LECTURES (3-4)

Manufacturing of Medical Devices

1.1 Introduction

Medical devices are defined by the US Food and Drug Administration (FDA) as any object or component used in diagnosis, treatment, prevention, or cure of medical conditions or diseases, or affects body structure or function through means other than chemical or metabolic reaction in humans or animals. This includes all medical tools, excluding drugs, ranging from tongue depressors to Computerized Axial Tomography (CAT) scanners to radiology treatments.

Due to the large amount of regulations in the industry, the production of medical devices presents significant challenges from both engineering and legal perspectives.

In medical device manufacturing, three things are paramount:

- **Efficiency,** efficiency is critical as device makers are racing to bring to new products to market as quickly as possible.
- **Quality,** quality is critical because no medical device can be marketed that is not fully compliant and approved by the FDA as safe and effective. This is especially true for complex Class III medical devices, which face some of the most stringent quality requirements in the industry.
- **Manufacturing facilities,** Medical device manufacturing facilities fall under the requirements of ISO 13485 and the FDA's Quality System. These requirements outline the criteria for successful quality programs for medical device manufacturers, and all facilities, equipment and processes must comply with these standards.

In the United States, medical device industry is one of the largest markets globally, exceeding $110 billion annually. In 2012 it represented 38% of the global market and currently more than 6500 medical device companies exist nationwide. These companies are primarily small-scale operations with fewer than 50 employees.

The medical device manufacturing industry is divided into the following branches:

- Electro-Medical Equipment,
- Irradiation Apparatuses,
- Surgical and Medical Instruments,
- Surgical Appliances and Supplies, and
- Dental Equipment and Supplies.

The fabrication of medical devices involves multiple components and materials, both synthetic and biological (e.g. nanotubes, polymers, stem cells, deoxyribonucleic acid).

Generally, productivity can increase significantly by improving the assembly process. And because medical devices require a series of material combinations, cell seeding/culturing, and have to be patient specific, the assembly of medical devices is considered to be a highly complex and time-consuming process, and the working environment has to be free from contamination during the process.

The assembly of medical devices is dependent on two main factors:

(a) highly skilled and well-trained workers and

(b) a sterile and conducive environment.

These dependencies, however, pose many underlying issues such as:

- High costs and time incurred to hire/train highly skilled workers,

- High costs and energy consumption required to maintain a cleanroom environment.

In addition, manufacturing facilities must adhere to ISO 14644 and/or FED STD 209E cleanroom requirements when relevant for the devices being manufactured. While a Class 7 or higher clean room is, for the most part, standard for Class III medical device manufacturing, cleanroom design and location can have a significant impact on both efficiency and quality.

1.2 Medical device regulation for manufacturers.

Manufacturers of medical devices are held to a higher standard than manufacturers of many other products due to the potential severity of the consequences of introducing inferior or unsafe products to the market-place. The medical device industry is regulated by a Country Health under the Medical Device Regulations of the Food and Drug Act.

The Medical Device Regulations define requirements of medical device design, development and manufacture to ensure that products reaching the public are safe and effective. A country Health also requires that medical device manufacturers maintain distribution records to ensure that devices can be traced to the source and consumers can be contacted successfully in the event that a device is recalled. Medical devices exported from any country must be compliant with the regulations of the country of import.

1.3 Medical Device Classification

1.3.1 Class I: General controls

General controls are the only controls regulating Class I medical devices. These state that a Class I medical device is "not intended to be:

1. For use in supporting or sustaining life;
2. Of importance in preventing impairment to human life; and may not
3. Present a potential unreasonable risk of illness or injury

Examples of Class I devices include bandages, bed-patient monitoring systems, medical disposable bedding, and some prosthetics such as hearing aids, tongue depressors, bedpans, elastic bandages, examination gloves, and hand-held surgical instruments and other.

1.3.2 Class II: General controls and special controls

Class II devices are subject to stricter regulatory requirements than Class I devices. The additional requirements are called "special controls" and were established for cases in which patient safety and product effectiveness are not fully guaranteed by the previously stated general controls. Special controls are specific to each device and classification guides are available for various branches of medical devices.

Devices in this class are typically non-invasive and include remote health care monitoring devices, x-ray machines, PACS, powered wheelchairs, infusion pumps, surgical drapes, surgical needles and suture material, acupuncture needles, and many medical lasers such as aesthetic lasers, dental lasers for soft and hard tissue procedures, and some ophthalmic surgical lasers.

1.3.3 Class III: General controls and premarket approval

Class III devices are those considered the most high-risk. These devices may be used in support or sustenance of human life, pose a potential risk of injury or illness, or are of great significance in preventative care. Prior to marketing such a device, the rights-holder(s) or person(s) with authorized access must seek FDA approval. The review process may exceed six months for final determination of safety by an FDA

advisory committee. Many Class III devices have established guidelines for Premarket Approval (PMA) and increasingly, must comply with unique device identifier regulations.

1.4 Choosing the Right Material for Medical Device Designing

In addition to all the usual material requirements for materials, biocompatibility presents a unique challenge for material choice for medical device manufacturing. For the designing of a medical device, each composing material should have certain characteristics, which should be in a harmony with the final properties of the medical device as well the target application. The manufacturing companies take into consideration the following criteria as bases for choosing each material towards their targeted applications:

1- The availability of the material in sufficient quantities to meet the market needs.

2- The second one is the flexibility of the material towards a targeted design, where the material can be needed in different forms (e.g., filaments, fibers, nanoparticles, etc.).

- For instance, the flexibility can be achieved using certain types of polymers, which can be processed as fibers, Nano fibers, hydrogels, etc.
- The usage of bioactive ceramics or glasses can be the best choice for others, especially in bone applications, which require implantation of rigid structures.
- Moreover, bioactive glass-based fibers can be also designed for bone grafting and drug delivery.

3- The material cost. This includes the costs of production, transportation, and amounts required for each device, the true lifecycle costs are essential.

4- The matching between the material properties and the required specifications of the designed device.

5- The choosing of the trusted/certified materials for the medical applications for shortening the period required for the device approval.

6- The biocompatibility of the finally designed device, as well as its components. It can be considered one of the most important factors for selecting the material. Moreover, the sterilization method, as well as the storage conditions, which can guarantee its optimum biocompatibility.

7- The used sterilization technique, where every type of medical devices requires a certain effective sterilization method, which can preserve the structure and properties of the constituting materials as well.

8- The usability of the device. However, this is only applied to the devices which are used without direct clinical supervision.

9- The choosing of the material which can guarantee efficient manufacturing.

10- The sustainability of the medical device, which starts from the designing stage, choosing of the material, the manufacturing method and its related economic issues, and finally the disposal of the device.

1.5 Medical Industry Sectors

1.5.1 Orthopedics

This is one of the fastest growing sectors in medical device manufacturing. It includes reconstructive devices, spinal implants, arthroscopy, orthobiologicals, hip implants and knee replacement. This sector utilizes manufacturing processes such as machining, casting, grinding, polishing, metal injection molding and rapid manufacturing.

1.5.2 Surgical Instruments & Technologies

One of the largest segments, this includes dilators, sutures and surgical robotics. Key technologies include micromachining, surface treatments and materials.

1.5.3 Diagnostic Apparatus

Endoscopic devices, ultrasound and magnetic resonance instruments are examples of this sector. Key technologies include imaging, IT and micromanufacturing.

1.5.4 Cardiovascular Devices

This highly competitive sector includes pacemakers, defibrillators and drug stents. Key technologies include power sources, micromolding and assembly.

1.5.5 Diabetes Devices

Continuous glucose monitoring (CGM) is a leading example of this sector. Key technologies include nanotechnology, sensors and assembly.

1.5.6 Dental Instruments & Technologies

Imaging equipment, implants, drills and instruments. Key technologies include machining, additive manufacturing and 3D imaging.

1.5.7 Other segments

Spinal devices, catheters, syringes and hypodermic needles, blood transfusion and IV equipment, internal fixation devices, neuromodulation devices and urology devices.

1.6 Some Examples of Precision Medical Technology:

- Stent Cutting & Milling
- Wire Stripping / Wire Joining
- Laser Welding
- Precision Wire Shaping
- Test Stands
- Tube Stretching
- Balloon Forming
- Device Coating
- Artificial Joint Manufacturing

- Prosthesis Manufacturing
- Catheter Assembly
- Pacemaker Assembly

1.7 Medical Devices Manufacturing Technologies and Processes

1.6.1 3D Imaging

Three-dimensional data capture refers to both the tools and the process for the collection of 3D digital data from physical objects. It is a process that combines hardware and software. The use is growing in medical manufacturing as the ability to manufacture custom, additive manufactured devices increases.

1.6.2 Quality Systems

In a highly regulated environment and a critical need for consistent quality, quality systems like FMEA are key to medical device manufacturing.

1.6.3 Measurement & Inspection

Maintaining quality requires consistent, reliable and verifiable measurement and inspection. Down to micron and submicron levels, medical device manufacturing can face unique technology and process challenges.

1.6.4 Additive Manufacturing/3D Printing

Combined with 3D imaging technologies, additive manufacturing allows for custom with reduced design and development time. Used for surgical guides (conjoined twins' separation) and prosthetics are two of the most common areas this technology is used.

Additive manufacturing (AM) processes are a dominant mode of production for medical devices that are used inside the body, such as implants, transplants and prostheses, for their ability to replicate organic shapes and enclosed volumes that are

difficult to fabricate. The inability of donation systems to meet the demand for organ transplantation in particular has led to the rise of AM in medical device manufacturing.

1.6.5 Assembly

From selecting appropriate joining methods to meet biocompatabilty requirements to handling what can be micron-sized components, medical device manufacturing assembly must be conducted often within clean room environments.

1.6.6 Lasers

Highly accurate and flexible, a narrow laser beam can cut, machine, mark or weld intricate details with accuracies to one micron.

1.6.7 Coatings and Surface treatments

Coatings serve numerous functions, such as increased wear resistance, increased bone in-growth, reduced friction and enhanced abrasion. Biocompatible coatings are used for passive and drug-eluting applications on cardiovascular stents and a broad range of other implantable medical devices. The ultra-thin coating formulation on implantable devices is designed to protect surrounding tissue from potential harmful interactions with bare metallic stents.

1.6.8 Machining

From components to other devices to joint implants, many require machining of medical grade materials. This includes the unique challenges of machining to extreme accuracies of titanium.

1.6.9 Micromanufacturing

For many reasons, devices continue to get
smaller and smaller. Features and components of just a few microns require the specialty processes of micromanufacturing including micromachining and micro molding.

1.6.10 Nanomanufacturing

Nanomanufacturing techniques provide a means of manufacturing cellular-scale medical devices (<100μm). They are particularly useful in the context of medical research, where cellular-scale sensors can be produced that provide high-resolution measurements of cellular-scale phenomena. Common techniques in the area are direct-write nanopatterning techniques such as dip-pen nanolithography, electron-beam photolithography and microcontact printing, directed self-assembly methods, and

1.6.11 Power Sources

With the advancement of implantable devices for monitoring and treatment, the selection and development of power sources has become a critical part of medical manufacturing.

1.6.12 Biocompatibility

The largest issue in integrating techniques into medical device manufacturing is biocompatibility. These issues arise from the stability of 3D printed polymers in the body and the difficulty of sterilizing regions between printed layers. In addition to the use of primary cleaners and solvents to remove surface impurities, which are commonly isopropyl alcohol, peroxides, and bleach, secondary solvents must be use in succession to remove the cleaning chemicals applied before them, a problem that increases with the porosity of the material used. Common compatibility materials include nylon and tissue material from the host patient.

1.6.13 Cybersecurity

Many medical devices have either been successfully attacked or had potentially deadly vulnerabilities demonstrated, including both in-hospital diagnostic equipment and implanted devices including pacemakers and insulin pumps. On 28 December 2016 the US Food and Drug Administration released its recommendations that are not legally enforceable for how medical device manufacturers should maintain the security of Internet-connected devices.