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Implementation of Risk Management in the Medical Device Industry

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IMPLEMENTATION OF RISK MANAGEMENT IN THE MEDICAL DEVICE
INDUSTRY

A Thesis

Presented to

The Faculty of the Department of Aviation and Technology

San Jose State University

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

by

Rachelo Dumbrique

December 2010

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The Designated Thesis Committee Approves the Thesis Titled

IMPLEMENTATION OF RISK MANAGEMENT IN THE MEDICAL DEVICE
INDUSTRY

by

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APPROVED FOR THE DEPARTMENT OF AVIATION & TECHNOLOGY

SAN JOSE STATE UNIVERSITY

December 2010

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ABSTRACT

IMPLEMENTATION OF RISK MANAGEMENT IN THE MEDICAL DEVICE INDUSTRY

by Rachelo Dumbrique

This study looks at the implementation and effectiveness of risk management (RM) activities in the medical device industry. An online survey was distributed to medical device professionals who were asked to identify RM-related activities performed during the device life cycle. RM activities and techniques included Establishing Risk Acceptance Criteria, Hazard Identification, Human Factors/Usability, Fault Tree Analysis (FTA), Design Failure Mode and Effects Analysis (DFMEA), Process Failure Mode and Effects Analysis (PFMEA), Hazard and Operability Study (HAZOP), Hazard Analysis and Critical Control Point (HACCP), Risk Benefit Analysis, and Risk Assessment of Customer Complaint. Devices were identified by type (therapeutic, surgical/clinical tools, diagnostic, instrument disposable, implantable, etc.), development history (new, second, third or later generation device), and time since market release. Respondents were also asked to indicate the degree of change made to the device as a result of RM activities and to rate the effectiveness of associated RM activities for the device. Survey results indicated that RM's impact and level of effectiveness on a medical device are dependent primarily on the device type and life-cycle stage (i.e., pre-market versus post-market). There is also some impact of development history and the time since the device was released to market.

Table of Contents

| | |
|---|----|
| Introduction..... | 1 |
| Statement of the Problem..... | 2 |
| Research Questions..... | 2 |
| Hypotheses..... | 3 |
| Review of the Literature | 4 |
| History of Risk Management..... | 4 |
| Risk Assessment Requirements and Management | 4 |
| Product Development Process | 10 |
| Risk Assessment Process | 14 |
| Medical Device Classification | 16 |
| United States Regulatory Pathway | 18 |
| Risk Analysis Techniques..... | 23 |
| Methodology..... | 32 |
| Data Analysis | 33 |
| Discussion..... | 37 |
| Survey Findings | 37 |
| Summary and Conclusion..... | 65 |
| References..... | 68 |
| Appendices..... | 74 |
| Appendix A: Examples of SR and NSR devices (CDRH, 2006) | 74 |
| Appendix B: “Scope of File Review by Submission Type” (WHO, 2003)..... | 82 |
| Appendix C: Typical PHA worksheet (ISO, 2007) | 83 |
| Appendix D: Snapshot of the survey questionnaire..... | 84 |
| Appendix E: Survey cover letter..... | 92 |
| Appendix F1: Chart for the count and degree of change of the risk management activities performed in the conceptualization phase of a medical device..... | 93 |
| Appendix F2: Chart for the count and degree of change of the risk management activities performed in the initial development phase of a medical device | 94 |
| Appendix F3: Chart for the count and degree of change of the risk management activities performed in the design verification and engineering validation phase of a medical device | 95 |

| | |
|--|-----|
| Appendix F4: Chart for the count and degree of change of the risk management activities performed in the design transfer phase of a medical device | 96 |
| Appendix F5: Chart for the count and degree of change of the risk management activities performed in the clinical validation phase of a medical device | 97 |
| Appendix F6: Chart for the count and degree of change of the risk management activities performed in the pilot production phase of a medical device | 98 |
| Appendix F7: Chart for the count and degree of change of the risk management activities performed in the manufacturing scale up phase of a medical device..... | 99 |
| Appendix F8: Chart for the count and degree of change of the risk management activities performed in the production monitoring and reporting phase of a medical device | 100 |
| Appendix F9: Chart for the count and degree of change of the risk management activities performed in the field production monitoring and reporting phase of a medical device | 101 |
| Appendix G1: Chart for the effectiveness and implementation scores of the risk management activities performed in the conceptualization phase of a medical device | 102 |
| Appendix G2: Chart for the effectiveness and implementation scores of the risk management activities performed in the initial development phase of a medical device | 103 |
| Appendix G3: Chart for the effectiveness and implementation scores of the risk management activities performed in the design verification and engineering validation phase of a medical device | 104 |
| Appendix G4: Chart for the effectiveness and implementation scores of the risk management activities performed in the design transfer phase of a medical device .. | 105 |
| Appendix G5: Chart for the effectiveness and implementation scores of the risk management activities performed in the clinical validation phase of a medical device | 106 |
| Appendix G6: Chart for the effectiveness and implementation scores of the risk management activities performed in the pilot production phase of a medical device | 107 |
| Appendix G7: Chart for the effectiveness and implementation scores of the risk management activities performed in the manufacturing scale up phase of a medical device | 108 |
| Appendix G8: Chart for the effectiveness and implementation scores of the risk management activities performed in the production monitoring and reporting phase of a medical device | 109 |

| | |
|---|-----|
| Appendix G9: Chart for the effectiveness and implementation scores of the risk management activities performed in the field production monitoring and reporting phase of a medical device | 110 |
| Appendix H1: Survey findings | 111 |
| Appendix H2: Survey findings | 112 |
| Appendix H3: Survey findings | 113 |
| Appendix H4: Survey findings | 114 |
| Appendix H5: Survey findings | 115 |
| Appendix H6: Survey findings | 116 |
| Appendix H7: Survey findings | 117 |
| Appendix H8: Survey findings | 118 |
| Appendix H9: Survey findings | 119 |
| Appendix H10: Survey findings | 120 |
| Appendix H11: Survey findings | 121 |

List of Tables

| | |
|--|----|
| Table 1: Common regulatory framework for medical device (WHO, 2003) | 10 |
| Table 2: 510(K) and PMA Submission Comparison (“Medical Devices: FDA,” 2009).. | 22 |
| Table 3: Summary of the Effectiveness of RM activities by Respondent | 54 |
| Table 4: Summary of RM Effectiveness from the Survey | 67 |

List of Figures

| | |
|--|----|
| Figure 1: Evolution of RM (G. Rao, personal communication, September 29, 2010) | 5 |
| Figure 2: Stages of a medical device life span (WHO, 2003) | 9 |
| Figure 3: Degree of change and RM effectiveness assessment (Respondent no. 1)..... | 40 |
| Figure 4: Degree of change and RM effectiveness assessment (Respondent no. 2)..... | 41 |
| Figure 5: Degree of change and RM effectiveness assessment (Respondent no. 3)..... | 42 |
| Figure 6: Degree of change and RM effectiveness assessment (Respondent no. 4)..... | 43 |
| Figure 7: Degree of change and RM effectiveness assessment (Respondent no. 5)..... | 44 |
| Figure 8: Degree of change and RM effectiveness assessment (Respondent no. 6)..... | 45 |
| Figure 9: Degree of change and RM effectiveness assessment (Respondent no. 7)..... | 46 |
| Figure 10: Degree of change and RM effectiveness assessment (Respondent no. 8)..... | 47 |
| Figure 11: Degree of change and RM effectiveness assessment (Respondent no. 9)..... | 48 |
| Figure 12: Degree of change and RM effectiveness assessment (Respondent no. 10)..... | 49 |
| Figure 13: Degree of change and RM effectiveness assessment (Respondent no. 11)..... | 50 |
| Figure 14: Degree of change and RM effectiveness assessment (Respondent no. 12)..... | 51 |
| Figure 15: Degree of change and RM effectiveness assessment (Respondent no. 13)..... | 52 |
| Figure 16: Degree of change and RM effectiveness assessment (Respondent no. 14)..... | 53 |

Introduction

The extensive innovations in medical device technology have supported the increasing demands of the health care industry over the past twenty years (Foote, 1988). Even in a highly technology-driven environment, it is still crucial that products are designed and developed to meet requirements of relevant International Organization for Standardization (ISO) standards and Food and Drug Administration (FDA) regulations that assure quality and safety.

Product liability and regulation have increasingly become major issues for the medical devices industry (Foote, 1988). For this reason, medical device manufacturers and the FDA face the challenging role of ensuring a stringent process is in place for medical device risk assessment. But with all the standards and regulations imposed for the assurance of a medical device's effectiveness and safety, the amount of risk involved is still in question on devices that are approved for market release (Dyadem International, 2008). A 100% risk-free device is never attainable (T. Chan, personal communication) but a systematic assessment of potential risks associated with a medical device can significantly reduce potential harm to the user, manufacturer, and the medical device industry in general.

This study focused on the implementation of selected risk-analysis activities and techniques over the life cycle of a medical device. This study studied its impact for an effective risk management, that, when effectively carried out, will help to significantly reduce product returns and litigations. The risk analysis techniques include Risk Acceptance Criteria, Hazard Identification/Preliminary Hazard Analysis (PHA), Human

Factors/Usability Analysis/Use Failure Mode and Effects Analysis (FMEA), Design FMEA, Process FMEA, Hazard Operability Study (HAZOP), Hazard Analysis and Critical Control Point (HACCP), Risk Benefit Analysis, and Risk Assessment of Customer Complaint. The use of these techniques was evaluated in the different phases of the design life cycle, which includes conceptualization, initial development, design verification and engineering validation, design transfer, clinical validation, pilot production, manufacturing scale up, production monitoring and reporting, and field production monitoring and reporting.

Statement of the Problem

Litigation and product recalls are still predominant in a heavily regulated industry such as the medical device industry (e.g., Medtronic pacemakers, Baxter pumps, Guidant defibrillator and pacemakers). Medical device manufacturers must be able to select the risk management activities that are suitable for their type of product, and employ them at phases where they are most appropriate and effective. This provides industry professionals with a basis for identification of potential hazards and means to effectively address the risks involved. The problem is to understand how risk management activities currently influence the development of a medical device.

Research Questions

- Do regulated risk management activities play a significant role in the medical device product development?
- What is the level of effectiveness of risk management activities in the medical device industry?

Hypotheses

- H1: Risk management activities drive the changes in the development of a medical device.
- H0: Risk management activities do not have any impact in the development of a medical device.

Review of the Literature

History of Risk Management

With no formal regulation to oversee RM, recognition of ISO 14971 and GHTF guidance came about in the late 20th century to help medical device manufacturers manage the risk associated with their medical device. The flowchart in Figure 1 depicts the evolution of risk management and the associated standards and guidance that support the framework of systematically applying risk management activities within the device life cycle process.

Risk Assessment Requirements and Management

It is critically important that medical device manufacturers do not only implement a full risk assessment process of a medical device but also ensure that a solid risk management is also implemented (Medical Device School, 2005). This way, the potential risk of a product can be readily addressed from the time it was being conceptualized to the moment when it is released and disposed. The many regulations and standards pertaining to risk management in medical devices, and the establishment of the Global Harmonization Task Force (GHTF) whose mission is to harmonize these regulations and standards globally, will ease the implementation of the risk management process (Global Harmonization Task Force [GHTF], 2009). GHTF includes Australia, Canada, European Union, Japan, and the United States (World Health Organization [WHO], 2003).

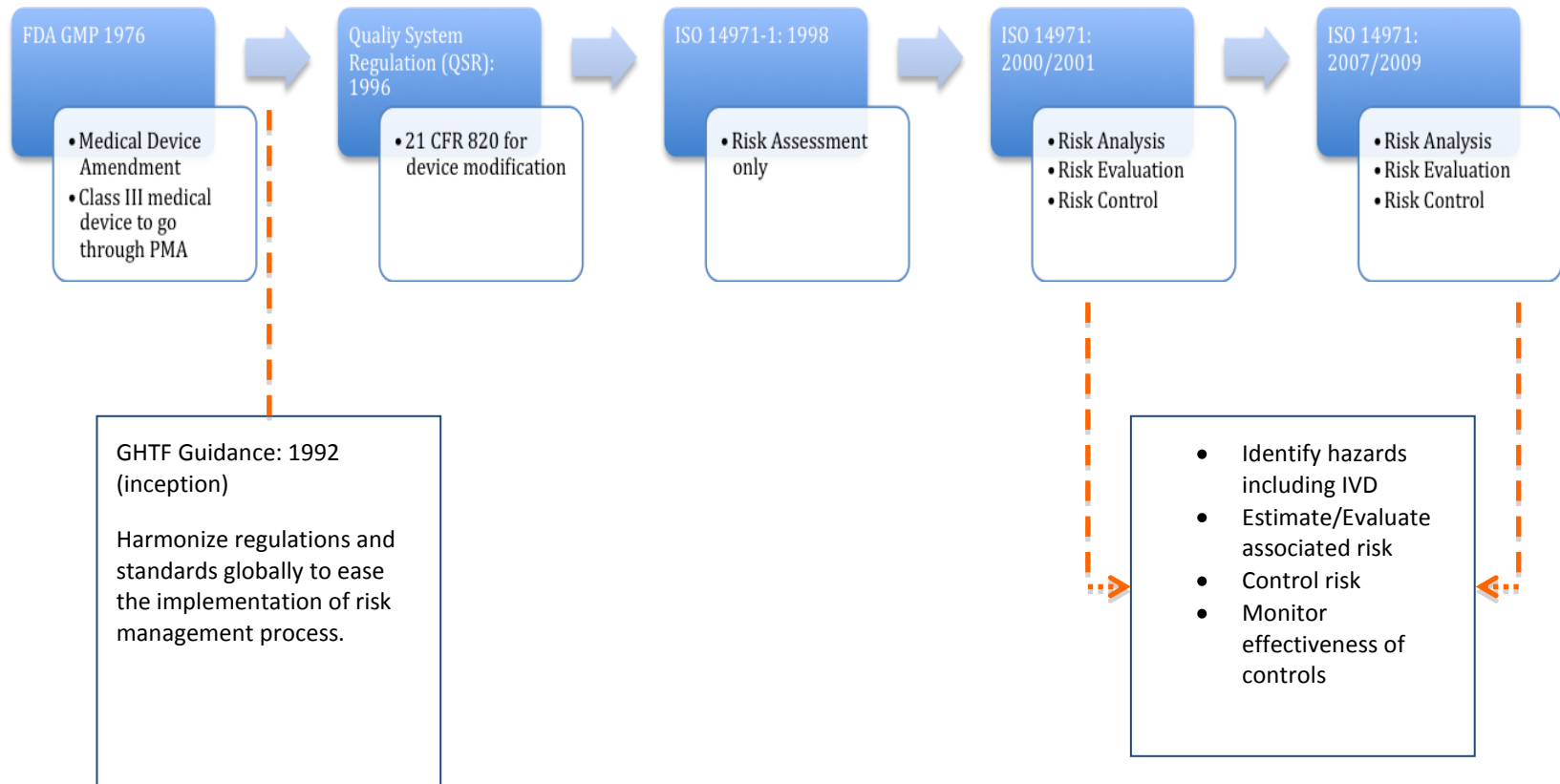


Figure 1: Evolution of RM (G. Rao, personal communication, September 29, 2010)

The international standard for risk management of medical devices is ISO14971. The standard covers the risk determination and application activities for the whole life cycle of a medical device from design, development, and manufacturing (International Organization for Standardization [ISO], 2007). The risk process determination stated in ISO 14971 has two important steps such as the collection and dissemination of information. The collection process engages in quality planning that covers the development of risk management plan, identification of potential hazards, estimation, and validation of risk. This information is then disseminated back through design input, design output, and design verification. Risk analysis (hazard identification), risk evaluation (risk acceptability), risk control, and risk monitoring (post market surveillance) are the critical parts of a medical device risk management (Medical Device School, 2005). It is also good to take into account that risk analysis and risk evaluation must be applied in all phases of the product life cycle (Emergo Group, 2009).

Pre-market product control. Pre-market handles the product's adherence to government regulations and thus falls within the scope of risk management. Different countries have different rules and standards for their product's approval, however it is the same risk management philosophy that governs these requirements, and that is to ensure device's safety and performance (WHO, 2003).

According to WHO (2003), the higher the complexity of the design, the higher the risk of user error. It is important that unwarranted risks are avoided at the design and conceptualization stage through adequate test validation, verification, and clinical trials.

Manufacturers are also responsible for ensuring that products meet the requirements and design specifications. This is done through good manufacturing management that implements the quality system regulations (GHMF, 2009). Good manufacturing practices (GMP) describe the quality system for FDA-regulated medical devices that includes process validation and design controls. These requirements are covered under 21 CFR Part 820 of the GMP regulations. FDA (1987) requires manufacturers to establish regulations applicable to their products' functions, as GMP regulations are broad and cover the general product market. It is the manufacturer's responsibility to follow the procedures suitable to the product being manufactured. GMP also needs to be consistent with the requirements set in ISO: 9001 "Quality Systems – Model for Quality Assurance in Design, Development, Production, Installation and Servicing" and ISO 13485 "Quality Systems – Medical Devices – Supplementary Requirements to ISO 9001 (FDA, 1987).

Also included in the pre-market control of a medical device are packaging and labeling. Manufacturers must ensure that safe handling of the device is observed at all times to avoid accidental tampering of information on the labels. The package must be well sealed with hazard warnings and clear instructions (WHO, 2003).

Placing on-market. This stage of the life span of a medical device is the responsibility of the vendor. Advertisements are powerful means to convince the users of the device's capabilities to meet their expectations. Thus, marketing of products must also be regulated to avoid mishandling when products are put into their intended use (WHO, 2003).

Post-market surveillance. User error is considered the most common cause of death or injury related to medical devices, according to WHO (2003). It is stated in ISO 13485 and FDA that companies must have processes in place to obtain customer feedback for trend monitoring and data review (Emergo Group, 2009). It is also noted that for the process to be effective, a regular review meeting must be held so that updates are disseminated and corrective and preventive actions (CAPA) are implemented when necessary. Data may also include product and process non-conformances, complaints, and customer survey. According to ISO 14971, post market surveillance should include the following (Emergo Group, 2009):

- Systematic process for product evaluation including customer complaints.
- New hazard evaluation.
- Objective evidence contained in the file for risk management.
- Determination of changes, if any, in the acceptance of the original risk.
- Revisions and feedback to the risk assessment and management as required.

In addition to monitoring the products risk it is important to note that a proof of documentation that shows how the data are analyzed, inspected, and studied must be readily on hand. It must also include information on who performs the investigation and how many times this process is performed. It is important that the medical devices industry has this on-going process for post surveillance trending and reporting of the product's condition to reaffirm its safety and be able to act suitably on any adverse effects that they may inflict on the user (Rodriguez, 2009).

Figure 2 (WHO, 2003) shows the life span of a medical device from conception to disposal. It also depicts the party responsible for ensuring that regulations are addressed appropriately to reduce, if not eliminate, potential risk through proper monitoring of the safety and performance of the device even after sale. An effective risk management emphasizes the different assignments for the responsible people in each stage of the life cycle. WHO (2003) also noted that product and use are the two critical elements that guarantee the safety and performance of a medical device. Pre-market review governs product control while the post market surveillance ensures its use to be continuously safe and effective. The placing on-market process in between which includes packaging, labeling, advertising and sale avoids misrepresentation. It is responsible to let the user know the device's intended use.

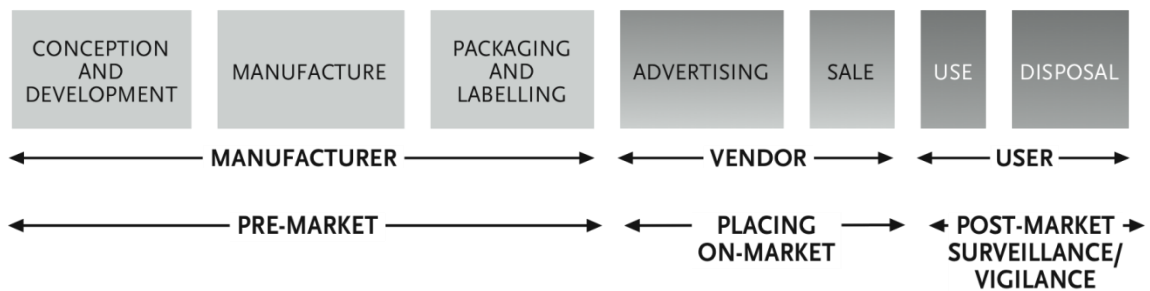


Figure 2: Stages of a medical device life span (WHO, 2003)

The regulatory framework in Table 1 summarizes the most common activities that require regulations in medical device. The different stages were tabulated with identification of the person in charge for controlling and monitoring the device, sale, after sale, and use.

Table 1: Common regulatory framework for medical device (WHO, 2003)

| Stage | Pre-Market | Placing On-Market | Post-Market |
|--------------------------------------|--|---|--|
| Control/Monitor | Product | Sale | After-Sale/Use |
| Person | Manufacturer | Vendor | Vendor/User |
| Items or Activities Regulated | Device Attributes - Safety and performance | Establishment Registration - List products available or in use. - Requires vendor to fulfill after-sale obligations. | Surveillance/Vigilance - After-sale obligations. - Monitoring of device's clinical performance. - Problem identification and alerts. |
| | Manufacturing - Quality systems | | |
| | Labeling (representation) - Accurate description of product. - Instructions for use. | Advertising (representation) - Prohibits misleading or fraudulent advertisement. | |

Product Development Process

The product development process of a medical device ensures that the device delivered to the customer has gone through rigorous steps to guarantee quality, safety and reliability. It is important that product requirements are clear so that design controls are defined and established. Design control as described by Gopaldaswamy & Justiniano (2003) is “a set of disciplines, practices, and procedures incorporated into the design and development process of medical devices and their associated manufacturing processes”. Discipline is what administers the performance of the design activities to be able to practice them as appropriate. The procedures, on the other hand, are the step-by-step guidelines that are followed accordingly. These set of controls, as well as the design inputs, are then converted into System Requirements Specifications (SRS), which are documented and maintained in the Design History File (DHF), together with the other

important processes. Production of the device comes forth when the final product and process specifications are completed and verified in conformance with the design controls and SRS. Risk management is performed alongside the design and development process to guarantee that the device being produced does not impose hazards onto the user (Gopaldaswamy & Justiniano, 2003).

Product requirements. The concept and development phase of product development contains the product requirements. Product requirements define the product's intended use and the target users. The requirements should also cover the following: device characteristics, quality and regulatory requirements, manufacturability, human factors, reliability, labeling, packaging, and all the other pertinent information that the designers find necessary to start the project. Information is obtainable from different sources like interviews, research studies, past records or device history, and regulatory requirements (Fries & King, 2009).

Design and development planning. Design and development planning includes program goals and the design and development elements. The plan details the ways to strategically align the team and the resources in terms of the needs defined by the product requirements. The plan contains the schedule of how each action item should be executed to meet the requirements. The plan is properly documented in the DHF. It has to be regularly updated so that every member of the team is attuned to the changes made until implementation is performed. Goals and objectives must also be clearly defined. It is usually the Program Manager's job to define the objective and to make sure that the plan is executed as defined, and that the scope, size, and complexity of the development

project are accurately addressed and understood. Revisions are signed and approved, and recorded for proper tracking (Fries & King, 2009).

Design and Development Elements

Design inputs. The needs and requirements of the users are converted into practical and technical design inputs.

Design activities. Refer to all activities that are performed in the product development. May involve activities related to suppliers and contractors, or activities that involve contingencies.

Design outputs. Determines activities to be developed for the desired design output. Accuracy and reliability must be defined with tolerance limits. Design outputs must also address quality, safety, and other factors as appropriate that are defined by design and risk analysis.

Formal design reviews. Identify the timing, content and reviewers for a formal design review. Every product must have at least one formal review to assess, at the very least, the completed design inputs, outputs, and design validation. Design reviews should also cover design issues and resolutions.

Design verification and test methods. Provides evidence that the required development activities have been met and that the design outputs meets the design inputs. Statistical techniques are employed at this stage. Includes integration testing, functional testing, and biocompatibility. Data analysis should cover design tolerance, worst-case scenarios, thermal analysis, as well as the outputs of risk analysis techniques like FMEA and FTA.

Design verification report. Contains the summary of design verification activities, device history file, and all issues that were identified and resolved.

Design validation. Provides validation activities on the project development activities performed like validation of test plans, test methods, software validation, risk analysis, validation of labeling and packaging, reporting, and reviewing. User's needs and the device's intended use are also part of design validation activities. The purpose is to determine discrepancies that may result between production and manufacturing units when operated in a simulated condition. Records and results of these activities are contained in the design validation report, which also includes information on the methods used and identification of the individuals who performed the validation. All these and other references reside in the device history file.

Design transfer. Design is transferred to manufacturing, service, production, or site location.

Design change control. Covers the criteria and responsibilities when approving a design change.

Device history file (DHF). This is where all program project records reside to provide ease of accessibility for everyone in the team. It contains previous DHF, revisions, and updates.

Risk management. Includes activities for risk management that involves hazard identification and detection of the degree of risk to the users.

System requirement specification (SRS). Details of the product design are translated into system requirement specifications, which also include inputs from the

activities performed in risk management. SRS requirements include (1) functional requirements that define the operational capabilities of the device, (2) physical and performance requirements that measure how well the device performs in terms of speed, strength, and reliability, (3) interface requirements define the criticality and compatibility of the device to its external interface, which includes the users, (4) system architecture denotes relationships of the various systems and their requirements, and if applicable, (5) software requirements for the product's functionality that will need to be implemented through software. SRS must also include the following as appropriate: toxicity, risk management, biocompatibility, EMC, human factors, etc.

Risk Assessment Process

There are four integral steps in the risk assessment process. They are hazard identification, dose-response assessment, exposure assessment, and risk characterization (Cammack, Eyre, White & Wilson, 1999).

Hazard identification. Hazard identification is the process that involves the determination of any adverse health condition upon exposure to an agent (e.g. chemicals). Birth defects, cancer, decreased fertility, and thyroid dysfunction are just few of the cited effects of one's exposure to toxicants (EM-Com, n.d.). Hazards may be identified using one of the following methods: (1) Epidemiological investigation, a study of the frequency and distribution of diseases within human population. It has the advantage of knowing and measuring the risk hazards that have direct effects on human (Daniels, Flanders & Greenberg, 2005). (2) Toxicological studies. It is a method of measuring health hazards affecting living organism. It is usually conducted in a controlled environment like the

laboratory. Animals are used for conducting the test (EM-Com, n.d.). (3) Ecological studies. This is a method of determining hazards based on the ecological studies of wildlife. It is believed that potential endocrine disrupters that have adverse affect on animals may be potentially harmful to human as well (EM-Com, n.d.).

Dose-response assessment. *“All substances are poisons: there is none which is not a poison. The right dose differentiates a poison and a remedy. Paracelsus (1493-1541)”* (EM-Com, n.d.). The characterization of dose-response relationship involves determination of the amount of agent that will not cause an effect. This is the determination of the upper limit, which is also called as the “allowable limit” (Gad & McCord, 2008). The response to the agent varies depending on the level of exposure, duration of contact or the agent’s level of toxicity (Cammack et al., 1999).

Exposure assessment. This is the estimation of the quantifiable dose of human exposure to an existing agent. Estimation includes that of the duration, frequency, and intensity of exposure (Gad & McCord, 2008). One’s exposure to different toxicants may come from the different sources in the environment, which may be synthetic or natural occurring. Synthetic sources of endocrine toxicants can be categorized as voluntary or involuntary exposure. The former includes exposure to commercial products like pesticides, cosmetics or medications. The latter may come from contamination in water, air or contact in the contaminated soil (EM-Com, n.d.).

Routes of exposure in the human body differ according to the chemical properties and human biology. Routes of exposure can be dermal (skin-absorbed), respiratory (inhaled), and gastrointestinal (ingested). Chemical toxicants that are insoluble in water

like PCB's can be skin absorbed while chemicals that are volatile can be inhaled. Once contaminants enter the body, they travel to organs and tissues through bloodstream. The measure of exposure to chemical contaminants in the body is done through blood sampling (EM-Com, n.d.).

Risk characterization. The final step of the risk assessment process includes the evaluations and results of the previous three steps. Risk characterization measures the overall risk of the agent towards human exposure. The allowable limit is then compared to the estimated limit of adverse health effects that determines the agent's safety (Gad & McCord, 2008).

Risk estimation is assessed in direct proportion for both levels of hazard and exposure. The presence of both assessments constitutes an end result that determines the amount of risk involved. If a hazard exists and the risk is known to be low, then it is an acceptable risk. In the context of the total risk assessment, the uncertainty of the hazard level is a pre-defined approach for a more extensive analysis on the amount of hazard involved in the compound (Gad & Jayjock, 1988).

The four risk assessment steps discussed are vital to the overall assessment of the medical device's exposure to risk. Thus, it is important to take into consideration the accuracy of the test data and results that will determine the device's acceptable safety level for market release.

Medical Device Classification

Part 860 is the medical device classification procedures defined by the Food and Drug Administration (2004). Medical devices are classified according to the potential

risk that they may impose on the user and are based on FDA's level of regulatory control to release and market the device. The higher the class, the higher is the risk and the higher is the number of regulatory controls.

Class I devices are considered the lowest risk devices as their design is not complicated; they are simple to manufacture and safe to users. These devices do not have histories of possible damages and are only subject to general controls. They also do not usually require pre market notification, as general controls are sufficient enough to guarantee their safety and effectiveness. FDA (2004) defines general controls as the inclusion of the following: "section 501 (adulteration), 502 (misbranding), 510 (registration), 516 (banned devices), 518 (notification and other remedies), 519 (records and reports), and 520 (general provisions) of the federal food, drug, and cosmetic act". Devices like handheld surgical instruments are considered Class I, as they are not life supporting devices (LEEDer Group, 2009).

Class II requires general controls and special controls. Devices under Class II are riskier than Class I and may be used for supporting human life. Thus, FDA (2004) requires manufacturers to fulfill sufficient evidence that these devices are assured to be safe and effective by establishing the following: proliferation of performance standards, post market surveillance, patient registries, development, and distribution of guidance documents that include pre market notification according to 510(K) act for market submission. More actions and evidence may be requested by the Commissioner should the manufacturer fail to build strong proof that the device is safe for use. Examples of Class II devices are x ray, pumps, and surgical drapes (LEEDer Group, 2009).

Class III devices are the riskiest among the classes of medical device as these devices are used for sustaining human life. Examples are replacement heart valves and silicone gel-filled breast implants. Devices under this category are usually required to have both a Pre-Market Approval (PMA) and 510(K) clearance for market submission (FDA, 2004). The Commissioner may also require additional evidence of safety and effectiveness when deemed necessary.

United States Regulatory Pathway

Regulatory requirements for clinical trials. The International Review Board (IRB) is defined as “...*any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of human subjects*” (Segal, 1998). IRB ensures that the rights of the subject matter are protected and that their risk to potential hazards is minimized. IRB also has the authority to grant approval or disapproval, to continue or discontinue a clinical trial. All clinical trials must be conducted according to the Investigational Device Exemption (IDE) regulations. Devices exempted from IDE regulations include pre amendment and SE devices, with provisions that they are not transitional devices and were investigated according to the labeling that was FDA reviewed at that time. An IDE application that was approved by FDA is required prior to a clinical trial on a device that has a significant risk. All approved clinical trials must be performed in accordance with the Good Clinical Practices (GCP). GCP refers to the approved standards and federal regulations relating to clinical studies that include

reporting and record keeping requirements, gathering of scientific data, subject's informed consent, and data that contains safety and effectiveness information required by the regulatory bodies. A standardized GCP called Guideline on Good Clinical Practice was formed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use to have a standardized set of guidelines for the U.S., European Union, Japan, Australia, Canada, the Nordic countries and WHO (Segal, 1998).

Significant risk (SR) and non significant risk (NSR) device. SR device is defined as “...*an investigational device that presents a potential for serious risk to the health, safety, or welfare of a subject and is an implant; or is used in supporting or sustaining human life; or is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or otherwise presents a potential for serious risk to the health, safety, or welfare of a subject*” (Segal, 1998). An NSR device, on the other hand, is one that does not meet the description of an SR device. Appendix A shows a list of examples of SR and NSR devices taken from the Center for Devices and Radiological Health (CDRH) (2006). Sponsors and IRB use this list in reference to their determination whether a device is SR or NSR. It is noted though that the list under NSR devices may not be considered final because the risk evaluation must determine the intended use of the device in a study.

The IRB reviews the sponsor's proposal for a clinical investigation based on the device description, investigation plan, reports of past investigations related to the device, and the criteria for subject selection. It is the IRB's discretion to classify whether a

device is SR or NSR. In this regard, FDA considers that IRB has the standard operating procedures (SOP) to conduct the clinical reviews on the subjects being studied for diagnostic or treatment purposes. Data confidentiality, impartial subject selection, a documented consent, and sufficient provisions that define the subject's protection of privacy are some of IRB's conditions for a clinical trial review. Any risks that may be imposed on the subject matter must be proven reasonable for the intention of the benefits and knowledge that are achieved at the end of the investigation. Thus, SR and NSR determination is based on the potential harm that may be inflicted on the subject participating in the investigation, plus the harm it entails in the use of the device, whereas IRB's approval for implementation of the clinical trial is based on the study's risk-benefit assessment (CDRH, 2006).

SR device studies should conform to the regulations set by IDE at 21 CFR 812 and an approved application from FDA before commencement. While NSR device studies has the abbreviated requirements at 21 CFR 812(b) for compliance (CDRH, 2006). Food and Drug Administration (FDA) Reviewing Process.

The FDA's role is to ensure that products released to market have sufficient evidence of safety (potential risk) and effectiveness (intended use) through clinical investigations conducted in accordance with the rules and regulations of the administration. Appendix B shows the scope of the review type and requirements according to the level of submission.

Pre-market review. In May 1976, Congress issued the Medical Device Amendments requiring FDA to have all Class III medical devices to go through the PMA

process before they can be commercially released. Devices released before May 1976 were classified as pre amendment devices while those marketed after were categorized as post amendment devices (“Medical Devices: FDA,” 2009). PMA review is conducted for post amendment devices that are deemed non substantially equivalent (NSE) to a pre amendment device and should submit adequate clinical investigations for the products release. Either that, or the Class III device will have to be reclassified as Class I or II. Substantially equivalent (SE) devices, on the other hand, that have the same intended use as the predicate device (pre amendment devices with approved 510(K)) with the same technological characteristic (TC), or with different TC but proved to be safe and effective as the predicate device, can submit a 510(K) clearance to market (“Medical Devices: FDA,” 2009). A less stringent 510(K) submission is seen to be dominantly favored than PMA by most medical device suppliers for grounds of faster turnaround time and enormous savings in cost. Moreover, 510(K) submissions only include comparative descriptions that includes performance data, and is more focused on the end product than the manufacturing process itself (“Medical Devices: FDA,” 2009). Table 2 shows GAO’s (2009) findings of FDA’s approved devices based on 510(K) and PMA submissions comparing turnaround time and cost.

Post-market surveillance. FDA’s post market surveillance guarantees that devices remain safe and effective after they are released to the market through the analysis of the annual reports that were submitted to them by users and manufacturers. Reports include serious device related injuries, device malfunctions, and death (“Medical Devices: Shortcoming,” 2009).

FDA agents are responsible for the research and investigation of issue trends in relation to the medical device safety, while FDA scientists are in charge for the review and follow up investigations based on the initial reports received. FDA scientists will issue necessary steps and actions for issue resolution and they can also issue product recalls, advisories or even require the manufacturers to change instructions in their device labeling as necessary (“Medical Devices: Shortcoming,” 2009).

Table 2: 510(K) and PMA Submission Comparison (“Medical Devices: FDA,” 2009)

| | Turnaround time (based on 2009 data) | Cost | |
|------------------------------|---|---------------------------------------|-----------------------------------|
| | | FDA reviewing submission (FY 2005) | Applicant submission (FY 2009) |
| 510(K) Submission | 90% within 90 days | \$ 18, 200 | \$ 3,693 |
| | 98% within 150 days | | |
| PMA Submission | 60% in 180 days | \$ 870,000 | \$ 200,725 |
| | 90% in 295 days | | |

Inspection of manufacturing establishments. For both pre market and post market supervision of medical devices, FDA also takes responsibility in making sure that the manufacturing establishments strictly follow the standard manufacturing requirements for device safety and effectiveness, and that local and international requirements are properly accounted for. It is also required that they inspect Class II and III device manufacturing establishments every two years (“Medical Devices: Shortcoming,” 2009).

The provisions included in Congress’ Medical Device User Free and Modernization Act of 2002 (MDUFMA) was instituted to support and increase the number of manufacturing establishments that are FDA inspected and to help manufacturers perform a single inspection that will cover both local and international

requirements. In response to these provisions, FDA formed the Accredited Persons Inspection Program and the Pilot Multi-purpose Audit Program (with Health Canada) that will allow manufacturers to acquire inspection services that will ease their compliance to the governing requirements in the US and abroad, as well as reduce the cost that would have been incurred if it were done in multiple inspections. (“Medical Devices: Shortcoming,” 2009).

Risk Analysis Techniques

Risk analysis is a fundamental requirement in the submission checklist for PMA and 510(K) and a significant guideline contained in GMP. The hazardous effects of a device are of great consideration before a product is approved for market release. Thus, the law requires the inclusion of risk analysis in the design phase of a medical device for early detection of adverse events that can cause serious harm to the user (Kamm, 2005).

Systematic methods for identifying and measuring the potential risk or hazard are specified in Annex G.6 of ISO 14971. These tools are used to effectively carry out the risk analysis of a medical device. Utilization of more than one tool may be necessary on an event that requires it (ISO, 2007).

Preliminary Hazard Analysis (PHA). PHA is a method of identifying potential hazards at the very early stage of design where a more extensive approach may not be suitable. It is importantly useful in the analysis of systems where preliminary design is underway as it identifies the harmful effects caused by an event or a situation. This helps lead the designers to take the steps necessary to alleviate the system’s or activity’s potential risk. Other names that are associated to PHA are Rapid Risk Ranking and

Hazard Identification (HAZID) (Rausand, 2005). PHA risk analysis takes the following characteristics into consideration: system interfaces, equipment used, environmental constraints, layout, and hazardous components (ISO, 2007). A typical PHA worksheet is shown in Appendix C.

The PHA risk analysis process can be broken down into four steps: (1) Establishment of PHA requirements, (2) Identification of potential hazard, (3) Measurement of frequency of occurrence and its severity, and (4) Risk ranking (Rausand, 2005).

Establishment of PHA requirements. PHA involves formation of the analysis team. This team should be able to clearly define and describe the potential problem according to system, equipment, environment, layout, and components involved and the subject being analyzed. The team must document the measures for detection and prevention for the establishment of design controls. Supporting data taken from past cases with related events are also good sources for investigation.

Identification of potential hazard. Every factor that is likely to cause danger must be identified. The list can go from maintenance operations to system safety, etc.

Measurement of frequency of occurrence and its severity. Events are ranked based on the severity of the failure outcome and the frequency of this outcome.

Risk ranking. Three categories (critical, major, minor) define the severity of failure in the PHA matrix and they are tabulated against the estimated frequency of occurrence. Recommended actions are based on the acceptability level.

The “as low as reasonably practicable” (ALARP) principle is the action determined for fairly acceptable cases. These are considered low-level risks that do not need further actions. The medium level acceptable situations will require further investigations and verification of the effectiveness of the corrective actions. A reassessment of the risk score may be required to verify improvements. The high-level or unacceptable risks take on the more rigorous actions to address the potential hazards involved. Verification of corrective actions is a requirement for risk reassessment.

The PHA process of risk analysis supports design resources like time and cost as it helps to ensure that potential risks are identified at the earliest time possible. However, it is also a challenge for designers to execute the plan of performing PHA as hazard interactions may not be easily recognizable and potential hazards may not always be foreseeable (Rausand, 2005).

Usability Engineering/Human Factors. Usability Engineering or Human Factors is a process of designing a device with high consideration on human accessibility and compatibility. Meeting the needs of the users and at the same time taking into account the standards and regulations that govern design implementation. Many companies now employ usability engineering into the product life cycle as it covers a systematic approach to design techniques and vast information on human characteristics. Greater customer satisfaction is also highly anticipated by companies that employ this technique. Users play a significant role through interview, user feedback and survey (Wiklund, 1995).

User studies. Most medical device manufacturers employ focus groups that study the type of users of the device. They are formed to study the needs of the users, how they will use the device, and how often the users will use the device. Interviews and survey questionnaires are often employed by the focus groups to obtain answers to these questions that will significantly help in getting the usability testing started.

Usability goal setting. This is the step wherein usability goals are defined and then compared to the design goals set. It usually involves a team of people who makes the realistic assessment of obtaining usability goals that will fit the design and vice versa.

Concept development. This step includes exploration of mental concepts, establishment of a user interface structure, concept modeling, and evaluation.

Detailed design. A realistic design is developed in this stage. All things considered such as usability test results, modeling, and evaluation.

Specification. Proper documentation of instructions and manuals is addressed in this step. Include drawings, reports and user interface descriptions.

Field activities. The practical use of the actual device is evaluated and user feedback is obtained. According to studies, most nurses make usability a requirement before actually using a device.

Though the usability test can be planned and performed in the various phases of the device life cycle, it is most effectively conducted when a device is ready to market and has proven reliable in meeting the customer's needs. A prototype of the actual device is more appropriately suitable to perform the test to get accurate information on the user's perspective on the device's ease of use and compatibility. Test plan should

include the objective, type of data to be collected, number, and type of test subjects, and upon completing these steps, the documented analysis of test results. Test objectives may contain collection of user's inputs on device improvement, determination of the device more preferred by the user and development of baseline upon user performance. Baseline considers incident and success rate and completion time. The place where the design must be conducted must also be defined be it in an office environment or a laboratory set up. Data analysis may employ statistical tools that can effectively separate the problems from successes like comparison of the mean and standard deviation. The use of statistical analysis makes it easier to convey the necessary information. Finally, usability report must cover a summary of the test results and recommendations for design improvement when appropriate (Wiklund, 1995).

Fault Tree Analysis (FTA). FTA is a top down approach of problem solving (O'Connor, 2002). It starts with identifying the potential hazard and breaks it down to failure modes that may have caused the hazard. This approach uses logic gates like “and” and “or” gates to relate potential failures to possible causes. It provides a systematic approach to problem solving as it visually details the causes and effects of activities or human related factors that may have caused a high level of risk if overlooked (Kamm, 2005). The tree like representation of root cause analysis gives the reviewer a clear picture, at a glance, of each of the possible scenarios that is taken into consideration. For large complex systems where failure modes may be enormous, software programs are now available to aid organizations in doing FTA (O'Connor, 2002).

FTA steps include the list of possible hazards like injury, electric shocks, and fire, and the identification of failures and failure modes that may have resulted in these hazards. Construction of a fault tree diagram may begin with these lists, and elimination of unacceptable events may then be carried out.

Failure Mode and Effects Analysis (FMEA)/Failure Mode, Effects, and Criticality Analysis (FMECA). Contrary to FTA, FMEA uses a bottom up approach of problem solving. It is performed in the early stage of design development, usually at the feasibility stage, to assess every component's possible risk (Bhote & Bhote, 2004). A component level assessment gives designers ideas on what they can improve in the design to improve the product's reliability and make it less susceptible to harmful failures. The failure modes and their severity are assessed based on risk index that will also determine the necessary actions for improvement, and this is where the term FMECA comes into play (Kamm, 2005). The two types of FMEA are Design FMEA (DFMEA) and process FMEA (PFMEA). DFMEA deals with design inadequacies and their effect on manufacturing operations, while PFMEA assesses the potential risks that may possibly transpire in the plant. While these two types have various potential problems that are different from each other, the FMEA approach is still similar, and takes into account the early signs of failure to avoid further changes on the later part of the design or process (Kamm, 2005). FMEA process steps include definition of the system being analyzed, identification of the failure modes and their effects associated with the system or component being investigated, measurement of risk index, and determination

of corrective and preventive actions for improvement. Implementation of these actions must be monitored to ensure that desired output is met (Kamm, 2005).

FMEA uses risk index to determine the severity of the failure. It is calculated based on the probability of occurrence versus the severity. The final score will reveal the acceptability criteria most suitable to the level of hazard of the failure mode (Kamm, 2005). Safety precautions that are significantly beneficial to using the FMEA in preliminary design include the use of sound judgment of the designer to only include the most unreliable parts and their potential failures. The attention is focused on the corrective actions that contribute most significantly in determining the part's reliability (Bhote & Bhote, 2004)

Hazard and Operability Study (HAZOP). HAZOP is a team approach problem solving method. It involves people with different expertise whose conviction of the process or system that is analyzed is what makes the HAZOP analysis effective and easily carried out.

The purpose is to identify the potential hazards that can come out of the system in review, and to be able to identify the methods and actions necessary to minimize the hazards (ISO, 2007). Guide words like “no/not, more, less, as well as, part of, reverse and other than” help to describe the failure or design deviation (O'Connor, 2002). The objectives of HAZOP analysis are to provide a full description of the medical device and its intended use, to review each of the intended use and determine how design deviations can possibly occur in each of the intended use. It is important to know the consequences of these deviations that can lead to possible hazards (ISO, 2007).

Hazard Analysis and Critical Control Point (HACCP). HACCP is a systematic approach for identifying, evaluating, controlling and monitoring of possible hazards that take place in the different life cycles of a medical device. Life cycle stages include design, manufacturing, service, use and disposal. HACCP is typically used in the latter part of the design phase to optimize design changes (ISO, 2007). HACCP is an approach that was first used by NASA to monitor food poisoning of the food being supplied to their astronauts, and was later adapted by WHO to include in the risk analysis methodology for drugs and pharmaceutical products (T. Chan, personal communication). HACCP's seven guiding principles as defined by ISO (2007) include: (1) Carry out a hazard analysis and identify preventive measures, (2) Determine critical control points (CCP's), (3) Generate critical limits, (4) Create a system for CCP monitoring, (5) Establish corrective actions for out of control CCP's, (6) Generate procedures for verification of HACCP effectiveness, and (7) Establish documentation and record keeping. An effective HACCP system is governed by continuous controlling and monitoring of the hazards identified (principles 2, 3 and 4), the manufacturer's ability to ensure that the system is in control and that corrective measures are effectively in place (principles 5 and 6), and establishment of effective documentation that includes process flowcharts, hazard analysis worksheet and HACCP plan. The process flowchart should be able to clearly describe the process as it serves as a guide to the team who is reviewing it. It is important that a step-by-step description of the process is stated for better understanding of the methods incorporated within. The hazard analysis worksheet contains the hazards that were identified in the process and their significance. A list of

the control measures, including the CCP's, is also visible in the analysis worksheet. The HACCP plan is formulated based on the seven principles and ensures that proper control is in place for the control and implementation of the procedures in relation to design, products, processes or procedures (ISO, 2007). Benefits include great reduction of customer complaints and product recalls, better time management as downtime is reduced, and increase employee awareness of process controls with ownership of product safety and effectiveness (T. Chan, personal communication).

Methodology

The survey design was established through the help of an industry expert, Dr. Geetha Rao, who also helped in the data analysis. Three medical device professionals were selected to validate the survey design and do a trial run. The feedback gathered from these 3 respondents helped to revise the survey with particular considerations on the number of questions, the type of questions asked, the time allotment to complete the survey, and the method to answer the survey.

Final revision of the survey is provided in Appendix D. This survey was posted online using Survey Monkey. It was designed as a 10-minute online survey consisting of 22 questions. The questions were divided into three sections: introduction (about the medical company), information on a selected medical device, and risk management assessment.

The actual email that was used to invite medical device professionals to participate in the survey is provided in Appendix E. This email, which also contains the link to the survey was initially distributed privately in March 2010 to 20 individuals who work at medical device companies or whose work is associated with medical devices. Later the survey was distributed more broadly through ASQ-NCBDG (American Society for Quality – Northern California Biomedical Discussion Group) out to its 400-member mailing list.

Answers to the survey were gathered over a period of two months. There were a total of 41 responses received over the total 3-month period. Sixteen of the respondents completed the entire survey but of those only 14 responses were considered valid as 2 of

the survey respondents either misunderstood a question or mistakenly answered a question on the rate of the effectiveness of RM. One out of the 14 respondents did not provide a clear definition of the medical type so only 13 medical device types were identified.

Qualitative data analysis for this type of non-experimental design was utilized, with supporting charts and tables to present the actual results gathered from the survey. Analysis charts were created for the following:

- The degree of change of the risk analysis technique used at every phase of the device life cycle.
- The effectiveness of the risk analysis technique used at each phase.

Data Analysis

With the different variables (development phase, RM activity, degree of change, effectiveness) that are factored in, it was initially difficult to discern the significance of each variable and come up with any immediate conclusion. Intermediate data analysis was used as a part of the initial assessment for the varying results gathered from the survey. The initial data analysis helped gauge whether the results that were collected would be able to provide any justification to the hypotheses. The results indicated some evidence to support the hypothesis that RM activities have an impact, but this was not true across the board. More detailed analysis was performed to understand the impact more granularly. The conclusions established from the survey results were done based on the method described in the Final Data Analysis.

Intermediate data analysis. Individual responses on risk management assessment (degree of change and effectiveness) were tabulated against the RM activities performed during each phase (see Appendices F1 to F9, and G1 to G9 for charts).

A numerical value was assigned to rate the effectiveness: 5 (*high*), 3 (*medium*), and 1 (*low*). The scores on effectiveness were based on the number of times the RM activity was used (implementation) at every phase, and the respondents' individual rating of its effectiveness (calculated). The scores provided an indication of how the different techniques can contribute to a change in design, manufacturing, and labeling.

Implementation score is the frequency of use of the RM activity at each phase, while effectiveness score was calculated by using the following formula: Sum of the rate of effectiveness / Implementation score.

For example, in the Conceptualization phase, 4 medical device professionals are using Hazard ID/PHA. The following ratings were obtained for the risk analysis technique's effectiveness in catching problems: two 5's (*high*) and two 1's (*low*). What is the effectiveness score?

- Implementation score = 4
- Sum of the Rate of Effectiveness = $5 + 5 + 1 + 1 = 12$
- Effectiveness score = Sum of the rate of effectiveness / Implementation score
- Effectiveness score = $12 / 4 = 3.0$

Thus, the effectiveness score of the risk analysis technique, Hazard ID/PHA in catching problems is 3 at the Conceptualization phase. A score of 3 means that Hazard ID/PHA is moderately effective in catching problems at the Conceptualization phase.

Final data analysis. A color coding scheme was used to distinguish the type of change that happened over the device's life cycle, as well as to rate the effectiveness of the RM activities for the following factors: catching problems, early identification of potential risk, identification of product improvements, saving cost, and overall design quality. Figures 3 to 16 show the charts for the 14 individual responses.

Degree of change. The number of labeling, design and manufacturing changes were counted and tabulated for each of the development phase. Colors used for the type of change are as follows: orange for labeling change, blue for design change, and brown for changes in manufacturing. The number of times (Y-axis) the type of change occurs at each phase tells us how much of the RM activities can contribute to these types of changes in the medical device life cycle.

Effectiveness. Effectiveness was rated high (red), medium (yellow) or low (green). The ratings were tabulated for each of the development phase, and put into a chart incorporating the colors associated with the ratings. The colors indicate the effect of the RM activities for the following factors: catching problems, early identification of potential risk, identification of product improvements, saving cost, and overall design quality.

This color coding scheme has helped to visualize a pattern on how effectiveness is rated high on some or all of the factors during the early stages, and how the ratings are shifted from high to low during the post-market stage. As the individual charts were laid out, common trends were observed on the effectiveness ratings based on three factors: medical device type, device development history and the time since the device was

market released. This led to the conclusion that the effectiveness of RM activities is significantly impacted by these three factors.

Discussion

Survey Findings

See Appendix H1 to H11 for the complete survey findings and results. The medical device industry is comprised of a wide range of functions that provides for the many different needs of the consumer population. The survey results revealed a high number of medical device manufacturers that comprised 73.7% of the total survey respondents. Medical device marketers placed as the second highest with 39.5%. Other groups of medical device professionals belong to component and service providers, wherein service providers are either consultants or educators. The responses gathered from the survey were able to create the necessary evidence that helps to validate our claim that the selection of risk analysis techniques over the life cycle of a medical device provides medical device manufacturers the needed confidence to effectively carry out a successful risk management. The percentage of respondents that perform risk management at their work place is 95%. The remaining 5% do not necessarily need to do risk management, as they are involved with either a consulting firm or an educational institution. This is, therefore, solid evidence that risk management is an activity performed in the medical device industry.

ISO 14971 is the international standard for risk management in the medical device industry. The standard provides a high level assessment of identifying, controlling, assessing, and accepting risk. About 83% of the respondents use ISO 14971 (2000, 2007). ISO 13845, which is the international standard for medical device quality system regulation, is as well observed to a great extent, with 84% of the respondents claiming

they are compliant. ICH Q9 compliant is 9.7%. One of the observations noted was how some respondents may have confused standards from guidance documents as revealed in survey question number 5, where others regarded ISO 14971 and ISO 13485 as guidance documents instead of standards. Industry awareness of standards therefore, needs to improve.

Survey results show 46% of the total population, operate with more than 5 product lines. While 33% have 2 to 5 product lines, and 7% with 1 product line. Other survey respondents skipped this question.

The foremost important aspect of this study is to know how the different risk management techniques affect the overall implementation of risk management throughout the device's life cycle. The degree of change and effectiveness brought about by the RM techniques were evaluated. A closer look at these three factors: (1) medical device type, (2) device development history, and (3) time since market release, have shown significant impact on these factors, which have also made this study more comprehensive.

Medical device types were divided into four categories: (1) surgical tools and catheters, (2) diagnostic devices, (3) implantables, and (4) other therapeutic devices. A total of 14 responses were analyzed based on the three significant factors mentioned, with focus on the degree of change and rate of effectiveness. Here is the breakdown of the medical device type of the 14 respondents:

- 4 Surgical tools and catheters
- 3 Diagnostic devices

- 5 Implantable devices
- 1 Other therapeutic device
- 1 Unknown (respondent was not clear on the medical device type)

Twelve out of 14 have rated the effectiveness of the risk management techniques used, while 13 were able to measure the degree of change. The preceding charts (Figures 3 to 16) show the individual assessments of the 14 survey respondents on the degree of change and rate of effectiveness of RM in catching problems, early identification of potential risk, identification of product improvements, saving cost, and overall design quality. Table 3 is the summary of results and observations gathered based on the survey response.

Medical Device Type:
Surgical/Clinical Tools

Approximate Time Since Market Release:
6 months to 18 months

Device Development History:
Revision of previous first generation device

| Phase | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring & Reporting |
|---|--|--|--|--|---|---|------------------------|--|--|
| Degree of Change | | | | | | | | | |
| Effectiveness in Catching Problems | High | High | Medium | Medium | Medium | Low | | | Low |
| Effectiveness in Early Identification of Potential Risk | High | High | High | Medium | Medium | Medium | | Low | Low |
| Effectiveness in Identification of Product Improvements | High | High | High | | High | | | High | Medium |
| Effectiveness in Saving Cost | High | High | High | High | High | Medium | Medium | Medium | High |
| Effectiveness in Overall Design Quality | High | High | High | High | Medium | Medium | Medium | Medium | High |
| Techniques Used | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA,DFMEA, Risk Benefit Analysis, Risk Assessment of Complaint Data/Customer Feedback | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA,DFMEA, Risk Benefit Analysis, Risk Assessment of Complaint Data/Customer Feedback | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA,DFMEA, Risk Benefit Analysis, Risk Assessment of Complaint Data/Customer Feedback | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA,DFMEA, Risk Benefit Analysis, Risk Assessment of Complaint Data/Customer Feedback | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, PFMEA, Risk Benefit Analysis, Risk Assessment of Complaint Data/Customer Feedback | Establish risk acceptance criteria, Hazard ID/PHA, PFMEA, Risk Assessment of Complaint Data/Customer Feedback | PFMEA | Establish risk acceptance criteria, PFMEA, | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, FTA, DFMEA, Risk Benefit Analysis, Risk Assessment of Complaint Data/Customer Feedback |

LEGEND

| Degree of Change | | Effectiveness | |
|------------------|--|---------------|--|
| Design | | High | |
| Manufacturing | | Medium | |
| Labeling | | Low | |

Figure 3: Degree of change and RM effectiveness assessment (Respondent no. 1)

Medical Device Type:
Surgical/Clinical Tools

Approximate Time Since Market Release:
Unknown

Device Development History:
Unknown

(No response on the degree of change)

| Phase | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring & Reporting |
|---|--|--|--|----------------------------------|----------------------------------|----------------------------------|----------------------------------|-----------------------------------|---|
| Degree of Change | | | | | | | | | |
| Effectiveness in Catching Problems | Green | Green | Yellow | Green | Yellow | Green | Green | Yellow | Red |
| Effectiveness in Early Identification of Potential Risk | Green | Green | Yellow | Green | Yellow | Green | Green | Green | Green |
| Effectiveness in Identification of Product Improvements | Green | Yellow | Yellow | Green | Yellow | Green | Green | Yellow | Red |
| Effectiveness in Saving Cost | Red | Yellow | Yellow | Green | Yellow | Green | Yellow | Green | Green |
| Effectiveness in Overall Design Quality | Green | Green | Yellow | Green | Yellow | Green | Yellow | Green | Green |
| Techniques Used | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, Risk Benefit Analysis, Risk Assessment of Complaint Data/Customer Feedback | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, Risk Benefit Analysis, Risk Assessment of Complaint Data/Customer Feedback | Risk Benefit Analysis | No specific technique identified | No specific technique identified | No specific technique identified | No specific technique identified | No specific technique identified | No specific technique identified |

LEGEND

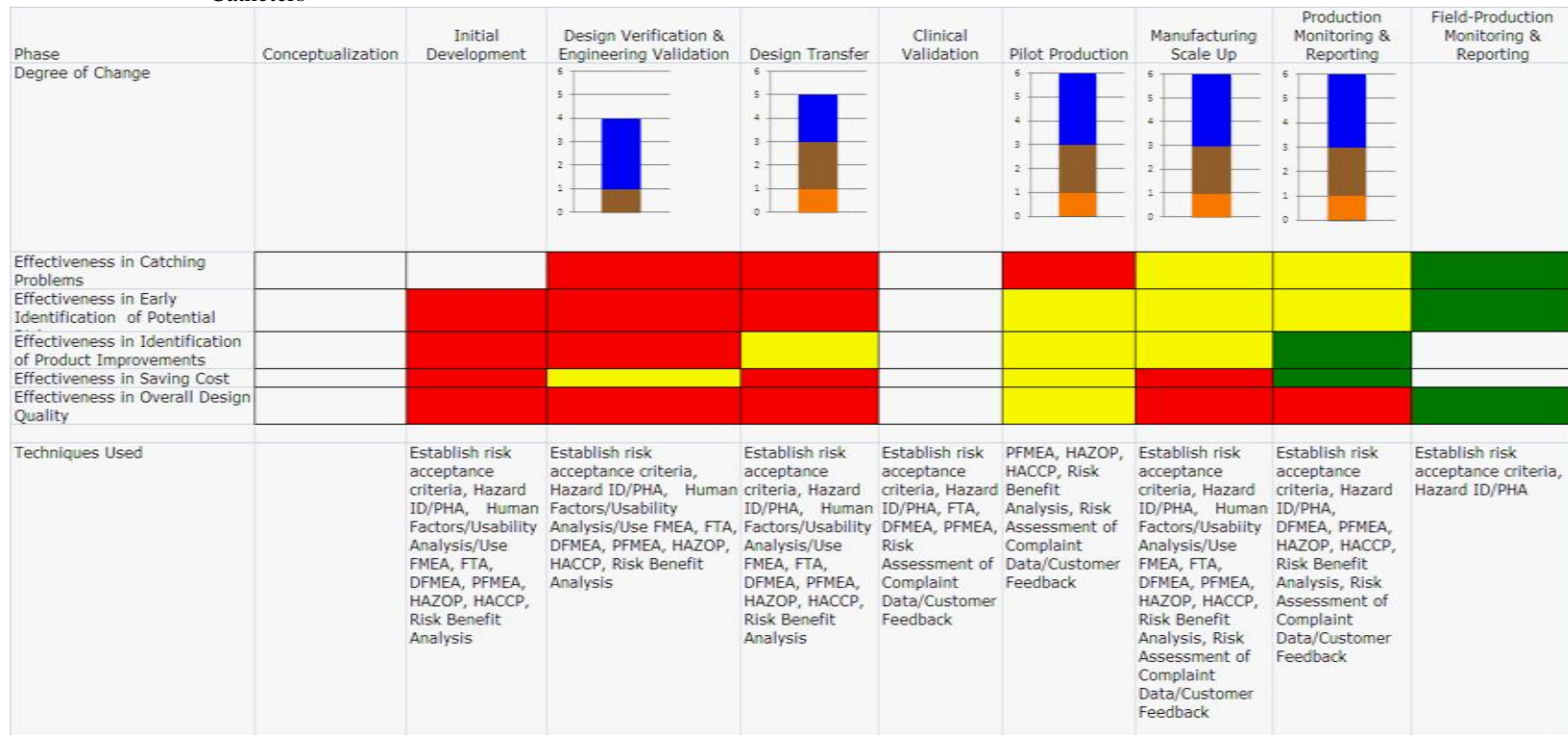
| Degree of Change | | Effectiveness | |
|------------------|--------|---------------|--------|
| Design | Blue | High | Red |
| Manufacturing | Brown | Medium | Yellow |
| Labeling | Orange | Low | Green |

Figure 4: Degree of change and RM effectiveness assessment (Respondent no. 2)

Medical Device Type:
Other (please specify) -
Catheters

Approximate Time Since Market Release:
18 to 36 months

Device Development History:
New, first generation device marketed for first time



LEGEND






| Degree of Change | | Effectiveness | |
|------------------|---|---------------|--|
| Design |  | High |  |
| Manufacturing |  | Medium |  |
| Labeling |  | Low |  |

Figure 5: Degree of change and RM effectiveness assessment (Respondent no. 3)

Medical Device Type:
Surgical/Clinical Tools
Instrument Disposable

Approximate Time Since Market Release:
6 months to 18 months

Device Development History:
Revision of previous first generation device

| Phase | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring & Reporting |
|---|---|--|---|-----------------|---|------------------|------------------------|--|--|
| Degree of Change | | | | | | | | | |
| Effectiveness in Catching Problems | High | High | High | Medium | High | Low | Low | Low | Low |
| Effectiveness in Early Identification of Potential Risk | High | High | High | Medium | Medium | Low | Low | Low | Low |
| Effectiveness in Identification of Product Improvements | Low | Low | Low | Medium | Medium | High | High | High | High |
| Effectiveness in Saving Cost | High | High | High | High | High | Medium | Medium | Medium | Medium |
| Effectiveness in Overall Design Quality | High | High | High | High | Medium | Low | Low | Low | Low |
| Techniques Used | Establish risk acceptance criteria, DFMEA, HACCP, Risk Benefit Analysis | Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA,DFMEA, HACCP, Risk Benefit Analysis | Human Factors/Usability Analysis/Use FMEA,DFMEA, HACCP, Risk Benefit Analysis | HACCP | Benefit Analysis, Risk Assessment of Complaint Data/Customer Feedback | FTA | Hazard ID/PHA | FTA, Risk Assessment of Complaint Data/Customer Feedback | FTA, Risk Assessment of Complaint Data/Customer Feedback |

LEGEND

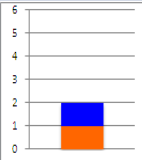
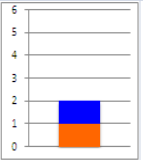
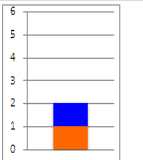
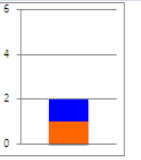
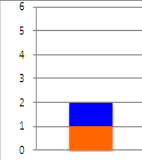
| Degree of Change | | Effectiveness | |
|------------------|--|---------------|--|
| Design | | High | |
| Manufacturing | | Medium | |
| Labeling | | Low | |

Figure 6: Degree of change and RM effectiveness assessment (Respondent no. 4)

Medical Device Type:
Diagnostic - Ophthalmic Imaging
Systems

Approximate Time Since Market Release:
6 months to 18 months

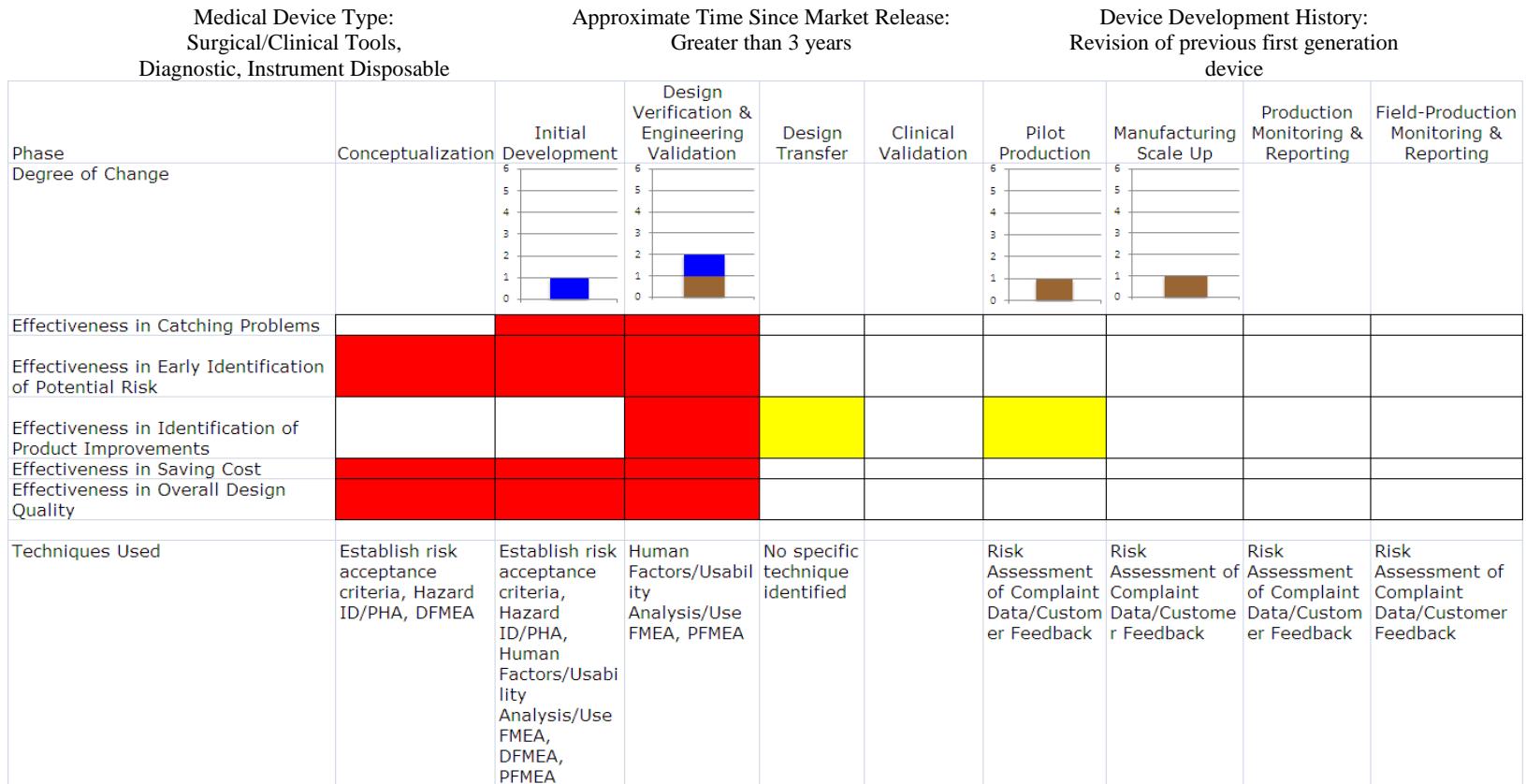
Device Development History:
Third or later generation device

| Phase | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring & Reporting |
|---|-------------------|---|---|---|---------------------|------------------|--|--|---|
| Degree of Change | | |  |  | | |  |  |  |
| Effectiveness in Catching Problems | | High | High | Medium | | | Low | Low | Low |
| Effectiveness in Early Identification of Potential Risk | | High | High | Medium | | | Low | Low | Low |
| Effectiveness in Identification of Product Improvements | | Low | Low | Low | | | High | High | High |
| Effectiveness in Saving Cost | | Medium | Low | Low | | | Low | Low | Low |
| Effectiveness in Overall Design Quality | | High | High | High | | | Low | Low | Low |
| Techniques Used | | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, DFMEA | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, DFMEA | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, DFMEA | | | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, Risk Assessment of Complaint Data/Customer Feedback |

LEGEND

| Degree of Change | | Effectiveness | |
|------------------|---|---------------|--|
| Design |  | High |  |
| Manufacturing |  | Medium |  |
| Labeling |  | Low |  |

Figure 7: Degree of change and RM effectiveness assessment (Respondent no. 5)



LEGEND

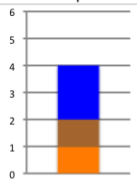
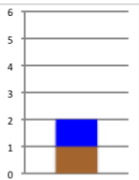
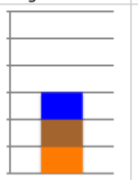
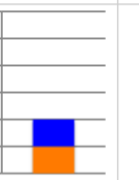
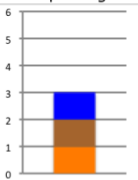
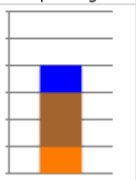
| Degree of Change | | Effectiveness | |
|------------------|--|---------------|--|
| Design | | High | |
| Manufacturing | | Medium | |
| Labeling | | Low | |

Figure 8: Degree of change and RM effectiveness assessment (Respondent no. 6)

Medical Device Type:
 Medical Device Type:
 Diagnostic - hematology instruments
 (blood cell counters)

Approximate Time Since Market Release:
 Greater than 3 years

Device Development History:
 Revision of previous first generation
 device

| Phase | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring & Reporting |
|---|----------------------------------|---|--|---|---|------------------|----------------------------------|---|--|
| Degree of Change | |  |  |  |  | | |  |  |
| Effectiveness in Catching Problems | | | | | | | | | |
| Effectiveness in Early Identification of Potential Risk | | | | | | | | | |
| Effectiveness in Identification of Product Improvements | | | | | | | | | |
| Effectiveness in Saving Cost | | | | | | | | | |
| Effectiveness in Overall Design Quality | | | | | | | | | |
| Techniques Used | No specific technique identified | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, Risk Benefit Analysis | No specific technique identified | Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, DFMEA | No specific technique identified | DFMEA | No specific technique identified | DFMEA, Risk Assessment of Complaint Data/Customer Feedback | Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, FTA, DFMEA, Risk Benefit Analysis, Risk Assessment of Complaint Data/Customer Feedback |

LEGEND





| Degree of Change | | Effectiveness | |
|------------------|---|---------------|--|
| Design |  | High |  |
| Manufacturing |  | Medium |  |
| Labeling |  | Low |  |

Figure 9: Degree of change and RM effectiveness assessment (Respondent no. 7)

Medical Device Type:
Therapeutic
Diagnostic
Implantable Electrophysiology at the San Jose
Campus

Approximate Time Since Market Release:
Greater than 3 years

Device Development History:
New, first generation device marketed for
first time

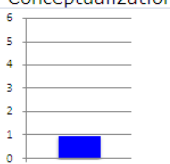
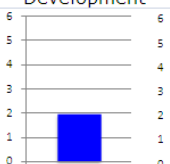
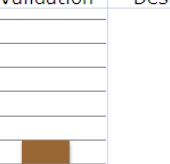
(Invalid response for effectiveness)

| Phase | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring & Reporting |
|---|-------------------|--|--|--|--|---|---|---|---|
| Degree of Change | | | | | | | | | |
| Effectiveness in Catching Problems | | | | | | | | | |
| Effectiveness in Early Identification of Potential Risk | | | | | | | | | |
| Effectiveness in Identification of Product Improvements | | | | | | | | | |
| Effectiveness in Saving Cost | | | | | | | | | |
| Effectiveness in Overall Design Quality | | | | | | | | | |
| Techniques Used | | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, FTA, DFMEA, HAZOP, HACCP | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, FTA, DFMEA, HAZOP, HACCP | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, FTA, DFMEA, PFMEA, Risk Benefit Analysis | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, FTA, HAZOP, HACCP, Risk Benefit Analysis | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, FTA, HAZOP, HACCP | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, FTA, DFMEA, PFMEA, HAZOP, HACCP | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, FTA, DFMEA, PFMEA, HAZOP, HACCP, Risk Benefit Analysis, Risk Assessment of Complaint Data/Customer Feedback | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, FTA, DFMEA, PFMEA, HAZOP, HACCP, Risk Benefit Analysis, Risk Assessment of Complaint Data/Customer Feedback |

LEGEND

| Degree of Change | | Effectiveness | |
|------------------|--|---------------|--|
| Design | | High | |
| Manufacturing | | Medium | |
| Labeling | | Low | |

Figure 10: Degree of change and RM effectiveness assessment (Respondent no. 8)

| Phase | Medical Device Type: Implantable | | Approximate Time Since Market Release: Not yet released – in clinical trial | | | Device Development History: Third or later generation device | | | |
|---|---|--|--|----------------------------------|---------------------|---|------------------------|-----------------------------------|---|
| | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring & Reporting |
| Degree of Change |  |  |  | | | | | | |
| Effectiveness in Catching Problems | | High | Medium | Low | | | | | |
| Effectiveness in Early Identification of Potential Risk | High | Medium | Low | | | | | | |
| Effectiveness in Identification of Product Improvements | High | Medium | | Low | | | | | |
| Effectiveness in Saving Cost | | High | Medium | Low | | | | | |
| Effectiveness in Overall Design Quality | Low | High | Medium | | | | | | |
| Techniques Used | No specific technique identified | Establish risk acceptance criteria, Human Factors/Usability Analysis/Use FMEA, DFMEA, PFMEA, Risk Benefit Analysis | No specific technique identified | No specific technique identified | | | | | |

LEGEND




| Degree of Change | | Effectiveness | |
|------------------|---|---------------|---|
| Design |  | High |  |
| Manufacturing |  | Medium |  |
| Labeling |  | Low |  |

Figure 11: Degree of change and RM effectiveness assessment (Respondent no. 9)

Medical Device Type:
Implantable

Approximate Time Since Market Release:
Not yet released – in clinical trial

Device Development History:
New, first generation device marketed
for first time

| Phase | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring & Reporting |
|---|------------------------------------|--|--|---|--|------------------|------------------------|-----------------------------------|---|
| Degree of Change | | | | | | | | | |
| Effectiveness in Catching Problems | | High | High | Medium | | | | | |
| Effectiveness in Early Identification of Potential Risk | | High | High | | | | | | |
| Effectiveness in Identification of Product Improvements | | High | High | | | | | | |
| Effectiveness in Saving Cost | | | Medium | Low | | | | | |
| Effectiveness in Overall Design Quality | | High | High | | | | | | |
| Techniques Used | Establish risk acceptance criteria | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, Risk Benefit Analysis | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, Risk Benefit Analysis, Risk Assessment of Complaint Data/Customer Feedback | | | | |

LEGEND

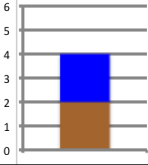

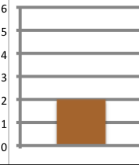
| Degree of Change | | Effectiveness | |
|------------------|--|---------------|--|
| Design | | High | |
| Manufacturing | | Medium | |
| Labeling | | Low | |

Figure 12: Degree of change and RM effectiveness assessment (Respondent no. 10)

Medical Device Type:
Therapeutic, Implantable

Approximate Time Since Market Release:
Not yet released – in clinical trial

Device Development History:
New, first generation device marketed
for first time

| Phase | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring & Reporting |
|---|----------------------------------|--|--|---|---|---|------------------------|-----------------------------------|---|
| Degree of Change | |  | | |  |  | | | |
| Effectiveness in Catching Problems | | High | High | Low | High | High | | | |
| Effectiveness in Early Identification of Potential Risk | | | | | | | | | |
| Effectiveness in Identification of Product Improvements | | | High | Low | High | High | | | |
| Effectiveness in Saving Cost | | | High | | | | | | |
| Effectiveness in Overall Design Quality | High | High | High | High | High | Low | | | |
| Techniques Used | No specific technique identified | No specific technique identified | Establish risk acceptance criteria, Human Factors/Usability Analysis/Use FMEA, DFMEA, PFMEA, Risk Benefit Analysis | Risk Assessment of Complaint Data/Customer Feedback | Establish risk acceptance criteria, Human Factors/Usability Analysis/Use FMEA, DFMEA, PFMEA, Risk Benefit Analysis, Risk Assessment of Complaint Data/Customer Feedback | | | | |

LEGEND





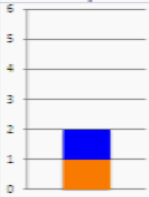
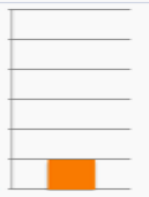
| Degree of Change | | Effectiveness | |
|------------------|---|---------------|--|
| Design |  | High |  |
| Manufacturing |  | Medium |  |
| Labeling |  | Low |  |

Figure 13: Degree of change and RM effectiveness assessment (Respondent no. 11)

Medical Device Type:
Implantable

Approximate Time Since Market Release:
Not yet released – in clinical trial

Device Development History:
New, first generation device marketed
for first time

| Phase | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring & Reporting |
|---|-------------------|---|---|-----------------|---------------------|------------------|------------------------|-----------------------------------|---|
| Degree of Change | |  |  | | | | | | |
| Effectiveness in Catching Problems | High | High | Medium | | | | | | |
| Effectiveness in Early Identification of Potential Risk | High | High | Medium | | | | | | |
| Effectiveness in Identification of Product Improvements | High | Medium | Medium | | | | | | |
| Effectiveness in Saving Cost | High | Medium | Low | | | | | | |
| Effectiveness in Overall Design Quality | High | Medium | Low | | | | | | |
| Techniques Used | Hazard ID/PHA | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, DFMEA | Establish risk acceptance criteria, Hazard ID/PHA, Human Factors/Usability Analysis/Use FMEA, DFMEA | | | | | | |

LEGEND







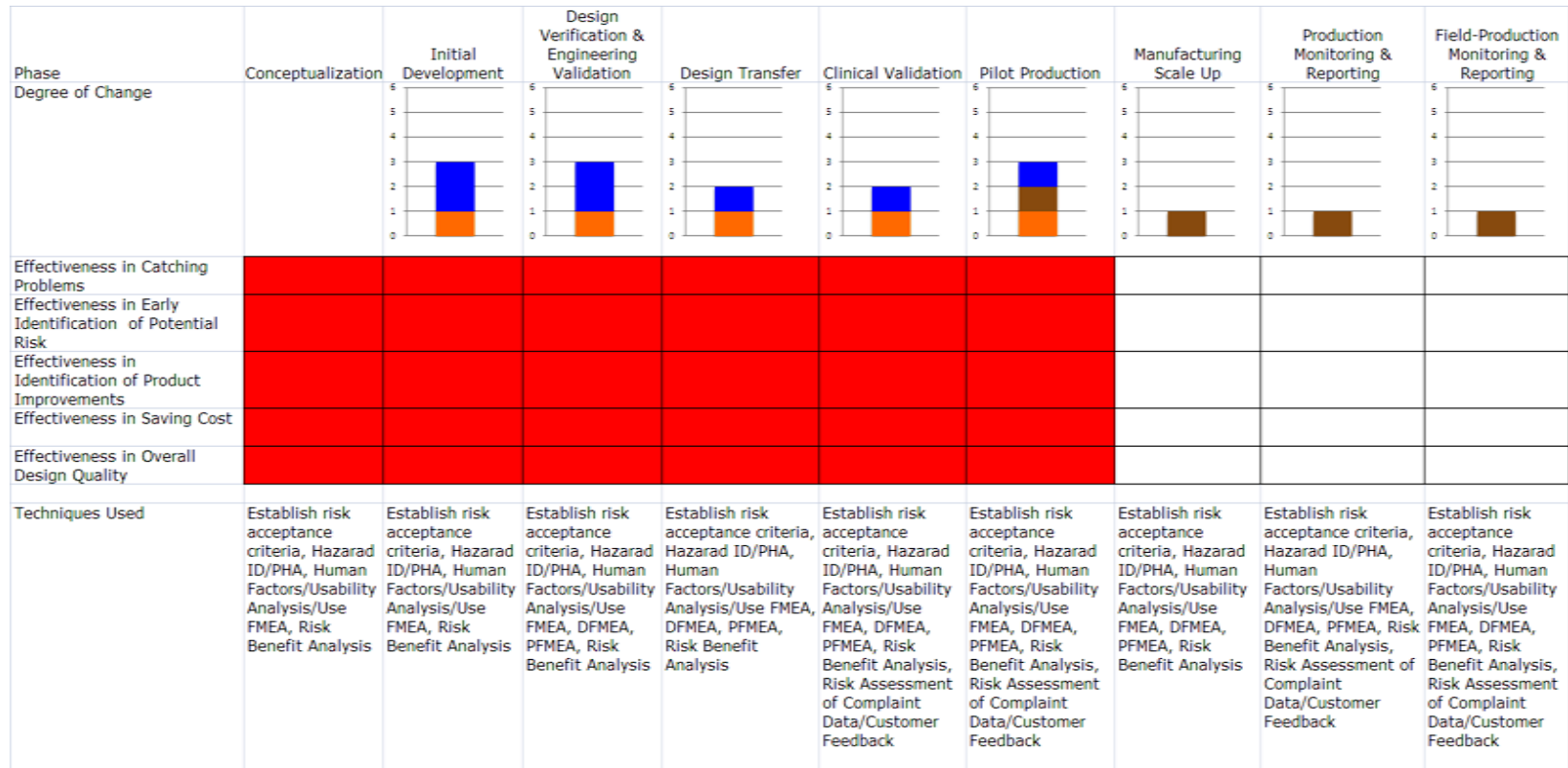
| Degree of Change | | Effectiveness | |
|------------------|---|---------------|--|
| Design |  | High |  |
| Manufacturing |  | Medium |  |
| Labeling |  | Low |  |

Figure 14: Degree of change and RM effectiveness assessment (Respondent no. 12)

Medical Device Type:
Therapeutic - investigational device
for migraine pain

Approximate Time Since Market Release:
Not yet released – in clinical trial

Device Development History:
New, first generation device marketed
for first time



LEGEND

| Degree of Change | | Effectiveness | |
|------------------|--|---------------|--|
| Design | | High | |
| Manufacturing | | Medium | |
| Labeling | | Low | |

Figure 15: Degree of change and RM effectiveness assessment (Respondent no. 13)

Medical Device Type:
 Therapeutic
 Surgical/Clinical Tools
 Diagnostic
 Implantable

Approximate Time Since Market Release:
 18 to 36 months

Device Development History:
 Revision of previous first generation
 device

(Invalid responses for effectiveness)

| Phase | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring & Reporting |
|---|--|--|--|--|----------------------------------|----------------------------------|----------------------------------|-----------------------------------|---|
| Degree of Change | | | | | | | | | |
| Effectiveness in Catching Problems | | | | | | | | | |
| Effectiveness in Early Identification of Potential Risk | | | | | | | | | |
| Effectiveness in Identification of Product Improvements | | | | | | | | | |
| Effectiveness in Saving Cost | | | | | | | | | |
| Effectiveness in Overall Design Quality | | | | | | | | | |
| Techniques Used | Establish risk acceptance criteria, Human Factors/Usability Analysis/Use FMEA, DFMEA, HAZOP, HACCP, Risk Benefit Analysis, Risk Assessment of Complaint Data/Customer Feedback | Establish risk acceptance criteria, Human Factors/Usability Analysis/Use FMEA, DFMEA, HAZOP, HACCP, Risk Benefit Analysis, Risk Assessment of Complaint Data/Customer Feedback | Establish risk acceptance criteria, Human Factors/Usability Analysis/Use FMEA, DFMEA | Establish risk acceptance criteria, Human Factors/Usability Analysis/Use FMEA, DFMEA | No specific technique identified | No specific technique identified | No specific technique identified | No specific technique identified | Establish risk acceptance criteria, Human Factors/Usability Analysis/Use FMEA |

LEGEND

| Degree of Change | | Effectiveness | |
|------------------|--|---------------|--|
| Design | | High | |
| Manufacturing | | Medium | |
| Labeling | | Low | |

Figure 16: Degree of change and RM effectiveness assessment (Respondent no. 14)

Table 3: Summary of the Effectiveness of RM activities by Respondent

| Respondent No. | Device Type | Development History | Time since Market Release | Summary of response |
|----------------|---------------|--|---------------------------|--|
| 1 | Surgical tool | Revision of previous first generation device | Greater than 3 years | <p>RM techniques used:</p> <ul style="list-style-type: none"> • Establish risk acceptance criteria • Hazard ID/PHA • Human Factors/Usability Analysis/Use FMEA • FTA • DFMEA • Risk Benefit Analysis • Risk Assessment of Complaint Data/Customer Feedback <p>Degree of change</p> <ul style="list-style-type: none"> • Design, manufacturing and labeling changes during the pre-market stage. <p>Effectiveness of RM</p> <ul style="list-style-type: none"> • Rated high on all factors during all pre-market stages. |
| 2 | Surgical tool | Unknown | Unknown | <p>RM techniques used:</p> <ul style="list-style-type: none"> • Establish risk acceptance criteria • Hazard ID/PHA • Human Factors/Usability Analysis/Use FMEA • Risk Benefit Analysis • Risk Assessment of Complaint |

| | | | | |
|---|-------------------|--|-----------------|--|
| | | | | <p>Data/Customer Feedback</p> <p>Degree of change (No response)</p> <p>Effectiveness of RM</p> <ul style="list-style-type: none"> • Cost savings was rated high at the conceptualization stage. • Highly effective in catching problems and identification of product improvements during field-production monitoring and reporting. |
| 3 | Other - Catheters | New, first generation device marketed for first time | 18 to 36 months | <p>(Not reliable data for techniques used)</p> <p>RM techniques used:</p> <ul style="list-style-type: none"> • Establish risk acceptance criteria • Hazard ID/PHA • Human Factors/Usability Analysis/Use FMEA • FTA • DFMEA • PFMEA • HAZOP • HACCP • Risk Benefit Analysis • Risk Assessment of Complaint Data/Customer Feedback <p>Degree of change:</p> <ul style="list-style-type: none"> • More design changes at both |

| | | | | |
|---|---------------|--|----------------|--|
| | | | | <p>pre-market and post-market stages.</p> <ul style="list-style-type: none"> • Design, manufacturing and labeling changes at both pre-market and post-market stages <p>Effectiveness of RM:</p> <ul style="list-style-type: none"> • Highly effective for all factors (except for cost savings) at the pre-market stage. • Cost savings and overall design quality were rated highly effective at the post-market stage. |
| 4 | Surgical tool | Revision of previous first generation device | 6 to 18 months | <p>RM techniques used:</p> <ul style="list-style-type: none"> • Establish risk acceptance criteria • Hazard ID/PHA • Human Factors/Usability Analysis/Use FMEA • FTA • DFMEA • HACCP • Risk Benefit Analysis • Risk Assessment of Complaint Data/Customer Feedback <p>Degree of change:</p> <ul style="list-style-type: none"> • Design and labeling changes during the early stages. |

| | | | | |
|---|-----------------|----------------------------------|----------------|--|
| | | | | <p>Effectiveness of RM:</p> <ul style="list-style-type: none"> • Highly effective for all factors (except for identification of product improvements) at the earlier stages. • Identification of product improvements was rated high at a later stage. |
| 5 | Diagnostic tool | Third or later generation device | 6 to 18 months | <p>RM techniques used:</p> <ul style="list-style-type: none"> • Establish risk acceptance criteria • Hazard ID/PHA • Human Factors/Usability Analysis/Use FMEA • DFMEA • Risk Assessment of Complaint Data/Customer Feedback <p>Degree of change:</p> <ul style="list-style-type: none"> • Design and labeling changes at V&V and post-market stage. <p>Effectiveness of RM:</p> <ul style="list-style-type: none"> • Catching problems was rated high at both pre- and post-market stages. • Overall design quality is highly effective at the pre-market stage. • Identification of product improvements was rated high at a later stage. |

| | | | | |
|---|-----------------|--|----------------------|---|
| 6 | Diagnostic tool | Revision of previous first generation device | Greater than 3 years | <p>RM techniques used:</p> <ul style="list-style-type: none"> • Establish risk acceptance criteria • Hazard ID/PHA • Human Factors/Usability Analysis/Use FMEA • FTA • DFMEA • PFMEA • Risk Assessment of Complaint Data/Customer Feedback <p>Degree of change:</p> <ul style="list-style-type: none"> • Design changes at initial development and V&V. • Manufacturing changes at a later stage. <p>Effectiveness of RM:</p> <ul style="list-style-type: none"> • Rated highly effective for all factors in the earlier stages. • Effectiveness was not indicated in the later stages, but it can be inferred that RM techniques were less effective during those stages. |
| 7 | Diagnostic tool | Revision of previous first generation device | Greater than 3 years | <p>RM techniques used:</p> <ul style="list-style-type: none"> • Establish risk acceptance criteria • Hazard ID/PHA • Human Factors/Usability Analysis/Use FMEA |

| | | | | |
|---|-------------|--|----------------------|--|
| | | | | <ul style="list-style-type: none"> • FTA • DFMEA • Risk Benefit Analysis • Risk Assessment of Complaint Data/Customer Feedback <p>Degree of change:</p> <ul style="list-style-type: none"> • Design, manufacturing and labeling changes at the earlier stages and at the production monitoring & reporting stage <p>Effectiveness of RM:</p> <ul style="list-style-type: none"> • Early identification of potential risk, identification of product improvements and overall design quality were highly effective during conceptualization. • All factors were highly effective for all factors during initial development. • Catching problems was rated high during manufacturing scale-up. (No technique identified at this stage but effectiveness was indicated.) |
| 8 | Implantable | New, first generation device marketed for first time | Greater than 3 years | <p>RM techniques used:</p> <ul style="list-style-type: none"> • Establish risk acceptance criteria • Hazard ID/PHA • Human Factors/Usability |

| | | | | |
|---|-------------|----------------------------------|--------------------------------------|--|
| | | | | <p>Analysis/Use FMEA</p> <ul style="list-style-type: none"> • FTA • DFMEA • PFMEA • HAZOP • HACCP • Risk Benefit Analysis • Risk Assessment of Complaint Data/Customer Feedback <p>Degree of change:</p> <ul style="list-style-type: none"> • Design was actually evolved. • Many later stage changes on design, manufacturing and labeling. <p>Effectiveness of RM (No response)</p> |
| 9 | Implantable | Third or later generation device | Not yet released – in clinical trial | <p>RM techniques used:</p> <ul style="list-style-type: none"> • Establish risk acceptance criteria • Hazard ID/PHA • Human Factors/Usability Analysis/Use FMEA • DFMEA • PFMEA • Risk Benefit Analysis <p>Degree of change:</p> <ul style="list-style-type: none"> • Early design changes. • Manufacturing change during |

| | | | | |
|----|-------------|--|--------------------------------------|--|
| | | | | <p>V&V.</p> <p>Effectiveness of RM</p> <ul style="list-style-type: none"> • Highly effective for all factors during the earlier stages of the pre-market phase. |
| 10 | Implantable | New, first generation device marketed for first time | Not yet released – in clinical trial | <p>RM techniques used:</p> <ul style="list-style-type: none"> • Establish risk acceptance criteria • Hazard ID/PHA • Human Factors/Usability Analysis/Use FMEA • Risk Benefit Analysis • Risk Assessment of Complaint Data/Customer Feedback <p>Degree of change:</p> <ul style="list-style-type: none"> • Design, manufacturing and labeling changes at the pre-market stage. <p>Effectiveness of RM</p> <ul style="list-style-type: none"> • RM techniques are highly effective for all factors during the pre-market stage (except for saving cost). |
| 11 | Implantable | New, first generation device marketed for first time | Not yet released – in clinical trial | <p>RM techniques used:</p> <ul style="list-style-type: none"> • Establish risk acceptance criteria • Human Factors/Usability |

| | | | | |
|----|-------------|--|--------------------------------------|--|
| | | | | <p>Analysis/Use FMEA</p> <ul style="list-style-type: none"> • DFMEA • PFMEA • Risk Benefit Analysis • Risk Assessment of Complaint Data/Customer Feedback <p>Degree of change:</p> <ul style="list-style-type: none"> • Labeling and manufacturing changes at the pre-market stage. • Some design change during clinical validation. <p>Effectiveness of RM</p> <ul style="list-style-type: none"> • Overall design quality is highly effective during the pre-market stage. • Catching problems and early identification of product improvements were rated highly effective during V&V and pilot production. |
| 12 | Implantable | New, first generation device marketed for first time | Not yet released – in clinical trial | <p>RM techniques used:</p> <ul style="list-style-type: none"> • Establish risk acceptance criteria • Hazard ID/PHA • Human Factors/Usability Analysis/Use FMEA • DFMEA |

| | | | | |
|----|-------------|--|--------------------------------------|--|
| | | | | <p>Degree of change:</p> <ul style="list-style-type: none"> • Only labeling changes were indicated from V&V. • Design and manufacturing changes at the initial development. <p>Effectiveness of RM</p> <ul style="list-style-type: none"> • Effectiveness was primarily indicated for cost savings and overall design quality. |
| 13 | Therapeutic | New, first generation device marketed for first time | Not yet released – in clinical trial | <p>RM techniques used:</p> <ul style="list-style-type: none"> • Establish risk acceptance criteria • Hazard ID/PHA • Human Factors/Usability Analysis/Use FMEA • DFMEA • PFMEA • Risk Benefit Analysis • Risk Assessment of Complaint Data/Customer Feedback <p>Degree of change:</p> <ul style="list-style-type: none"> • Very active design changes in RM. <p>Effectiveness of RM</p> <ul style="list-style-type: none"> • Rated very highly effective. |
| 14 | Unknown | Revision of previous first generation device | 18 to 36 months | <p>RM techniques used:</p> <ul style="list-style-type: none"> • Establish risk acceptance criteria |

| | | | | |
|--|--|--|--|--|
| | | | | <ul style="list-style-type: none"> • Human Factors/Usability Analysis/Use FMEA • DFMEA • HAZOP • HACCP • Risk Benefit Analysis • Risk Assessment of Complaint Data/Customer Feedback <p>Degree of change:</p> <ul style="list-style-type: none"> • Very active design changes in RM. <p>Effectiveness of RM (No response)</p> |
|--|--|--|--|--|

Summary and Conclusion

Risk management activities are employed by medical device companies to ensure that the intended use and purpose of the medical device are properly addressed and the known and foreseeable hazards are well identified. Regardless of the medical device classification, the use of the appropriate RM activities according to device type and maturity play a significant role in determining the effectiveness of the activities utilized. This risk management survey was conducted to understand the use and effectiveness of the risk management activities and how these activities impact the medical device development.

The 14 respondents may not be enough to arrive at a statistically significant evaluation of RM activities. However, a trend is evident in the survey showing a switch of the effectiveness ratings in the entire life cycle, and how the degree of change was measured throughout the device phase. Therefore, these results may be used as a guide to improve risk management practices.

A survey on the implementation and effectiveness of risk management activities was carried out in this research to achieve an accurate assessment of how RM activities can contribute to the level of change in the design and manufacturing processes and how RM activities are recognized as vital to the medical device design and manufacturing operations.

The degree of change and measure of effectiveness of RM activities based on survey results were significantly impacted by the following factors: device type, time

since market release, and device development history. Table 4 summarizes the RM effectiveness based on survey results.

Further studies on the impact of RM activities in the medical device industry is highly encouraged to achieve a better understanding of the significance that these activities bring to influence the development of a medical device.

Table 4: Summary of RM Effectiveness from the Survey

| Device Type (Number of respondent) | Pre-Market Effectiveness of RM Activities | Post-Market Effectiveness of RM Activities |
|------------------------------------|--|---|
| Surgical Tools & catheters (4) | Relatively more effective for all purposes especially second generation devices | Some effectiveness especially for costs savings and product improvement |
| Diagnostic devices (3) | Relatively more effective for early identification and overall design quality | Relatively less effective (except for catching problems and cost savings where RM has some effectiveness) |
| Implantables (5) | Generally rated less effective than for other device types. Most effectiveness was indicated for overall product quality | (Not enough respondents had devices in post-market stage) |
| Other therapeutic devices (1) | Rated highly effective on all factors | (No data) |

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Appendices

Appendix A: Examples of SR and NSR devices (CDRH, 2006)

A. Nonsignificant Risk Devices

- Caries Removal Solution
- Contact Lens Solutions intended for use directly in the eye (e.g., lubricating/rewetting solutions) using active ingredients or preservation systems with a history of prior ophthalmic/contact lens use or generally recognized as safe for ophthalmic use
- Conventional Gastroenterology and Urology Endoscopes and/or Accessories
- Conventional General Hospital Catheters (long-term percutaneous, implanted, subcutaneous and intravascular)
- Conventional Implantable Vascular Access Devices (Ports)
- Conventional Laparoscopes, Culdoscopes, and Hysteroscopes
- Daily Wear Contact Lenses and Associated Lens Care Products not intended for use directly in the eye (e.g., cleaners; disinfecting, rinsing and storage solutions)
- Dental Filling Materials, Cushions or Pads made from traditional materials and designs
- Denture Repair Kits and Realigners
- Digital Mammography

- Electroencephalography (e.g., new recording and analysis methods, enhanced diagnostic capabilities, measuring depth of anesthesia if anesthetic administration is not based on device output)
- Externally Worn Monitors for Insulin Reactions
- Functional Non-Invasive Electrical Neuromuscular Stimulators
- General Biliary Catheters
- General Urological Catheters (e.g., Foley and diagnostic catheters) for short term use (< 28 days)
- Jaundice Monitors for Infants
- Low Power Lasers for treatment of pain
- Magnetic Resonance Imaging (MRI) Devices within FDA specified parameters
- Manual Image Guided Surgery
- Menstrual Pads (Cotton or Rayon, only)
- Menstrual Tampons (Cotton or Rayon, only)
- Nonimplantable Electrical Incontinence Devices
- Nonimplantable Male Reproductive Aids with no components that enter the vagina
- Ob/Gyn Diagnostic Ultrasound within FDA approved parameters
- Partial Ossicular Replacement Prosthesis (PORP)
- Total Ossicular Replacement Prosthesis (TORP)
- Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of pain (except for chest pain/angina)
- Ureteral Stents
- Urethral Occlusion Device for less than 14 days
- Wound Dressings, excluding absorbable hemostatic devices and dressings (also excluding Interactive Wound and Burn Dressings that aid or are intended to aid in the healing process)

B. Significant Risk Devices

1. General Medical Use

- Catheters for General Hospital Use - except for conventional long-term percutaneous, implanted, subcutaneous and intravascular
- Collagen Implant Material for use in ear, nose and throat, orthopedics, plastic surgery, urological and dental applications
- Surgical Lasers for use in various medical specialties
- Tissue Adhesives for use in neurosurgery, gastroenterology, ophthalmology, general and plastic surgery, and cardiology

2. Anesthesiology

- Breathing Gas Mixers
- Bronchial Tubes

- Electroanesthesia Apparatus
- Epidural and Spinal Catheters
- Epidural and Spinal Needles
- Esophageal Obturators
- Gas Machines for anesthesia or analgesia
- High Frequency Ventilators greater than 150 BPM
- Rebreathing Devices
- Respiratory Ventilators and new modes of ventilation
- Tracheal Tubes

3. *Cardiovascular*

- Annuloplasty Rings
- Aortic and Mitral Valvuloplasty Catheters
- Arterial Embolization Devices
- Atherectomy and Thrombectomy Catheters
- Cardiac Assist Devices: artificial hearts, ventricular assist devices, intra-aortic balloon pumps, cardiomyoplasty devices
- Cardiac Bypass Devices: oxygenators, cardiopulmonary blood pumps, axial flow pumps, closed chest devices (except Class I cardiovascular surgical instruments), heat exchangers, catheters/cannulae, tubing, arterial filters, reservoirs
- Cardiac Mapping and Ablation Catheters
- Cardiac Pacemaker/Pulse Generators: antitachycardia, esophageal, external transcutaneous, implantable
- Cardiopulmonary Resuscitation (CPR) Devices
- Cardiovascular Intravascular (vena cava) Filters
- Coronary Artery Retroperfusion Systems
- Distal Embolic Protection Devices
- Extracorporeal Counterpulsation Devices
- Extracorporeal Membrane Oxygenators (ECMO)
- Implantable Cardioverters/Defibrillators
- Intravascular Brachytherapy Devices
- Intravascular Stents
- Laser Angioplasty Catheters
- Organ Storage/Transport Units
- Pacing Leads
- Percutaneous Conduction Tissue Ablation Electrodes
- Percutaneous Transluminal Angioplasty Catheters
- Replacement Heart Valves
- Transcatheter Cardiac Occluders for atrial and ventricular septal defects, patent foramen ovale and patent ductus arteriosus

- Transmyocardial Revascularization, Percutaneous Myocardial Revascularization Devices
- Ultrasonic Angioplasty Catheters
- Vascular and Arterial Graft Prostheses
- Vascular Hemostasis Devices

4. *Dental*

- Absorbable Materials to aid in the healing of periodontal defects and other maxillofacial applications
- Bone Morphogenic Proteins with and without bone, e.g., Hydroxyapatite (HA)
- Dental Lasers for hard tissue applications
- Endosseous Implants and associated bone filling and augmentation materials used in conjunction with the implants
- Subperiosteal Implants
- Temporomandibular Joint (TMJ) Prostheses

5. *Ear, Nose And Throat*

- Absorbable Gelatin Sponge
- Auditory Brainstem Implants
- Cochlear Implants
- Endolymphatic Shunt Tubes with or without valve
- ENT Cements/Adhesives
- Implantable Bone Conduction Hearing Aids
- Implantable Middle Ear Hearing Device
- Injectable Teflon Paste
- Laryngeal Implants
- Synthetic Polymer Materials
- Tissue Autofluorescent Devices
- Vocal Cord Medialization (Augmentation) Devices

6. *Gastroenterology And Urology*

- Anastomosis Devices
- Balloon Dilation Catheters for benign prostatic hyperplasia (BPH)
- Biliary Stents
- Components of Water Treatment Systems for Hemodialysis
- Dialysis Delivery Systems
- Electrical Stimulation Devices for sperm collection
- Embolization Devices for general urological use
- Extracorporeal Circulation Systems
- Extracorporeal Hyperthermia Systems
- Extracorporeal Photopheresis Systems

- Femoral, Jugular and Subclavian Catheters
- Hemodialyzers
- Hemofilters
- Implantable Electrical Urinary Incontinence Systems
- Implantable Penile Protheses
- Injectable Bulking Agents for incontinence
- Lithotripters (e.g., electrohydraulic extracorporeal shock-wave, laser, powered mechanical, ultrasonic)
- Mechanical/Hydraulic Urinary Incontinence Devices
- Penetrating External Penile Rigidity Devices with components that enter the vagina
- Peritoneal Dialysis Devices
- Peritoneal Shunt
- Plasmapheresis Systems
- Prostatic Hyperthermia or Thermal Ablation Devices
- Retention Type (Foley) Balloon Catheters for long term use (≥ 28 days)
- Suprapubic Urological Catheters and accessories
- Urethral Occlusion Devices for greater than 14 days use
- Urethral Sphincter Protheses
- Urological Catheters with anti-microbial coatings
- Urological Stents (e.g., urethral, prostate, etc.)

7. *General And Plastic Surgery*

- Absorbable Adhesion Barrier Devices
- Absorbable Hemostatic Agents
- Artificial Skin and Interactive Wound and Burn Dressings
- Breast Implants
- Injectable Collagen
- Implantable Craniofacial Protheses
- Repeat Access Devices for surgical procedures
- Sutures

8. *General Hospital*

- Implantable Vascular Access Devices (Ports) - if new routes of administration or new design
- Infusion Pumps (implantable and closed-loop - depending on the infused drug)

9. *Neurological*

- Electroconvulsive Therapy (ECT) Devices
- Hydrocephalus Shunts
- Implanted Intracerebral/Subcortical Stimulators
- Implanted Intracranial Pressure Monitors

- Implanted Spinal Cord and Nerve Stimulators and Electrodes
- Neurological Catheters (e.g., cerebrovascular, occlusion balloon, etc.)
- Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of chest pain/angina

10. *Obstetrics And Gynecology*

- Abdominal Decompression Chamber
- Antepartum Home Monitors for Non-Stress Tests
- Antepartum Home Uterine Activity Monitors
- Catheters for Chorionic Villus Sampling (CVS)
- Catheters Introduced into the Fallopian Tubes
- Cervical Dilation Devices
- Contraceptive Devices:
 - Cervical Caps
 - Condoms (for men) made from new materials (e.g., polyurethane)
 - Contraceptive *In Vitro* Diagnostics (IVDs)
 - Diaphragms
 - Female Condoms
 - Intrauterine Devices (IUDs)
 - New Electrosurgical Instruments for Tubal Coagulation
 - New Devices for Occlusion of the Vas Deferens
 - Sponges
 - Tubal Occlusion Devices (Bands or Clips)
- Cryomyolysis
- Devices to Prevent Post-op Pelvic Adhesions
- Embryoscopes and Devices intended for fetal surgery
- Endometrial Ablation Systems
- Falloposcopes and Falloposcopic Delivery Systems
- Fundal Pressure Belt (for vaginal assisted delivery)
- Gamete and Embryo Surgical Systems
- Intrapartum Fetal Monitors using new physiological markers
- New Devices to Facilitate Assisted Vaginal Delivery
- Operative Hysteroscopy and Laparoscopy
- Uterine Artery Embolization

11. *Ophthalmics*

- Aniridia Intraocular Lenses (IOLs) or Rings (for iris reconstruction)
- Capsular Tension Rings
- Class III Ophthalmic Lasers

- Contact Lens Solutions intended for direct instillation (e.g., lubrication/rewetting solutions) in the eye using new active agents or preservatives with no history of prior ophthalmic/contact lens use or not generally recognized as safe for ophthalmic use
- Corneal Storage Media
- Extended Wear Contact Lens (i.e., including a single overnight use)
- Glaucoma Treatment Devices (e.g., trabeculoplasty devices, devices that treat ciliary bodies, devices that raise or lower intraocular pressure, aqueous shunt/drainage devices, etc.)
- Implants for Refractive Purposes (e.g., intraocular lenses, corneal implants, scleral expansion bands, etc.)
- Intraocular Lenses (IOLs)
- Keratoprotheses
- Refractive Surgical Devices (e.g., lasers, electrical current devices, thermal and non-thermal keratoplasty devices, ablation devices, expansion rings, treatment of ciliary bodies, etc.)
- Retinal Disease Treatment Devices (e.g., electrical stimulation devices to treat macular degeneration, lasers to ablate epiretinal membranes and vitreous strands, etc.)
- Retinal Prosthesis (implant)
- Retinal Reattachment Devices (e.g., fluids, gases, perfluorocarbons, perfluoropropane, silicone oil, sulfur hexafluoride, balloon catheter for retinal reattachment)
- Viscosurgical Fluids (viscoelastics)

12. Orthopedics And Restorative

- Anti-Adhesion Gels
- Bone Growth Stimulators
- Bone Morphogenetic Proteins/Biodegradable Scaffolds combination products, with or without allograft/autograft combinations and with or without metallic implant
- Bone Void Fillers (hydroxyapatite and other materials)
- Bovine Collagen Meniscus Implants
- Computer Guided Robotic Surgery
- Implantable Peripheral Neuromuscular Stimulators
- Implantable Protheses (ligament, tendon, hip, knee, finger)
- Implantable Spinal Devices
- Injectable Sodium Hyaluronate

13. Radiology

- Boron Neutron Capture Therapy
- Hyperthermia Systems and Applicators

Appendix B: “Scope of File Review by Submission Type” (WHO, 2003)

| Characteristic of 510(k) submission | Included in file review? | Reason |
|--|--------------------------|---|
| Submission type | | |
| Traditional | Yes | Traditional 510(k) submissions are the conventional 510(k) submission type used to clear new devices for market. Traditional submissions constituted the majority of 510(k) submissions made to FDA during the time of our review. |
| Abbreviated | Yes | Abbreviated 510(k) submissions are a streamlined version of the traditional 510(k) process. In an abbreviated 510(k) submission, applicants use guidance documents, special controls, or performance standards to assess and then report on the performance of their new device to expedite review. |
| Special | No | Special 510(k) submissions are submitted for a modification to a device that has been cleared through the 510(k) process. We excluded them from our review because this type of submission is only used for modifications to a device which has already cleared the 510(k) process. |
| Review decision | | |
| Substantially equivalent (SE) | Yes | The submissions completed the 510(k) review process and were cleared for market. |
| Not substantially equivalent (NSE) | Yes | The submissions completed the 510(k) review process and were not cleared for market. |
| Withdrawn | No | Withdrawn submissions did not complete the 510(k) review process. |
| Deleted | No | Deleted submissions did not complete the 510(k) review process. |
| FDA office or center | | |
| Center for Devices and Radiological Health, Office of Device Evaluation | Yes | This office administers the 510(k), PMA, Humanitarian Device Exemption, and Investigational Device Exemption programs. It processes the majority of 510(k) submissions each year: for example, in FY 2007, it processed 85 percent of all 510(k) submissions. |
| Center for Devices and Radiological Health, Office of In Vitro Diagnostic Device Evaluation and Safety | No | This office oversees the regulation of devices such as in-home and laboratory diagnostic tests, and processes relatively few 510(k) submissions each year. In FY 2007, it processed 13 percent of all 510(k) submissions. |
| Center for Biologics Evaluation and Research | No | This office oversees devices such as those used for licensed blood collection and processing, and processes relatively few 510(k) submissions each year. In FY 2007, it processed 2 percent of all 510(k) submissions. |

Source: GAO.

Appendix C: Typical PHA worksheet (ISO, 2007)

System: _____ Operating mode: _____ Analyst: _____
Date: _____

| Ref. | Hazard | Accidental event (what, where, when) | Probable causes | Contingencies/ Preventive actions | Prob. | Sev. | Comments |
|------|--------|---|--------------------|--------------------------------------|-------|------|----------|
| | | | | | | | |

Appendix D: Snapshot of the survey questionnaire

Risk Management Survey

Introduction

1. Please tell us about you. (OPTIONAL)

Name:

Company:

Address:

Address 2:

City/Town:

State:

ZIP:

Country:

Email Address:

Phone Number:

2. Which of the following best describes your company. (Check all that apply)

- Market medical device
- Manufacture medical device
- Provide components for medical device
- Provide design and development services for medical device
- Other (please specify)

* 3. Are medical device design and risk management activities performed in your company?

- Yes
- No

4. From the list below, please indicate to which standards your company is in compliance.

- ISO 13485
- ISO 14971:2000
- ISO 14971:2007
- ICH Q9
- Other (please specify)

5. Please indicate the guidance documents that you use for risk management.

- GHTF Guidance
- Other (please specify)

6. Please indicate the number of product line your company deals with.

- 1 product line
- 2 to 5 product lines
- More than 5 product lines

7. Please indicate the medical device type. (Check all that apply)

- Therapeutic
- Surgical/Clinical Tools
- Diagnostic
- Instrument Disposable
- Implantable
- Other (please specify)

8. Please provide a brief description. (OPTIONAL)

9. Please indicate the FDA risk classification.

- Class I
- Class II
- Class III

10. What is the EU MDD risk classification?

- Class I
- Class IIa
- Class IIb
- Class III

11. Please indicate the US pre-market regulatory pathway.

- Exempt
- 510(k): Traditional
- 510(k): Special
- 510(k): Abbreviated
- 510(k): De Novo Process
- PMA: Traditional
- PMA: Modular
- PMA: Streamlined
- Humanitarian Device Exemption (HDE)

12. Please select the description of the device development history.

- New, first generation device marketed for first time
- Revision of previous first generation device
- Second generation device with significant design or manufacturing change from previous model
- Third or later generation device

13. What is the approximate time since market release of this model?

- Not yet released – in clinical trial
- Less than 6 months
- 6 months to 18 months
- 18 to 36 months
- Greater than 3 years

14. Please indicate the number of units sold or used in clinical trials.

- Less than 5
- 5 to 30
- 30 to 100
- Greater than 100

15. What is the level of user competence needed to operate this device?

- Lay user
- Professional user (nurse, physician, medical tech, etc.)
- Device-specific training or certification

Risk Management Assessment

16. For the selected device, please indicate all phases during which the risk management activity (left column) was performed, including initial and update.

| | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring & Reporting |
|---|--------------------------|--------------------------|--|--------------------------|--------------------------|--------------------------|--------------------------|-----------------------------------|---|
| Establish Risk Acceptance Criteria | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Hazard ID/PHA | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Human Factors/Usability Analysis/Use FMEA | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| FTA | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| DFMEA or FMECA | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| PFMEA or FMECA | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| HAZOP | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| HACCP | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Risk Benefit Analysis | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Risk Assessment of Complaint Data/Customer Feedback | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Other | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Please specify

17. For the selected device, please indicate the degree of change (left column) that resulted from the output of the above risk management activities during each life cycle phase.

| | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring & Reporting |
|----------------------------------|--------------------------|--------------------------|--|--------------------------|--------------------------|--------------------------|--------------------------|-----------------------------------|---|
| No Change | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Labelling Change | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Minor Design Changes | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| One or More Major Design Changes | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Redesign | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Minor Manufacturing Changes | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Major Manufacturing Changes | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

18. For questions 18 to 22, we would like your assessment of the effectiveness of the above risk management activities in each phase for the selected device.

Effectiveness in catching problems.

| | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring and Reporting |
|--------|--------------------------|--------------------------|--|--------------------------|--------------------------|--------------------------|--------------------------|-----------------------------------|---|
| High | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Medium | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Low | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

19. Effectiveness in the early identification of potential risk.

| | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring and Reporting |
|--------|--------------------------|--------------------------|--|--------------------------|--------------------------|--------------------------|--------------------------|-----------------------------------|---|
| High | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Medium | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Low | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

20. Effectiveness in the identification of product improvements.

| | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring and Reporting |
|--------|--------------------------|--------------------------|--|--------------------------|--------------------------|--------------------------|--------------------------|-----------------------------------|---|
| High | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Medium | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Low | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

21. Effectiveness in saving cost.

| | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring and Reporting |
|--------|--------------------------|--------------------------|--|--------------------------|--------------------------|--------------------------|--------------------------|-----------------------------------|---|
| High | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Medium | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Low | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

22. Effectiveness in the overall design quality.

| | Conceptualization | Initial Development | Design Verification & Engineering Validation | Design Transfer | Clinical Validation | Pilot Production | Manufacturing Scale Up | Production Monitoring & Reporting | Field-Production Monitoring and Reporting |
|--------|--------------------------|--------------------------|--|--------------------------|--------------------------|--------------------------|--------------------------|-----------------------------------|---|
| High | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Medium | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Low | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Appendix E: Survey cover letter

Risk Management Survey

Dear Participant,

I am conducting a study regarding the selection of risk analysis techniques in establishing effective risk management programs for medical devices. I would appreciate your help. The purpose of this study is to enhance understanding of the different risk analysis techniques that are used over the life cycle of a medical device for effective risk detection and prevention. Emphasis is on the selection of suitable risk analysis techniques and their impact on successful risk management.

I am contacting medical device professionals to participate in this study. I believe that your knowledge and understanding of your own device will significantly contribute to the quality of the results obtained from this study.

Your participation on this survey is vital. I would sincerely appreciate it if you would share a few minutes of your time in responding to the questions as completely as you can. Since I will be compiling the survey information by end of April 2010, your prompt response would be very helpful. I will be happy to share the findings of the survey with you.

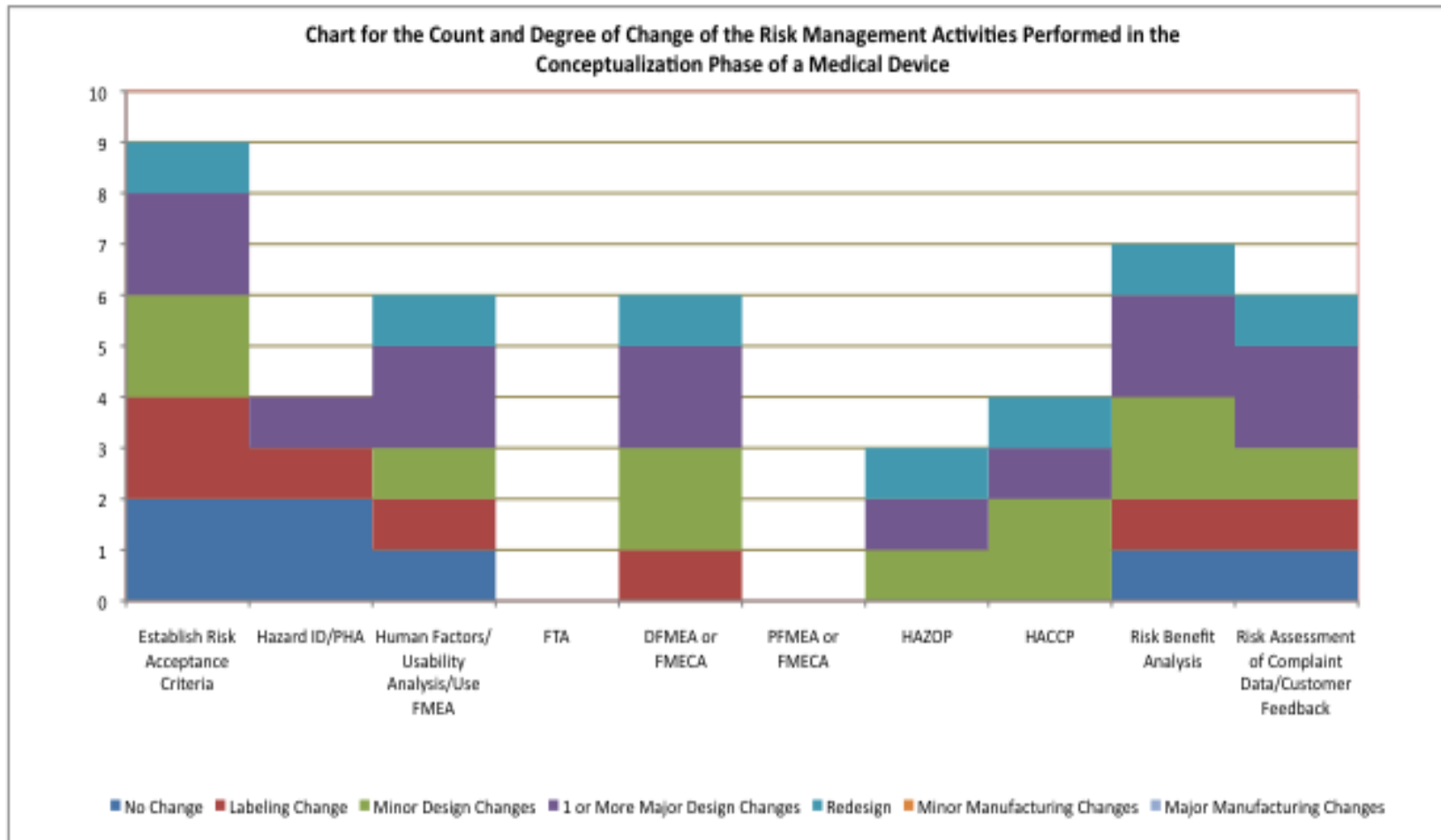
Here is the survey link: <http://www.surveymonkey.com/s/RiskManagement>

You should understand that your participation is voluntary and that choosing not to participate in this study, or in any part of this study, will not affect your relations with San Jose State University. Although the results of this study may be published, any information that could result in identification of you, your company, or your specific device will remain confidential.

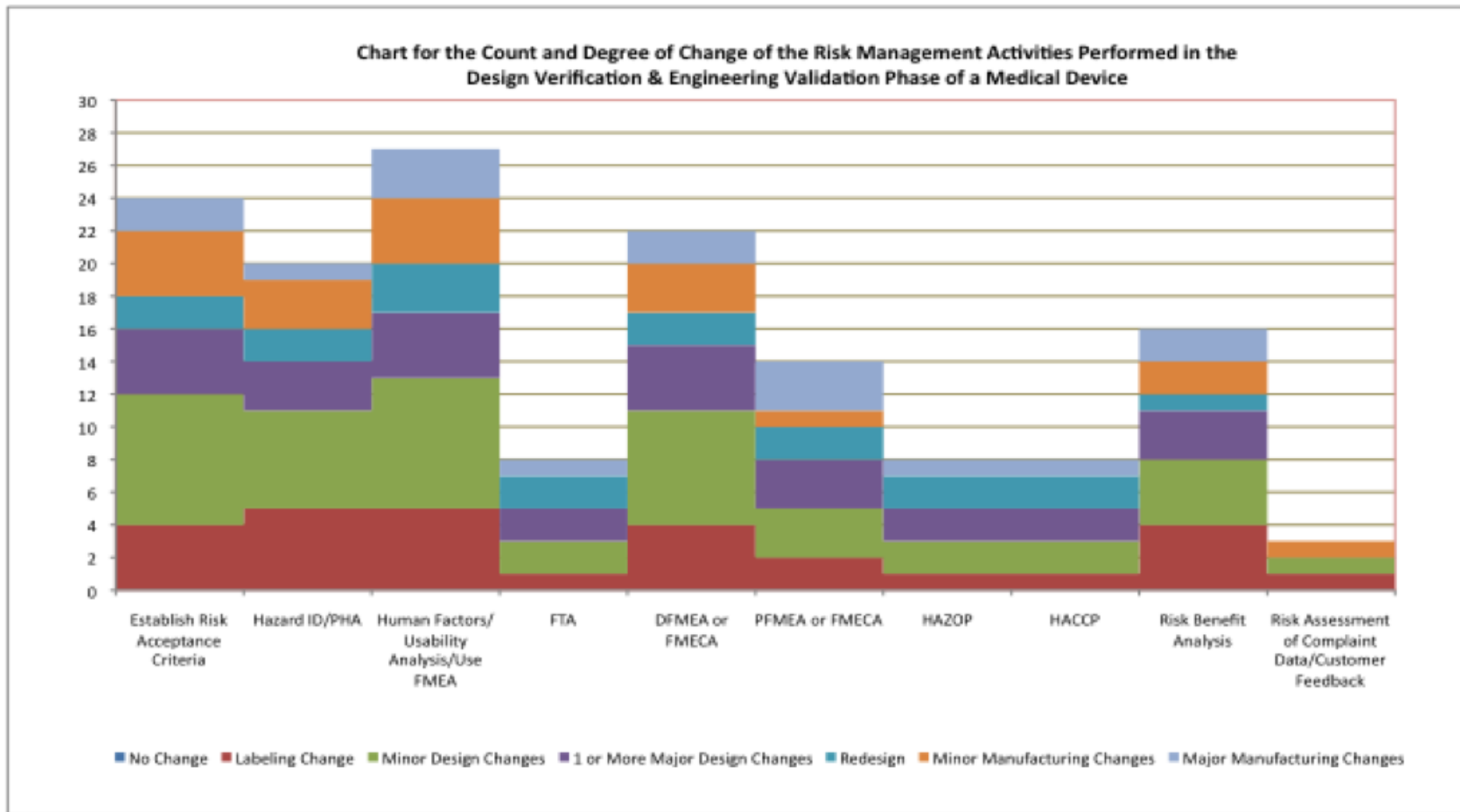
If you have questions about this study, I will be happy to talk with you. I can be reached at (408) 914-0189 or through e-mail at rachelod21@gmail.com. Complaints about the research may be presented to Dr. Seth Bates, Department Chair for Aviation and Technology, at (408) 924-3227. Questions about a research subjects' rights, or research-related injury may be presented to Dr. Pamela Stacks, Associate Vice President, Graduate Studies and Research, at (408) 924-2427.

Very truly yours,
Rachelo Dumbrique
Responsible Investigator
MSQA Candidate
San Jose State University

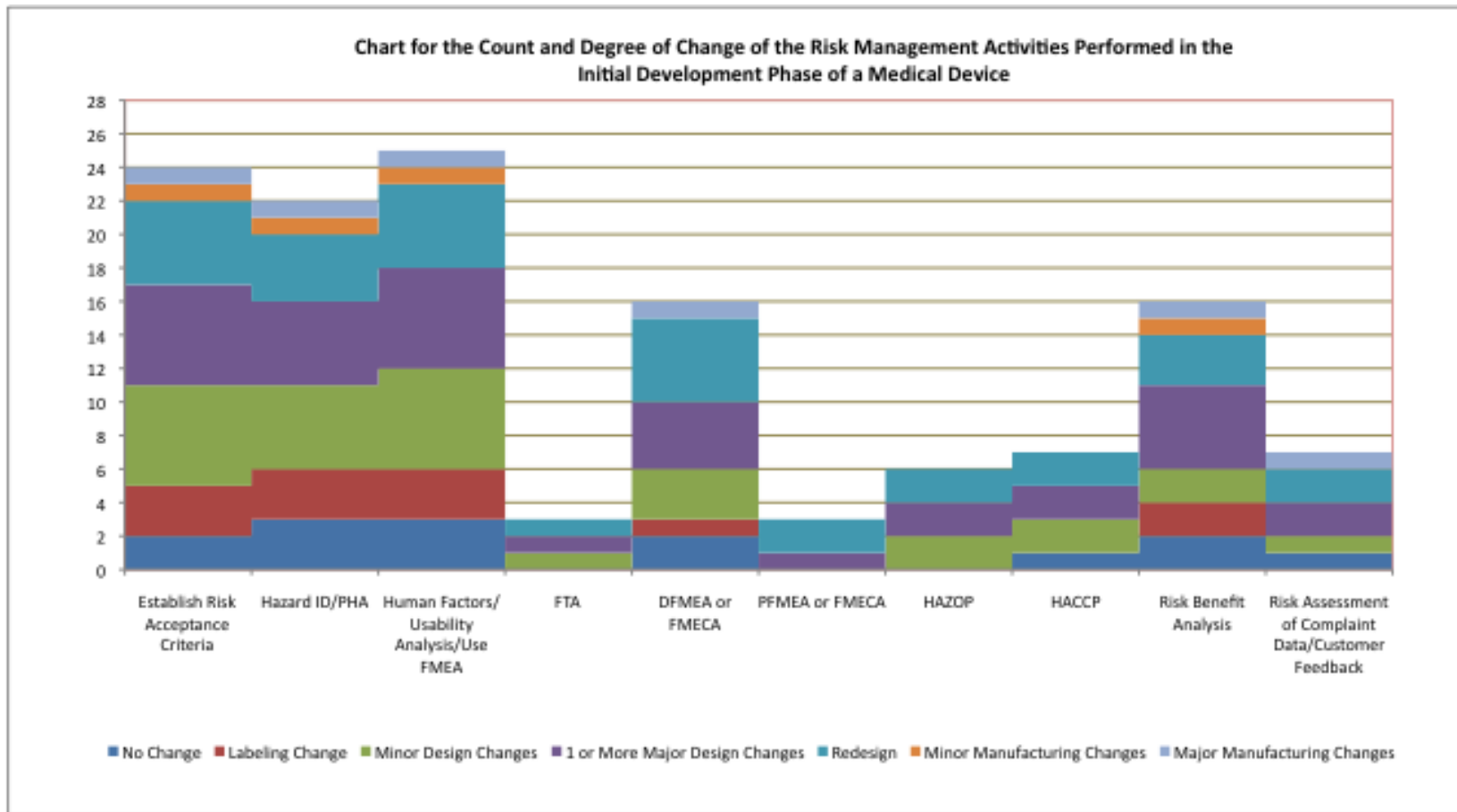
Appendix F1: Chart for the count and degree of change of the risk management activities performed in the conceptualization phase of a medical device



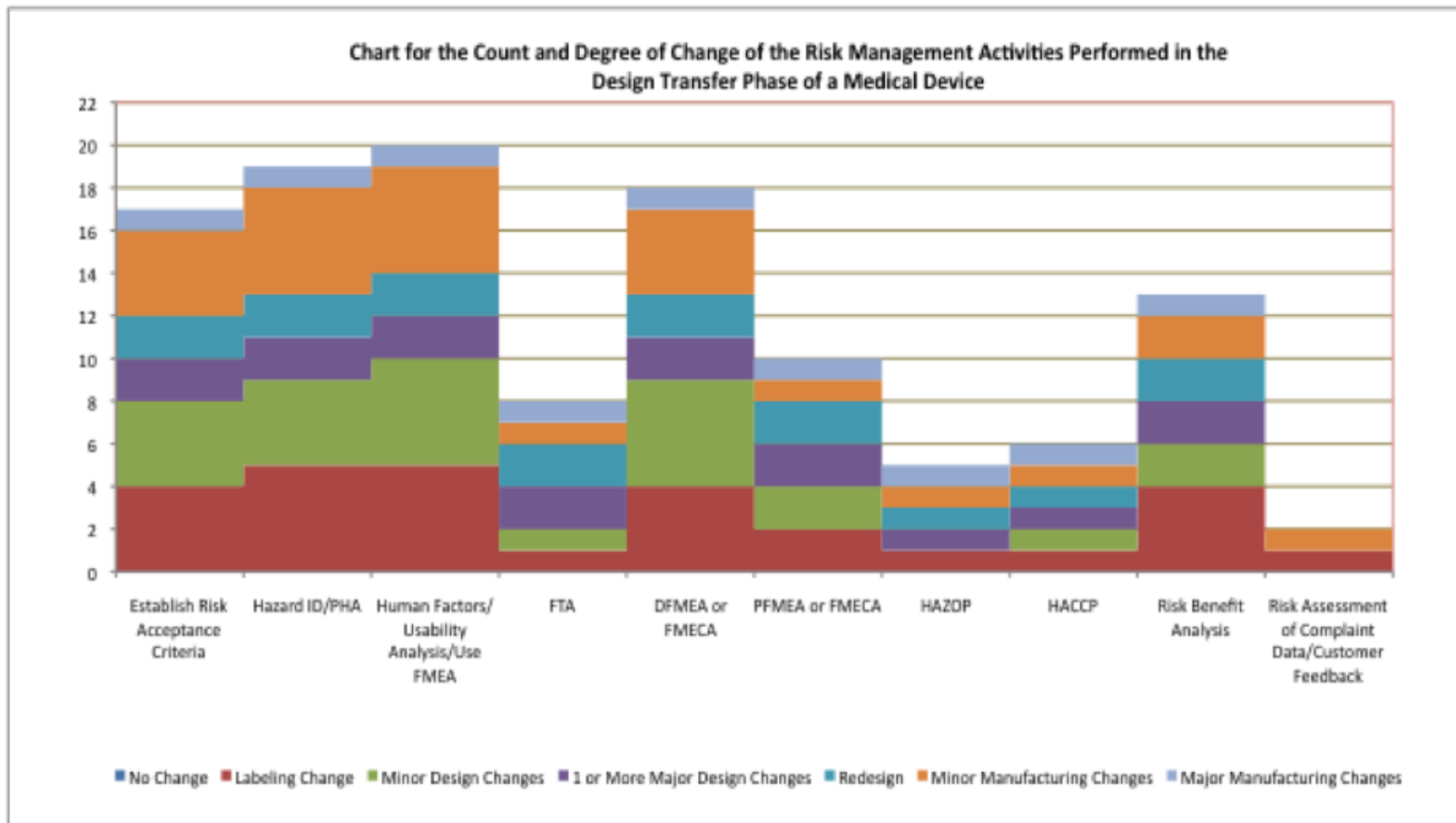
Appendix F2: Chart for the count and degree of change of the risk management activities performed in the initial development phase of a medical device



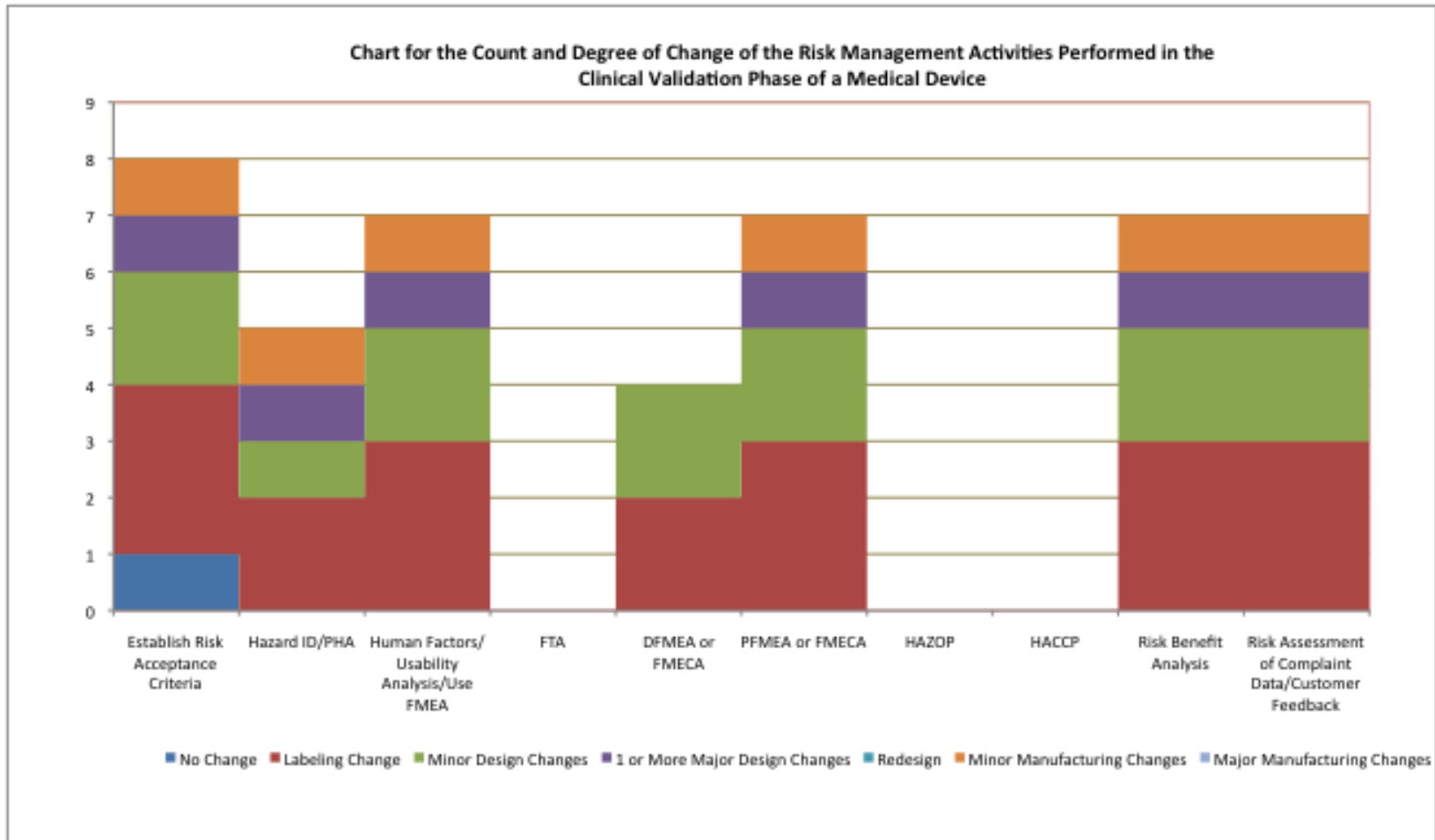
Appendix F3: Chart for the count and degree of change of the risk management activities performed in the design verification and engineering validation phase of a medical device



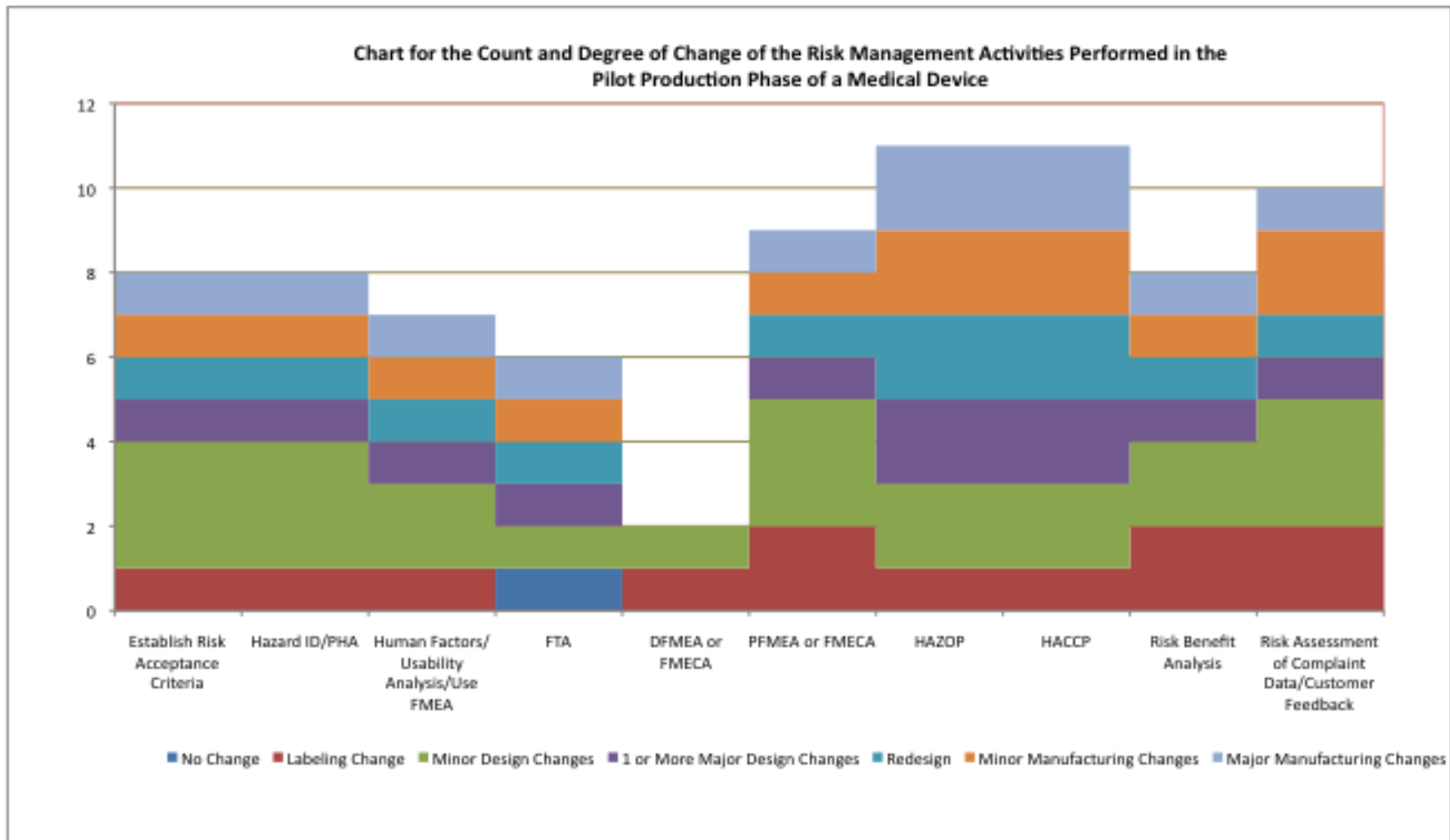
Appendix F4: Chart for the count and degree of change of the risk management activities performed in the design transfer phase of a medical device



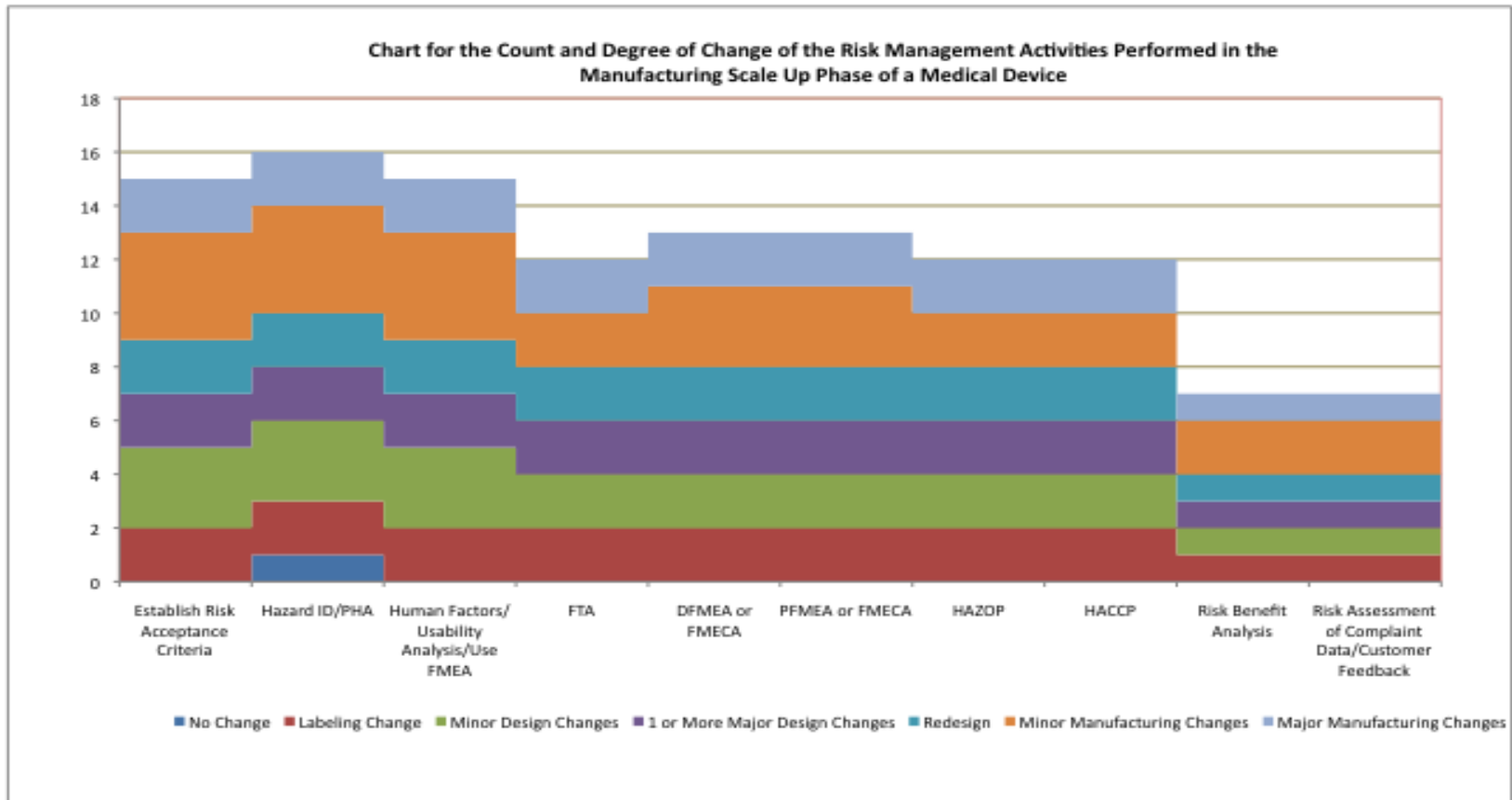
Appendix F5: Chart for the count and degree of change of the risk management activities performed in the clinical validation phase of a medical device



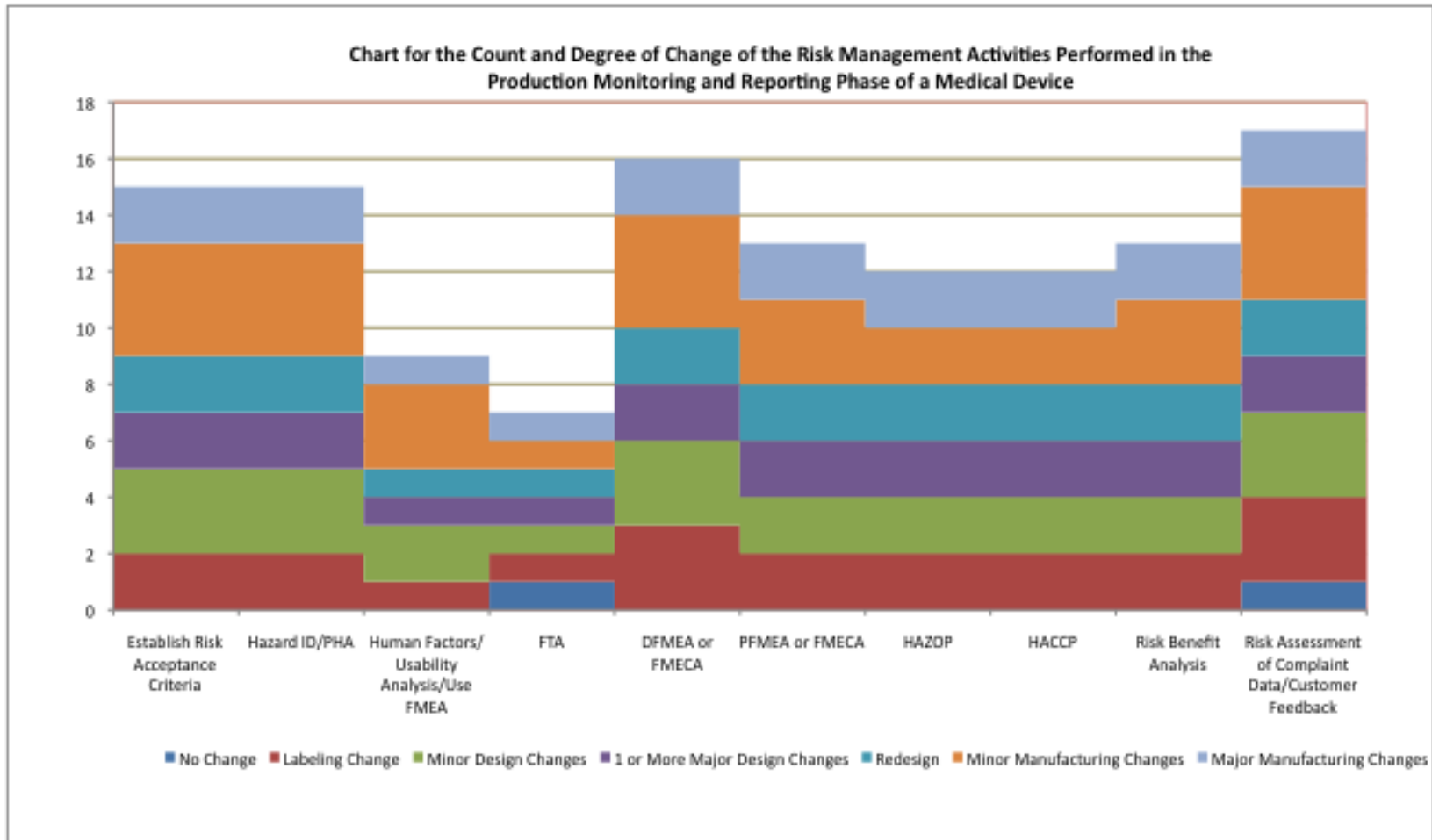
Appendix F6: Chart for the count and degree of change of the risk management activities performed in the pilot production phase of a medical device



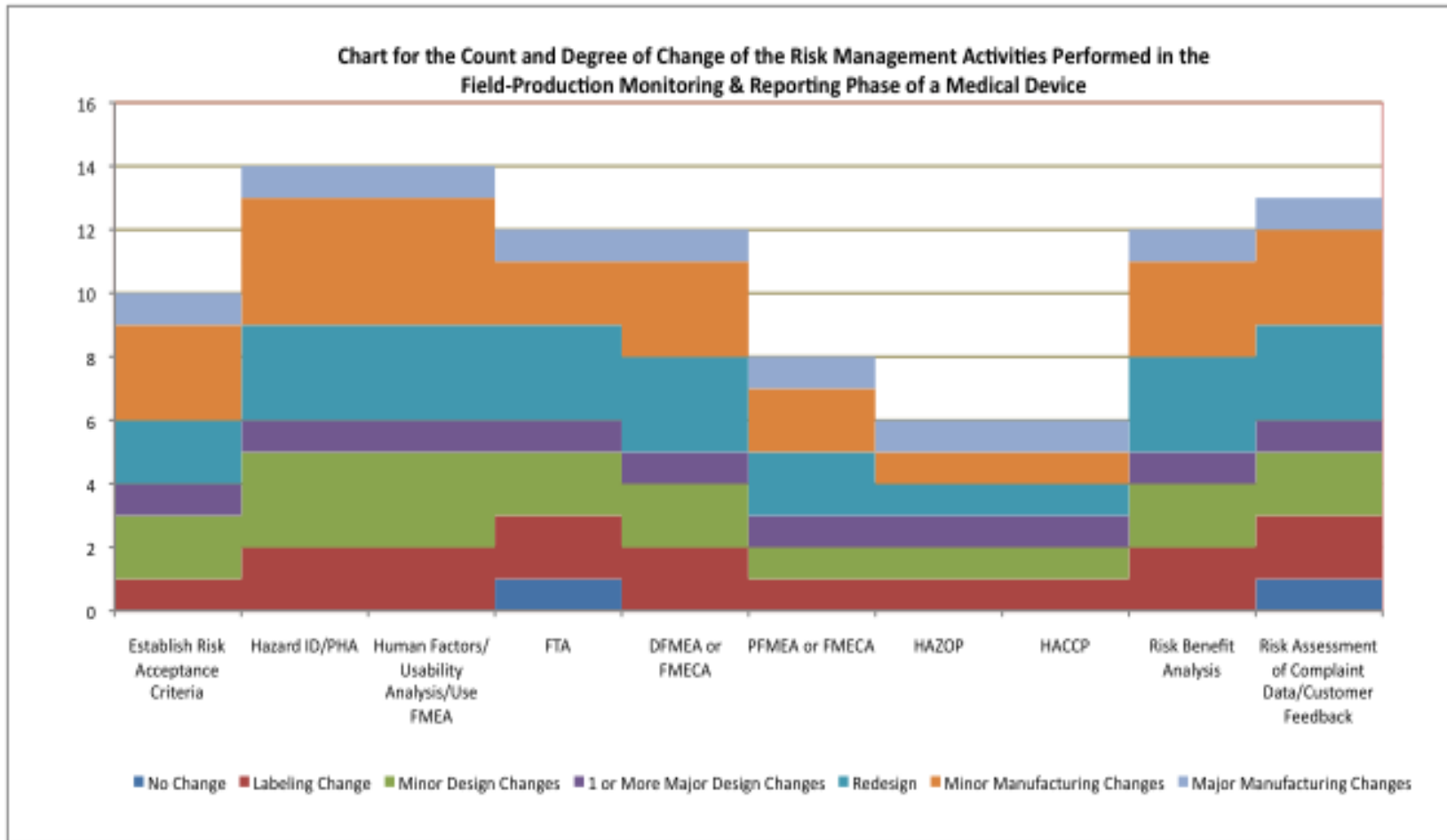
Appendix F7: Chart for the count and degree of change of the risk management activities performed in the manufacturing scale up phase of a medical device



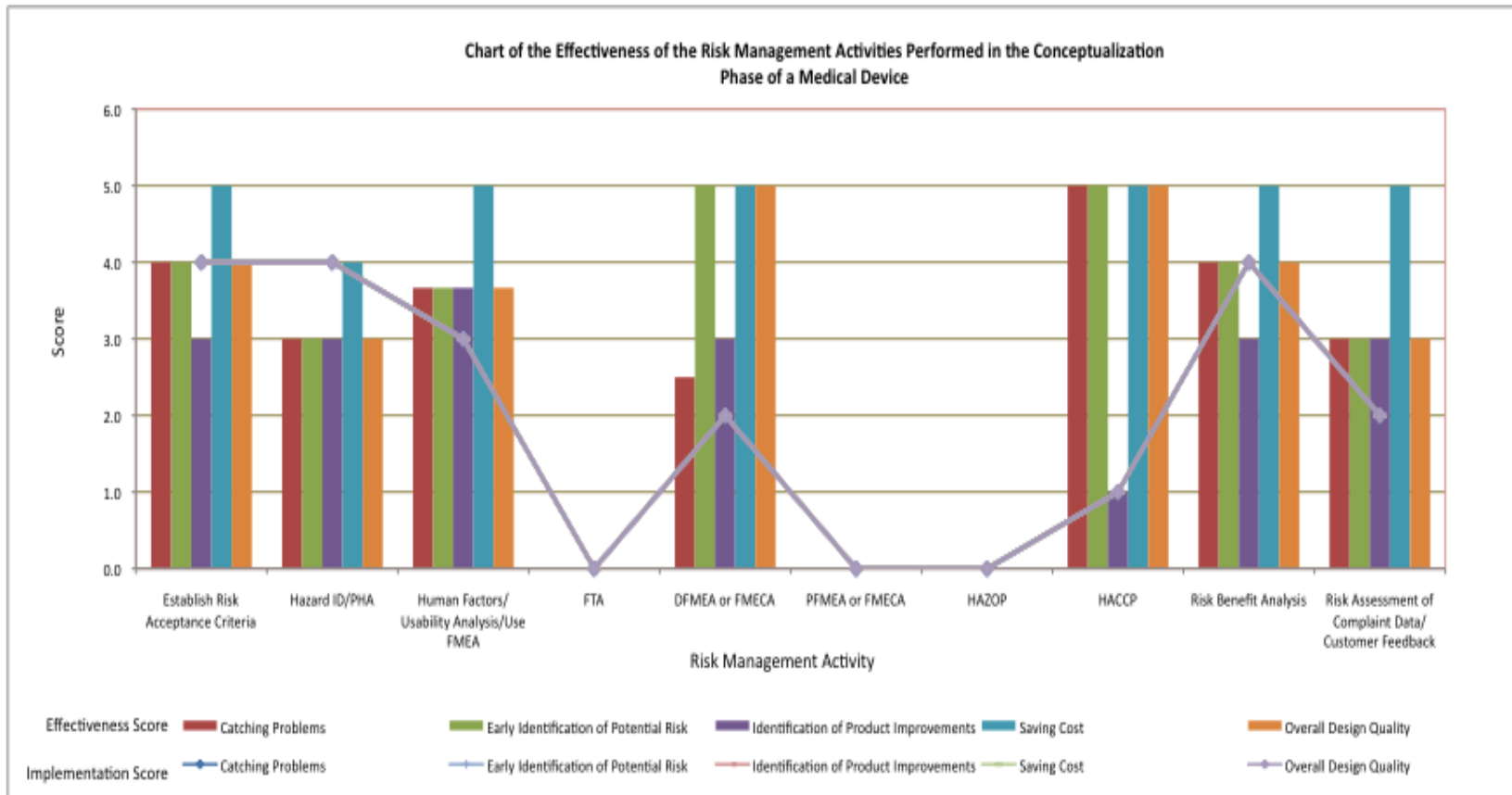
Appendix F8: Chart for the count and degree of change of the risk management activities performed in the production monitoring and reporting phase of a medical device



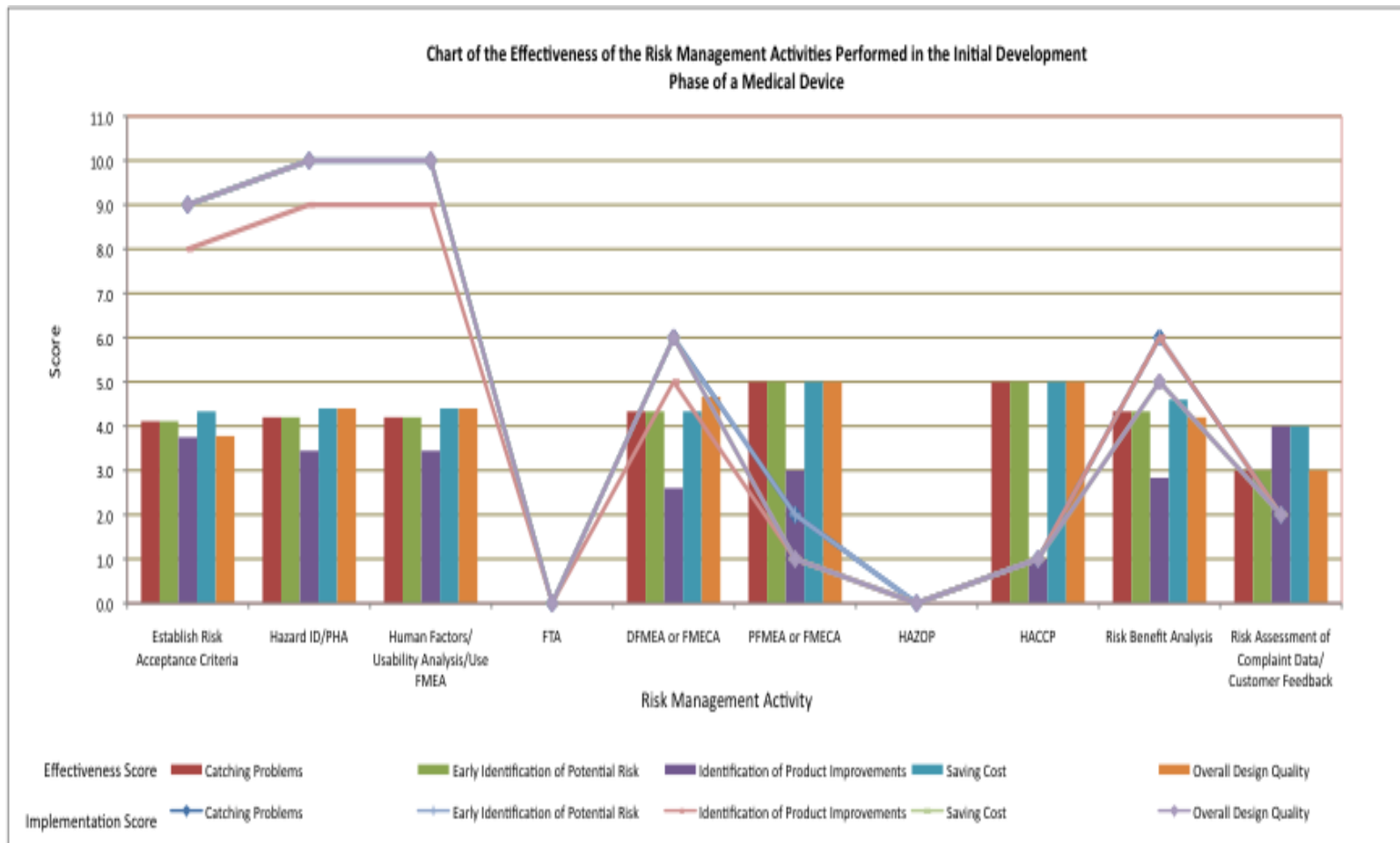
Appendix F9: Chart for the count and degree of change of the risk management activities performed in the field production monitoring and reporting phase of a medical device



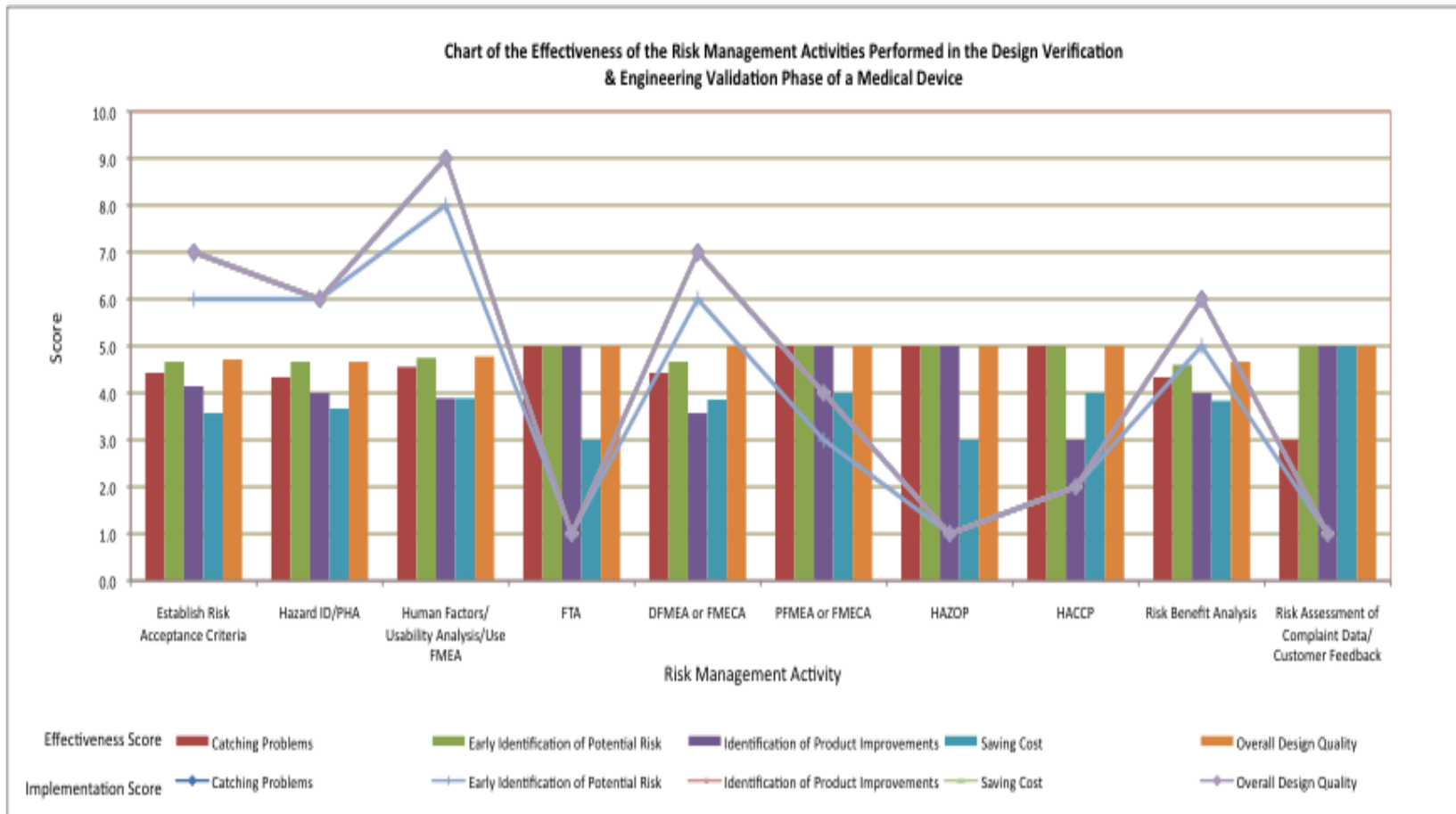
Appendix G1: Chart for the effectiveness and implementation scores of the risk management activities performed in the conceptualization phase of a medical device



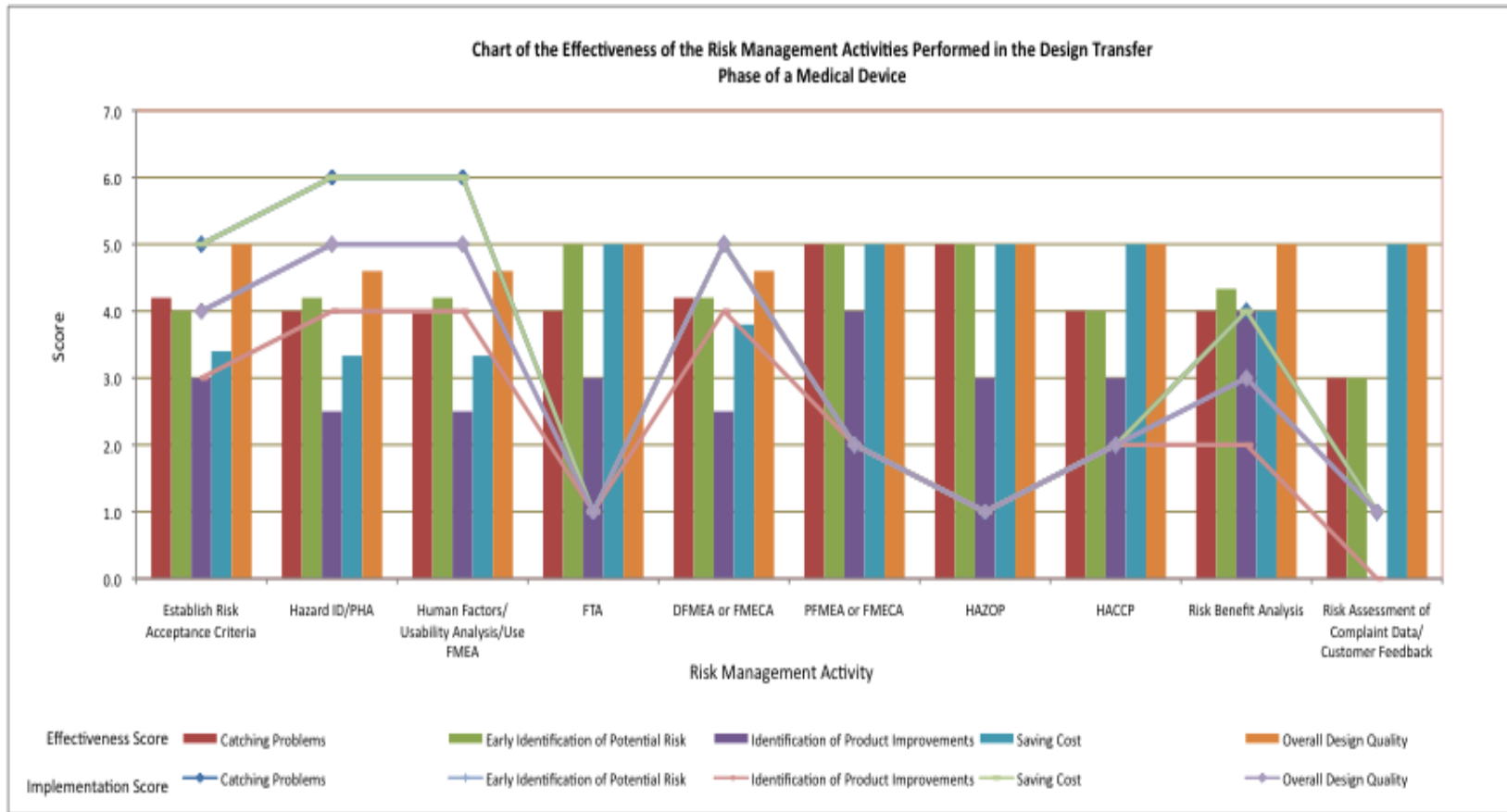
Appendix G2: Chart for the effectiveness and implementation scores of the risk management activities performed in the initial development phase of a medical device



Appendix G3: Chart for the effectiveness and implementation scores of the risk management activities performed in the design verification and engineering validation phase of a medical device



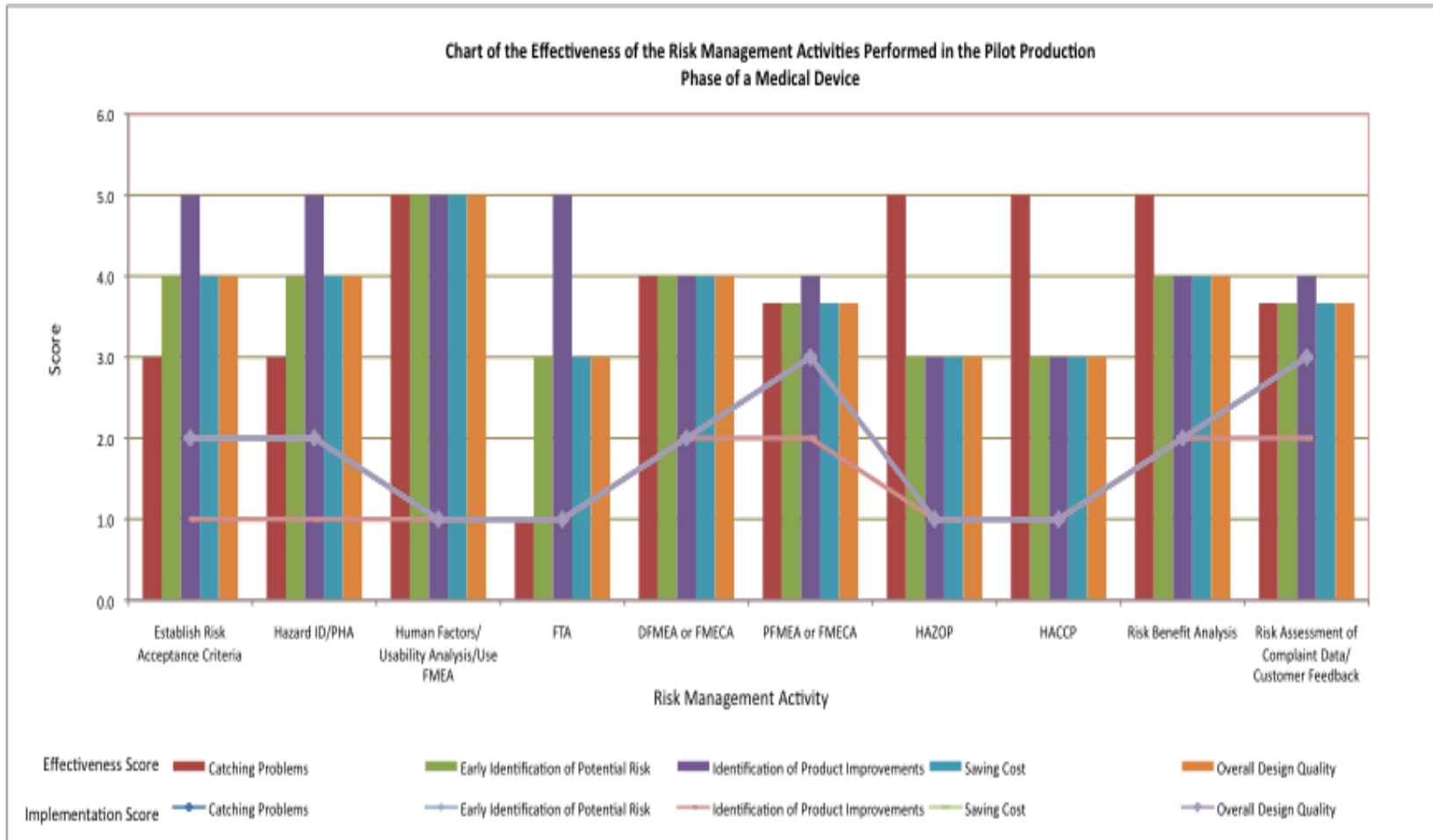
Appendix G4: Chart for the effectiveness and implementation scores of the risk management activities performed in the design transfer phase of a medical device



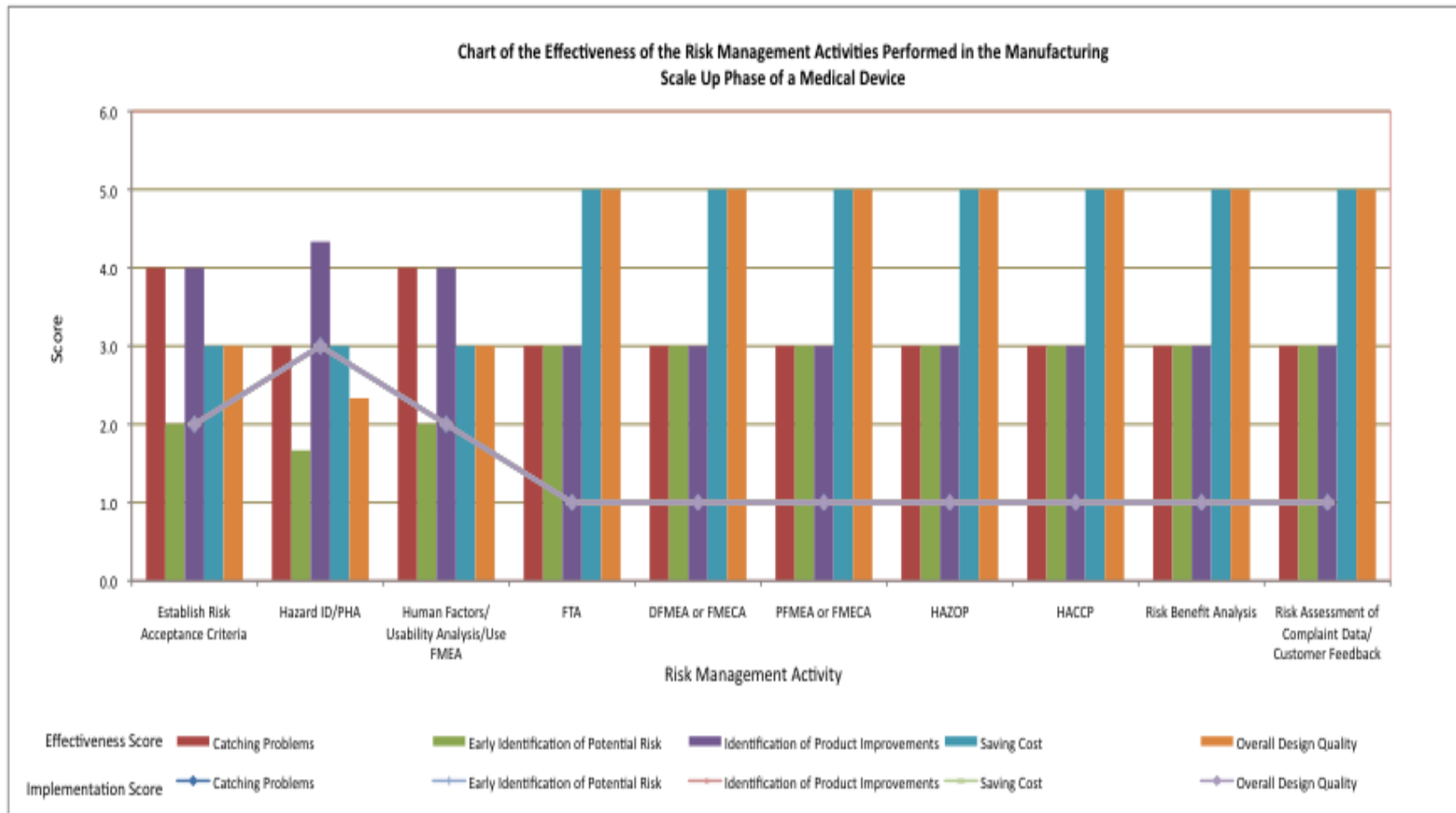
Appendix G5: Chart for the effectiveness and implementation scores of the risk management activities performed in the clinical validation phase of a medical device



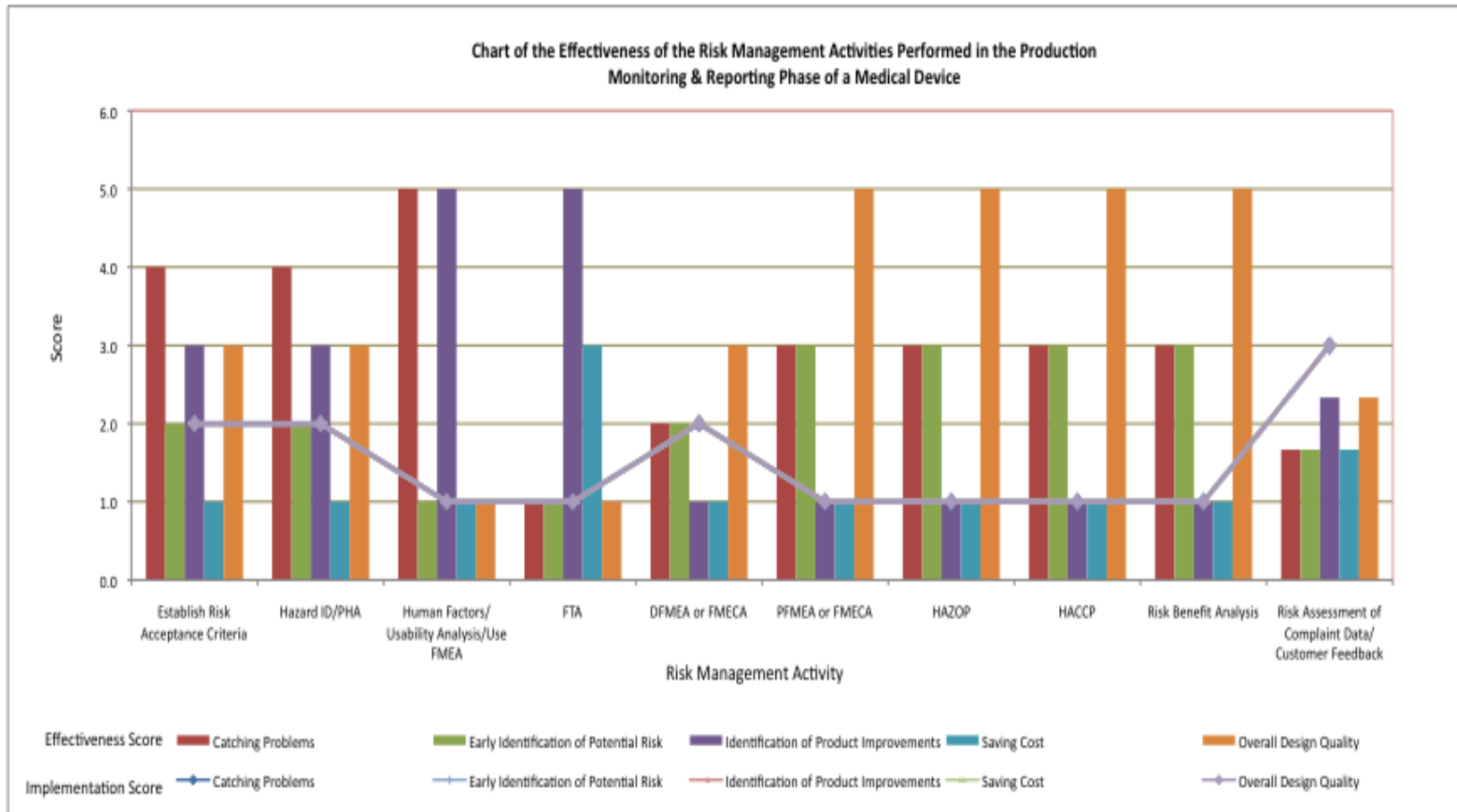
Appendix G6: Chart for the effectiveness and implementation scores of the risk management activities performed in the pilot production phase of a medical device



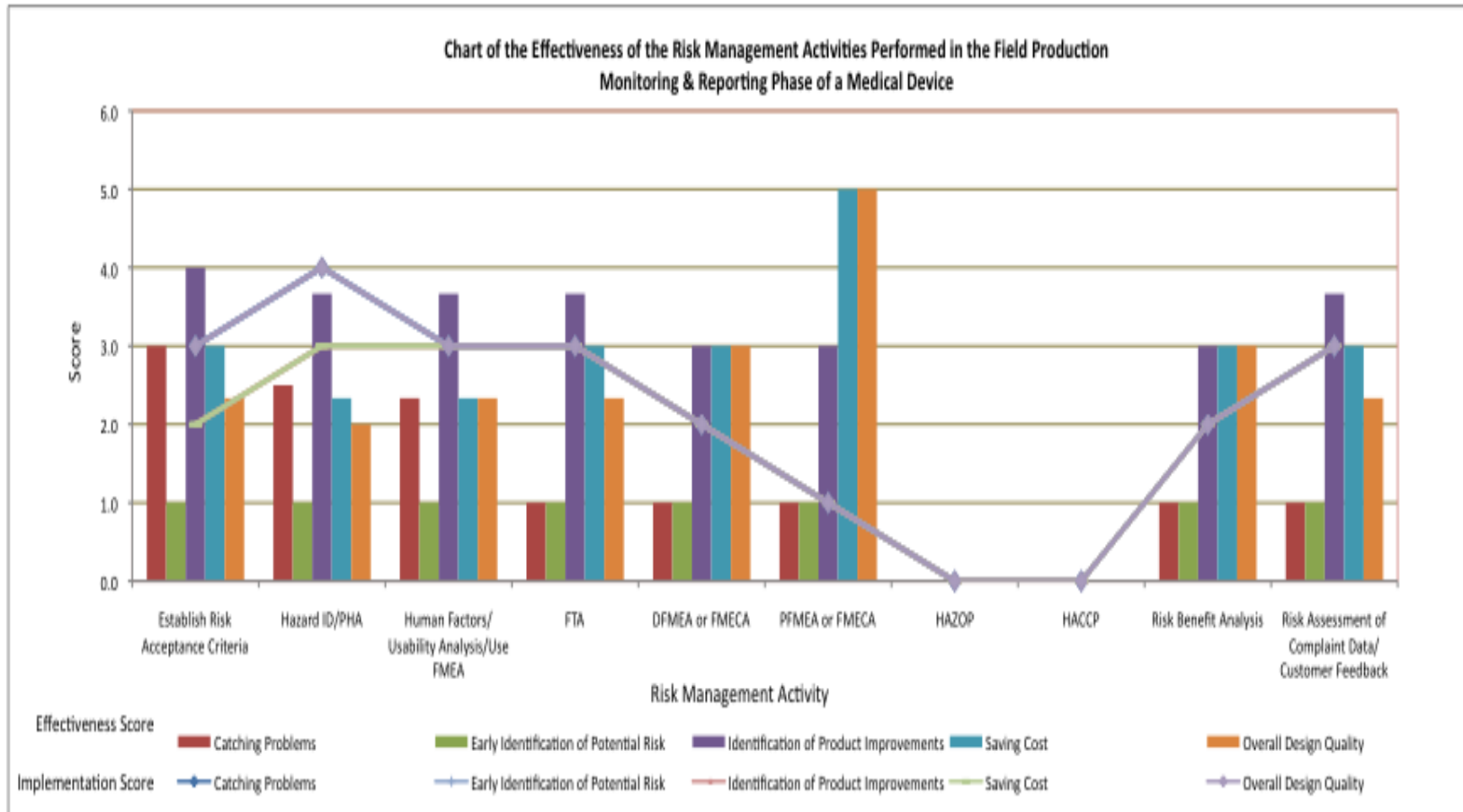
Appendix G7: Chart for the effectiveness and implementation scores of the risk management activities performed in the manufacturing scale up phase of a medical device



Appendix G8: Chart for the effectiveness and implementation scores of the risk management activities performed in the production monitoring and reporting phase of a medical device



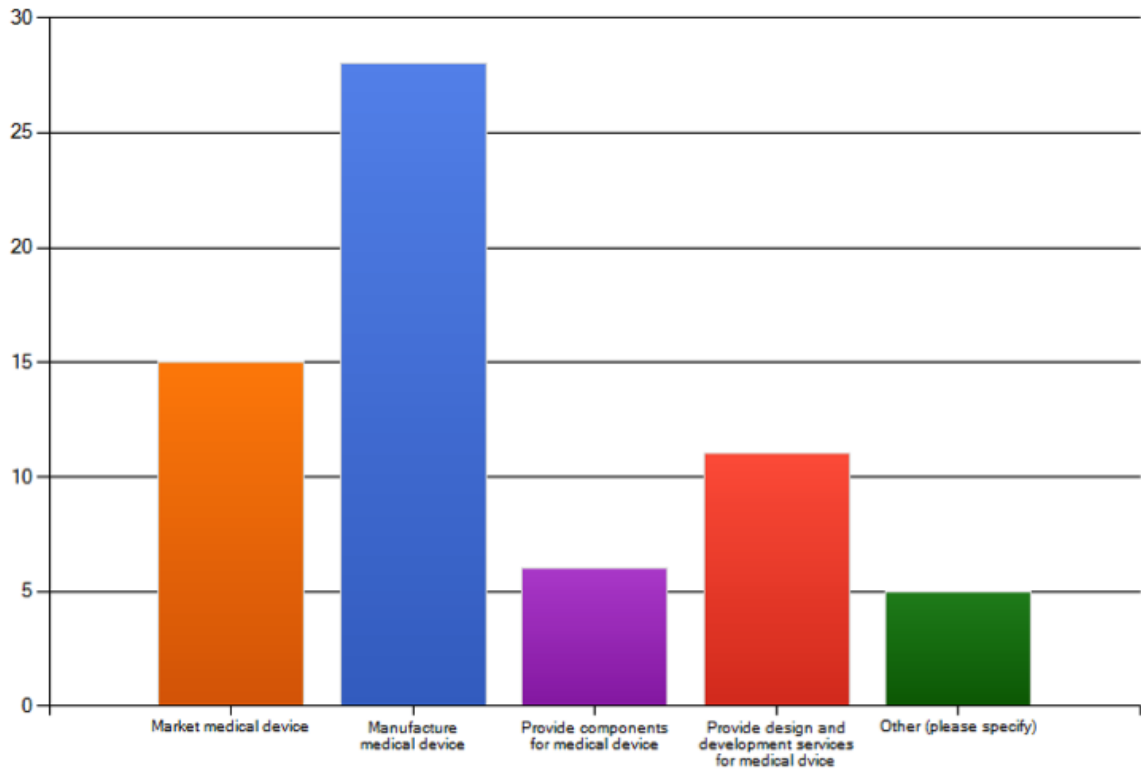
Appendix G9: Chart for the effectiveness and implementation scores of the risk management activities performed in the field production monitoring and reporting phase of a medical device



Appendix H1: Survey findings

| Which of the following best describes your company. (Check all that apply) | | | |
|--|----------------------|-----------------------------------|----------------|
| Answer Options | | Response Percent | Response Count |
| Market medical device | | 39.5% | 15 |
| Manufacture medical device | | 73.7% | 28 |
| Provide components for medical device | | 15.8% | 6 |
| Provide design and development services for medical dvice | | 28.9% | 11 |
| Other (please specify) | | 13.2% | 5 |
| <i>answered question</i> | | | 38 |
| <i>skipped question</i> | | | 3 |
| Number | Response Date | Other (please specify) | |
| 1 | Apr 15, 2010 9:49 AM | Consulting Services | |
| 2 | Apr 16, 2010 9:43 PM | Provide consultants | |
| 3 | Apr 17, 2010 2:28 AM | Consultant for numerous companies | |
| 4 | Apr 19, 2010 3:57 AM | Educational | |
| 5 | Apr 29, 2010 4:00 PM | Medical Device Consultant | |

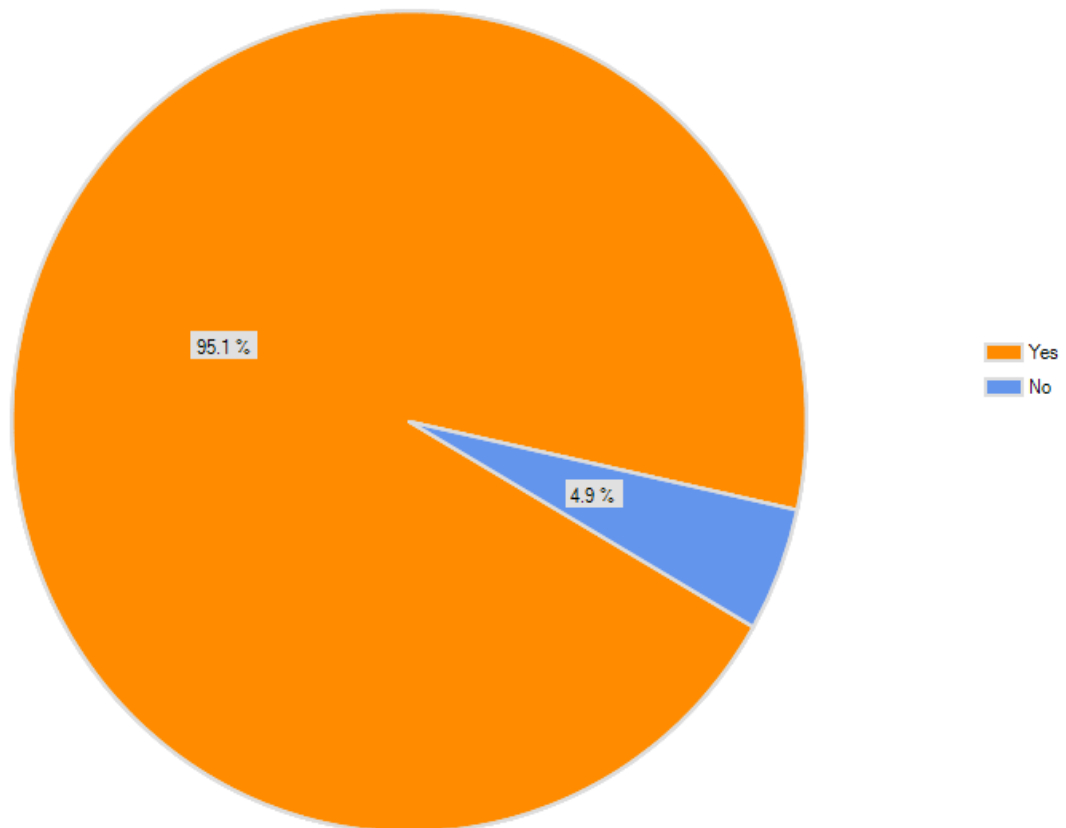
Chart for the Type of Medical Device Company



Appendix H2: Survey findings

| Are medical device design and risk management activities performed in your company? | | |
|---|--------------------------|----------------|
| Answer Options | Response Percent | Response Count |
| Yes | 95.1% | 39 |
| No | 4.9% | 2 |
| | <i>answered question</i> | 41 |
| | <i>skipped question</i> | 0 |

Percentage of Medical Device Companies That Perform Design and Risk Management Activities

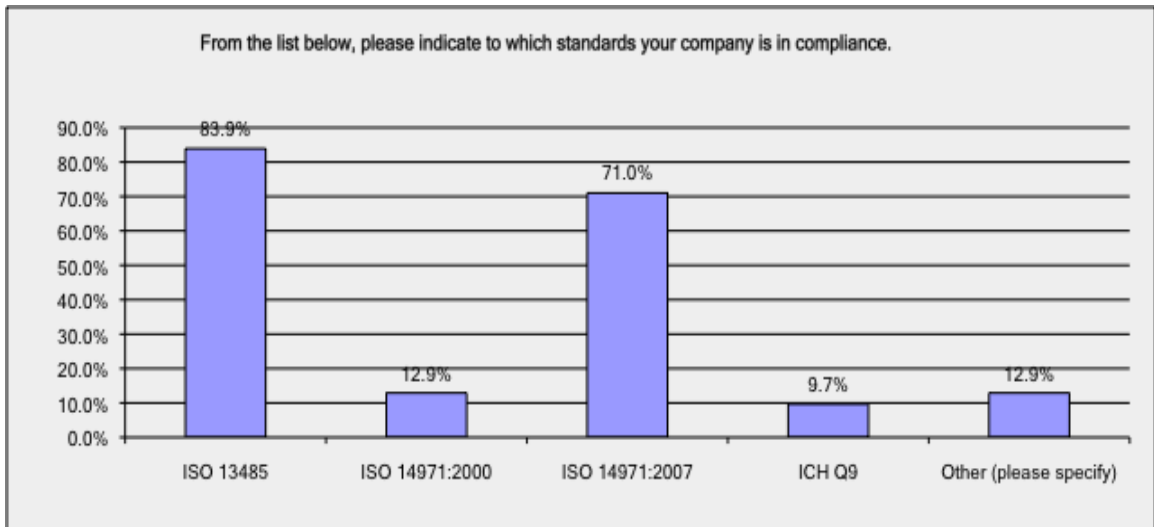


Appendix H3: Survey findings

From the list below, please indicate to which standards your company is in compliance.

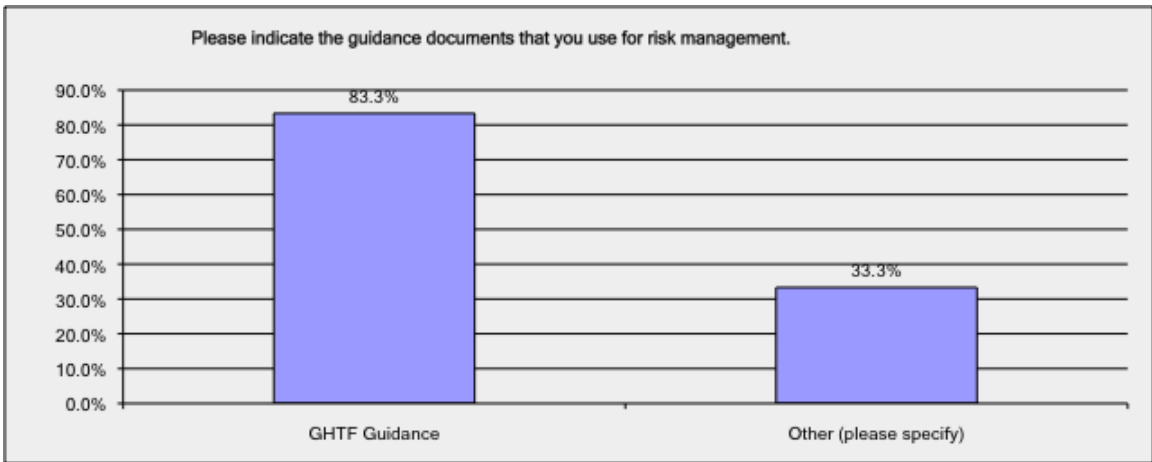
| Answer Options | Response Percent | Response Count |
|--------------------------|------------------|----------------|
| ISO 13485 | 83.9% | 26 |
| ISO 14971:2000 | 12.9% | 4 |
| ISO 14971:2007 | 71.0% | 22 |
| ICH Q9 | 9.7% | 3 |
| Other (please specify) | 12.9% | 4 |
| <i>answered question</i> | | 31 |
| <i>skipped question</i> | | 10 |

| Number | Response Date | Other (please specify) |
|--------|----------------------|---|
| 1 | Apr 8, 2010 4:35 AM | use documents defined by medical device clients |
| 2 | Apr 16, 2010 5:08 PM | Non Significant Risk IDE; FDA QSR |
| 3 | Apr 17, 2010 2:57 PM | Many others |
| 4 | Apr 25, 2010 6:54 PM | 14971:2009 |



Appendix H4: Survey findings

| Please indicate the guidance documents that you use for risk management. | | |
|--|-----------------------|---|
| Answer Options | Response Percent | Response Count |
| GHTF Guidance | 83.3% | 20 |
| Other (please specify) | 33.3% | 8 |
| | | <i>answered question</i> |
| | | 24 |
| | | <i>skipped question</i> |
| | | 17 |
| Number | Response Date | Other (please specify) |
| 1 | Apr 1, 2010 3:11 PM | ISO 13485 and ISO 14971 |
| 2 | Apr 8, 2010 4:35 AM | use documents defined by medical device clients |
| 3 | Apr 15, 2010 9:49 AM | GAMP Guide |
| 4 | Apr 16, 2010 5:08 PM | Design and Process FMEA Guidances -multiple |
| 5 | Apr 16, 2010 5:28 PM | Product specific but follows ISO 14971 |
| 6 | Apr 17, 2010 12:40 AM | FDA |
| 7 | Apr 17, 2010 2:57 PM | ISO 14971 |
| 8 | Apr 22, 2010 3:31 PM | ISO 14971 |

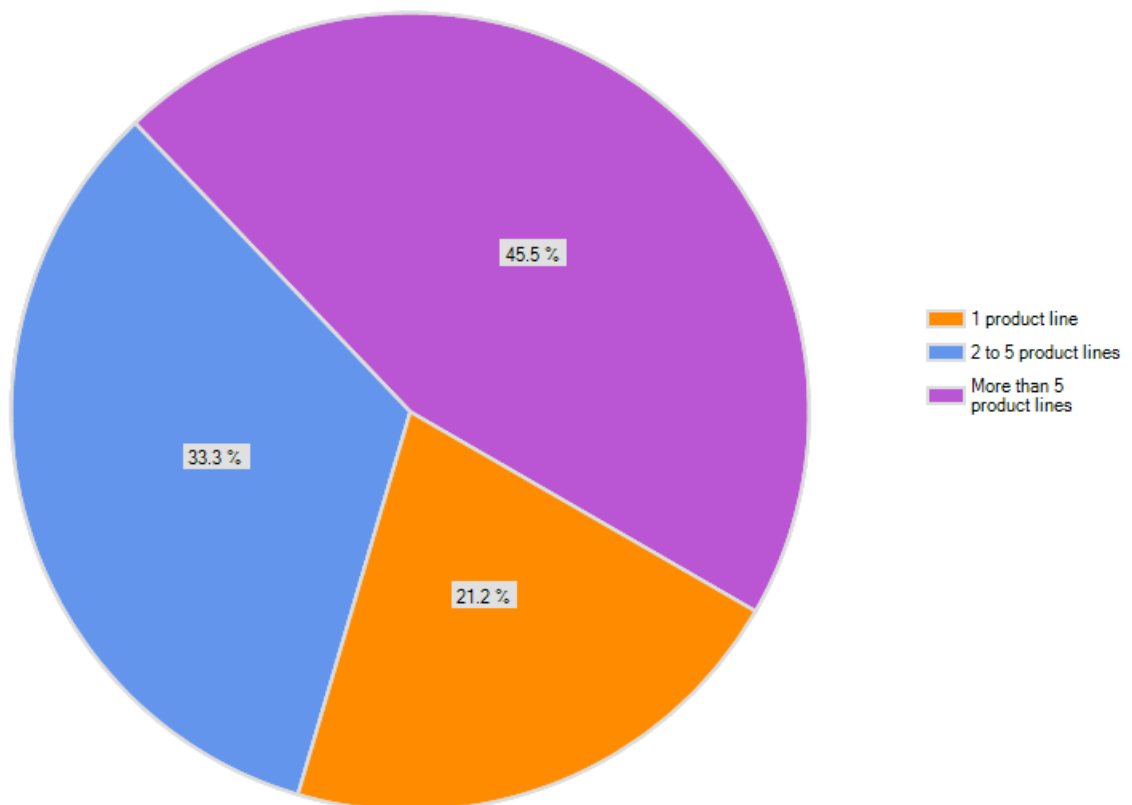


Appendix H5: Survey findings

Please indicate the number of product line your company deals with.

| Answer Options | Response Percent | Response Count |
|---------------------------|--------------------------|----------------|
| 1 product line | 21.2% | 7 |
| 2 to 5 product lines | 33.3% | 11 |
| More than 5 product lines | 45.5% | 15 |
| | <i>answered question</i> | 33 |
| | <i>skipped question</i> | 8 |

Percentage of the Number of Product Lines in a Medical Device Company

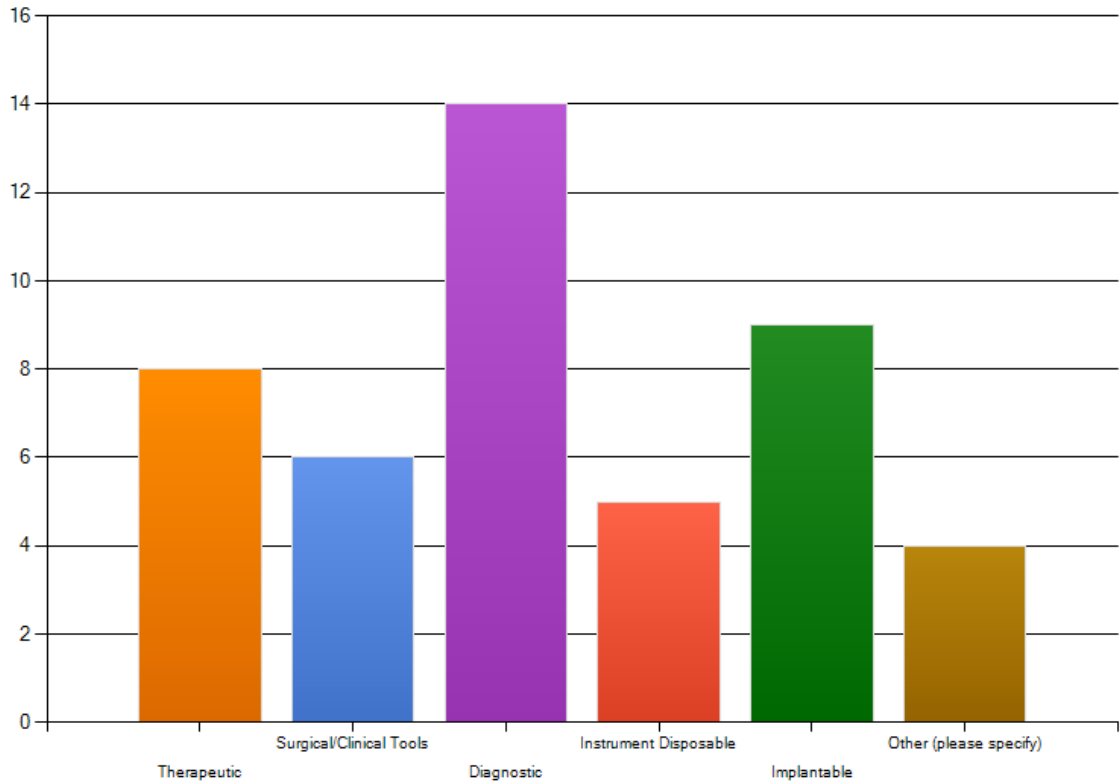


Appendix H6: Survey findings

| Please indicate the medical device type. (Check all that apply) | | |
|---|------------------|----------------|
| Answer Options | Response Percent | Response Count |
| Therapeutic | 28.6% | 8 |
| Surgical/Clinical Tools | 21.4% | 6 |
| Diagnostic | 50.0% | 14 |
| Instrument Disposable | 17.9% | 5 |
| Implantable | 32.1% | 9 |
| Other (please specify) | 14.3% | 4 |
| <i>answered question</i> | | 28 |
| <i>skipped question</i> | | 13 |

| Number | Response Date | Other (please specify) |
|--------|-----------------------|--|
| 1 | Apr 8, 2010 4:36 AM | various medical device clients |
| 2 | Apr 15, 2010 9:50 AM | Business & Decision does not manufacture devices |
| 3 | Apr 16, 2010 10:35 PM | Catheters |
| 4 | Apr 16, 2010 11:03 PM | IVD |

Chart for the Medical Device Type



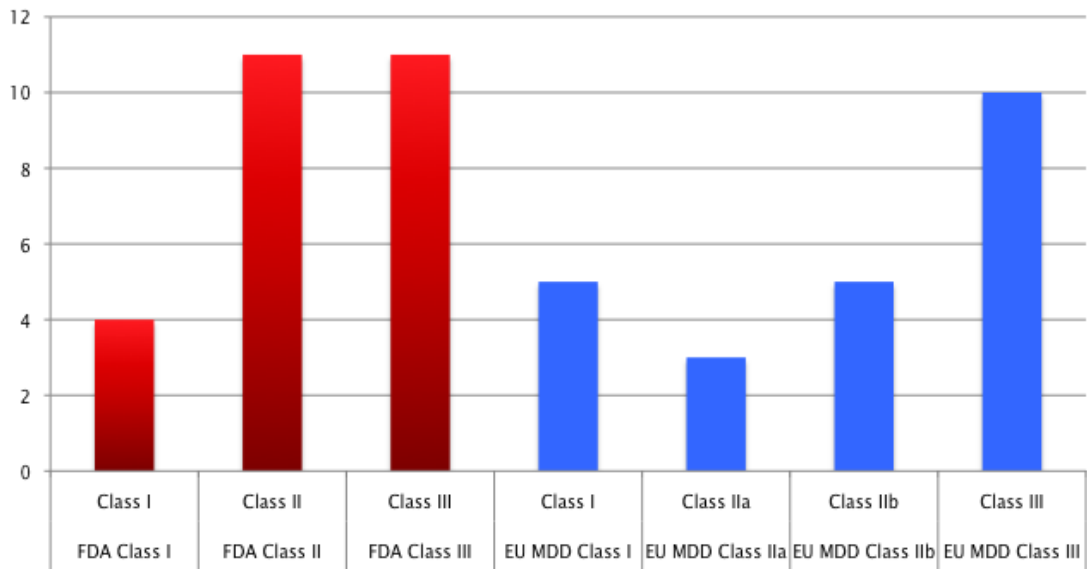
| Please provide a brief description. (OPTIONAL) | | |
|--|----------------|----|
| Answer Options | Response Count | |
| | 10 | |
| <i>answered question</i> | | 10 |
| <i>skipped question</i> | | 31 |

| Number | Response Date | Response Text |
|--------|-----------------------|---|
| 1 | Mar 28, 2010 9:19 PM | asthma diagnosis |
| 2 | Mar 29, 2010 9:49 PM | Ophthalmic Imaging Systems |
| 3 | Apr 8, 2010 4:36 AM | all device classifications are used |
| 4 | Apr 16, 2010 5:15 PM | Continuous Glucose Monitoring |
| 5 | Apr 16, 2010 11:03 PM | Test kits for professional users |
| 6 | Apr 17, 2010 12:41 AM | hematology instruments (blood cell counters) |
| 7 | Apr 17, 2010 2:59 PM | Cardiac Diagnostic and Therapeutic ablation catheters, RF Generators, and ancillary devices |
| 8 | Apr 17, 2010 10:22 PM | Pharmaceutical electromechanical compounder |
| 9 | Apr 19, 2010 6:27 PM | investigational device for migraine pain |
| 10 | Apr 25, 2010 6:55 PM | Electrophysiology at the San Jose Campus |

Appendix H7: Survey findings

| Please indicate the FDA risk classification. | | |
|--|------------------|----------------|
| Answer Options | Response Percent | Response Count |
| Class I | 15.4% | 4 |
| Class II | 42.3% | 11 |
| Class III | 42.3% | 11 |
| <i>answered question</i> | | 26 |
| <i>skipped question</i> | | 15 |

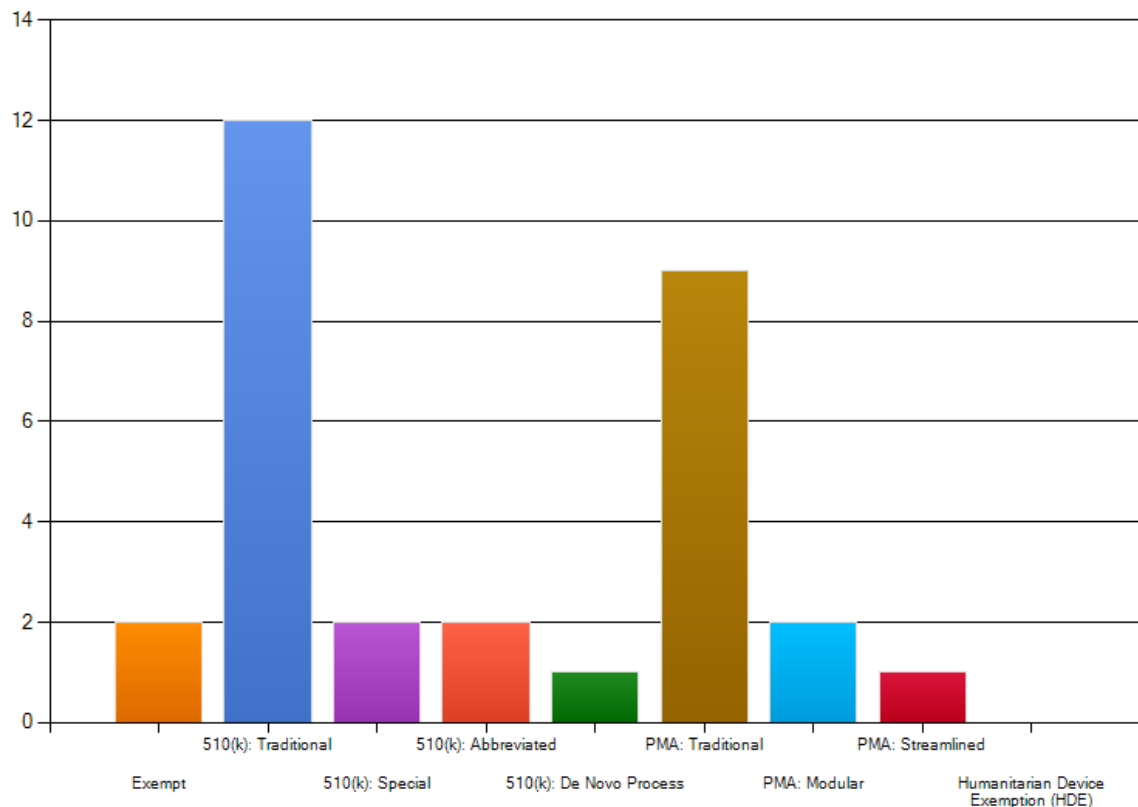
| What is the EU MDD risk classification? | | |
|---|------------------|----------------|
| Answer Options | Response Percent | Response Count |
| Class I | 21.7% | 5 |
| Class IIa | 13.0% | 3 |
| Class IIb | 21.7% | 5 |
| Class III | 43.5% | 10 |
| <i>answered question</i> | | 23 |
| <i>skipped question</i> | | 18 |



Appendix H8: Survey findings

| Please indicate the US pre-market regulatory pathway. | | |
|---|--------------------------|----------------|
| Answer Options | Response Percent | Response Count |
| Exempt | 8.0% | 2 |
| 510(k): Traditional | 48.0% | 12 |
| 510(k): Special | 8.0% | 2 |
| 510(k): Abbreviated | 8.0% | 2 |
| 510(k): De Novo Process | 4.0% | 1 |
| PMA: Traditional | 36.0% | 9 |
| PMA: Modular | 8.0% | 2 |
| PMA: Streamlined | 4.0% | 1 |
| Humanitarian Device Exemption (HDE) | 0.0% | 0 |
| | <i>answered question</i> | 25 |
| | <i>skipped question</i> | 16 |

Chart for the US Pre-Market Regulatory Pathway



Appendix H9: Survey findings

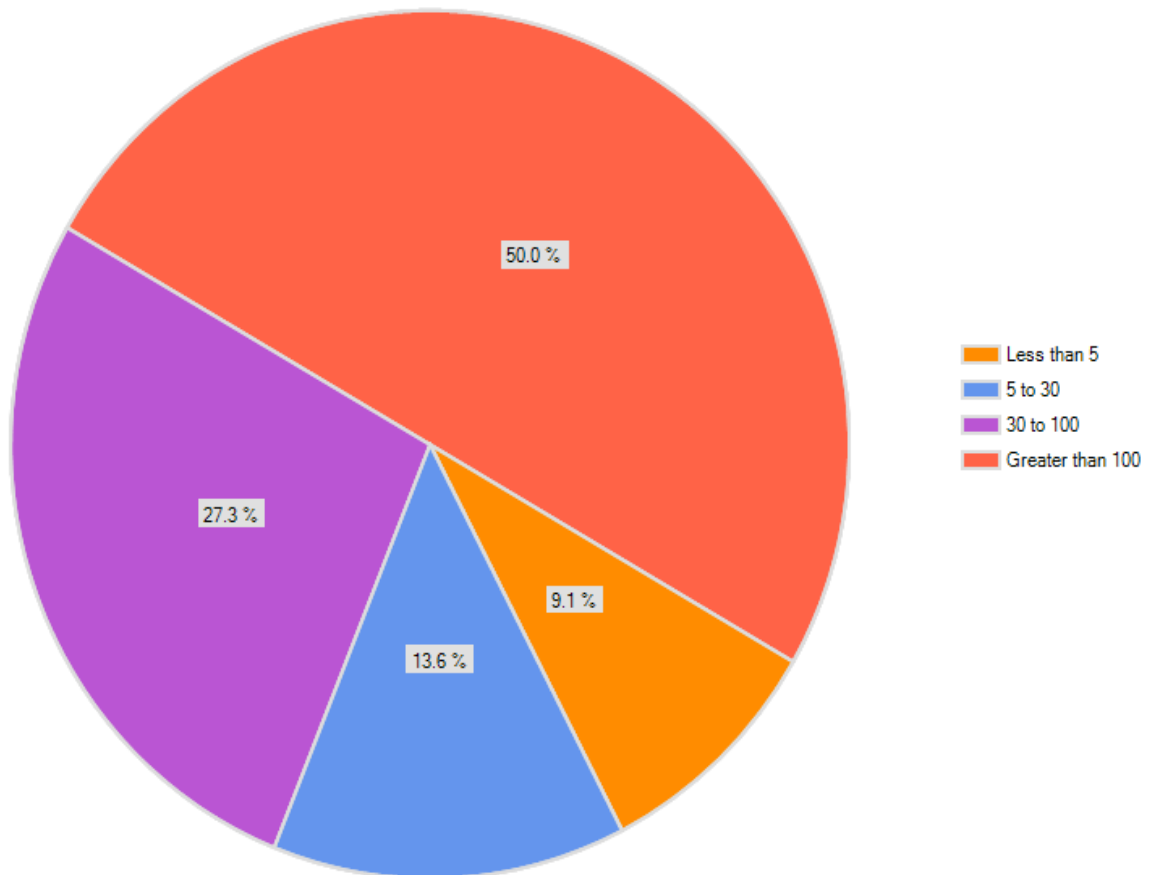
| Please select the description of the device development history. | | |
|--|--------------------------|----------------|
| Answer Options | Response Percent | Response Count |
| New, first generation device marketed for first time | 50.0% | 12 |
| Revision of previous first generation device | 29.2% | 7 |
| Second generation device with significant design or | 4.2% | 1 |
| Third or later generation device | 16.7% | 4 |
| | <i>answered question</i> | 24 |
| | <i>skipped question</i> | 17 |
| What is the approximate time since market release of this model? | | |
| Answer Options | Response Percent | Response Count |
| Not yet released - in clinical trial | 45.8% | 11 |
| Less than 6 months | 4.2% | 1 |
| 6 months to 18 months | 16.7% | 4 |
| 18 to 36 months | 12.5% | 3 |
| Greater than 3 years | 20.8% | 5 |
| | <i>answered question</i> | 24 |
| | <i>skipped question</i> | 17 |

Appendix H10: Survey findings

Please indicate the number of units sold or used in clinical trials.

| Answer Options | Response Percent | Response Count |
|------------------|--------------------------|----------------|
| Less than 5 | 9.1% | 2 |
| 5 to 30 | 13.6% | 3 |
| 30 to 100 | 27.3% | 6 |
| Greater than 100 | 50.0% | 11 |
| | <i>answered question</i> | 22 |
| | <i>skipped question</i> | 19 |

Percentage of the Number of Units Sold or Used In Clinical Trials



Appendix H11: Survey findings

What is the level of user competence needed to operate this device?

Percentage of the Level of User Competence Needed to Operate the Device

