production units is conducted under actual or simulated use conditions; and that the design validation results are documented, as required by 21 C.F.R. § 820.30(g). Specifically,

a. During the design development of the Elta® Silver Antimicrobial Wound Gel, your firm has not validated the mixing process nor tested the finished devices to ensure that they contain the correct and homogenous silver nitrate concentration of **[redacted]** as

your firm verbally stated during the inspection and documented in your device labeling that was included in your firm's Supplement 1 of the 510(k) submission.

b. Your firm has not conducted and documented a risk analysis for the Elta® Silver Antimicrobial Wound Gel, where appropriate."

As stated in the Warning Letter above, Company official at Swiss American Products, Inc. may have thought the manufacturing process is simple and did not need to validate the mixing process. However, the FDA described violation in the Warning Letter for not validating the mixing process and not testing the finished devices to ensure that they contain the correct and homogenous silver nitrate concentration.

Similarly, the Warning Letters issued to 120 medical device companies during the period from January 2008 thru August 2010 included numerous examples and recommendations for violations affecting performance of Design Controls, CAPA, and Complaint files of the quality system. These examples provided interpretation of FDA regulations and included them as requirements in the implementation plan to prevent such deficiencies at the start up small medical device company. The researcher also discussed findings from the Warning Letters during the structured interviews with the experts in the device industry for their views for the recurrence of violations in the area of Design Controls, CAPA and Complaint files.

Each participant the Researcher interviewed had number of years experience in medical device company. Input from participants was important based on their experience with quality systems to develop a robust quality system implementation plan. Review of Warning Letters and discussion of the issue with the experts was an active way of learning about trends in the FDA data. The methodology helped obtain information from the Warning Letters by means of examples and experts' perspective about how to mitigate the risk of recurring violations

observed from data analysis. Each participant was interviewed approximately 60 minutes and the interviews were audio recorded for careful analysis for research purpose.

In order to systematically analyze information from interviews, researcher employed the constant comparative method as recommended for this type of research in the articles "Teaching the analysis of textual data: an experiential approach" by Phillip Burnard [26] and "Enthnographic Research and the Problem of Data Reduction" by Judith Preissle Goetz and Margaret D. LeCompte[27]. The researcher transcribed quotes of recommendations or opinions from each interview specific to the issues discussed about three quality systems and documented information in two columns identified as 'Participants' and 'Recommendations/Opinions'. All data relevant to each category (Design Control, CAPA, and Complaint files) were identified and examined using the constant comparison, in which each recommendation or opinion was checked or compared with all other data to determine common findings per categories or quality system.

4.2. Transcribed quotes from interviews

The following sections highlight key concepts identified from the interview analysis. In addition, sample sections copied from the interview transcripts are used as evidence to emphasize the primary interview findings. Please refer to the Appendix 5 for additional quotes from each participant.

[26] Teaching the analysis of textual data: an experiential approach by Phillip Burnard; Nurse Education Today (1996) 16, 278-281

[27] Enthnographic Research and the Problem of Data Reduction by Judith Preissle Goetz and Margaret D. LeCompte; Anthropology &Education Quarterly, Vol. 12, No. 1, Issues in Social Ethnography (Spring, 1981), pp. 51-70

4.2.1 Design Controls

Design controls are a component of a comprehensive quality system that covers the life of a device. The changes are part of a continuous, ongoing effort to design and develop a device that meets the needs of the user and/or patient. Thus, the design control process is revisited many times during the life of a product. The following were recommendations or opinions from experts for the handling of design controls:

Table 4-1: Design Controls- Summary of Interviews

Participants	Deficiencies /Remarks
1	o Lack of design of experiments and documentation of development work o Lack of management commitment o Companies push to finish through the development and manufacturing so they can start clinical studies and ultimately to the market to prove return on their investment Quotes from interview: "…..companies tend to push to finish through the development phase to start clinical studies and ultimately to the market to prove return on their investment….."
2	o Lack of organization of design plan and data generated during the design stage o Resource constraints within organization cause more issues in this system o Companies create so much information that it becomes overwhelming to manage the data. It is extra work but the imperative for the company is to prove return on investment as soon as possible and therefore companies push to finish through the development and manufacturing so they can

Participants	Deficiencies /Remarks
	prove return on their investment. o Medium to large companies may have procedures but may fail to follow, whereas small firms may fail to have design control procedures o Managing the information is important and there is software available to organize these information, but it costs money. Quote from interview: "…everybody wants to make product and move forward and that sort of thing it hurts intellectually, that you have to go back in time and figure out what we did wrong and try to fix it…it's all sort of backward thinking…"
3	o Information for each design change should be properly named and described so one can locate the information easily. o Lack of management commitment and lack of resources affects these systems not being managed well o Companies push to finish the development and manufacturing so they can start marketing the device and prove return on their investment. Company should have design/quality plan per product or an overall quality plan that may have sections (e.g. sterilization process, SOPs, validation and qualification plan.) o When FDA visits companies for inspection they tend to look more at CAPA, Complaints and Design Controls and therefore there are more findings within these three systems. o Organization of the information is important and there is software available

Participants	Deficiencies /Remarks
	to manage this information Quotes from interview: 1. "…..I do not think companies have done very good job of organizing the information that they developed during the design control…" 2. "…..the push from the company is to finish the design, get it in the manufacturing, and get it out so (the) company can start making money and to provide return on the investment……."
4	o Small companies start manufacturing device at risk to rush to market o Management commitment is very important. o Design control depends on the classification of the device. Procedure is typically more comprehensive for class III then class II or I devices. Quote from interview: "……to do the things right in my opinion its three separate different things- one is management commitment that upper management has to be committed to get your paperwork done in order to do right design control…."

4.2.2 CAPA

Based on the findings from review of Warning Letters, CAPA had the second largest number of violations. Any problems related to the quality of the products in marketplace can have a financial impact on the company. Troubleshooting problems and attempting to identify and prevent potential problems is a typical activity for most businesses. A Company's ability to correct existing problems or implement controls to prevent potential problems is essential for

continued customer satisfaction and efficient business practice. The following were recommendations or opinions from experts for the handling of CAPA:

Table 4-2: CAPA - Summary of Interviews

Participant	Suggestions/Remarks
1	o The critical item for CAPA process is the closing loop of any cause of existing non-conformity or defect to prevent recurrence and an action taken to eliminate the cause of existing non-conformity or defect to prevent an occurrence. o There are regulations to include CAPA in the organization but there is no defined process on how to do CAPA. o The following three fundamental components that must be established first at any start up company. These three basic components are the backbone of all systems in the Quality Systems: I. Document Management, II. Change Control, and III. Training Quote from interview: "…..companies fail to close loop of any defect or quality related issues to prevent recurrence and fail to check the effectiveness of action taken…."
2	o When FDA visits companies for inspection they tend to look more in CAPA, Complaints and Design Controls and, therefore, there are more findings within these three systems. o Companies tend to skip steps during CAPA process and fail to

Participant	Suggestions/Remarks
	identify legitimate cause. o Companies fail to follow up to see if the corrective action is effective and may also fail to implement the preventive action o Lack of resources also affects these systems not being managed well. o Use of electronic system could be very effective way of managing CAPA but these systems cost money and small companies may not have funding to support the system. Quotes from Interview: "….head count available to you and assigned somebody to do multiple task is an issue…. lack of resources also affects these systems not being managed well..."
3	o Ideal CAPA system will fit into from all and to the other systems. Some of the sources for CAPA could be Audits, complaints, internal quality finding, high waste, high rejects of finished goods. Quote from Interview: "CAPA to this day is not used correctly; we concentrate on the corrective action, we do not use the information that we have to use it as preventive opportunity…..we use the corrective part of CAPA but we do not use the preventive part of CAPA"
4	o The violation of lack of procedures may mean that lack of implementation of procedures that are difficult to follow or the SOPs are so cumbersome.

Participant	Suggestions/Remarks
	o Typically Companies have the procedures but fail to follow due to lack of resources. o Companies should have a SOP stating clear process of periodic schedule of supplier audits

In summary, for the CAPA system a common theme of opinion was that companies fail to close loop of corrective action to prevent recurrence and lack an effectiveness check of the preventive action. Another point that all participants made was that the companies tend to skip steps during CAPA process and fail to identify legitimate cause.

4.2.3 Complaint Files

The third highest number of violations that the FDA issued related to the Complaint Files.

According to the CustomerExpressions web site, consumers who complain about products and services tend to buy the products they complained about if they believe the complaint was resolved fairly.[28] This means consumers give businesses an opportunity to correct the immediate problem and restore goodwill. A careful complaint process system can save the company unwanted costs.

Table 4-3: Complaint files- Summary of Interviews

Participant	Suggestions/Remarks
1	o Complaint files and CAPA are typically managed under one system. o Lack of resources is typically the root cause of not maintaining compliance status of this system Quote from interview: "….three basic components may be considered (documentation management, training, and change control) for successful establishment of the Quality Systems…."
2	o Complaints files goes together with CAPA and normally managed under one system o Lack of resources is the main cause for failed to follow the procedures
3	o Complaint files and CAPA systems are "windows to the soul" of QS.

[28] http://www.customerexpressions.com/cex/cexweb.nsf/(GetPages)/f0807e646e0c9bb885256ff20069fb8e

	Complaint provides the issues from end users. o Small firm tend not to have established procedures for CAPA and/or Complaint file QSs. Quotes from Interview: "…..in recent years companies have laid off a lot of people….companies do not readjust the quality system including the work load…. . now less people will have to the work …you literally do not have enough hours of the day…" "……Developing decision tree or flow chart and use it as a template. This process can help determine how to manage flow of information step-by-step…"
4	o Complaint files and CAPA are normally managed under one system o Small companies may have the procedures as to establish a procedure is inexpensive. However, they mostly fail to follow the procedures due to lack of resources. Quote from Interview: "…..small company's struggle is really just one person or two people doing it all and so it gets dropped and so as your sales ramp up you stand a chance to get more complaints and so complaints that were two, three weeks old or two three months old gets behind…..as you do this… new complaints we forget about the old ones……so this (is) due to lack of resources…" "…..a lot of CAPA and Complaint files get managed within one

	system…"

The participants were asked during the interviews about the reasons for FDA issuing a lot of recurring violations related to Complaint files. There was a common theme of response from all participants that lack of resources typically the root cause of not maintaining compliance status of the Complaint files. They also stated that Complaint files and CAPA typically managed under one system. One of the participant stated that the Complaint files and CAPA systems are "windows to the soul" of Quality Systems.

4.3. Summary of interviews

Analytical conclusion drawn through qualitative analysis of the Warning Letters and constant comparison of the interview data, suggested the following three common themes as being a major concern affecting performance of Design Controls, CAPA, and Complaint files of the quality system:

- Lack of resources (insufficient resources)- negatively affect management of the quality system
- Rush to the market- Companies push to finish through the development and manufacturing so they can start clinical studies and ultimately to the market to prove return on their investment.
- Lack of management commitment (uncommitted management)- negatively affects all parts of the quality system.

This information is further captured in the next Chapter for the quality system implementation plan. The researcher utilized information from FDA guidance documents,

Compliance manuals, literatures, the FDA provided examples in the Warning Letters and the recommendations or opinions from each interview participants and prepared a comprehensive implementation plan described in Chapter 5.

5 CHAPTER – Implementation Plan

The research was focused on preparing quality system plan for a class II medical device. 21 CFR Part 820 and other FDA guidance documents provide quality system requirements; however, the researcher prepared a comprehensive quality system implementation plan to help meet these requirements based on the findings through qualitative action research of the literature and FDA issued Warning Letters, and through application of the constant comparison analysis of recommendations and opinions from interviews. This comprehensive list should be easy to follow and could help establish Design Control requirements, processes for CAPA, and processes to effectively handle Complaint Files at any small start-up class II medical device company. This comprehensive plan may also be used as a check list to prepare, for example, Design Control package to include in the quality manual. It should be noted that any start up medical device company should consider gathering additional information as there may be additional requirements they need to consider in order to comply based on the nature of the type of device to be manufactured.

Design Controls	
Points to consider	**Actions required** [29], [30], [31], [32], [33], [34], [35], [36], [37]
Management responsibilities	Provide adequate resources with expertise in managing the quality systems for the design controls required to support the device being manufactured.
Documentation requirements for each phase of device process	Documentation should include at a minimum the design planning, design input, design output, design verification/ validation, design review, device history files, design transfer , and design change control attributes that the design released to production meets the approved requirements.
Electronic systems or software for data management	o According to the experts from industry, use of electronic systems or software for data management should be considered. o Ensure that the electronic systems supporting the collection, trending or assessment of data is validated with security through limited administrated access o Ensure that audit trails are available as required. o Example of electronic system would be TrackWise® quality management application by Sparta

[29] http://www.janosko.com/documents/GMP%20Design%20Controls/June%201998%20Design%20Control%20Inspection%20Guidance/FDA-CDRH%20design%20control%20report%20and%20guidance.htm –accessed January 2011

[30] http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm070627.htm - accessed January 2011

[31] www.ghtf.org/documents/sg3/sg3_fd_n99-10_edition2.pdf - accessed January 2011

[32] Expert opinion as stated in the Section-4 of this document

[33] Review of Warning Letters from Jan 2008 through August 2010

[34] http://www.rmbimedical.com/RegulatoryAffairs/CAPAMain.aspx

[35] UGA course PHAR 6100; CAPA Systems by Ron Arkin

[36] http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm

[37] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/MedicalDeviceQualitySystemsManual/default.htm

Design Controls	
Points to consider	**Actions required** [29], [30], [31], [32], [33], [34], [35], [36], [37]
System for device design planning	Design planning stage to include: o Describe the device. What is it used for? Who will use it (e.g., doctors, nurses, patients, etc.)? o Document the goals, objectives, design schedule and timelines of the design and development o Outline organization responsibilities and interface with contractors (if any) o Identify tasks, deliverables, resources, and schedule o Conduct a major review and stage-gate decision points o Design validation should be conducted using the production unit o Identify company policy, processes, and standards o Establish procedures for documentation requirements and change controls (electronic change control system is preferred) o Document any deviation from the plan and the revised plan should be reviewed, and approved
System for device design Input	Define process to prepare design requirements and to identify regulatory requirements specific to the design input requirements. Consider the following for design input requirements: o Design input requirements are inputs to the creation of top-level specification documents

Design Controls	
Points to consider	**Actions required** [29], [30], [31], [32], [33], [34], [35], [36], [37]
	o Identify law, rules and regulatory requirements and a set of principles to be followed o Describe intended use o Outline limits and tolerances of the device and define standards for the device o Identify engineering and manufacturing needs based on the device physical and performance characteristics and efficacy requirements o Perform user needs and wants per device physical and performance requirements o Perform risk analysis o Consider labeling/packaging requirements o Conduct reliability study of the device (e.g. stability study) o Manufacturing processes o Consider the following health and safety requirements (as applicable): • Chemical Safety • Electrical Safety • Mechanical Safety • Radiation Safety • Thermal Safety • Toxicity and biocompatibility

Design Controls	
Points to consider	**Actions required** [29], [30], [31], [32], [33], [34], [35], [36], [37]
	• Electromagnetic compatibility • Device Compatibility with accessories/auxiliary devices • Device compatibility with the environment of intended use • System Compatibility • Environmental Compatibility • Sterility o Review and approve the design input requirements and monitor through change control process o Review and monitor MDRs/complaints/failures and other historical data o Maintain device history files o Store approved (electronic copy preferred) design input documents to use for design output and for device master record.
System for device design output	Consider the following for design output requirements: o Establish the design output procedure(s) o Confirm how design outputs are expressed in terms that allow comparison to design inputs o Demonstrate assurance of user/patients requirements and include proper references to acceptance criteria o Review how the characteristics are essential to the proper functioning

Design Controls	
Points to consider	**Actions required** [29], [30], [31], [32], [33], [34], [35], [36], [37]
	of the device o Identify purchasing controls including quality requirements o Review production and process engineering related information o Review and approve the design output reports, data and any supporting documents o Archive documents to use for device master record
System for device design review	o Establish process and procedures for the systematic design review starting with the design phase and continuing through validation of initial production batch. o Confirm the documentation exists to demonstrate that the manufacturer has conducted formal design reviews at identified stages o Assure an independent and objective review include producibility and production documentation such as assembly drawings, manufacturing instructions, test specifications, test procedures, etc. o Employ skilled reviewers or a qualified person to perform an analysis of the device design to check that the design input is satisfied by the design output. o Evaluate the adequacy of the design requirements and evaluate the capability of the design to meet these requirements o Confirm that problems or action items identified during a formal

Design Controls	
Points to consider	**Actions required** [29], [30], [31], [32], [33], [34], [35], [36], [37]
	design review were addressed o Identify area of concerns and prepare resolution
System for design verification and design validation	Verification provides theoretical proof of the appropriateness of the final design relative to the design input requirements. The following should be considered for the design verification: o Finished device test procedure(s), specifications, qualifications study reports, manufacturing and packaging batch records, validation protocol, etc should be current and approved. A list of documents with designated references may be provided as an Attachment o Conduct test of finished device for design outputs and verify that the devices are functioning as intended. o Verify that a document is established for the qualification of components and provide reference to the documents. o Create an inspection check list and acceptance criteria for verification of the manufacturing and packaging processes o Verify the manufacturing building is designed for the intended use and contains sufficient space to perform necessary operations to prevent mix-ups, and assure orderly handling of materials as required by 21 C.F.R. § 820.70(f)

Design Controls	
Points to consider	**Actions required** [29], [30], [31], [32], [33], [34], [35], [36], [37]
	o Hand washing sink and gowning area for operators should be adjacent to gowning room and provide reference to the SOPfor gowning procedure. o Verify that microbiology and analytical testing lab for product sterility and release tests have been qualified and certified. Attach a copy of testing lab certificate or provide a preference. o Assure facility maintenance schedule is current. Provide reference to the SOPfor the maintenance of the facility including HEPA filter air supply and wet line sprinkler head. o Verify that all utensils, vessels, and equipments are cleaned and sanitized as required. Refer to the SOP for the cleaning and sanitization of the utensils, vessels, and equipments. o Verify Device History File (DHF) and confirm that includes all documentation with established acceptance criteria. The following should be considered for the design validation: o Perform design validation on a production units or its equivalent o Review the manufacturer's procedure(s) for design validation. For the design project chosen, confirm the design validation was accomplished in accordance with established procedures

Design Controls	
Points to consider	**Actions required** [29], [30], [31], [32], [33], [34], [35], [36], [37]
	o Review the evaluations (clinical or other activities) performed to assist in validating that the device design meets defined user needs and intended use(s). o Validation activities may include the following and need to make sure the relevant documents are approved: • Clinical evaluation in clinical or non-clinical settings • Clinical studies approved via IRB and IDE or IRB alone as appropriate • Historical evidence: 510(k) historical database search and literature search • Evaluate mixing process and test the finished devices to ensure that they contain the correct and homogenous mixture • Testing production units in the actual or simulated use environment • Statistical justification or rational for selected sample size • Description of how test materials and product will be dispositioned at the end of the test procedure • Review of labels and labeling, packaging, and other historical product information

Design Controls	
Points to consider	**Actions required** [29], [30], [31], [32], [33], [34], [35], [36], [37]
	• Analysis of the production unit and inspection data • User needs and intended uses o Identify any risk analysis tools and/or techniques such as Failure Mode Effects Analysis (FMEA), Failure Mode Effects and Criticality Analysis (FMECA) and any Risk Analysis Standards used. o Conduct and document design risk analysis o Ensure acceptance criteria have been established prior to performing validation activities o Prepare, review and approve validation protocol, report, and supporting information o Confirm that design validation data show the approved design meets the predetermined user needs and intended use(s) and that the completed design validation did not leave any unresolved discrepancies o Update and maintain device history file
System for design transfer	Transfer of the device design to the manufacturing for production should consider the following: o Evaluate if the transfer from an in-house or contract facility requires the designing, or re-designing, of the process at the Receiving Site o Outline at a minimum, descriptions for –

Design Controls	
Points to consider	**Actions required** [29], [30], [31], [32], [33], [34], [35], [36], [37]
	• Source and destination of transfer • Device and processes being transferred • Persons and titles responsible for transfer at the manufacturing facility and the inter-relationships needed for transfer o Determine and document how the following will be addressed– • Process and QA Procedures • In-coming, in-process, finished product • Control of prototype units • Control of prototype components, raw materials • Nonconformances and discrepancies during the production of prototype builds o A comprehensive manufacturing plan should be developed, reviewed, approved and controlled for changes o Tooling & Equipment - Need to be properly qualified, identified, controlled (storage and handling), calibrated, and maintained o Make sure of adequate controls established for packaging and labeling (pre-printed boxes, instructions for use (IFU), etc) o Establish design transfer procedure and confirm that procedures for design transfer were followed

Design Controls	
Points to consider	**Actions required** [29], [30], [31], [32], [33], [34], [35], [36], [37]
	o Conduct review of completed design output documents and associated Device Master Record (DMR) o Identify required training of production employees o Ensure that the transfer meets acceptance criteria for input and output requirements o Describe steps to take in the event the transfer is not successful and a need for a change control o Prepare, review and approve design transfer protocol and report o Confirm that design transfer is successful and that the completed design transfer did not leave any unresolved discrepancies o Update device history file to include design transfer.
System for design changes	Define the following items in the change control procedure: o Describe in what conditions change control is required o Describe how to manage change control process when outside parties are involved such as gather change criteria and the reason for the change from the Requester o Allow the Requester to review the complete design change report o Design control site need to review and approve any permanent changes that affect design including CAPA changes o Evaluate and analyze the design to identify other elements that are

Design Controls	
Points to consider	**Actions required** [29], [30], [31], [32], [33], [34], [35], [36], [37]
	impacted by the change o Identify significant changes which includes any change requiring verification and/or validation o Describe the initiations, review and approval of change control documents into the document control system o Update design history file along with the required design verification, validation and review documentation o Establish requirements for removal and deletion of obsolete documents o Establish process to accept, reject, or defer a change request and corrective action o Perform identification, documentation, validation or verification, review, and approval of design changes before implementation of any design change o Describe implementation strategy of changes in such a manner that the original problem is resolved and no new problems are created o Define communication process so all persons whose work might be impacted by the change are informed in timely manner
System for design history	Design history files (DHF) should include the following: o DHF may contain more than one device within the same family o DHF should include unique identification and with some logical

Design Controls	
Points to consider	**Actions required** [29], [30], [31], [32], [33], [34], [35], [36], [37]
	scheme for revision control for documents such as: • meeting minutes • testing summary • analytical procedures • device design records • design drawings • device history records • labeling • manufacturing records • specifications • executed validation protocols and reports and • design output and DMR documents o DHF may contain a reference to the location of the above mentioned documents o The documents should be linked to the product or component from development lab to manufacturing for commercial distribution o Define design problem reporting including assign category of the problem (i.e. importance and urgency) and the review process o Define investigation procedure and change control process for the CAPA process

Design Controls	
Points to consider	**Actions required** [29], [30], [31], [32], [33], [34], [35], [36], [37]

Complaints Handling [38], [39], [40], [41], [42], [43], [44]	
Points to consider	**Actions required**
A system of receipt For complaints	Documentation of complaint should include: o Date received, by phone/fax/e-mail/other, o Received from: Patient/ Pharmacy/ Physician/ Nurse/ Relative/ Address/ other o Product Information: Name/ Strength/ Lot# and Expiration date/ Amount returned o Complaints should be sequentially numbered o Name, date and signature of person collecting all these information o Collection of adverse events/ any safety related information/ complaint with cause, open or closed unit, complainer, criticality
A system of verification of complaints	o Verify if sample to be tested o Verify receipt of return sample including pick-up address/is there a return sample logbook/ contact information and inform QA o For controlled substance complete DEA documentation o Determine and verify testing to be performed; i.e. analytical, performance, packaging etc.

[38] Expert opinion as stated in the Section-4 of this document
[39] Review of Warning Letters from Jan 2008 through August 2010
[40] http://www.rmbimedical.com/RegulatoryAffairs/CAPAMain.aspx
[41] UGA course PHAR 6100; CAPA Systems by Ron Arkin
[42] http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm
[43] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/MedicalDeviceQualitySystemsManual/default.htm
[44] http://www.hc-sc.gc.ca/dhp-mps/compli-conform/prob-report-rapport/gui_md_chr-dir_tpr_mm_tc-tm-eng.php

Complaints Handling [38], [39], [40], [41], [42], [43], [44]	
Points to consider	**Actions required**
	o Classification of complaint and decision tree to determine if the investigation is required
A system for investigation of Complaints	The following items were determined to be critical for complaints from this research: o There should be formally designated unit handling complaints o Process all complaints in uniform and timely manner and maintain all complaint files o Determine if the complaint represents an event, isolated event, location of event, manufacturing and analytical and release for lot and associated lots, risk assessment o Consider the following for investigation to be performed by QC Lab: a. Examine the defective product b. Perform any tests suitable to investigate the reported defect and possible causes of it c. If necessary, examine and test retain samples of the relevant batches
Investigation process and determine possible cause	o Consider the following for investigation to be performed by Production: a. Investigate the possible causes of the defect b. Examine the batch records, all relevant logbooks, and any other

Complaints Handling [38], [39], [40], [41], [42], [43], [44]	
Points to consider	**Actions required**
	relevant documentation c. Interview any production personnel involved with the concerned batches (if necessary) d. Any other actions to fully investigate the causes of the defect o Consider the following when investigation to be performed by Contractor: a. QA to inform the contractor of the complaint and request an investigation to be performed b. Clarify investigation time depend on the nature of the complaint and the extent of the investigation required o Mechanism to verify instance of counterfeiting
A process for trending of complaints	Is the complaint representative of a trend if so are there CAPA in place or action to be taken, is this isolated to one site or multiple locations
A system of determining severity of complaints	o Review of the matrix of all safety, health possibilities that could be associated o Is the complaint an adverse reaction and requires regulatory input or medical assessment o Evaluation of potential adverse event and reporting of adverse event
A system of	o Evaluate against the adverse event process as well as develop a letter

Complaints Handling [38], [39], [40], [41], [42], [43], [44]	
Points to consider	**Actions required**
communicating to the customer and regulatory authorities	to communicate back to the complainer o Acknowledgement letter to complainant and define timeline the letter should be sent to complainant o Define sample replacement and form to be filled out o Issuance of final report by QA, compiling all the information received from other departments. The report need to cover details of the investigation, determination of potential or probable root cause and conclusion o Customer Complaint close-out process
Establish a risk assessment process	o Risk assessment should include all parts of the manufacturing process as well as medical implementation o An evaluation of all customer complaints on an annual basis and its communication and review of all open Customer Complaints o QA to issue report covering details of the investigation including determination of potential or probable root cause and conclusion with corrective and preventive actions

Corrective and Preventive Actions [45], [46], [47], [48], [49], [50], [51]	
Points to consider	**Actions required**
System for CAPA	The following should be considered for a successful CAPA process: o Management should provide adequate resources for handling of CAPA o Assign a person with specific responsibility to oversee and carry out CAPA procedures o Establish a training module for proper handling of CAPA o Establish document management and Change control systems o Use of electronic system (such as TrackWise®) can be very effective to manage CAPA o CAPA system should be tied to risk management program o CAPA procedure to define terms such as nonconforming product, quality audit, correction, prevention, quality records, service records, complaints, and return products o Statistical method to isolate root cause o Training module for proper handling of CAPA o Define in the procedure to close loop of corrective action to prevent

[45] http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm070627.htm - accessed January 2011
[46] www.ghtf.org/documents/sg3/sg3_fd_n99-10_edition2.pdf - accessed January 2011
[47] Expert opinion as stated in the Section-4 of this document
[48] Review of Warning Letters from Jan 2008 through August 2010
[49] http://www.rmbimedical.com/RegulatoryAffairs/CAPAMain.aspx
[50] UGA course PHAR 6100; CAPA Systems by Ron Arkin
[51] http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm - accessed on September 2010

Corrective and Preventive Actions[45],[46],[47],[48],[49],[50],[51]	
Points to consider	**Actions required**
	recurrence and an effectiveness check of the preventive action o Emphasis the implementation of preventive actions and to follow up to determine the effectiveness of the preventive action
System for identification of the problem, nonconformity, or incident	Documentation of the problem or incident should include: **Report source:** o Input product or quality problems into the CAPA subsystem o Product Information: Name/ Strength/ Lot# and Expiration date/ Packaging configuration o Problem identified should be sequentially numbered o Name, date and signature of person collecting all these information o Collection of problem, nonconformity, or incident related information/ criticality o Clearly define the problem and accurately and completely describe the situation as it exists o Document the external or internal source of the information, a detailed explanation of the problem, the available evidence that a problem exists o Situations that require corrective or preventive actions may come from external and/or internal sources o Example of external sources that require corrective action may come

Corrective and Preventive Actions [45], [46], [47], [48], [49], [50], [51]	
Points to consider	**Actions required**
	from: • Customer concerns or service requests. o Example of internal sources that may require corrective actions could be: • Internal quality audits • Staff observations • Quality assurance inspections • Trending data, and • Management review. o Examples of sources that lead to preventive actions may include: • Service Request • Internal Quality Audit • Customer Complaint / Concern • Quality Assurance Inspection • Staff Observation • Trending Data • Risk Assessment • Process Performance Monitoring • Management Review • Failure Mode Analysis

Corrective and Preventive Actions [45], [46], [47], [48], [49], [50], [51]	
Points to consider	**Actions required**
	Explanation of the Problem: Document a complete description of the problem so the problem can be easily understood from reading the explanation. **Evidence:** List the specific information available that demonstrates that the problem does exist. **Corrective/Preventive Action Request form:** If electronic change control system has not been implemented, refer to Appendix 6 for a sample form that can be used to initiate a CAPA action and to collect the initial information.
System for evaluation of the problem	A documented procedure shall be established to define requirements for: o Describing process for the proper evaluation of the problem o Reviewing nonconformities (including customer complaints) o Determining the causes of nonconformities o Evaluating the need for action to ensure that nonconformities do not recur o Determining and implementing action needed, including, if appropriate, updating documentation Consider the following for the evaluation of the problem that has been identified:

Corrective and Preventive Actions[45],[46],[47],[48],[49],[50],[51]	
Points to consider	**Actions required**
	Review of historical records: Review trending data, component history records, process control records, finished product testing and other quality system records for unfavorable trends. **Potential Impact:** Specify and explain why the problem is a concern. This may include the possible impact that the problem may have in terms of costs, function, product quality, safety, reliability, and customer satisfaction. **Assessment of Risk:** o Based on the documented evidence of the impact evaluation assess the seriousness of the problem and determine the level of risk that is associated with the problem. o Assessment should be reviewed by the team to determine whether a record or report should be established for corrections and removal of the product or for medical device reporting. **Remedial Action:** o Based on the review of historical records and impact and risk evaluations above, determined if immediate remedial action is required to remedy the situation until a thorough investigation and a permanent solution is implemented.

Corrective and Preventive Actions [45], [46], [47], [48], [49], [50], [51]	
Points to consider	**Actions required**
	o If remedial actions are necessary, identify the actions and the resources required and explain steps that must be taken immediately to avoid any further adverse effects. **Remedial Action form** If electronic change control system has not been implemented, refer to Appendix 6 for a sample "Remedial Action" form that can be used to document steps that must be taken to avoid any further adverse effects.
System for investigation of the problem	There must be a written procedure for conducting an investigation into the problem. The following procedures shell be established to define requirements for investigation: • Objective for the actions that will be taken, • The procedure to be followed, • The personnel that will be responsible, and • Any other anticipated resources needed, **Objective** Document the desired outcome of the corrective or preventive action. In the "Identification" section define and state the current situation of the problem. Document what the situation will be when the action is complete. **Investigation Procedure**

Corrective and Preventive Actions [45], [46], [47], [48], [49], [50], [51]	
Points to consider	**Actions required**
	o Objective and the instructions for conducting the investigation o Outline what must be done to determine the contributing and root cause of the problem o Documentation requirements of person or persons responsible for the investigation o Specify within how many days an investigation should be initiated and completed o Must incorporate a comprehensive review and analysis of all of the circumstances related to the problem. Consider equipment, materials, personnel, procedures, design, training, software, and external factors o Rationale for determining if a failure analysis should be conducted as part of the investigation, and the depth of the failure analysis o Recording of the results of investigation and of action taken o Review and approval of the investigation data and report **Responsibilities / Resources** It is very important that the investigation procedure includes assignment of responsibility for conducting each aspect of the investigation. The procedure should also require identifying and documenting for any additional resources that may be required.
System for analysis	Consider the following for the analysis of the cause problem:

Corrective and Preventive Actions [45], [46], [47], [48], [49], [50], [51]	
Points to consider	**Actions required**
of the cause of the problem	o Analyze and determine the root cause of the problem o Use the information available to determine the cause of the problem. o Identify any contributing causes for the problem o Collect relevant data o Investigate all possible causes, and o Distinguish between the observed symptoms of a problem and the fundamental (root) cause of the problem. **Possible Causes / Data Collection** Create a list of all possible causes and determine the basis to collect relevant information, test data, etc. A comprehensive list of possible causes, appropriate information and data collected should be used to determine the root cause of the problem. **Results and Data** o Document the results of the data collected such testing results and/or a review of records, processes, service information, design controls, operations, and any other data that may lead to a determination of the fundamental cause of the problem. o Evaluate the results and completed documents and narrow down the possible cause. o This information should be used to determine the root cause of the

Corrective and Preventive Actions [45], [46], [47], [48], [49], [50], [51]	
Points to consider	**Actions required**
	problem. **Root Cause Analysis** o To determine the root cause often requires answering a series of 'why?' questions and digging deep into the situation until the fundamental reason for the problem is found o Document the root cause of the problem and determine the appropriate corrective and/or preventive actions that must be taken o During the root cause analysis consider the following areas: • Methods (Lack of process, incorrect instructions, etc.) • Machinery (Equipment not calibrated, malfunction, major service/repair performed, etc.) • Materials (raw materials not received or not suitable, etc.) • Manpower (Lack of training, illness, etc.) • Environment (Poor lighting, temperature instability, etc.) **Failure Mode Analysis** o Provisions for identifying the failure modes o Determine the significance of the failure modes (using tools such as risk analysis) and o Rationale for determining if a failure analysis should be conducted as part of the investigation, and the depth of the failure analysis

Corrective and Preventive Actions[45],[46],[47],[48],[49],[50],[51]	
Points to consider	**Actions required**
	Problem Analysis form Refer to Appendix 6 for a sample form that can be used to document information related to the analysis of the problem.
System for action plan	o CAPA procedure shell include the following for proper execution of an Action Plan: • Requirements to identify a set of written procedures that detail all of the actions that must be done to resolve the problem and prevent it from recurring • Inclusion of corrective and preventive activities, document changes, training, etc. • Qualified person or persons should be responsible for the execution of an action plan • Identify the person or persons responsible for completing each task • Define expected completion date and communicate for timely completion of the action plan • Define method for determining verification or validation • Establish implementation plan and record changes in methods and procedures • Identify experienced people to follow up monthly to check that the problem has been solved and the action plan has been

Corrective and Preventive Actions [45], [46], [47], [48], [49], [50], [51]	
Points to consider	**Actions required**
	implemented • Define method for disseminating information on the quality problem or nonconforming product to those responsible o According to the results from the analysis of the cause of the problem, determine optimum method for correcting the situation (or preventing a future occurrence) o Identify, as appropriate, the items to be completed, document changes, any process, procedure, or system changes required, employee training, and any monitors or controls necessary to prevent the problem or a recurrence of the problem. **Actions to be Completed** List all of the activities and tasks that must be accomplished to either correct the existing problem or eliminate a potential problem. Identify all actions that will be required to address everything related to the situation. **Document or Specification changes** List any documents to be modified and describe what the modifications will be. **Process, Procedure, or System changes** Describe in detail any changes that must be made to processes,

Corrective and Preventive Actions [45], [46], [47], [48], [49], [50], [51]	
Points to consider	**Actions required**
	procedures, or systems so that it is clearly understood what must be done. Explain what will be the expected outcome of these changes. **Employee Training** Communicate and train all persons or departments that may be affected of any modifications made to documents or processes.
System for action implementation	Consider the following for the implementation of action taken during the CAPA process: o CAPA procedure(s) should explain how design changes may interact with design change control system and risk management program o Initiate, complete, and document all of the required tasks listed and described in the action plan o Implement the corrective / preventive action plan that has been created under action plan **Implementation Summary** o List and summarize all of the activities that have been completed as required in the "Action Plan" o Document all the actions that were taken to correct the problem and assure that it will not recur. This may include changes, preventive measures, process controls, training, etc. **Documentation**

Corrective and Preventive Actions [45], [46], [47], [48], [49], [50], [51]	
Points to consider	**Actions required**
	o List all documents or other specifications that have been modified o Attach the updated documentation with the final printed report of this CAPA action. This will facilitate verification of the changes for the follow up.
System for follow up	The following follow up questions must be answered to evaluate the actions taken during the CAPA process o Did the actions correct or prevent the problem and are there assurances that the same situation will not happen again? o Have all recommended changes been completed and verified? o Has appropriate communications and training been implemented to assure that all relevant employees understand the situation and the changes that have been made? o Is there any chance that the actions taken may have had any additional adverse effect on the product or service? **Verification Results** Verify and record the implementation and completion of all changes, controls, training, etc. **Results / Effectiveness of the Actions** o Check for effectiveness of the actions taken o Thoroughly evaluate that the root cause of the problem has been solved

Corrective and Preventive Actions [45], [46], [47], [48], [49], [50], [51]	
Points to consider	**Actions required**
	o Any resulting secondary situations have been corrected o Proper controls have been established o Adequate monitoring of the situation is in place o Investigate and determine if the actions taken could result in any other adverse effects and the investigation and the results of it are documented.
A system of communicating to the customer and Regulatory authorities	o Procedure for the mechanism to disseminate relevant CAPA information to those individuals directly responsible for assuring product quality and the prevention of quality problems should include documentation of the correspondence(s) to the customers and timely reporting and follow up response to the regulatory authority

6 Conclusion and Impact

In this research, the researcher first determined the current trend in medical device industry regarding the quality system by reviewing literature and analyzing the last three years of Warning Letters. Compilation of data from Warning Letters showed significant increase in violations in three areas of the quality system: Design Controls, CAPA, and Complaints. Therefore, the focus for this research was limited to these three areas. Second, experts in the medical device industry were interviewed to delineate the potential underlying causes responsible for recurring violations in these three quality systems. The data from interviews were examined using the constant comparison methodology resulting in three common themes affecting the performance of Design Controls, CAPA, and Complaint files.

The first theme and possible cause for recurring violations was that insufficient resources could negatively affect the management of quality system. In this situation the management needs to provide adequate resources to perform necessary tasks so the products meet quality standards.

The second possible cause for recurring violations in these areas could be that companies try to push through the development and manufacturing so they can start clinical studies and ultimately bring products to the market to prove a return on their investment. A combination of the first and second themes could make it very difficult for employees to manage these quality systems adequately. Further study is needed to determine whether these situations tend to occur more in small companies compared to large companies.

The third possible cause, which the researcher and experts from the device industry believe is the most prevalent one, is lack of management commitment. It is the management's

responsibility to provide adequate resources to produce products that meet quality system regulations. Although, this research was mainly focused on three areas of the quality system found in published Warning Letters to have the largest most number of violations, additional work should be performed to check if violations observed in other areas of the quality system might also be due to the same reasons.

This observation of increased number of violations adds to evidence with the article titled "FDA Worried That Class I Recall Jump Reflects Industry Rush To Market," published in The Silver Sheet- May 2010 the FDA raised concerns over a recent spike in recalls, questioning whether manufacturers are sacrificing quality to rush products to the market.[52] These concerns are consistent with the findings of this thesis. The FDA is in the process of closely examining recall data to specify where recalls occur, the reason for recalls and their classification criteria. Once their assessment is published, it will provide a more comprehensive perspective of recall issues.

The Researcher prepared a comprehensive implementation plan to help establish requirements for Design Controls, CAPA, and Complaint files of the quality system. Understanding the reasoning behind medical device companies' violations of quality system regulations as they increasingly incur is important and could be further extended. The action research and constant comparison methodology that was employed in results analysis for this thesis could be applied in other areas of the quality system as well.

There were some limitations during this research in terms of difficulty finding more experts in the industry and lack of resources with regards to available funding and time for in-depth interviews. Therefore, the research can be further continued with interviewing more experts to further validate the findings. Inspectors at the FDA CDRH division may also be

[52] "The Silver Sheet" - May, 2010 - May, 2010

interviewed to include their opinion, recommendations and current thinking. Any additional research in this area should help increase validity of the project by performing constant comparison of any new data with the data from Warning Letters and recommendations and opinions from experts reported in this thesis.

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Appendix 1: List of Violations from Warning Letters

Citations from Warning Letters from

Appendix 2: Information Letter

:
Dear :

I am a graduate student at University of Georgia College of Pharmacy, Regulatory Affairs under the direction of professor Dr. Paul Brooks. I invite you to participate in a research study entitled "Developing a Comprehensive cGMP/Quality System Program to Meet the FDA Regulations for Class II Medical Device," which is being conducted for my graduate program thesis project. The scope of this study is to develop a set of recommendations to implement an effective quality system (QS) and corresponding operational document support system for a small start-up biomedical device industry.

I am interviewing a targeted number of individuals from within the biomedical device manufacturing industry to obtain an industry perspective for quality system requirements. The findings from the interviews and a complete literature review will be used to recommend implementation steps for a robust quality system.

Your participation will involve discussing your experience in developing and establishing quality systems and should take only about 60 minutes. Participation in the study is voluntary, and you may choose not to participate or to stop at any time without penalty or loss of benefits to which you are otherwise entitled. No individually-identifiable information about you or provided by you during the research will be shared with others without your written permission. The results of the research study may be published, but your name will not be used. In fact, the published results will be presented in summary form only. Your identity will not be associated with your responses in any published format. E-mails will be printed but your name and e-mail address will be redacted. In addition, your e-mail(s) will be deleted from the Sent Items and from the Inbox of the e-mail account as soon as the research project is completed. Audio recordings will not be publicly disseminated and the audio recordings will be destroyed upon completion of the research.

The final quality system model of this research project will assist those in the industry, who are responsible to set up biomedical device manufacturing facility that should meet the FDA requirements. There are no known risks or discomforts associated with this research.
In order to evaluate eligibility to participate in this research, please review the following questions and simply type yes or no to the following questions,

1. Are you 18 years and older?
2. Do you have two or more years experience working in a biomedical device industry or a pharmaceutical industry?
3. Have you been involved in establishing cGMP/QS for pharmaceuticals or medical device manufacturing facility?

If your responses indicate that you are not eligible for further participation, your e-mail(s) will be deleted immediately and any printed copy will be shredded.
After typing your answers to the questions, please hit the reply button so that I can send you a copy of the consent form and schedule a time to interview you. If you have any questions about this research project, please feel free to call me at 770-578-5952 or send an e-mail to naran.patel@abbott.com.

Thank you for your consideration! Please keep this correspondence for your records.
By responding to the above questions you are agreeing to be considered for participation in the above-described research study

Sincerely,
Naran Patel

Appendix 3: Interview Questions

1 Tell me a little about your experience in establishing cGMP/QS for biomedical device manufacturing facility?

2 Discussion: I have evaluated Warning Letters issued to medical device companies within the last three years and the following are the most citations FDA issued during this time period:

21 CFR Part 820.30- Design Controls
21 CFR Part 820.100- Corrective and preventive action
21 CFR Part 820. 198- Complaint files

2.1 How do you suggest the affected systems should be managed to prevent these types of citations?

2.2 Any other critical requirements that must be included for each of the above Quality Systems?

3 Other than the following FDA guidance documents can you help identify regulations and guidelines to consider while developing QS for biomedical device manufacturing facility?

3.1 Quality System (QS) Regulation/Medical Device Good Manufacturing Practices; http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/default.htm

3.2 http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm

3.3 MEDICAL DEVICE QUALITY SYSTEMS MANUAL: A SMALL ENTITY COMPLIANCE GUIDE, First Edition: December 1996; http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/MedicalDeviceQualitySystemsManual/default.htm (extracted 18 July 2010)

3.4 Guidance for Industry- ICH Q9 Quality Risk Management; June 2006

3.5 HHS Publication FDA 97-4179; MEDICAL DEVICE QUALITY SYSTEMS MANUAL: A SMALL ENTITY COMPLIANCE GUIDE- First Edition

3.6 Guide to Inspections of Quality Systems: August 1999 ; http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm

4 Can you please identify useful resources such as publications, books, etc that can be used while developing QS for biomedical device manufacturing facility?

Appendix 4: Consent Form

I, _____, agree to participate in a research study titled " Developing a Comprehensive cGMP/Quality System Program to Meet the FDA Regulations for Class II Medical Device " conducted by Naran Patel from the University of Georgia College of Pharmacy, Regulatory Affairs under the direction of Dr. Paul Brooks, University of Georgia College of Pharmacy. I understand that my participation is voluntary. I can refuse to participate or stop taking part at anytime without penalty or loss of benefits to which I am otherwise entitled. I can ask to have all of the information about me returned to me, removed from the research records, or destroyed.

The goal of this project is to develop a set of recommendations to implement an effective quality system (QS) and corresponding operational document support system for a small start-up biomedical device industry. The recommendations will be based on the researchers' investigation of best practices in biomedical device manufacturing operations.

If I volunteer to take part in this study, I will be asked to discuss the following items for the duration of about 60 minutes (this interview may be audio recorded):
(for example)

4. Answer questions about my years of experience in biomedical device industry and my knowledge and expertise in Quality System requirements
5. Have I been involved in establishing cGMP/QS for pharmaceuticals or medical device manufacturing facility?
6. Am I familiar with cGMP/QS regulations and FDA expectations for biomedical device manufacturing facility?
7. What are/were the challenges encountered during the development of the QS?
8. What are/were the challenges encountered during the implementation of the QS?
9. Identify regulations and guidelines for developing comprehensive QS.
10. Identify good resources such as publications, books, etc that can be used when developing QS for biomedical device manufacturing facility?
11. Name documents that may be required for each quality system I developed.

There is no risk or discomfort expected during the research participation.

There are no expected direct benefits to me for my participation. The researcher hopes to learn about the FDA requirements and industry standards to develop a comprehensive quality system for biomedical device manufacturing facility. I understand that there is no financial or other compensation/incentive offered to participate in this research.

No individually-identifiable information about me, or provided by me during the research, will be shared with others without my written permission. The results of this participation will be confidential, and will not be released in any individually identifiable form, unless otherwise required by law. E-mails will be printed but your name and e-mail address will be redacted. In addition, your e-mail(s) will be deleted from the Sent Items and from the Inbox of the e-mail account as soon as the research project is completed. Audio recordings will not be publicly disseminated and the audio recordings will be destroyed upon completion of the research. The investigator will answer any further questions about the research, now or during the course of the project.

I understand that I am agreeing by my signature on this form to take part in this research project and understand that I will receive a signed copy of this consent form for my records.

_____	_____	_____
Name of Researcher	Signature	Date

Telephone: _____ Email: _____

_____	_____	_____
Name of Participant	Signature	Date

Please sign both copies, keep one and return one to the researcher.

Additional questions or problems regarding your rights as a research participant should be addressed to The Chairperson, Institutional Review Board, University of Georgia, 612 Boyd Graduate Studies Research Center, Athens, Georgia 30602-7411; Telephone (706) 542-3199; E-Mail Address IRB@uga.edu

Appendix 5: Quotes from Interviews

All participants had about similar views for the violations observed in all three quality systems (Design control, CAPA, and Complaint files). Participants commented centering around the reality that employees at small companies are sometimes forced to manage QA, RA, Complaint Files, CAPA, handling CMOs, etc. Most of the times the employee may not even have proper training or experience to perform some of the job responsibilities. Therefore, lack of resources is major concern at small companies. When the participants were asked individually what they meant by the lack of resources they said the following:

Participant-2 said "….head count available to you and assigned somebody to do multiple task is an issue…. lack of resources also affects these systems not being managed well..."

Participant-3 stated that "…..push from the company is finish the design, get it in the manufacturing and get it out so they can start making money and to prove return on the investment and all these effort…." and similarly

Participant-4 stated "…..You have to have adequate resources to properly execute a process. So if the process is not well understood it's a problem. If the process is not well managed it's a problem. And if the process does not have enough resources that's a problem." When Participant-4 was asked for an example that could demonstrate an example of lack of resources it was explained as "….for example, I use myself, so I am the Director of Quality but I also take on Regulatory piece which I do not have regulatory person. I design/implement/and maintain QS and with that much work when a complaint comes in what do I do with it? OK, So I have to talk on phone to interview the complainer, then I have to document that, then I have to

investigate that. Investigation mean try to get a return samples and that it self is a process. Then take that return sample and do something with it. Did you have the expertise to review to study the return sample and if not then you have to send that out and manage that investigation- right! So you have to instruct that outside lab to do something with your sample. You have to discuss with the lab about the findings from investigation. And that takes additional time and effort- right! Once you have that information then you have to go back and summarize all that in investigation report. In the mean time you have to decide also is that a reportable event. If it is reportable event then you kick it in the MDR process which takes whole set of resources. So as I am seeing small companies struggle is just one person doing it all."

The following quotes transcribed from interviews to document what each participants thought were the major issues for recurring violations affecting the following three systems:

Design Control:

Participant-1:

"…..companies tend to push to finish through the development phase to start clinical studies and ultimately to the market to prove return on their investment….."

Participant-2:

"…everybody wants to make product and move forward and that sort of thing it hurts intellectually, that you have to go back in time and figure out what we did wrong and try to fix it…it's all sort of backward thinking…"

Participant-3 stated the following:

3. "……companies create so much information when we are doing design of the product that we just become overwhelm with and ……..later on when you are working on a

complaint or you are involved in a CAPA situation you can expeditiously impossible to go back and be able to look at the right report to get you the right information…"

4. "…..because it gets so complex I do not think companies have not done very good job of organizing the information that they developed during the design control…"
5. "…..the push from the company is finish the design, get it in the manufacturing, and get out so company can start making money and to provide return on the investment……."

Participant-4:

"…..go back and look at things that you have to have in place to do the things right in my opinion its three separate different things- one is management commitment that upper management has to be committed to get your paperwork done in order to do right design control…."

CAPA and Complaint files:

Participant -1:

"…..the critical item for CAPA process is that companies fail to close loop of any defect or quality related issues to prevent recurrence and fail to check the effectiveness of action taken to eliminate the cause of existing defect or problem to prevent an occurrence…."

Participant-2:

1. "…..a lot of people skip different phase of the CAPA during the investigation process….. such as trying to actually eliminating solid root cause and then making sure that corrective action cover root cause."
2. "…..another thing people screw up in CAPA a lot is at the end going back to make sure that a corrective action that was implemented were effective. That's a big part of it gets

skip a lot of time and that's one of the thing that need to close out for correct CAPA process…."

Participant-3:

1. "CAPA to this day is not used correctly; we concentrate on the corrective action, we do not use the information that we have to use it as preventive opportunity…..we use the corrective part of CAPA but we do not use the preventive part of CAPA"
2. "…..many many companies do not clearly define what type of scenarios or what the triggers are and decision points that means decide to go to CAPA….many accompanies put everything in CAPA…"
3. "…..in recent years companies have laid off a lot of people….companies do not readjust the quality system including the work load…. . now less people will have to the work …you literally do not have enough hours of the day…"
4. "……Developing decision tree Or flow chart and use it as a template. This process can help manage how to manage flow of information step-by-step…"

Participant-4:

"…..small company's struggle is really just one person or two people doing it all and so it get dropped and so as your sales ramp up you stand a chance to get more complaints and so complaints that were two, three weeks old or two three months old gets behind…..as you do this new complaints we forget about the old ones……so this due to lack of resources…"

Appendix 6: Attachments for CAPA Process

Attachment 6- 1: Corrective / Preventive Action Request

Date: _____ □ Corrective Action □ Preventive Action

Request Source

□ Service Request
□ Customer Compliant / Concern
□ Staff Observation
□ Risk Assessment
□ Management Review
□ Internal Quality Audits
□ Quality Assurance Inspection
□ Trending Data
□ Process Performance Monitoring
□ Failure Mode Analysis

Description of the Problem

_____
_____
_____
_____

Evidence Observed

_____
_____
_____
_____

Preliminary Assessment of Potential Impact and/or Risk

_____
_____
_____
_____

Action initiated by _____

Attachment 6- 2: Corrective / Preventive Action Remedial Action Required

CAPA Action #:_____

Date: _____ □ Corrective Action □ Preventive Action

Description of the Problem:

Evidence Observed:

Potential Impact of the Problem:

Remedial Actions Required:

Actions Completed Date_____ By_____

Results

Attachment 6- 3: Corrective / Preventive Action Problem Analysis

CAPA Action #:_____

Date: _____

List of Possible Causes and Supporting Data:

Analysis Results and Data:_____

Supporting Documents Attached:

Root Cause Determination:_____

Supporting Documents Attached:

Analysis Complete Date _____ By _____