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ADDRESSING SAFETY CONCERNS: A CRITICAL EXAMINATION OF MEDICAL DEVICE SAFETY ASSESSMENT IN THE US MARKET

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ABSTRACT

Medical devices play a vital role in modern healthcare, facilitating diagnosis, treatment, and patient care. As the complexity and diversity of medical devices grows it is essential to ensure the safety of the medical devices. This article presents a comprehensive review of the different testing methods followed for the safety assessment and process which needs to be followed to achieve a more effective and systematic approach to evaluating medical device safety. The review encompasses of existing safety assessment techniques include pre-market testing, risk management, quality management system, post marketing surveillance. The potential benefits of the proposed framework are significant, as it promises to enhance the overall safety and reliability of medical devices, reducing the occurrence of adverse events and improving patient outcomes.by enabling a more comprehensive and data-driven approach to safety assessment, healthcare systems can gain valuable insights into device performance, facilitate informed decision making, and foster innovation in the medical device industry.

Keywords: Medical Devices, Safety Assessment, Risk management, Post marketing Surveillance

INTRODUCTION

Medical equipment can easily be replaced by comparable goods with higher efficacy. Because of this, the creation and commercialization of new goods and technology are essential for market success **[1]**. Consumer spending in the US is governed by the Food and Drug Administration (FDA) to the tune of about 25 cents of every dollar, of which 75% is spent on food. The focus of this article is

medical devices and radiological products, but the FDA also regulates food (Centre for Food Safety and Applied Nutrition), tobacco (Centre for Tobacco Products), veterinary medicine and feed (Centre for Veterinary Medicine), drugs, and biologics (Centre for Drug Evaluation and Research and Centre for Biologics Evaluation and Research) (Centre for Devices and Radiological Health) **[2]**. The formal regulation of devices was not implemented until May 1976, when Congress passed the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act (FFD&C) of 1938, in contrast to medicines, which have been subject to federal control since the early 1900s **[2]**.

The revisions were made in order to guarantee that medical devices were reliable, efficient, and appropriately labelled for their intended use**[3]**Prior to the Medical Device Amendments, the FDA had the right to file complaints about adulteration or misbranding but was not able to ask for pre-market testing, review, or approval. FDA's authority over medical device regulation has been altered by later legislation, most recently the FDA Safety and Innovation Act of 2012 **[2]**. The U.S. Food and Drug Administration (FDA) is responsible for policing more than 1700 different categories of medical equipment, 500 000 different medical device models, and 23,000 different producers throughout the country **[3]**. The intricacy of medical devices varies widely, from implantable life-sustaining devices like pacemakers and defibrillators to simpler "devices" like bedpans and gloves. Many device accessories, including plastic tubing and computer software, as well as some human tissues, such as heart valve allografts, are regulated as devices **[3]**. According to their intended purpose, whether they are invasive or implantable, and the risk they pose to the user, the FDA categorizes devices into one of three regulatory classifications **[4]**.

MEDICAL DEVICES

Simple tongue depressors and sophisticated technology like computer-assisted (robotic) surgical systems are examples of medical equipment **[2]**. The term medical device is defined by the U.S. Congress as (6) “an instrument . . . which is . . . intended for use in the diagnosis, . . . the cure, . . . treatment, or prevention of disease . . . and which does not achieve any of its intended purposes through chemical action within or on the body. This definition creates a distinction between medical devices and drugs **[5]**.

RISK-BASED CLASSIFICATION

The majority of devices are categorized from class I (lowest risk) through class III based on their level of risk (highest risk) **[6]**. They recognized that some degree of risk is inherent in the development of devices. They also realized that: (1) All hazards cannot be eliminated; (2) There is often little

or no prior experience on which to base judgments about safety and effectiveness; (3) That devices undergo performance improvement modifications during clinical trials; and (4) That results also depend on the skill of the user (2). The risk a medical device poses to a patient and the degree of regulatory oversight the FDA deems necessary for the device to be sold legally determine the classifications. The risk to the patient and the extent of FDA regulatory oversight both rise as the classification level does **[2]**.

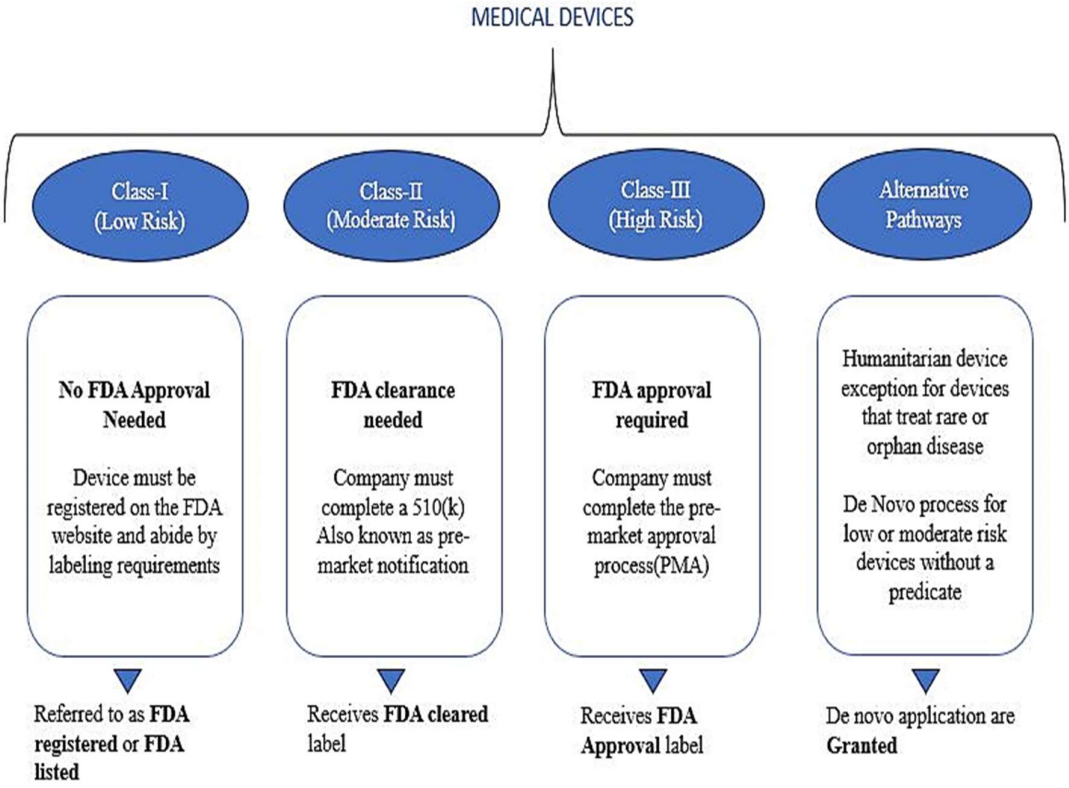

Figure 1: Classification of medical devices

SAFETY ASSESSMENT FOR MEDICAL DEVICES

BIO COMPATIBILITY TESTING

These items need to have strong physical and chemical qualities as well as good biocompatibility because they come into direct touch with body tissues and cells **[7]**. The FDA's Bluebook Memorandum G95-1 and ISO 10993, Part 1 both list twelve categories of biocompatibility tests (Centre for Devices and Radiological Health 1995). Standards have been created to evaluate cytotoxicity, sensitization, irritation, systemic, sub-chronic, genotoxic, implantation, hemocompatibility, carcinogenic, and degrading toxicity. For each assay, these standards outline a specific methodology or cross-reference other

existing standards. The selection of test methods is based on the kind, level, frequency, and conditions of human exposure to the gadget during normal intended use as well as the chemical and physical makeup of the item. When a toxicity profile is known and acceptable or when the presence of leachable compounds has been ruled out, some biocompatibility studies may be performed **[8]**.

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 **[9]**.

CYTOTOXICITY

Cytotoxicity testing is necessary for all medical devices. Culture medium with serum, culture medium without serum, 0.9 percent sodium chloride, or another nontoxic solvent are all acceptable extraction solvents. It is generally accepted that adding a serum to the extraction vehicle will improve the extraction of compounds with lipophilicity. The bioavailability of extracted lipophilic substances that bind to serum albumin, however, might be constrained. There are four assay techniques offered: direct contact, agar diffusion, filter diffusion, and tests of extracts.

SENSITIZATION

The maximal and closed-patch assays are described in Part 10 of ISO 10993, Tests for Irritation and Sensitization, and are used to assess the possibility of delayed contact sensitization of extracts of medical devices. All medical gadgets must be tested using a guinea pig delayed contact sensitization experiment. The maximization assay is preferred, but if a sufficient extract cannot be generated for the maximization assay, the closed-patch (Buehler) test may be employed. An interesting history of sensitization tests and a list of substitute assays are provided in the appendix to Part 10. The intradermal induction, topical induction (priming dose), and challenge phases of the maximizing assay all involve a preparatory test to determine a non-irritating concentration of the test substance.

IRRITATION

Part 10 of ISO 10993, Tests for Irritation and Sensitization, contains procedures for assessing the potential for irritation of medical devices. Most medical equipment needs to be tested for irritation. The assays for skin, eye, and intracutaneous (intradermal) irritation are done using the techniques in Part 10. The procedures for the oral, penile, rectal, and vaginal irritation tests are outlined in Appendix D of this standard. It is announced that test compounds that have a pH of 2 or less or greater than 11.5 are irritants, and no

additional testing is necessary. The intracutaneous irritation assay in rabbits assesses if an extract of the test substance will result in skin tissue necrosis, ulceration, erythema, or edema.

GENOTOXICITY

ISO 10993-3, A battery of three genotoxicity assays is necessary for testing for genotoxicity, carcinogenicity, and reproductive toxicity. A genotoxicity assessment is necessary for most medical devices with ongoing or permanent interaction. The most often used in vitro assays are the sister chromatid exchange in mammalian cells, the chromosome aberration assay in mammalian cells, and the Ames test for bacterial reverse mutations using Salmonella typhimurium. The Organization for Economic Cooperation and Development (OECD) standards outline the test methodology. For some medical devices, in vivo genotoxicity experiments such as the rodent micronucleus, rodent bone marrow, or dominant lethal assay may be applicable.

HEMOCOMPATIBILITY

Several test categories for evaluating interactions of medical devices with blood are described in Part 4 of the ISO standards, "Selection of tests for interactions with blood." Medical instruments that come into touch with the blood directly or indirectly must undergo hemocompatibility testing. Thrombosis, coagulation, hematology, effects on platelets, and complement activation are testing categories that are covered by the standard (i.e., immunology). These studies are often carried out when the ready-to-use medical gadget is exposed to animal models either ex vivo or in vivo. By using light microscopy, thrombosis measurements assess the presence of blood clots, adherent leucocytes, erythrocytes, fibrin, etc.

CARCINOGENICITY

Because the criterion is only applicable to new materials applied in implanted devices and those with a permanent or cumulative contact of at least 30 days, testing of medical devices for carcinogenicity is very uncommon. Unless there exist data on the identification and biological effects of the degradants, carcinogenicity assays may be required for resorbable materials and devices, according to ISO 10993-3, Tests for genotoxicity, carcinogenicity, and reproductive toxicity. Before moving further with clinical trials, substances that are discovered to be genotoxic in mammalian cells must first undergo carcinogenicity testing in animals. In OECD standards, assay methodologies are described.

IMPLANTATION

Tests for local effects after implantation, Part 6 of the ISO standards, evaluate the local effects of a material placed on living tissue at the macroscopic and microscopic levels. Medical devices that come into touch

with blood, tissues, bone, or dentin for an extended period need to be implanted for testing. The approach in Part 6 is used to evaluate both long-term and short-term impacts (lasting up to 12 weeks). For a typical wound to heal around the specimens, a minimum implantation period of one week is advised. After an acute wound has healed, the tissue response more properly depicts the biological reaction to the implanted material in its steady state, including the reshaping of the wound tissue surrounding the implant

DEGRADATION

The procedures for the identification and quantification of degradation products from polymers, ceramics, metals, and alloys are provided in ISO 10993 Parts 13, 14, and 15, respectively. The examination of the release or leaching of chemicals and elements from the materials under standardized conditions is required for each of these criteria. Suitable procedures are used to identify and quantify the degradation products. To determine the safety of the components in medical devices, a risk assessment based on health will be done on the chemicals and elements that can be extracted.

STERILIZATION AND PROCESS RESIDUES

The completed medical device may contain processing agents and sterilant residues from the various sterilizing and manufacturing operations. International restrictions on the amount of ethylene oxide residues allowed in medical equipment were defined by Part 7 of ISO 10993, Ethylene oxide sterilization residuals. Since ethylene oxide is a gas, the diffusion of the substance continues after the product has been released, hence the quantity of residue that the patient may be exposed to is potentially almost non-existent. A tissue xenograft for a blood vessel or heart valve, as well as other sterilization residues like peracetic acid, formaldehyde, chlorine dioxide, ozone, and hydrogen peroxide, as well as cleaning chemicals like solvents, are examples of what might be left behind.

RISK MANAGEMENT

However, if these gadgets break down or are utilized improperly, they pose a serious risk. If the manufacturer fails to put a strong risk management approach in place, there is a very real possibility that a medical device will injure patients and/or the people using it. Medical devices - The application of Risk Management to Medical Devices is one such international standard. The standards for a risk management process are outlined in the ISO 14971 standard, which encourages enterprises to identify and manage risks related to the medical device that is currently being developed. However, this standard simply outlines what organizations must do, not how this must be done, giving companies some latitude for the procedure that is modified to satisfy the standards **[10]**.

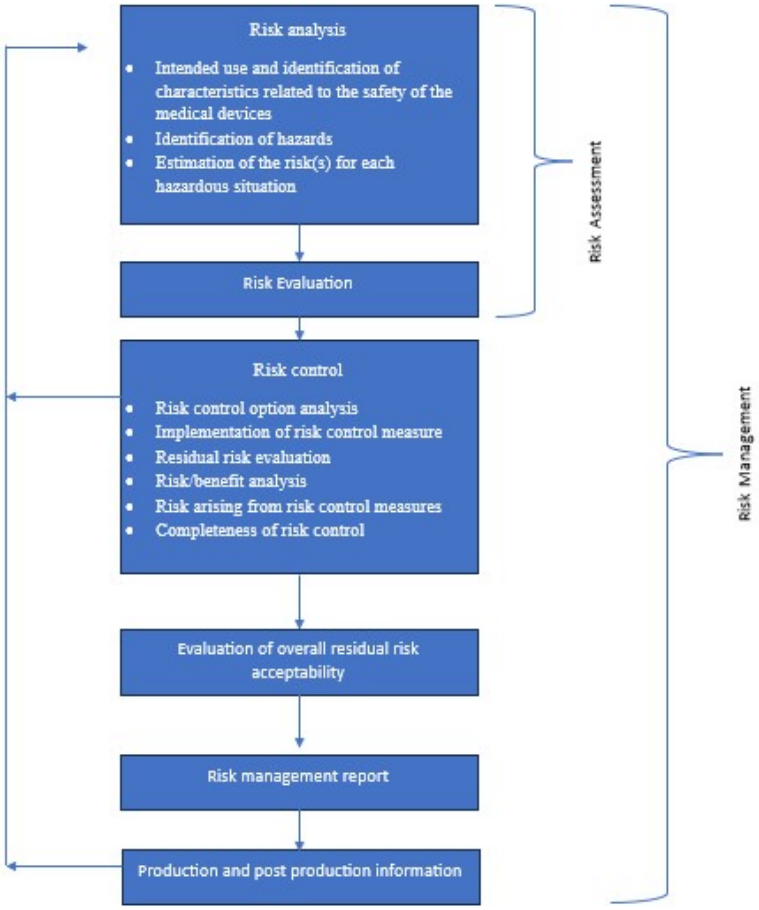

Figure 2: Overview of the risk management process

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) **[11]**. The manufacturer shall establish, document, and maintain throughout the life-cycle an ongoing process for identifying hazards associated with a medical device, estimating and evaluating the associated risks, controlling these risks, and monitoring the effectiveness of the controls **[12]**.

QUALITY MANAGEMENT SYSTEM

A standard called ISO 13485 was first released in 1996 and then updated in 2003. It stands for the fundamental needs of an extensive quality management system targeted at the development and production of medical devices. This offers a benchmark against which the industry can be judged in terms of its capacity to consistently provide medical devices and related services that meet the defined requirements and relevant regulatory specifications **[13]**. Every

industry can use the ISO Quality Management System (QMS), which is recognized as the "gold standard" for quality systems worldwide. The International Organization for Standardization (ISO) has created various industry-specific standards based on this standard, including those for the medical device industries **[14]**. FDA has issued specific GMP requirements for individual categories of products. Dietary supplements must adhere to 21 Code of Federal Regulations (CFR) 111. Pharmaceutical products are regulated by 21 CFR 210/211. Medical devices are governed by 21 CFR 820 **[15]**. In cGMP practices, it is fundamental to have a manufacturing process that is clearly defined and controlled. The critical manufacturing process must be validated to ensure consistency and compliance with specifications **[16]**.

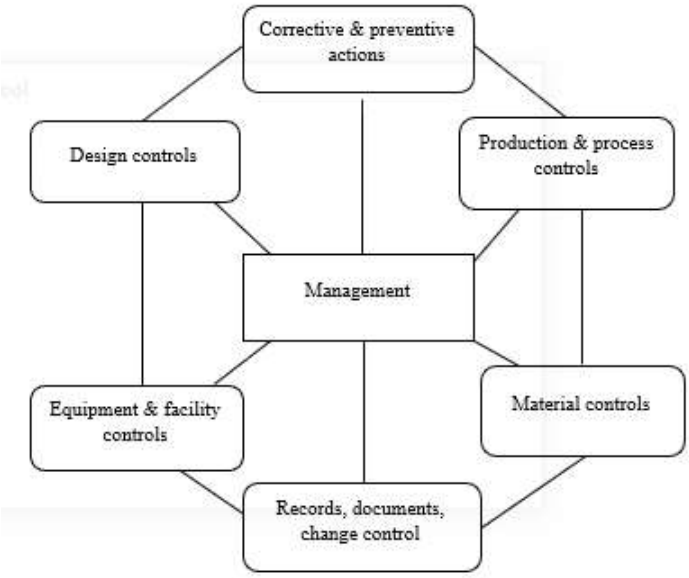

Figure 3: Overview of the Quality management system

POST MARKETING SURVEILLANCE

Companies are required to maintain quality production control systems once a device has received US approval. Additionally, they are required to report any adverse occurrences that are brought to their knowledge by their staff or user facilities to the US Food and Drug Administration (FDA), including patient demographics, clinical data, and procedure specifics. Despite having varying substance and quality, reports are compiled in a database that is publicly searchable. Specific time limits for reporting have been set (5 calendar days for any report of a device-related death, serious injury, or malfunction requiring

immediate remedial field action to prevent recurrence or 30 days if no remedial action is required). In addition, so-called "522 studies" for specific devices, such as those mediums **[17]**. Using the Manufacturer and User Facility Device Experience (MAUDE) database to hunt for un favourable incidents involving privacy or security issues **[18]**. The Medical Device Reporting system has been used by doctors, hospitals, manufacturers, and patients to report medical device failures and complications as part of the FDA's safety surveillance strategy **[19]**.

A strategy in which a thorough post-market surveillance strategy is established as part of the approval dialogue between the FDA and the businesses that market medical products may allow for a more streamlined approval process and could give the governing bodies, doctors, and patients more relevant data to guide the use of new devices as they are released onto the market **[20]**.

CONCLUSION

The assessment of medical device safety is a critical and evolving process that plays a pivotal role in safeguarding patients' health and well-being. This article delved into the key aspects of medical device safety assessment, highlighting the major stages and methodologies involved. Firstly, we explored the importance of regulatory frameworks and standards and medical device classification and then the different safety testing methods for the assessment of medical device and the article examined the significance of risk management and quality management in the medical device industry which is also important for the safety of medical devices. Furthermore, we explored the importance of post-market surveillance, emphasizing that medical device safety assessment does not end with regulatory approval. Finally, it should be noted that providing patients around the world with safe, efficient, and cutting-edge medical technologies depends on an extensive and thorough process for medical device safety assessment. We can improve medical device safety and make sure that people throughout the world have a better and safer future by adhering to strict rules, using risk management techniques, performing rigorous clinical research, and encouraging teamwork.

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CONFLICT OF INTEREST

Authors declare no conflict of interest amongst themselves.

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