REGULATORY REQUIREMENTS FOR MEDICAL DEVICE MANUFACTURERS

SINCLAIR COLLEGE

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Executive Summary

The purpose of this document is to provide an overview of the U.S. regulatory requirements for medical device manufacturers. The document specifically addresses the FDA requirements that should be considered by companies interested in entering into the space of medical device manufacturing or contract manufacturing. The regulatory requirements vary based on the classification of the product and the desired establishment type. Preparation to achieve and maintain compliance with the requirements are highly dependent on the size of the organization, complexity of the device, scope of any existing quality system, and most important, commitment by senior management. This document provides general guidance on how to assess these variables in order to develop a regulatory and quality plan to achieve compliance. Compliance with the FDA regulations is necessary prior to registering the manufacturing facility, listing the medical device, and releasing the product into commercial distribution.

Items addressed in this document include:

1. An overview of FDA medical device regulatory classifications, submission types, and the registration and listing process. General guidance for manufacturers is included to address how they can determine whether the product they are planning to manufacture is Class I, Class II or Class III.

2. Individual certification programs applicable to professionals in the medical device industry that are desired competencies of employees working for manufacturers. The recommendation is to begin with non-certification training curriculum that will be beneficial for individuals entering into the medical device industry.

3. Guidance on how to determine the regulatory requirements associated with the classification of the medical device the organization plans to manufacture. The document outlines a general process for achieving compliance with the FDA QSR and ISO 13485 certification, if appropriate.

4. An overall estimate of time to complete the recommended professional certification programs. The document provides general guidelines on the estimated timeline to become ISO 13485 certified given key variables.

5. An estimate of costs associated the professional certification programs. An estimate of the direct cost associated with becoming an ISO 13485 certified medical device.

Many manufacturers today are considering diversifying their product lines into new market sectors that are financially viable. As the medical device manufacturing industry continues to grow, this report provides detail in terms of the expected pathway a manufacturer needs to follow to pivot operations into medical devices.

A medical device is defined by the Food & Drug Administration (FDA) as "any instrument, machine, contrivance, implant, or in vitro reagent that is intended to treat, cure, prevent, mitigate, or diagnose disease in man." Examples of medical devices range from a simple tongue depressor, or a thermometer, to a robotic surgical tool. The definition goes on to include the statement that a medical device does not achieve its primary intended use through a chemical activation on or within the skin, and it is not required to be metabolized to achieve the primary intended use.

Establishing a manufacturing facility to produce a medical device for sale in the U.S. market requires that a company comply with current FDA regulations for medical devices. Devices that are intended for markets in other countries must be manufactured according to that country's medical device regulations.

Important elements to consider for manufacturing medical devices in the US include:

- FDA Pre-Market Product Clearance/ Approval Requirements
- Quality System Regulation Compliance
- Qualified Workforce and Training
- Type of Establishment (e.g. Manufacturer, Contract Manufacturer, or Component Manufacturer)

This document will describe the requirements that must be followed for medical device manufacturing in the US. The FDA bases regulations for medical devices on a device classification and product code system. This information includes the regulations governing the medical device and the pathway for approval from the FDA that is needed to market the product. Depending upon the classification of the device, a 510(k) pre-market notification submission package may be required; a device may be classified as exempt from a 510(k) submission; or a device may require Pre-Market Approval (PMA). Pre-Market Approval includes preclinical studies and clinical investigations.

Once the medical device is classified, a manufacturer or contract manufacturer of the finished device must register and list the device with the FDA before it can be marketed and put into commercial distribution. A finished device is any device or accessory to any device that is suitable for use or capable of functioning, whether or not it is packaged, labeled, or sterilized. Component manufactures are not required to register. A component means any raw materials, substance, piece, part software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged and labeled device.

The time and cost to the manufacturer differs for each of the regulatory pathways depending upon the complexity of the device, level of supporting documentation needed to demonstrate safety and efficacy and involvement of the FDA. In addition, the time and cost to the manufacturer is influenced by the rigor of the Quality System that is required to effectively comply with the Quality System Regulation (QSR) Title 21 CFR Part 820. Often medical device companies decide to obtain ISO 13485 certification.

This certification specifies requirements for a quality management system for medical device manufacturers to enable them to consistently meet customer requirements and regulatory requirements. The ISO standard encompasses most aspects of the FDA QSR.

As in any industry, employees of medical device manufacturers require training specific to their assigned duties within the company. Employees may be hired who have completed a medical device training curriculum through an educational institution. This training may include earning a certification from one of the third party certification bodies related to regulatory and quality monitoring such as the American Society for Quality (ASQ) or the Regulatory Affairs Professionals Society (RAPS). Training must also include company specific training to an employee's job responsibilities and the Quality System of that company including annual training on FDA regulations.

More specifically, this document will cover:

1. FDA Pre-Market Product Clearance / Approval Requirements

a) Medical device manufacturing and marketing is regulated in the United States by the FDA.

b) Medical devices are classified into Class I, II or III, based on the risk associated with the device.

c) The device classification level determines the premarket submission/application to the FDA.

d) Prior to manufacturing a medical device a regulatory strategy is developed.

e) Company size, the type of establishment and the class of medical device are factors that guide the regulatory strategy.

f) The time and cost to the manufacturer differs for each of the regulatory pathways depending upon the complexity of the device, level of supporting documentation needed to demonstrate safety and efficacy and involvement of the FDA.

2. Quality System Regulation Compliance

a) Medical device manufacturers are required to produce their product under an established Quality System that meets FDA Quality System Regulation.

b) Augmenting an existing Quality System following a gap assessment, often performed by a qualified third party, may be an option.

c) An ISO 13485 Quality Management System, while not required or recognized by the FDA, is the most commonly chosen path used to establish a Quality System.

d) Time and cost to the manufacturer for establishing a Quality System is influenced by the rigor of the Quality System that is required to effectively comply with the Quality System Regulation (QSR) Title 21 CFR Part 820.

3. Type of Establishment

a) A manufacturer, contract manufacture or marketer of medical devices in the United States must register with the FDA and list the generic category of the device(s) they are producing.

b) This information is used by the FDA to know what devices are on the market, and to plan inspections of the manufacturing facilities.

c) There are exemptions from registration and listing requirements.

d) Annual registration user fees are charged to the device manufacturer.

4. Qualified Workforce and Training

a) Training for individuals employed in the medical device industry is required.

b) Training is conducted by each company to allow an employee to fulfill the specific job requirements for which they are responsible.

c) Employees who have completed a medical device training curriculum through an educational institution are desired by employers.

d) Industry recognized certification programs in the areas of regulatory and quality skills are provided by established organizations.

FDA Medical Device Classifications

In the United States, medical devices are regulated by FDA. The specific branch within FDA that is charged with regulating medical devices is the *Center for Devices & Radiological Health (CDRH)*.

The mission of CDRH is to protect and promote public health, ensuring that medical devices are safe.

Medical devices are classified based upon the risks associated with the device. Devices are typically classified into one of three categories—Class I, Class II, and Class III.

Devices are typically classified into one of three categories:

Class I
Class II
Class III

Class I devices are assessed as low risk and subject to the least regulatory controls. For example, dental floss is a Class I device. About 47% of medical devices are included in this category.

Many medical devices fall into the Class II category. These devices are higher risk devices than Class I and require greater regulatory controls to provide a reasonable assurance that the device will be safe and effective. About 43% of medical devices fall into this class of products. Hearing aids and orthodontic wire are Class II devices.

Class III devices make up about 10% of medical devices. These are the highest risk devices and are subject to the most stringent regulatory control. Class III devices must typically be approved by FDA before they are marketed. For example, replacement heart valves are classified as Class III devices.

Class I Examples

- Tongue depressors
- Elastic bandages
- Hand held dental instruments
- Examination gloves

Class II Examples

- X-ray machines
- Powered wheelchairs
- Infusion pump
- Surgical and acupuncture needles

Class III Examples

- Implanted pacemakers
- Heart valves
- Implanted cerebral simulators

Why Is Classification Important and How is Classification Determined?

Identifying the classification of a medical device is important because the classification assigned will guide the design and development plan for the product and the quality plan for the organization's Quality System. Determining the product class will also determine the premarket submission/ application required for FDA clearance to market.

1. Product classification helps determine what must be done before the product is brought to market.

2. Product classification guides the product development phase to establish design controls and a quality system.

3. Product classification helps to determine the cost and investment of time it will take to bring a product to market.

Device classification is determined based on the intended use of the device and also upon indications for use. For example, a scalpel's intended use is to cut tissue. A subset of intended use arises when a more specialized indication is added in the device's labeling such as, "for making incisions in the cornea". Product classification is also risk based, as discussed previously. The risk the device poses to the patient and/or the user is a major factor in the class the medical device is assigned. Most medical devices are classified through the use of FDA databases and documents. The FDA has classified and described over 1,700 distinct types of devices and organized them into 19 medical specialty panels such as cardiovascular devices or ear, nose, and throat devices. For each of the devices classified by the FDA, general description is provided, including the intended use, the class to which the device belongs (i.e., Class I, II, or III), and information about marketing requirements.

The FDA document where this classification information can be found is Title 21 of the Code of Federal Regulations (CFR), Parts 862-892.

FDA Device Classification Panels

How to Locate Classification Regulations

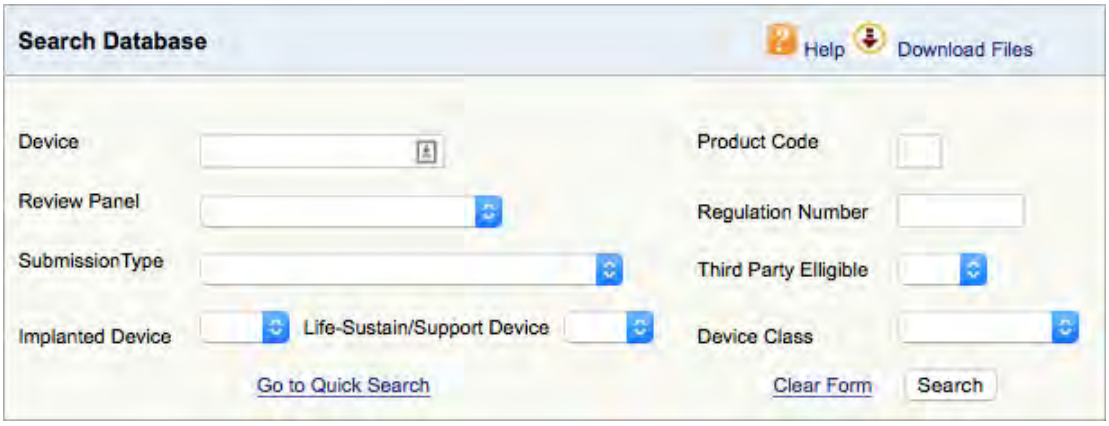
Medical Specialty		Reg. Citation (21CFR)
73	Anesthesiology	Part 868
74	Cardiovascular	Part 870
75	Chemistry	Part 862
76	Dental	Part 872
77	Ear, Nose, and Throat	Part 874
78	Gastroenterology and Urology	Part 876
79	General and Plastic Surgery	Part 878
80	General Hospital	Part 880
81	Hematology	Part 864
82	Immunology	Part 866
83	Microbiology	Part 866
84	Neurology	Part 882
85	Obstetrical and Gynecological	Part 884
86	Ophthalmic	Part 886
87	Orthopedic	Part 888
88	Pathology	Part 864
89	Physical Medicine	Part 890
90	Radiology	Part 892
91	Toxicology	Part 862

In addition to identifying the device class, the device product code also needs to be determined. Product codes allow medical devices to be identified accurately. They also provide a way to track current medical devices and to identify predicate devices. A predicate device is a medical device that is currently or has been previously legally marketed and is substantially equivalent to the device being identified.

Classification product codes are used by FDA to obtain accurate data about devices for purposes of reporting and analysis. Classification product codes are used throughout the total product life cycle (TPLC) because they provide consistent information across all medical device databases.

The FDA Product Classification Database contains medical device names, the product codes associated with the device and additional information developed by the Center for Devices and Radiological Health (CDRH).

FDA Product Classification Database Search



Bringing the Medical Device to Market

Once the device classification and product code are determined for the medical device, the type of premarket submission/application, if required for FDA approval of the device, can be pursued.

All medical devices must be manufactured under a quality assurance program, be suitable for the intended use, be adequately packaged and properly labeled, and have an establishment registration and device listing in the FDA Unified Registration and Listing System.

As the device class increases from Class I, to Class II to Class III, the regulatory controls also increase. Class I devices are subject to the least regulatory control, through Class III devices being subject to the most stringent regulatory control. The regulatory controls for each device class include:

Class I (low to moderate risk): General Controls
Class II (moderate to high risk): General Controls and Special Controls
Class III (high risk): General Controls and Premarket Approval (PMA)

Class I

Class I Medical Devices and General Controls

The FDA has exempted almost all Class I devices from the requirement to provide a 510(k) premarket submission. A 510k is a document provided to the FDA by the medical device manufacturer that demonstrates that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device and that the new device is not subject to premarket approval (PMA). Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices.

Class I devices are not intended for use in supporting or sustaining life. They are not meant to be of substantial importance in preventing impairment to human health, and they may not present a potential unreasonable risk of illness or injury.

General controls apply to all medical devices, unless exempted by regulations. General controls govern device registration and listing; premarket notification; good manufacturing practices; records and reports; other notifications relating to repair, replacement, or refund; adulteration of product; misbranding; banned devices; and restricted devices.

Some Class I devices are also exempted from the GMP (Good Manufacturing Practice) regulations, except for general requirements concerning records (820.180) and complaint files (820.198), as long as the device is not labeled or otherwise represented as sterile.

FDA General Controls For Medical Devices

Class II

Class II Medical Devices and Special Controls

The FDA Class II devices are devices for which general controls alone are not sufficient to provide reasonable assurance of the safety and effectiveness of the device. Special controls are regulatory requirements for these devices and may include: performance standards, post-market surveillance, patient registries, special labeling requirements, pre-market data requirements and guidelines for use. The FDA maintains a list of Class II devices that are exempt from 510(k) pre-market notification requirements. These devices are not exempt from GMP requirements. The research done to determine the classification and product code for a device is the guide to determining the regulatory requirements for the device.

FDA Medical Device Exemptions 510(k) and GMP Requirements

510(k) Pre-Market Notification

A 510(k) is a premarket submission made to the FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device (21 CFR 807.92(a)(3)) that is not subject to PMA.

In order to be eligible for 510(k) clearance, a new device must closely resemble the safety and effectiveness characteristics of the predicate device to which it is being compared. An example of technological advancement under this process was marketing clearance of lasers for “cutting or ablation” of tissues when compared with a heated wire cautery device.

The FDA provides guidance documents which describe the information and the format that is required for a 510k premarket notification submission, but does not provide a specific form to be used for the submission. It is up to the company applying for FDA clearance to follow the regulations and guidance documents and to provide the FDA with the information required.

Electronic Code of Federal Regulations Part 807 Premarket Notification Procedures

FDA’s goal is to make a 510(k) decision within 90 days. Within 60 days the FDA conducts a substantive review. If additional information is needed the submitter is notified and the 510(k) is placed on hold. The average time to get a 510(k) decision is 5 months. A 510(k) submission that is accepted by the FDA does not provide approval of the medical device. It is clearance from the FDA to legally market a medical device. Approximately 80% of submissions are designated substantially equivalent to existing devices cleared by the FDA.

Class III

Class III Medical Devices and Pre-Market Approval

Class III medical devices are the most regulated devices. These devices fall into one or more of the following categories:

- some devices that have not been marketed prior to 1976;
- devices intended to be used to support or sustain human life or prevent impairment of human health;
- devices that may present a potential unreasonable risk of illness or injury and for which general controls and special controls are insufficient to provide reasonable assurance of the safety and effectiveness of a device;
- devices for which there is insufficient information to make such a determination.

Pre-Market Approval Application

The FDA requires Premarket Approval (PMA) for high-risk Class III medical devices and may also require PMA for new technology where no identifiable predicate exists. The FDA PMA approval process is an involved process and requires considerable preparation and resources. Approvals can take up to 12 months after pre-submission. The following are the steps involved in a PMA:

- Pre-Submission (pre-sub)
- Investigational Device Exemption (IDE)
- Premarket Approval
- Quality System Inspection to 21 CFR Part 820
- Registration of your medical device with FDA

The FDA requires Premarket Approval (PMA) for high-risk **Class III** medical devices

Clinical trials of the medical device are required before submitting a premarket approval application to the FDA. A modest medical device clinical trial can cost $1 million and a major trial $5-10 million. In order to conduct clinical trials an Investigational Device Exemption (IDE) is needed if the device is considered to have "significant risk." An IDE application must include an investigational plan and information on any prior clinical investigations that were conducted with the medical device under consideration. Documentation requirements for the IDE application are substantial. To guide the process, the FDA follows a pre-submission process which allows for a preliminary review of the IDE documents and guidance from the FDA prior to submission. At this time the FDA will work with the device company to discuss testing requirements for the device, the clinical trial design and testing methods to be used, and the designation of the device as one of "significant risk" or "non-significant risk". To proceed with clinical trials, Institutional Review Board (IRB) approval will also need to be obtained from the medical institution at which the clinical trials will be conducted. The FDA reviews the PMA and conducts a site visit of the major suppliers involved in the design and production of the medical device under consideration. When approval of the PMA is obtained, the FDA issues a PMA approval letter and posts it online. When this approval is obtained, the device must be listed and the company producing the device registered with the FDA. The average time to get a PMA decision is 12 months. Approximately 70% of these submissions receive approval as safe and effective.

Medical Device User Fee Amendments (MDUFA)

Premarket review by FDA – both 510(k) and PMA - require the payment of a user fee. FDA typically evaluates more than 4,000 510(k) notifications and about 40 original PMA applications per year. The fees for fiscal year 2016 (October 1, 2015 through September 30, 2016) are as follows:

Application Type	Typical Class ◊◊	Standard Fee	Small Business Fee ◊
510(k)	Class II	$5,228	$2,614
PMA	Class III	$261,388	$65,347

◊ Small businesses with annual sales of no more than $100 million are provided a discount on fees.
◊◊ Refer to the specific product classification for exceptions.

What is a Regulatory Strategy?

A regulatory strategy is a first step towards defining the plan for obtaining regulatory approval of a medical device. The regulatory strategy is a formal document that aligns the regulatory activities to bring a new or modified product to market with the business strategy for that product. It provides overall definition and direction to the company for the product being developed by identifying the important regulatory elements to be addressed to market the device. A regulatory strategy typically assesses the following:

- Research "product classification" for the product; Determine if ongoing dialogue with the regulatory agency is needed;
- Review the regulations and guidance documents related to the product category (if available);
- Review performance standards, guidance documents, etc. related to the product code(s)/product classifications;
- Search competitor products (if any) or products utilizing similar modalities;
- Assess product claims with multiple predicates (if possible)
- Review warning letters, advisory committee meetings, letters to health care providers, consumer updates, etc. for potential impact/alerts;
- Determine if pre-clinical or clinical testing is required;
- Determine if specific testing requirements are applicable and state their relationships to established standards and guidance, if applicable.

The regulatory strategy takes into consideration internal company resources and challenges to obtaining regulatory approval. Once this information is obtained and analyzed, a determination can be made about the best pathway to follow to bring the product to market. Pathways include the 510(k) submission and the premarket approval application discussed previously. There are other pathways available for medical devices that fall into categories that are not discussed in this document. Low to moderate risk devices for which there is no predicate device can follow a de novo classification pathway. There are also regulatory pathways for investigational devices, and there are humanitarian device exemptions. The FDA regulations are subject to change and adaptation as new technologies and products are brought forward for classification and clearance.

Third party organizations specializing in regulatory processes and documentation are often the best source of current information related to product classification and the submission process.

The regulatory strategy is a document internal to a company and is not submitted to the FDA for approval. It is shared with a project team and any stakeholders in the company who require information about the medical device being brought to market.

Medical Device Quality Systems

Manufacturers must establish, implement and maintain a Quality System to help ensure that their products consistently meet established regulations. The Quality System for FDA-regulated products (food, drugs, biologics, and devices) is known as current good manufacturing practices (cGMP's).

Since FDA regulations apply to a broad array of devices, they do not define in detail how a manufacturer must produce a specific device. Rather, the regulation provides a general framework for manufacturers to follow. Each are required to develop Quality System policies and procedures suitable for their organization to ensure their device is produced following cGMP's.

In order for a manufacturer to demonstrate that a Quality System has been established, implemented and maintained, objective evidence is required in the form of a Quality System Record (QSR). This should include documents and records that can be examined by the FDA at the time of an inspection. The QSR applies to finished device manufacturers who intend to commercially distribute medical devices. A finished device is defined in 21 CFR 820.3(l) as any device or accessory to any device that is suitable for use or capable of functioning, regardless of whether it is packaged, labeled, or sterilized.

Facilities, machinery and quality training, among other things, need to be analyzed and verified on a regular basis to meet minimum tolerances and requirements and then recorded in the QSR. It is worth noting that the FDA has determined certain types of medical devices are exempt from GMP requirements by FDA classification regulations discussed above. However, exemption from the GMP requirements does not exempt manufacturers of finished devices from keeping complaint files (21 CFR 820.198) or from general requirements concerning records (21 CFR 820.180).

Quality System Regulation

In order to achieve FDA Quality System Regulation compliance a Quality System addressing the design, manufacture, packaging and labeling, storage and delivery of the medical device is required. 21 CFR Part 820 details the requirements of the Quality System.

Elements addressed in the Quality System include but are not limited to:

- Management responsibilities
- Internal quality audits
- Personnel qualification and training
- Design controls
- Document and purchasing controls
- Identification and traceability
- Production and process controls
- Acceptance activities
- Nonconforming product
- Corrective and preventative action
- Labeling and package control
- Handling, storage, distribution, and installation
- Records
- Servicing
- Statistical techniques

In addition, compliance to 21 CFR 803 and 806 are required:

- Medical device reporting
- Corrections and removals

A company that chooses to manufacture a medical device will be required to establish a new Quality System, or may be able to augment their existing Quality System. A common approach is to have a qualified third party perform a gap assessment of the existing system with the FDA regulations which can be used to develop a custom quality plan appropriate for the organization. Quality plans are typically phased in based on the maturity of the organization, life-cycle of the product and complexity of the design and manufacturing.

Electronic Code of Federal Regulations Part 820 Medical Devices Quality System Regulation

ISO 13485

specifies organizational requirements to provide quality medical devices that consistently meet customer and regulatory requirements.

ISO 13485 Quality Management System

ISO 13485 is an International Organization for Standardization (ISO) that represents the requirements for a comprehensive Quality Management System for the design and manufacture of medical devices. While not required or recognized by the FDA, ISO 13485 Certification provides an organization with an objective way to demonstrate its ability to provide medical devices that consistently meet customer and applicable regulatory requirements. It is the most commonly chosen path for companies to meet the Quality Management System (QMS) medical device requirements in Europe, Canada, and Australia, and serves as the basis for QMS compliance in other countries.

ISO 13485 certification requires effort to attain and maintain which allows customers to have confidence that the company can be trusted to fulfill their quality requirements. The approach used to implement the ISO 13485 standard typically occurs in phases as follows:

PHASE 1

Analysis, Planning, Scope and Exclusions Phase

- Define scope of implementation
- Appoint management representative
- Conduct a gap analysis audit to determine areas of focus
- Define objectives and create a quality plan
- Conduct training for employees on ISO 13485

PHASE 2

Documentation Development and Implementation Phase

- Develop quality policy, objectives and manual
- Review current policies and procedures
- Write new Standard Operating Procedures (SOP) and review Work Instructions
- Start using new procedures to generate auditable records

PHASE 3

Internal Auditing and Management Review Phase

- Conduct internal audits
- Conduct management review meeting
- Train internal auditors

PHASE 4

Audit Readiness and Certification Phase

- Conduct pre-certification audit and final readiness review
- Certification audit stage I (desk top)
- Certification audit stage II (on-site)
- Address any remaining issues

Development of a Medical Device Quality System

Development of a Medical Device Quality System compliant with ISO 13485 and the applicable sections of 21 CFR 820 will allow a company to achieve certification to ISO 13485 and enable registration with FDA as a Manufacturer. The amount of time required to achieve compliance can vary widely. Commitment by senior management is key. Delays in full implementation can occur when senior management views the Quality System as just another regulatory hurdle, not recognizing the benefits of the system to the organization, such as ensuring customer requirements are met, reducing risk and maintaining effective processes. Upper management must allocate sufficient in-house resources. Hiring an experienced outside consultant can help the process move more quickly, but without a dedicated management representative who has the full support of senior management, change will happen slowly.

Developing a Medical Device Quality System enables a company to register with the FDA.

Quality System development tasks include the preparation of a Quality System manual, careful crafting of an estimated 20 – 30 Quality System procedures, implementing the procedures via releasing them per the established document control process in the new QMS, and providing Quality System training to employees. It's important that the Quality System be appropriately developed for the size and complexity of the organization. An overly burdensome system may become resource intensive and difficult to maintain. A "template" based system may not be well adapted to the products and needs of the organization. While implementation and ISO 13485 certification may be possible in both cases, the Quality System may not be effective, resulting in compliance issues, additional cost and potential regulatory violations when inspected by the FDA.

If your company has 5 employees and one location, it often takes less time to implement a QMS than if you have 500 employees and three locations or if you have complex manufacturing processes or high risk medical devices. Once the QMS is developed and implemented, it takes time to generate quality records in accordance with those policies and procedures that can be used as objective evidence to demonstrate compliance during an audit to support full implementation of the system.

For most small to mid-size medical device manufactures it is possible to achieve ISO 13485 certification within 4 to 7 months if the company has hired an experienced medical device professional or using outside consults. For companies less familiar with the requirements of medical devices an average or 12 months is typical. If an existing ISO 9001 Quality System, or similar, is well established and implemented within the company this can be leveraged to reduce the amount of new procedures; however careful consideration should be made to the impact of the existing business when trying to integrate a more a stringent Quality System.

The cost of ISO 13485 certification depends primarily on three factors:

1. Fees of the certification body

Certification body fees can range from $6,000 - $30,000 and may be recurring. Cost depends on many factors and include:

- Number of employees
- Complexity of the medical device and variants
- Certification body selected
- Traveling fees
- Auditor accommodations and daily expenses

2. Implementation or additional resource costs

- Anything purchased or added to the organization as part of the implementation (i.e. resources, equipment, software, etc.) should be considered and are dependent on the maturity of the organization.
- New equipment, staffing of Quality Engineer(s), added maintenance costs, certification maintenance, document management, staff training, etc. as required

3. Technical consultancy cost, if needed

- Consultant charges
- Consultant traveling and other related charges

FDA Registration and Listing

Regardless of the medical device class, a company intending to manufacture, contract manufacture, or market medical devices in the United States must inform the FDA of its facility location, and must list its product with the agency for monitoring purposes. Registration requires payment of a registration fee and is required to be done through the FDA Unified Registration and Listing System (FURLS)/ Device Registration and Listing Module (DRLM).

Manufacturers are required to register annually following the initial registration.

If a device requires premarket clearance or premarket approval prior to marketing (i.e., the medical device is not exempt), the device firm must wait until it receives FDA clearance or approval before registering and listing.

Registration of a device establishment, assignment of a registration number, or listing of a medical device does not in any way denote clearance or approval of the establishment or its products by the FDA.

Exemptions from registration and listing requirements include component manufacturers who provide raw materials and/ or components used in the manufacture or assembly of a device. Manufacturers whose devices are used solely in research, teaching, or analysis and are not introduced into commercial distribution are also exempt.

Establishment Registration

Each owner/operator is required to create an electronic account; they may also appoint a designee who will be the official correspondent with the FDA. A subaccount is created with a separate ID and password for the designee.

Registration with the FDA is required initially when a manufacturer brings a medical device to market. Manufacturers are required to register annually following the initial registration. If a manufacturer's information changes (i.e. address, owner/operator, official correspondent, establishment type, etc.) the information included in the annual registration should be updated during the course of the year.

Other manufacturing related establishment types required to register with the FDA include the following:

- **Contract Manufacturer** – Manufacturers a finished device to another establishment's specifications. (See section 8 of this document for a more detailed description.)
- **Repackager** – Packages finished devices from bulk or repackages devices made by a manufacturer into different containers (excluding shipping containers).
- **Relabeler** – Changes the content of the labeling from that supplied from the original manufacturer for distribution under the establishment's own name. A relabeler does not include establishments that do not change the original labeling but merely add their own name.
- **Remanufacturer** – Any person who processes, conditions, renovates, repackages, restores, or does any other act to a finished device that significantly changes the finished device's performance or safety specifications, or intended use.
- **Specification Developer** – Develops specification for a device that is distributed under the establishment's own name but performs no manufacturing. This includes establishment's that, in addition to developing specifications, also arrange for the manufacturing of devices labeled with another establishment's name by a contract manufacturer.

Device Listing

The product listing provides the generic category of the device being marketed. This information is used by the FDA to conduct inspections and it ensures that the FDA knows what products are on the market. There is a separate regulation number for most types of devices.

Owner/operators or their official correspondents are responsible for keeping data on their listing forms current. The following types of changes require an update:

- marketing a new device with a classification name that is different from the classification name currently listed.
- the intended use of the device changes sufficiently that a different classification name is required.
- models or variations of the listed device are no longer on the market.

Annual Registration User Fees

Congress authorized the FDA to collect annual registration fees for device establishments. These are recurring fees which adjust each year. The schedule of annual registration user fees for fiscal years 2013 through 2017 follows.

Year	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Fee	$2,575	$3,313	$3,646	$3,845	$3,382

Medical Device Regulatory and Quality Training

As in any industry, employees of medical device manufacturers require training specific to their assigned duties within the company. These are typically company sponsored non-certification training programs or training provided by outside consultants. Employees may be hired who have completed a medical device training curriculum through an educational institution. These credentials are desired by employers, as well as prior medical device experience.

Non-Certification Training Curriculum

The FDA quality system requirement 820.25 Personnel (b) Training states: "Each manufacturer shall establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities. Training shall be documented."

The benefit to hiring employees with a regulatory/quality background is that they come prepared to work in the medical device industry.

Each employee must be trained in their job function by specifically using what is written in the Standard Operating Procedures (SOPs) developed by the company. The employees should read the appropriate SOPs. When new SOPs are written or significant or complex changes are made to existing SOPs, training with an instructor or in a group setting is suggested. Training may be delivered electronically. Each employee's work should be reviewed to make certain that the work is being performed properly. All training must be documented.

If an employee performs a specific task that requires outside training, i.e. soldering or welding, that training must be documented and a copy of the documentation will need to be kept on file.

Employees responsible for detecting defects are to be trained in the defects that they are looking for so that they have a solid understanding of potential problems. This is very important for production line employees as well as for quality control/assurance employees. In this, as in other training scenarios, having hands-on examples available will reinforce the training information had help employees to retain what they have learned. For example: what constitutes a bad solder joint, a cold joint, and a good joint is critical to solder inspection training and to the job function. Having examples of the solder joints available is key to the employees' training.

All employees do not require training on all of the quality system requirements. Best practice is to provide employees with an overview of the requirements, the reasons for their importance and how they directly relate to their job and the consequences of non-compliance to the regulations. The sections of the quality system requirements that pertain to the employee's job responsibilities and documentation of that training are what is required to be compliant with FDA training requirements.

Regulatory and quality courses of study are offered at many colleges and universities. These courses provide students with a foundation of knowledge that can be applied to regulated industries. Through these courses students gain and understand the issues, terminology and requirements that need to be fulfilled in an FDA regulated environment. The benefit to hiring employees with a regulatory/quality background is that they come prepared to work in the medical device industry. They have studied the regulations and the reasons for the regulations and come prepared to immediately contribute to business of manufacturing medical devices.

Certification Programs for Medical Device Personnel

There are industry recognized certification programs for both regulatory and quality skills. Certification in these areas is formal public recognition by a respected professional organization that the individual has demonstrated proficiency within the discipline; is credible; has proven their knowledge and is recognized by their peers for achieving a high level of competence. Individuals who achieve certification are also committed to further develop their knowledge and skills and to remaining current with industry practices in order to retain and renew their certification.

American Society for Quality

The American Society for Quality (ASQ) is the global professional organization of individuals who work in the quality profession. ASQ brings together diverse quality experts who provide training and professional credentials to the global quality community.

ASQ certification is a formal recognition by ASQ that an individual has demonstrated a proficiency within, and comprehension of, a specific body of knowledge. ASQ currently offers certifications in 18 areas of quality systems. These certifications include the areas of quality manufacturing, quality auditing, quality management, software, systems and analytical tools.

Each certification area has specific eligibility requirements which include academic and work experience requirements. ASQ provides a recommended order in which to earn certifications based on an individual's career path. The order of certification is not required but in most cases allows the professional to build on the bodies of knowledge of prior certifications.

Exam fees range from $244 to $2229, depending upon the exam topic and ASQ membership. To achieve the highest level of quality proficiency, the Master Black Belt, a portfolio review is required in addition to the exam. The cost of the portfolio review ranges from $495 for ASQ members to $650 for non-members. Most exam candidates also purchase the recommended study materials.

American Society For Quality Website

Regulatory Affairs Professional Society

The Regulatory Affairs Professional Society (RAPS) is the largest global organization for those involved with the regulation of healthcare and related products, including medical devices. RAPS helped to establish the regulatory profession and continues to actively support and lead the profession as a neutral, non-lobbying, nonprofit organization.

The Regulatory Affairs Certificate (RAC) granted by RAPS is the only globally recognized certification for the regulatory profession. A regulatory affairs certificate can be earned for the US, EU, Canada and for international practices with a Global certificate.

Individuals are eligible to take the certification exam after completing educational and work experience requirements. Most individuals who take the exam also complete a plan of study that includes content directly related to the exam topic.

Exam fees range from $425 for RAPS members to $525 for non-members. Most candidates for the RAC exam also purchase study materials.

Regulatory Affairs Professional Society Website

Contract Manufacturing

A contract manufacturer manufactures a finished device to another company's specifications.

Contract manufacturers are required to register with the FDA and list the medical devices they produce and the activities they perform on those devices. Contract manufacturers who do not develop the specifications for a finished device are not required to obtain FDA clearance for that device. The responsibility for obtaining FDA clearance for a medical device resides with the entity that designs and develops the device. The FDA also states that the product owner is responsible for making sure that the products introduced into interstate commerce are neither adulterated nor misbranded, particularly as the result of failing to meet cGMPs.

The guidance clarifies that FDA considers contract facilities an extension of the manufacturer's own facility. While manufacturers are only required to comply with the FDA regulations that govern the activities performed, certain product responsibility and liability may rest with not just the designer, but with the manufacturer as well.

The FDA currently recommends the establishment of quality agreements between a device owner and contract manufacturers who perform functions for the device owner. Quality agreements must require the manufacturer to comply with cGMP regulations, while making clear that it is ultimately the distributing entity that must ensure the products are manufactured to those standards. All responsibilities for both parties are explicitly stated in the quality agreements.

A quality agreement describes the owner's and the contract facility's roles and manufacturing activities under cGMP. A well-written quality agreement will use clear language, define key manufacturing roles and responsibilities and establish expectations for communication. It will specify which products and/or services the owner expects from the contract facility and who has final approval for various activities. Most quality agreements feature:

- **Purpose/Scope** — to cover the nature of the contract manufacturing services to be provided
- **Roles and Responsibilities** — to define key stakeholders and their commitments to the engagement
- **Definitions** — to ensure that the owner and contract facility agree on precise meaning of terms in the quality agreement
- **Regulatory Compliance** — to outline necessary compliance concerns and ensure regulatory issues are addressed
- **Change Control** — to explain how the parties will resolve disagreements about product quality issues or other problems
- **Manufacturing Activities** — to document quality unit and other activities associated with manufacturing processes as well as control of changes to manufacturing processes
- **Duration** — Lifecycle of, and revisions to, the quality agreement

Conclusion

FDA medical device regulations and quality systems provide a means to document processes, procedures and responsibilities so that a medical device manufacturer can be trusted to consistently meet customer requirements and specifications and to produce a safe and effective product.

Obtaining clearance from the FDA to bring a medical device to market is the driving force behind the manufacturing of a medical device. The pathway to FDA clearance determines the requirements and responsibilities of each entity involved in the design, manufacturing and distribution of the medical device.

Establishing a quality system ensures that controls are implemented and completed satisfactorily during all stages of the manufacturing and distribution process. Building a product of acceptable quality mitigates risks that may arise during the production of the product and during its use.

In addition to the QSR established by the FDA, many medical device manufacturers opt to obtain ISO 13485 certification to demonstrate to their customers their commitment to the safety and quality of the medical devices they manufacture.

Employee training and certification helps to ensure that the company is developing personnel capable of making defect-free products that safely and effectively meet customer needs and expectations, while reducing falloff, rework, and time to market. Each company has the responsibility to provide this training for their employees. Some employees will expand their knowledge base and contribute even more significantly to this company goal.

The investment of time and money into a substantive regulatory and quality system for the manufacture of medical devices pays off in customer confidence and patient safety. A “doing it right the first time” approach to FDA regulations and quality system best practice development allows the manufacturer to plot their own course through positive growth. Investing in quality mitigates risk, lowers long term costs by reducing rework and discarded product, results in a consistent and reliable manufacturing and most importantly, patients benefit from a safe and effective product.

Appendix

Center for Devices & Radiological Health (CDRH)

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/

FDA Device Classification Panels

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051530.htm

FDA Product Classification Database Search

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm

FDA General Controls For Medical Devices

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/ucm055910.htm

FDA Medical Device Exemptions 510(k) and GMP Requirements

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm

Electronic Code of Federal Regulations Part 807 Premarket Notification Procedures

http://www.ecfr.gov/cgi-bin/text-idx?SID=5dd5e413eb481e5b88afaaf3ee7063ab&mc=true&node=sp21.8.807.e&rgn=div6

Electronic Code of Federal Regulations Part 820 Medical Devices Quality System Regulation

http://www.ecfr.gov/cgi-bin/text-idx?SID=9ea37f40915ebabfece4ba431c9d7f40&mc=true&tpl=/ecfrbrowse/Title21/21cfr820_main_02.tpl

American Society For Quality Website

http://asq.org/index.aspx

Regulatory Affairs Professional Society Website

http://www.raps.org/