Industry-specific Guidebook for Opto-mechatronics Industries to Enter Medical Device and Healthcare Market

Project Applicant:

香港光機電行業協會
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1.1.1 Introduction to HKOMIA

Introduction to HKOMIA

Formerly known as The Hong Kong Photographic and Optics Manufacturers Association (HKPOMA), The Hong Kong Opto-Mechatronics Industries Association (HKOMIA) has successfully been renamed in 2010 for better serving our members and coordinating with the industry. From the past twelve year's continuous effort, HKOMIA has assisted many Hong Kong industrialists who are interested in optics and opto-mechatronics industry to explore, diversify into the business and to develop a close network and collaboration relationship with mainland China and overseas industries as well as related organizations. HKOMIA members heavily engaged in the high value-added manufacturing activities including opto-mechatronics design, manufacturing and business investment.

Aim of HKOMIA:

- To foster the communication, interaction and co-operation among members and to establish liaison with and convey the collective opinions to the government, industrial or trade association
- To serve the interest, build up the reputation and promote the image and capabilities of Hong Kong's opto-mechatronics industry.
- To assist in upgrading the technology, engineering, and management skills of the industry so as to improve its performance and enhance its competitiveness in the international market.
- To establish contacts with overseas organizations of similar nature and to provide platforms for members to develop business relationships with overseas buyers and potential joint venture partners.

1.1.2 Introduction to HKOMIA SDF Project

Introduction to HKOMIA SDF Project

Hong Kong opto-mechatronics industry has been one of the fastest growing industry sectors in the past. However, as the competition in the opto-mechatronics industry has become extremely vigorous in recent years (contributing from the shortening of product-life as well as keen competition in the Asian region), local opto-mechatronics SMEs are facing great challenges to sustain their business.

Competition with our regional counterparts, for instance, South Korea, Taiwan, Singapore and our mainland counterparts are substantially increased. Hong Kong opto-mechatronics SMEs are gradually losing their competitive edge, and urgently needed to transform their business in order to survive. It is crucial for our local opto-mechatronics SMEs in expanding their business into the high value-added market, by leveraging our strong industry foundation and know-how in opto-mechatronics design, manufacturing and assembly.

1.1 Introduction

It is common to find opto-mechatronics components being the critical components of many medical and healthcare devices. For instance, the endoscopic devices which are widely employed in minimally invasive surgery are composed of precision optics, mini-motors/ actuators, illumination source, micro-gears, etc., which are supplied by opto-mechatronics manufacturers, who have the know-how on high-precision manufacturing, optics design and opto-mechatronics system assembly.

Since the entry-barrier for migration from the traditional opto-mechatronics industry into medical and healthcare industry is relatively high, a lot of local opto-mechatronics SMEs are facing great challenges to overcome such barrier, which includes the medical device risk management, regulatory requirement (e.g. pre-market approval, US FDA clearance requirement, MHRA requirement, EU medical device directive 93/42/EEC, etc.), medical device quality management system (e.g. ISO13485, QSR, cGMP, etc.), post-market surveillance requirement, etc. Local opto-mechatronics SMEs are in need of support to overcome the mentioned barrier, in order to open up the medical and healthcare device market.

Therefore, HKOMIA has been granted with a government funding to assist the opto-mechatronics industry to expand their business into the high value-added medical and healthcare device market through a series of deliverables, including:

1. **Implementation of Pilot Scheme**
   To guide 3 pilot companies to establish and upgrade their quality management system for the manufacturing and distribution of medical devices through hands-holding implementation by HKPC.
2. **Compilation of Industry-specific Guidebook**
   To highlight the strategy and know-how in transforming the manufacturing and distribution operations from opto-mechatronics complied into medical-grade complied requirements.
3. **Organization of 8 Half-day Training Workshops and 1 Half-day Experience Sharing Seminar**
   To enable the knowledge transfer of opto-mechatronics related medical device information to the industry for future business expansion into high value-added medical and healthcare device market.
4. **Construction of Project Website**
   To disseminate project deliverables and results to all the SMEs of the opto-mechatronics industries, SMEs of the other related industries and the public. Project deliverables, including this industry-specific guidebook and the materials presented during the aforementioned training workshops will be uploaded to this project website for the public to download.
5. **Set-up of Help Desk Services**
   To provide the industries on the know-how for upgrading and transformation the current business to the medical and health device business.

1 Introduction and Overview of Medical Device Industry

1.1 Introduction

1.1.3 Introduction to Opto-mechatronics Industry

Hong Kong opto-mechatronics industry has been one of the fastest growing industry sectors in the past. However, as the competition in the opto-mechatronics industry has become extremely vigorous in recent years (contributing from the shortening of product-life as well as keen competition in the Asian region), local opto-mechatronics SMEs are facing great challenges to sustain their business. Competition with our regional counterparts, for instance, South Korea, Taiwan, Singapore and our mainland counterparts are substantially increased. Hong Kong opto-mechatronics SMEs are gradually losing their competitive edge, and urgently needed to transform their business in order to survive.

As a result, it is crucial for our local opto-mechatronics SMEs in expanding their business into the high value-added market, by leveraging our strong industry foundation and know-how in opto-mechatronics design, manufacturing and assembly.

One of the examples of high value-added market is medical and healthcare device market which is highly correlated with opto-mechatronics industry. It is common to find opto-mechatronics components being the critical components of many medical and healthcare devices. For instance, the endoscopic devices which are widely employed in minimally invasive surgery are composed of precision optics, mini-motors/actuators, illumination source, micro-gears, etc., which are supplied by opto-mechatronics manufacturers, who have the know-how on high-precision manufacturing, optics design and opto-mechatronics system assembly.

1.1.4 Introduction to Medical Device Industry

According to the report “Medical Device Market in 2016: Challenges In The Traditional Markets And New Opportunities In Asia Pacific”, written by Giedre Liorancaite, Global medical device production value will record strong growth of almost 6% in 2016, to reach US$315 billion. [26]

The medical devices industry will witness significant opportunities for growth in the coming decade. It is expected that the market expansion will be driven by the rising prevalence of chronic diseases and related increase in disability-adjusted life years (DALYs), technological advancements in medical devices, and growing aging population. [28] For example: cardiac and respiratory diseases generally affect people above the age of 65, and with the global over-65 population expected to rise up to 1 billion by 2020, devices used in the treatment of age-related illnesses will see significant growth in their revenues.

When comparing to other regions, Asia Pacific presents unique opportunities for medical device producers. The region was the fastest growing medical device market, rising at a CAGR of 10% over 2008-2014 and settling at US$90,916.5 billion in 2014. The market growth was spurred by rapid expansion of the healthcare industry, as the hospital, medical

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and dental service industry's revenue in Asia Pacific has been rising at a CAGR of 8% (in US$ terms) over 2008-2014, representing the highest growth among regions. The region's healthcare industry is expected to continue to grow rapidly over 2016 as well. For instance, China's and India's healthcare service revenues are expected to advance by 12% and 9%, respectively, in 2016 alone, resulting in a large number of new hospital construction projects and thus soaring demand for medical and surgical equipment. [26]

2 Medical Device Regulatory Requirement in U.S., E.U. and China

2.1 US Regulation for Opto-Mechatronics Medical Devices

2.1.1 Overview of US FDA Regulation System

US Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) regulates firms who manufacture, repackage, re-label, and/or import medical devices sold in the United States. In addition, CDRH regulates radiation-emitting electronic products (medical and non-medical) such as lasers, x-ray systems, ultrasound equipment, microwave ovens and color televisions. [1] As a result, in order to be legally marketed in the United States, many medical devices (including opto-mechtronics related medical devices) must be reviewed by the FDA, the agency responsible for protecting the public health by overseeing medical products, including devices. [2]

Before selling medical devices in US, FDA requires all medical product manufacturers to 1) register their facilities, 2) list their devices with FDA, and 3) follow general controls requirements. [2] However, apart from the end-product manufacturers, there are still a lot of accessory or component manufacturers providing their products either to the end users or the finished device manufacturers. For the manufacturers of accessories or components that are packaged or labeled for commercial distribution for health-related purposes to an end user, registration and listing in FDA are required as same as the end-product manufacturers. However, for those manufacturer of components, that are not otherwise classified as a finished device, that are distributed only to a finished device manufacturer, registration and listing in FDA are not necessary required. [4] For example: micro-gears and micro motors/ actuators for endoscopic devices are not required to be registered or listed in FDA if they are sold to the end-product manufacturers instead of end users.

FDA classifies devices (including accessories/components) into one of the three categories (Class I, II and III) according to the risk they pose to consumers and the level of control necessary to provide reasonable assurance of safety and effectiveness. [2] As a result, the regulatory control increases from Class I to Class III. [1] Detailed device classification rules and examples would be further discussed in the following chapters.

Classified devices are subjected to different regulatory control. Most Class I devices are exempt from Premarket Notification 510(k); most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval (PMA). [1] A 510(k) is a premarket submission made to 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 that is not subject to PMA. [5] While PMA is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. [6] Further elaboration on the applicability and application for 510(k) and PMA would be made in the following chapters.

For most medical devices which are sold in the U.S., manufacturers must establish and follow quality systems to help ensure that their products consistently meet applicable requirements and specifications. The quality systems for FDA-regulated products (food, drugs, biologics, and devices) are known as current good manufacturing practices (CGMP's).

2.1 US Regulation for Opto-Mechatronics Medical Devices

[7] Many opto-mechatronics manufacturers have already established quality management system with compliance to different requirements such as ISO9001 or TS 16949, therefore these manufacturers may need to enhance their current quality management systems in order to comply with the requirements for medical device manufacturing before entering US market. Major requirements for cGMP and their importance to the realization of medical devices would be further introduced in the later chapters.

There are still a lot of regulatory requirements for medical device manufacturing and marketing in the US, such as labeling, reporting, clinical trials before device marketing. However, only the overall regulation system on medical devices, quality management system (21 CFR 820) would be discussed in detail in this industry guidebook.

As mentioned earlier, if the medical device is also radiation emitting electronic product, it must comply with two independent sets of regulations. Apart from device regulations, which may include establishment registration, device listing, and premarket notifications and approvals, the device must comply with the radiation safety regulations specified under 21 CFR 1000-1050. [17]

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2.1 US Regulation for Opto-Mechatronics Medical Devices

2.1.2 FDA Regulation System

2.1.2.1 Medical Device Definition

Medical devices range from simple tongue depressors and bedpans to complex programmable pacemakers with micro-chip technology and laser surgical devices. In addition, medical devices include in vitro diagnostic products, such as general purpose lab equipment, reagents, and test kits, which may include monoclonal antibody technology. [12]

Certain electronic radiation emitting products with medical application and claims meet the definition of medical device. Examples include diagnostic ultrasound products, x-ray machines and medical lasers. If a product is labeled, promoted or used in a manner that meets the following definition in section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act (the Act) it will be regulated by the Food and Drug Administration (FDA) as a medical device and is subject to premarketing and post-marketing regulatory controls. [12]

According to the definition of medical devices in FDA website, a device is: [12] "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

Therefore, whether the device is regarded as medical devices mostly based on its intended purpose of the devices and how the manufacturers claim the function and the use of the products when market in the US market.

2.1 US Regulation for Opto-Mechatronics Medical Devices

2.1.2.2 Medical Device Classification

FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Devices will be classified depends on the intended use of the device and also upon indications for use. For example, an endoscope's intended use is to view the inside of a person's body through body's natural opening. A subset of intended use arises when a more specialized indication is added in the device's labeling such as, "for doctors' detection of digestive problem". Indications for use can be found in the device's labeling, but may also be conveyed orally during sale of the product. In addition, classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned. Class I includes devices with the lowest risk and Class III includes those with the greatest risk. [9]

Table 1: Examples of Opto-Mechatronics Medical Device Classification:

Classification	Examples
I	Microscopes, Mechanical Wheelchair*
II	Endoscopes, Surgical Lamp, Insulin Pump, Blood Pressure Monitor
III	Pacemakers, Automated External Defibrillators

*510(k) is required for mechanical wheelchair

As device class increases from Class I, to Class II to Class III, the regulatory controls also increase accordingly, with Class I devices subject to the least regulatory control, and Class III devices subject to the most stringent regulatory control. Most Class I devices are exempt from Premarket Notification 510(k); most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval. The regulatory controls for each device class include: [11]

Table 2: Regulatory Control for Medical Devices of Different Classes

Classification	Risk		Regulatory Control
I	Low to Moderate Risk	- With Exemptions - Without Exemptions	General Controls
II	Moderate to High Risk	- With Exemptions - Without Exemptions	General Controls Special Controls
III	High Risk		General Controls Premarket Approval (PMA)

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If the device is classified as Class I or II, and if it is not exempt, a Premarket Notification 510(k) will be required for marketing. All devices classified as exempt are subject to the limitations on exemptions. Limitations of device exemptions are covered under 21 CFR xxx.9, where xxx refers to Parts 862-892. For Class III devices, a premarket approval application (PMA) will be required unless your device is a preamendments device (on the market prior to the passage of the medical device amendments in 1976, or substantially equivalent to such a device) and PMA's have not been called for. In that case, a 510(k) will be the route to market. [9]

As mentioned in Table 2, general controls are regulatory requirements authorized by the FD&C Act, under sections 501, 502, 510, 516, 518, 519, and 520. General controls apply to all medical devices, unless exempted by regulations. If a device is exempted from one of the general controls, such exemption is stated in the classification regulation for that device. [11] For example, the classification regulation for articulator, 21 CFR 872.3150, states the device is exempt from the current good manufacturing practice requirements of the quality system regulation if the device is not labeled or otherwise represented as sterile and it is exempt from 510(k) under certain limitations. Also, microscope and accessories, 21 CFR 864.3600, also states that the devices are exempt from the current good manufacturing practice requirements of the quality system regulation in part 820 of this chapter, with the exception of 820.180, with respect to general requirements concerning records, and 820.198, with respect to complaint files. As a result, opto-mechatronics manufacturers should check the corresponding classification regulations in FDA for any exemption. If no exemption is mentioned, then it should be regarded as general control with the inclusion on the following key items:

- Premarket notification or 510(k), if not exempt;
- Register and Listing;
- Labeling requirements;
- Prohibit Misbranding;
- Prohibit Adulteration;
- Quality Systems /GMP;
- Records and Reports;
- Report device failures;
- Corrective action plans.

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Apart from general controls, special controls are regulatory requirements for class II devices. FDA classifies class II devices for which general controls alone are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance. [11] For example: the classification regulation for ingestible telemetric gastrointestinal capsule imaging system, 21 CFR 876.1300, states the system is classified as Class II with special controls. Special controls refers to FDA's guidance, "Class II Special Controls Guidance Document: Ingestible Telemetric Gastrointestinal Capsule Imaging Systems; Final Guidance for Industry and FDA." Apart from having guidance documents, there are still different special controls for applicable devices. Examples are listed as below:

- Performance standards
- Postmarket surveillance
- Patient registries
- Special labeling requirements
- Premarket data requirements
- Guidelines [11]

In general, medical devices need to comply with general controls while special controls or premarket approval depending on corresponding classification regulation, etc. according to their classification. Manufacturers are advised to check the device-specific regulatory requirements in the FDA website in a regular manner in order to ensure full compliance of all requirements.

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2.1.2.3 Regulatory Control: Registration and Listing

FDA has Registration and listing enables FDA to know the location of medical device establishments and the devices manufactured in those establishments. Having such registered and listing information can increase U.S.'s ability to prepare for and respond to public health emergencies. As a result, all owners or operators of places of business (also called establishments or facilities) that are involved in the production and distribution of medical devices intended for use in the U.S. are required to register annually with the FDA. [13]

Most establishments that are required to register with the FDA are also required to list the devices that are made there and the activities that are performed on those devices. If a device requires premarket approval or notification before being marketed in the U.S., then the owner/operator should also provide the FDA premarket submission number (510(k) and PMA...). [13]

Manufacturers must list their devices with the FDA. Establishments which are required to list their devices include:

- manufacturers,
- contract manufacturers that commercially distribute the device,
- contract sterilizers that commercially distribute the device,
- repackagers and relabelers,
- specification developers,
- reprocessors single-use devices,
- remanufacturer,
- manufacturers of accessories and components sold directly to the end user,
- U.S. manufacturers of "export only" devices.

2.1.2.4 Regulatory Control: Premarket Notification, 510(k)

Each manufacturer who wants to market in the U.S., a Class I, II, and III device intended for human use, for which a Premarket Approval (PMA) is not required, must submit a 510(k) to FDA unless the device is exempt from 510(k) requirements of the Act and does not exceed the limitations of exemptions in .9 of the device classification regulation chapters (e.g., 21 CFR 862.9, 21 CFR 864.9). [5] There are several types of 510(k), namely Traditional, Abbreviated and Special 510(k) for manufacturers to submit. However, traditional 510(k) will be discussed in focus in this industry guidebook.

2.1 US Regulation for Opto-Mechatronics Medical Devices

Most Class I devices and some Class II devices are exempt from the Premarket Notification 510(k) submission. At the same time, there are also some situations where 510(k) exemption is allowed, table 3 has listed some 510(k) exemption situations for reference:

Table 3: Examples of 510(k) Exemption [5]

Situation 1: You sell unfinished devices to another firm for further processing or sell components to be used in the assembling of devices by other firms. However, if your components are to be sold directly to end users as replacement parts, a 510(k) is required.
Situation 2: Your device is not being marketed or commercially distributed. You do not need a 510(k) to develop, evaluate, or test a device. This includes clinical evaluation. Please note that if you perform clinical trials with your device, you are subject to the Investigational Device Exemption (IDE) regulation (21 CFR 812).
Situation 3: Your device was legally in commercial distribution before May 28, 1976 and you have documentation to prove this. These devices are "grandfathered" and have Preamendment Status. You do not have to submit a 510(k) unless the device has been significantly modified or there has been a change in its intended use.
Situation 4: In most cases, if you are a repackager or a relabeler you are not required to submit a 510(k) if the existing labeling or condition of the device is not significantly changed. The labeling should be consistent with the labeling submitted in the 510(k) with the same indications for use and warnings and contraindications.
Situation 5: Your device is exempted from 510(k) by regulation (21 CFR 862-892). That is, certain Class I or II devices can be marketed for the first time without having to submit a 510(k). A list of the Class I and II exempted devices can be found on Medical Device Exemptions 510(k) and GMP Requirements. However, if the device exceeds the limitations of exemptions in .9 of the device classification regulation chapters (e.g., 21 CFR 862.9, 21 CFR 864.9), such as the device has a new intended use or operates using a different fundamental scientific technology than a legally marketed device in that generic type of device, or the device is a reprocessed single-use device, then a 510(k) must be submitted to market the new device.

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As a result, opto-mechatronics medical device/accessory/component manufacturers need to decide whether their products need to go through 510(k) or PMA before marketing to U.S. For example: a lens module, which is going to be sold to endoscope manufacturers, may not require any 510(k) or PMA before selling to US endoscope manufacturers.

If the device is confirmed that 510(k) is required, then manufacturers need to proceed with the 510(k) application while a series of preparation work should be performed for 510(k) application. There are a few critical elements which should be included in the 510(k) submission for FDA evaluation on its safety and effectiveness, below are some examples for reference:

A : Administrative

B : Device Description

C : Substantial Equivalence Discussion

D : Proposed Labeling

E : Sterilization

F : Shelf Life

G : Biocompatibility

H : Safety

I : Electronic Safety and EMC performance

J : Performance Data in General

K : Performance Characteristics – In Vitro Diagnostic Devices Only

The main idea for submitting 510(k) is to demonstrate the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device distributed in the U.S.: (1) before May 28, 1976; or (2) to a device that has been determined by FDA to be substantially equivalent while the legally marketed device(s) to which equivalence is drawn is commonly known as the "predicate". Therefore, 510(k) submitters can show its substantial equivalence by comparing with a legally marketed devices distributed in the U.S. from different field of areas such as electronic safety, biocompatibility, etc. A device is substantially equivalent if, in comparison to a predicate it:

- has the same intended use as the predicate; and
- has the same technological characteristics as the predicate; or
- has the same intended use as the predicate; and
- has different technological characteristics and the information submitted to FDA;

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- does not raise new questions of safety and effectiveness; and
- demonstrates that the device is at least as safe and effective as the legally marketed device.

Submitters must compare their devices to one or more similar legally marketed devices and make and support their SE claims while a claim of SE does not mean the new and predicate devices must be identical. SE is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable. As a result, manufacturers can demonstrate SE by comparing their performance data in order to enable FDA to evaluate whether the device is at least as safe and effective as the legally marketed device.

Apart from showing the performance data, demonstrating device safety and/or effectiveness via the compliance of consensus standards is possible as FDA believes that the conformance with recognized consensus standards can support a reasonable assurance of safety and/or effectiveness for many devices. Also, using recognized consensus standards for showing SE in 510(k) also help to minimize the amount of data as well as documentation required during submission.

The tables 4 and 5 below are some examples of 510(k) summaries of opto-mechatronics related medical devices for reference. Opto-mechatronics manufacturers are advised to perform comprehensive search in FDA website for finding SE products and their respective classifications in order to support the 510(k) application.

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Table 4: 510(k) Summary of Disposable Anoscope: [15]

Device Name:	Sapimed Self Light Disposable Anoscope		
Regulation Number	21 CFR 876.15		
Classification Name	Anoscope and accessories Endoscope, AC-powered and accessories		
Product Code	FER/GCP		
Predicate Devices	CFR21:876.1500 Code:FER/GCP Device Class: II Legally Marketed Device:		
	Company	Product	510(k) #
	Patrick J. O'Regan	O'Regan Disposable Anoscope	K020702
	Welch Allyn, Inc	Model #53110 Disposable Anoscope	K810227
	North EOS Industries	EOS Brand Disposable Proctoscope	K954614
Device Description	The Sapimed Self Light® Disposable Anoscopes are clear, transparent plastic anoscopes in a range of sizes to suit varying clinical needs. Illumination is provided by either coldlight source GLF 100 or pen-light. The anoscopes are provided in the following configurations: Models A.4018 and 4019 are clear anscopes for a clear and easy rectal examination. Models A.4023 and 4024 are anoscopes for examination and use in surgical procedures. The Self-Light® Disposable Operating Anoscopes are clear, transparent disposable anoscopes for various proctological procedures. Illumination is provided by either coidlight source GLF 100 or pen-light. Model A.4081 is an operating anoscopes with a curved shape, transparency and length suitable for open and close hemorrhoiectomy, spincterotomy , coico/ileo anastarnosis, anoplasty, etc. Model A.4082 Basile's cone shaped operating anoscope has a graduated scale visible on the internal part of the instrument. ModelA.4083 The Beak is a surgical anoscope with a closed and rounded tip and a kulllength open channel 2-2.5cmn wide		
Intended Use	The Sapimed Self Light® Disposable Anoscopes are intended for physician use to examine the anal sphincter and anus, and, using additional accessories, to perform various diagnostic and therapeutic procedures.		

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Shelf Life	Accelerated aging testing was performed to substantiate an expiration of 5 years.				
Biocompatibility Testing	ISO 10993 standard.				
Regulatory Class	II				
Predicate Product Comparison Chart	Parameter				
	Device Name	Sapimed Disposable Anoscope	O'Regan Disposable Anoscope	Welch Allyn Disposable Anoscope	North Eos Industries Disposable Proctoscope
	Product Code	FER	FER	FER	GCP
	K Number		K020702	K810227	K954614
	Common Name	Disposable Anoscope	Disposable Anoscope	Disposable Anoscope	Disposable Proctoscope
	Intended Use	Intended for physician use to examine the anal sphincter and anus, and, using additional accessories, to perform various diagnostic and therapeutic procedures	Intended for physician use to examine the anal sphincter and anus, and, using additional accessories, to perform various diagnostic and therapeutic procedures	Intended for physician use to examine the anal sphincter and anus, and, using additional accessories, to perform various diagnostic and therapeutic procedures	Intended for physician use to examine the anal sphincter and anus, and, using additional accessories, to perform various diagnostic and therapeutic procedures
	Material	Plastic	Plastic	Plastic	Plastic
	Single Use	Yes	Yes	Yes	Yes
	Packaged	Clean, non-sterile/Sterile	Clean, non sterile	Clean, non sterile	Sterile
Similarities and differences between Self-Light Disposable Anoscope and Predicate Products	The Sapimed disposable anoscopes have a similar intended use, technological characteristics and mode of operation as the predicate products, both disposable and reusable and presents no new questions concerning safety and efficacy.				

2 Medical Device Regulatory Requirement in U.S., E.U. and China

2.1 US Regulation for Opto-Mechatronics Medical Devices

Table 5: 510(k) Summary of Surgical Light: [16]

Proprietary Name	TRIOP VOLISTA® Surgical Light System
Common Name	Surgical Light
Device Classification	Class II, according to regulation number 21 CER 878.458
Predicate Device Identification	- MAQUET POWERLEDTM Surgical Light System - 510(k) No. K070442 - MAQUET LUCEA LED® Surgical Light System - 510(k) No. K113679
Device Description	MAQUET TRIOP VOLISTA® Surgical Light Systems have been developed in order to provide any operating room with LED technology. An innovative design combined with a functional shape offers an efficient product to the surgical staff. The TRIOP VOLISTA " Surgical Lights are well-suited for installation in surgical suites, examining rooms, doctor's surgeries and external consultations. The TRIOP VOLISTA " product family is composed by two different lightheads, Volista 400 and Volista 600. The System is available on ceiling versions and may be composed by one, two or three lightheads. Accessories such as integrated cameras and screen supports can be included to the TRIOP VOLISTA® Surgical Light System.
Intended Use	MAQUET TRIOP VOLISTA Surgical lights are intended to be used to provide visible illumination of the surgical area or the patient during surgical operations, diagnosis and treatment.
Nonclinical Comparisons to Predicate Device	The TRIOP VOLISTA' Surgical Light (subject device) is similar to the predicate devices with the following modifications: 1) a minor redesign of the lighthead, 2) change in the type of camera (optional) that can be integrated to the lighthead, 3) a new type of suspension arms and mechanical connections that allows the users to easily place either a cupola or an accessory to the arms, 4) A touch-screen interface that allows the user to switch the lights on/off, control the optical parameters of the devices and the optional cameras.

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Conclusion	The modifications incorporated into the MAQUET TRIOP VOLISTA® Surgical Light System designs use those desired design features from MAQUET POWERLED TM and MAQUET LUCEA LED® Surgical Light Systems. Based upon the information provided herein this 510(k) Premarket Notification, it is conclude that TRIOP VOLISTA® Surgical Light Systems are substantially equivalent to the predicate devices.
Test Data	Test data support conformance to: - UL 60601-1, 1st Edition, 2006-04-26 (Medical Electrical Equipment, Part 1: General Requirements for Safety, includes National Differences for USA) - IEC 60601-2-41:2000, Medical electrical equipment - Part 2-41: Particular requirements for the safety of surgical luminaires and luminaires for diagnostics - IEC 60601-1:1988 + A1:1991 + A2:1995, Medical electrical equipment - Part 1: General requirements for basic safety and essential performance - IEC 60601-1-2:2007: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests - FCC Part 15 (10) Code of Federal Regulations, Title 47 - Telecommunication, Chapter I - Federal Communications Commission, Padt 15 - Radio frequency devices, Subpart B - Unintentional Radiators, limits and methods of measurement of radio disturbance characteristics of information technology equipment
Clinical Data	No clinical data is required for this device classification submission.

The above two 510(k) summary examples have generally stated their intended purposes as well as the corresponding predicate devices. Basic comparisons have been made between the submitted devices and their predicated in these 510(k) summaries. Also, some complied standards are listed in order to allow FDA to evaluate devices on their safety and/or effectiveness as compared to predicate devices. However, the above tables are just the summarized version of submitted 510(k) which should provide more comprehensive performance data and comparison between the submitted device and proposed predicate. With more detailed information, the device can be evaluated whether it will raise any new questions in safety and effectiveness, such that proving the device is at least as safe and effective as the legally marketed predicate devices.

2 Medical Device Regulatory Requirement in U.S., E.U. and China

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With the completion of preparation work for 510(k) application, manufacturers can submit all information to FDA for 510(k) clearance. Manufacturers are not allowed to proceed to market their devices until they receive an order declaring a devices SE by FDA. Once the device is determined to be SE, manufacturers may market the device immediately after 510(k) clearance is granted. Apart from having 510(k), FDA quality system (21 CFR 810) is also required for marketing medical devices in the US. Therefore, manufacturer should be prepared for an FDA quality system (21 CFR 820) inspection at any time after 510(k) clearance. FDA quality system will be further discussed in the following chapters.

2.1 US Regulation for Opto-Mechatronics Medical Devices

2.1.2.5 Regulatory Control: Premarket Approval (PMA)

PMA is the most stringent type of device marketing application required by FDA and PMA process is more involved and includes the submission of clinical data to support claims made for the device. [1] Product requiring PMAs are Class III devices are high risk devices that pose a significant risk of illness or injury, or devices found not substantially equivalent to Class I and II predicate through the 510(k) process. [1]

Due to the level of risk associated with Class III devices and devices which are not substantially equivalent to any Class I or II predicates, FDA has determined that general and special controls alone are insufficient to assure the safety and effectiveness of these devices. Therefore, these devices require a PMA application under section 515 of the Act in order to obtain marketing clearance. [6]

The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). Therefore, a PMA application is a scientific, regulatory documentation to FDA to demonstrate the safety and effectiveness of the class III devices and devices which are not substantially equivalent to any Class I or II predicates. [6] Below are the brief descriptions of some general elements of a PMA application:

- The name and address of the applicant.
- A table of contents that specifies the volume and page number for each item referred to in the table.
- A summary section in sufficient detail to provide a general understanding of the data and information in the application.
- A complete description of:
  - the device, including pictorial representations;
  - each of the functional components or ingredients of the device;
  - the properties of the device relevant to the diagnosis, treatment, prevention, cure, or mitigation of a disease or condition;
  - the principles of operation of the device; and
  - the methods, facilities, and controls used in the manufacture, processing, packing, storage, and where appropriate, installation of the device in sufficient detail.
- Reference to any performance standard or voluntary standard
- Technical sections (for example: results of clinical and nonclinical investigations) containing data and information in sufficient detail to permit FDA to determine whether to approve or deny the application

2.1 US Regulation for Opto-Mechatronics Medical Devices

- For a PMA supported solely by data from one investigator, a justification showing why data and other information from a single investigator is sufficient to demonstrate the safety and effectiveness of the device and to ensure reproducibility of test results
- A bibliography of all published reports not already submitted under §814.20(b)(6), whether adverse or supportive, that are known to or should reasonably be known to the applicant and that concern the safety or effectiveness of the device.
- One or more samples of the device and its components, if requested by FDA.
- Copies of all proposed labeling for the device
- Environmental assessment (EA) or environmental impact statements (EIS)
- A financial certification or disclosure statement or both as required by 21 CFR 54.
- Such other information as FDA may request.

In order to demonstrate the device is safe and effective for its intended use(s), submitters should provide complete, accurate and consistent critical information regarding to the device in their PMA application. Any unqualified PMA application may result in delays in approval or denial of PMA applications. Therefore, it was suggested by FDA that submitters should have quality checking for the PMA documents before submission in order to ensure that the information is presented scientifically and in a well-organized format.

2.2 EU Regulation for Opto- Mechatronics Medical Devices

2.2.1 Overview of EU Regulation System

The European Union (EU) includes the following 28 member counties: Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and United Kingdom. These member countries have different constitutional and legal systems, however, some legal requirements have been harmonized by the establishment of European Commission (The executive body of the European Union) and acceptance from European Council while these harmonized legal requirements are called Council Directive or simply Directives. These Directives describe the consensus that has been achieved and provides a deadline for the transposition of this consensus into the national laws of each Member State. The flow of goods within the region of EU member countries has been facilitated by the harmonization of some legal requirements.

For medical devices being sold within EU countries, they are under the control of several Directives (where applicable). There are three directives for medical devices:

- the Active Implantable Medical Device (AIMD) Directive - 90/385/EEC
- the Medical Device Directive (MDD) - 93/42/EEC (with amendment being 2007/47/EC)
- the In Vitro Diagnostic Device Directive (IVD) - 98/79/EC

This industry guidebook will mainly focus on the MDD (with inclusion of amendment from 2007/47/EC) as this covers most of the medical devices in the industry while most provisions are much the same under the other two medical device directives.

Under MDD, medical devices are classified into 4 groups (Class I, Class IIa, Class IIb and Class III) based on different criteria, such as intended purposes, the duration of contact with the patient (Transient, Short Term or Long Term), the degree of invasiveness (Invasive Devices, Body Orifice, Surgically Invasive Device and Reusable Surgical Instrument, etc.) and the part of the body affected by the use of the device, etc. Developers are required to classify their devices into corresponding Classes according to the classification rules while the detailed rules would be further elaborated in the later chapters.

Regardless of which class should the device belong to, all medical devices are required to fulfill the applicable essential requirements on safety, performance and labeling as outlined in Annex I of the MDD as well as preparing technical documentation for their devices. Unlike the compliance model in the U.S., developers should demonstrate the fulfillment of essential requirements by their devices no matter they are new devices or have similar devices on the market.

2.2 EU Regulation for Opto- Mechatronics Medical Devices

Apart from the compliance of essential requirements, medical devices are required to fulfill specific requirements (conformity assessment procedures) according to their classification in accordance with the Annexes II, III, IV, V, VI and VII of the MDD.

During the conformity assessment procedures, all Class I (Except non-sterile and non-measuring devices), IIa, IIb and III medical devices all require the intervention of third party: Notified Bodies. With intervention of Notified Bodies, manufacturers can only place the CE Mark together with the identification number of Notified Bodies to the products. For Class I devices in which Notified Bodies are not required, manufacturers should place the CE Mark to their products with a Notified Body number under the manufacturers' sole responsibility.

2.2.2 EU Regulation System

2.2.2.1 Medical Device Definition

"Medical devices" means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
- investigation, replacement or modification of the anatomy or of a physiological process;
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

Apart from having the whole functional medical devices, accessories are also entitled certain control under MDD. In MDD, the definition of accessories means an article which whilst not being a device is intended specifically by its manufacturer to be used together with a device to enable it to be used in accordance with the use of the device intended by the manufacturer of the device. As a result, the wordings "medical devices" being used in this chapter would imply medical devices with inclusion of accessories.

As for opto-mechatronics medical components, since MDD aims essentially at the protection of patients and users and the medical purpose relates in general to finished products regardless of whether they are intended to be used alone or in combination.

2.2 EU Regulation for Opto- Mechatronics Medical Devices

However, since components or intermediate products are not regarded as finished products, so in general, components or intermediate products are not under the control of MDD. [24]

Apart from fulfilling the definitions of “medical” devices, some of the opto-mechatronics medical devices are also entitled to comply with other Directives (such as Radio Equipment Directive, etc.) based on their device characteristics. For example: hearing aid and wireless imaging system, etc. These are the devices which should comply with MDD as well as R&TTE when their device designs and functions fall within the scope of these two Directives. As a result, manufacturers of opto-mechatronics medical device are advised to go through different other Directives under EU based on their device characteristics before placing CE mark onto the products.

2.2.2.2 Medical Device Classification

According to the Annex IX of MDD, medical device and accessories are classified into one of the four classes I, IIa, IIb and III while class I is further divided into 1) Non sterile and measurement devices, 2) Sterile devices and 3) Measuring devices. The classification rule of medical device is based on the risk level associated with the devices on human body. Different criteria are taken into account for classification determination such as

- Intended Purpose
- Duration of Contact with the Human Body
- Degree of Invasiveness
- Active Medical Devices
- Devices with Measuring Functions
- Procedure Pack

During device classification process, manufacturers should take all the criteria in Annex IX of MDD into considerations to ensure the conformity assessment procedures of the appointed class could provide enough control on the risks of devices. It would be hard to find one rule fitting all the device characteristics and therefore, manufacturers are advised to go through all rules in Annex IX of MDD and identified the highest class which fits the device characteristic or combination of characteristics in accordance with the device intended purpose.

There are 18 rules in Annex IX of MDD while rule 1 to 12 are the general rules and rule 13 to 18 are the specific one. Table 6 is the classification rule and their corresponding classes.

2.2 EU Regulation for Opto- Mechatronics Medical Devices

Table 6: Classification Rules for Medical Devices and Their Corresponding Classes under EU Regulations

Rule 1 - Devices that either do not touch the patient or contact intact skin only - All non-invasive devices are in Class I, unless one of the rules set out hereinafter applies.
Rule 2 - Channeling or storing for eventual administration **All non-invasive devices intended for channeling or storing blood, body liquids or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body are in Class IIa:** ▪ if they may be connected to an active medical device in Class IIa or a higher class, ▪ if they are intended for use for storing or channeling blood or other body liquids or for storing organs, parts of organs or body tissues - in all other cases they are in Class I.
Rule 3 – Non-invasive devices that modify biological or chemical composition of blood, body liquids or other liquids intended for infusion into the body **All non-invasive devices intended for modifying the biological or chemical composition of blood, other body liquids or other liquids intended for infusion into the body are in Class IIb** - unless the treatment consists of filtration, centrifugation or exchange of gas or heat, in which case they are in Class IIa.
Rule 4 - Non-invasive devices which come into contact with injured skin **All non-invasive devices which come into contact with injured skin:** - are in Class I if they are intended to be used as a mechanical barrier, for compression or for absorption of exudates - are in Class IIb if they are intended to be used principally with wounds which have breached the dermis and can only heal by secondary intent - are in Class IIa in all other cases, including devices principally intended to manage the micro-environment of a wound.
Rule 5 - Devices invasive with respect to body orifices **All invasive devices with respect to body orifices, other than surgically invasive devices and which are not intended for connection to an active medical device or which are intended for connection to an active medical device in Class I:**

- are in Class I if they are intended for transient use,
- are in Class IIa if they are intended for short term use
- except if they are used in the oral cavity as far as the pharynx, in an ear canal up to the ear drum or in a nasal cavity , in which case they are in Class I,
- are in Class IIb if they are intended for long term use,
- except if they are used in the oral cavity as far as the pharynx, in an ear canal up to the ear drum or in a nasal cavity and are not liable to be absorbed by the mucous membrane, in which case they are in Class IIa.
- All invasive devices with respect to body orifices, other than surgically invasive devices, intended for connection to an active medical device in Class IIa or a higher class, are in Class IIa.

Rule 6 - Surgically invasive devices intended for transient use *(< 60 minutes)*

All surgically invasive devices intended for transient use are in Class IIa unless they are:

- intended specifically to control, diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body, in which case they are in Class III;
- reusable surgical instruments, in which case they are in Class I
- intended specifically for use in direct contact with the central nervous system, in which case they are in Class III;
- intended to supply energy in the form of ionizing radiation in which case they are in Class IIb,
- intended to have a biological effect or to be wholly or mainly absorbed in which case they are in Class IIb,
- intended to administer medicines by means of a delivery system, if this is done in a manner that is potentially hazardous taking account of the mode of application, in which case they are Class IIb.

Rule 7 - Surgically invasive devices intended for short-term use *(>60 minutes, <30 days)*

All surgically invasive devices intended for short term use are in Class IIa unless they are intended:

- either specifically to control, diagnose, monitor or correct a defect of the heart or of the central circulatory system through direct contact with these parts of the body, in which case they are in Class III,
- or specifically for use in direct contact with the central nervous system, in which case they are in Class III,

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- or specifically for use in direct contact with the central nervous system, in which case they are in Class III,
- intended to have a biological effect or to be wholly or mainly absorbed in which case they are in Class III,
- or to undergo chemical change in the body, except if the devices are placed in the teeth, or to administer medicines, in which case they are Class IIb.

Rule 8 - Implantable devices and long-term surgically invasive devices *(> 30 days)*

All implantable devices and long-term surgically invasive devices are in Class IIb unless they are intended:

- to be placed in the teeth, in which case they are in Class IIa,
- to be used in direct contact with the heart, the central circulatory system or the central nervous system, in which case they are Class III,
- to have a biological effect or to be wholly or mainly absorbed, in which case they are in Class III,
- or to undergo chemical change in the body, except if the devices are placed in the teeth, or to administer medicines, in which case they are in Class III.
- Directive 2003/12/EC introduced a derogation from this rule, reclassifying breast implants in Class III
- Directive 2005/50/EC introduced a derogation from this rule, reclassifying hip, knee and shoulder joint replacements in Class III

Rule 9 - Active therapeutic devices intended to administer or exchange energy

All active therapeutic devices intended to administer or exchange energy are in Class IIa

- unless their characteristics are such that they may administer or exchange energy to and from the human body in a potentially hazardous way, taking account of the nature, the density and the site of application of the energy, in which case they are in Class IIb.
- All active devices intended to control or monitor the performance of active therapeutic devices in Class IIb or intended to influence directly the performance of such devices are in Class IIb.

Rule 10 - Active devices for diagnosis

Active devices intended for diagnosis are in Class IIa:

- if they are intended to supply energy which will be absorbed by the human body, except for devices used to illuminate the patient's body, in the visible spectrum,

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- if they are intended to image in vivo distribution of radiopharmaceuticals,
- if they are intended to allow direct diagnosis or monitoring of vital physiological
- Gamma cameras - Positron emission tomography and single photon emission computer tomography processes,
- unless they are specifically intended for monitoring of vital physiological parameters, where the nature of variations is such that it could result in immediate danger to the patient, for instance variations in cardiac performance, respiration, activity of CNS in which case they are in Class IIb.
- Active devices intended to emit ionizing radiation and intended for diagnostic and therapeutic interventional radiology including devices which control or monitor such devices, or which directly influence their performance, are in Class IIb.

Rule 11 - Active devices intended to administer and/or remove medicines, body liquids or other substances to or from the body

All active devices intended to administer and/or remove medicines, body liquids or other substances to or from the body are in Class IIa,

- unless this is done in a manner: that is potentially hazardous, taking account of the nature of the substances involved, of the part of the body concerned and of the mode of application, in which case they are in Class IIb.

Rule 12 - All other active devices

- All other active devices are in Class I

Rule 13 - Devices incorporating, as an integral part, a medicinal product or a human blood derivative (See MEDDEV. 2.1/3 for further guidance)

- All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product as defined in Article 1 of the Directive 2001/83/EC, and which is liable to act on the human body with action ancillary to that of the devices, are in Class III.
- All devices incorporating as an integral part, a human blood derivative are in Class III

Rule 14 - Devices used for contraception or prevention of sexually transmitted diseases

- All devices used for contraception or the prevention of the transmission of sexually transmitted diseases are in Class IIb,
- unless they are implantable or long term invasive devices, in which case they are in Class III.

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Rule 15 - Specific disinfecting, cleaning and rinsing devices

- All devices intended specifically to be used for disinfecting, cleaning, rinsing or, when appropriate hydrating contact lenses are in Class IIb.
- All devices intended specifically to be used for disinfecting medical devices are in Class IIa
- unless they are specifically to be used for disinfecting invasive devices in which case they are in Class IIb.
- Directive 2003/12/EC introduced a derogation from this rule, reclassifying breast implants in Class III
- This rule does not apply to products that are intended to clean medical devices other than contact lenses by means of physical action.

Rule 16 - Devices to record X-ray diagnostic images

- Devices specifically intended for recording of X-ray diagnostic images are in Class IIa.

Rule 17 - Devices utilizing animal tissues or derivatives

- All devices manufactured utilizing animal tissues or derivatives rendered non- viable are Class III except where such devices are intended to come into contact with intact skin only.

Rule 18 - Blood bags

- By derogation from other rules, blood bags are in Class IIb.

Take electronic blood pressure measuring equipment as an example:

Rule 1 : Applicable (Class I)

Rule 2 : No channeling or storing for eventual administration (Class I)

Rule 3 : No modification to the biological or chemical composition of blood, body liquids or other liquids intended for infusion into the body (Class I)

Rule 4 : The electronic blood pressure measuring equipment is not intended to contact with injured skin (Class I)

Rule 5 : This equipment is not intended to be used with body orifices (Class I)

Rule 6 : This equipment is not a surgically invasive device for transient use (Class I)

Rule 7 : This equipment is not a surgically invasive device for short term use (Class I)

Rule 8 : This equipment is not an implantable device and long-term surgically invasive device (Class I)

Rule 9 : This equipment is not an active therapeutic device intended to administer or exchange energy (Class I)

Rule 10 : This equipment is intended to allow direct diagnosis or monitoring of vital physiological processes. (Class IIa)

Rule 11 : This equipment is not an active device intended to administer and/or remove medicines, body liquids or other substances to or from the body (Class IIa)

Rule 12 : Applicable (Remain as Class IIa as Class IIa is higher than Class I)

Rule 13 : Not Applicable (Class IIa)

Rule 14 : Not Applicable (Class IIa)

Rule 15 : Not Applicable (Class IIa)

Rule 16 : Not Applicable (Class IIa)

Rule 17 : Not Applicable (Class IIa)

Rule 18 : Not Applicable (Class IIa)

As a result, according to the classification rule in MDD, electronic blood pressure measuring equipment should be regarded as Class IIa instead of Class I since this equipment fulfills the description in Rule 10 while the description in the above table has identified any equipment fulfilling its criteria are regarded as Class II. Manufacturers should adopt the highest identified Class as the final classification decision.

2.2.2.3 Medical Device Conformity Assessment

As mentioned in the previous paragraphs, devices are divided into different classes according to the device characteristics. The reason for device classification is to enable the performance of different conformity assessments to ensure the device's safety to the patients. For all medical devices, manufacturers are required to provide technical documentation, risk analysis and a proof of the compliance to the essential requirements of MDD before placing a CE Mark to the devices and marketing the devices within EU countries. Also, manufacturers are required to issue a product-related declaration of conformity for declaring the compliance of requirements under MDD.

For issuing a declaration of conformity, the involvement of Notified Bodies is required for all medical devices except non-sterile Class I devices. For non-sterile Class I devices, manufacturers could place a CE Mark onto the products under their sole responsibility without stating the Notified Bodies number. Any other devices except non-sterile Class I devices require Notified Bodies to issue a certificates before the manufacturers issuing the declaration of conformity as well as placing CE Mark onto the products with the Notified Bodies number on the devices.

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The role of Notified Bodies is to ensure a high level of health and safety protection, the free movement of medical devices in the internal market, and citizens' confidence in the regulatory system. As a result, the involvement of Notified Bodies is to verify the fulfillment of the legal requirements by the manufacturer. Notified Bodies would carry out different types of assessment according to the respective conformity assessment procedure of different medical devices.

There are five types of conformity procedures in total for manufacturers to choose to comply and they are listed in the Annex II, IV, V, VI, and VII of the MDD respectively. Figure 1 has shown the possible conformity assessment routes according to the class of device.

Annex II : EC Declaration of Conformity (Full Quality Assurance System)

Annex III : EC Type Examination

Annex IV : EC Verification

Annex V : EC Declaration of Conformity (Production Quality Assurance)

Annex VI : EC Declaration of Conformity (Product Quality Assurance)

Annex VI : EC Declaration of Conformity

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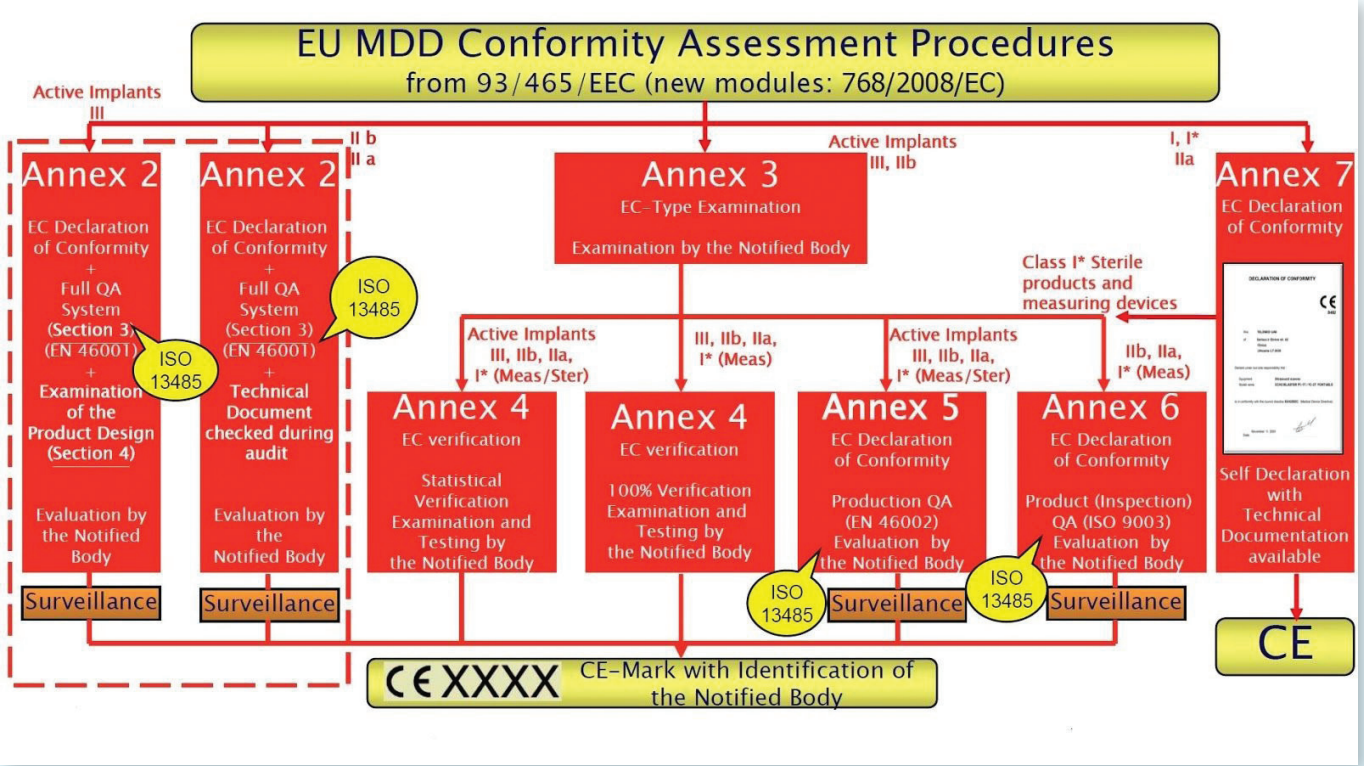
Figure 1: Conformity Assessment Routes under 93/42/EEC



Manufacturers should take note that there may be more than one allowable conformity assessment routes for the device, and manufacturers could choose the either one according to their preferences.

Take electronic blood pressure monitoring equipment (Class IIa) as an example. According to the Article 11 of MDD, having devices falling within Class IIa, other than devices which are custom-made or intended for clinical investigations, the manufacturer shall, in order to affix the CE marking, follow the procedure relating to the EC declaration of conformity set out in Annex VII, coupled with either:

a. the procedure relating to the EC verification set out in Annex IV; or

b. the procedure relating to the EC declaration of conformity set out in Annex V (production quality assurance); or

c. the procedure relating to the EC declaration of conformity set out in Annex VI (product quality assurance).

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As a result, manufacturers can choose one of the conformity assessment routes with the involvement of Notified Bodies:

Option 1 : Annex VII (EC Declaration of Conformity) + Annex IV (EC Verification)

Option 2 : Annex VII (EC Declaration of Conformity) + Annex V (EC Declaration of Conformity (Production Quality Assurance)

Option 3 : Annex VII (EC Declaration of Conformity) + Annex VI (EC Declaration of Conformity (Product Quality Assurance)

Take external defibrillator (Class IIb) as an example. According to Article 11 of MDD, having devices being Class IIb, other than devices which are custom-made or intended for clinical investigations, the manufacturer shall, in order to affix the CE marking, either:

a. follow the procedure relating to the EC declaration of conformity set out in Annex II (full quality assurance); in this case, point 4 of Annex II is not applicable; or

b. follow the procedure relating to the EC type-examination set out in Annex III, coupled with:

   i) procedure relating to the EC verification set out in Annex IV; or

   ii) procedure relating to the EC declaration of conformity set out in Annex V (Production Quality Assurance)

   iii) procedure relating to the EC declaration of conformity set out in Annex VI (Product Quality Assurance)

As a result, manufacturers can choose one of the conformity assessment routes with the involvement of Notified Bodies:

Option 1 : Annex II (with exclusion of Point 4) EC Declaration of Conformity (Full Quality Assurance System)

Option 2 : Annex III (EC Type Examination) + Annex IV (EC Verification)

Option 3 : Annex III (EC Type Examination) + Annex V (Production Quality Assurance)

Option 4 : Annex III (EC Type Examination) + Annex VI (Product Quality Assurance)

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2.2.2.4 Conformity Assessment – Annex Introduction

As mentioned in the previous chapters, manufacturers need to choose the conformity assessment route according to the class of device. With selected conformity assessment, manufacturers need to comply with the requirements in the selected conformity assessment route (Annex). In this chapter, all conformity assessment route (Annex) would be discussed and their corresponding requirements would be elaborated for opto-mechatronics industry to identify the major tasks required for marketing their devices within the EU countries.

Conformity Assessment Route – Annex I (Essential Requirements)

All medical devices being sold in EU countries must comply with the applicable essential requirement as outlined in Annex I of the MDD regardless of their class of device. Essential requirements are divided into two big categories: 1) General Requirements and 2) Requirements regarding Design and Construction. Manufacturers are advised to go through all essential requirements and identified all applicable ones. In Table 7, some examples of the essential requirements are listed below:

Table 7: Essential Requirements – General Requirements

The devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety. **This shall include:** - reducing, as far as possible, the risk of use error due to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety), and - consideration of the technical knowledge, experience, education and training and where applicable the medical and physical conditions of intended users (design for lay, professional, disabled or other users.
The devices must be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected during transport and storage taking account of the instructions and information provided by the manufacturer.
Any undesirable side effect must constitute an acceptable risk when weighed against the performances intended. - Demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X.

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Essential Requirements – Requirements regarding Design and Construction
The devices must be designed and manufactured in such a way that they can be used safely with the materials, substances and gases with which they enter into contact during their normal use or during routine procedures; if the devices are intended to administer medicinal products they must be designed and manufactured in such a way as to be compatible with the medicinal products concerned according to the provisions and restrictions governing those products and that their performance is maintained in accordance with the intended use.
The devices and manufacturing processes must be designed in such a way as to eliminate or reduce as far as possible the risk of infection to the patient, user and third parties. The design must allow easy handling and, where necessary, minimise contamination of the device by the patient or vice versa during use.
Devices delivered in a sterile state must have been manufactured and sterilised by an appropriate, validated method.
Devices with a measuring function must be designed and manufactured in such a way as to provide sufficient accuracy and stability within appropriate limits of accuracy and taking account of the intended purpose of the device. The limits of accuracy must be indicated by the manufacturer.
Where devices are designed to emit hazardous levels of radiation necessary for a specific medical purpose the benefit of which is considered to outweigh the risks inherent in the emission, it must be possible for the user to control the emissions. Such devices shall be designed and manufactured to ensure reproducibility and tolerance of relevant variable parameters.
Devices where the safety of the patients depends on an internal power supply must be equipped with a means of determining the state of the power supply.
Devices intended to monitor one or more clinical parameters of a patient must be equipped with appropriate alarm systems to alert the user of situations which could lead to death or severe deterioration of the patient's state of health.
Devices must be designed and manufactured in such a way as to avoid, as far as possible, the risk of accidental electric shocks during normal use and in single fault condition, provided that the devices are installed correctl
Devices must incorporate suitable means to prevent, as far as possible, the accidental release of dangerous levels of energy from an energy and/or substance source.

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The above are some of the requirements extracted from the Annex I of MDD. Manufacturers should go through the Annex and make sure to identify all applicable essential requirements.

After identifying applicable essential requirements, manufacturers are suggested to perform testing or establish procedures in the current quality management system in the companies in order to demonstrate companies' ability to fulfill such requirements. In order demonstrate the conformity with essential requirements and enable the conformity to be verified, a list of harmonized standards has been recognized by European Committee for Standardization (CEN) and the European Committee for Electrotechnical Standardization (Cenelec) as a way to demonstrate the companies' ability to protect against the risks associated with the design, manufacture and packaging of medical devices while the adoption harmonized standards is voluntary-based.

Since many harmonized standards represent the state-of-the-art or the international benchmark for safety, and in some cases for performance, and the market will have expectations of conformance. The conformance to appropriate harmonized standards can be regarded as the easiest, clearest, and in many cases the cheapest approach. It should be noted that very few harmonized standards can be considered a presumption of compliance with all the essential requirements, so harmonized standards should be seen by manufacturers as just part of the requirements to be met for CE marking. [20]

All harmonized standards will contain an Annex ZZ for each EC Directive under which they are harmonized. Under such circumstances, manufacturers can use Annex Z to indicate precisely the Essential Requirements where compliance can be presumed. Manufacturers should be aware that they cannot use harmonized standards to claim compliance using a presumption of conformity where no such correlation is shown in Annex ZZ. [20]

Technical Documentation

All medical devices (All Class I, Class IIa, Class Iib and Class III) require the preparation of technical documentation. Particular requirements are given in the MDD, Annex II.3.2 (c) and 4.2, Annex III.3, Annex VII.3, and Annex VIII.3.1 and 3.2., Annex V.4.2 and Annex VI.4.2.

The recommended essential content of a technical file is as follows:

- A table of contents
- Manufacturer's declaration of conformity
- A general description of the device/device family, including any variants planned
- Design drawings, specifications, methods of manufacture, including method of sterilization and validation data
- Results of risk analysis

2.2 EU Regulation for Opto- Mechatronics Medical Devices

- Results of calculations and test reports
- Reference to applicable harmonized standards
- Evidence that the essential requirements have been met
- Clinical data
- Label and instructions for use
- Results of database researches and copies of relevant literature, etc.

The MDD increases the responsibility of medical device manufacturers beyond previous regulations by strictly requiring a formal risk analysis for each device/device family. A preferred standard to be used is the harmonized standard EN 14971 about the risk management of medical devices. [21]

Conformity Assessment Route – Annex II (Full Quality Assurance System)

This conformity assessment procedure is the most comprehensive one and this refers to the establishment and maintenance of a full quality system which includes the design process of new devices or changes of existing devices. However, only Class III devices are required to exam the design process as stated in Section 4 of this Annex.

Most comprehensive conformity assessment procedure referring to a full quality system including the design phase for new devices or changes of existing devices; Section 4 (Examination of the Design of the Product) applies only to class III devices; this Section is similar to Annex III - EC Type-Examination with the difference that in-house test results obtained by the manufacturer under his full quality management system may be used as the basis of certification;

The manufacturer may choose the harmonized standard EN ISO 13485 in combination with the respective guidance standard as the basis of his quality system or use an equivalent quality system suitable to fulfill the requirements of the MDD.

As this stage, Notified Bodies would check the compliance of the quality management system as well as assess the technical documentation to see whether the manufacturers have complied with the essential requirements as well as the conformity assessment route requirements.

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Conformity Assessment Route – Annex III (EC Type Examination)

This conformity assessment procedure is the most comprehensive one and this refers to the establishment and maintenance of a full quality system which includes the design process of new devices or changes of existing devices. However, only Class III devices are required to exam the design process as stated in Section 4 of this Annex.

Most comprehensive conformity assessment procedure referring to a full quality system including the design phase for new devices or changes of existing devices; Section 4 (Examination of the Design of the Product) applies only to class III devices; this Section is similar to Annex III - EC Type-Examination with the difference that in-house test results obtained by the manufacturer under his full quality management system may be used as the basis of certification;

The manufacturer may choose the harmonized standard EN ISO 13485 in combination with the respective guidance standard as the basis of his quality system or use an equivalent quality system suitable to fulfill the requirements of the MDD.

As this stage, Notified Bodies would check the compliance of the quality management system as well as assess the technical documentation to see whether the manufacturers have complied with the essential requirements as well as the conformity assessment route requirements.

Conformity Assessment Route – Annex III (EC Type Examination)

It is the procedure whereby a Notified Bodies ascertains and certifies that a representative sample of the production fulfilling the requirements in the relevant provisions of MDD while EC Type Examination is applicable only to class IIb and III devices.

Technical documentation would be examined, assessed and verified whether the products have been manufactured in conformity with that documentation. Apart from documentation assessment, Notified Bodies would also perform on-site inspections and tests necessary to verify whether the solutions adopted by the manufacturers meet the essential requirement of MDD.

If the representative sample conforms to the requirements under MDD, Notified Bodies would issue an EC type-examination certification to the manufacturers. On this certificate, it should show the name and address of the manufacturers, conclusion of inspection by the Notified Bodies, conditions of validity as well the data needed for identification of the representative sample approved. The relevant parts of the documentation must be annexed to the certificate and a copy kept by the Notified Bodies.

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Conformity Assessment Route – Annex IV (EC Verification)

In addition to the examination and verification carried out in Annex III, Annex IV is the procedure where Notified Bodies examines and tests every single device or devices taken on a statistical basis while EC Verification may be applied to class IIa, IIb and III devices.

At this stage, Notified Body would carry out the appropriate examinations and tests in order to verify the conformity of the type described in the EC type-examination certificate and to the requirements in MDD which apply to them either by examining and testing every product or by examining and testing products on a statistical basis, as the manufacturer decides.

Conformity Assessment Route – Annex V (EC Declaration of Conformity – Production Quality Assurance)

In addition to the examination and verification carried out in Annex III, Annex V is the conformity assessment procedure for the quality system of the manufacturer excluding the design phase of new devices but including all other aspects of conformity with the MDD. Also, the manufacturer must ensure application of the quality system approved for the manufacture of the products concerned and carry out 1) final inspection and is subject to the 2) community surveillance. With the use of the harmonized standard EN ISO 13485, manufacturers could establish and maintain their quality system accordingly.

Manufacturers should ensure that the application of quality system ensures the products conforming to the type described in the EC type-examination certificate. After making an official application to the Notified Bodies regarding to the quality system assessment, the Notified Bodies must perform an inspection to audit the quality system and determine whether it meets the corresponding requirements.

As for the surveillance, it is to ensure the fulfillment of obligation stated in the approved quality system by the manufacturers. Therefore, Notified Bodies must periodically carry out appropriate inspections and assessments or pay unannounced visits to make sure that the manufacturer applies the approved quality system and supply the manufacturer with an assessment report.

Conformity Assessment Route – Annex VI (EC Declaration of Conformity – Product Quality Assurance)

In addition to the examination and verification carried out in Annex III, Annex VI is the conformity assessment procedure for the quality system on devices whose relevant properties can be assessed in the final inspection. Similar to Annex V, manufacturers could establish and maintain their quality system based on the harmonized standard EN ISO 13485. Manufacturers should take note that this Annex is not suitable for devices which

involve special manufacturing processes and require validation to verify its effectiveness (such as sterilization). Also, this Annex is not advised to used for the assessment of Class III products.

The major difference between Annex V and VI is that in Annex V, manufacturers should focus on quality system for the whole manufacturing process while in Annex VI, manufacturers should focus on the quality system for the final inspection and testing of the products.

Under such circumstances, every product or a representative sample of each batch would be examined. Also, appropriate tests would be carried out to ensure the products conform to the type described in the EC type-examination certificate and fulfill the provisions of MDD.

After making an official application to the Notified Bodies regarding to the quality system assessment, Notified Bodies would audits the quality system to determine whether it meets the requirements referred in Annex VI.

As for the surveillance, it is to ensure the fulfillment of obligation stated in the approved quality system by the manufacturers. Therefore, Notified Bodies must periodically carry out appropriate inspections and assessments or pay unannounced visits to make sure that the manufacturer applies the approved quality system and supply the manufacturer with an assessment report.

Conformity Assessment Route – Annex VII (EC Declaration of Conformity)

Annex VII is a conformity assessment procedure in which manufacturers could declare the compliance of their devices with the MDD on their own. For Class I devices, this Annex could be used independently while for Class IIa devices, this Annex should be used in combination with one of the Annexes IV, V or VI.

As mentioned earlier, technical documentation is also required for Class I devices. Manufacturers or their authorized representatives must make this documentation, including the declaration of conformity, available to the national authorities for inspection purposes.

It is necessary for manufacturers to review the experience gained from devices in the post-production phase and to implement any necessary corrective actions in an appropriate timeframe. Opto-mechatronics manufacturers should note that any Class I products placing on the market in sterile condition or equipped with measuring functions, manufacturers should also fulfill the corresponding procedures as stated in Annexes II, IV, V or VI.

2 Medical Device Regulatory Requirement in U.S., E.U. and China

2.3 China Regulation for Opto- Mechatronics Medical Devices

2.3.1 Overview of China Regulation System

All medical devices are required to obtain pre-market approval from the China Food and Drug Administration (CFDA) before entering the market in China. The whole life cycle of medical devices is mainly regulated by the "Regulations on Supervisory Management of Medical Devices" (Decree of the State Council of the People's Republic of China No. 650)《医疗器械监督管理条例》(国务院令第 650 号).

Medical devices are divided into three main categories: Class I, Class II and Class III according to "Rules of Classification of Medical Devices" (Decree No.15 of China Food and Drug Administration)《医疗器械分类规则》(国家食品药品监督管理总局令第 15 号). This classification is based on the risk level associated with the devices. With higher risk class, stricter requirement would be imposed on the design, manufacturing and usage of medical devices. Detailed requirements for each risk class device would be discussed in detail in the later chapters.

All medical device sold and used within the territory of the China shall be subject to application for notification (备案) or registration (注册) while Class I medical devices are required to submit documentation for notification and Class II and Class III medical devices are required to submit documentation for registration.

According to the "Provisions for Medical Device Registration" (Order of China Food and Drug Administration No. 4)《医疗器械注册管理办法》(国家食品药品监督管理总局令第 4 号), the applicant or the person who files for record shall carry out notification or registration application according to the basic requirements for the safety and effectiveness of the medical device and ensure the normalization of design cycle and the authenticity, integrity and traceability of all data.

During the application of notification and registration, manufacturers should submit the Quality Assurance System documents related to product research & development and manufacture while these documents should complied to the "Medical Device Good Manufacturing Practice"《医疗器械生产质量管理规范》.

2.3 China Regulation for Opto- Mechatronics Medical Devices

2.3.2 China Regulation System

2.3.2.1 Medical Device Definition

Medical devices refer to those instruments, equipment, tools, materials and other objects, including the software attached to them, that are designed to be used either independently or in combination on human body. These devices are used for:

1. Prevention, diagnosis, treatment, monitoring or remission of diseases;
2. Diagnosis, treatment, monitoring, remission or compensation of injury or physical disability;
3. Research, replacement or adjustment of anatomical or physiological process;
4. Control of pregnancy.

Basically, the effect of these devices on human body is not achieved through means of pharmacology, immunology or metabolism; though they might be resorted to in order to bring about certain supplementary effect.

2.3.2.2 Medical Device Classification

According to “Rules of Classification of Medical Devices” (Decree No.15 of China Food and Drug Administration), medical devices are divided into three major classes: Class I, Class II and Class III according to their risk classes, while Class III devices having highest risk among the three classes.

The risk degree of a medical device shall be determined comprehensively according to the intended purpose, structural characteristics, pattern of use, status of use as well as whether the device is body contacting. CFDA has published a Table for Determination of Medical Device Classification (Table 8) for the public to determine the device risk class according to different criteria. Also, CFDA has also listed some situations where classification should be made in combination with the Table and the following principles are listed below:

1. Where two or more classes are applicable to one medical device, the one representing highest risk degree shall be adopted; the class of a medical device kit composed of multiple medical devices shall stay with the one representing highest risk degree in the kit.
2. For a medical device which may be used as an accessory, its classification shall be made with comprehensive consideration of the impact of the accessory to the safety and effectiveness of the major medical device used with. If the accessory has significant impact on the major medical device used with, the class of such an accessory shall not be lower than the major medical device used with.

2.3 China Regulation for Opto- Mechatronics Medical Devices

3. A medical device used to monitor or influence the essential functions of another medical device, its class shall be identical to the medical device being monitored or influenced.
4. A drug-device combination product with its major effects is as a medical device, it shall be regarded as a class III medical device.
5. A medical device which may be absorbed by human body shall be regarded as a class III medical device.
6. An active body-contacting device with significant impact on medical results shall be regarded as a class III medical device.
7. In any of the following cases, medical dressings shall be regarded as a class III medical device: the medical dressing is intended to have a function to prevent tissue/organ adhesion; is used as artificial skin; is to contact with the deep dermis or the injured trauma of tissue below dermis; is used to heal chronic wound, or may be wholly/partially absorbed by human body.
8. A medical device supplied in sterile state, its class shall not be lower than class II.
9. An orthopedic medical device which is used to actively apply a sustained action force to human body in such action modes as pulling, strutting, twisting, holding and bending and may dynamically adjust the fixed position of limb (not including a medical device with fixation and supporting function only, a medical device used in conjunction for temporary orthopedics in the surgery or a medical device used for limbs orthopedics after surgery or in other treatment), its class shall not be lower than class II.

   A medical device with measuring function, its class shall not be lower than class II.

   A medical device intended for the treatment of a certain disease, its class shall not be lower than class II.

   A reusable surgical device used in surgical operations under endoscope, such as tissue picking up, cutting or stone removing, etc., shall be regarded as a class II medical device.

2.3 China Regulation for Opto- Mechatronics Medical Devices

Table 8: Table for Determination of Medical Device Classification

Body-contacting device										
	Status of use		Temporary use			Short-term use			Long-term use		
	Patterns of use		Skin /Orifice (openings)	Trauma /Tissue	Blood circulation /Central	Skin /Orifice (openings)	Trauma /Tissue	Blood circulation /Central	Skin /Orifice (openings)	Trauma /Tissue	Blood circulation /Central
Non-active device	1.	Liquid transportation device	II	II	III	II	II	III	II	III	III
	2.	Blood and other body fluids alternation device	-	-	III	-	-	III	-	-	III
	3.	Medical dressing	I	II	III	I	II	II	-	III	III
	4.	Invasive device	I	II	III	II	II	II	-	-	-
	5.	Reusable surgical device	I	I	II	-	-	-	-	-	-
	6.	Implantable device	-	-	-	-	-	-	III	III	III
	7.	Contraceptive and family planning device (excluding reusable surgical device)	II	II	III	II	III	III	III	III	III
	8.	Other non-active devices	I	II	III	II	II	III	II	III	III
Active device	Status of use		Minor injury			Moderate injury			Serious injury		
	Patterns of use										
	1.	Energy treatment device	II			II			III		
	2.	Diagnostic and monitoring device	II			II			III		
	3.	Liquid transportation device	II			II			III		
	4.	Ionizing radiation device	II			II			III		
	5.	Implantable device	III			II			III		
	6.	Other active devices	II			II			III		

Non-body-contacting device					
Non-active device	Status of use		little impact	Minor impact	Significant impact
	Patterns of use				
	1.	Nursing device	I	II	-
	2.	Device for medical device sterilization and cleaning	-	II	III
	3.	Other non-active devices	I	II	III
Active device	Status of use		little impact	Minor impact	Significant impact
	Patterns of use				
	1.	Clinical laboratory instruments	I	II	III
	2.	Stand alone software	-	II	III
	3.	Instruments for medical devices disinfection and sterilization	-	II	III
	4.	Other non-active devices	I	II	III

2.3 China Regulation for Opto- Mechatronics Medical Devices

Apart from Table 8, opto-mechatronics manufacturers could also determine the class of the device from the official medical device database established by CFDA (医疗器械分类目录). For example, for electronic blood pressure monitor, it is classified as Class II device while surgical light is classified as Class II device. Below are some of the extracts (Table 9) from the database regarding to some opto-mechatronics medical devices.

Table 9: Extracts from CFDA Medical Device Classification Database

醫療器械分類目錄	
编码代号	6820 普通诊察器械
分类编号	6820-02
管理类别	II 类 (Class II)
品名举例	无创性电子血压计，台式，立式血压计，血压表，小儿血压表
分类名称	血压计 (Blood Pressure Monitor)

醫療器械分類目錄	
编码代号	6854 手术室，急救室，诊疗室设备及器具
分类编号	6854-13.1
管理类别	II 类 (Class II)
品名举例	无影灯，医用冷光纤维导光手术灯
分类名称	手术灯 (Surgical Lamp)

醫療器械分類目錄	
编码代号	6822 医用光学器具，仪器及内窥镜设备
分类编号	6822-01
管理类别	III 类 (Class III)
品名举例	眼人工晶体、角膜接触镜（软性、硬性、塑形角膜接触镜）及护理用液、眼内填充物（玻璃体等）、粘弹物质、灌注液（重水、矽油）
分类名称	植入体内或长期接触体内的眼科光学器具

2.3 China Regulation for Opto- Mechatronics Medical Devices

醫療器械分類目錄	
编码代号	6822 医用光学器具，仪器及内窥镜设备
分类编号	6822-05
管理类别	II 类 (Class II)
品名举例	诊断用纤维内窥镜（上消化道镜、结肠镜、大肠镜、支气管镜）、观察用硬管内窥镜（喉镜、鼻镜、膀胱镜、子宫镜、直肠镜、羊水镜）、内窥镜冷光源
分类名称	光学内窥镜及冷光源 (Optical Endoscope and Cold Light Source)

醫療器械分類目錄	
编码代号	6821 医用电子仪器设备
分类编号	6821-01
管理类别	III 类 (Class III)
品名举例	植入式心脏起搏器、体外心脏起搏器、心脏除颤器、心脏调搏器、主动脉内囊反搏器、心脏除颤起搏仪
分类名称	用于心脏的治疗、急救装置 (Devices used for Treatment or Emergency Treatment for Heart)

Opto-mechatronics manufacturers are advised to check the device risk classes regularly from the online database in order to ensure the control for corresponding devices are appropriate [22]

2.3 China Regulation for Opto- Mechatronics Medical Devices

2.3.2.3 Medical Device Notification (備案) and Registration (註冊)

To ensure the safety and effectiveness of devices in China, it is required that all medical devices sold and used within the territory of China shall be subject to application for notification or registration.

Medical device notification is a process for Class I devices where the applicant or person submits the filing materials to CFDA and CFDA keeps the submitted materials in the archives for future reference. On the other hand, medical device registration is a process for Class II and III devices under which CFDA carries out the systematic review towards its safety, validation study as well as the related result of the validation study. CFDA would make the decision for application approval based on the result in review.

As mentioned earlier, applicants should submit documentations for CFDA's actions for notification or registration. According to "Regulations on Supervisory Management of Medical Devices" 《医疗器械监督管理条例》, the below information should be provided by the applicants to CFDA:

1. Analysis on risks of the product; 产品风险分析资料
2. Technical requirements for the product; 产品技术要求
3. Test report of the product; 产品检验报告
4. Clinical evaluation data; 临床评价资料
5. The Instructions for Use and the sample of product labels for the product; 产品说明书及标签样稿
6. Quality Assurance System documents related to product research & development and manufacture; 与产品研制、生产有关的质量管理体系文
7. Other documents necessary to prove the safety and effectiveness of the medical device. 证明产品安全、有效所需的其他资料

After the preparation of the above documentation, applicants need to submit the prepared documents to different levels of regulatory authorities in China based on the device risk class. For Class I medical devices, the person to submit the product for notification should submit all the required documents to the food & drug administration department of the local municipal-level people's government. While for Class II medical devices, the person to submit the product for registration should submit all the documents required for registration to the food and drug administration department of the local government of the province, autonomous region or municipality directly under the central government where the applicant is located. For Class III medical devices, the person to submit the product for registration should submit the application documents to the Food & Drug Administration department of the State Council.

However, for the filing of the Class I imported medical device, the applicant shall submit the application documents to Food & Drug Administration department of the State Council for filing. On the other hand, Food & Drug Administration department of the State Council shall review the Class II and Class III imported medical device and issue the medical device registration certificate upon the approval.

For any Class I medical devices which is submitted for notification, the conduction of clinical trials is not required while for a Class II or III medical device which is submitted for registration, clinical trials should be conducted and related results should be summited for CFDA's review on its safety and effectiveness. However, there are some cases in which clinical trials may be exempted:

1. The medical device is a product having definite working mechanism, finalized design and mature production processes, while there have been similar medical devices of similar specifications already applied clinically for many years without severe effect and its regular usage would not be changed;
2. The safety and effectiveness can be proven through non-clinical assessment;
3. The safety and effectiveness of the medical device can be proven through the analysis and evaluation by using the data obtained from the clinical trial of similar product or during clinical application.

2.3.2.4 Notification and Registration – Product Technical Requirements and Registration Inspection

One of the main requirements for device notification or registration is the submission of product technical requirements. The person who submits the product for notification or registration should prepare the product technical requirements to CFDA.

Product technical requirements generally include the performance index as well as the inspection method of the finished medical device while performance index refers to product functionality and security index as well as other indexes related to the quality control that can be objectively determined.

For Class I medical devices, the product technical requirement shall be submitted by the person who files for record to the food and drug regulatory authorities during the application of notification and it can be in the form of self-inspection report with no registration inspection performed .

As for Class II and III medical devices, the submitted product technical requirement shall be evaluated along with the registration by the food and drug regulatory authorities while their registration application will be subject to the result of registration inspection.

Registration inspection is a process performed by the medical device inspection body towards the related product according to the submitted product technical requirements. Registration applicants of Class II or III devices should provide the inspection body with the related technical materials, a sample for registration inspection as well as any product

technical requirements necessary for registration inspection. Manufacturers should note that the production of the sample, which is used for registration inspection, shall accord with the registration by the food and drug regulatory authorities.documents to different levels of regulatory authorities in China based on the device risk class. For Class I medical devices, the person to submit the product for notification should submit all the required documents to the food & drug administration department of the local municipal-level people's government. While for Class II medical devices, the person to submit the product for registration should submit all the documents required for registration to the food and drug administration department of the local government of the province, autonomous region or municipality directly under the central government where the applicant is located. For Class III medical devices, the person to submit the product for registration should submit the application

2.3.2.5 Quality Management System for Manufacturing

All applicants engaged in the production of medical devices should submit an application for notification or registration for getting approval from CFDA to start the manufacturing process. Below are the application submission route according to "Regulations on Supervisory Management of Medical Devices"《医疗器械监督管理条例》

	Submission Route
Class I Device:	Food & drug administration department of the municipal-level government of the region
Class II or III Device:	Food and Drug Administration Department of the people's government of the province, autonomous region and municipality directly under the central government

With submitted documents, the regulatory authority will examine these documents and conduct field inspections according to the requirements of the "Medical Device Good Manufacturing Practice" (医疗器械生产质量管理规范). As a result, manufacturers should comply with the requirements in "Medical Device Good Manufacturing Practice" (医疗器械生产质量管理规范). Manufacturers should establish and perfect its quality management system while ensuring its effectiveness. Also, the technical requirements submitted for notification or registration should be strictly followed for manufacturing while the manufacturers should ensure the device meeting the mandatory standards as well as the technical requirements submitted for notification or registration.

Manufacturers should note that all medical devices and products should comply with the mandatory standards of the state for medical devices. If there is no mandatory national standard, the compulsory standards of medical devices industry should be executed. Since YY T 0287-2003 《医疗器械 质量管理体系 用于法规的要求》" is recognized as the standard of medical devices industry by CFDA, therefore, manufacturers should follow this standard to fulfill the requirements on quality assurance system established by CFDA. [23]

2.4 Highlights of Good Manufacturing Practices (GMP) for Medical Devices

2.4.1 Overall GMP Description in U.S. E.U. and China

2.4.1.1 U.S.

Manufacturers must establish and follow quality systems (QS) to help ensure that their products consistently meet applicable requirements and specifications. The quality systems for FDA-regulated products (food, drugs, biologics, and devices) are known as current good manufacturing practices (CGMP's). The QS regulation provides the framework that all manufacturers must follow by requiring that manufacturers develop and follow procedures and fill in the details that are appropriate to a given device according to the current state-of-the-art manufacturing for that specific device. [7]

It is the responsibility of each manufacturer to establish requirements for each type or family of devices that will result in devices that are safe and effective, and to establish methods and procedures to design, produce, distribute, etc. devices that meet the quality system requirements. It is left to manufacturers to determine the necessity for, or extent of, some quality elements and to develop and implement specific procedures tailored to their particular processes and devices. [7]

FDA has determined that certain types of medical devices are exempt from GMP requirements. These devices are exempted by FDA classification regulations published in the Federal Register and codified in 21 CFR 862 to 892. Opto-mechatronics manufacturers are advised to review the classification regulation for each specific medical device for any exemptions on GMP before taking real actions.

2.4.1.2 E.U.

Basically, all medical devices (except Class I non-sterile, non-measuring devices) require Quality Management System (QMS) as the minimum market entry requirement. With ISO13485 (Medical devices -- Quality management systems -- Requirements for regulatory purposes) being the recognized harmonized standards under 93/42/EEC, manufacturers are advised to follow the guidelines in ISO13485 for easy compliance to the QMS requirements under 93/42/EEC. Manufacturers are advised to have Notified Body, which is a third party accredited by European authorities to audit medical device companies and products, to review and audit whether their existing QMS meet the minimum requirements of MD in order to ensure the ISO13485 certification is under recognition of European authorities.

There are two types of Quality Assurance Systems for manufacturers to choose while their difference lies between whether the manufacturers involve in the design process. If development process involves design session, then Annex V should be followed, otherwise, Annex VI should be followed. As mentioned earlier, manufacturers can make use of ISO13485 to fulfill the requirements for QMS under 93/42/EEC, thus the manufacturers can decide whether the inclusion Section 7.3 (Design and Development) of ISO13485 is required or not.

2.4 Highlights of Good Manufacturing Practices (GMP) for Medical Devices

2.4.1.3 China

According to Article 9 of Regulations on Supervisory Management of Medical Device of Medical Device (State Council Order No. 650), Quality Assurance System documents related to product research, development and manufacturing are one of the requirements for device registration in China. [18][19] Referring to Quality Management Practices for Medical Device Manufacturing (CFDA Order No. 64 2014), a series of requirements are listed including documentation, design control, purchasing, quality control and handling of nonconforming products, etc. Manufacturers are advised to incorporate these requirements into the current QMS in order to comply the requirements for manufacturing medical devices in China.

In the following sessions, several key items in the good manufacturing practices / quality management system will be discussed in detail to enable the opto-mechatronics manufacturers to identify the major gaps for upgrading the current operation to cater for the requirements for medical device manufacturing.

2.4.2 Key Elements in Good Manufacturing Practices

2.4.2.1 Traceability

Regulatory Requirements in Different Regions:
FDA Requirements: Each manufacturer shall establish and maintain procedures for identifying product during all stages of receipt, production, distribution, and installation to prevent mix-ups. (21 CFR 820.60) Each manufacturer of a device that is intended for surgical implant into the body or to support or sustain life and whose failure to perform when properly used in accordance with instructions for use provided in the labeling can be reasonably expected to result in a significant injury to the user shall establish and maintain procedures for identifying with a control number each unit, lot, or batch of finished devices and where appropriate components. The procedures shall facilitate corrective action. Such identification shall be documented in the Device History Record (DHR). (21 CFR 820.61)

2.4 Highlights of Good Manufacturing Practices (GMP) for Medical Devices

EU Requirements:

In the essential elements required by 93/42/EEC, clauses of 13.5 in Annex I of 93/42/EEC states that "Wherever reasonable and practicable, the devices and detachable components must be identified, where appropriate in terms of batches, to allow all appropriate action to detect any potential risk posed by the devices and detachable components." As a result, manufacturers should ensure all devices/components are identified, where "identified" means each batch of devices/components has their own batch number, and manufacturers should be able to identify all process records as well as used raw material according to the batch number, in order to facilitate the traceability requirements.

In ISO13485:2003, traceability requirements appear in many clauses. For example, in clause 7.5.3.2, "The organization shall establish documented procedures for traceability. Such procedures shall define the extent of product traceability and the records required (see 4.2.4, 8.3 and 8.5)." and "Where traceability is a requirement, the organization shall control and record the unique identification of the product (see 4.2.4)." As a result, manufacturers are advised to maintain the unique identification for their products and ensure all involved processes contain the element of product unique identification for achieving traceability.

China:

Under the Article 50 and 53 of China Food and Drug Administration in accordance with Order No. 64, "Each batch shall have production records, and meet traceability requirements. Production records include product name, specifications, raw material batch number, batch number or product number, production date, the number of major equipment, process parameters and operating personnel." and "An enterprise shall establish traceability procedures to provide product traceability scope, extent, logos and necessary records." Therefore, manufacturers should ensure traceability is attained in accordance with the requirements in China.

In the coming paragraphs, the importance of traceability will be discussed and thus allowing opto-mechatronics industries to understand the role of traceability in medical device industries with an aim to upgrade the current manufacturing operation for fulfilling traceability requirements in different countries.

2.4 Highlights of Good Manufacturing Practices (GMP) for Medical Devices

Traceability is not commonly implemented in traditional opto-mechatronics companies as there are no such requirements for the operation. However, traceability of medical devices is one of the critical elements in the quality management system as this allows manufacturers to take corrective and preventive actions, recall related products and provide advisory notices to affected customers effectively if there are any adverse events. As a result, opto-mechatronics medical device manufacturers should enhance their current quality management system in order to fulfill the traceability requirements for medical device manufacturing.

There are two common ways to realize traceability: Forward Traceability and Backward Traceability. Forward traceability is the one using raw material information (such as date of receipt and lot number, etc.) or in-process information (such as job order number and etc.) to trace the affected final products as well as the affected customers. In reverse way, backward traceability is the one using final product information to trace back the root cause of problem (for example deteriorated raw material, or any human error) such that other affected final products and customers can be traced for taking corresponding corrective and preventive actions and minimizing the consequences of adverse events.

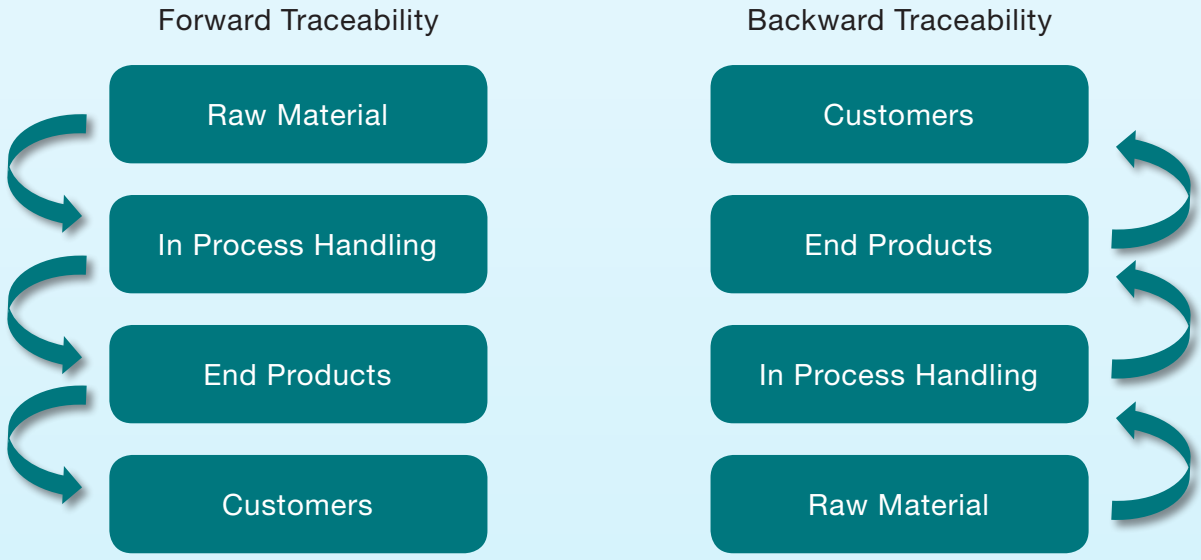


Figure 2: Flow of Forward and Backward Traceability

As a result, traceability should be maintained through documented records or software system starting from the purchasing of raw material, design & development, production, quality control, packing, storage to product delivery, etc. In such case, manufacturers are advised to ensure that there is a common element (such as job order number or invoice number, serial number, etc.) available throughout the whole realization process.

2.4 Highlights of Good Manufacturing Practices (GMP) for Medical Devices

Starting from the purchase of raw material, the lot number / purchase order / incoming date of the purchased raw material should be recorded such that the future use of any material for manufacturing session can be traced. It was common to find that manufacturers only record the amount of used raw material without recording the lot number of the used raw material. If problems are found with the final products which have been delivered to several clients and the manufacturer decide to recall the products, then the manufacturer will need to figure out the root cause of the problem by backward traceability and perform forward traceability to reach the affected clients. Therefore, lack of raw material lot number information may hinder the cause-finding process and may delay the recall process at the end.

Apart from raw material, traceability should also be maintained to the manufacturing process. Information such as used equipment, handling person, in-process quality control records and delivery records, etc. should be recorded properly in order to enable the completeness of traceability system and facilitate the process of finding root cause when adverse event happens.

Apart from tracing the affected products / customers effectively, comprehensive traceability system also help to minimize the number of products that must be recalled when a manufacturing problem is found by identifying only the specific serial numbers that were built with the faulty component or material or by the faulty process.

Therefore, opto-mechatronics medical devices manufacturers should review the current daily operation and check whether forward and backward traceability can be achieved throughout the whole medical device realization process.

2.4 Highlights of Good Manufacturing Practices (GMP) for Medical Devices

2.4.2.2 Customer Feedback and Complaint

Regulatory Requirements in Different Regions:

US Requirements:

A series of requirements on complaint are established by USFDA under 21 CFR 820.198.

A. Each manufacturer shall maintain complaint files. Each manufacturer shall establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit….

B. Each manufacturer shall review and evaluate all complaints to determine whether an investigation is necessary…

C. Any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications shall be reviewed, evaluated, and investigated, unless such investigation has already been performed for a similar complaint and another investigation is not necessary.

D. Any complaint that represents an event which must be reported to FDA under part 803 of this chapter shall be promptly reviewed, evaluated, and investigated by a designated individual(s) and shall be maintained in a separate portion of the complaint files or otherwise clearly identified….

E. When an investigation is made, a record of the investigation shall be maintained by the formally designated unit identified in paragraph (A) of this section…

F. Etc…

EU Requirements:

ISO 13485: 2003, Clause 8.2.1 “The organization shall establish a documented procedure for a feedback system to provide early warning of quality problems and for input into the corrective and preventive action processes.” and Clause 8.5.1 “Records of all customer complaint investigations shall be maintained (see 4.2.4). If investigation determines that the activities outside the organization contributed to the customer complaint, relevant information shall be exchanged between the organizations involved (see 4.1). If any customer complaint is not followed by corrective and/or preventive action, the reason shall be authorized (see 5.5.1) and recorded (see 4.2.4).”

2.4 Highlights of Good Manufacturing Practices (GMP) for Medical Devices

China Requirements:

Under the Article 66 and 73 of China Food and Drug Administration in accordance with Order No. 64, “An enterprise shall establish customer feedback procedures, and shall track and analyze customer feedback.” and “An enterprise shall establish a data analysis program, for the collection and analysis of, product quality, adverse events, customer feedback and quality management system operating data relating to validation of product safety and efficacy; relevant records shall be maintained.

In general, all three regions require manufacturers to record any received feedback and complaints, as well as investigating and following up with corrective and/or preventive actions if necessary. Proper handling of customer feedback and complaints enables manufacturers to be aware of the root causes of the problem and thus taking appropriate corrective and/or preventive actions. As a result, manufacturers would be able to evaluate and improve the devices according to the feedback and complaints received, and thus enhancing the overall device quality and minimizing the chances of experiencing same/similar problems.

It is common to find that opto-mechatronics manufacturers handle feedback and/or complaint cases with evaluation, investigation and corrective actions for individual customers, however, preventive actions are not commonly implemented after receiving customer feedback and/or complaint. Manufacturers are advised to note that a series of preventive actions should be considered in order to reduce the chances of re-occurrence, for example, revision of procedural documents and/or work instructions, re-evaluation of risk management and revision of device design or manufacturing process, etc.

2.4.2.3 Documents / Records Retention Time

Regulatory Requirements in Different Regions:
US Requirements: According to 21 CFR 820.180, "All records required by this part shall be retained for a period of time equivalent to the design and expected life of the device, but in no case less than 2 years from the date of release for commercial distribution by the manufacturer."
EU Requirements: According to ISO13485:2003 Clause 4.2.3 and 4.2.4, "This period shall ensure that documents to which medical devices have been manufactured and tested are available for at least the lifetime of the medical device as defined by the organization, but not less than the retention period of any resulting record (see 4.2.4), or as specified by relevant regulatory requirements." and "The organization shall retain the records for a period of time at least equivalent to the lifetime of the medical device as defined by the organization, but not less than two years from the date of product release by the organization or as specified by relevant regulatory requirements."
China Requirements: According to Article 4 and 37, etc. of China Food and Drug Administration Order No. 64, "record retention period shall be equivalent to at least the life of the enterprise, but no less than 2 years from the date of product release, or in accordance with applicable regulatory requirements, and traceable."

With the requirements as stated above, manufacturers should be careful on the documents and records retention time in order to fulfill the regulatory requirements and achieve the completeness of the QMS. Importance of the retention period of documents and records will be elaborated in the following paragraphs in order to enable opto-mechatronics companies to understand the reasons of having such requirements.

Documents and records retention time is important to the whole medical device realization process since documents and records facilitate the completeness of traceability and these allows manufacturers to trace any necessary records if needed. It is required in many counties that records should be kept at least longer than the life span of the devices. This is essential because once there are any adverse events or recall cases, manufacturers can make use of their records and documents to trace any other affected devices and customers, and thus minimizing the consequences of adverse events. Without any documents or records, the real root cause(s) of adverse ev ents cannot be identified and rectified and under such circumstances, same problems may happen again and this should be avoided in medical device realization process. Therefore, opto-mechatronics companies

are advised to determine the life span of the devices/components, such that deciding the number of years for document retention. To comply with the requirements, manufacturers should consider enhancing staff awareness in document retention as well as revising procedural documents for maintaining documents and records.

All in all, opto-mechatronics should consider enhancing the current operation process to retain necessary documents and records according to the regulatory requirements in different countries.

2.4.2.4 Risk Management

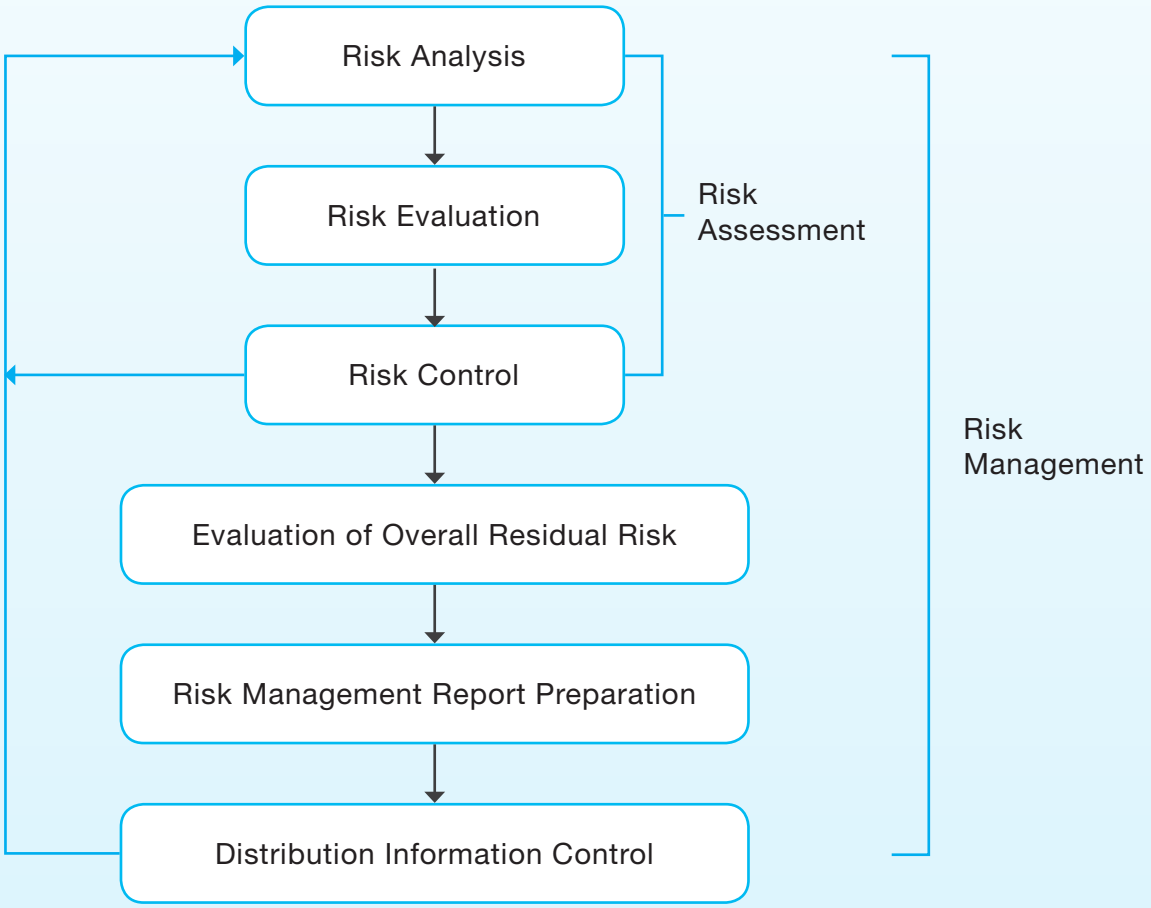
Regulatory Requirements in Different Regions:
US Requirements: According to 21 CFR 820.30 (g), "Design validation shall include software validation and risk analysis, where appropriate." ISO 14971:2007 has been adopted by FDA as recognized standards.
EU Requirements: According to 21 CFR 820.30 (g), "Design validation shall include software validation and risk analysis, where appropriate." ISO 14971:2007 has been adopted by FDA as recognized standards.
China Requirements: According to Article 4 and 37, etc. of China Food and Drug Administration Order No. 64, "The enterprise shall implement risk management throughout the design, development, production, sales and after-sales service as well as throughout the whole process; any mitigation measures taken shall be appropriate for the risk of the product." and "When changes to the materials, parts or functions of the product may affect the safety of medical products, the risk shall be evaluated against the changes and, if necessary, steps shall be taken to reduce the risk to an acceptable level, and comply with the relevant regulatory requirements."

Risk Management is a process assisting manufacturers to identify potential hazards, analyze the arised risks and thus implementing risk control measures with effectiveness monitoring. In such practices, risks involved in medical devices can be controlled as low as possible and thus ensuring safety for the device.

Risk management involves a series of stages including Risk Analysis, Risk Evaluation, Risk Control, Residual Risk Acceptability, Risk Management Report as well as Production & Post Production Information. Figure 3 shows the flow chart of the above stages.

2.4 Highlights of Good Manufacturing Practices (GMP) for Medical Devices

Figure 3: Flow Diagram of Risk Management Process



It is suggested that risk management should be started at the beginning of the medical device realization process and consider all possible risks that would arised during the design & development process as well as the servicing process with an aim to detect risks involved and take appropriate actions as early as possible.

However, it is sometimes misunderstood that risk management only applies to the initial stage of medical device realization process, however, it should be noted that risk management should be implemented at all times. Whenever there are any adverse events, complaints, internal audit findings and nonconforming products, etc., risk analysis should be triggered to evaluate whether any other risks have been missed from the original risk analysis or any risks have been created during the realization process. Thus, risk management should be performed throughout the whole device realization process instead of just at the design and development stage.

Risk analysis plays an important role in the device realization as this allows developers to evaluate any potential problems which could be encountered. There are many risk

2.4 Highlights of Good Manufacturing Practices (GMP) for Medical Devices

analysis tools available in the market, such as Failure Modes & Effects Analysis (FMEA), Fault Tree Analysis (FTA) and Preliminary Hazards Analysis (PHA), etc., such that manufacturers can choose to adopt any tools that fits its daily operation. FMEA will be used as an example below to demonstrate the risk evaluation.

FMEA can be applied to design and development stages respectively. With FMEA, the potential hazards, possible risks arised due to the hazards and the possible consequences of the risks are listed in a table format. With calculating the risk value (R), probability of happening (P) and detectability (N), the final value of R x P x N (Risk priority number) can be evaluated in a way to see if any control measures are required. Manufacturers should set their acceptable value before risk analysis and if the risk priority number is larger than the acceptable value, then manufacturers should implement corresponding control measures. After taking control measures, risk analysis should be performed again to check if the residual risk value could be lowered to be smaller than the acceptable value.

The result of risk analysis and any corresponding control measures for the unacceptable risks should be included in the risk management report which will be used as production and post-production information throughout the product lifecycle. One more important element for the risk management report is the post-market surveillance and it should be considered as part of the overall risk assessment process throughout whole device life cycle. The main idea of post-market surveillance is to collection information from real end-users regarding to the problems in device design and usage. As a result, the real risks incorporated in the device can be identified and manufacturers can take corresponding risk control measures to enhance the device safety.

2.4.2.5 Verification and Validation

Regulatory Requirements in Different Regions:

US Requirements:

21 CFR 820.30(f) - Design Verification

- Each manufacturer shall establish and maintain procedures for verifying the device design.
- Design verification shall confirm that the design output meets the design input requirements.

21 CFR 820.30(f) - Design Verification

- Each manufacturer shall establish and maintain procedures for validating the device design.
- Design validation shall be performed under defined operating conditions on initial production units, lots, or batches, or their equivalents.
- Design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions.
- Design validation shall include software validation and risk analysis, where appropriate. The results of the design validation, including identification of the design, method(s), the date, and the individual(s) performing the validation, shall be documented in the DHF.

21 CFR 820.80(c) - In-process Acceptance Activities

- Each manufacturer shall establish and maintain acceptance procedures, where appropriate, to ensure that specified requirements for in-process product are met. Such procedures shall ensure that in-process product is controlled until the required inspection and tests or other verification activities have been completed, or necessary approvals are received, and are documented.

21 CFR 820.75 - Process Validation

A. Where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures. The validation activities and results, including the date and signature of the individual(s) approving the validation and where appropriate the major equipment validated, shall be documented.

   Each manufacturer shall establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met.

2.4 Highlights of Good Manufacturing Practices (GMP) for Medical Devices

EU Requirements:

ISO13485 Clause 7.1 c)

In planning product realization, the organization shall determine the required verification, validation, monitoring, inspection and test activities specific to the product and the criteria for product acceptance.

ISO13485 Clause 7.3.1 b)

During the design and development planning, the organization shall determine the review, verification, validation and design transfer activities (see Note) that are appropriate at each design and development stage

ISO13485 Clause 7.3.5

Verification shall be performed in accordance with planned arrangements (see 7.3.1) to ensure that the design and development outputs have met the design and development input requirements. Records of the results of the verification and any necessary actions shall be maintained

ISO13485 Clause 7.3.6

Design and development validation shall be performed in accordance with planned arrangements to ensure that the resulting product is capable of meeting the requirements for the specified application or intended use. Validation shall be completed prior to the delivery or implementation of the product

ISO13485 Clause 7.5.2.1

The organization shall validate any processes for production and service provision where the resulting output cannot be verified by subsequent monitoring or measurement. This includes any processes where deficiencies become apparent only after the product is in use or the service has been delivered. Validation shall demonstrate the ability of these processes to achieve planned results.

The organization shall establish arrangements for these processes including, as applicable

a) defined criteria for review and approval of the processes,

b) approval of equipment and qualification of personnel,

c) use of specific methods and procedures,

d) requirements for records (see 4.2.4), and

e) revalidation.

2.4 Highlights of Good Manufacturing Practices (GMP) for Medical Devices

China Requirements ("Medical Device Good Manufacturing Practices" (医疗器械生产质量管理规范) (including but not limited to):

Article 29

During the design and development planning, an enterprise shall determine the stage of design and development, and evaluate the various stages of verification, validation and design conversion and other activities; the enterprise shall identify and determine the design and development stages and interfaces, with clear responsibilities and division of labor.

Article 34

Enterprises shall carry out design verification to ensure that the design and development outputs meet the input requirements, and maintain records of results and any necessary actions.

Article 37

Design and development changes shall be identified and records maintained. When necessary, the design and development changes shall be reviewed, verified and validated, and approved before implementation.

Validation means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled. While verification means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled. Figure 4 has shown the interrelationship between Verification as well as Validation.

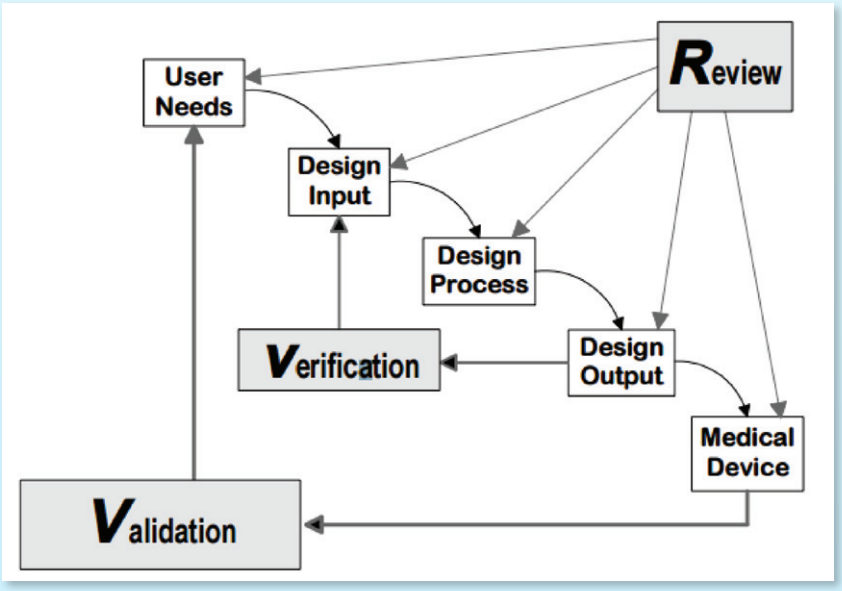


Figure 4: Interrelationship between Verification and Validation in Design Stage [25]

2.4 Highlights of Good Manufacturing Practices (GMP) for Medical Devices

Verification and Validation (V&V) should be implemented in all phases of product development including design & development as well as manufacturing process and many different technologies. For examples, injection molding, thermal systems, electronics, instrumentation, fluids, mechanical/physical, electromechanical component evaluation, biologic aspects, etc. It is extremely important to consider V&V early in the design stage when developing requirement specifications for the product. For example, adding test points on circuit boards, having accessible connectors, providing data storage/ retrieval capabilities, and making products modular can enhance the ability to test a product, which saves time and money. V&V costs can also be reduced if previously tested materials or coatings are used for the product. Clarity, conciseness, measurability, appropriate tolerances, accuracy, and testability can all impact the final design and overall manufacturability. These specifications also provide the acceptance criteria for later V&V activities.

As mentioned earlier, V&V should be implemented in all phases of product development. However, it is common to find that process validation is sometimes being missed out by opto-mechatronics manufacturers as there are no such requirements in the past while process validation is one of the critical stages for medical device production.

Take injection molding as an example: It is common to find that in the trial production stage, manufacturers would verify the specification of the intermediate products after the completion of injection according to the product design. However, it is not common to find manufacturers to validate the equipment used for injection molding while this process validation could ensure the equipment is operating as expected and producing expected products under the parameters set by the manufacturers. For process validation of injection molding machines, manufacturers could consider undergoing three main stages, which are 1) Installation Validation, 2) Operational Validation and 3) Performance Validation. For Installation Validation, the injection molding machine should be inspected to see if they are installed appropriately and conform to the manufacturers' requirements. For Operation Validation, the injection molding machine should be inspected to see if it operates as expected by going through test runs to check under what conditions the equipment will continue to operate as expected. As a result, by varying different equipment parameters such as temperature, time duration and pressure, etc. for the test runs, manufacturers would be able to identify the conditions during which the equipment operates out of expectation.

As a result, opto-mechatronics manufacturers are suggested to conduct process validation for their critical processes such as injection molding, coating and diamond turning, etc. to ensure the process provide result as expected and thus maintaining product quality.

3 Case Studies from Pilot Scheme

3.1 Background and Purpose of Pilot Scheme

This government-funded project aims to enhance the ability of opto-mechatronics industry and thus enabling them to expand their business into the high value-added medical and healthcare device market. As a result, to demonstrate the know-how to the industry effectively, a pilot scheme have been conducted to guide three selected pilot companies to establish and upgrade their quality management system for the manufacturing and distribution of medical devices through hands-holding implementation by HKPC.

As mentioned earlier, three companies would be selected as pilot companies. These companies cover various business aspects and business models of local SMEs in the opto-mechatronics business. As a result, these pilot companies can act as role models in opto-mechatronics industry to demonstrate the effectiveness of medical device quality management system establishment.

In this industry-specific guidebook, case studies in the pilot scheme will be shared to illustrate the process and methodology of gap assessment and gap bridging requirement for migration from a particular category of opto-mechatronic product design and production into particular risk class and category of medical device design and production.

3.2 Methodology of Pilot Scheme

For the pilot scheme, gap assessment on the current operation would be conducted via site visits to pilot companies as well as documentation review based on the requirements of ISO13485:2003 (Medical devices -- Quality management systems -- Requirements for regulatory purposes).

For on-site gap assessment, the current design and manufacturing processes were identified through discussion with front-line & management staff and on-site observation during site-visits, etc. Gap assessment was made between the observation of site visits and the requirements as stated in ISO13485:2003. Recommendations have been provided to pilot companies as well for future consideration on system enhancement.

Apart from on-site visit, internal documentation such as quality manual, quality objectives, procedural documents, work instructions and records, etc. are reviewed as well, such that providing recommendations to upgrade their current operation approach to “medical-grade ready”.

3.3 Pilot Company Introduction

In the coming chapters, the company background as well as their product scope would be introduced to allow the opto-mechatronics industry to use as reference for their future business migration from opto-mechatronics side to medical grade. Also, the summary of pilot scheme gap assessment and corresponding recommendations would be elaborated in the coming chapters as well. As a result, opto-mechatronics industry could make use of this chapter to identify the major gap between current operation and medical grade requirements, and thus, getting prepared for future migration to medical and healthcare industry.

Under this pilot scheme, three companies were selected for being pilot companies. Under the hands-holding services provided by HKPC, these companies have enhanced their current quality management system to accommodate the requirements for medical device quality management system. Below is the introduction of company background of the three pilot companies:

Diffractive Optics Limited

In the new era, the rapid development of imaging technology accelerates the precision optical system and its accompanying optical components, an unprecedented development. Diffractive Optics Limited is in this development and has played a pivotal role.

The company has over 20 years solid design and manufacture of precision lenses basis of practical experience, equipped with the most advanced processing equipment, but there stands the concept of continuous innovation. Currently the company is implementing the project involves the following areas: 1) Diffractive Optical Element (DOE), 2) Aspheric Optics and 3) Micro-optics.

In addition, the company is committed to developing products that are widely used in optical industry, for example:

1. Digital imaging lens.
2. Microdisplay-ray machines and goggles display system.
3. Far infrared thermal imaging optics array.
4. Laser level and DVD reading head.
5. Special LED lighting and displays, automotive taillights.

3.3 Pilot Company Introduction

Forward Electronics Co., Ltd.

Forward Electronics Company Limited is committed to the R&D and production of supercapacitor (also known as EDLC: Electric Double Layer Capacitors) and Lithium-ion Rechargeable Battery modules and systems. This new energy products are widely used in the areas of Wind/Solar Energy Storage System (ESS), voltage regulation for electrical equipment, energy regeneration system for rail transportation and heavy industrial equipment, smart grid, power system, electric vehicles (E-Bike, E-Motor, HEV/EV), UPS, start-up power (telecommunication and industrial application), as well as digital applications such as power tools, portable power supply and so on.

Sanwa Biotech Limited

The company was created in December 2012 from a core team of founders with entrepreneurial spirits and cross-functional backgrounds in business, biotechnology, advanced micromachining & microfluidic Lab On Chip (LOC) platform. Their backgrounds and experiences formed the basis for this concept of bringing forth a rapid diagnostic, mobile platform for faster and more accurate diagnosis for time critical and life threatening diseases.

Sanwa believes that impending changes are coming to the way to conventional clinical diagnostic & academic R&D for bio-discoveries. Sanwa aims to become a driving force for these changes to revolutionize healthcare solutions into the future. Sanwa delivers accurate and actionable information through our disposable Lab-On-Chip (LOC) rapid diagnostic platform, resulting in transformative diagnostic tests for faster clinical decisions and better economic outcomes.

3.4 Case Sharing from Pilot Scheme

3.4.1 Requirements on the Endoscope's Camera Module

For the camera module developed, it is one of the components of a medical-use endoscope. There are three main requirements for developing medical grade camera module:

1. Optical Requirements
2. Sterilization / Cleanliness Requirement
3. Coating Requirements

For optical requirements, since the end product (endoscope) is used to visualize the internal body channels and this is used to assist the physicians for diagnostic or treatment purpose. As a result, the efficiency of the camera module will be of paramount importance to the intended use of the endoscope. Under such circumstances, the optical specification of camera module will be essential during the consideration of product design and manufacturing process. In general, the camera module must provide consistent and accurate visual image as the final output in order to ensure no risk could be imposed on end user.

With the end products being endoscopes, which will be placed in the human body for diagnostic or treatment purpose, the requirement for sterilization or cleanliness is also one of the critical concerns for the design and production of end products. Even though the concerned product is only a component of the end product, sterilization or cleanliness requirements may still being applied on the camera module. If such requirements are required from the clients, then companies may need to consider incorporating such working procedures to the current operation to achieve sterilization or cleanliness requirements.

Surface treatment for the camera module may also be one of the design and production concerns before launching to medical device market. During the use of endoscope in liquid environment, air bubbles may be created if the external surface has not gone through any surface treatment while the created air bubbles may affect the image captured by the camera module. As a result, companies may need to consider performing surface treatment for their camera module or endoscope.

3.3 Pilot Company Introduction

3.4.2 Requirements on the ELDC Electrical System

For the ELDC module developed, it is one of the components of the back-up battery power system supplied for health-care organizations. There are two main requirements for developing medical grade ELDC Electrical System:

1. Electrical Requirements
2. Reliability

Being a part of the back-up battery power system, the electrical requirement for the ELDC module will be the main concern to the product design and development process. The electrical performance of the module must be able to provide safe and effective output to the end user. Companies are advised to perform some electrical related testing according to international standards (such as IEC60601-1) in order to demonstrate the compliance of basic safety and essential performance.

Apart from electrical requirements, consistent performance of repeated certain key functions is also essential to medical device. Any unreliable device may affect the overall device performance and may even lead to potential harm to end user (such as electric shock, in extreme case). As a result, companies may consider performing product reliability testing for their products in order to demonstrate its reliability performance and fulfill regulatory requirements for some regions.

3.4.3 Requirements on the In Vitro Diagnostic Device (IVD) Platform

For the In Vitro Diagnostic Device (IVD) platform developed, there are three main requirements for compliance.

1. Electrical Performance
2. Reliability

For an IVD device, electrical supply is required for reading the collected samples, processing the samples as well as showing the diagnostic results, etc. Therefore, the performance of electrical components may be critical to the effectiveness of the device's function. Any mal-function of the electrical part may lead to incomplete analysis and accurate results may not be shown. Therefore, companies may need to consider specific design for the electrical part in order to ensure the electrical output is capable for producing accurate results to end users.

Taking up the role of diagnosis, product reliability plays an important role in IVD performance. As this product is not a single-use item and it is expected to be used for a certain period of time. Therefore, the ability to provide consistent and accurate diagnosis result is crucial to the product in the long run. Companies may consider incorporating product reliability element into the design and production stage.

3.5 Summary of Gap Analysis and Recommendations

3.5.1 Traceability

- During site visits, the effectiveness of traceability was checked. By going through the whole production processes, starting from incoming of raw material, storage of raw material, in-process handling, QC control, storage of end products and delivery of end products to clients, the traceability effectiveness was evaluated in the forward and backward approach.

  It was common to find that companies usually had several identification elements (such as pur chase order number, job number and invoice number, etc.) throughout the whole production processes. Comprehensive linkage of these identification elements could facilitate the effectiveness of traceability and therefore, during the site visits, the linkage between these identification elements were re-confirmed via written documents to evaluate the traceability effectiveness in the pilot companies.

  Two approaches (Forward Traceability and Backward Traceability) were adopted for evaluating the traceability effectiveness. For Forward Traceability, the starting point of evaluation usually would be raw material. By selecting the identification elements (such as incoming date, purchase order number or lot number, etc.) as well as identifying amount of raw material in the stock, all involved lot as well as the amount of the intermediate products, which incorporated selected raw material, needed to be full identified. Usually companies would demonstrate the linkage of these two stages by having a record of “Raw Material Collection Sheet” while this record would show the identification element as well as the amount of collected raw material. Also, other identification element(s) (such as job number or order number, etc.) would be shown on this record as well to connect the identification elements between two stages.

  For the later stages of production, the existence of identification element would be checked via written records (such as Quality Control records) to ensure all related intermediate products or raw material could be identified and traced. Apart from identifying the affected products, traceability also facilitates the cause-finding process if all involved equipment, personnel and time, etc. are all recorded in documentation. Therefore, this information would be checked as well during the traceability evaluation

  After identifying the related intermediate products, the linkage between later stages of production would be checked again to ensure all production and quality control records can be traced.

  At the end, all customers, who have received that lot of end products, should be able to be identified to ensure any information could be passed to all related parties when adverse events, or recall cases or any other situations happen. If all customers could be identified in Forward Traceability approach, then this is regarded as successful.

3.5 Summary of Gap Analysis and Recommendations

- For Backward Traceability, it should be achieved by tracing the identification element of the final products (such as invoice number, product serial number or lot number, etc.) to the previous production stage until the corresponding identification element of raw material is identified. If the final products only constitutes a part of the involved raw material, companies may consider perform Forward Traceability again to identify all involved customers with the involved raw material. Backward Traceability is performed often because when companies receive complaints from customers with respect to a specific product lot, companies may want to identify the reason behind and perform corrective actions (such as recall or provision of notices to all related customers), then backward traceability could assist them to identify all involved production records and assist the companies to figure out the root cause of problems.

- Since there are no such strict requirements on traceability for opto-mechatronics companies before, therefore during the site visits to pilot companies, it was not surprised to see the incomplete documentation showing the connection between production stages. Therefore, it was suggested that companies could enhance the documentation requirements by revising the record forms, procedural documents and work instructions, etc., such that the identification elements of the raw material, intermediate products or end products should be recorded in all production records to facilitate traceability.

3.5 Summary of Gap Analysis and Recommendations

3.5.2 Quality Control

- Quality control is one of the critical processes for medical device manufacturing as it can help ensure the output meeting the input requirements while ensuring the output consistency. Therefore, in order to make final products complying to input requirements, comprehensive quality control should be conducted at all production stages with complete documentation. Complete documentations for quality control could assist companies to trace and identify the root cause of problem effectively.

- For some in-process quality control which require quantitative measurements, it was good to see the front-line staff in companies following the procedural documents and work instructions to perform quality control processes, however, some of the recorded results are not shown in quantitative format, but instead, only “OK” is written in the record. Under such circumstances, critical data could not be recorded and traced back in the future, this may lower the effectiveness of cause-finding process if problem happen in the future.

  During site visits, different quality control record (including incoming quality check of raw material, production in-process and final quality control, etc.) are checked for their effectiveness as well as comprehensiveness. It is essential to have the identification element of the handled products (as mentioned in previous paragraphs) being written on the quality control records in order to allow future trace back on the quality issue regarding to a specific group of products. However, it was common to found that the identification element was not recorded in every quality record which may led to failure in traceability. Therefore, it was recommended that companies could revise the current record format as well as providing training to corresponding staff, such that recording necessary data in an appropriate method.

- Apart from in-process quality control, final quality control is also essential to the medical device manufacturing process as it acts as the final inspection point for ensuring product quality. However, it was noted that some of the final quality control results are based on the results of in-process quality control. Personnel in final quality control department would check

  the in-process quality record and see if they fulfill the input requirements. Final quality control was regarded as complete when the in-process quality control written records complied to the input requirements. Under such circumstances, the role of final quality control could be enhanced by conducting further quality checking with appropriate measurements and documentation.

3.5 Summary of Gap Analysis and Recommendations

3.5.3 Verification and Validation

- Both verification and validation are important to medical device realization process while these processes should be implemented for product design as well as production process.

- For design verification and validation, it is required that the product design should be reviewed, approved by the corresponding person. Also, client confirmation on product design should be received before adopting the design for further action. For the review and approval process, it was good to see that some companies adopted computer system (project management system) to get approval from authorized person for all design input requirements. These computerized system help ensure all design inputs are appropriately approved before adoption while the approval date and approved person could be shown via the computer system. From the computer system, it was also good to see that only the latest version of documents (including design graphs) can be opened by working staff and this function can lower the chances of misusing outdated design graphs and producing products, which do not fulfill latest requirements.

  As a result, it is suggested that companies may consider using computer system to upload the design graphs, authorize specific person for approval and maintain the most updated design graphs, etc.

- Apart from getting internal approval for the product design and production process, having client confirmation on the product design requirement before processing is also crucial to the medical device realization process. It was common to see that companies usually sign agreement with the client with reference to a specific version of product design. However, when the product design is changed, confirmation from the client is required as well (with documentation) to ensure the client is aware of the updated product design and confirm the updated design could meet his/her requirements, while having documentation for re-confirming with client on the updated design is not common in the current practices. Therefore, it is suggested that companies could enhance the current practices on client re-confirmation for updated product design by requiring staff to have written record on the re-confirmation.

- Apart from design verification and validation, process verification and validation are also important throughout the whole production process. Process verification is the process verifying the output with reference to the input requirements while process validation is the process validating the process/equipment whether it can produce reliable output of certain standard. During site visit, it was complemented to note that companies are performing comprehensive process verification for most of the production processes, however, process validation is not commonly found in the current practices. As a result, it is suggested that companies should incorporate process validation into the daily practices such that ensuring the critical processes (such as sterilization, injection molding and packaging, etc.) are validated and are available to produce reliable results consistently.

3.5 Summary of Gap Analysis and Recommendations

3.5.4 Customer Complaint Handling

- Effective customer feedback and complaint handling is important to the improvement to company processes as well as product itself. During site visits, it was good to see that companies generally handled customer feedback and complaint with prompt actions by providing new and improved products and revising internal working procedures for reducing the chance of having similar feedback and complaints. However, more comprehensive preventive actions (such as review of risk management file and amendments to internal audit plan, etc.) could be performed for further enhancement of current processes in view of the received feedback and complaint. As a result, it is suggested that companies could consider enhance the role of risk management in the current practices such that any feedback or complaint received would initiate the review of risk management, which allows a macroscopic as well as microscopic review on the whole realization process and revision of current practices.

- Apart from the interrelationship between customer complaint handling and risk management, it was also noted that companies may not fully record all received feedback and complaint. It is understood that companies may consider some of the feedback and complaints as external problems at the first place and therefore, companies may decide not to record these cases in the internal file. However, since all feedback and complaints (even those being regarded as external problems or unreasonable) have to go through evaluation right after receiving such cases and then companies can decide the following actions towards the cases. As a result, it is suggested that companies should record all received feedback and complaints, regardless of the reasons behind. After generating a file for such case, companies could evaluate the root cause of such case and decide any appropriate actions (close file or continue with corrective and preventive actions) accordingly.

3.5 Summary of Gap Analysis and Recommendations

3.5.5 Risk Management

- The implementation of comprehensive risk management throughout the whole medical device product life-cycle could lower the consequence of risk involved to the end user. During site visits, it was complimented to see that companies have performed risk management for their devices as the most common type of tool used is Failure Mode and Effects Analysis (FMEA). However, companies should note that the implementation of risk management should be started at the beginning of the device development stage and should be maintained and updated throughout the whole medical device life-cycle. Early implementation of risk management could assist companies to early detect some potential risks and carry out corrective and preventive actions accordingly to lower the risk level to acceptable level in a more effective way. Also, early risk management implementations allows companies to make changes to the product design as well as production process according to the risk control measure as early as possible to minimize wasted efforts.

- Apart from the schedule of risk management implementation, the effectiveness of risk management is also a big concern to the medical device realization process. All risks involved throughout the design and development stages should be identified and evaluated while the depth of risk identification and evaluation has remained uncertain to most companies. During site visits, it was observed that different companies were evaluating the risk involved in different depth level. Some of them were performing comprehensive risk identification and conduction of risk control measures, however, the risk management measures of some other companies were relatively simple such that not all major risks are listed in the risk management report.

- With implementation of comprehensive risk management in current practices, regular review and update of risk management file is required as well as this enables companies to continuously enhance the product design and production processes according to the risks identified along the medical device life-cycle. Throughout the whole medical device life-cycle, there are a lot of potential inputs for the consideration of risk management such as customer feedback or complaints, notice from regulatory authorities, comments from internal / external audits or identification of nonconforming products, etc. It was noted that companies may not have strong awareness on continuous review and update risk management and thus, the risk management file was generated at the start of product development but no continuous actions were taken towards risk management. Companies should realize that the continuous review, update and implementation of risk management could enhance the safety factor of the product and this would in turn reduce the damages caused by the potential risks. As a result, it is suggested that companies could enhance the current process by requiring staff to regularly review the risk management file accordingly

4 Conclusion

This industry guidebook provides an overview of the regulatory requirements in U.S., E.U. and China with inclusion of examples of opto-mechatronics devices regarding to device classification, conformity assessment route, etc. Opto-mechatronics companies may take this regulatory part as reference for entering medical device market in the future. Apart from the device classification and conformity assessment route, information on the manufacturing practices was also discussed such that opto-mechatronics companies may compare the current operation to different regional requirements and get prepared for future business migration.

This industry guidebook also provides case studies according to the experience in pilot scheme, which will be crucial for other opto-mechatronics companies to learn from these case studies and identify the major gap for improvement before business migration.

Appendix 5

[1]: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/

[2]: https://www.fas.org/sgp/crs/misc/R42130.pdf

[3]: http://www.qrasupport.com/FDA_MED_DEVICE.html

[4]: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/RegistrationandListing/ucm053165.htm

[5]: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm

[6]: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm

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

[8]: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLabeling/default.htm

[9]: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm

[10]: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/CardiovascularDevices/ExternalDefibrillators/ucm232302.htm

[11]: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/ucm2005378.htm

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5 Appendix

[20]: http://www.sgs.com/en/news/2013/01/application-of-european-harmonised-standards

[21]: https://www.mdc-ce.de/fileadmin/user_upload/Downloads/mdc-Dokumente/Broschueren/040100_basic_info_93-42-EEC_06_e.pdf

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[23]: http://www.sda.gov.cn/WS01/CL1105/9394.html

[24]: http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_1-1___04-1994_en.pdf

[25]: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070642.pdf

[26]: http://blog.euromonitor.com/2016/02/medical-device-market-2016-opportunities-in-asia-pacific.html

[27]: https://www.visiongain.com/Press_Release/498/%E2%80%98The-global-medical-devices-market-will-reach-398-0bn-in-2017%E2%80%99-predicts-new-visiongain-report

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