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USFDA BIOLOGICAL EVALUATION AND SAFETY ASSESSMENT OF MEDICAL DEVICES

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ABSTRACT

In this paper, I will give an extensive account of the regulatory process governing the food and Drug administration (FDA) of United States; dealing with the safety, efficacy, and quality control of the medical devices. It draws the reader's attention to the history of the regulation of using medical devices with references to such legislations as Medical Device Amendments of 1976 and the FDA Safety and Innovation Act of 2012. The division of the devices according to the level of risks into Classes I, II, and III is mentioned, and the biocompatibility and safety testing with detailed description as provided in ISO 10993 portrays. The similarity between ISO 14971 corresponded to risk management procedures and ISO 13485 and cGMP to quality management systems in order to demonstrate regulatory stringency. Post-market surveillance processes are also discussed such as the MAUDE database and the 510 (k) / 522 pathways. In general, this paper supports the necessity of effective and changing regulation system to find the balance between medical innovations and the safety of population.

INTRODUCTION

Medical devices are very substitutable to the products of high efficacy that offer similar products. Due to this, the success in the market lies in the new product and technology development as well as commercialisation. To be in line with their duties and responsibilities of regulation in order to keep their patients and customers out of harm, the medical device industry and actually the regulators are largely seen as conservative towards any changes(Slattery et al., 2022). The U.S. Food and drug administration FDA statutory mission protecting and promoting the public health. In that same context, all medical devices available in the United States are subject to control by the FDA. The rules are supposed to monitor all safely and effective devices sold in the market (Pietzsch et al., 2007)

About 25 cents of every dollar used by consumers in the US are regulated by the food and drug administration (FDA) and 75 percent of this is food. The reviewed activities of the FDA embrace food (Center for Food Safety and Applied Nutrition), tobacco (Center for Tobacco Products), veterinary medicine and feed (Center for Veterinary Medicine), drugs and biologics (Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research), and the topic of the current paper medical devices and radiological products (Center for Devices and Radio logical Health). CDRH (Center for Devices and Radiological Health) safeguards the Americans by putting in place measures to protect the people by allowing Americans a reason able safety to use medical devices and radiation-emitting products, and to be safe and effective when used. This review aims to give an overview of a top-level of the medical device regulation. Congress adopted the Food Drug and Cosmetic (FD&C) act Medical Device Amendments of 1976, which gave the FDA the authority to regulate the devices [2,3]. Prior to the Medical Device Amendments, the FDA had the power to file charges of adulteration or misbranding, but a request of premarket testing, review, or approval was not within its powers. FDA medical device authority has since been altered by subsequent laws, the latest being the FDA Safety and Innovation Act of 2012 (Jarow & Baxley, 2015)

The responsibility of the U.S Food and Drug Administration (FDA) is to maintain the safety and efficiency of the medical devices in the United States and it regulates over 1700 categories of devices, 500 000 types of medical devices and 23 000 producers(Maisel, 2004). FDA has classified and listed more than 1700 different kinds of such devices and groups them in the CFR into 16 of medical specialty such as Cardiovascular devices or Ear, Nose, and Throat devices(FDA2018).

Relative to the case of the pharmaceuticals that the Federal Government had been regulating since the early 1900s, it was not until in May 1976, that the Congress signed the Medical Device Amendments to the Federal Food, Drug and Cosmetic Act FFD&C of 1938 into law, the actual regulation of the devices. As it is

stated by Fries 1, the main purpose of the amendments was to ensure that patients are safe and effective and effectiveness have adequate labels about the intended purposes of the devices used in medicine. To implement this mandate, these amendments empowered the FDA with the mandate to exert authority in the regulation of the devices in most of the product development, testing, manufacture, distribution and use. A medical device can be highly complicated as in the lifesaving implantable devices like the pacemakers and defibrillators and others can be as simple as a bedpan or a glove. Accessories Many accessories that we use on medical devices are themselves devices, along with some human tissue medical products (like heart valve allografts) (Jarow & Baxley, 2015)

MEDICAL DEVICES:

Medical device A medical device is defined as an instrument, apparatus, implement, machine contrivance, implant, in vitro reagent or other similar or related article(Jarow & Baxley, 2015). The proposed to be used in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, in man or other animals(Kramer, Xu, et al., 2012)

Medical devices include finger splints and tongue depressors on the one end of the spectrum, and computer-assisted (robotic) surgical systems on the other end of the spectrum. Also, the medical devices incorporate the in-vitro diagnostic products and radiation products used in therapy and medical imaging(Jarow & Baxley, 2015)

Risk based classification:

There are commonly three different categories of devices depending on their risk as determined by course I (least risk devices) to course III (highest risk devices)(Maak & Wylie, 2016) Any medical device is of 3 FDA regulatory classifications: Class I, Class II, and Class III. The risk the medical device poses to the patient and the degree of control over such medical device that the FDA indicates necessary to market the device legally are the designations that classify the medical device(Jarow & Baxley, 2015)

They realized that there is some amount of risk that is associated in the development of such devices. They also learnt that: 1 not all the risk can be eliminated; 2 that the previous experiences might be very few or none to build on a base of opinion on efficacy and safety; 3 that the acceptable performance of the devices sometimes have an improvement update during the studies under clinical trials; and 4 that even the performance could be different depending on the competency of the reader(Pietzsch et al., 2007) The higher the level of the classification, the more is the risk to the patient and the higher the level of the FDA regulation control. FDA had classified the categories of medical devices that had been marketed in the United States at May 28, 1976, the date at which the medical device Amendments were enacted, and these were allowed to continue marketing. Duly introduced medical devices into the market after May 28, 1976, will be categorized by comparing the intended use and technology attributes of the new medical device against those of the products that are in the market but legally marketable medical devices(Jarow & Baxley, 2015)

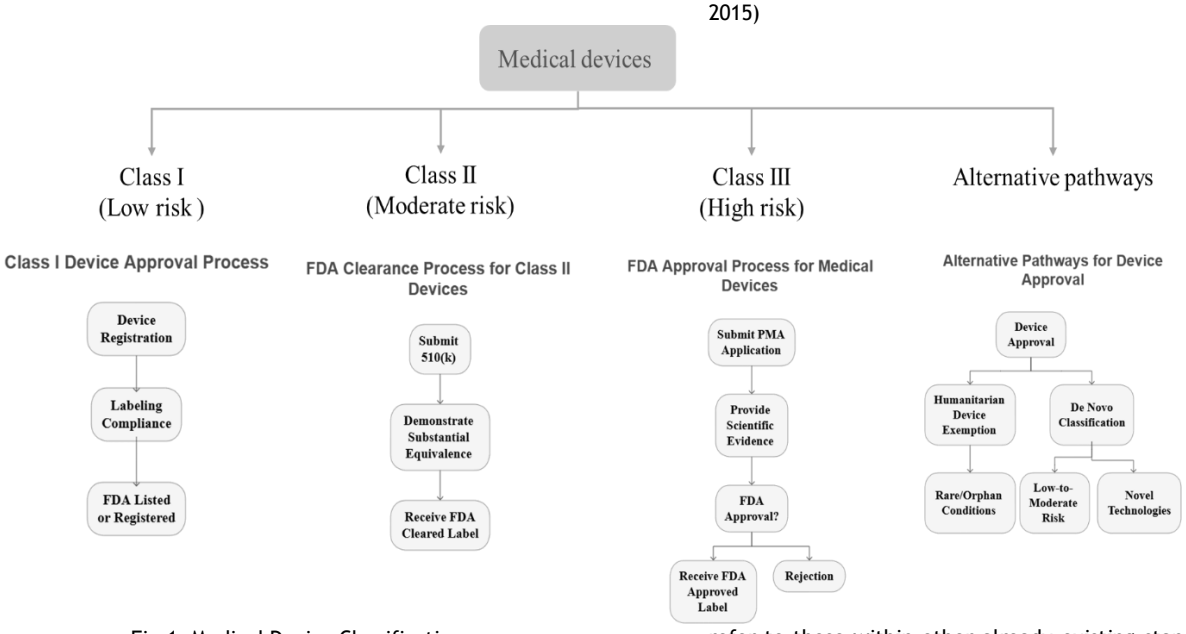

Fig.1: Medical Device Classification

Safety assessment of medical device

Biocompatibility Testing:

Biocompatibility refers to the reaction of a medical device when in a certain environment and condition of the body, it contacts directly or indirectly with the body and interacts with the host, either alone or in combination, as implanted in the body, living or deceased, and the dynamic process of change in vivo on the surface of biomaterials, and the ability to adapt to all functions of the host in a long-term host reaction, with the exception, and not excluded (1-3). As per the International Organization for Standardization (ISO) and national standards although the mechanical, physical and chemical properties or they are the best, but biocompatibility assessment is required when medical devices come into contact with the body(LI et al., 2015)

According to the ISO 10993, Part 1 and the Bluebook Memorandum G95-1 by FDA, there are twelve types of biocompatibility tests (Center for Devices and Radiological Health 1995). Assessment methods for data on cytotoxicity, sensitization, irritation, systemic and sub chronic toxicity, genotoxicity, implantation, hemocompatibility, chronic toxicity, carcinogenicity, reproductive toxicity and degradation have been produced, which give specific details on the methodology to be followed in each test, or which refer to those within other already existing standards. Limits of sterilization and sterilization residue, risk assessment, sample and reference materials, characterization of materials, explanation of data, clinical test results are among the other standards in ISO10993series(Northup, 1999)

Biocompatibility assays are used to prove the absence of any negative effects of the substance and to forecast and stop unwanted reactions. These tests aid in identifying any possible risks that a substance might present to a patient. By doing biocompatibility tests correctly, potentially harmful materials can be rejected while safe materials can be employed to make the device(Gad, 2011)

Cytotoxicity:

The part 5 of the iso 10993 sets out methods in vitro to evaluate the cytotoxicity of medical devices and their extracts. Suitable solvents that are used in preparation of extracts include culture medium (with or without serum) or saline. Serum may improve the extraction of the lipophilic substances, but the addition of serum can decrease their bioavailability through binding of serum proteins. The Four assays methods available are given Extract test Quantitative, which is good when dealing with measurable parameters. Direct contact Extraction and exposure together; is useful on solid materials. Agar diffusion Materials that do not

leach well should be used. Filter diffusion This can be applied to study fill-able bioactive chemicals. The different methods show a similar sensitivity with the difference in the ease, application and appropriacy depending on the properties of the materials. The standard is flexible to give the option to choose the most suitable test. In this regard, the test of cell viability is to be preferably used instead of total protein content on the use of formaldehyde-releasing material.

Sensitization:

ISO 10993-10 gives the procedure to test of delayed contact sensitization of medical device, and normally the animal to use is guinea pig. There are two principal assays; Maximization assay (preferable) Intradermal and topical induction, with a challenge phase. It evaluates skin irritation (erythema/edema), 10 animals are used and the test is performed with the aid of the Draize scale. Any positive case needs additional risk evaluation or testing. Closed-patch (Buehler) test: It is the one employed when extracts cannot be used in the maximization test. Topical application of the test material and occlusion is scheduled 3 times over a 3week period after which the test material is allowed to challenge and analyse the results of the skin on repeat evaluation. Validating test sensitivity Often test sensitivity is validated using Positive Control 10% dinitrochlorobenzene. Rechallenge can be undertaken when the results are inconclusive. Not in ISO 10993 In chronic studies, immunotoxicity is Not specifically investigated, although effects such as inflammation and immune system suppression may be cause to pursue it. Testing of anaphylaxis may be necessary in the devices which come in prolonged contact with blood but a standard test has not yet developed.

Irritation:

ISO 10993-10 specifies protocols to assess the potential of medical devices to cause irritation on the skin, eyes, and elsewhere with skin, eye, and intracutaneous (intradermal) tests, although some additional intracutaneous (intradermal) tests are given in Appendix D; protocols to determine oral, vaginal, rectal, and penile irritation are given in Appendix D. Test sample is topically applied with an occlusion of 4hours in rabbits. The erythema and edema are scored at 1, 24, 48 and 72 hours on the sites. There is calculation of a Primary Irritation Index (PII). Intracutaneous Irritation (Rabbits) At 5 places,0.2ml of the extracts in saline or oil are injected. Such groups of reactions scored on Draize scale at 0, 24, 48 and 72 hours.PII identifies severity (negligible to severe). The eyes are scrutinised in an attempt to detect the presence of corneal, iris, and conjunctiva damages, chemosis, and discharge. When the response is more than 50 percent of animals, a material is an irritant. This is permissible in post application rinsing, which is much more humane.

Systemic toxicity:

Purpose Determines the presence of toxic effects of medical devices systemic (whole body). Test Types Single dose on the blood path exposure devices. Repeated-dose Subacute: 1 month/ or less Sub chronic, 90 days/ or less, Chronic Modelled after cancer studies needed in the case of devices which remain in contact with blood, mucosa, or damaged skin. The pyrogenicity Testing checks whether devices are febrile (pyrogens). Rabbit test Value temperature injecting by a device extract. Endotoxin-detector In vitro alternative of LAL test. When Tested is called for on devices that have direct/indirect contact with the blood (e.g. IV sets, heart valves). Not necessary where there is no vascular contact (endotoxins can be destroyed by the tissues).

Genotoxicity:

The ISO 10993-3 provides the requirements of genotoxicity testing of medical devices, carcinogenicity testing of medical devices, and reproductive toxicity of medical devices. Products that have extended or permanent contact are normally-at-risk candidates that should have their genotoxicity evaluated. A suite of typical tests consists of three assays, and are generally run in vitro Ame's test (bacterial reverse mutation using Salmonella typhimurium) Sister chromatid exchange Sister chromatid exchange Sister chromatid exchange Sister chromatid exchange in mammalian cells Chromosome aberration assay Chromosome aberration assay Chromosome aberration assay in mammalian cells These assays are regulated by the OECD. Depending on the device used, in vivo tests may be deployed depending on the test. In vivo tests include the rodent micronucleus test, bone marrow assay, or dominant lethal assay. A supplement shall be provided to justify the reasons of choosing each type of test and assist in the guidance of usage according to the types of devices.

Implantation:

Application Measures local tissue response (a short-term, and chronic) of implanted medical device materials. Devices required when there is prolonged/permanent contact of tissue, bone, dentin or blood. Length of Implants Procedure 1 week; 12 weeks at maximum. Animal Model Mice, rats, rabbits, dogs, pigs etc. selected by the size and type of device to be tested. Implantation Sites Which can be subcutaneous or muscle; or bone-dependent on the intended clinical use. Macroscopic Tissue response (inflammation, necrosis, haemorrhage) is included in the evaluation. Microscopic Fibrosis, formation of capsules, inflammatory cells, in-growth of tissues and debris material. The common test 7-day intramuscular test in rabbits. Special Notes Test aims at non-degradable materials. In the case of degradable material, ISO considers different guidelines. Some of the important aspects in radiolabel studies, undestroyable labelling, poor mounting on plastic to be used in analysis of interface, and frequent tissue observation.

Hemocompatibility:

Part 4 provides a description of hemocompatibility studies of medical devices in contact with blood with emphasis on thrombosis, coagulation, haematology, platelet effect, and complement activation when they are in the contact of blood. Such tests are normally done ex vivo or in vivo (using animal models) and determine the interactions of the devices with components of blood. The Key tests are a Thrombosis Blood clot counting and cellular attachments with the use of a microscope. Coagulation Partial thromboplastin time (PTT) of clotting. Platelet Assessment Counts why it is used in measuring platelet activation and attachment. Haematology Leucocyte counts and haemolysis. Complement Activation Classical/alternative pathway The ISO standard includes a table of applicable hemocompatibility tests with medical devices

Carcinogenicity:

Evaluation of carcinogenicity of medical devices is not common and is generally reserved, unless specifically requested, for materials that are new in implants that are in long or cumulative contact (30 days). According to ISO 10993-3, resorbable material may require such testing unless the degradant information is present. Genotoxic substances need to be obtained, tested in terms of animal carcinogenicity prior to clinical trials. OECD-guided guidelines are applied, but species-specific effects on creating tumour's allow further interpretation to be complex. ISO requires two levels of doses on the basis of prolonged human worst-case exposure. They also have a draft standard given by ASTM and any other method of testing used should be scientifically defendable.

Degradation:

Degradation ISO 10993 Parts 13, 14 and 15 give guidance on identification and quantification of degradation products of polymers, ceramics and metals and alloys. All those standards are related to testing the discharge or leaching of chemicals and elements of those materials in a control atmosphere. The suitable methods are used to identify and determine the amount of degradation products. Health-based risk assessment of the extractable chemicals and elements is seen to be carried out to determine the safety of the materials in medical devices.

Sterilization and Process Residues:

Other manufacturing process and sterilization procedures can cause residue of processing agents and sterilant in the finished medical device. The international limits of the amount of ethylene oxide residues allowed to be contained in medical device were determined by part 7 of ISO 10993; Ethylene oxide sterilization residuals. These restrictions have to be achieved when the machine spreads to the market. Since the ethylene oxide is a gas, the diffusion process happens even after the release of a product thus the residue that the patient comes into contact with can be practically untouchable. Other process residues: A health-based risk assessment process, which is presented in ISO 10993-17, Establishment of permissible limits for sterilization and process residues, establishes limits on other process residues. These may be glutaraldehyde tissue xenograft residues of a blood vessel or

heart valve, other sterilization residues: per acetic acid, formaldehyde, chlorine dioxide, ozone, and hydrogen peroxide, and cleaning agents: solvents and detergents(Northup, 1999)

Immunotoxicity:

Injections with a material that produce immune toxic effects may be detected using systemic toxicity studies. ISO/TS 10993-20 (2006) proposes a framework to the assessment of immunotoxicity with hazard identification of first stages. The in vitro tests lack the ability to identify the immune response due to the complexity of the immune system as opposed to the in vivo rodent response that is essential in identifying immune response including variation in the weight of lymphoid organs, animal histological characteristics, cell population size, or susceptibility to infections. Immunotoxicity testing - Nonfunctional assays (e.g. organ weight, cell counts, immunoglobulin levels) are the first choice in defining the early indicators. Functional assays (e.g. mitogen stimulation, immune challenge with pathogens) are aimed to show the performance of the immune response. Systemic effects are inflammation and immunosuppression, hypersensitivities, and autoimmunity. Other ISO 10993 parts cover some of these endpoints, and the ISO/TS 10993-20 directs other immune system assessment(De Jong et al., 2020)

RISK MANAGEMENT:

Nevertheless, when they fail or are overworked these gadgets can be dangerous. Thus, unless the manufacturer employs a powerful risk management practice, it is quite likely that a medical device will harm both patients and/or users of the device. Medical devices - One such international standard is the application of Risk Management to Medical devices. The ISO 14971 standard provides the criteria of an effective process of risk management and urges businesses to address and deal with risks of the medical device under development. But this standard just presents what should be done and not how this should be done which presents companies with some freedom on how they carry out the process which is adjusted to meet the requirements(Flood et al., 2015)

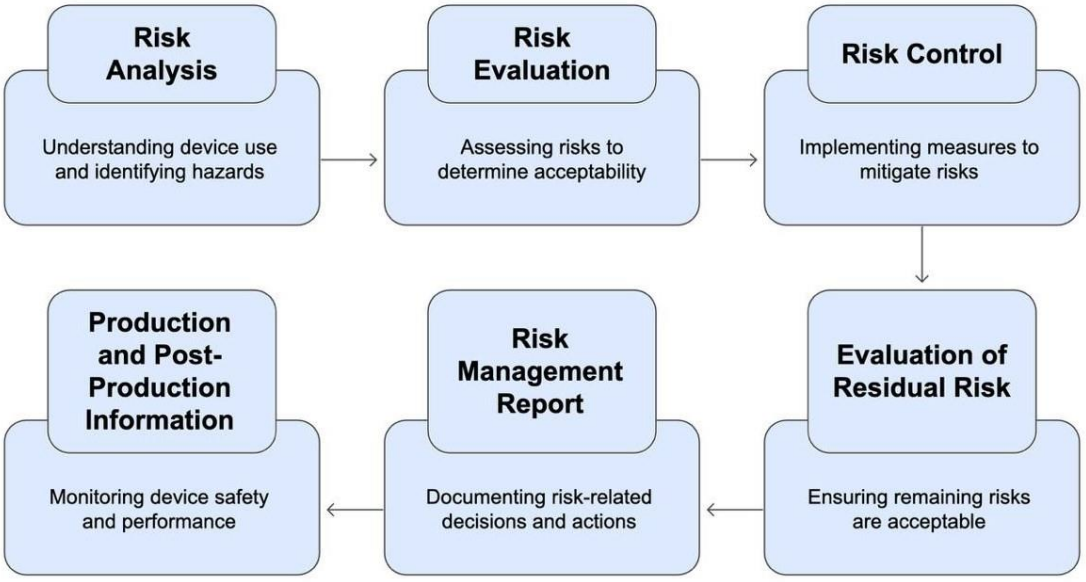

Fig.2: Risk management Process of Medical devices

An overview of the 13 steps in the ISO 14971 standard for risk management activities carried out at the various stages of the risk management process Risk Analysis (step 1,2,3), Risk evaluation (Step 4), Risk control (Steps 5 to 10), Overall residual risk evaluation (Step 11), Risk management report (Step 12), Post production information (Step 13)(Hegde, 2011)

The manufacturer will determine, describe and keep through life-cycle a process of continuous improvement on identifying hazards relating to a medical device; estimate and evaluate the associated risks and control these risks; and monitor the effectiveness of the controls in relation to the identified hazards(Chan T & Tong RK, n.d.)

Risk analysis: In the risk analysis segment, identification of all potential hazards of the clinical equipment is carried out. These risks are in turn assessed as far as their viability to materialize and as far as level of damage. The standard does not tell which metrics to deploy to ensure the assessment of the likelihood and the level of harm to enable organisations to choose an approach that best fits their needs. The organisation can decide to do this evaluation qualitatively or quantitatively according to the device being developed and the organisational culture.

Risk evaluation: The organisation is required to ascertain whether risk-control measures are called upon using probability of occurrence and severity of harm. When the probable deed of harm is minimal and the resulting harm being not severe then an organisation can choose to adopt the IS acceptable. The acceptable level of risk may depend on the utility that the medical device provides and hence it may differ among medical devices. To illustrate, in the instance of a computerised tomography scanner, the level of acceptable risk would be much more than that of blood pressure monitor because the benefits derived out of the computerised tomography scanner would be very high.

Risk control: After the risk has been ascertained to be unacceptable the organisation must undertake a risk control measure to deal with the risk. The standard details three categories of risk control that are broad subjects.

Overall residual risk acceptability effects: After ensuring that all the risk control measures are under control, then the organisation should assess the other risks to ascertain whether they are acceptable or not. Otherwise, the organisation should decide whether the advantages of the medical device supersede the risks of the device.

Risk management report: The organisation ought to conduct a review of the risk management process before releasing the product and it should submit a risk management report. During this review, the organisation must make sure that the process of risk management has been conducted in a proper manner, the total residual risk acceptable, and the right mechanisms that should be in place in a bid to get the right information pertaining to production and post-production safety.

Post-production and information: At this stage(s) of the product life the medical device should be checked within the organisation so that it does not contain any other unidentified risks or risky situations earlier, and that the number of estimated risks caused by a hazardous situation remain as tolerable. In case it is not, the information ought to be recycled into the risk management process(Flood et al., 2015)

Factors for the Assessment of Medical Device Benefits:

To enhance compliance and safeguard the quality of medical devices and patients, FDA considers a total benefit of the device via diverse aspects during development and its widespread productiveness. Such changes, that can change over time, concern not only direct health effects, but also their effect on planning of treatment, relieving of symptoms, quality of life and prevention

of the disease. Such extra clinical uses can also add value to a device through off label or expanded clinical use

Magnitude of benefit(s) is the extent of benefit (s) of treatment to patients or the efficacy of a medical device. The shift in the state of patients or the shift in required clinical treatment may enable FDA to ascertain the extent of consequent advantage. Magnitude of benefit can be measured relative to standards of care as well as anticipated performance and it could vary with time.

Probability of patient benefit of a medical device is the extent to which it is to be expected to be able to treat of diagnose a condition successfully. Patients do not receive the same number of benefits. The calculation of this probability is arrived at by dividing the number of successful outcomes with the total number of treated populations. Manufacturers are obliged to consult with FDA in as far as presentation of relevant data is concerned. Perhaps FDA can also take into consideration subpopulations, which have more benefit compared to the general population. Adding the subgroup benefits to the benefit-risk analysis should be done under the overall single benefit-risk analysis.

Duration of effects: The length of duration of a treatment advantage. Therapeutic interventions tend to deliver lasting effect. The long-term benefits may be extended than those previously depicted in the clinical reports with real world use.

Patient Perspective: Patients are interested in the usefulness of a device according to the severity of the condition. People suffering with severe or terminal illnesses can attach a great deal of importance to the short-term benefits, but this is not necessarily the case with people with less severe illnesses.

Healthcare Professionals/Caregivers: These advantages are enhancement of patient care, which is shortening the procedure time, and versatile usage at various levels of skills. Clinical practice can be improved with devices that promote new techniques or superior continued care.

Medical Necessity: Think whether the device responds to the needs that cannot be satisfied by the other forms of therapy or whether there are alternatives. Academic evaluation ought to consider availability of substitutes.

Factors for the Assessment of Medical Device Risks:

In ranking its compliance and enforcement activities to develop a medical device and to guarantee patient safety, FDA considers several risk factors simultaneously to develop an understanding of whether the device will cause direct or indirect risks to patients. These factors are to be evaluated at early stages in the device lifecycle and updated once the device had broader use with relative changes of risk being reported by the manufacturer. The unexpected hazards, variation in the environment in which the device is used, presence of nonconformity identified as well as the problems related to the design and manufacture may result into variations in risk. There are risks on all the devices in relation to whether the device is in compliance or not, and it may happen either given the proper functioning or not. Nonconformities and regulatory non compliances have the potential to increase the risks in question or introduce additional risks, whereas post market data can lead to discovering risks higher than was previously realized without necessarily initially identifying a problem in question. In that way, risk is a dynamic phenomenon, and it should be assessed on an ongoing basis in the light of all these facts and applied to regulatory measures.

The process of likelihood of risk looks at the risk factors that deal with the possible number of patients who may be at risk of being subjected to harm; likelihood of a medical device having problems, likelihood of a patient being subjected to harm, and the total number of patients. Manufacturers who want to submit data and calculations to be used in the assessment of this factor are requested to contact FDA about what information is potentially relevant and germane to the question under consideration.

Distribution of nonconforming devices entails; is nonconforming product distributed and is so, how many nonconforming devices are available in the market.

Duration of exposure to population is the time between the first exposure of patients to device with identified risk of harm and when this risk of harm has been dealt with.

The risk factors of diagnostics are false-positive or false-negative. An erroneous diagnosis, e.g. the diagnosis of a severe disease when the patient is not actually sick, may happen when a diagnostic medical device produces a false-positive result, and proceeding with such a misdiagnosis may entail all the risks of the medical procedure involved. In case a diagnostic medical device produces a false-negative result, then the patient may fail to be assigned with the right disease or condition and may fail to receive efficacy treatment (thereby he/she could miss the effects of the treatment itself). The risks related to false positives and false negatives may be multiple but are measured by FDA with consideration to likely risks

Patient tolerance of risk is also the extent to which patients are willing to accept risks of adverse harm caused by a medical device even when the product is nonconforming (or non-compliant). This differs per individual and is moderated by the estimations of advantages, levels of dangers, and knowledge of dangers oftentimes with the assistance of clinicians in the effects of prescription devices. This can also be classified as risk to healthcare professionals or care givers where it may affect the professionals and care givers safety(USFDA 2018)

Quality management system:

ISO 13485 is a standard of quality management system that is specific to designing and production of medical devices. It was first published in 1996 and updated in 2003 and defines minimum requirements necessary to ensure that an organization can continually satisfy the regulations and customers' requirements. It superseded older standards such as EN 46001, EN 46002 and ISO 13488. Although ISO 13485 is related to the ISO 9001, it is different because it is aimed at conforming compliance with the regulation instead of being result-focused on continual improvement, which is also the objective of the ISO 9001(MICHELLE A. WHITTAKER, n.d.)

Though roughly 70 percent of the ISO 13485:2003 has been adopted as ISO 9001:2000, it pays more attention to quality of products, their compliance to regulations and risk management. The goal of the standard is to deliver medical devices which are proven to be safe and effective in their diagnosis, treatment or prevention and capable of meeting the regulation as well as the needs of the customers. Though it somewhat parted with ISO 9000, bringing both standards together would be much beneficial to implement regulatory emphasis along with continuous enhancement and customer satisfaction(Hamimi Abdul Razak et al., 2009)

The FDA has written certain Good Manufacturing Practice (GMP) controls to the different types of products Dietary supplements Should satisfy the requirements of 21 CFR Part 111 Pharmaceutical products fall within the provisions of 21 CFR Parts 210 and 211 Medical devices are addressed in 21 CFR Part 820Every set of regulations contains the quality and safety requirements that manufacturers need to achieve in their respective product types(Lincoln JE, n.d.)

Medical device products are accustomed to the requirements of Current Good Manufacturing Practice (cGMP) (FDA, 1996). One of the concepts of cGMP is that well-defined and exactly-regulated manufacturing processes are needed. Processes that are considered critical should also be validated, and this is done to make sure that such processes always perform as per agreed specifications and standards. Guaranteed manufacturing quality and process reliability are some of the main current barriers towards introducing Additive Manufacturing (AM) as a mainstream production process. In this paper, a thorough review of the AM application in the medical device business is done(Wai Yee Yeong, n.d.)

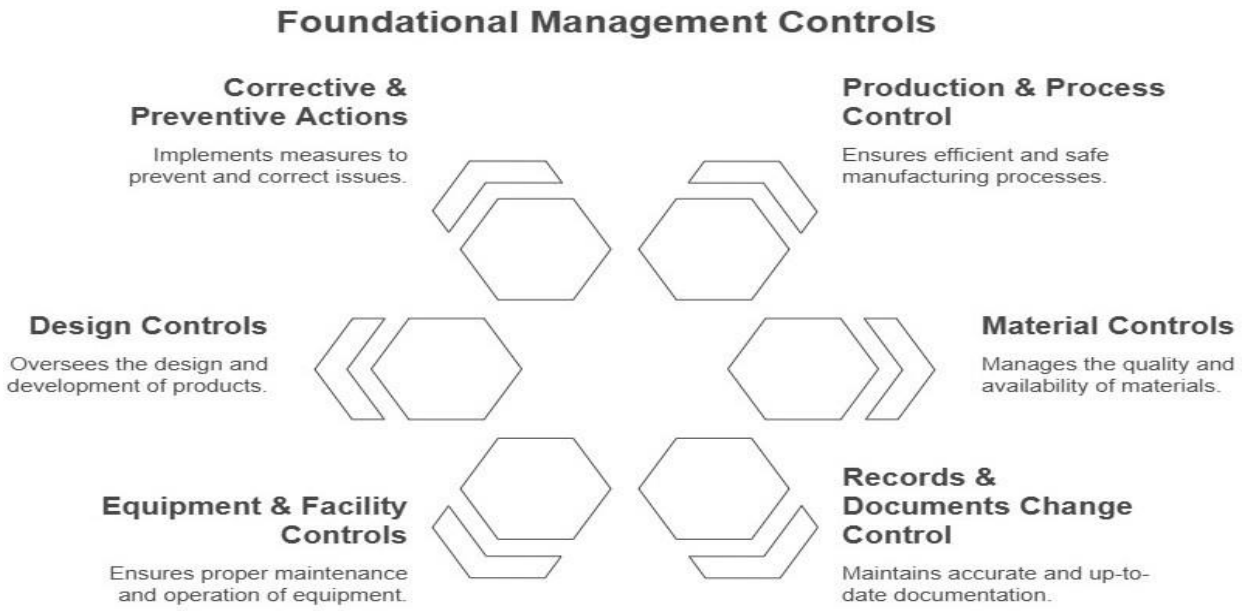

Fig.3: Overview of the Quality Management System

Post marketing surveillance:

Once medical devices are licensed in the U.S., the manufacturers are expected to have quality control systems and report all cases of adverse events to FDA and most likely not through healthcare providers but through the representatives of the company instead. Post market surveillance (PS) by FDA may be required as a post-approval study of high-risk or rare-disease device, or as a 522 study of a selected device cleared under the 510(k) pathway. The 510(k) normally does not involve new clinical data, but uses substantial equivalence to current devices.

The FDA delivers the safety communications or alerts when the relevant potential safety issues are found by PS. The manufacturers may have recalls and the FDA may request recalls, serious ones expected to be closely observed. The FDA monitors recalls and alerting in the public databases as well. There is a proposed Unique Device Identifier (UDI) system to enhance reporting, tracking of adverse events as well as coordination of recall of the devices(Kramer et al., 2013)

The Safe Medical Devices Act of 1990 was passed creating the MAUDE database, under which the sites where the medical devices are used (hospitals, nursing homes, physicians' offices, etc.) must report the device related fatalities and serious adverse events directly to FDA and also report the same to the manufacturers (FDA1990). The serious cases which require urgent action have a deadline of 5 days, otherwise 30 days. Since 1996 reports have been compiled in the MAUDE database where it is both mandatory and voluntary to be contributed by a variety of sources (FDA2006). Data focused on finding Unfavourable events related to privacy or security problems was found by searching the Manufacturer and User Facility Device Experience (MAUDE) database (Kramer, Baker, et al., 2012)

The safety-surveillance program of FDA has depended on physicians, health care institutions, manufacturers and patients to report the launch of failures and complications of medical devices via the Medical Device Reporting system. This system has the ability to track unpredicted failures and complications of medical devices but some limitations are that it ought to undergo numerous analytic reviews and is not intended to replace a clinical practice review (Hauser, 2012)

A course of action that includes the establishment of a comprehensive post-market surveillance plan as part of the approval process between the FDA and the companies that sell medical devices could lead to an easier approval process and could also provide the regulating bodies, the physicians and the patients with a much needed set of data to direct the use of the new devices after they have been placed on the market(Mehran et al., 2004)

CONCLUSION

The safety and the regulation of medical equipment's are key to the health of the people, as well as innovation. Standards such as ISO 10993 and ISO 14971, as well as the risk-based classification system of FDA, form an excellent background on which safety, biocompatibility and performance can be assessed. Quality standards (the International Organization for Standardization ISO 13485 and cGMP) guarantee that manufacturing is carried out in consistent ways, but market surveillance (the MAUDE database) can monitor actual results of the products in real-world conditions. Medical regulation is a very dynamic process which needs to keep up with modern changing medical technology so that patients are given unquestionable and competent medical devices.

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