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COMMERCILISATION AND QUALITY REQUIREMENTS OF BIOMEDICAL WEARABLE AND IMPLANTABLE DEVICES

Master's thesis

Examiner: Professor Heimo Ylänen
Examiner and topic approved by the Faculty Council of the Faculty of Natural Sciences on 6 June 2012.

ABSTRACT

TAMPERE UNIVERSITY OF TECHNOLOGY
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Due to growing old age population and increase in chronic diseases at all the ages across the world, there is an opportunity for Biomedical device companies for a vital investment and address the problems by introducing risk free, effective, and safe devices into the market. Presently, the market for Biomedical Wearable and Implantable devices is in high demand due to wider applications and advance in computing algorithms in Medical industry.

The current thesis has been focused on commercialising and quality requirements of Biomedical Wearable and Implantable devices by understanding the market requirements and increase in global demand for quality devices. In order to manufacture an effective Biomedical device, manufactures have to establish quality management systems in every phase of product development phase to produce safe and effective devices, and meet the requirements of regulatory authorities who in turn are answerable to the public. These Biomedical devices can extend and give quality life to the patient sufferings.

Though companies see a profitable business for these innovative Biomedical devices, stringent requirements and longer approval time process from regulatory authorities are making the Biomedical device companies to rethink to enter the market in these Biomedical devices. Moreover, regulatory authorities should consider adopting the global nomenclature and standards due to increasing global demand supply chain management for these devices.

PREFACE

The current thesis is the diploma work for master's degree in Biomedical Engineering at Tampere University of Technology. This document focuses on commercialising and quality requirements in two of the growing markets in Biomedical device industry: Wearable and Implantable devices. Due to increase in old age population and chronic diseases across the world, these innovative devices can be a solution in future due to its safer and wider applications. This thesis was done under the guidance of Professor Heimo Ylänen who works in the department of Biomedical Engineering at Tampere University of Technology, and who has extensive knowledge and wide experience in Biomedical Implants and drug-delivery devices field whose courses have inspired me to take up thesis on this subject. He gave me lot of flexibility and freedom to choose the scope and depth of the subject. I also thank the department of Biomedical Engineering and Industrial Management of Tampere University of Technology for my learning curve and depth in different subjects for my future career.

The reason I have chosen to work on this topic is due to interest I have in quality management when I have first started working as consultant to GE Healthcare. This work made me familiarise with the Biomedical industry regulatory affairs and quality system requirements in USA, EU, and International standards. In addition, through this work I have also learnt the ways how the manufacturer of Biomedical devices should devise business strategies at various stages of product development for successful commercialising of the product. This work gives opportunity for the readers as a guideline in understanding the commercialising and regulatory requirements of these Biomedical Wearable and Implantable devices.

Finally I thank the almighty God, my parents, my siblings, my fiancé Rufiya, my dearer friend Hilda Fülöp for effort shown in cessation of smoking, my dear friends, and people from everyday life who have given me enormous support, motivation, and inspiration to complete this thesis throughout my insomniac sleepless nights, depression, and hibernation period. I also thank Finnish government and Finnish people for giving me an opportunity to study in one of the world's best environment with good hospitality.

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LIST OF SYMBOLS

$	Monetary in US dollars.

ABBREVIATIONS AND ACRONYMS

3Q	Three Questions
ADME	Absorption, Distribution, Metabolism, or Excretion
AIMDD	Active Implantable Medical Device Directive
ANS	The National Regulatory Agency for Private Health Insurance and Plans
ASME	American Society for Mechanical Engineers
CAGR	Compound Annual Growth Rate
CEN	The European Committee for Standardization
CIP	Clinical Investigational Plan
cGMP	current Good Manufacturing Practices
CMO	Contract Manufacturer Organisations
CPM	Critical Path Method
CPT	Current Procedural Terminology
CRO	Clinical Research Organisation
DHF	Design History File
DHR	Device History Record
DI	Device Information
DMR	Device Master Record
DS	Device Specifications
EC	European Commission
ECG	Electrocardiography
EMEA	European Medicinal Agency
EPO	European Patent Office
ERP	Enterprise Resource Planning
EU	Europe Union
FMEA	Failure Mode Effect Analysis
FP7	Seventh Search Program
GCP	Good Clinical Practices
GDP	Gross Domestic Product
GE	General Electric
GLP	Good Laboratory Practices
GMDN	Global Medical Device Nomenclature
GMP	Good Manufacturing Practices
GxP	Good Practices
HCPCS	Healthcare Common Procedure Coding System
HMO's	Health Maintenance Organization's
IACUC	Institutional Animal Care and Use Committee
IB	Investigational Brochure
ICD	International classification of disease
ICH	International Conference on Harmonisation of Technical Requirements

ABBREVIATIONS AND ACRONYMS

	for Registration of Pharmaceuticals for Human Use International Conference on Harmonisation
IDE	Investigational Device Exemption
IDMC	Independent data-monitoring Committee
IEC	Independent Ethics Committee
IMDRF	International Medical Device Regulators Forum
IP	Intellectual Patent
IQ	Installation Qualification
IMS	Installation, Maintenance, and Servicing
IRB	Institutional Review Board
ISO	International Standards Organization
IVDD	In-vitro Diagnostic Device Directive
LOS	Length of Stay
MDD	Medical Device Directives
mm	millimetre
MP	Manufacturing Process Specifications
NB	Notified Body
NCA	National Competent Authorities
NHS	National Health Service
NOC	Not Otherwise Classified
NPD	New Product Development
OQ	Operational Qualification
ORDT	Operating Room Device Technician
PCT	Patent Cooperation Treaty
PESTEL	Political, Economic, Socio-cultural, Technological, Environmental, and Legal
PI	Product Information
PL	Packaging and Labelling Specifications
PMA	Pre-market application
PMCF	Post Market Clinical Follow Up
PMDA	Pharmaceuticals and Medical Devices Agency
PQ	Performance Qualification
QA	Quality Assurance Procedures and Specifications
QAU	Quality Assurance Unit
QMS	Quality Management System
R&D	Research and Development
RPN	Risk Priority Number
SAEs	Serious Adverse Events
SCM	Supply Chain Management
SFDA	State Food and Drug Administration
SME's	Small and Medium-sized enterprises
SOP	Standard Operating Procedures

ABBREVIATIONS AND ACRONYMS

SWOT	Strength, Weakness, Opportunities, and Threats
UID	Unique Device Identification
USA	United States of America
USPTO	The United States Patent and Trademark Office
WCE	Wireless Capsule Endoscopy
WHO	World Health Organization
WIPO	World Intellectual Property Organization

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1. INTRODUCTION

1.1. Motivation

The motivation for doing thesis in this particular subject is an idea gathered during my work experience during my tenure as ERP consultant for GE Healthcare where I have experienced quality systems of GE Healthcare software system. As per the Food and Drug Agency(FDA) requirements the GE Healthcare Company should confront the software system in regards to quality requirements. This provided me an insight of the regulations and quality requirements of FDA to a Healthcare company. This was also my motivation point to take up my master degree course in Biomedical Engineering field while Industrial Management as minor field. I have envisaged learning the regulations in Medical devices and implementing qualities to confront the regulatory authorities and improve the quality system internal to the company.

1.2. Healthcare and Medical Industry

Medical field has been diversified(as shown in figure 1.1) and technologies from other fields have been implemented in Medical and Healthcare industries which have been evolving by inventing new technologies and increasing the life expectancy and quality of life of the public. But, the major concern for these technologies has been with safety issues, because of which regulatory bodies have been formed over time across countries for the benefit of the public health. The purpose of the regulatory bodies is to follow the product development process of the companies and make sure that they implement the quality requirements as governed by the regulatory bodies. Table 1.1 shows various(important) regulatory bodies across word-wide, while figure 1.2 shows the Healthcare markets in the world.

Table 1.1. *Regulatory bodies across world-wide [1].*

Country	**Regulatory Agency**
USA	FDA
Europe	EU Notified Bodies and National Competent Authorities
Japan	PMDA
China	SFDA
Brazil	ANS

It is therefore important for the companies to thoroughly gather the necessity requirements of the regulatory bodies to market the products from the beginning of the product development process. Adhering to the requirements of the regulatory authorities can reduce a stipulated amount of time and expenses incurred during the course of product development.

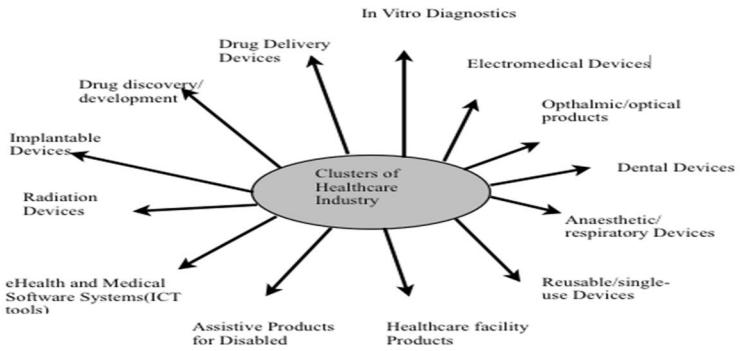

Figure 1.1. *Diversification of Medical field [2].*

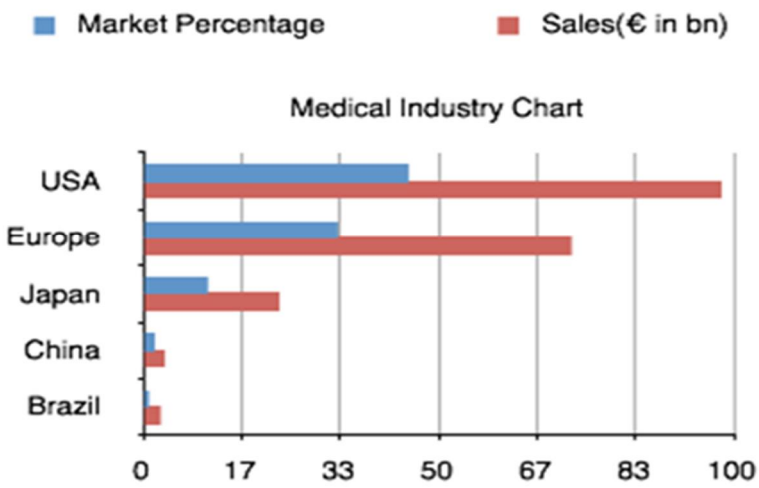

Figure 1.2. *Competitiveness facts and figures(2007) [1].*

1.3. Biomedical Wearable and Implantable Devices

Medical industry is a vast subject and involves pharmaceutical, drug delivery, Medical equipment's, Medical orthopaedics, Medical support, Medical ambulatory interests. Further due to increase in the ageing population who need assistance, and increase in number of chronic diseases who require continuous monitoring/treatment, companies have found new ways to give a better life and rapid diagnosis/treatment by focusing on Wearable and Implantable devices.

1.INTRODUCTION

Before explaining the definition of Biomedical Wearable and Implantable devices it is better to have insight of the definition of Medical device. FDA states “a Medical Device is an instrument, apparatus, machine, contrivance, Implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognised in the official National Formulary, or the United States Pharmacopoeia
- 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 for the achievement of any of its primary intended purposes”. [3]

Any Biomedical Wearable device is a device that is being worn by a person and assists in Medical monitoring or support over a long period of duration. The Wearable device is non-invasive which is an accessory or is embedded within the garments of the patient. These devices have physiological sensors which can process the data through complex algorithms and can be transmitted through wireless communication systems. The receiver end can be doctors or Healthcare monitoring units where they can study the subject’s data and provide treatment whenever required as outpatient units. These Wearable devices are small in size, light in weight, unobtrusive, and basically designed for patients with prolonged chronic diseases or disability or people with congenital disorder which are designed to give real-time feedback to the doctors for Medical decision/assistance [4].

Further Wearable devices can be classified into Medical care equipment (termed as Medical device data systems by FDA) [5] and home Health and consumer devices, current thesis focuses on Medical care equipment as these devices should pass the regulatory compliance for marketing the device and require physician intervention. Since, home health and consumer devices do not require any physician intervention and these devices do not require tedious process of compliance of the regulatory system, however they are regulated for safe use by the public.

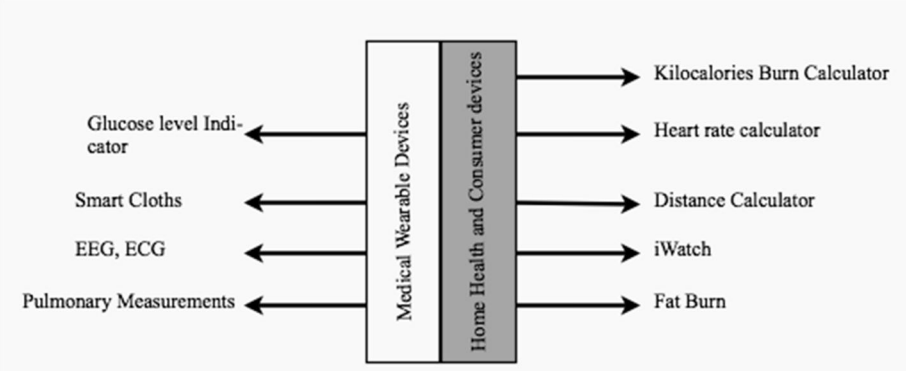

Figure 1.3. *Examples of Medical care vs. home Health Wearable devices.*

1.INTRODUCTION

Biomedical Implants are artificial devices which are in contrast to transplants which are manufactured to replace a missing biological structure, support a biological structure, or enhance the operation of an existing structure. In current thesis the following Implantable devices have been discussed;

- general Implants
- Active Implants with medicinal products
- Active Implants for clinical monitoring/treatment (e.g. pacemakers)
- Implants with drug delivery devices

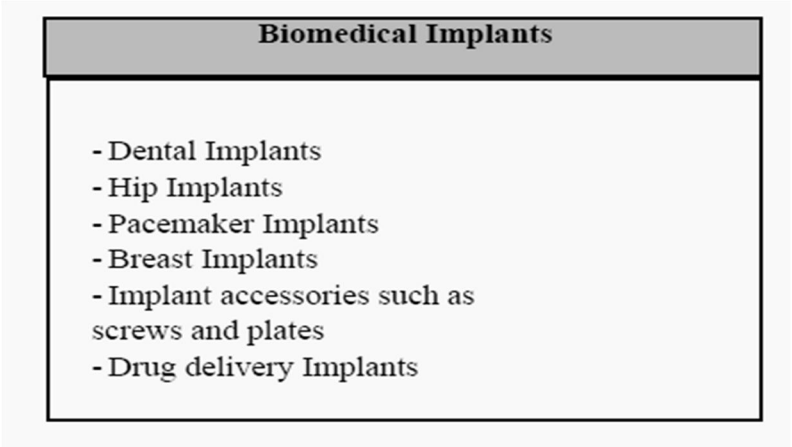

Figure 1.4. *Examples of Biomedical Implantable devices.*

1.4. Safety and Compliance

Though articles with advanced Medical technologies have been published over period of time, many research works could not enter the market due to failure in product development process and risk of the devices for the public health. The regulatory agencies make sure that the Medical devices available in the market have more benefits than risks, so the public can trust on these regulatory bodies in terms of buying the device to be used safe enough. Therefore, these bodies have to assure the public that the related technology or Medical device is safe upon application for treatment or diagnosis.

1.5. Research Method

Though current thesis is based upon c*ommercialisation and quality requirement of Biomedical Wearable and Implantable devices,* I have started with literature review of process related to FDA. Though going through each and every step of FDA was tedious, time taking, and confusion, I had an overview of the FDA process. Further, I started reading the quality requirements of some of the Implants which got approved through both Pre-Market Application(PMA) and 510(k) approval. This gave me further hint of quality requirements on Medical devices.

The next step was to concentrate on commercialisation of the Medical devices into the market. I have gone through the book *"Commercialising successful Biomedical Technologies"* written by Shreefal S. Mehta which is based on FDA process. The author thoroughly explained about the contemporary methods and process used by various companies to get approval from the FDA and also highlights different ways for reimbursements invested by the companies by involving the stakeholders from the start of the product development. Shreefal S. Mehta in his book stated that companies trying to market their product in USA have to involve with Medicare, insurance companies, hospitals and other 3rd parties so the product/device is given preference or the device should be placed in the Healthcare provider catalogues for the treatment.

Since companies market the device differently depending on the organisations value-chain there is no particular commercialisation process for marketing the Medical device. Hence, I followed the book *"Biomedical Technology Assessment: The 3Q Method"* written by Phillip Weinfurt(Marquette University). The three question(3Q) Method basically gives hindsight about how a company which is developing a product, or an organisation which is buying the product should answer the following three question: "Is it Real?, Can We Win?, and Is It Worth It?"

Once acquiring knowledge of commercialisation process in USA and quality requirements of the Medical devices with respect to FDA, I moved on with Europe Union Medical Device Directives(EU MDD) to have an basic understanding of the processes involved between EU notified bodies and FDA agencies. Further, thinking of future prospective trade of inter-continent businesses, I had a detailed view on International Medical Device Regulatory Forum(IMDRF) and World Health Organisation(WHO) documents. The sole purpose is to understand how the IMDRF can minimise the compliance or regulatory works for companies intending to market globally. The common goal of IMDRF is to focus on common regulatory works that a company has to follow to market their devices across continents or countries.

1.6. Goals

The goal of the current thesis is to analyse and layout the commercialisation process involved in marketing a Biomedical Wearable and Implantable devices(through same process is used for other Medical devices) and to define quality requirements of these devices. There is no single correct process that a company follows, but I have generalised the basic approach for commercialising the Biomedical Wearable and Implantable devices. During commercialisation process companies have to involve with different stakeholders, internal and external to company. Though product development is tip of the iceberg, external stakeholders play a vital role in making companies to generate their revenues. Further, the current thesis focusses on quality requirement for these Biomedical devices in order to achieve the feasible final product and comply with the norms of

the regulatory bodies. In addition, the thesis work focuses on the good practices that are mandatory for any Medical device companies to endorse their final product and get approved from regulatory agencies for marketing.

1.7. Document Structure

While the objective of the thesis has been discussed in chapter 1, the remainder of thesis is organised in the following way. Chapter 2 presents the future market growth and applications of these Biomedical devices. Chapter 3 covers different product development and commercialisation stages, including future scope of demand-based manufacturing and Unique Device Identification(UDI) for global traceability of Medical devices. In chapter 4 various quality requirements of Biomedical Wearable and Implantable devices to be adopted by manufactures' have been discussed extensively, while chapter 5 discusses the good practices to be maintained by the manufacturers' during product development stages so the results are accurate, repeatable, trustable, and efficient. Further in chapter 6, the EU vs. FDA regulatory affairs, the future role of IMDRF, future complexity in applications of these devices, and challenges in Biomedical Wearable and Implantable devices have been briefly discussed. The last chapter summarizes the work that he been done and gives a hint of challenges that exists.

2. MARKET AND APPLICATIONS OF BIOMEDICAL WEARABLE AND IMPLANTABLE DEVICES

The applications of Biomedical Wearable and Implantable devices are in numerous and have increased the life expectancy and given quality of life to the public by generating accurate data to the clinicians. Though there are certain risks of using these devices, the benefits are more when compared to risks associated with these devices. Over the years companies have used advanced technologies in design processing, enduring risks for marketing, increasing the life cycle of the device, biocompatibility nature of the Implantable devices, using microchips for monitoring and diagnosis of the patients, and increasing the quality of life of the public. In the past, there were failures associated with the Implants, but companies through learning process from the predicate devices and capital spending in R&D department, have definitely changed the scope of the Medical technologies, earned the trust of regulatory authorities and public, and found better solutions for both the public Health as well as profits.

2.1. Biomedical Implantable Devices

2.1.1. Biomaterial Implants

Biomaterial is a synthetic material which is biocompatible, non-toxic, and non-carcinogenic which has physical and mechanical characteristics, can be degradable or non-degradable material to be used as augmentation or replacement of body tissues. Biomaterial have found applications in orthopaedics, cardiovascular applications, dental applications, wound healing purpose(sutures), opthamalics, gastrointestinal, plastic surgery, and drug delivery systems. Most of the ingredients used in Biomaterials are metals, polymers, ceramics, and composites. The market for cardiovascular is expected to grow at Compound Annual Growth Rate(CAGR) of 14.5% from 2009 to 2014, where the market value in 2008 was $9.8billion. The overall Biomaterial Implant industry is going to be worth $22.8 billion in USA with CAGR of 13.6%, while in EU $17.7 billion with CAGR of 14.6% and global worth of US $58.1 billion by 2014[6].

2.1.2. Orthopaedic and Dental Implants

Orthopaedic Implants are most commonly used in patients who are suffering from osteoporosis, osteoarthritis, bone cancer, and patients who have undergone accidents/trauma. Osteoporosis is most common in old people above age 50, and due to

growing old age population world-wide which is estimated to be 31.4% by 2020 in EU-27 and 25.3% by 2020 in USA[7]. There is huge demand for orthopaedic Implants and companies have to deliver risk free and safe Medical devices. Globally, one in every three women, and one in every five men above age 50 suffer osteoporosis, of which 33% of these adults who suffer from hip fractures are disabled in year and are dependent for support to continue their normal life[8].

In USA it is estimated that in the year 2013, around 3,010 patients shall be diagnosed with bones and joint cancer which represents 0.2% of all cancers[9] of which 1,440 shall die. Though this is a smaller figure the estimated rate shall increase in forthcoming years. Patients suffering from bone cancer(primary bone cancer) have to go through enormous side effects through chemotherapy process and other surgical methods. If the bone cancer resides in the areas of arm, shoulder, leg, or hip the surgeon can decide to operate “limb sparing surgery”[10] where the affected area is removed and is replaced by orthopaedic Implant.

Another area of application is use of orthopaedic Implants for patients who have gone through accidents/trauma, where there is requirement for the fixation of the bones to continue their normal physical activity. Moreover, surgeons also use screws, plates, and other accessories for the treatment of fracture encountered in the trauma.

Dental Implants are used world-wide for better appearance, improved speech; ease in eating, higher self-esteem, and for oral health. The industry of dental Implant shall rise from $3.5 billion in 2011to $7 billion in 2020 with CAGR of 10%. It is estimated that penetration of dental Implants is going to rise by 25% to 30% of USA population by the year 2020[11]. Most of the dental implant industry is used for cosmetic changes of facial expression.

2.1.3. Active Implants

Active Implants are biocompatible Medical Implants that are embedded with chips which are used for treatment, or diagnosis on implanting it inside the body using bio-feedback system. The modern applications of the active Implants are monitoring of diabetics, treating eye disease such as glaucoma, neuro-simulator for patients with nervous disorders, and are used in heart rhythm management[12]. For example, in USA alone 325,000 deaths occur due to Sudden Cardiac Arrest(SCA) [13], this can be prevented by using implantable defibrillators. The future of active Implants involves implantable nano-robots or sensors which transmit data through wireless communication with the physician to generate data of the state of patient and the Implant itself. Further, research work is going on in the area of active implants where the biocompatible sensors can be implanted inside the body in order to detect the cancer at early stages.

2.2. Biomedical Wearable Devices

Applications of Biomedical Wearable devices have just started to boom due to advance in microelectronics, wireless transmission network, and advance computing algorithms in Medical industry. Biomedical Wearable devices can be used for the patients who are suffering from chronic diseases such as heart, epilepsy, related to nervous system, diabetic's detection, pulmonary measurements, and rehabilitation purpose. For example, patients suffering from weak muscles or paralysis can use Wearable device to trigger the impulse for the movement of the muscle. It is estimated that 1 in every 25 children aged between 6months to 5years experience febrile seizures[14], application of Wearable devices on this children can alert the parents or care givers as they need regular monitoring. The sensors are mounted on the designated area of the body, this reads the information and transfers the data through wireless transmission to the clinicians, healthcare units, or alert the care takers for the action to be taken on these patients[15]. In addition, Wearable devices can be used in ambulance services to monitor the key functioning of the patients and this data can be transmitted to hospitals so that the doctors are ready to serve the patient quickly soon after the arrival of the patient. Further, future active Implants can be connected to these Wearable devices for transmitting the data and controlling the parameters of the implanted active device.

3. COMMERCIALISATION

Commercialisation of a Medical device is a product development process where the product is released into the market for the benefit of the society to diagnose/treatment and to cure the illnesses, and generate revenues to the company. Product development in Medical industry starts with the research in customer requirements or market specifications. More than the time invested in creating a new product, most of the companies do analysis or survey to estimate the scope of the device. The analysis should include demographics, survey of how many people are suffering from the disease or need of the product, and how well the product can be distributed through various modes of distribution. The final step in product commercialisation is where most of the companies spend money in advertising, sales promotion, and other marketing efforts.

The three key steps in commercialisation of a product are:

- to look into the many product development ideas and choose one or two products that can benefit the company both in short-term and long-term
- to devise a proper plan and have stage-wise objectives(checkpoint clearance) and analysis in further developing the product
- to involve all the stakeholders in early stages of the product development. Further, it is important that the customers participate in the product development process using prototypes

The commercialisation process should consider:

- decision on the release time of the product(studying the competition and patent)
- region of release of the product
- target group where the product should be released through research and test marketing the device

3.1. Modern Healthcare Industry

Health sector is one of the most rapid growing industries in the world. In modern world many unknown diseases have been diagnosed and various medicines have been invented for cure. But human science is not so easy to understand and it takes time to recognize the cause of the disease and then invent the cure for the disease. Modern medicines with advanced technologies have allowed researchers to invent medicines to cure forthcoming diseases despite a huge challenge in risks associated with the use of the product. Companies invest time and money in development of Healthcare industry as the profits

generated in Medical industries are enormous. Current trend shows that USA has largest Healthcare service sector with revenues approximating $1.75 trillion while the market for Medical device industry sector accounts $110 billion and is estimated to grow due to rapid development in technologies and increase in population with diseases[16].

3.2. Concept of Commercialisation

For Biomedical Wearable or Implantable device companies, the figure 3.1 indicates the basic paradigm life cycle of product development from idea to commercialisation of the product. The propulsion to commercialise the device is invention/idea through market trends or customer needs. Secondly, in order to make the invention/idea to be marketable, companies have to plan if the product is viable and suits the strengths of organisation to build and sell the product. Later, organisations have to make decisive strategies to plan the product development process which involves business model, personnel allocation, financial plans, prototypes, future development strategies, pre-clinical trials, clinical trials, compliance to regulatory laws, manufacturing, distribution, and stakeholders.

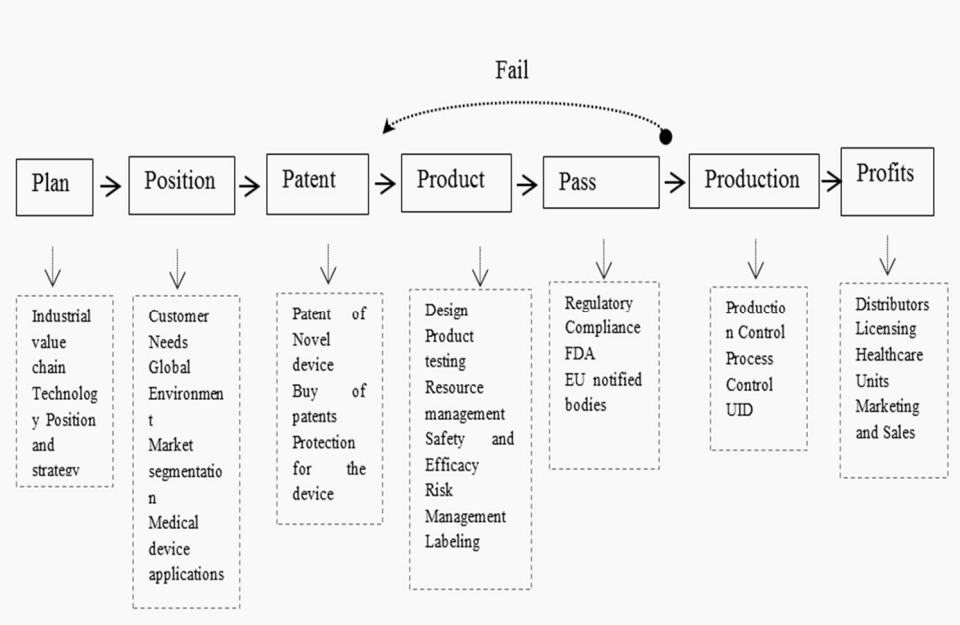

Figure 3.1. *Product development check point's [17].*

3.3. Market Research

Market research is the genesis for understanding the requirement to commercialise the product as many innovative Medical technologies have failed to make an impact in the market. The process of product development should be started with understanding of requirements of the product as per the market needs. For organisations to make the in-

vention commercialisable they have to define the market potential of the new idea to convince the management or sponsors in their business plan. The market research helps to identify: the market, opportunity to new invention, product characteristics, competitors, and projection of sales, profits, and pricing. Finding early market size of the new invention can help the management to go forward with production or to drop the idea of new invention to commercialise.

3.3.1. Market Research Methodologies

Medical market research information for Biomedical Wearable and Implantable devices can be gathered using primary or secondary information. Primary information can be gathered by going through past records of predated products and listing down the success and failure of each of the products. For example for *hip fracture*, the company can list own all the available treatments and can chart down the best procedures adopted, the cost of the product, the cost for treatment, and adverse side effects or deaths using those technologies. The other approach is testing of prototype using simulation and advanced techniques by involving the customers, clinicians, and other stake holders. This approach can help the companies to define design parameters and spread knowledge to the public. In case of Wearable devices, users can be asked to use the prototype technology for observation and self-assessment.

The secondary information for research can be found at public sources which include reports published by regulatory agencies, notified bodies, and physician associations. Other sources include hospitals, insurance companies, internet search, commercial research sources especially marketing the statistics for profits, and journals.

3.3.2. Market Segmentation Approach

Once the market statistics and requirements are recorded the next step is to segment the market in terms of demographics and technology competent. For instance, companies have to predict the reachable population for device, known as sizing of the market. The sizing of market should be in numbers, and should consider the similar products and competitors in the market. For example, aging population across Europe which is estimated to be 31.4% by 2020 in EU-27 and 25.3% by 2020 in USA[18] respectively requires lot of attention towards old age problems, which means lot of scope for companies marketing in Biomedical Wearable and Implantable devices. In addition, companies have to list down the market size in terms of value i.e., $100million, or $1billion or greater. Then the companies have to chart down the list of existing treatments in the market, treatments that are niche, and the survival time period of the new invention before other new treatments race into the market.

In segmentation approach companies have to also consider factors such as targeted age, pricing, marketing geographic region, stage of illness where the new invention can

be introduced to the patient, market acceptance, risks associated with the product, hurdles to introduce the product, treatment costs at various geographies, and growth of the product. Though it is difficult to predict the scope of future of the product, statistics can give hint for companies using historical data.

3.3.3. Market Assessment Techniques

SWOT Analysis

Considering the market position and other competitors in the existing market, companies have to assess Strength, Weakness, Opportunities, and Threats(SWOT). The figure 3.2 lists the SWOT analysis for both Biomedical Wearable and Implantable devices.

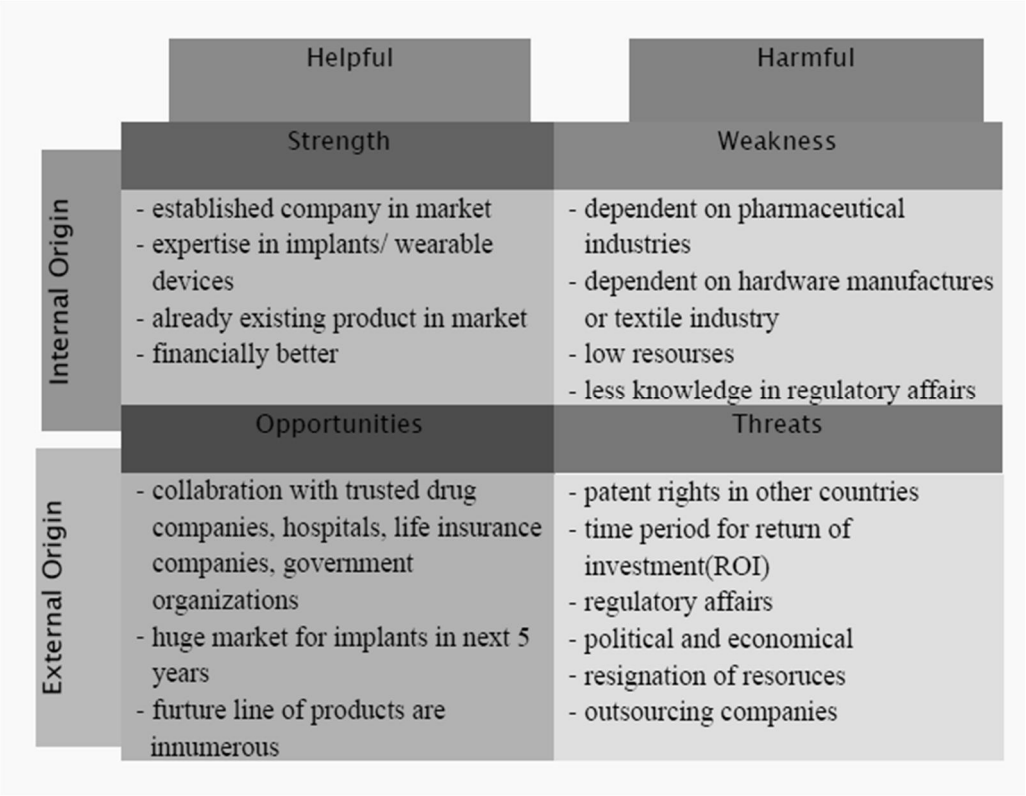

Figure 3.2. *SWOT analysis of Biomedical Wearable and Implantable devices [19].*

PESTEL Analysis

PESTEL stands for Political, Economic, Socio-cultural, Technological, Environmental, and Legal. When introducing a new product in to the macro-environment manufacturers have to consider many factors that affect the decisions, market value-chain, and brand value of the company. Using these factors managers can make appropriate decisions about the product. Table 3.1 highlights factors that have effects on the product and company for Biomedical Wearable and Implantable devices.

3.COMMERCIALISATION

Table 3.1. *PESTEL analysis of Biomedical Wearable and Implantable devices [20].*

Issue	Impact on business
Political	
•pressure on price control •funding to small organizations •regulatory policies for implant and Medical wearable devices •aging population agenda •length of patent protection •infrastructure for eHealth •different policies during different regimes of government tenure •cross-border business trade impact •global forum for regulatory compliance •growing aging population	•loss of revenues to the companies •pressure to deliver the product •loss of business due to cutbacks •cannot introduce the product in developing countries due to high prices and infrastructure •recoup the invested money in less time due to protection of patents •tax deduction
Economic	
•global economic crisis •government sponsored public care •insurance companies •income per capita(individual income) •pressure from buyers for price reduction	•reluctance from patients to spend on expensive treatments •increased pressure from stakeholders to decrease costs which effects revenues of the company due to global crisis •price control by insurance companies and hospitals
Sociocultural	
•acceptance of technology in developing world •acceptance of technology by surgeons and general practitioners •awareness of treatment •increasing aging population •increasing dental treatments, bone cancers, and heath diseases •local ethics	•sales of devices •easy reimbursement for the company
Technological	
•rapid growth of technology •customized products •Supply chain management •well trained personnel's in advanced technologies •competition of the similar, predated and advanced products •infrastructure for eHealth •better tools and techniques	•advanced approach to build customize products •service centres for both patients and doctors •low impact of sales due to competition •integration with all stakeholders using ERP(enterprise resource planning) •new application products
Environmental	
•growing concern to reduce wastes	•ecological business
Legislation	
•bills passed by governments to Medical device companies •death or adverse effects on patients •change in regulatory affairs	•adoption to change in policies •compensation to the patients

Fish-Bone Analysis

Companies can use Fish-Bone analysis(also known as cause and effect analysis) as shown in figure 3.3 when implementing the New Product Development(NPD) to analyse the competence within the internal environment. The Fish-Bone analysis helps in identifying the problem and factors that affect the product development. This way the companies can discover the problems before the start of development process.

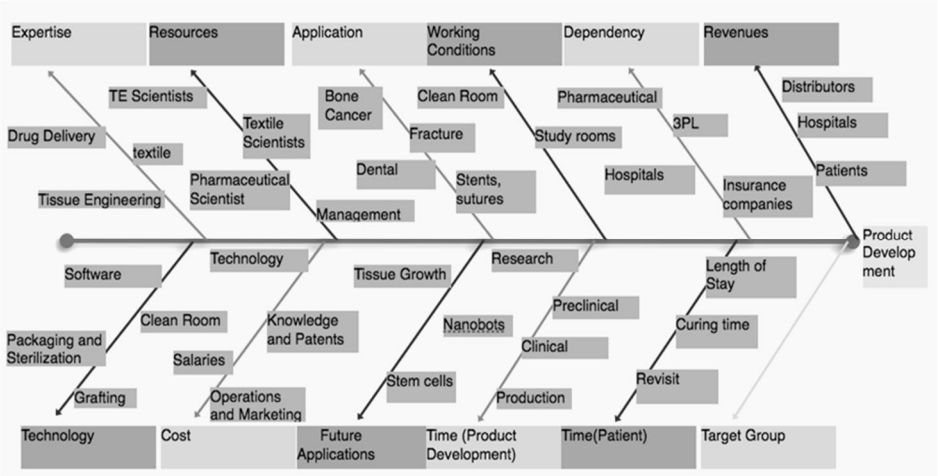

Figure 3.3. *Fish-Bone analysis for analysing internal company competence to start a venture in Biomedical Wearable and Implantable devices [21].*

3.3.4. Drivers and Hurdles

In order to establish a well product commercialisation plan, companies have to run checks on driving forces and hurdles involved in product development and marketing process. The foremost drivers for Medical Implants are the aging population in Europe and rest of the developed countries, demand in cosmetic industry, and increasing dental industry penetration. An increase aging population means a strong market for innovative products that can increase the life expectancy and physical Health. The second driving force is investment by government organizations and other venture capitals in Medical Wearable and Implantable devices. It is estimated that EU grants 20% of the budget for research, education and training, and transport and energy[22]. In the Medical field research, the Seventh research Program(FP7) which is funded by EU supports the following areas: brain research, human development and aging population, major diseases and disorders, severe chronic diseases, and various other applications[23]. Small and Medium-sized Enterprises(SME's) who are looking for funding in Biomedical Wearable and Implantable devices can make proposal to be funded by EU grants.

The other driving force for the marketing of the product is the referral chain involved in making the product available through referral chain system. Companies should identify the stage where the clinicians can use the device for the treatment. It is

also important for the companies to identify the referral system of other existing treatments or products in the current market. Using this method companies can define their own referral chain system during the product development process. A brief referral chain for hip replacement Implants is shown in figure 3.4. Moreover, implementing Operating Room Device Technician(ORDT) from the company to assist the doctors during the transition phase of implanting the device rather physicians depending on sales representative[24], or advertising programs for the benefits of Wearable device can be a huge driving factor for the sales.

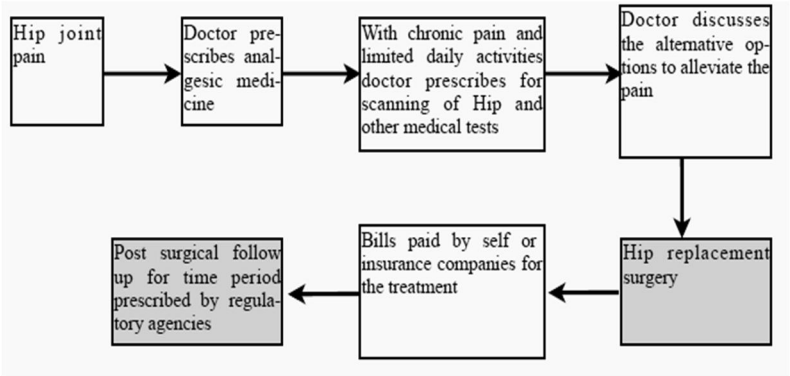

Figure 3.4. *Referral chain of hip replacement Implants.*

Another key concept involved in the research is identification of indication for the Medical device. Indication is defined as the Medical device used for treatment for that particular disease or stage of the referral chain system. Identification of indication is the foremost key element during product development and approval from regulatory agencies. As shown in figure 3.5, doctor prescribes Wearable ECG unit to reduce the Length of Stay(LOS) in hospitals while continuously monitoring the chronic heart pain through wireless transmission of data. The indication here is chronic heart pain with murmurs.

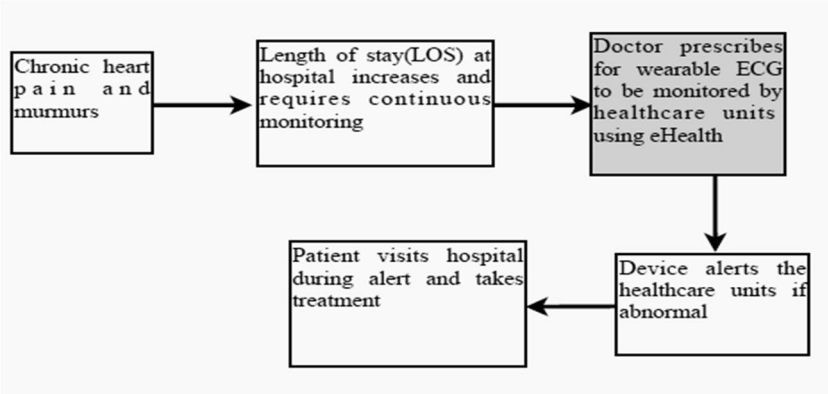

Figure 3.5. *Indication for usage of Wearable ECG device.*

The hurdles in commercialising the Biomedical Wearable and Implantable devices are delay in getting the product approved by regulatory bodies, repetitive submissions of documents, and time period to wait for approval in different phases of product development etc. Other hurdles include the buying power of the product by Healthcare providers. These providers which include Health Maintenance Organisations (HMO's), insurance companies both public and private, and hospitals can dictate the price terms and pressurise the companies to cut-off the actual prices. This may adversely hamper the revenues of the companies for future planning of other product developments.

3.4. Intellectual Property(IP), Patenting, and Licensing

Biomedical device companies have to invest time in finding out if their devices are patentable before product development process as this may hamper sales of product due to competition from generic devices. Having patents gives full rights to commercialise the product in the market with no competition or issuing license to the other companies to manufacture the product to generate huge profits, and maintain the monopoly in the business. IP can be registered as patents, trademarks, copyrights, and trade secrets. IP's are huge profits to the companies as they can be competitive and withhold other companies from entering the market using same technology or they can license the IP to other organizations for profits.

3.4.1. Patenting

There are three types of patents: utility patents, design patents, and plant patents. The Biomedical Wearable and Implantable devices fall under utility patents. Patents are granted under three circumstances i.e., the product should be useful, or the product should be novel, or the product should be non-obvious. Most the Biomedical Wearable and Implantable devices fall under the novelty or non-obvious due to the reasons:

- Medical Implants are novel due to biocompatibility in nature and have different applications to both human and animals
- Medical Wearable devices are non-obvious because they use the existing technology for diagnosis
- Medical Implants are also non-obvious because they are modified versions of predated devices with new indications
- active Medical Implants are also used in transmitting vital information of the patients through wireless technology, for instance Wireless Capsule Endoscopy(WCE)[25]
- Medical Wearable devices might be novel because of the computing algorithms used for the diagnosis and treatment
- Medical Implants are also novel because they use drug delivery system imbibed in the device

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A Medical device can be novel if the product is new of its kind when compared to previous inventions which is also called as prior art[26]. A device is non-obvious if the product has significant development or changes compared to the existing product. Under Biomedical devices, the devices can be classified in terms of composition of matter, application or method of treatment(referral chain system), and device or machine used in production process or diagnosis purpose.

Necessity of Patenting

The patenting gives monopoly to the inventor or any other companies to market the device and it also prevents other companies or inventors to publish similar claims. It also gives protection from infringement of the novelty of the device. In order to achieve the complete right of novelty of the device, inventor or companies have to make sure that no such prior art exists or have been filed for patenting. Since SME's through ventures and funding are involved in innovations they totally relay on patents for profits[27]. It allows the inventor the freedom to practice rights or licensing of the device to other companies. Moreover, Biomedical Wearable and Implantable devices apply more than one technology in the device, the inventors have to buy patents or get license from the patentee's to exclusively commercialise their device. But however, the patentee has certain limitations those include:

- territorial limitations: the patent holds exclusively to the geographical regions filed
- time limitation: the patent holds a time limit of 20years
- limitation in scope: the patent is limited to the indications or application to that particular disease, treatment, or diagnosis

Process of Patent filing

In USA patent is filled under the United States Patent and Trademark Office(USPTO), while in EU the patent is filled under European Patent Office(EPO), which covers all the countries under EU, and also an inventor can patent the invention globally under World Intellectual Property Organization(WIPO) under Patent Cooperation Treaty(PCT) process where 185 countries have been enrolled. Under WIPO the inventor can choose the countries where the patent can be valid and allows complete monopoly for marketing the product[28][29]. The patent filling process is shown in figure 3.6.

3.COMMERCIALISATION

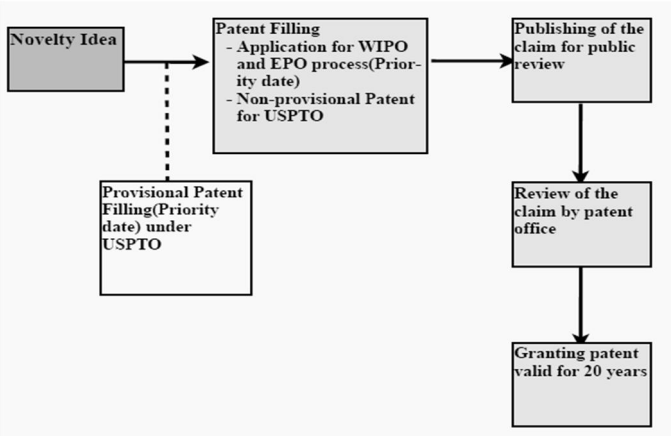

Figure 3.6. *Process for filing a patent.*

Step1: Once a Biomedical Wearable or Implantable device has been invented, to claim the patent the inventor or companies should evaluate if the same novelty exists or if the invention has significant change compared to the existing product.

Step2: The next step is filing a patent (provisional if required more supporting documents in case of USPTO). The date of filing is called as priority date and it is the most significant when multiple person's apply for similar invention in other countries. In case of filing for EPO the patent application should have information supported in English, French, or German.

Step3: The patent office shall publish the claim and in due time if any other inventor claims the same invention then the legal process proceeds.

Step4: The patent office shall award the patent to inventor by reviewing of the invention.

In USA first to invent has proper rights to claim the patent if the inventor has proof of records and documents, while WIPO follows first to file for patenting. If an inventor has already filed a patent in one country, and wants to file in some other country and founds out that someone is claiming the same invention of the device then as per the PCT act the person filed first in any of the WIPO representative countries(priority date) can claim the patent rights, also called as priority rights. In case of USA, patent filed at the time of non-provisional patent is priority date.

The inventors have to make sure that the ideas, basic drawings, thoughts, and other trivial evidence should be recorded as this might be useful in case if more than one claim exists for the similar product. Also, the language used for application of the device should be precise and indicative. Even a slight alteration in the language, an inventor can lose the claim. For Biomedical devices the inventor should name proper indications and usage of the devices. Also, the organisations or inventor should monitor if any infringement of the invention at regular interval of time throughout the life cycle of the product until the patent expires.

For inventors working in universities or research centres, the technology strategic managers in the university or third party assess the commercial potential of the invention. The invention is filed for patent rights and in due process approaches a right investor for the product development, which may take months to years. In case the patentee is from university, the university receives payments or gratuities from the companies which are shared among the inventor, and the departments. In USA, according to Bayh-Dole act the government sponsored inventions are licensed to small businesses.

3.4.2. Licensing

If an invention has to be converted in to commercial business, the inventor or small companies shall require huge capital for product development and production. Rather they prefer to license their patents to other bigger companies for mass production and commercialising the product. The grant of rights can be classified according to exclusivity of rights, territorial or geographic distribution of rights, and field of use. Box 3.1 shows different licensing grant of rights that a company can issue.

Box 3.1. *Classification of grants of rights to produce and sell [17].*

Exclusivity of rights: - *Exclusive license:* only the licensee has rights(not even the inventor) - *Non-exclusive license:* one or more licensee have rights - *Sole license:* Both licensor and licensee can market but licensor cannot grant rights for other licensee's - Partially exclusive license: the licensor can grant the licensee in partial application of the invention
Territorial or geographic distribution of rights: - All inclusive(world-wide) - Conditional or geographically limited
Field of use: - All application, disease, and diagnostic area - Limited application

Trademark also helps to place the Medical devices quick in to the shelves of the distributors or Healthcare units. Smaller companies can exclusively get license from the larger companies to market the Biomedical Wearable or Implantable devices for a specific geographical region for commercialising. Moreover, companies outsourcing for mass production have to share specific aspects of the design and the trade secrets should not be disclosed as it may affect the sales of product.

3.5. New Product Development(NPD)

3.5.1. NPD Planning

In Biomedical Wearable and Implantable devices defining the characteristics at the beginning of product development is significant through research, clinical indications, and identifying customer requirements. Most of the products fail to enter the market due to non-feasibility in the development stages of the device. While large companies have special multidisciplinary teams as shown in figure 3.7 to study and review the stages of product development, contrary to this small companies have to perform extra work in analysing the product characteristics through external sources. It is better to establish a structured process beforehand to move the product concept towards commercialising the product more efficiently and in organized manner. Early planning and designing the processes involved in NPD can:

- reduce the time of approval at regulatory agencies
- increases successful progress of NPD at different stages
- minimise the costs involved
- ensures quality and safety in every stage of NPD an final product

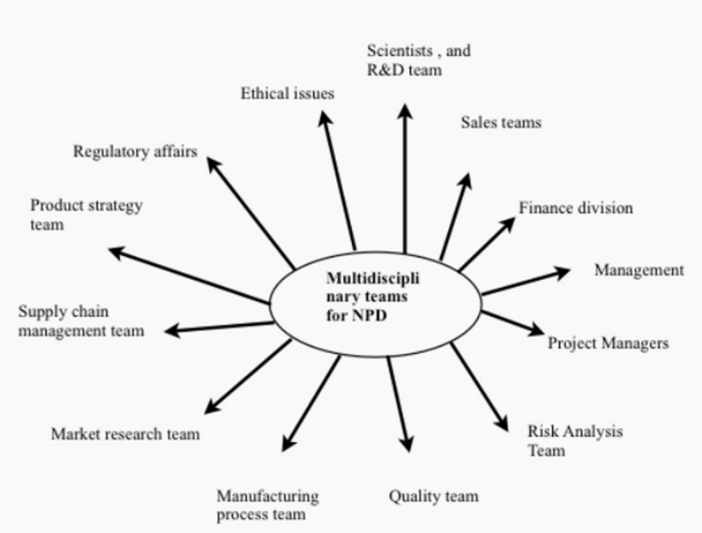

Figure 3.7. *Multidisciplinary teams involved in NPD.*

The NPD process in Medical industry starts with market research by understanding the requirements of the customers and doctor specifications. The marketing team should study the failures and efficacy of the existing products in the market. And based on these details manufacturers have to design and frame the characteristics of the device including the indications. The NPD starts with project proposal to convince the management or investors for funding as shown in figure 3.8.

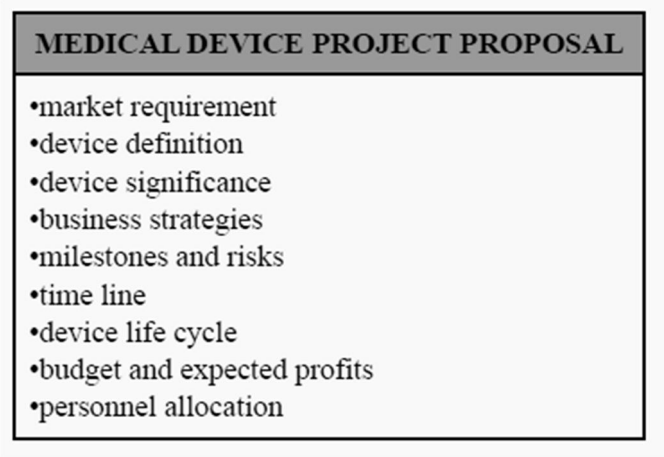

Figure 3.8. *Biomedical device project proposal list.*

Business strategies should be established either in long-term or short-term. Because most of the SME's have very few product lines, building a right strategy and good planning to extend the product line for different applications can add them a value chain in that particular Medical device market. The figure 3.9 shows the new product lines using similar technology but for various other indications. From the figure 3.9, companies have to release a new product before the existing product enters into matured market. Competition and innovation are high in Biomedical device industry, companies have limited time period to earn maximum profits using minimum costs. Further, due to volatile market in Biomedical device industries no single technology can stay long-term in the market; companies have to decisively start NPD for other applications before the existing technology expires as shown in figure 3.9.

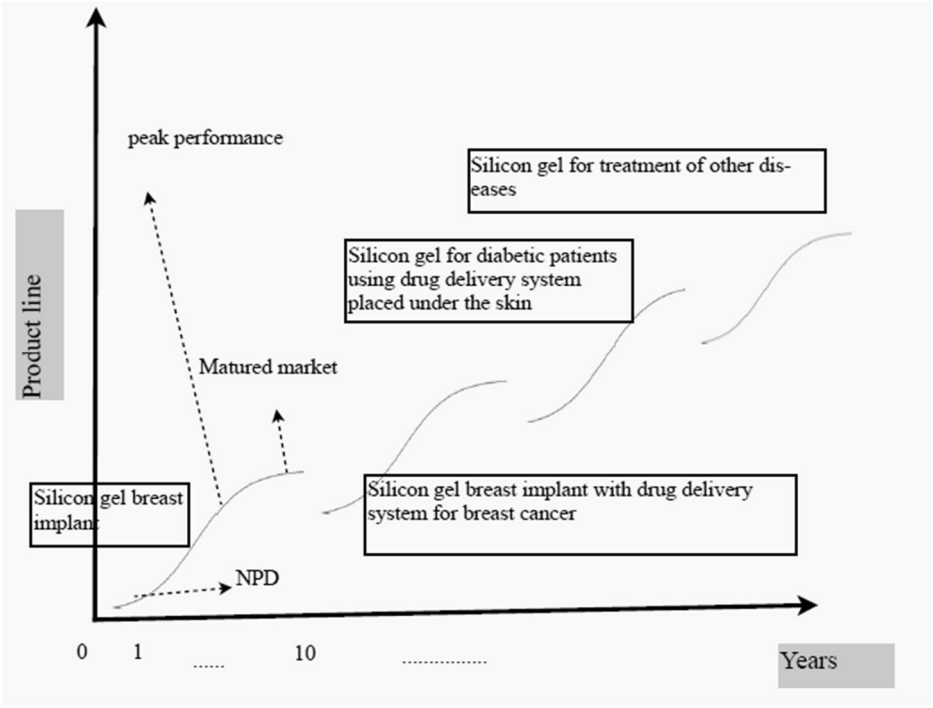

Figure 3.9. *Technology development for line of products to stay alive in the market [30].*

During the product development cycle, early identification of risks during the design phase can make the product successful for clearance by the regulatory agencies. Moreover, listing down of risk factors can be helpful during the design and pre-clinical trial phases. Critical milestones should be determined beforehand as it holds the crucial phase of NPD process. For example in Biomedical Wearable devices, the critical milestones are accuracy and sensitivity of the device to process the signal using the algorithm, despite external noise generated by the patients, and for Biomedical Implantable devices the critical milestone can be biocompatibility and toxicity tests in pre-clinical trials and no contra-indications in clinical trials. Certain risks associated with Biomedical Wearable and Implantable devices are listed in figure 3.10. In case of orthopaedic Implants it is necessary to determine the biocompatibility and wearablity of the device due to physical activity.

Risk factors of medical implants and wearable devices	
Medical Implants	- implants with drug delivery system : ADME(absorption, distribution, metabolism, or excretion) in clinical trials are low - toxicity - biocompatibility - residual risks(post surgery risks) are high - market capture is low - treatment costs are high
Medical Wearable devices	- accuracy and sensitive are not achieved - reliability and repeatability are not achieved - needs lot of licenses(software and hardware) - risk of data security while transmission

Figure 3.10. *Risk factors associated with Biomedical Wearable and Implantable devices.*

3.5.2. Killing the Project

Since Medical devices have high risks and costs involved in development stage it is always better to identify the risks associated beforehand and take decision whether to kill the project or continue the project by reducing the risks. Sometimes companies have to kill the project in the early stages of product development than later stages to reduce the costs incurred. Companies should also consider clinical trials during risk analysis as it costs millions of dollars for clearance during regulatory confrontation. For example, Stryker Orthopaedics has to pay for Rejuvenate and ABG II hip patients[31] because there was risk due to wearing out of metal joints causing and subsequently leading to corrosion. The reason of withdrawal, metal hip Implants caused severe damage to soft tissue and bones, because of which FDA has to halt further manufacturing of hip Implants until proper steps have been taken to re-design[32] and perform further clinical trials. This is complete failure in terms of costs associated to the companies. The failure

of hip implant(Stryker Orthopaedics) was because of inadequate design controls and clinical trials. Failure Mode Effect Analysis(FMEA) and Stage-Gate approach are analysis methods to define whether the companies have to quit the project or reassess the risks and continue the NPD process.

Failure Mode Effect Analysis(FMEA)

FMEA should be conducted early during the product development process during the design phase, preclinical trial phase, clinical trial phase, and production phase[17]. FMEA analysis identifies the most likelihood failure at each phase of the NPD. The main elements of the FMEA analysis are severity levels, occurrence of failure levels, and current controls(detection) of the failures which have a scale of 1 to 10 where 1(easy to detect) means not severe and 10(not easy to detect) means very severe. Once listed down, Risk Priority Number(RPN) is calculated by multiplying severity, occurrence, and detection. The highest RPN should be given preference and control methods should be listed down. Similarly each control methods should be listed down for each failure mode in descending order of RPN[33].

Stage-Gate Approach

Another approach is the Stage-Gate approach which is decision making by evaluating at the end of each stage, where next stage of development is progressed only after the clearance of earlier stage[17]. This approach determines if the project has to be stopped/reassessed or continued to the next stage of NPD. Also combining the FMEA approach at each stage can solve the problems encountered in developing Medical devices. Once evaluated at each stage, a decision is made whether to move on to next stage or needs more assessment of device in the current stage or the project should be killed.

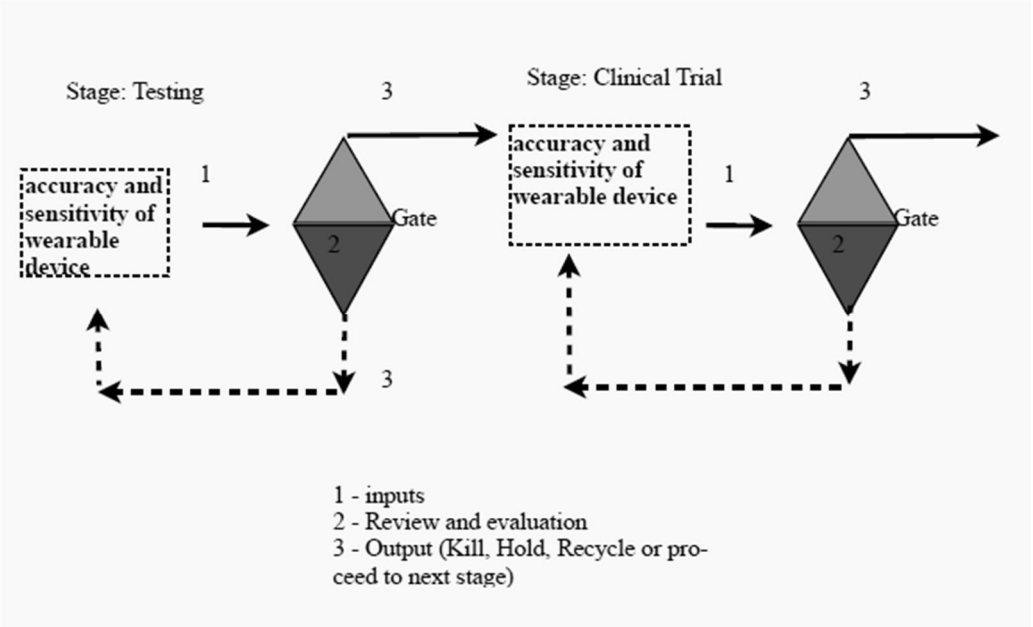

Figure 3.11. *Stage-Gate approach for Biomedical Wearable device[17].*

3.5.3. Product Development Process

Product development process of Biomedical Wearable and Implantable devices are quite different, where the former requires less time for development on contrast the later requires more time from development to commercialisation of the product due to pre-clinical and clinical trials. Biomedical Implants are prone to high expenditure and are heavily subjected to rules and regulations from regulatory bodies when compared to Wearable devices. The expertise levels of developers are high in Biomedical Implants, while Wearable devices require integration from different technologies such as textile technology, mobile technology, electronics, embedded systems, information technology, software systems, hardware systems, and computing algorithms.

Biomedical Implantable devices

Biomedical Implants are diverse in nature and depending on the risk of the Implant; the regulatory bodies dictate the extent of safety and efficacy of the device to be approved for clearance for marketing. Companies have to understand the classification of Medical devices before NPD process. The average time taken for Biomedical Implant to enter the market is about 8 years(as seen in figure 3.13), and an Implant with slight modification from already existing similar device can decrease the costs and time taken to enter the market. During the Biomedical Implant device development process there are many stages involved as shown in figure 3.12. For Biomedical Implantable devices the average time for concept and design is up to 12months, for development and pre-clinical engineering is between 24 to 36 months, for clinical trials it up to 36 months, and for approval process it is between 12 to 24 months. In case of 510(k), in USA, the 510(k) notification review can take 3 to 5 months[34].

In Biomedical Implants most of the design is based on the requirements of the customers or market driven specifications. Hence at the time of designing the device it is important to analyse the customer needs or market driven specification, endpoints, and indications. Before designing an Implant, companies have to spend time in analysing the success and failures of already existing devices as this helps the design engineers to prioritise the design where there is huge risk of failure. For example, around 10000 people who have used ASR Implants have filed for lawsuit as the design of Johnson & Johnson hip Implants went wrong and nearly 40% of ASR hip Implants are estimated to fail within 5 years of time prematurely as the hip Implant life cycle was estimated to be 15 years[35]. During the product development phase, companies have to consider risk factors, manufacturing process, regulatory laws, maintenance of the records, and adhering to standards (ISO, ASME in USA, CEN in Europe etc.). Also, companies have to lock the design phase before the clinical trials as this may lead to unambiguity in development process. Companies can also expect some capital returns on selling their prod-

ucts to animal care units once the safety and efficacy in animal subjects are tested in pre-clinical trials.

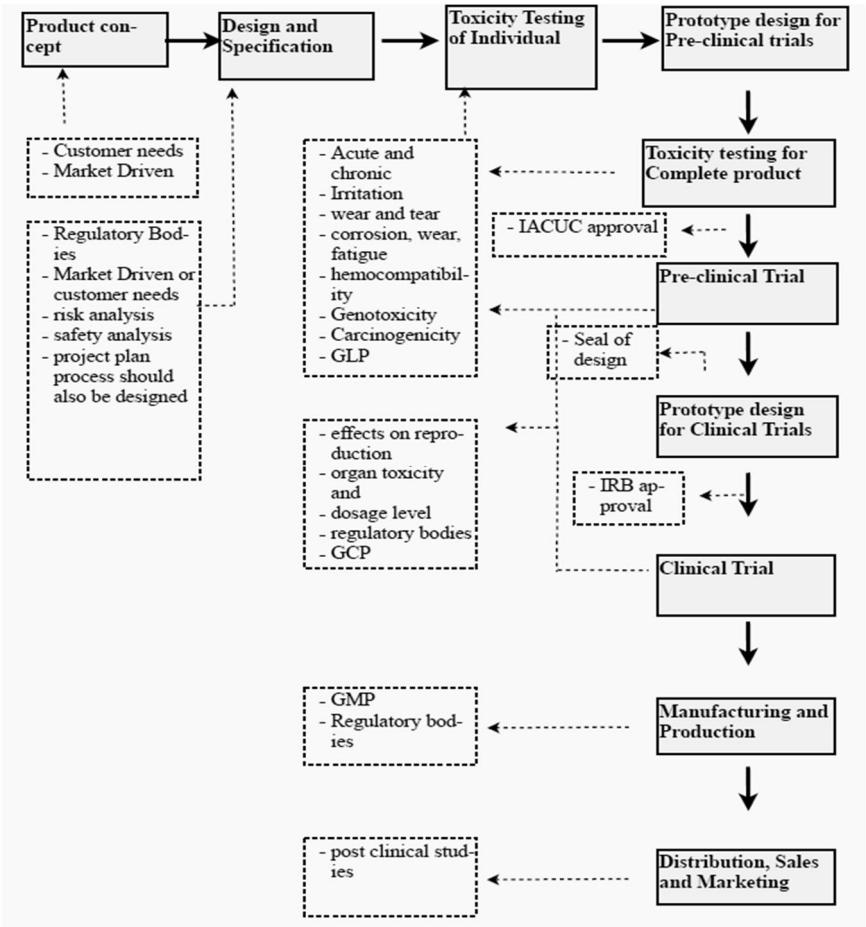

Figure 3.12. *Biomedical Implant development process.*

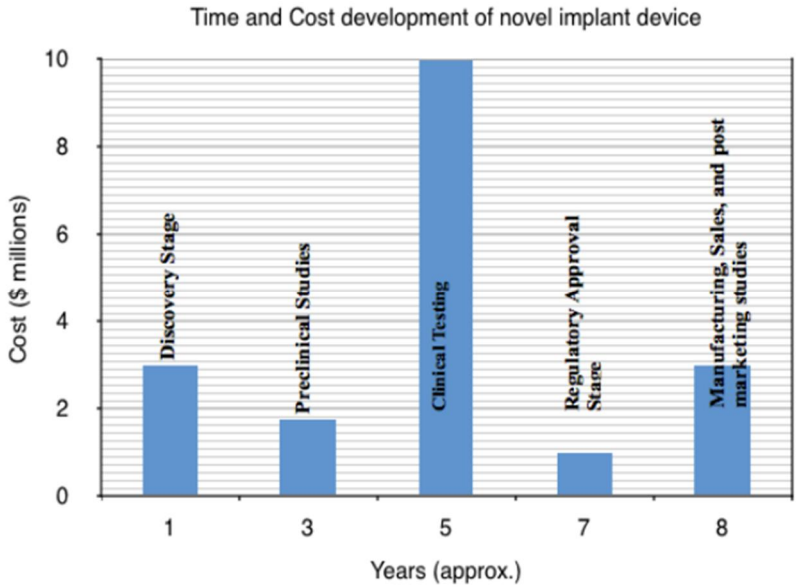

Figure 3.13. *Time and cost development of Biomedical Implantable devices[17].*

Biomedical Wearable Devices

The development process for Biomedical Wearable devices have short span because most of these devices are used for diagnostic purpose, and these devices need not go for pre-clinical trials if unless stated by regulatory bodies. The most important phases of Wearable devices are design phase and clinical trials to determine if the Wearable device is accurate and the results are repeatable. The time period for development of Wearable devices are usually between 3 to 8 years(same as in-vitro devices[17]) and cost associated in phases of product development varies depending on the complexity of the device and computing algorithms used. Drug companies have already been adopting(co-developing) of diagnostic devices for the therapeutic purpose(pairing of diagnostics and drugs)[36]. In future, drug companies may adopt Wearable devices for therapeutic treatment and because of this the complexity of product development can change leading to new regulatory laws.

Other aspects to consider while developing Biomedical Wearable devices are:

- ergonomics of use
- wearablity of the device due to exposure to environment
- information handling and processing
- integration of the device data with healthcare unit software systems
- secure data transmission
- power consumption

3.5.4. Ethical Requirements

During the preclinical and clinical trials, all the Biomedical Wearable and Implantable devices should follow certain ethical requirements which are mandatory for approval of the device. The ethical boards committee's include *Institutional Animal Care and Use Committee(IACUC)* and *Institutional Review Board(IRB)*.

The purpose of IACUC is to ensure that the animals used for laboratory testing are properly taken care. The committee shall review the physical wellness of the animals; only on approval from the IACUC committee the pre-clinical trials should be started. Some of the protocols include:

- minimisation of pain and distress caused during animal testing
- proper care of both physical and physiological states of animals
- protocols should ensure the decrease in number of animals for testing

Whilst IRB reviews the clinical investigation protocols, and grant permission for the clinical trials on human subjects. IRB in regular intervals interacts with human subjects, to ensure the rights of human subjects are protected, and also make sure that the safe

levels of dosages are used on human subjects. More information about roles of IRB and IACUC is given in GxP(Chapter 5).

3.5.5. Indications and End Points

Indications and end points play a vital role for clearance of the product by regulatory agencies. Indication is defined as the disease for which the product is approved. There might be several indications for the single device but companies have to separately get approval for each indication and device should be marketed as per the approved label. End points are the final reports or statistics during the clinical trials due to usage of the device on human subjects to estimate safety and efficacy. In clinical end points there might be primary, secondary or composite end points. The primary end points are used to convince the authorities that the device is safe and better than the existing treatment methods[37]. It is important to design Biomedical Wearable or Implantable devices keeping the end points, indications, and customer needs during the NPD process.

Box 3.2. *End points for breast Implants and Wearable ECG device.*

Breast Implants(With anti-cancer drugs)

Primary End point:
- reoccurrence of cancer after the removal of cancer tissue is <5% with breast Implants with anti-cancer drug when compared to women with breast implants with no anti-cancer drugs (40% in detection)
- better shape to the body
- life cycle of implant is increased by 2 years compared to other existing implant

Secondary End point:
- decrease in cost for treatment
- reduced doctor visit

Wearable ECG device in synchronisation with eHealth systems

Primary End point:
- early detection of heart disease compared to standard treatment
- accuracy and sensitivity is greater

Secondary End point:
- reduced hospital visit
- data in continuously transmitted
- security is established

3.6. Regulatory Compliance Planning

Unlike free flow of electronic gadgets into the market through lenient regulatory laws, every Medical device has to strictly adapt to the regulatory compliance pertaining to the country of sales. The regulatory authorities are catalysts who ensure the final product in market is safe and shows performance as stated by the manufacturer. A Medical device manufacturer before starting the product development, he/she has to define the Class of the device according to regulatory compliance. Unable to classify the Medical device at the start of product development process can lead to killing the project, can make huge losses to the company, or increase the development process time. Regulatory bodies

acting on behalf of the countries have classified the Medical device depending upon the risks and application associated with the device. This section shall give an outline of classification of Biomedical Wearable and Implantable devices, and approval process with regards to FDA and EU regulatory affairs.

3.6.1. FDA Regulatory Affairs

FDA classifies Medical devices under Class I, Class II, and Class III devices. Most of the Medical Implantable devices fall under category of Class II and Class III. FDA usage term for Biomedical Wearable devices is MDDS which was reclassified to Class I device in 2011 from Class III devices. Manufactures of MDDS devices should adhere to requirements of Class I device and are not required for PMA approval. The MDDS should adapt the QSR 820 for good practices[38]. A manufacturer can sell a Biomedical Implantable device in USA, under 510(k) or PMA approval from FDA. For 510(k) approval the manufacturer should demonstrate a substantial equivalent device in the market that has been marketed before 1976 or a predicate device which was approved through 510(k) process. If the manufacturer could not find the predicate device, but can prove that the device has fewer risks and not required to for the prolonged PMA clinical trials process, the manufacturer can get approval through "de novo 510(k)" process. Though 510(k) process is shorter on comparison to PMA process, sometimes clinical physicians or insurance companies or buyers of the device require a strong clinical evidence of the device to sponsor the treatment. Hence, manufacturers of the Implantable device approved through 510(k) should also perform additional clinical trials to convince third parties and increase in sales of the device. Manufacturers should make sure that they schedule meetings with FDA at regular time basis during product development. It is mandatory to schedule meetings before the start of pre-clinical and clinical trials. During the scheduled meetings the manufacturer has to submit all the required quality documents, records, and protocols followed during the product development phase of the device. Manufacturers of Biomedical Implant should adapt *"21 CFR Part 820 quality system regulations(QSR)"* as per the quality requirements of Medical devices. While, quality requirements for combinational products has been discussed in GxP (Chapter 5).

3.6.2. EU Regulatory Affairs

EU system classifies Medical devices under Class I, Class IIa, Class IIb, and Class III. The Biomedical Wearable and Implantable devices fall under the category Class IIa, Class IIb, or Class III. Dental Implants and Wearable devices come under Class IIa devices. Classification of device is important for the manufacturer as it defines the conformity assessment route through annexes of the Medical device directives. Any company marketing their device in EU should have CE trademark. If the manufacturer is outside the EU, it is his/her responsibility to appoint an authorised representative who can handle regulatory issues. A CE mark is given to the Medical device only after going

through the conformity assessment done by Notified Bodies (NB) that are hired by the manufacturers. Manufactures should adhere to the guidelines of Medical device directives for conformity assessment of Medical devices as shown box 3.3. Many companies in EU adapt ISO 13485 standards for Quality Management System(QMS). For CE marking, manufacturers of Class IIa, Class IIb, and Class III have to get certification from NB which includes:

- EC Type Examination Certificate (issued during the design phase)
- EC Design Examination Certificate (issued covering design and production phase)
- EC Certificate Full Quality Assurance System
- EC Certificate Production Quality Assurance
- EC Certificate Product Quality Assurance
- Certificate of Conformity (after product has been verified) [39]

For Biomedical Implantable devices having medicinal products, the NB shall review the importance of the substance governing the application of the device and shall take a scientific opinion from designated European Medicinal Agency(EMEA) authorities. EMEA shall review the dosage levels, any modification to the actual substance, manufacturing process, and benefit/risk factor. Only once approved from the EMEA of the use of medicinal product and other quality requirements the NB can give the CE marking.

Box 3.3. *Medical device directive as per EU system.*

- 93/42/EEC on Medical devices (MDD)
- 98/79/EC on in vitro diagnostic Medical devices (IVDD)
- 90/385/EEC on active implantable Medical devices (AIMDD)
- 2003/32/EC for Medical devices utilizing tissues or derivatives originating from animals susceptible for TSE

3.7. Project Management

Project management is important task in controlling the various phases during NPD process. Project managers have to formulate timelines for every phase and assign personnel's, and are responsible that the tasks are being completed according to the planned schedules. The most modern methods used for project management is Gantt chart and Critical Path Method(CPM). The Gnatt chart allows calculating the timeline of the project with every phase of the project, when to start and when to move on with next phase with every task being allocated to the responsible team member. CPM is used for identification of specific critical tasks that has effects on the timeline of the project. In larger organisations there are experienced mangers working on each phase of

the project while in smaller organisations individuals have to take more responsibility in completing the tasks. Since every Medical product development is allotted with limited budgets, managers have to formulate both success and failure scenarios by calculating the risks involved during NPD process.[17]

3.8. Outsourcing the Product Development

Outsourcing of Biomedical Wearable and Implantable devices can be done at various stages of product development:

- *Pre-clinical trials and Clinical trials:* for animal testing the companies have to inform the regulatory bodies the address of the animal testing laboratories and human trial care centres such as Clinical Research Organisation(CRO). While testing the device, laboratories have to adhere to the compliance of the concerned regulatory bodies. The regulatory bodies, IACUC, and IRB shall audit the laboratory and then approve the protocols for the trials. Outsourcing clinical trials predominately reduces time in recruiting the human subjects and makes the product development process quicker due to expertise.
- *Manufacturing process:* SME's who have less expertise in manufacturing a product in accordance to guidelines of regulatory bodies or problems of capital to establish a manufacturing unit can outsource the device who already are in compliance with regulatory agencies. Sometimes larger companies may outsource the production of the Medical devices in other geographic regions. But there are certain risks of IP associated for outsourcing the manufacturing of the product. A company whose device is novel, highly complex, and expensive, it is better to outsource only certain parts of the device as know-how can be disseminated to other industry players through contractors. Contrary, if the risk of IP of the device is low, then it is better idea to outsource the manufacturing of the device. Personnel's from the company should be appointed to communicate with the outsource companies to monitor the process and make sure that the production process is adhered to regulatory compliance. Figure 3.14 is the matrix that allows mangers to make decision of outsourcing the production process.

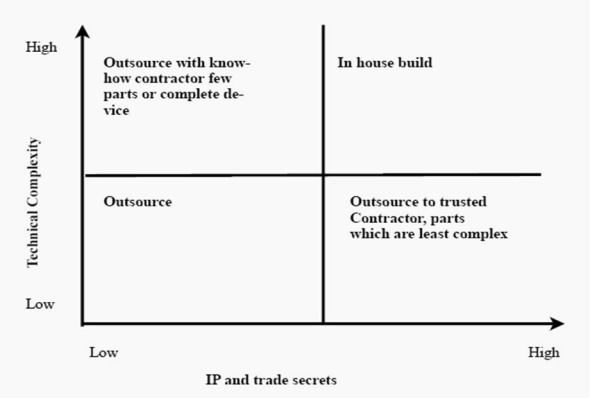

Figure 3.14. *Outsource decision making matrix [17].*

3.9. Manufacturing

The manufacturing of Biomedical Wearable and Implantable devices is transition phase from NPD to large scale production after undergoing pre-clinical trials, clinical trials, and approval from regulatory bodies for production in large scale. This means that the device is safe to be used on humans and ready for the production in large scale. Sometimes the device that has been developed in laboratories under small R&D studies may not be feasible at the time of technology transfer from laboratory to production because of different set of parameters and controls in laboratory and production process. The laboratories look for scientific evidence, innovation, reliability, and predictability while the production process involves reduction of defection per thousand devices made, reproducibility of the process, adhering to Good Manufacturing Practices(GMP), and other international standards. Technology transfer from laboratory to production control can be failure because:

- lack of capital for mass production
- cultural differences between R&D and operation personnel's
- lack of communication between R&D and operation personnel's
- lack of ownership between R&D and operation personnel's
- market is very bleak for the device or better product is already available
- lack of proper Supply Chain Management(SCM)
- device not feasible for mass production

During NPD process, companies have to involve multi-disciplinary teams and start planning for production control. Moreover, the design of the device should be sealed completely before entering the clinical trials as shown in figure 3.12. For better technology transfer, companies should start preparing documentation, look for distributors, involve R&D and operation personnel's together, marketing should be done rigorously for profits in future, and search for right suppliers and sub-contractors etc.

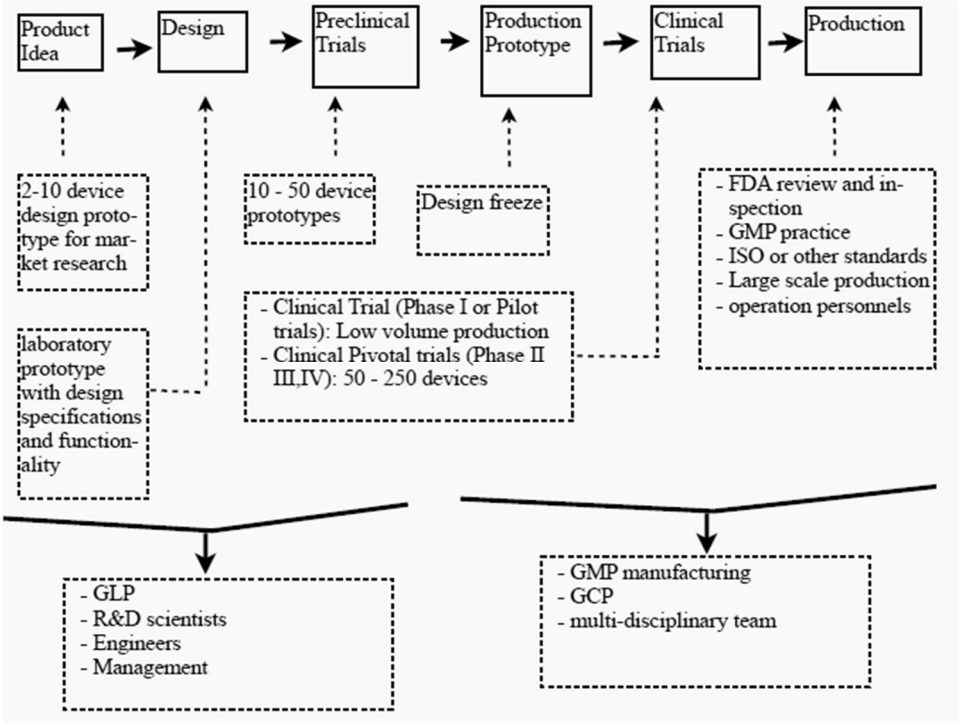

Figure 3.15. *Manufacturing scale-up of Biomedical Implants and Wearable Devices.*

For scaling up the production units, companies can decided if the production should be down in house or to be contracted. If contracted, companies have to re-consider some critical factors as explained in figure 3.14. Many SME's approach Contract Manufacturing Organisations(CMO's) until clinical trials, once approval is obtained these companies build their own production process or can decide in licensing the manufacturing process to CMO's. Companies have to make a decision in manufacturing process either in-house build or giving to contractors depending on the market size, company strategies, and company competence. Companies have to establish Standard Operating Procedures(SOP's) which are mandatory for production and process control as per regulatory compliance and international standards. Suppliers and contractors should be selected based on their credentials in compliance with the regulatory agencies. The suppliers have to strictly adopt the design specifications as agreed mutually between the manufacturer and supplier. Companies have to audit the supplier/contractor manufacturing units for quality and check if they are adhering to regulatory standards. Companies should reject the suppliers/contractors if they have found to supply low quality materials, or any deviation from the manufacturer's requirements.

3.9.1. Demand-based Manufacturing

Demand-based manufacturing is the term used for designing a Biomedical Wearable or Implantable device to the specifications of the clinicians or surgeons depending upon the condition and requirement of the patient. Most of the Medical companies still manufacture the product traditionally using standard sizes, for instance orthopaedic and den-

tal Implants; due to advance in technology many niche companies are coming up new ways to meet the demand of customer's specifications. Due to standard sizes, surgeons have to alter the Implantable devices in the body due to which the life cycle of the product can decrease. Most of the younger patients who are undergoing orthopaedic Implants tend to have limited physical activity due to the limitations in the Implants. Considering these factors, manufacturers have to develop and design according to the anatomical structure of these patients. In case of Wearable devices, computing algorithms and design of the device can be manufactured as per the patient's parameters and condition of disease. The term generally used for demand-based manufacturing is "Addictive manufacturing". Andy Christensen, President and Owner, Medical Modelling Inc states that CAGR for orthopaedic Implants grows at 13.5% between the periods 2012 to 2017 and the market value for such products shall raise to $3.5 billion in 2017[40]. Moreover, patients are allergic to certain substance in the Implants; using addictive manufacturing the materials suited for the patient can be applicable. Figure 3.15 outlines the basic approach of demand-based manufacturing. Advantages in using demand-based manufacturing are [41]:

- design of Implant is according to specifications as per anatomy and pathology
- disappearance of stress shielding effect(bone requires constant stress or load for proper bone remodelling, in case of standard orthopaedic Implants the stress is absorbed by the hard element Implants which has side-effect on bone remodelling, where the bone material is reabsorbed into the body making the bone more porous and not holding the implant[42]
- avoiding carpentry job by the orthopaedic surgeons for manual adjustment
- ability to design complex shapes
- minimizing inventory which in turn reduces obsolete devices
- manufacture what is required [43]

Whilst there are huge benefits for this kind of niche marketing, there are challenges to be met both from the manufacturers, the clinical healthcare providers, and the regulatory authorities which are:

- improvement in technology for 3D imaging and designing process
- infrastructure across the stakeholders
- up-link and down-link communication between the parties
- pricing of the Biomedical device
- competitive standard Biomedical devices with cheaper prices
- JIT(just in time) approach and SCM

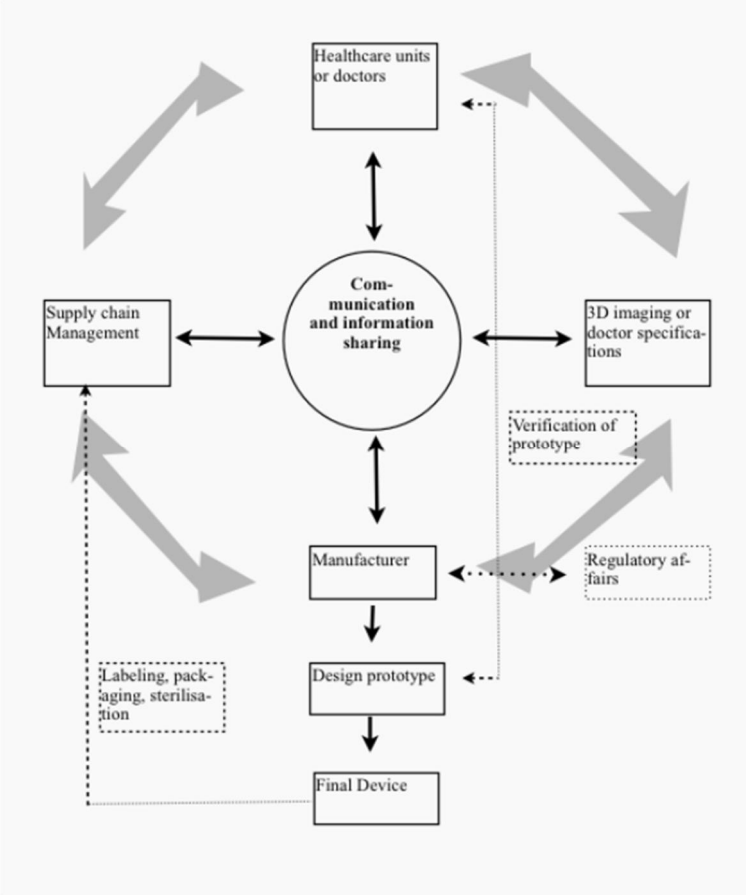

Figure 3.15. *Outline of demand-based manufacturing.*

3.10. Reimbursement, Sales, and Distribution

Companies planning to market the device should also consider the Healthcare providers and payers. Healthcare providers and payers play an important role for the reimbursement of device and increase in sales. Also Gross Domestic Product(GDP) and government spending on Healthcare system have impacts in placing the device in market for treatment.

In USA, the Healthcare system is complex and involves:

- Medicare System(>65years)
- Medicaid System(low income people)
- Private insurers(<65years)
- Self-Pay(for non-insurers)
- Hospitals and Healthcare providers
- Distributors, Wholesalers

If the Medical device has to enter the market in USA, companies have to influence the insurance companies to pay for treatment costs, and Healthcare providers to enrol

their device for treatment by the surgeons or physicians. Sometimes these third parties may influence the cost price of the device, generating lesser profits to the companies. Companies can also influence the coverage decision to these third parties by proper product development planning, education to payers, publishing the articles related to the product, co-operation between manufacturers and distributors or local wholesalers etc.

The three main components for reimbursement are coverage, coding, and payment. In coverage phase, the insurance companies who are going to pay for the treatment require proof on the clinical evaluation of the device which is more effective than existing treatment. The treatment should be listed within the insurance company's catalogue if the reimbursement has to be done and coverage decision has to be made. Another component is entering the treatment in to International Classification of Disease system(ICD-9 code) and Healthcare Common Procedure Coding System(HCPCS II) or Current Procedural Terminology(CPT) as these codes identify the specific treatment carried out by physicians for the indications. Many hospitals adopt this coding system to capture the diagnosis or treatment for administrative transactions and claim the insurance companies. The Biomedical Wearable or Implantable device treatment procedures have to be enrolled into the existing codes for market potential of the device. If the procedure is not described into the existing codes then lobbying with certain physician groups can help to get Not Otherwise Classified(NOC) for application of the device in the treatment for the indication. But having NOC for the device, the manufacturer and organisation providing the Healthcare have to work out for billing each time the treatment has been done which may increase reimbursement time to the manufacturer. Hence, not having CPT code leads to low sales of the Medical device which may hamper the development process of other product lines. Manufacturers have to decisively establish strategies at the time of clinical trials with wholesalers, distributors, insurance companies, and Healthcare providers for reimbursement. For instance, orthopaedic companies spend $37 on every $100 they earn on sales and marketing [44].

In Finland, companies wanting to sell their products must have CE marking, and also register at Valvira. Valvira is the national supervisory authority for welfare and health, which can have influence in promoting the sales of device[45]. In England, National Health Service(NHS) has influence in procurement of the Medical devices and other Healthcare services by evaluation of the technology[46]. Also, local wholesalers can play a major role in promoting the Medical device in private Healthcare providers.

3.11. Unique Device Identification(UDI)

UDI consists of Device Information(DI) such as company address and product identity, and Product Information(PI) such as shelf life, serial or lot number, manufacturing date, single use, or sterilised product. The nomenclature used for coding of the device is Global Medical Device Nomenclature(GMDN). As defined in ISO 15225 standards,

GMDN has three level structures: device category, generic device group, and device type. The ambition of GMDN is to provide single naming system to furnish the authorities, Healthcare units, manufacturers, suppliers, and other bodies for the patient safety[47]. UDI should be created and maintained by the manufacturer for his/her Medical device, and provide all the necessary information pertaining to the device. The purpose of UDI for global commercialising of the Medical devices is to facilitate.

- traceability of the device
- to identify the device for distribution and use
- reducing Medical errors
- to capture the statistics of Medical devices[48]

The main challenge of UDI is to integrate all the regulatory authorities and provide unambiguous identity to the device through Unique Device Identification Database(UDID). Though UDI is still under proposal format, implementation of UDI can help the Medical device industries to easily enter the market through globalisation of supply chain, which requires support from politics and other stakeholders. The communication between different entities in UDI approach is shown in figure 3.16.

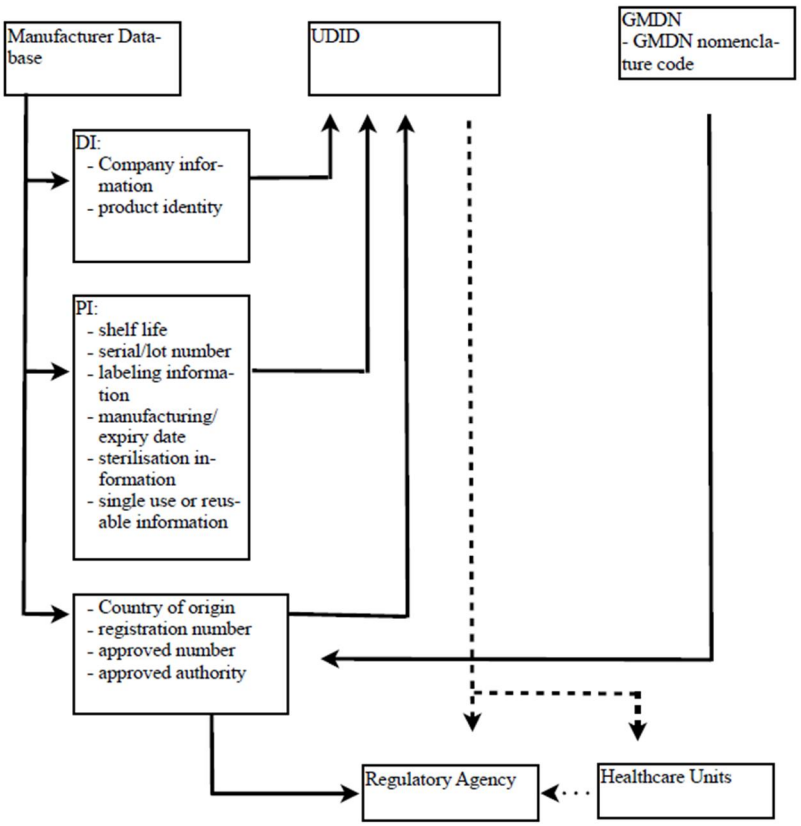

Figure 3.16. *Outline of UDI approach [49n].*

4. QUALITY REQUIRMENTS

Quality requirements are mandatory for every Medical device in order to improve the efficiency and effectiveness, and deliver the product that meets the expectations of the customers. In current thesis, the quality requirements combined from FDA, EU MDD, ISO, and IMDRF quality management systems for Biomedical Wearable and Implantable devices have been discussed. ISO 13485 standards should be adopted by manufactures of Medical device as indicated in QMS for design and production process of Medical devices.

4.1. Documents

There are three documents to be established by the manufacturer during product development stages:

- Design History File(DHF): The DHF contains all the records pertaining to design of the final product such as user needs, design input, design process, design output etc.
- Device Master Record(DHF): The DMR contains all the design methods, specification, production process specifications, SOP's, packaging, labelling, sterilisation, etc.
- Device History Record(DHR): The DHR is used at the time of production of the device, to check if each batch or unit of the device is in accordance with DMR.

4.1.1. Design Control Documents

Design control is the quality system that covers the life cycle of the product during product development stage, preclinical trials, clinical trials, and post-market stage. The design controls help the mangers and product developers for more visibility of the product at all stages of development process. The design control includes design inputs, design outputs, design validation, manufacturing process, changes to existing device, labelling, sterilisation methods etc.

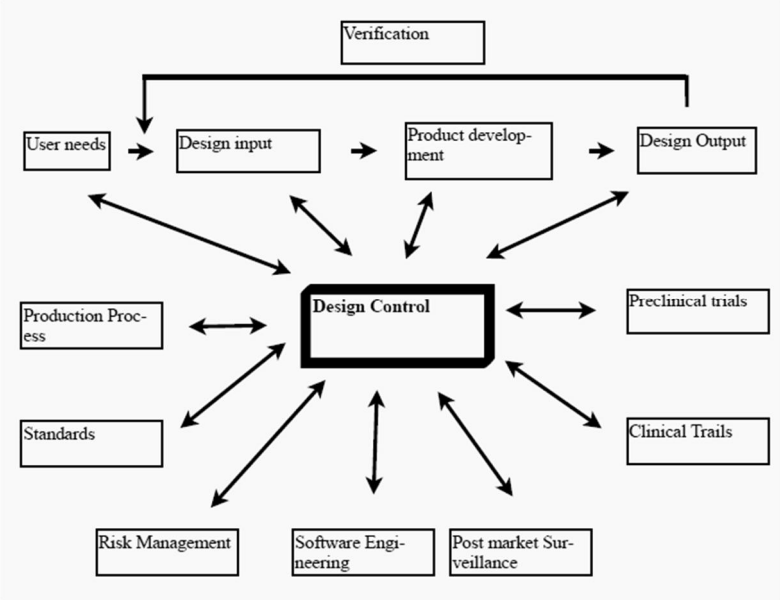

Figure 4.1. *Design control and quality systems outline.*

In the design control document the manufacturer should determine the design and development stages of the device, including the design transfer activities, and should ensure clear assignment of individual responsible. The design inputs should address the performances, safety, regulatory requirements, literature review, and associated risks. The design output should be in accordance to design inputs, should have information of purchasing, processing, production, servicing, and safety of the device. The design validation should address that the device meets the requirements, and identify any further problems to be solved[50]. DHF should show that the design of the device was developed in accordance to the planned stages of product development[51].

4.1.2. Device Master Record(DMR)

For each model of the device the DMR file should have the following list of documents:

- Device Specifications(DS)
- Manufacturing Process specifications(MP)
- Quality Assurance procedures and specifications(QA)
- Packaging and Labelling specifications(PL)
- Installation, Maintenance, and Servicing specifications(IMS) [52][53]

A more comprehensive requirement is shown in Appendix1.

4.1.3. Device History Record(DHR)

The manufacturer of the device for the batch or unit shall ensure that the following information should be included in DHR:

- date of manufacturing
- number of units manufactured

- number of units released for distribution purpose
- acceptance record showing that the device in production is under strict compliance as shown in DMR
- traceability/identification/control number
- labelling and sterilisation methods[54]

4.2. Labelling

The intention of labelling is to communicate the safety, operational details, and traceability of the device. Any printed or graphical matter within the packaging of device should address the application and identification of the device[55]. For a device, country specific labelling should be adhered to its format along with the language which is understood by user population, for example USA labelling should have FDA approved mark while EU should have CE mark on the device for marketing.[56]

4.2.1. Biomedical Implants

The Biomedical Implants labelling should have the particular details on the package of the device[55]:

- the device should have the company's name, address of manufacturer, and its intended purpose. In case if the device is being imported the address of the importer or in case if the device is manufactured in the importing country then the details of authorised representative in the marketing country.
- indication for which the device can be used
- sufficient information for the user to identify the device
- lot or batch number, serial number, or control number for traceability of the device
- indication of manufacturing date, usable date, and expiry date represented in terms of year and month
- storage or handling conditions of the package
- warning or precautions of the device
- the intended application of the device and undesirable hazards, risks, or side-effects
- information related to verification for safety and operation of the device after installation
- information detailing the treatment of the device before application of device, e.g., sterilisation, calibration, tailoring of the Implant, final assembly with accessory components
- indication of sterility of the Implant, and in case during damage of the package extra information concerning the sterilisation methods to be used or contact information
- indication of single-use of device
- if addictive manufacturing devices, the indications should exclusively state the single individual and prescription details

- indication of risks associated with the Implants
- information regarding the risks associated with reciprocal interference such as electrical interference from electro-surgical devices or magnetic interference from imaging techniques
- precautions at the event of change of function of Implants
- precautions when exposed to environmental conditions such as magnetic field, electrical field, mechanical pressure etc.
- information of medicinal products used along the Implants(combinational device)
- information of any medicinal products to administer along the Implant at the time of surgery
- precautions for the disposal of the Implants
- degree of accuracy for installation of the Implants
- information concerning the handling of the Implants, such as selecting suitable devices or corresponding accessories or software
- information concerning the trained personnel to install the Implant or any training required for installation
- contact information of company authority during the adverse event occurrence

4.2.2. Biomedical Wearable Devices

The Biomedical Wearable devices other than stated in the section 3.2.1 should have additional details as mentioned below[55]:

- intended use of the device
- procedures for installation
- operation principles
- performance indications and specifications
- instructions for operation of the device
- calibration procedures
- manual to change any external components
- precautions for operations
- limitations for the use of device
- hazards and risks related to the device
- service information
- maintenance information
- clinical evaluations for the clinicians

4.2.3. Investigational Device Exemption(IDE)

- clinical protocol document which has details of sponsor, clinical investigators, monitoring authorities, and procedures

- if the Implant is used for IDE(investigational device exemption), it should indicate for clinical purpose only. Example "*CAUTION: Investigational Device. Limited by Federal (or United States) law to investigational use*"
- information concerning contra-indications, hazards, risks, adverse effects, warnings and precautions
- in case for preclinical trials on animal use "*CAUTION - Device for investigational use in laboratory animals or other tests that do not involve human subjects*" [55]

4.3. Packaging and Sterilisation

For packaging and sterilisation of Biomedical devices ISO proposes relevant standards, ISO 11607-1 "Requirements for materials, sterile barrier systems and packaging systems" and ISO 11607-2 "Validation requirements". The objective of packaging and sterilisation is to have physical protection, and present the Medical device in an aseptic manner until the use. Depending upon the state of the Medical device, single or multiple packaging can be used. For proper packaging and sealing process Installation Qualification(IQ), Operational Qualification(OQ), and Performance Qualification(PQ) validating methods should be used. The proper use of packaging and sterilisation methods should be justified pertaining to the Medical device such that physical and chemical properties do not change beyond the threshold limits.

Design development of packaging should be documented and consider many factors such as customer requirements, sensitivity of the product to external environment, labelling of the package, sterilisation compatibility, distribution, handling, and storage environments. Documents related to packaging system must be retained for a time period depending on the competent authorities, expiry date of the device, and for traceability of the device. The SOP's used for validation methods, process control methods, and other quality system methods must be reliable and should be signed by the concerned authority.

For packaging material the following characteristics should be considered to meet minimum standard: temperature range, cleanliness, bio-burden, electrostatic conductivity, pressure range, humidity range, and exposure to sunlight. The materials used for packaging must be non-leaching, odourless, and impermeable to microorganisms, and the materials should not have adverse effects on the Medical devices.

The evaluation of sterilisation effects as listed below should be done[57][58][59]:

- physical and chemical properties
- compatibility in regards to sealing process
- shelf-life limitations before and after sterilisation
- microbial barrier

- toxicity and biocompatibility

According to EU Medical directives for active Implantable devices, the devices should be packed using non-reusable material and should be sterile at the time of marketing the device. The sterile pack should have the method of sterilisation method used along with other information details while the sales packaging should contain as said in section 4.2.1.

4.4. Preclinical Studies

Preclinical studies are determining factor for the safe application of the Biomedical Implants on human subjects in clinical trials and to determine the risks associated with the Implants. Preclinical studies include study of Biomedical Implants under in-vitro, in-vivo, and ex-vivo environment. ISO 10993 standard is associated to determine the safety and efficacy of any Biomedical device. There are overall 20 parts under ISO 10993 standard; where part 1 is associated with in-vitro studies while part 6 is about local effects after the implantation is done. Though other parts(as shown in appendix 3) of ISO 10993 include various studies to be performed about the risks of Medical devices, in this chapter the current thesis shall discuss about ISO 10993-1 and ISO 10993-6 briefly. Figure 4.2 indicates brief outline of preclinical trials.

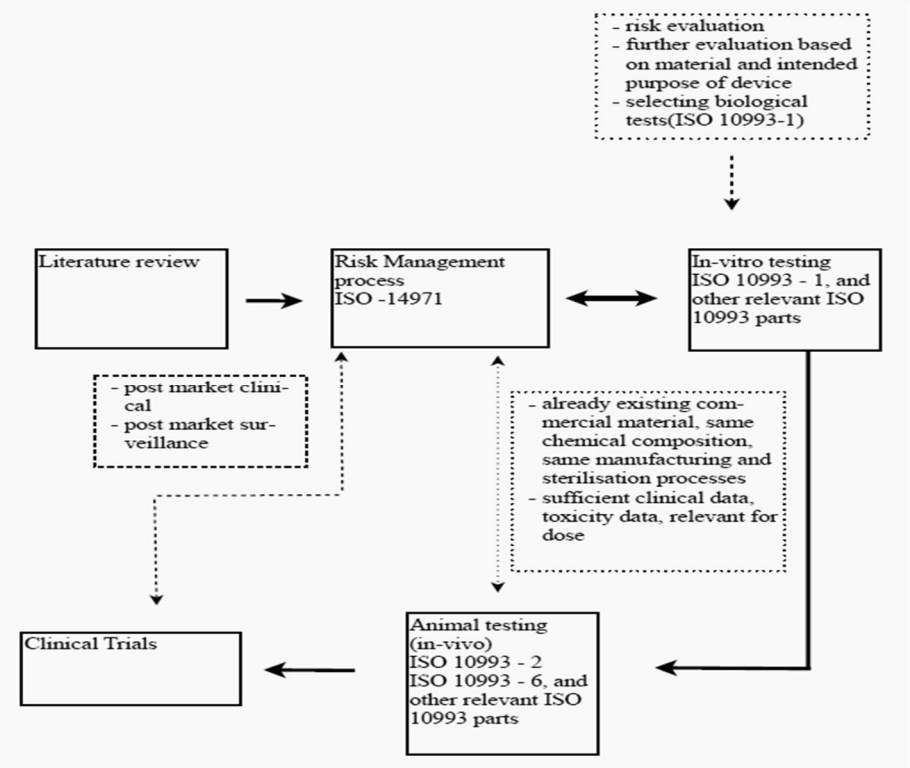

Figure 4.2. *Outline of preclinical trial quality requirements.*

4.4.1. Literature Review

Before starting preclinical studies, literature review should be done extensively for the biological evaluation of the Biomedical Implants and be verified by the third parties or external agencies. Performing literature review can minimise the tests and assess the risks/benefits associated with the Implant. The objective of the literature review should be legible and a plan is established for the selection and exclusion of the articles to be reviewed. The assessment of literature documents should be based on similar technology devices, critical performance, design and operation of the device, relevant animal testing studies, current Medical practice, and intended use of device in question.[60]

4.4.2. In-vitro Biological Evaluation Process

The in-vitro biological evaluation process should assess the physical and chemical characteristics if the Biomedical Implants intended to use on humans and animals using existing clinical records, existing toxicology and biological safety data, test procedures in preclinical trials, and risk management process to determine the hazards. In case any relevant preclinical and clinical data exists no testing of the device is required as it has demonstrated the safe history use that is equivalent to the device in question. The risk management process(ISO-1497) shall take in to consideration of biological hazards for every material, combined material, and final product. The in-vitro or in-vivo tests shall be related to the intended purpose of the device and should strictly adhere to Good Laboratory Practices(GLP). In order to minimise the preference of the in-vivo tests, in-vitro tests should be validated, should depend on the already tested data of the same Medical device characteristics, and the methods should be reliable and reproducible. According to ISO 10993-1, Medical Implants are classified into devices which comes in contact with bones(tissue/bones) and devices which come in contact with blood(blood).

Material characterisation is pivotal step during biological evaluation process. The manufacturer should address the materials, chemical constituents of the material, and additional additives used for manufacturing of the device. If the materials, chemicals, and similar technology process have history of safety and efficacy then biological evaluation is not required. Risk management process is mandatory for material characterisation during biological evaluation. Table 4.1 shows the linkage between the material characterisation and biological evaluation in order to take the decision for the use of such materials and chemicals.

A brief list of biological evaluation tests that should be considered during the evaluation of Biomedical Implant devices in-vitro is shown in table 4.1. And additional set of evaluation tests might be required depending on Medical devices if stated by regulatory authorities. The risk assessment for determining hazards should also consider chronic

toxicity, carcinogenicity, biodegradation, toxicokinetics, immunotoxicity, reproductive/developmental toxicity or other organ-specific toxicities [60].

Table 4.1. *Biological evaluation chart for Biomedical Implants [60].*

Evaluation Test ***Contact duration: (A-limited(≤24h), B-prolonged(>24h to 30days), C-permanent(>30days))***	**Tissue/Bone Medical Implants**			**Blood related Medical Implants**		
	A	**B**	**C**	**A**	**B**	**C**
Cytotoxicity	x	x	x	x	x	x
Sanitization	x	x	x	x	x	x
Irritation or intracutaneous reactivity	x	x	x	x	x	x
Systemic toxicity(acute)		x	x	x	x	x
Sub-chronic toxicity(subacute toxicity)		x	x	x	x	x
Genotoxicity		x	x		x	x
Implantation				x	x	x
Haemocompatibility				x	x	x

4.4.3. In-vivo Biological Evaluation after Implantation

The purpose of preclinical trials is to estimate overall effects of the Implant in the living environment of animals before testing it on human subjects. Adhering to ISO-10993-2 standards and GLP is necessary for preclinical animal trials. Before the start of biological evaluation in animals the protocols should be approved by IACUC and respective regulatory authorities. For Biomedical Implants smaller animals such as mice, rats, hamsters, and rabbits are usually preferred, implantation on larger animals such as dogs, sheep, goats, and pigs should be justified. In most preclinical animal trials smaller animals are used for short-term testing while larger animals are used for long-term testing. The time period of testing an implantation depends on short-term or long-term analysis, non-degradable/non-resorbable or degradable/resorbable Implants, and post-surgery trauma effects. In general the short-term assessment for non-degradable/non-resorbable is between 1week to 4weeks, and for long-term assessment it is over 12 weeks. For degradable/resorbable Implants the estimated time period for assessment depends on degradation time of the Implant. Prior to implantation of degradable/resorbable Implants, degradation studies should have been done in-vitro. The evaluation of degradation should be done at various time points:

- when there is no or minimal degradation(1week to 12 weeks after implantation)
- during the occurrence of degradation
- during the tissue restoration or degradation ending point

The Implant specimens used should be manufactured, processed, and sterilised by the same methods used for final Implants and follow GMP. The specimen should be handed-over aseptically for planting the Implant inside the animal with labelled as "*CAUTION - Device for investigational use in laboratory animals or other tests that do not involve human subjects*"[55]. The surgery should be performed under general anaesthesia and the size of specimens should be in accordance to ISO 10993-6 standards. In In order to yield valid evaluation, many Implant devices should be implanted in the animals. The control and test Implants should not be implanted in the same animals. Evaluation of Implants should be macroscopic and histopathological(microscopic assessment) response as function of time. Evaluation should also be done to assess the response to test sample and control sample at the same operating sites in different animals.

- ***Macroscopic assessment:*** During the macroscopic assessment the Implants should be evaluated depending on the change in structure, tissue reaction towards the Implant, any possible presence of degradation materials, animal health signs or reactions towards the placement of Implant, and macro-photography should be documented.
- ***Microscopic assessment:*** The microscopic assessment includes the histological evaluation in regards to the Implant. The parameters to be recorded are extent of fibrosis(layer in mm), inflammation, degeneration of tissue morphology, necrosis, other tissue alterations, tissue growth levels. For degradable/resorbable Implants intermediate levels, near completion of material, and residual debris of Implant should be presented in tissue samples, and for non-degradable/non-resorbable Implants in bone the interface between tissue and bone should be examined. Any adverse histological responses should be presented in photomicrograph.[60]

4.5. Clinical Studies

Clinical studies for Biomedical Implants are more complex when compared to clinical studies in Biomedical Wearable devices, because Implants are used within the living environment of the human body while Biomedical Wearable devices are used for diagnosis, or monitoring, or mitigation of disease, or treatment for a disease that have influence(results) for clinicians towards the care of the patient from external environment. In clinical studies of Implants the safety, efficacy, and performance are measured while in Wearable devices sensitive, accuracy, and other measurement characteristics are measured. Though the below sections are more applicable for Implantable devices, some of the quality requirements in clinical studies can be also applied for Wearable devices.

4.5.1. Clinical Investigation Plan(CIP)

The objective of the clinical investigation is to determine the safety, efficacy, and accuracy of the Medical device that is going to be placed in the market and evaluates its in-

tended purpose. In order to start clinical trial of the device a proper CIP should be framed with objective and goal of the clinical investigation. The general requirements have been discussed in chapter 5 under Good Clinical Practices(GCP) as per ISO 14155-1:2003. The CIP should have details(ISO 14155-2:2003) of:

- objective of the clinical investigation
- end points to assess the objective of the clinical investigation
- stages of clinical trials
- follow up time period and adverse events reporting
- mode of recruitment of the subjects, identification of the subjects for clinical trials
- anticipated risk analysis during clinical trials(ISO 14971)
- residual risks after placing the Biomedical Implant in the patient[61]
- control groups to be tested
- inclusion and exclusion criteria of the subjects
- measurement variables, statistical methods, pass/fail criteria of the tests
- subject identification procedures

The CIP shall have names and addresses of the sponsor, and patient management personnel's should be clearly stated. The sponsor along with the clinical investigators and coordinators shall agree to the CIP and sign the document with date and if any changes are made to the CIP all the parties should agree and the document should be approved. The CIP document should also address the monitoring path and data verification methods with database management, data verification, data analytic methods, data storage, and data archiving. The CIP shall also include manufacture's name of the Implant, Implant identification number, and software details if used for identification and traceability. The CIP should also include indications and contra-indications, material and medicinal products used in Implants, sterilisation methods, storage and handling details, surgical procedures and training methods for the application of the Implant.

The CIP should include a strong justification for use on human subjects through pre-clinical evaluation and literature data. The pre-clinical evaluation should have summary of all the tests that have carried on the Implant. For adverse reporting, the document should have contact details of the responsible personnel details. The document should have details of foreseeable adverse events and their effects, reporting procedures to sponsor, regulatory agencies, and ethical committee(IRB).[62]

4.5.2. Clinical Investigation

Once CIP is documented the clinical investigation is approached to assess the safety and efficacy of the Implant in the human subjects. The clinical investigations should be carried on unknown risks of the Implant beyond the literature studies, available clinical data, post-market studies, and adverse event reports. The data generated through clinical investigation is used for clinical evaluation of safety and efficacy of the device in hu-

man subjects. Risk management process should be carried out to determine the residual risks of the Implants as per ISO 14971 standards. The clinical investigation design should be done according to intended purpose of the device in question, considering subject population, dosage levels(in case medicinal product used in Implants), clinical end points, analysis methods for clinical evaluation, and statistical approach. Also, the clinical investigation design should consider ethical requirements to safeguard the human subjects. GCP(ISO 14155) should be adopted during the clinical investigation. The final document of clinical investigation should have data pertained during clinical investigation on human subjects for conformity assessment of the Implant.[61]

4.5.3. Clinical Evaluation

During clinical evaluation, the data acquired through clinical investigation is used to assess the risk/benefit ratio, safety, efficacy, and performance of the Implants for human use. For clinical evaluation of the Implant a well-qualified evaluator should be adopted, and justification is required for the choice of evaluator in regards to the implanted device technology, application, and treatment knowledge. The clinical evaluation should be assessed throughout the life cycle of the Implant from clinical trial stages to post-marketing stage for continuously assessing the safety of the device, and this data must be inputted to risk management for any changes in the Implants to control the risks. Clinical evaluation can be done using:

- data obtained through literature search
- data obtained from previous clinical investigation studies
- date obtained through clinical investigation of the Implant
- data obtained through identical Implant using same material or technology

And by using the data as mentioned above, a comprehensive decision can be made if there is sufficient evidence for conformity of the device or further data should be acquired through clinical investigation

Evaluator should assess the selection criteria for published articles/reports related to Implant as these articles become part of clinical evaluation. For data obtained for the similar devices in the market, the data should have clinical evaluation results, post-market surveillance data for residual risks, adverse events, cohort studies, and other clinically relevant data. Once the data is generated from various sources and the clinical investigation results, the evaluator should assess the benefits and limitations of clinical data(appraisal of clinical data) for demonstration of safety, efficacy, performance, and intended use of the Implant. Once clinical data is appraised and relevant clinical evaluation should show:

- that the Implant is working as intended by the manufacturer and claims made about the safety and efficacy of the Implant

- that the clinical data gathered from sources is relevant for the safety of the device for human use
- that the benefits are outnumbered compared to the risks associated with the Implant [63]

4.5.4. Post Market Clinical Follow up(PMCF)

PMCF should be conducted according to jurisdiction of regulatory affairs or competent authorities. PCMF is performed on the human subjects who have undergone the clinical trials. The PMCF should use appropriate methods to draw the end points and report of adverse events. PMCF documentation should have related clinical trial questions, objectives, and end points. To address the clinical safety and clinical performance of the device the residual risks should be identified and risk controls should be documented. The study plan of PMCF should include:

- number of clinical trial subjects
- subject inclusion or exclusion criteria
- justification of study design and use of control groups
- appoint of investigators and study sites
- endpoints and statistical methods
- time period of follow-up
- justification for termination of clinical trials
- quality measures undertaken

The data gathered from PMCF is used as justification for the safety on human subjects.[64]

4.6. Post-market Surveillance

The manufacturer after marketing the device has to do post-market surveillance in order to protect the safety of public health and to prevent the adverse events related to the device. An event related to device during the post-market surveillance can occur through manufacturer or misuse of the device. The adverse event due to the device through manufacturer may be because of malfunction or deficiency in the performance of the device, flaws in design, inaccurate labelling or packaging, and not giving enough information prior to use. Figure 4.3 highlights the post-market surveillance of the Medical device.

The manufacturer has to report an event:

- if there is flaw in the design and cause serious injury or death of the patient. For example, a software error in the pacemaker or premature failure in hip Implants.

- if the labelling information is given wrong and no proper information has been put on label for the proper use of the device. For example, the label of caution is placed in inside packaging rather outside packaging
- if the device prematurely fails before the shelf/service life. For example, the service life of hip Implant as stated by manufacturer is around 15 years, and if the Implant fails before the service life, the event has to be reported
- if the device is being used against the intended purpose as labelled by the manufacturer
- in case of death caused due to mistake caused by doctor

The manufacturer no need to report of the adverse event:

- if already existing side effects are known upon the use of the device
- if adverse event occurred due to patient condition not related to the device. For example hip Implant failed due to osteoporosis.
- if the manufacturer has taken proper control procedures against the malfunctioning of the device. For example, one of the ECG sensor failed to gather the signal and the device has alarmed the user, but still the user did not act upon the warning and led to injury or death.
- in case if the advisory notice has been sent to all the Healthcare providers for the recall or not to be used purpose and still the device has been used

The adverse events have to be reported to National Competent Authorities(NCA) in 30days and for unanticipated deaths the event has to be reported immediately. In USA the adverse event should be reported to FDA, while in Finland it has to be reported to Valvira and VTT(Notified body). The report should have information of device manufacturer, operator of the device at the time of adverse event, single use / reusable type of device, current device location or disposition, patient information, and device approval information(authority who approved the device). [65]

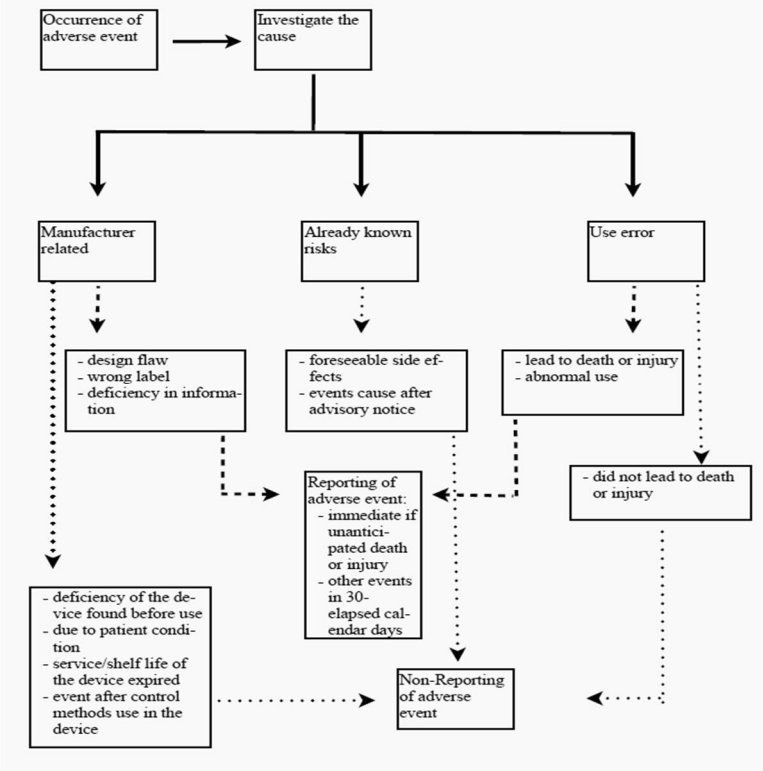

Figure 4.3. *Reporting of post-market surveillance.*

4.7. Wearable Devices

Though quality requirements are discussed inclusively for both Biomedical Wearable and Implantable devices, the following quality requirements are exclusive for Biomedical Wearable devices. FDA states that "A Medical device data system (MDDS) is a device that is intended to provide one or more of the following uses, without controlling or altering the functions or parameters of any connected Medical devices:

- the electronic transfer of Medical device data
- the electronic storage of Medical device data
- the electronic conversion of Medical device data from one format to another format in accordance with a preset specification
- the electronic display of Medical device data.

A MDDS may include software, electronic or electrical hardware such as a physical communications medium (including wireless hardware), modems, interfaces, and a communications protocol. This identification does not include devices intended to be used in connection with active patient monitoring"[38]

Most of the Biomedical Wearable devices are related to physiological state or congenital abnormality. Wearable devices should be manufactured in such a way to reduce the risk of infection, for ease of handling the device, and to avoid leakage of device. Since most of the Wearable devices interact with other devices, the performance of the

device should not be impaired. The Wearable devices should be designed in such a manner as:

- to reduce the risk of physical features
- effects of foreseeable effects of external environment such as magnetic fields, electrical fields, temperature changes, pressure changes etc.
- to avoid risks of explosion or fire
- to facilitate the safe disposal of the device
- the display , measurements, or monitoring scales/indicators should follow ergonomic principles
- to show accuracy and stability of the measurements, and the values as per the country competent authorities
- to design, to be manufactured, and packaged to minimize the effects of the radiation
- to design instruments emitting radiation's as not to have any effects on users, or controlling or adjustment of radiation should be adopted
- to show repeatability, reliability, and intended performance for the software used in the device
- the information supplied by manufacturer should adequately discuss about the safety, proper user instructions(including version number), and training of the device [59]

4.8. Risk Management of Medical Devices

Risk management has to be adapted to all Biomedical Wearable and Implantable devices at all stages of life cycle of the device in accordance to ISO 14971 standards. Risk analysis can be done using the published data of predicate devices already available in the market. Risk management is of four distinctive features that the manufacturer has to identify the hazards associated:

- risk analysis
- risk evaluation
- risk control
- post-production adverse events

The risk management have to document the scope of risks associated with the device using the predicate devices, international standards, and country related standards. It is also responsible to allot personnel’s to work on risk management activities at regular intervals of time for assessing the risks of the device. The management should prepare risk management plan associated with particular Biomedical Wearable or Implantable device at all stages of the lifecycle of the device and to review the acceptable criteria of risks for the device. The management should record all the risk management activities and plans to reduce the risk of the device.

4.QUALITY REQUIREMENTS

During risk analysis of the device, the management should estimate the foreseeable use of the device and list the characteristics that can affect the safety of the device. In addition, the manufacturer has to estimate the foreseeable hazards for the device in both normal and faulty conditions. After identifying the related hazards the management has to estimate the risk associated with each hazard. Estimating risks can be done using qualitative and quantitative analysis, or information from external sources such as published standards from various international organisations, scientific data, existing predicate devices, clinical trials, post production reports, and opinions of experts and external quality assessment organisations.

Once risks associated for the hazards have been identified, the management has to evaluate the design and production process of the device. Once evaluated the management have to implement risk control measures at all stages of lifecycle of the device. Once the control measures are taken, the risk control verification has to be done and should be well documented. If any residual risks are associated with the device, control measures have to be taken and should be implemented. Moreover, the management should analyse if the overall residual risks are acceptable for the device for its intended purpose, if not the management have to re-evaluate the risks and take control measures. The post production data obtained through post-market surveillance is mandatory in all the regulatory compliance, it helps the manufacturers know if there are any unforeseeable risks of the device[66] . More information about the hazards associated with the Biomedical Wearable and Implantable devices are shown in appendix2.

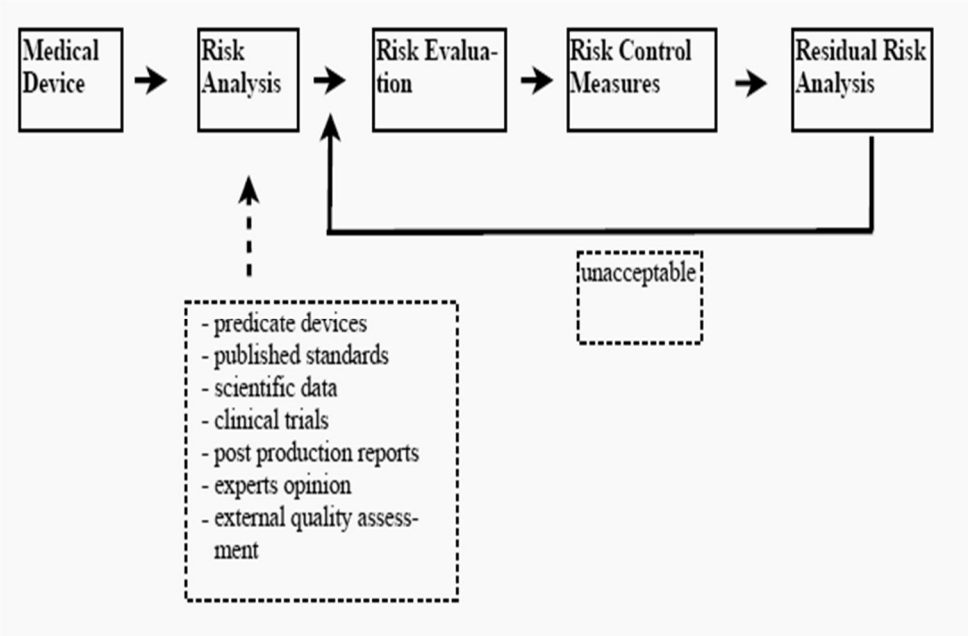

Figure 4.4. *Risk management process of a Medical devices.*

4.9. Validation of Standalone Software

Another important aspect to consider about the active Implants and Wearable device is standalone software. Any software or computer program that is designed to incorporate the Implant or Wearable device that is used for treatment or monitoring the performance or used for decision making by the clinicians comes under standalone software for regulatory process. Standalone devices should be approved from the regulatory authorities such as:

- software in active therapeutic devices, which are intended to direct energy source or exchange data from inside the body. Example include monitoring of pacemakers which can transmit data
- software intending to measure the vital physiological state of the organs. Example include monitoring of the heart rate
- software's used for designing the Biomedical Wearable and Implantable devices. Example include hip implant designing software
- software algorithms that are used for monitoring, diagnosis, treatment, or prognosis of individual patient
- pre-hospital ECG system that are used to transmit data to doctor at remote location
- health care environment
- telemedicine software's for monitoring of patients by healthcare units from remote locations [67]

5. GOOD PRACTICES(GXP)

This chapter includes good practices to be practiced by companies and research organisations to show that the product is safe and efficacy, and results are repeatable for the approval of the regulatory bodies and process followed are in correspondence to regulatory compliance.

5.1. Good Laboratory Practices(GLP)

The purpose of GLP is to assure that the management of the companies or research organisation have adopted quality system to ensure that non-clinical tests are validated, uniform, reproducible, and consistent. Companies selling products in USA or EU require that they follow strict GLP standards as prescribed by FDA or EU notified agencies[68n] as non-clinical laboratory studies support applications for further research development in clinical trials or marketing of device[70n]. In addition, clinical trials and manufacturing of the products requires the approval in non-clinical studies, organisation adhering to these GLP's can reduce time and effort as it makes easy for the regulatory bodies to audit and approve the tests. GLP's key elements include study director, Quality Assurance Unit(QAU), SOP's, reagents and solutions, test and control articles, raw data, storage and archiving, personnel, equipment validation, and statistical procedures for data evaluation. [68][69][70]

5.1.1. Organisation and Personnel

The management or sponsor should allocate study director and trained personnel's for the non-clinical studies. Study director is responsible for the conduct of the non-clinical analysis, documentation, and presentation of results[69]. The individuals working in the preclinical/clinical studies should be experienced and should be allotted the job that is fulfilled on time. Individuals working in laboratory should adhere to protocols and be sanitised. Individual personnel suffering from illness should be excluded if there is impact on tests.[69][70]

5.1.2. Quality Assurance Unit(QAU)

QAU is an internal control function team that should assure the management that the facilities, equipment, personnel, methods, practice, records, and controls are in conformance as per the regulatory bodies[69][70]. The laboratory management should prepare written procedures that should be carried out by QAU, and should submit the procedures to regulatory bodies when notified. QAU should update the management of the

inspections carried out as per schedule and duly report any problems encountered during the non-clinical studies. The main responsibilities of QAU include:

- to maintain the copy of master file containing all the tests being conducted at the test facility containing information about nature of study, initiated date, status of the study, sponsor identity, and study director.
- to maintain written procedures pertaining to QAU
- to periodically inspect the undergoing tests
- to submit written document to management about the progress of the study
- to find out if any deviations from the SOP's carried on with proper authorization
- to review the final report and to check if the personnel's followed as per the protocols
- to audit and validate laboratory equipment [69][70]

5.1.3. Facilities

Facilities for laboratory testing should be of suitable size for proper laboratory tests. There should be enough degree of separation between the tests, so in case of adverse events the other tests should not be disturbed or contaminated. The facilities of animal care should have enough rooms and animals should be separated as per the tests carried out. There should be separate areas for diagnosis and treatment of animals. Animal facilities should also have proper disposal of wastes so contamination is minimised. Facilities should also provide separate areas for storage and mixing to avoid contamination.

SOP's shall be established and should be reviewed to ensure the quality and integrity of the study. The SOP's should have unique number and revision number. Deviation from SOP must be authorised by the study director.[69]

The reagents and solutions used in laboratory should be labelled with identity, concentration, storage temperatures, and expiration date [70]

5.1.4. Equipment

Equipment's used in laboratory tests should be of appropriate design and should allocate proper space for cleaning and maintenance. Equipment's should be validated as per the laboratory protocols. Copy of SOP's of each equipment should be placed next to the equipment which contains procedures for maintenance, application, cleanings, and troubleshooting. Records of maintenance should be written and should be provided when required for auditing.

5.1.5. Test and Control Articles

Test article means any drug or biologic product for human use while *Control article* means any drug or biologic product other than test article that is administered during the course of non-clinical studies established for the comparison with test article [71].

Procedures should be documented for each batch of test control articles to determine the identity, strength, purity, composition, and other characteristics. Also, synthesis and fabrication methods should be documented. These documents must be submitted to regulatory bodies for inspection. Storage container used for the test or control articles must be labelled by name, batch number, chemical extract number, expiration date and any if applicable[69][70]. Also, stability of these articles should be performed before the start of studies and during the studies for every batch of test control articles[70].

5.1.6. Protocol for conduct of a Non-clinical Laboratory Study

The study director should prepare the protocols for every test being conducted. The information in protocol should include:

- title and objective of the studies
- identification of test and control articles
- sponsors details
- testing design, description of materials and chemicals used, and dosage levels should be indicated in country specific units as required by regulatory authorities
- statistical methods adhered
- approval of study director for the protocols, and sign of study director if any changes are made to the protocol[70]

5.1.7. Records and Reports

The final report of each laboratory tests should include name and address of facility, objectives and procedures, statistical procedures for data evaluation, description of materials and drugs used, any adverse events, study director and individuals involved, signed and dated reports, location of reports, specimens and raw data, and the sign of study director. In addition, the raw data, documentation, protocols of the test, and specimens used for the test should be stored with few exceptional in orderly manner and should be accessible only by specific individuals.[70]

5.1.8. Disqualifications of Testing Facilities

The sponsor should intimidate the regulatory bodies about the testing facilities. On audition the regulatory agency can disqualify the testing facility for not complying with the regulations, any change in results, or in case it is understood that the testing facility may adverse effect the results.[70]

5.2. Good Clinical Practices(GCP)

The purpose of GCP is to assure the public that the rights, safety and wellbeing of human subjects involved are protected[72]. The goals of GCP are also to provide reliable data to the review board and the regulatory agencies pertaining to clear the Medical device in a qualitative environment. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use(ICH) adopted GCP, whose task is to provide unified standards to the EU, United states, and Japan and then later followed by other countries. The ISO 14155 standards are adopted for GCP as general requirements for clinical investigation [73]. The guidelines provided by ICH is set of instructions to the companies generating clinical data to be submitted to the regulatory agencies[74]. In this section brief information about GCP has been covered which are taken from ICH standard document other than discussed in GLP section. [72][74]

5.2.1. Duties of Institutional Review Board(IRB)

The principles of ICH covers the ethics in clinical trials, submitting a comprehensive report to IRB or Independent Ethics Committee(IEC) about the benefits and risks involved in the investigational drug for the proposal of clinical trial, adopting the compliance of IRB/IEC, educating and training the individuals involved in clinical trials such as investigators, monitoring agents, physicians, human subjects etc., storage of records and data concerning to the clinical trials, maintaining the confidentiality of the reports concerned to human subjects, and adopting GMP to the investigational products.[74]

The responsibilities of the IRB/IEC include:

- to see that the sponsors adhere to the clinical ethics of the human subjects
- to obtain the documents of trial protocol, consent forms, information provided to the subjects, Investigator's Brochure (IB), safety and quality information, investigator's information. In addition after obtaining these documents, IRB/IEC should state its views on conduction of clinical trials is favourable or unfavourable, modifications to the clinical trial protocol or any amendments if required, or termination of clinical trials
- to audit the clinical trials in intervals and determine to continue or terminate
- to store the records for a period or 3 years or longer and be shared with regulatory authorities on request [74]

5.2.2. Investigator

The investigator who is going to perform clinical trials should be qualified and experienced person whose responsibilities include adopting the clinical trial protocol and having knowledge of GCP and regulatory requirements. The investigator also should recruit well qualified persons responsible for clinical trials and inform them about the proto-

cols. The investigator should adhere to the trial time period. The investigator should monitor the human subjects and be responsible and provide Medical care if in case of adverse events and also should ascertain the reasons if the human subject is withdrawing from trial though the human subject has rights to withdraw from the trials at any given time.

Investigator should also be responsible for communication with IRB/IEC and submit the documents when asked by the authorities. The investigator should also inform the IRB/IEC bodies of any changes or amendments to the clinical protocol and justify the reasons. The investigators should adapt strictly to the clinical protocols agreed by the sponsors and regulatory authorities and should not deviate from the protocol. If any deviation from the actual protocols the investigator should document and justify the reasons.

In addition the responsibilities of investigator include accountability of investigational products. The investigator should record the investigational products used, and follow the instructions provided by sponsor for application and storage. The investigator is also responsible for talking to human subject physicians if the protocol denotes(blinding).

The investigator responsibilities also include to submit the progress reports to the IRB/IEC frequently as requested and reports about Serious Adverse Events(SAEs) immediately. [74]

5.2.3. Sponsor

The sponsor is responsible for quality assurance and control of the clinical trials. The sponsor should provide enough information to the investigators or Contract Research Organisations(CRO's) to implement the clinical trials. The sponsor can recruit Medical experts to prepare the clinical trial protocols and involve them at every stage of clinical trials. The sponsor can also assign the Independent Data-Monitoring Committee (IDMC) to monitor the progress. The sponsor is also responsible for financing the clinical trials and human subjects involved.

The sponsor should notify the regulatory bodies about the information of investigators and submit the reports when asked by these authorities. The sponsor should also submit data that pertains to non-clinical studies to support the start of clinical trials. The sponsor should assure that the investigational products manufactured on small scale follow GMP and show efficacy. The sponsor also should provide information on how the investigational products are packaged and stored for the human trials.

The sponsor should share adequate information to the investigators such as protocols, SOP's, Investigator's Brochure(IB) etc. before the start of the trial. The sponsor

can allocate auditors who are independent of clinical trials to audit the progress of human trials. The auditors should prepare a report of their findings carried out by investigators and the report should be submitted to the regulatory authorities when required.[74]

5.2.4. Clinical Trial Protocol and Amendments

Clinical trial protocol is a document which states the objective(s), design, methodology, statistical considerations, and organisation of a trial[74]. The document contains the trial design process, number of human subjects to be tested, SOP's to the investigators, dosage levels, duration and sequence of trials, and storage, packaging, and labelling of investigational products.

The protocol should also justify the selection and exclusion criteria of human subjects, terminating of trial for any reasons, and assessment of efficacy and safety. In addition, the document should state what kind of statistical approaches are imbibed during the trial process. [74]

5.2.5. Investigator's Brochure

IB is a document that presents clinical and non-clinical data to the investigator's and other personnel's involved during the investigational product. The IB should support enough non-clinical data for the understanding of persons involved in clinical trials. While preparing the IB the sponsor has to involve medically qualified persons. Also, sponsor should be responsible to update IB annually[74].

5.3. Good Manufacturing Practices(GMP)

GLP and GCP which predates GMP analyse toxicity, stability, and drug development activities of individual components and whole investigational product while GMP's help during producing mass or bulk investigational products and final products with stability, consistency and quality to ensure that good quality Medical devices are marketed to the public. Biomedical Implants which are combinational devices have to undergo both drug and Medical device GMP's while Wearable devices needs to adopt Medical device GMP's. Drug companies in USA should adopt part 211, current Good Manufacturing Practices(cGMP) while Medical device companies marketing in USA should adopt part 820, Quality System Regulations(QSR). Also there are available WHO GMP's which are being adopted by several countries while companies in EU adopt EU-GMP. While few of the key elements have been discussed in the GLP's the most important aspects of GMP's are validation, design controls, Installation Qualification(IQ) and Operational Qualification(OQ), method validation, on-going performance, data security, integrity, traceability, and vendor validation[69].

5.3.1. Validation

Validation is the process of evaluation of products, equipment's, and analytical methods used in the manufacturing of the product. Validation is not one time requirement but a continuous process at various intervals of time to validate the stability of the process during manufacturing. In validation process the sensitivity and reproducibility is analysed for the hardware systems, software systems, and analytical methods individually and combined. SOP's had to be written for validation process and should be continuously reviewed in course of time. Personnel validating the process should be educated and well trained.

Hardware systems used in the process should be validated prior to the use, during the regular intervals, and after the repair. While computer systems should be validated in modules and at the end of development process. Analytical methods should be validated in ideal scenarios and if any parameters are being changed. It is always a good practice for the manufacturing managers to have a validation master plan and document it thoroughly.

5.3.2. Design controls

Medical devices coming under Class II(Class IIa and Class IIb under EU regulations) and Class III should have manufacturing design control documents established. Design controls play an important role in selecting the right equipment's, computer systems, and analytical methods. It has impact on business and life cycle of the products. During the design phase the manufacturing have to make a chart for every equipment, computer systems, and analytical methods as below:

- selection of facility, environmental selection
- documenting planning phase of equipment's, computer systems, and analytical methods
- risk analysis
- technical specification of requirements
- material quality
- vendor selection for material and equipment[69][75]

The design input and output should be validated and documented for the intended purpose. Any changes in design should be documented and approved before implementation. DHF should be established and documented for every equipment, computer system, and analytical methods[76].

5.3.3. Purchasing Controls

Manufactures who are buying the products or services should ensure that the suppliers, contractors, and consultants match the quality requirements of the manufacturers and

strictly adhere to the specifications. Before the purchase, manufactures should thoroughly inspect the facility, instruments, and processes followed by the suppliers and contractors. Any changes made to the process design or changes in the product or services the supplier or contractor should notify and get approval of the manufacturer[76].

5.3.4. Identification and Traceability

Manufacturers should establish a process to identify the products during the process of production, distribution, and installation. In order to trace the product after production each manufacturer has to allocate a unit, lot and batch number[76].

5.3.5. Production and Process Control

Manufacturers should develop, conduct, control, and monitor production processes to achieve the stability, integrity, and quality of the products. Though deviations are normal occurrences of the production process manufacturers should establish and maintain process control procedures to adhere to the specifications[76]. Since Implants are more prone to contamination, manufacturer should make sure to have procedures for contamination control. Proper validation of automated systems should be documented. Other production controls include regular maintenance schedules, inspection of materials and equipment's, adjustment of the equipment's to the specifications, training of personnel handling the production, environmental controls, and calibration of equipment's[76].

5.3.6. Acceptance Activities

Manufacturers shall make sure that any material from vendors should be in acceptable criteria and match the specification. The manufacturer shall inspect, test and then only confirm for the incoming products for manufacturing and these activities of acceptance or rejection should be documented. When the materials are in process, the product should be matching the specifications in each stage of production. Finally, the finished goods should be verified and tested. Also, after the final product the personnel responsible should clearly document each every step carried during acceptance activities and should be signed as these documents should be part of DHR[76].

5.3.7. Corrective and Preventive Action

Manufacturer should ensure that after thorough audits are being done in manufacturing process, if any non-conformity activities of the product are found shall thereby be recorded, have taken proper action to correct, and prevent the activities to happen again. For these reasons the manufacturer shall audit analysing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of non-conforming product, or other quality problems[75]. The managers should ensure that the responsible person shall correct the actions. All these audits should be docu-

mented and should be submitted to regulatory bodies on request or during auditing process[76].

5.3.8. Labelling and Packaging Control

Each manufacturer shall make sure that the label printed is legible and shall have right applications of the product, endpoints, expiration date, control number for traceability, storage instructions, handling instructions, and other information applied to the product. Labelling for every product in the manufacturing unit should be stored in right manner with identification numbers to avoid mix ups, on release of the labels the personnel who is examining it shall sign and shall be documented in DHR[76]. The packaging material used on the products should maintain the stability and integrity of the components while shipping and distribution[76].

5.3.9. Handling, Storage, Distribution, and Installation

The manufacturer shall ensure that the products should not mix up with other products and prevent contamination while handling as this have adverse effects on entire batch of products. In addition, manufacturer should ensure proper storage facilities for the products and should prevent mixing up of other products. Also, manufacturer should avoid distribution of obsolete, deteriorated, or untested product to reach the final customer. While distributing the product the manufacturer should maintain proper records of the distributor details such as name of the distributor, control number, batch number, lot number and identification number of the product, number of quantities distributed, shipment date, and any other information if applicable by regulatory bodies. Person who is installing the product should use the product as intended and any deviation from the intended use shall be responsible for any adverse effects[76].

5.3.10. Record and Servicing

Manufacturer should make sure that the records related to design of the product such as device master record(DMR) and device history record(DHR) should be thoroughly updated and signed. It includes the design specifications, drugs used, computer systems, packaging and labelling specifications, quality procedures, audit procedures, SOP’s, and procedures for IMS. The manufacturer shall maintain the records of complaints filed by the customers. The complaints should be recorded and processed as per the procedures; any adverse events in the complaint shall be reviewed and controlled in production and process control. The complaint records should be sent to regulatory agencies in regular intervals to safeguard the public[76].

Manufacturer should ensure that the personnel involved in servicing are well trained and capable to solve the problems. The service records should be well maintained and shall be reported using statistical approach to the regulatory agencies. The service rec-

ords should include name of the device served, control number of the device, date of inspection, personnel serviced the product, and other applicable details.

5.3.11. Combinational Product

The word combinational product is defined as any product which combined with drug and Medical device or biological product and Medical device. Many companies are finding new ways to design and market an Implant using combinational products where drug or biological products are included within the Medical Implant device. However, confusion exits for the companies regarding the GMP of the combinational products. In this scenario FDA states that the companies can demonstrate in two ways:

i. Manufacturers can demonstrate both cGMP requirements for drug and quality regulation for Medical device as per FDA (or)
ii. Manufactures intending to market as drug device should demonstrate cGMP as well few of QSR as shown in table 4.1 or manufactures intending to market as Medical device shall demonstrate QSR and few of cGMP as shown in table 4.2.

Box 5.1. *Product intended to market as drug [77][78].*

QSR demonstration of the drug
• Sec. 820.20. Management responsibility.
• Sec. 820.30. Design controls.
• Sec. 820.50. Purchasing controls.
• Sec. 820.100. Corrective and preventive action.
• Sec. 820.170. Installation.
• Sec. 820.200. Servicing.

Box 5.2. *Product intended to market as Biomedical device [77][78].*

cGMP demonstration of the device
• Sec. 211.84. Testing and approval or rejection of components, drug product containers, and closures.
• Sec. 211.103. Calculation of yield.
• Sec. 211.132. Tamper-evident packaging requirements for over the-counter (OTC) human drug products.
• Sec. 211.137. Expiration dating.
• Sec. 211.165. Testing and release for distribution.
• Sec. 211.166. Stability testing.
• Sec. 211.167. Special testing requirements.
• Sec. 211.170. Reserve samples.

6. DISCUSSION'S

6.1. FDA vs. EU Approval Authorities

For higher risk devices, the approval process is quite faster in EU on comparison to FDA approval. This has impact on the health benefits of the public and reimbursement on the capital spent for the development of the Medical devices as the latest treatments are not reaching the public in USA. Moreover companies commercialise first in EU than in USA due to scrutinised regulatory path by FDA. The gap between devices getting approval for commercialising is three to four years[79] between EU and FDA making the stakeholders to consider the marketing geographic regions. This is also due to regulatory path process where in USA, FDA is a centralised organisation working on different Medical devices while in EU, the regulatory path is decentralised manner where the companies can work with 72 notified bodies(NB) across EU.

The PMA approval period by FDA has been increased by 135%, 12.5 months in 2000 to 29.3 months in 2010, due to increase in repetitive submission by the companies in the preclinical and clinical evaluation. This has impacted the development of new devices in USA, which has limited the treatment choices, improved quality of life, and limited physician choices for treatment to the patients in USA when compared to EU[79]. The recall rates of the device are significantly same between speedy approval process of EU when compared to delayed approval process by FDA, despite FDA seeking more information and review time from the companies to safeguard the public health.

The studies done by Dr Josh Makower, America's leading Medical entrepreneurs by interviewing 200 small and medium Medical devices companies indicated that:

- 85% of participants feel EU authorities are more predictable on comparison with 22% for FDA
- 91% of participants feel EU authorities are more likely reasonable on comparison with 25% for FDA
- 85% of participants found that EU authorities are more transparent on comparison with 27% for FDA
- while 75% of participants feel experience with EU authorities as excellent on comparison to 16% for FDA[80]

But most recently EU approval process came in to question when 12 of the high risk Medical devices were approved in EU, while the same devices have been disapproved in USA which are found to cause serious adverse effects during clinical evaluation for approval of FDA and many believed that EU has lower standards for high risk devices on comparison to FDA PMA approval process[81]. Due to this European Commission(EC) has made a proposal for PMA just like FDA PMA for Class IIb and Class III devices, novel technologies, and high risk devices[82]. Table 6.1 shows a comparison of USA and EU regulations for high risk devices.

Table 6.1. *USA vs. EU regulations for high risk devices [81].*

	EU	**FDA**
Approval Standard	Safety of the device, technical performance, no clinical evidence required	Safety, and clinical evidence required
Evidence required	literature studies, data from laboratory studies, and small clinical trials	valid clinical trials
Approval authority	Notified bodies(NB) and national competent authorities	FDA(centralized authority)
post-market and adverse reporting transparency	adverse events, and recalls must be reported to NB and displayed for public	adverse events, and recalls must be reported to FDA, and is displayed for public

Due to extended delayed regulatory process by both FDA and EU there will be less spending in R&D, decrease in value of smaller companies due to funding and resources, non-persuasion of risky devices(more opting for less risky devices), and non-availability of the device to the public for quality life.

6.2. Role of International Medical Device Regulators Forum(IMDRF)

Due to global nature of trade, Medical companies have real challenge to get approval from regulatory authorities and go through the time taking repetitive procedures for getting approval of the Medical device across different regulatory authorities. This can affect the global trade by not making availability of advanced innovative Medical devices to the public, but also extra burden to the companies in terms of reimbursements and competition. The purpose of IMDRF which was earlier called as Global Harmonisation Task Force(GHTF), is to harmonise the national standards across the borders to minimise regulatory barriers, facilitate trade, lowering time to enter the market for inno-

vative devices, reducing market for substandard products, and access for new Medical technologies[83]. The challenges of IMDRF is the convergence of all the regulatory standards to single international standard while still maintaining certain local jurisdiction laws where Medical companies are required to adhere. In order to achieve single international standard for Medical devices, it requires commitment from governments and cross border regulatory authorities, involvement of stakeholders at all levels, and global traceability of Medical device.

6.3. Complex Medical Technologies

Due to increase in complex technologies used in Medical devices, the approval process from regulatory authorities is being more scrutinised and subject to delay in marketing the technology. The future in Medical technology is combination of both Implantable and Wearable devices which works together. These devices are far more efficient and can be used in early detection of cancer, diabetic patients, neurostimulator Implants for epilepsy/paralysed patients, heart disease patients, drug delivery procedures for the targeted organ which eliminates side-effects. Medical nanotechnologies using nano-robots/Implantable sensors that can be connected wirelessly to the wearable devices for communication where the parameters for drug delivering can be controlled by the physicians, or for monitoring the performance characteristics of the Implantable device which in turn sends collected data wirelessly to the physicians. These kind of Medical devices which uses biomaterial's and electronics, needs to be encouraged and regulatory authorities needs to define standards and be prepared for the future Medical technology to reduce the time for approval and companies have to take responsibility to show safety and efficacy of such advance devices. These complex technologies can be used for the diagnostic/treatment of modern diseases which can increase the life expectancy and quality of life of the public.

6.4. Challenges

6.4.1. Biomedical Implantable Devices

The future of Biomedical Implants is combination of drug delivery with miniaturization of circuits to target the drug to the specific organ of the body, though challenges exists in terms of risks, Medical Implants can be used for diagnosis and treatment of the diseases which can give quality life to the public. Due to heavy profits in this area of product development companies have to make sure that all the necessary tests are carried out to ensure the safety and efficacy of the product. Active Medical Implants should consider the durability of the device which has long battery life, biocompatibility in long stay of the product in the body, and interface between the device and body environment.

6.4.2. Biomedical Wearable Devices

Biomedical Wearable devices are new entry to the market and regulatory authorities are still working on the standards. Companies have to concentrate in increasing the sensitivity and accuracy despite noises generated in patients during movement or physical activity and the right computing algorithms and hardware systems to detect the disease. Since Wearable devices are always worn, power consumption and “wear and tear” factors should be considered for long usage of the device. For Wearable devices used for transmitting data, companies have to secure the data from hackers as this data is used for diagnosis/treatment of the patient. Companies and Healthcare units should work together to integrate the device data into software system of the hospitals. Moreover, Healthcare units should dedicate resources for monitoring of the patients with Wearable devices and provide quick treatment.

7. CONCLUSION

This thesis has extensively focussed on the commercialising and quality requirements of Biomedical Wearable and Implantable devices by discussing market analysis and strategies, various product development stages of these Biomedical devices, importance of stakeholders, and future role of harmonising the Biomedical device quality standards by IMDRF due to global demand of supply chain management and reduction of approval time by regulatory authorities across border. Further, the thesis has discussed the market value of these devices and how they can shape and give quality of life to many people world-wide due its wider applications.

Concurrently due to vast applicability and huge profits involved in the sales of these devices, company and university researchers are establishing R&D methods for these devices involving multi-disciplinary teams for safe entry into the market. Though many of these devices are replacing standard procedures carried out by physicians, challenges still exists for these devices in terms of risks, accuracy, sensitivity, and stringent requirements by regulatory due to complex technologies adopted in these Biomedical devices. The future prospects of these Biomedical devices are high, both for the companies and patients, but care must be taken by the companies to thoroughly evaluate the safety, efficacy, and accuracy, and adhere to the requirements of regulatory systems. At the same time, regulatory systems should harmonise the standards world-wide while maintaining minimum regional regulatory requirements for these devices, and government organisations should encourage the industries to develop these devices and educate both the public and doctors for the safer applications of these devices.

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APPENDIX1: DEVICE MASTER RECORD(DMR) REQUIREMENTS

Device Specifications(DS)

- product trade and common names intended uses
- performance characteristics and theory of operation
- physical characteristics
- environmental limitations, product stability and storage requirements
- software specifications
- user safety characteristics;
- component, subassembly and assembly drawings and specifications
- bills of materials (or lists of ingredients)
- compositions
- formulations
- wiring and piping diagrams[52]

Manufacturing Process Specifications(MP)

- process flow charts
- process/assembly lines diagrams
- equipment, tools, molds
- manufacturing environment specifications
- setup procedures
- operator instructions
- equipment maintenance procedures
- validation reports for special processes
- sterilization specifications, procedures, and validation reports
- blank work orders, non-conforming product/process forms, and other reporting forms[52]

Quality Assurance Procedures and Specifications(QA)

- quality system manual (QM)
- quality system operational procedures (QOP)
- quality system forms (QF)
- process control specifications/charts
- control plans, instructions and acceptance criteria for incoming, in-process, and finished device inspection and testing
- procedures and acceptance criteria for the verification of packaging, labeling, installation, and servicing activities;
- blank work order forms for recording inspection/testing activities, traceability, and other data for device history records;
- device release review/evaluation checklists[52]

APPENDIX

Packaging and Labelling Specifications(PL)

- package drawings and specifications
- filling/packaging procedures
- label/labeling drawings
- instruction manuals[52]

Installation, Maintenance, and Servicing Specifications(IMS)

- installation, specifications and instructions
- maintenance instructions
- servicing specifications and manuals[52]

APPENDIX

APPENDIX2: ASSOCIATED HAZARDS

Wearable Devices

- non-accuracy and not-repeatable
- electro-magnetic noise
- electricity conducting problems
- erroneous errors
- software or hardware or user operational problems
- wireless transmission problems or data security issues
- inadequate labelling and operating instructions
- non-breathable textile problems
- sensor instability problems
- high temperature problems
- improper re-use and packaging
- improper charging
- water proof problems[66]

Implantable Devices

- Energy Hazards
    - Electricity and heat
    - mechanical force
    - unintended motion
    - ionising and non-ionising radiations
    - magnetic fields
- Biological Hazards
    - bio-incompatibility
    - bio-contamination
    - degradation, toxicity
    - carcinogenicity
    - mutagenicity
    - oncogenicity
    - pyrogenicity
    - allergic
- Environmental Hazards
    - electromagnetic fields
    - susceptibility to electromagnetic interference
    - electromagnetic emissions
    - storage or operation outside stated environmental conditions
    - incompatibility towards secondary devices
    - mechanical damage

APPENDIX

- contamination problems

- incorrect production and process control problems
- lack of correct labelling of device
- insufficient warning of side effects
- inadequate packaging[66]

APPENDIX3: ISO 10993

Part 1	Evaluation and testing in the risk management process
Part 2	Animal welfare requirements
Part 3	Tests for genotoxicity, carcinogenicity and reproductive toxicity
Part 4	Selection of tests for interactions with blood
Part 5	Tests for in vitro cytotoxicity
Part 6	Tests for local effects after implantation
Part 7	Ethylene oxide sterilization residuals
Part 8	Selection of reference materials
Part 9	Framework for identification and quantification of potential degradation products
Part 10	Tests for irritation and delayed-type hypersensitivity
Part 11	Tests for systemic toxicity
Part 12	Sample preparation and reference materials
Part 13	Identification and quantification of degradation products from polymeric Medical devices
Part 14	Identification and quantification of degradation products from ceramics
Part 15	Identification and quantification of degradation products from metals and alloys
Part 16	Toxicokinetic study design for degradation products and leachables
Part 17	Establishment of allowable limits for leachable substances
Part 18	Chemical characterization of materials
Part 19	Physico-chemical, morphological and topographical characterization of materials
Part 20	Principles and methods for immunotoxicology testing of Medical devices

APPENDIX4: LIST OF IMPORTANT DOCUMENTS AND STANDARDS

- Council Directive 93/42/EEC of 14 June 1993, concerning Medical devices (MDD) as amended by Directive 2007/47/EC. [84]
- Council Directive 90/385/EEC of 20 June 1990, on the approximation of the laws of the Member States relating to active implantable Medical devices (AIMDD).
- Commission Directive 2003/12/EC of 3 February 2003, on the reclassification of breast Implants in the framework of Directive 93/42/EEC concerning Medical devices (Breast Implant Reclassification Directive).
- Commission Directive 2003/32/EC of 23 April 2003, introducing detailed specifications as regards the requirements laid down in Council Directive 93/42/EEC with respect to Medical devices manufactured utilizing tissues of animal origin (Animal Tissues Directive).
- Guide to the Implementation of Directives Based on New Approach and Global Approach (European Commission).
- European Parliament and Council Directive 94/62/EC of 20 December 1994, on Packaging and Packaging Waste (PPW).
- Directive 2005/32/EC of the European Parliament and of the Council of 6 July 2005,
- establishing a framework for the setting of Eco design requirements for energy-using products and amending Council Directive 92/42/EEC and Directives 96/57/EC and 2000/55/EC of the European Parliament and of the Council (EuP Directive).
- Directive 2002/96/EC of the European Parliament and of the Council of 27 January 2003 on waste electrical and electronic equipment (WEEE) - Joint declaration of the European Parliament, the Council and the Commission relating to Article 9.
- List of European Harmonized Standards (Official Journal of the European Communities).
- European Commission Europa web site for Medical devices and all guidance documents.
- ISO 9001: 2008 Quality Management Systems. Requirements.
- ISO 13485: 2003 Medical devices - Quality management systems - Requirements for regulatory purposes.
- PD ISO/TR 14969: 2004 Medical devices - Quality management systems - Guidance on the application of ISO 13485: 2003.
- ISO 14971: 2009 Medical devices – Application of risk management to Medical devices.
- EN 12442-1: 2007 Medical devices utilizing animal tissues and their derivatives. Application of risk management.
- EN 12442-2: 2007 Medical devices utilizing animal tissues and their derivatives. Controls on sourcing, collection and handling.

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- EN 12442-3: 2007 Medical devices utilizing animal tissues and their derivatives. Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents.
- FDA’s Quality System Regulation, Part 820 of 21 CFR (US Code of Federal Regulations).
- FDA’s CDRH web site and all guidance, especially that provided by Device Advice.
- IMDRF. Website: www.imdrf.org