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Enhancing Patient Safety Under The US and The EU Medical Device Regulations

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Enhancing Patient Safety Under The US and The EU Medical Device Regulations

Medical devices have improved and continue to improve the quality of life of patients. Medical devices undergo strict control under the US and the EU medical device regulations and the EU medical device directives. The control of medical devices in both the US and the EU aims to continuously ensure the patient safety.

Once medical devices are cleared in the US and the EU markets, the safety of these medical devices cannot be fully guaranteed. Fortunately, the manufacturers are required to continuously generate data regarding complications or problems which may only become apparent after long-term use of these devices. However, the generated data is not fully reliable as it does not capture the real performance of medical devices that are used by patients.

The US and the EU have different approaches in the application of risk management for medical devices. This research proposes a postmarket risk control periodic review framework that will serve as tool to ensure patients safety. The proposed framework can be adapted by any health authority of medical device around the globe.

Keywords:

Risk, patients safety, medical devices, vigilance, MedWatch.

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List of abbreviations

ASTM	American Society for Testing and Materials
BMI	Body mass index
BS	British Standards
BSI	British Standards Institution
CDRH	Center for Devices and Radiological Health
CE	Conformité Européenne (European Conformity)
CEN	European Committee for Norm
CFR	Code Federal regulation
DFMEA	Design failure mode and effect analysis
EEA	European Economic Area
EN	European Norm
EU	European Union
EUDAMED	European Database on Medical Devices
FDA	Food and Drug Administration
HDE	Humanitarian Device Exemption
ICD-10	International Classification of Diseases 10th revision
ISO	International Organization for Standardization
MAUDE	Manufacturer and User Facility Device Experience
MDCG	Medical Device Coordination Group
MDR	Medical Device Regulation

MIR	Manfacturer Incident Report
NB	Notified Body
NANDO	New Approach Notified and Designated Organizations
PMA	Pemarket Approval
PMCF	Post-Market Cinical Follow-up
PMS	Post Market Surveillance
PD	Published Document
QMS	Quality Management System
SNOMED CT	Systematized Nomenclature of Medicine -Clinical Terms
THA	Total hip arthroplasty
TR	Technical Report

1 Introduction

Medical devices have improved and continue to improve the quality of life of the patients. Medical devices undergo strict control under EU medical device directives and US medical device regulations. The new EU medical device regulation 2017/745 (MDR) replaced EU medical device directives. The new MDR with date of application on 26th of May 2021 promises further strict control of medical devices in the EU. The control of medical devices in both the US and the EU aims to continuously ensure the safety of patients. The control of medical devices in both the EU and the US is demonstrated by the US FDA, the EU Competent Authorities, the EU Notified bodies and manufacturers of medical devices through different mechanisms. The US FDA is referred here as FDA. These different mechanisms follow risk-based approach that addresses the safety and performance of medical devices. There are several recognized medical devices standards by the EU Commission and the FDA that are used by manufacturers to support the safety of the patients. The commonly used standard to address risk-based approach is the ISO 14971: 2019 Medical devices - Application of risk management to medical devices (FDA, 2022) and (EU Commission, 2022).

Once medical devices are cleared or approved in the US and the EU markets, the safety of these medical devices cannot be fully guaranteed. Fortunately, the manufacturers are required to continuously generate data regarding complications or problems which could only become noticeable after these devices have been released to the markets or during the long-term use of these devices. The generated data is therefore assessed and reported to the FDA, the relevant EU competent authority and if applicable to the notified body by the manufacturers of medical devices. There is a gap on the generated data related to the performance of medical devices in the US and the EU markets. The gap is that this generated data in not fully reliable as it does not capture the real performance of medical devices that are used by patients.

Since the EU medical device regulation is new, this research emphasized heavily on investigating the new EU regulation and identify gaps that are related to the safety of patients. In similar way, the investigation of similar gaps that exist in the US medical device regulation was carried too. The focus was only on hip implants class III passive medical devices. The reason for the focus of this research is that the class III hip implants represent medical devices with high risk.

2 Objectives and importance of research

The objectives of this research were as follow:

1) Analyze how patient safety is addressed in both the US and the new EU medical device regulations.

2) Identify potential gaps in both, the US and the new EU medical device regulations related to the safety of the patients.

3) Conduct full risk management investigation as per ISO 14971: 2019 to identify the weakness of medical devices reporting systems in the US and the EU.

4) Propose appropriate harmonized solutions to enhance the safety of the patients under the US and the EU medical device regulations.

The overall aim of this research is to find adequate solutions to capture reliable data of the devices that are released in the US and the EU markets. Consequently, the FDA and the EU competent authorities will be able to accurately identify the level of safety of the medical devices in their markets. The outcome of this research is to propose solution such as harmonized mechanism that will enhance patient safety under the US and the EU Medical Device Regulations. This mechanism can be used to support both FDA and EU competent authorities, EU notified bodies and the manufacturers of medical devices to improve the safety and performance of medical devices.

The proposed solution can be adopted by other medical devices regulations or laws around the world. The solution can serve as benchmark or foundation for harmonizing medical devices risk practices worldwide. The proposed solution will enable the manufacturers of medical devices to produce safer devices and will get quick market access in any country. In return, patients in any country will benefit from quick access of the safe medical devices.

3 Literature review

3.1 Total hip arthroplasty

The procedure related to hip replacement is referred as total hip arthroplasty (THA) (Migliorini et al, 2019). Sometimes total hip arthroplasty is referred as total hip replacement (Bishi,et al, 2022). THA is performed to treat patients with osteoarthritis (Mellon, et al, 2013). “Osteoarthritis is the most common form of arthritis, affecting millions of people worldwide. It occurs when the protective cartilage that cushions the ends of the bones wears down over time” (Mayo Clinic, 2022). Osteoarthritis symptoms often develop slowly and worsen over time. Signs and symptoms of osteoarthritis include (Mayo Clinic, 2022):

- Pain: Affected joints might hurt during or after movement.
- Stiffness: Joint stiffness might be most noticeable upon awakening or after being inactive.
- Tenderness: The joint of patient might feel tender when he/she apply light pressure to or near it.
- Loss of flexibility: Patient might not be able to move his/her joint through its full range of motion.
- Grating sensation: Patient might feel a grating sensation when he/she use the joint, and he/she might hear popping or crackling.
- Bone spurs: These extra bits of bone, which feel like hard lumps, can form around the affected joint.
- Swelling: This might be caused by soft tissue inflammation around the joint.

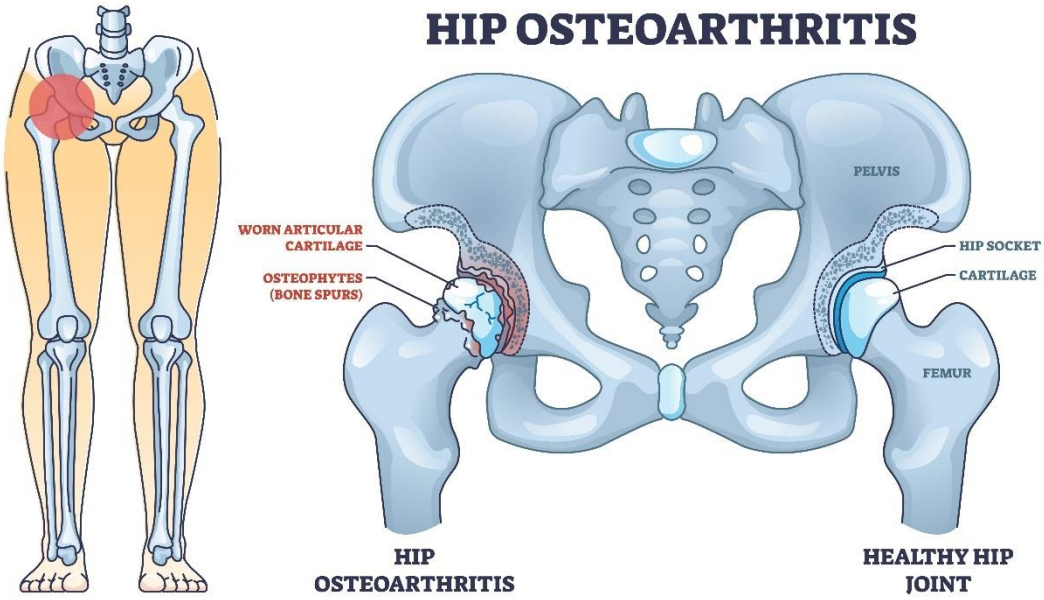

Figure 1. Osteoarthritis of the hip.
(Source: Adobe Stock, education licence, 2023).

The hip joint shown on the right side (HEALTHY HIP JOINT) of the Figure 1 in blue is normal hip joint. The hip joint shown on the left side (HIP OSTEOARTHRITIS) of the Figure 1 shows worn of cartilage and the formation of bone spurs due to osteoarthritis.

According to Johns Hopkins University (2022) “Hip replacement, also called hip arthroplasty, is a surgical procedure to address hip pain. The surgery replaces parts of the hip joint with artificial implants. The hip joint consists of a ball (at the top of the femur, also known as the thigh bone) and a socket (in the pelvis, also known as the hip bone). Hip replacement surgery includes replacement of one or both parts. The goal of the procedure is to allow patient to resume daily activities and exercise with less pain.” Hip implants defined by the FDA (2019) as “medical devices intended to restore mobility and relieve pain usually associated with arthritis and other hip diseases or injuries. Every hip implant has benefits and risks. Every hip implant system has unique device design features such as size, shape, and material, and dimensions.”

The hip osteoarthritis disease like other known diseases has code in the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT). The hip osteoarthritis disease codes in the SNOMED CT[1] are as follow: Name: Osteoarthritis of hip. Concept ID: 239872002, Read Codes: N0535 N05zJ X703K, and ICD-10 Codes: M158 M153 M154 M169 M167 M150 M161 M151 M166 M160 M159 M162 M165 M152 M164 M163. The used SNOMED CT can be used to detect comorbidities among patients that underwent THA (Bae et al, 2022).

Nowadays there are available technologies and sciences such as Deep Learning that can be used to solve hip joint issues related to preoperative component position for patients that will undergo THA (Jang, et al, 2022). Physical X-ray is traditional method that is used by surgeons to plan a surgery (Gómez et al, 2021). There are various validated software that can be used by surgeons to plan a surgery and select the right hip implant size that fit each patient. Such software are mediCAD software (Mirghaderi et al, 2022) and Altair SimSolid (Moscol et al, 2022).

3.2 Safety of hip implants

The safety of hip implants follows same approach of all other medical devices. All medical devices are assessed for their safety prior they are put into the market. Safety of the hip implants prior to their release to the market is usually addressed during the clinical trial phases. A literature review was conducted on THA showed that the outcome measures used to report results in THA clinical trials varied and lack of comprehensiveness (Vajapey et al, 2020). There is no secret about the fact that medical devices are marketed before conducting a deep study on their efficacy (Haute Autorité de Santé, 2021). Which means that the safety results of

[1] https://snomedbrowser.com/Codes/Details/239872002

medical devices during clinical trial does not guarantee that the medical devices are fully safe when they are released to the market.

During the clinical trial there were studies showing that THA introduced or can introduce side effects to the patients (Golladay et al, 2017), (Zhu, et al, 2018), (Arthur and Spangehl, 2019), (Bonner et al, 2019), (Hannon et al, 2019), (Laigaard et al, 2021), (Stone et al, 2021) and (Simonsson et al, 2022). There are other researchers that took an interesting approach on how to minimize the side effects of THA. The efficacy and safety of multiple-dose oral tranexamic was used to address blood loss side effect of THA (Cao et al, 2019). The outcome of the clinical trial showed that multiple-dose oral tranexamic could further reduce blood loss, haemoglobin and haematocrit drop, and restrain post-operative fibrinolysis in primary THA without increasing the risk of thrombotic diseases, stroke, cardiac infarction and infection (Cao et al, 2019). Other obvious side effect of THA is the one associated to the pain due to the surgery. It was reported that THA surgical procedures to be one of the most painful (Götz et al, 2022). The pain is usually alleviated using appropriate medications (Li et al, 2017). Some medication that are used to reduce surgery pain may also introduce adverse side effects to the patients. Opioid is one type of medication that is used to reduce pain. There is a high concern on the potential of overprescribing this medication after surgery that may contribute to opioid-related adverse event such as addiction or death (Padilla et al, 2019) and (Shah et al, 2020). There are other medications that can be used to alleviate the patients' pain such medications are dexmedetomidine (Yang et al, 2020). Fortunately, there are other drugs such as non-steroidal anti-inflammatory drugs that are used to treat postoperative pain to reduce opioid consumption (Gürkan et al, 2019).

Dislocation is one common potential failure that can occur after THA. In the year 2019, another systematic review and meta-analysis of 125 studies involving approximately five million hip replacements was carried out by Kunutsor et al (2019), this systematic review showed that dislocation following primary total hip replacement has declined over time using alternative bearings such as dual mobility that can be used in individuals at high risk of dislocation. Modifiable risk

factors such as high Body mass index (BMI) and comorbidities might also be amenable to optimization before surgery (Kunutsor et al, 2019).

Overall, the THA is proven to be reliable, the reliability of THA is supported by a systematic review of 17 studies about THA between 1966 and 2005 (Montin et al, 2008). In their results, Montin et al (2008) showed that THA enhanced health-related quality of life of the patients by relieving the pain and improving physical function of the hip. The latest studies showed that THA continue to be a reliable procedure for patients with end-stage osteoarthritis (Okafor and Chen, 2019). However, satisfaction of the patients that undergo the THA remain unclear subject and require further research (Okafor and Chen, 2019) and (Galea et al, 2020). Fortunately, the patients' satisfactions remain high after THA at long-term follow-up (Schmitz et al, 2019).

The safety of hip implants as medical devices is often addressed by following the risk management process. The standard ISO 14971 Medical devices- Application of risk management to medical devices is the standard recognized by the FDA[2] and the European Commission[3]. This standard is one common guidance used by manufacturers of medical devices to address failures that could potentially impact safety and effectiveness of hip implants (Weininger et, 2010), (Sujan et al, 2013), (Pane et al, 2019) and (Marcus et al, 2022).

[2]https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/detail.cfm?standard__identification_no=41349

[3]https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32022D0757

4 Methods and Material

4.1 Medthods

R programing text mining techniques was used to analyze adverse events that are reported in Manufacturer and User Facility Device Experience (MAUDE) data base for devices that contains hip implants class III reports. The adverse events of hip implants medical devices of each of the following major manufacturers was used:

- Johnson and Johnson
- Stryker
- Smith and Nephew

The selected three major manufacturers sell their hip implants in the US and the EU markets. The targeted data consists of the results from 1st of January 2013 to 31st of December 2022.

The target groups of this research are the US FDA, the EU Medical Device Coordination Group (MDCG), the EU Competent Authorities, the EU notified bodies, the manufacturers of medical devices and the patients who use or will use hip implants medical devices or other medical devices.

4.2 Material

The material that supported this research is based on:

- The US FDA Medical device regulation.
- The New EU MDR.
- The ISO 14971 application of risk management to medical devices.
- The US FDA publicly available data in Manufacturer and User Facility Device Experience database (MAUDE).
- The European Database on Medical Devices (EUDAMED).

The selection of MAUDE data base is appropriate because this database contains all the medical devices incident reports that occurred in the US and the EU for the same devices that are sold in both the EU and the US markets. “FDA considers an event that occurs in a foreign country reportable under the medical devices reporting regulation if it involves a device that has been cleared or approved in the U.S. — or a device similar to a device marketed by the manufacturer that has been cleared or approved in the U.S. — and is also lawfully marketed in a foreign country. Devices may be manufactured to slightly modified specifications to meet standards in different countries. If these changes do not substantially alter the performance of the device, then any adverse events that are medical devices reporting are reportable events relating to such modified devices should be reported under the MDR regulation.” (FDA, 2016).

4.3 Medical device in the EU

4.3.1 Definition and classification of medical devices under MDR

Medical devices in the EU are currently regulated under the EU medical device regulation (MDR) 2017/745. The definition of medical device according to MDR article 2 section (1) is “‘medical device’ means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

— diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,

— diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,

— investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,

— providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices:

— devices for the control or support of conception;

— products specifically intended for the cleaning, disinfection or sterilization of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point."

All medical devices that are planned to be market in the EU market are required to undergo the classification rules to determine their risk classification (MDR Annex II Section 1.1(f)). The risk level of medical device determines the level of control over them. All medical devices under MDR are divided into four classifications as per MDR article 51. The medical devices under MDR article 51 are classified as follow: class I low risk, class IIa low medium risk, class IIb high medium risk and class III high risk medical devices. Medical devices under MDR can be either active device or non-active device. Active device is defined in MDR article 2 section (4) as "'active device' means any device, the operation of which depends on a source of energy other than that generated by the human body for that purpose, or by gravity, and which acts by changing the density of or converting that energy. Devices intended to transmit energy, substances or other elements between an active device and the patient, without any significant change, shall not be deemed to be active devices."

Hip implants fall under the medical devices that are defined as in MDR article 2 sections (5) and (6) as "'implantable device' means any device, including those that are partially or wholly absorbed, which is intended:

— to be totally introduced into the human body, or

— to replace an epithelial surface or the surface of the eye,

by clinical intervention and which is intended to remain in place after the procedure.

Any device intended to be partially introduced into the human body by clinical intervention and intended to remain in place after the procedure for at least 30 days shall also be deemed to be an implantable device" (MDR article 2, section 5)

And "'invasive device' means any device which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body;" (MDR article 2, section 6)

All medical devices classification depends on the intended use of the medical devices. The classification of medical devices is associated with their duration of use, invasiveness and being active or nonactive devices. Based on the definition of hip replacement from Johns Hopkins University (2022) and the definition of hip implant from FDA (2019), it can be concluded that the hip implants are artificial implants that can be used to restore mobility and relieve pain associated with arthritis or osteoarthritis. The hip implants are intended to be implanted in human body for duration that is more than 30 days. Following the classification rules of medical devices as per MDR annex VIII, the invasive rules apply. The appropriate rule that applies to the hip implant is rule 8 section 8. Therefore, the classification of the hip implants is class III under the MDR.

4.3.2 CE marking of hip implants in the EU

All medical devices that are intended to be sold in the EU market must have a CE mark certificate. CE certificate means that marking CE on a product to signify that it meets the legal requirements to be sold on the extended Single Market in the European Economic Area (EEA) (MDCG 2021-6, p 4)[4].

[4] https://health.ec.europa.eu/system/files/2021-04/mdcg_2021-6_en_0.pdf

In the EEA CE mark certificate is issued by regulatory body called Notified Body (NB) that is designated by applicable EEA competent authority. For example, BSI Group the Netherlands B.V. is a NB designated by the Dutch competent authority to issue CE mark for medical devices under MDR. All designated NBs can be found in the European Commission website called New Approach Notified and Designated Organizations (NANDO)[5]. There are 34 NBs designated by different competent authorities from different EEA countries for MDR (Figure 2).

Body type ▲	Name ▲	Country ▲
NB 2265	3EC International a.s.	Slovakia
NB 2797	BSI Group The Netherlands B.V.	Netherlands
NB 1370	BUREAU VERITAS ITALIA S.P.A.	Italy
NB 0633	Berlin Cert Prüf- und Zertifizierstelle für Medizinprodukte GmbH	Germany
NB 2409	CE Certiso Orvos- és Kórháztechnikai Ellenőrző és Tanúsító Kft.	Hungary
NB 0318	CENTRO NACIONAL DE CERTIFICACION DE PRODUCTOS SANITARIOS	Spain
NB 0546	CERTIQUALITY S.r.l.	Italy
NB 0344	DEKRA Certification B.V.	Netherlands
NB 0124	DEKRA Certification GmbH	Germany
NB 2460	DNV Product Assurance AS	Norway
NB 0297	DQS Medizinprodukte GmbH	Germany
NB 1282	ENTE CERTIFICAZIONE MACCHINE SRL	Italy
NB 0537	Eurofins Electric & Electronics Finland Oy	Finland
NB 0477	Eurofins Product Testing Italy S.r.l.	Italy
NB 0459	GMED SAS	France
NB 0051	IMQ ISTITUTO ITALIANO DEL MARCHIO DI QUALITÀ S.P.A.	Italy
NB 0373	ISTITUTO SUPERIORE DI SANITA'	Italy
NB 0426	ITALCERT SRL	Italy
NB 2862	Intertek Medical Notified Body AB	Sweden
NB 0476	KIWA CERMET ITALIA S.P.A.	Italy
NB 1912	Kiwa Dare B.V.	Netherlands
NB 0483	MDC MEDICAL DEVICE CERTIFICATION GMBH	Germany
NB 0482	MEDCERT ZERTIFIZIERUNGS- UND PRÜFUNGSGESELLSCHAFT FÜR DIE MEDIZIN GMBH	Germany
NB 0050	National Standards Authority of Ireland (NSAI)	Ireland
NB 1434	POLSKIE CENTRUM BADAN I CERTYFIKACJI S.A.	Poland
NB 1639	SGS Belgium NV	Belgium
NB 0598 (ex-0403)	SGS FIMKO OY	Finland
NB 1304	SLOVENIAN INSTITUTE OF QUALITY AND METROLOGY - SIQ	Slovenia
NB 2274	TUV NORD Polska Sp. z o.o	Poland
NB 1936	TUV Rheinland Italia SRL	Italy
NB 0044	TÜV NORD CERT GmbH	Germany
NB 0197	TÜV Rheinland LGA Products GmbH	Germany
NB 0123	TÜV SÜD Product Service GmbH	Germany
NB 2696	UDEM Adriatic d.o.o.	Croatia

Figure 2. List of designated NBs from different EEA countries.

To gain CE mark certificate, the manufacturers of medical devices class III such as hip implants must follow so called the conformity assessment route or conformity procedure as per Article 52 of MDR. The example of conformity assessment route for the hip class III implants is shown in Figure 3.

[5] https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=34

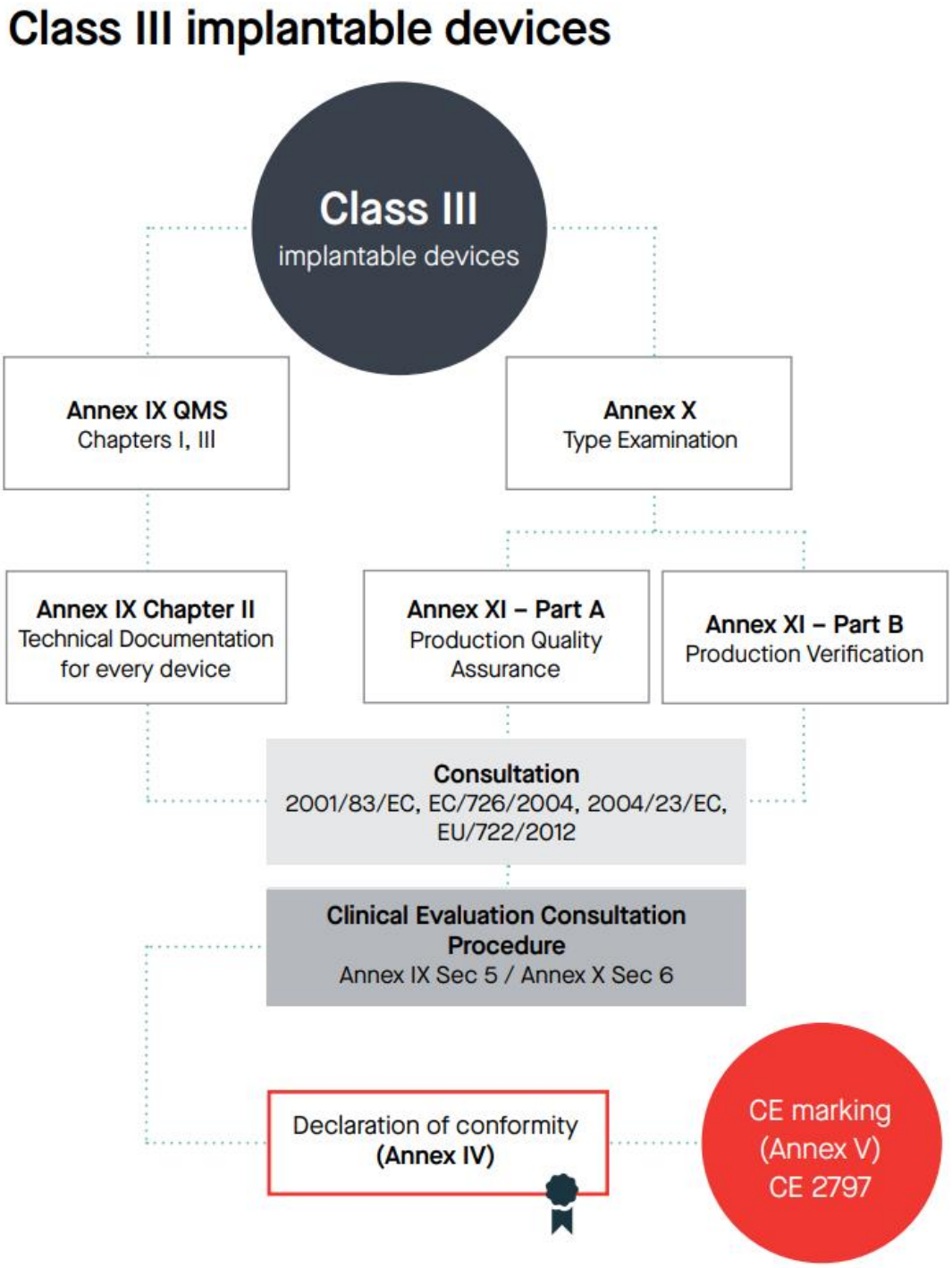

Figure 3: Class III Implantable devices conformity assessment route (BSI,2023).

Figure 3 shows the appropriate conformity assessment to gain CE mark certificate for the class III implantable devices. The manufacturer of the hip implants is required to select the right NB from the NANDO website. The NB must have the right codes to be able to conduct a conformity assessment of the hip

implants and issue the CE mark certificate. For the hip implants the appropriate NB is expected to have these codes: MDN 1102 Non-active osteo- and orthopedic implants, MDS 1005 Devices in sterile condition, MDT 2001 Metal processing, MDT 2002 Plastic processing, MDT 2002 Plastic processing, MDT 2011 Packaging, including labelling and MDN 1208 Non-active non-implantable instruments (MDCG 2019-14). Other codes may apply, NB can confirm its suitability to conduct the conformity assessment of the medical device based on the intended use of the hip implants. Once the manufacturer finds the right NB to conduct the conformity assessment toward CE mark certificate, the manufacturer will agree with the NB about what conformity assessment route to follow as per Figure 3. Usually, the use of appropriate conformity assessment route is demonstrated by having in place a quality management system (QMS) using the EU harmonized EN ISO 13485:2016/A11:2021[6] standard and technical documents as per Annex IX chapter I, II and III of MDR. In other words:

CE certificate = QMS certificate issued by notified body + technical file assessed by notified body.

Once, the manufacturer will receive CE mark certificate, he must issue a declaration of conformity as per article 19 of MDR and start to sell hip implants in the EEA market.

4.4 Medical device in the US

In the US medical devices are regulated through the US medical devices regulation. The FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States (FDA, 2020). FDA (2018) defines medical device as" an instrument, apparatus, implement, machine, contrivance,

[6] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32022D0757&qid=1669309320540

implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is

(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(2) 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

(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes."

Similar to the EU MDR, medical devices are classified under the FDA are based on their intend use. Medical devices are classified under FDA (2018) medical devices regulation as class I (low-risk devices), class II (medium to moderate risk devices) and class III (high risk, generally life-supporting, life-sustaining devices). The hip implants fall under medical device definition. Therefore, hip implants are considered as medical devices in the US. The FDA identifies all medical devices with three letter codes. The pathway to bring new medical devices to the US market also depends on the intended use of the device which ultimately defines the classification of the device. There are four basic pathways that manufacturers can use to bring new medical devices to the US market (Torpa, 2019). These four pathways are: the premarket approval application (PMA) for class III medical devices, the premarket notification usually referred as 510(k) for class II medical devices, the De Novo for devices with new intended use or devices that are not similar to any existing device in the US market, and the Humanitarian Device Exemption (HDE) pathways (Torpa, 2019). The Figure 4 represents an overview of FDA regulatory pathway for medical devices.

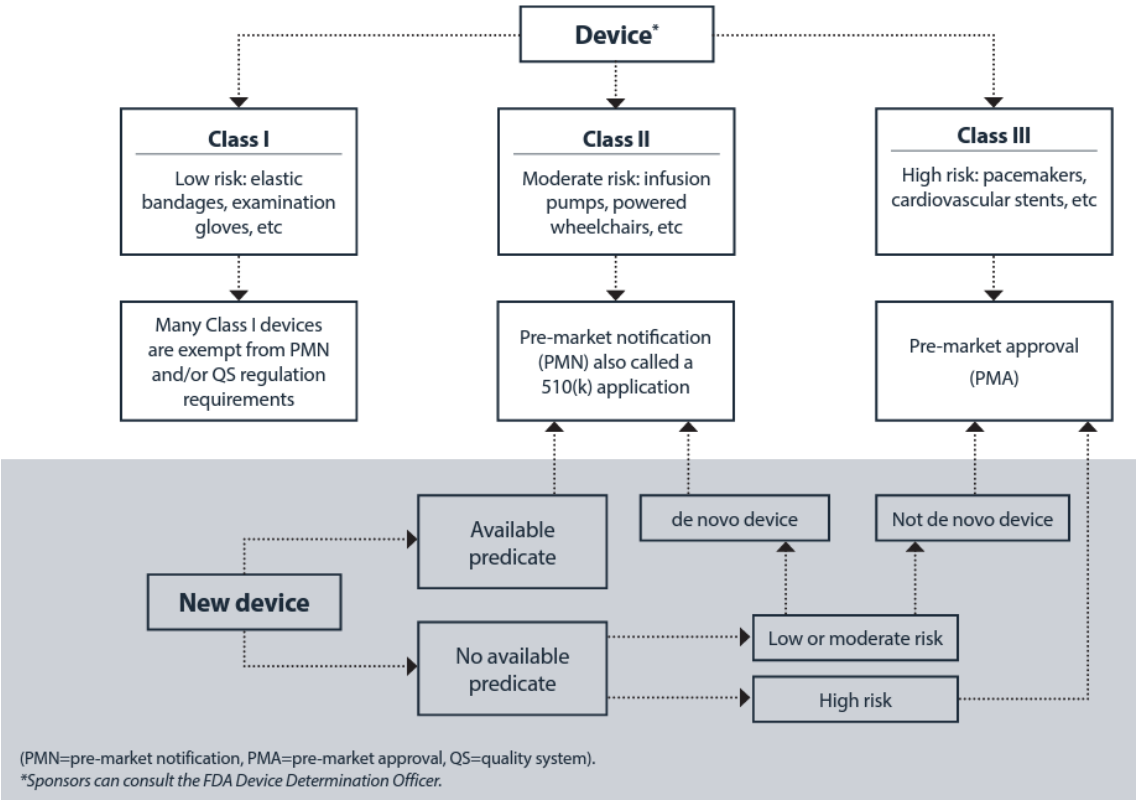

Figure 4. Overview of FDA regulatory pathway for medical devices (source: Torpa, 2019).

In the year 2017, an interesting article was published by an expert in medical device about how the medical devices are marketed in the US (Buch, 2017). The article claimed that the hip implant metal on metal medical devices are cleared to the US market through 510(K) (Buch, 2017, p.409). However, already in the year 2016 the FDA issued a final order[7] requiring manufacturers to submit a PMA application for metal-on-metal total hip replacement device. The article can lead to noncompliance that can be rejected by the FDA if the manufacturers will fill metal-on-metal total hip replacement devices following 510(k) pathway. The associated three code letters with hip implants high risk class III that are the

[7] https://www.federalregister.gov/documents/2016/02/18/2016-03331/effective-date-of-requirement-for-premarket-approval-for-total-metal-on-metal-semi-constrained-hip

scope of this research are NXT[8], KWA[9] and MRA[10]. These devices will require PMA.

All medical devices have different level of risks that is why in both the US and the EEA, manufacturers of medical devices follow the guidance of ISO 14971 standard to identify the hazards associated with hip implants. The ISO 14971 standard was developed specifically for manufacturers of medical devices on the basis of established principles of risk management that have evolved over many years (ISO 14971:2019, p 6). Following ISO 14971 entails that the manufacturers of medical device to establish so called risk management system.

4.5 Risk management system

Risk management system refers to the establishment, implementation, documentation and maintenance of risk management process (ISO 14971:2019 clause 4.1). There are three versions of ISO 14971 standards. ISO 14971:2007, EN ISO 14971: 2012 and ISO 14971:2019. The ISO 14971:2007 is used in the US and the EN ISO 14971: 2012 is used in the EEA. EN stands for European Norms, which means the standards that are accepted by European Commission and other members of the EEA to show the compliance with MDR. Often the standards ISO accompanied by EN in front of them, are referred as the EU harmonized standards. In both versions ISO 14971:2017 and EN ISO 14971:2012 the application of risk management is referred as risk management process. But, in the current ISO 14971:2019 the risk management process is expressed as risk management system that includes risk management process. ISO 14971:2019 defines the requirements of risk management systems best practices throughout the entire lifecycle of medical device.

[8] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=NXT
[9] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?id=4764
[10] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=MRA

The state of the art is at the heart of developing and controlling medical devices. The state of the art was mentioned 12 times in MDR. The state of the art implies using the lasted updated standards. Therefore, the manufacturers of the hip implants are required to implement ISO 14971:2019 and have a risk management system in place. In the US, FDA set 23rd of January 2023[11] as the date entry of the ISO 14971:2019. The compliance with ISO 14971:2007 is no longer accepted by the FDA.

Under both the FDA and the EU medical device regulations, manufacturers of medical devices are required to address the hip implants risk prior to marketing the hip implants devices and after marketing the hip implants devices. Prior to marketing the hip implants devices process is referred as premarket and after marketing the hip implants devices process is referred as postmarket.

4.5.1 Premarket

In the US, the FDA is interested during the premarket process in assessing the safety and effectiveness of the hip implants prior approving these types of medical devices. The PMA process is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices (FDA, 2019). The premarket process is based on two main technical sections. The technical sections containing data and information should allow the FDA to determine whether to approve or disapprove the application. These sections are usually divided into non-clinical laboratory studies and clinical investigations (FDA, 2019).

Non-clinical laboratory studies section includes information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests. Non-clinical studies for safety evaluation are required

[11]https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/detail.cfm?standard__identification_no=41349

to be conducted in compliance with 21 CFR Part 58 (Good Laboratory Practice for Nonclinical Laboratory Studies) (FDA, 2019). The FDA provides guidance documents and standards to help manufacturers to determine the appropriate non-clinical bench studies for the hip implants (FDA, 2019). The applicable technical guidance documents and standards can be identified in the product classification database[12] for hip implants using the code NXT (Figure 5).

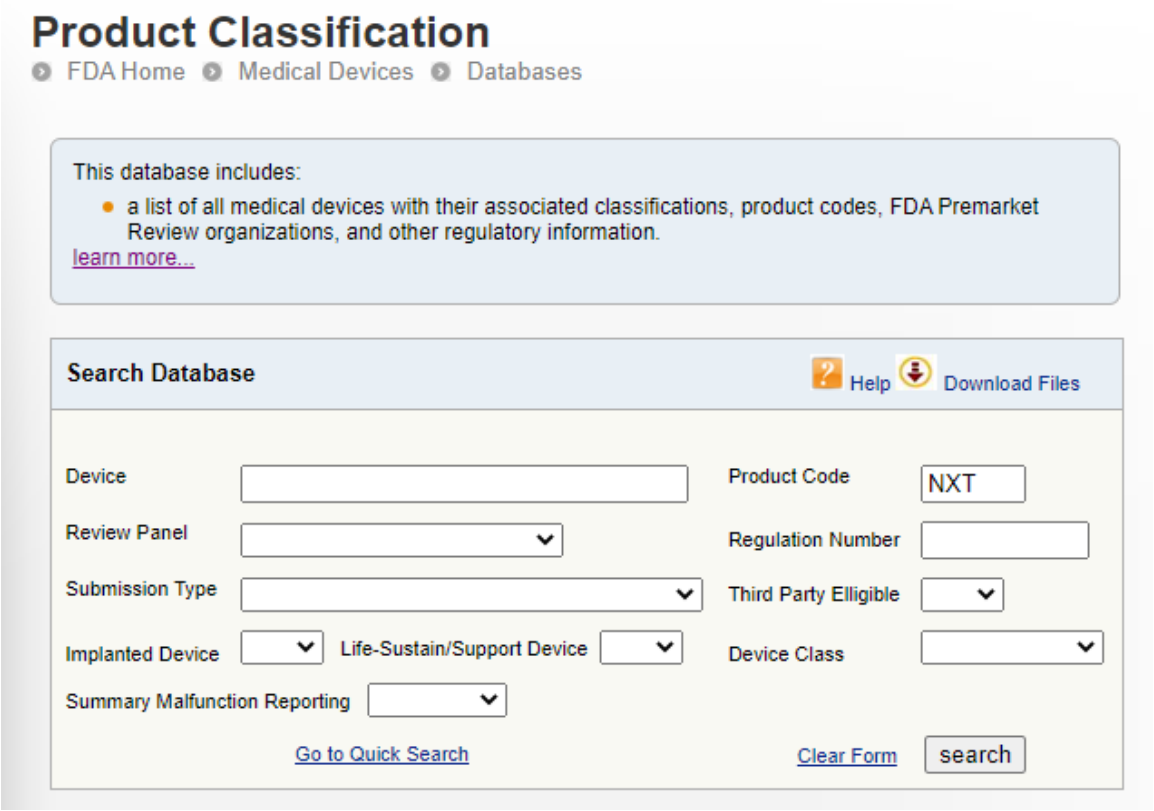

Figure 5. The FDA product classification database.

The result of search for guidance documents and standards in Figure 5 for code NXT produced the list of the FDA Recognized Consensus Standards[13] as follow:

11-306 ASTM F1814-15: Standard Guide for Evaluating Modular Hip and Knee Joint Components

[12] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm
[13] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm?id=4967

11-314 ISO 14242-2 Second edition 2016-09-15: Implants for surgery - Wear of total hip-joint prostheses - Part 2: Methods of measurement

11-319 ISO 7206-12 First edition 2016-10-01: Implants for surgery - Partial and total hip joint prostheses - Part 12: Deformation test method for acetabular shells

11-337 ISO 16087 First edition 2013-10-01: Implants for surgery - Roentgen stereophotogrammetric analysis for the assessment of migration of orthopaedic implants

11-339 ISO 7206-2: Third edition 2011-04-01 AMENDMENT 1 2016-09-15: Implants for surgery - Partial and total hip joint prostheses - Part 2: Articulating surfaces made of metallic, ceramic and plastics materials [Including AMENDMENT1 (2016)]

11-340 ASTM F3018-17: Standard Guide for Assessment of Hard-on-Hard Articulation Total Hip Replacement and Hip Resurfacing Arthroplasty Devices

11-349 ISO 14242-3 First edition 2009-03-15: Implants for surgery - Wear of total hip-joint prostheses - Part 3: Loading and displacement parameters for orbital bearing type wear testing machines and corresponding environmental conditions for test [Including AMENDMENT 1 (2019)]

11-352 ISO 14242-1 Third edition 2014-10-15: Implants for surgery - Wear of total hip-joint prostheses - Part 1: Loading and displacement parameters for wear-testing machines and corresponding environmental conditions for test [Including AMENDMENT 1 (2018)]

11-358 ISO 14242-4 First edition 2018-05: Implants for surgery - Wear of total hip-joint prostheses - Part 4: Testing hip prostheses under variations in component positioning which results in direct edge loading

11-376 ASTM F2033-20: Standard Specification for Total Hip Joint Prosthesis and Hip Endoprosthesis Bearing Surfaces Made of Metallic, Ceramic, and Polymeric Materials

11-379 ASTM F2978-20: Standards Guide to Optimize Scan Sequences for Clinical Diagnostic Evaluation of Metal-on-Metal Hip Arthroplasty Devices using Magnetic Resonance Imaging

11-380 ASTM F2979-20: Standard Guide for Characterization of Wear from the Articulating Surfaces in Retrieved Metal-on-Metal and other Hard-on-Hard Hip Prostheses

11-381 ASTM F2582-20: Standard Test Method for Dynamic Impingement Between Femoral and Acetabular Hip Components

11-382 ASTM F3090-20: Standard Test Method for Fatigue Testing of Acetabular Devices for Total Hip Replacement

11-383 ASTM F3143-20: Standard Test Method for Determination of Frictional Torque and Friction Factor for Hip Replacement Bearings under Standard Conditions Using a Reciprocal Friction Simulator

11-384 ASTM F3446-20: Standard Test Method for Determination of Frictional Torque and Friction Factor for Hip Implants Using an Anatomical Motion Hip Simulator

11-394 ASTM F1820-22: Standard Test Method for Determining the Forces for Disassembly of Modular Acetabular Devices

11-395 ASTM F1814-22: Standard Guide for Evaluating Modular Hip and Knee Joint Components.

Clinical investigations section includes study protocols, safety and effectiveness data, adverse reactions and complications, device failures, device replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations (FDA, 2019). Also, manufacturer of medical device can seek input from the FDA review division through a Pre-Submission process (FDA, 2019).

In the EU premarket is the process of assessing the device prior gaining CE mark of the device. The process of premarket for hip implants in the EU follows similar

approach of the US FDA in terms of non-clinical laboratory studies and clinical investigations. The requirements for premarket in the EU are laid down in MDR, Annex II section 6.1 pre-clinical and clinical data and 6.2 additional information required in specific cases. The manufacturers of medical device usually need to follow similar standards that are used for the FDA PMA process of hip implants of class III. The standards are therefore used to produce records of different tests such as biocompatibility tests, fatigue test etc. For example, the biography of the ISO/TR 24971:2020 the guidance of the ISO 14971:2019 refers to all necessary standards that can be used to show the safety of the medical devices in general. Not all the standards that are listed in the biography of the ISO/TR 24971:2020 guidance apply to hip implants. The reason is that the ISO/TR 24971:2020 guidance is a general guidance issued to be used for all active and passive medical devices regardless of their risk classifications. The legal manufacturer of hip implant is responsible to select the right general and specific standards and guidance to generate records that are used to build the technical file of the hip implants. In the US it is easy to find the applicable standards and guidance to use to gain PMA. In the EU the applicable standards are usually referred as harmonized standards but there is no clear specific list of standards that can be used for hip implants. Overall, in the US and the EU the risk associated with medical devices are the main concern of health authorities such as FDA, notified bodies, competent authorities and the manufacturers of medical devices too. According to both the US and the EU medical device regulations, all manufacturers of any class of medical devices are required to have a risk management system in place as per ISO 14971:2019 and to ensure the implementation of proper risk management process.

4.5.2 Risk management process

Risk management process is part of risk management system. The risk management is defined in ISO 14971:2019 clause 3.24 as systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating, controlling and monitoring the risk. ISO 14971 uses standardized

terms to facilitate a proper implementation of risk management. These terms can be found in section 3 “terms and definitions” of ISO 14971:2019. The risk is defined in ISO 14971:2019 clause 3.18 as combination of the probability of occurrence of harm and the severity of that harm. The harm is defined in ISO 14971: 2019 clause 3.3 as injury or damage to the health of people, or damage to property or the environment. Furthermore, the safety is defined in ISO 14971:2019 clause 3.26 as freedom from unacceptable risk. The requirements of risk management process encompass structured steps as it shows in the Figure 6. A risk management necessitate a risk management plan to include a framework of the following steps: risk analysis, risk evaluation, risk control, evaluation of overall residual risk, risk management review and production and post-production activities (Figure. 6).

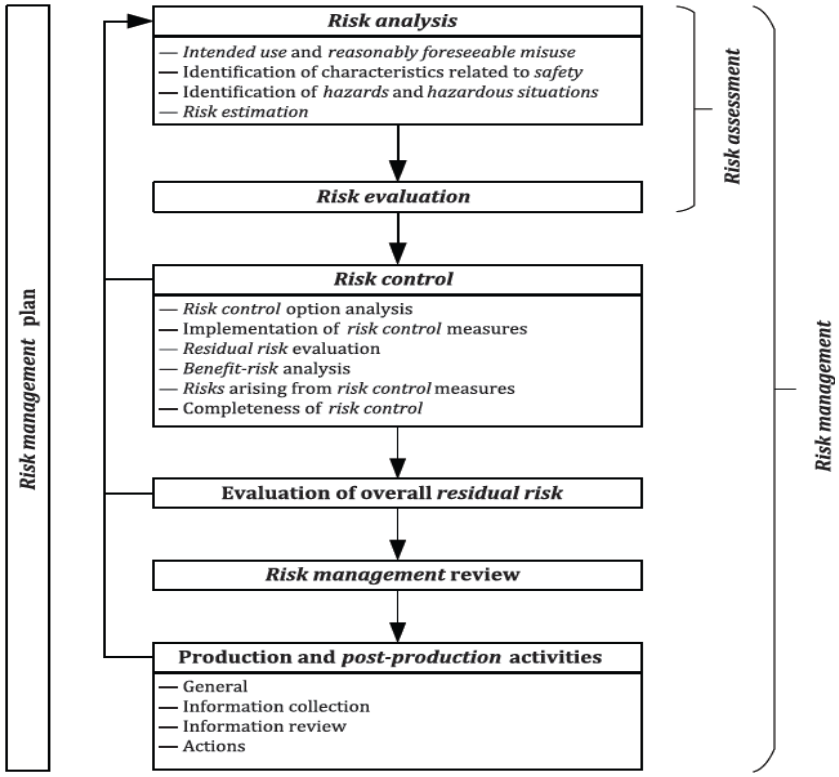

Figure 6. Schematic representation of risk management process (source: figure A1 of ISO 14971:2019 + A 11:2021).

4.5.3 Inherent safety by design

Inherent safety is mentioned in Article 89 section 5 of MDR. Inherently safety by design implies that the manufacturers of medical device must take into account safety in Design Controls as per FDA 21 CFR 820.30, Design and Development Planning as per ISO 13485:2016 clause 7.3, Usability Engineering or Human Factors Engineering as per IEC 62366-1:2015 Medical devices - Part 1: Application of usability engineering to medical devices, ISO 14971:2019 risk control option analysis clause 7.1 section a) and BS PD ISO/IEC GUIDE 63:2019 Guide to the development and inclusion of aspects of safety in International Standards for medical devices. FDA has fully recognized the use of ISO 14971:2019 which implies that the FDA also consider inherent safety by design to be a mandatory requirement. The essence of controlling risks in medical devices is specified in ISO 14971:2019 clause 7.1 as:

a) inherently safe design and manufacturer
b) protective measure in the medical device itself or in the manufacturing process
c) information for safety and, where appropriate, training to users.

The three points a), b) and c) of ISO 14971:2019 risk control option analysis clause 7.1 can be summarized as follow: a) incorporate safety in design of hip implants, b) ensure the part implant parts are manufactured with material that are biocompatible with human body (as per ISO 10993-1:2018), free of contamination and c) ensure that the surgeons who will perform THA are trained properly and patients are advised by surgeon to take precautions after the surgery. The implementation of the inherent safety by design is usually demonstrated by using several risk management tools from IEC 60812 Failure modes and effects analysis guidance. Example of risk management tools are Design Failure Mode Effect Analysis (DFMEA) and /or Fault Tree Analysis (FTA). The most common used risk management tool to address risk control options is DFMEA. The DFMEA includes the requirements of risk management process of ISO 14971 presented in Figure 6. The DFMEA includes all known possible and potential

failure of hip implant. Common possible and potential failure of hip implants can be found under FDA Total Product Life Cycle database. For example, for hip implant with product code NTX[14] common possible and potential failure of hip implants are, but not limited to, crack, degraded, break, fracture, noise and loose. These failures usually serve as input for DFMEA. In practice an example of DFMEA can look like appendix 1.

After gaining CE mark in the EU or PMA in the US, the manufacturers of hip implants are required also to show that they have process in place to comply with so called postmarket. DFMEA correspondingly is used to support the postmarket activities. DFMEA is living document that is needed to be updated periodically by the manufacturers following ISO 14971:2019 clause 10.4 actions.

4.5.4 Postmarket

Once, the hip implants meet the required safety aspects they are allowed to be sold in the EEA and in the US markets. Nevertheless, the hip implants are continuously monitored for their safety. The process or activities of continuous monitoring of hip implants safety is called postmarket surveillance (PMS). In the US as part of PMS, the manufacturers of medical devices are required to have in place a tracking system, reporting of device malfunctions, serious injuries or deaths, and registering the establishments where devices are produced or distributed (FDA, 2018). Additionally, the manufacturers of medical devices need to provide PMS studies required under section 522 of the act as well as post-approval studies required at the time of approval of a PMA (FDA, 2018, 2022).

In the EU PMS is required under the MDR, chapter VII post-market surveillance, vigilance and market surveillance and Annex III. PMS in the EU is almost similar to the US PMS. The PMS process is an essential part of QMS. The PMS is usually divided into two categories: reactive and proactive PMS (Figure. 7).

[14] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTPLC/tplc.cfm?id=4970

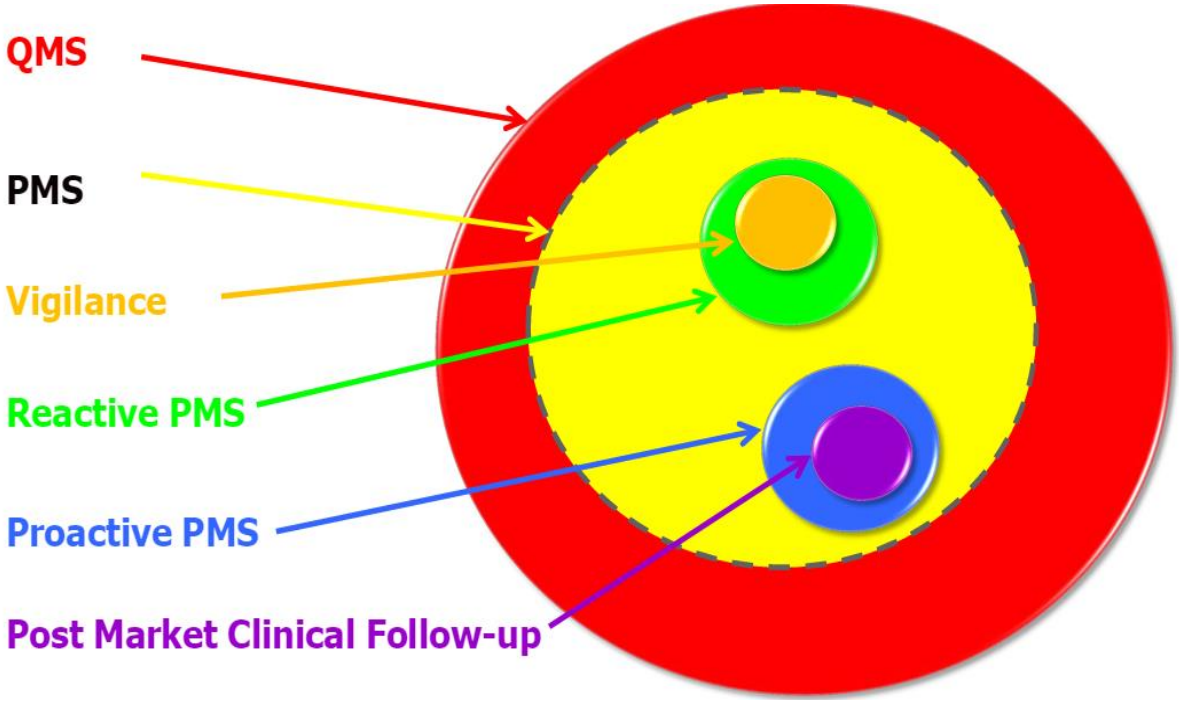

Figure 7. PMS setting in QMS. (Source: BSI, 2015).

Although, the Figure. 7 was created by BSI (2015) based on old MDD, the picture continues to reflect the PMS requirements under MDR Annex III, section 1.1 (a) that states: “The post-market surveillance plan shall address the collection and utilization of available information, in particular:

- information concerning serious incidents, including information from Periodic safety update reports, and field safety corrective actions;
- records referring to non-serious incidents and data on any undesirable side-effects;
- information from trend reporting;
- relevant specialist or technical literature, databases and/or registers;
- information, including feedbacks and complaints, provided by users, distributors and importers; and
- publicly available information about similar medical devices.”

The vigilance continues to be part of reactive PMS in the MDR. The vigilance is described in detail in Article 87 of MDR.

Reactive category includes:

- information, including feedbacks and complaints, provided by users, distributors and importers; and
- information concerning serious incidents, including information from Periodic safety update reports, and field safety corrective actions;
- records referring to non-serious incidents and data on any undesirable side-effects;
- information from trend reporting;

Proactive category includes:

- relevant specialist or technical literature, databases and/or registers;
- publicly available information about similar medical devices."

The post-market clinical follow-up (PMCF) in the Figure 7 as per MDR ANNEX XIV part B point 5, is a continuous process that updates the clinical evaluation of medical devices. The PMCF belongs to reactive category of PMS in MDR. The EU commission provides the manufacturer of medical devices and notified bodies with guidance for PMCF template and report templates under MDCG 2020-7 Post-market clinical follow-up (PMCF) Plan Template A guide for manufacturers and notified bodies and MDCG 2020-8 Post-market clinical follow-up (PMCF) Evaluation Report Template A guide for manufacturers and notified bodies. There is an ISO Guide ISO/TR 20416 issued with the aim to provide guidance on the post-market surveillance process for the manufacturers of medical device.

Overall, the postmarket is considered to be tied to risk management and quality management system. The Figure 8 shows the inter-relationship between PMS, risk management system and quality management system.

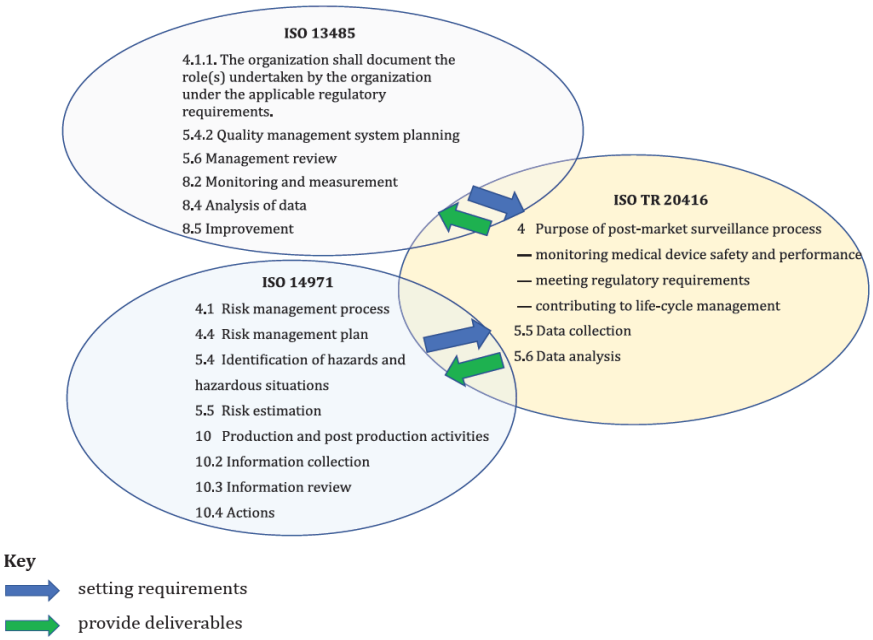

Figure 8. Inter-relationship of ISO TR 20416 (PMS) with ISO 13485 (QMS) and ISO 14971 (Risk management system) standards (Source: BS PD CEN ISO/TR 20416:2020, p vi).

Monitoring medical device safety and performance is major task that manufacturers of medical devices perform under postmarket activities. This task enables the manufacturers of medical devices to assess the experience of medical devices that are or will be used by large population. The experience of medical devices is related mainly to risk control measures effectiveness that are underlined in risk management tools DFMEA (appendix 1). The experience of medical devices in the market are reflected in the FDA MAUDE database (Figure. 9). Therefore, the selected codes of hip implants NXT, KWA and MRA are used to collect the data of class III hip implants for the following manufacturers: Johnson and Johnson, Stryker and Smith & Nephew. The link to the FDA MAUDE is:

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/Search.cfm

Figure 9. MAUDE - Manufacturer and User Facility Device Experience.

Since the lifetime of the hip implants is between 10 and 25 years, the data that will be used from the FDA MAUDE the recorded data for 10 years. The data that is used for this research is from the 1st of January 2013 to 31st of December 2022. The Figure 9 shows an example of how to use the product code and retrieve all reported incidents or complaints to the FDA. The results of the hip implants with products codes NXT, KWA and MRA are listed in the results chapter 5 of this research.

4.6 Reporting medical devices incidents or complaints

Once the medical devices are market for sale in the EU and/or the US. The manufacturers of medical devices are required to report all applicable incidents, complaints or medical devices problems to the FDA and/or EU competent authorities in some cases to notified body who issued their CE mark certificate.

The reporting mechanism can be performed using the so called MedWatch in the US as per the FDA 21 CFR Part 803 and/or Vigilance mechanisms as per EU MDR Chapter VII Post-market surveillance, Vigilance and market surveillance, section 2 Vigilance. In the US, the manufacturers of medical devices are required to use a form called MedWatch 3500A[15] form. Also, FDA has other reporting incident voluntary forms for patients (From 3500B) and healthcare professionals (form 3500). These voluntary forms are made available online[16] for both patients and healthcare professionals. FDA provides detailed instruction on how to report medical device problems for manufacturers, healthcare professionals and patients[17]. In the EU the reporting of all applicable incidents, complaints or medical devices problems is performed using the Manufacturer Incident Report from[18] (MIR). MIR can be seen as the equivalent of the FDA MedWatch 3500A form. All applicable medical device problems that require reporting to the FDA are recorded in MAUDE. Both forms MIR and MedWatch 3500A have different content but they are used by both the FDA, the EU competent authorities and in some cases by notified bodies to assess the actions taken by the manufacturers of medical devices to resolve or contain the medical devices problems that occur in the market. Also, EU commission has published guidance on how to use the MIR form and communicates the medical devices problems to the EU competent authorities. Nevertheless, the EU commission so far has only guidance for reporting medical device problem for the manufacturer of medical devices and not for patients or healthcare professionals. The applicable medical devices that require reporting to the EU competent authorities are recorded in European Database on Medical Devices (EUDAMED). Currently, EUDAMED in not yet ready to show all applicable medical devices problems that are reported by the manufacturers of medical devices. According to EU commission (2022) “EUDAMED will be composed of six modules related to: actor registration, unique

[15] https://www.fda.gov/media/69876/download
[16] https://www.accessdata.fda.gov/scripts/medwatch/
[17] https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems
[18] https://ec.europa.eu/docsroom/documents/41681

device identification (UDI) and device registration, notified bodies and certificates, clinical investigations and performance studies, vigilance and market surveillance.” There is no indication so far that patients are aware of EUDAMED or patients will be able to report medical devices problems to competent authorities through EUDAMED.

5 Results

5.1 Device problems using product codes NXT, KWA and MRA

The NXT product code MAUDE results from 1st of January 2013 to 31st of December 2022 are summarized in the Table 1.

Table 1. NXT product code results (Source FDA MAUDE, 2023).

Device Problem	**Total**
Adverse Event Without Identified Device or Use Problem	86
Adverse Event Without Identified Device or Use Problem; Loosening of Implant Not Related to Bone-Ingrowth	1
Adverse Event Without Identified Device or Use Problem; Migration	3
Biocompatibility	316
Biocompatibility; Adverse Event Without Identified Device or Use Problem	13
Biocompatibility; Adverse Event Without Identified Device or Use Problem; Migration	3
Biocompatibility; Device Dislodged or Dislocated; Adverse Event Without Identified Device or Use Problem	1
Biocompatibility; Insufficient Information	2
Biocompatibility; Loosening of Implant Not Related to Bone-Ingrowth	3
Biocompatibility; No Apparent Adverse Event	2
Biocompatibility; Noise, Audible	1
Break	22
Component Misassembled	1
Crack	1
Degraded; Biocompatibility	1
Device Dislodged or Dislocated	1
Fracture	7
Fracture; Material Twisted/Bent	1
Fracture; Migration	1
Improper or Incorrect Procedure or Method	2
Loosening of Implant Not Related to Bone-Ingrowth	10
Loosening of Implant Not Related to Bone-Ingrowth; Migration	1
Loss of Osseointegration	3
Loss of Osseointegration; Biocompatibility	1
Loss of Osseointegration; Device Dislodged or Dislocated; Adverse Event Without Identified Device or Use Problem	1
Malposition of Device; Biocompatibility	2
Malposition of Device; Biocompatibility; Migration	3
Malposition of Device; Migration	1
Material Disintegration; Biocompatibility	2
Material Fragmentation	1
Mechanics Altered; Adverse Event Without Identified Device or Use Problem	1
Migration	2
Osseointegration Problem	2
Positioning Failure	1
Total	**499**

The table shows that there are 499 device problems recorded under medical device reporting cases related to hip implants marketed by Smith & Nephew. All records in MAUDE for hip implants with code NXT were only of Smith & Nephew and other manufacturers of similar hip implants which are not Johnson & Johnson (J&J) or Stryker. The Table 1 contains device problems of Smith & Nephew only. The Table 1 shows most of the device problems were biocompatibility with 316 cases, adverse event without identified device or use problem with 86 cases, break with 22 cases, biocompatibility; and loosening of implant not related to bone-ingrowth with 10 cases.

The KWA product code MAUDE results from 1st of January 2013 to 31st of December 2022 are summarized in the Table 2.

Table 2. KWA product code results (Source FDA MAUDE, 2023).

Device Problem	**Total**
Adverse Event Without Identified Device or Use Problem	203
Adverse Event Without Identified Device or Use Problem; Osseointegration Problem	1
Device Contaminated During Manufacture or Shipping	1
Device Damaged Prior to Use	1
Device Dislodged or Dislocated	15
Device Dislodged or Dislocated; Naturally Worn	1
Device Dislodged or Dislocated; Noise, Audible	2
Device-Device Incompatibility	3
Difficult to Open or Remove Packaging Material	1
Difficult to Remove	1
Difficult to Remove; Adverse Event Without Identified Device or Use Problem	1
Illegible Information	1
Improper or Incorrect Procedure or Method	1
Loss of or Failure to Bond; Osseointegration Problem	2
Migration	2
Naturally Worn	8
Naturally Worn; Adverse Event Without Identified Device or Use Problem	2
Naturally Worn; Osseointegration Problem	1
No Apparent Adverse Event; Inaccurate Information	4
Noise, Audible	1
Off-Label Use; Difficult to Remove; Adverse Event Without Identified Device or Use Problem	1
Osseointegration Problem	14
Osseointegration Problem; Migration	1
Tear, Rip or Hole in Device Packaging	1
Use of Device Problem	2
Use of Device Problem; Device Dislodged or Dislocated	1
Use of Device Problem; Osseointegration Problem	1
Use of Device Problem; Osseointegration Problem; Migration	1
Total	**274**

The table shows that there are 274 device problems recorded under medical device reporting cases related to hip implants marketed by DePuy Synthes owned by J&J. All records in MAUDE for hip implants with code KWA were only of J&J and other manufacturers of similar hip implants which are not Smith & Nephew or Stryker. The Table 2 contains device problems of J&J only, most of the device problems were adverse event without identified device or use problem with 203 cases, device dislodged or dislocated with 15 cases, off-label use;

difficult to remove; osseointegration problem with 14 cases and naturally worn with 8 cases.

The MRA product code MAUDE results from 1st of January 2013 to 31st of December 2022 are summarized in the Table 3.

Table 3. MRA product code results (Source FDA MAUDE, 2023).

Device Problem	**Total**
Adverse Event Without Identified Device or Use Problem	98
Biocompatibility	4
Biocompatibility; Adverse Event Without Identified Device or Use Problem	1
Break	173
Break; Adverse Event Without Identified Device or Use Problem	2
Break; Component Missing	1
Break; Fracture	1
Break; Material Twisted/Bent	2
Crack	5
Degraded	1
Degraded; Insufficient Information; Noise, Audible	1
Degraded; Material Frayed	1
Device Appears to Trigger Rejection	1
Device Dislodged or Dislocated	12
Device Slipped; Device Damaged by Another Device; Unintended Movement	1
Device Slipped; Material Twisted/Bent	1
Device-Device Incompatibility	2
Device-Device Incompatibility; Material Twisted/Bent	2
Device-Device Incompatibility; Material Twisted/Bent; Naturally Worn	1
Difficult to Insert	1
Difficult to Remove; Device Dislodged or Dislocated	1
Fitting Problem	1
Fracture	34
Fracture; Device Dislodged or Dislocated	3
Fracture; Device Dislodged or Dislocated; Migration	1
Fracture; Difficult to Open or Remove Packaging Material	1
Fracture; Difficult to Remove	1
Fracture; Naturally Worn; Noise, Audible	1
Fracture; Noise, Audible	8
Inadequacy of Device Shape and/or Size	1
Insufficient Information	9
Loose or Intermittent Connection; Appropriate Term/Code Not Available	1
Loosening of Implant Not Related to Bone-Ingrowth	4
Loss of or Failure to Bond	1
Loss of Osseointegration	5
Material Deformation	1
Material Deformation; Material Twisted/Bent	1
Material Erosion	2
Material Twisted/Bent	12
Naturally Worn	1

Naturally Worn; Adverse Event Without Identified Device or Use Problem	1
Naturally Worn; Noise, Audible	2
Noise, Audible	6
Osseointegration Problem	2
Patient Device Interaction Problem	1
Patient-Device Incompatibility	1
Unsealed Device Packaging	1
Unstable	2
Use of Device Problem	1
Use of Device Problem; Malposition of Device	1
Use of Device Problem; Malposition of Device; Naturally Worn; Noise, Audible	1
Use of Device Problem; Osseointegration Problem	1
Total	**420**

The table shows that there are 420 device problems recorded under medical device reporting cases related to hip implants marketed by DePuy Synthes owned by J&J, Smith & Nephew and Stryker. All records in MAUDE for hip implants with code MRA were J&J, Smith & Nephew and Stryker and other manufacturers of similar hip implants which are not Smith & Nephew or Stryker or J&J. The Table 3 contains device problems of J&J, Smith & Nephew and Stryker only, most of the device problems were break with 173 cases, adverse event without identified device or use problem with 98 cases, fracture with 34 cases, device dislodged or dislocated with 12 cases, material twisted/bent with 12 cases and insufficient information with 9 cases. The Table 4 contains 301 cases that were reported by J&J.

Table 4. MRA product code results of J&J only (Source FDA MAUDE, 2023).

Device Problem	**Total**
Adverse Event Without Identified Device or Use Problem	35
Break	170
Break; Adverse Event Without Identified Device or Use Problem	1
Break; Component Missing	1
Break; Material Twisted/Bent	2
Crack	4
Device Dislodged or Dislocated	8
Device Slipped; Device Damaged by Another Device; Unintended Movement	1
Device Slipped; Material Twisted/Bent	1
Device-Device Incompatibility	2
Device-Device Incompatibility; Material Twisted/Bent	2
Device-Device Incompatibility; Material Twisted/Bent; Naturally Worn	1
Difficult to Remove; Device Dislodged or Dislocated	1
Fitting Problem	1
Fracture	29
Fracture; Device Dislodged or Dislocated	1
Fracture; Device Dislodged or Dislocated; Migration	1
Fracture; Difficult to Open or Remove Packaging Material	1
Fracture; Difficult to Remove	1
Fracture; Noise, Audible	8
Inadequacy of Device Shape and/or Size	1
Loss of or Failure to Bond	1
Loss of Osseointegration	5
Material Deformation; Material Twisted/Bent	1
Material Twisted/Bent	12
Naturally Worn	1
Naturally Worn; Adverse Event Without Identified Device or Use Problem	1
Naturally Worn; Noise, Audible	2
Noise, Audible	1
Osseointegration Problem	1
Use of Device Problem	1
Use of Device Problem; Malposition of Device	1
Use of Device Problem; Malposition of Device; Naturally Worn; Noise, Audible	1
Use of Device Problem; Osseointegration Problem	1
Total	**301**

In the Table 4, most of the device problems were break with 170 cases, fracture with 29 cases, material twisted/bent with 12 cases and Device Dislodged or Dislocated with 8 cases. In Table 5 contains 19 cases that were reported by Stryker.

Table 5. MRA product code results of Stryker only (Source FDA MAUDE, 2023).

Device Problem	**Total**
Adverse Event Without Identified Device or Use Problem	1
Degraded	1
Degraded; Insufficient Information; Noise, Audible	1
Degraded; Material Frayed	1
Device Dislodged or Dislocated	2
Fracture	2
Insufficient Information	3
Material Erosion	2
Noise, Audible	4
Unstable	2
Total	**19**

In Table 5 most of the device problems were unstable with 4 cases, insufficient information with 3 cases, noise, audible with 2 cases, material erosion with 2 cases, noise, fracture with 2 cases and device dislodged or dislocated with 2 cases. The Table 6 contains 100 cases that were reported by Smith & Nephew.

Table 6. MRA product code results of Smith & Nephew only (Source FDA MAUDE, 2023).

Device Problem	**Total**
Adverse Event Without Identified Device or Use Problem	62
Biocompatibility	4
Biocompatibility; Adverse Event Without Identified Device or Use Problem	1
Break	3
Break; Adverse Event Without Identified Device or Use Problem	1
Break; Fracture	1
Crack	1
Device Appears to Trigger Rejection	1
Device Dislodged or Dislocated	2
Difficult to Insert	1
Fracture	3
Fracture; Device Dislodged or Dislocated	2
Fracture; Naturally Worn; Noise, Audible	1
Insufficient Information	6
Loose or Intermittent Connection; Appropriate Term/Code Not Available	1
Loosening of Implant Not Related to Bone-Ingrowth	4
Material Deformation	1
Noise, Audible	1
Osseointegration Problem	1
Patient Device Interaction Problem	1
Patient-Device Incompatibility	1
Unsealed Device Packaging	1
Total	**100**

In Table 6 most of the device problems were adverse event without identified device or use problem with 62 cases, insufficient information with 6 cases, loosening of implant not related to bone-ingrowth with 4 cases, biocompatibility with 4 cases, break with 3 cases and fracture 3 cases.

5.2 Text mining using R programing

The objective of text mining is to explore the hidden patterns among all medical devices reports from all three selected manufacturer of hip implants (Smith & Nephew, J&J and Stryker). Studio Programing R version 2022.12.0-353 was used to perform a text mining of the event description of medical device reports

that covered the period of 1st of January 2013 to 31st of December 2022. The results of records from MAUDE related to device problems using product codes NXT, KWA and MRA was exported as excel sheets. The event description related to device problems from each product codes NXT, KWA and MRA was compiled in one text document and saved as .txt format. The .txt format was uploaded to Studio Programing R. A word cloud technique was used to analyze the compiled text related to the event of device problems. The results of word cloud word technique are presented in the Figure 10:

Figure 10. Word cloud of event description of medical device reports.

From the Figure 10, the hidden patterns can be identified by using the most frequent words that were contained in the event description of medical device problems. The hidden patterns are that depuy (J&J) received most complaints about their hip implants. This can be related to the fact that J&J sold high number of medical devices related to the selected medical devices codes. If not, then J&J hip implants have more issues with their hip implants that are sold by Smith & Nephew or Stryker. “Unknown”, “information” combined with “complaint”, “follow”, “potential” and patient indicate that there are unknown potential risks on the patient due to lack of information. Also, the text mining revealed that a large of THA required a revision. The large revisions indicate that large of hip implants failed to perform as intended otherwise it will not be considered as reportable complaints.

In section 5.1 Device problems using product codes NXT, KWA and MRA there are adverse event without identified device or use problem with 86 cases in Table 1, 203 cases in Table 2, 98 cases in Table 3, insufficient information with 3 cases in table 5 and 6 cases in Table 6. Adverse event without identified device or use problem and insufficient information require an immediate action from health authorities to ensure that there will be no risk that might lead to impairment or deterioration in the health of the patients. The FDA and the EU medical device regulations both have a requirement of traceability and identification of all medical devices. Usually, the identification of the device can be traced to the hip implants’ unique device identifier. Failure to identify such large number of hip implants is gap that require attention of both the FDA and the EU health authorities. There is a need for a clear guidance on how the manufacturer will acquire additional information about the complaints related to adverse event without identified device or use problem and insufficient information.

6 Findings and limitation of the study

6.1 Findings and discussion

The state of the art was mentioned 12 times in the MDR. However, there was no clear definition of the state of the art in the MDR. The definition of the state of the art can be found in the ISO 14971:2019 clause 3.28 which states that “developed stage of technical capability at a given time as regards products, processes and services, based on the relevant consolidated findings of science, technology and experience. The state of the art embodies what is currently and generally accepted as good practice in technology and medicine. The state of the art does not necessarily imply the most technologically advanced solution. The state of the art described here is sometimes referred to as the generally acknowledged state of the art” (ISO 14971:2019, p 13). The state of the art usually implies the use of the latest updated standards. However, it was identified that several updated standards referred to old withdrawn standards. For example, the EN ISO 10993 -1: 2020 referred to the ISO 14971:2007 in clauses 3.18 risk analysis, 3.19 risk assessment, 3.20 risk evaluation, 3.21 risk management and 4 general principles applying to biological evaluation of medical devices section 4.1. EN ISO 10993 -1: 2020 (issued in the year 2020) as per sate of the art need to refer to ISO 14971:2019 (issued in the year 2019) instead of the ISO 14971:2007 (issued in the year 2007). To solve this issue, it is highly recommended to the ISO technical committees to add a general disclaimer to advise the manufacturers of medical devices to implement the latest in use ISO version. The disclaimer can be a simple general sentence stating: Please use the latest ISO standards if not a justification shall be documented.

In the implementation of ISO 14971:2019 following the US FDA requirements and the EU MDR requirements is different. The US FDA does not require to reduce risks if they are assessed as acceptable risks. In the EU according to MDR, the manufacturers of hip implants or medical devices in general are required to remove or reduce risks as far as possible (Annex ZA of EN ISO

14971:2019/A11:2021). Assessing risk as acceptable is not enough to show the safety of the hip implants. As far as possible means if the acceptable risks can be reduced further or removed then the manufacturer must document a record evidence to demonstrate the requirement in MDR Annex I section 5(a), section 10.4.1. Design and manufacture of devices, section 10.4.5. Labelling and section 14. Construction of devices and interaction with their environment.

Several studies such as Garriga et al, (2019) claimed to observe an improvement in patient outcomes after hip replacement over the last decade. This claim is judged to be weak. The reason is the study of Garriga et al, (2019) evaluated the rate of revision surgery up to 5 years after primary hip replacement. The lifetime of the hip implant is expected to be twice than 5 years. There are several studies that showed that the lifetime of the hip implants can be up to 15 or 25 years (Evans et al, 2019), (Sodh and Mont, 2019). Therefore, the study of Garriga et al, (2019) should take all revisions that occurred by before lifetime of the hip implants.

The reporting of medical devices problem is seen to be stricter in the US while it is loose in the EU. The reason is if a same hip implant or any medical device that is sold in both the EU and the US markets and the medical device problem of that device occurred or will occur in the US or other country which is not EU country and met the reporting criteria to the EU competent authorities, this type of reporting is not required to be reported to the EU competent authorities. Additionally, the FDA provided instruction for reporting medical device problems to patients, whereas in the EU, patients are left in dark without any mechanism that will enable them to communicate the medical devices issues to the competent authorities or notified bodies. Furthermore, the EU MIR form does not show that the MIR is shared with the patients or the patient is kept informed especially the MIR has four types of reports: initial report, follow-up report, combined initial and final report and final report. It is highly recommended that EU commission to introduce additional MIR form reserved to patients. The reason is that it is not evident that all complaints raised by patients to the manufacturer

medical devices are fully captured, recorded and assessed. Also, not all complaints of patients are communicated in time to the manufacturers of medical devices.

The examination of the FDA MedWatch forms and the EU MIR form revealed that risk criteria are not well integrated in these forms. For example, the 316 device problems of Smith and Nephew that were related to biocompatibility issues should be clearly assessed for their occurrence and assess their risk acceptability and link it to current in use DFMEA or other risk management tools that is used by Smith and Nephew in both MedWatch and MIR forms. In other words, the risk associated to biocompatibility issues should be re-quantified and reassessed for their acceptability. Biocompatibility can cause infection that could lead to impairment or death of the patients. All other risks for Smith and Nephew such as 86 of break cases and 13 loosing cases in the Table 1 need to be reviewed and assessed based and verify if the risk acceptability is still valid. Additionally, all other risks with high number of occurrences in Tables 2, 3, 4, 5 and 6 need to be reviewed and assessed and verify if the risk acceptability still is valid. If any risk is assessed as not valid then the introduced risk control measures need to be modified and find new solutions to reduce the risks as far as possible to the acceptable risk levels.

All medical devices problems recorded in the MAUDE do not necessary reflect the actual medical devices problems that occurred in the market. The reason is that there is no evidence that all patients or healthcare professional report all medical devices problems. Therefore, it can be argued that the risk acceptability for medical devices is not fully accurate. The accuracy of the risk acceptability can be ensured if all the medical devices problems will be fully captured, reported to the FDA and the EU competent authorities and re-assessed for their acceptability.

6.2 Postmarket Risk Control Periodic Review framework

The proposed framework in the Figure. 11 represents postmarket risk control periodic review. The proposed framework has sequence of points from 1 to 10. This framework can serve as solution or a method to enable the FDA, the EU competent authorities and notified bodies to capture complaints directly from patients. Postmarket risk control periodic review for class III is performed usually at least once a year as part of PMS activities. The proposed framework sequence of points from 1 to 11 are as follow:

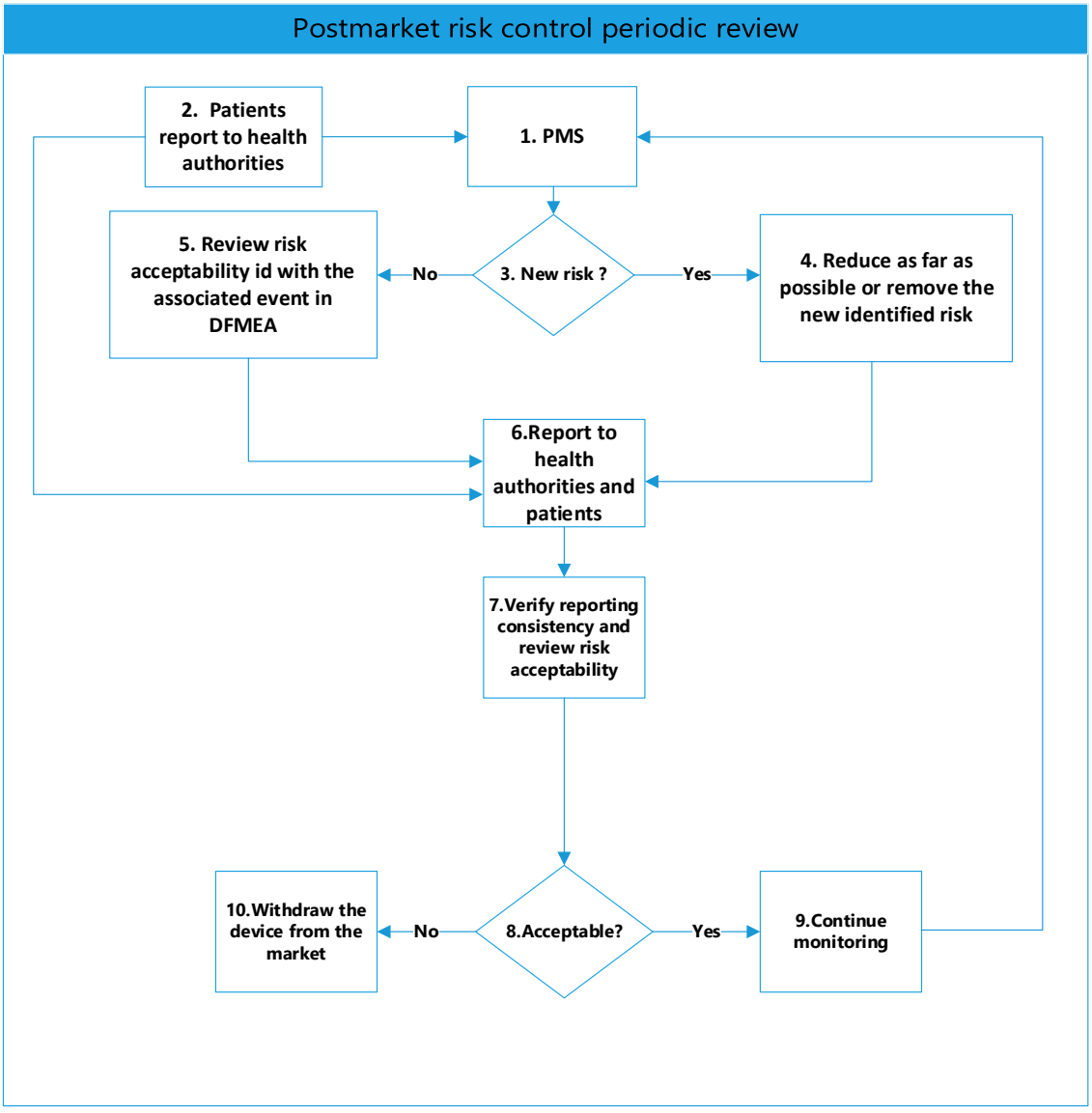

Figure 11. Postmarket risk control periodic review framework.

1.PMS: The points 1 represent the PMS that is the conventional well-established compliant process each manufacturer of medical device has in place. The compliant PMS process is usually audited or inspected by health authorities or notified bodies and proven to meet both the medical device regulations in the EU and the US. Health authorities in the proposed framework are the FDA and the EU competent authorities.

2. Patients report to health authorities: There is no evidences that the complaints or medical device problems identified by the patients are fully reported to health authorities and notified bodies. In this point 2, the patients will be able to send complaints to the manufacturers of medical devices through PMS. Eventually the patients' complaints will be addressed under the PMS process of the manufacturers of medical devices. In same time, the patients will be able to send the complaints to the FDA using the voluntary form and hopefully in the future patients will be able to send complaints to the competent authorities through EUDAMED using an electronic form.

3. New risk: In the point 3, the manufacturers of medical devices assess all complaints, medica device problems or any feedback received from the patients. The feedback, complaints or any medical device problems is done as per ISO 13485:2016 clauses 8.2.1, 8.2.2 and 8.2.3. Usually, all manufacturers of medical devices that have approval to sell their devices in the EU or the US have in place a process on how to report complaints or medical devices problems to the FDA, the EU competent authorities and/or notified bodies. Complaints or medical device problems that meet the reportability requirements are therefore communicated to the FDA, the EU competent authorities and/or notified bodies using applicable form. Both the European Commission MIR and the FDA MedWatch do not have a clear section where to assess risk. It is highly recommended to add informative section in both forms MIR and MedWatch where the manufacturer of medical device will point to their DFMEA.

4. Reduce as far as possible or remove the new identified risk: In the point 4, in case the reported complaints or the reported medical device problems will result in the identification of new risk that was not known prior putting the medical device in the market and this risk was identified through complaints or the reported medical device problems. The new identified risk must be added in the DFMEA. The new identified risk therefore must be reduced as far as possible or removed following the ISO 14971:2019 and the annex I of MDR. Any action of reducing as far as possible or removing new risk must be assessed on its impact on existing risks.

5. Review risk acceptability id with the associated event in DFMEA: in point 5, if no new risk was identified, which means the reported complaints or reported medical device problems have know risks. The risks needs to be reviewed for their occurrence and ensure that the occurrence of these risks are still within the acceptance window as per the approved risk management plan.

6.Report to health authorities and patients: in this point 6, the manufacturers of medical devices assess the complaints and medical device problems for their reportability and report to the health authorities within predefined time as required by both the article 87 of MDR and the US 21CFR 803.

7 and 8 Verify reporting consistency and review risk acceptability: In these points 7 and 8 when the patients report complaints and medical device problems to both the FDA and the EU competent authorities. These health authorities, therefore, will be able to capture all the complaints and medical devices as reported by the patients and verify the consistency in the complaints or medical devices problems narratives of both the manufacturers and the patients. Additionally, the health authorities and notified bodies will be able to verify if the manufacturer of medical devices report within the required time laid down in the article 87 of MDR and the US 21CFR 803. Health authorities and notified bodies will be able to verify the risk accessibility and assess the action taken by the manufacturers of medical devices to contain and mitigate the new identified risk or other risks.

9.Continue monitoring: In the point 9, if the new or existing risks are judged to be acceptable by the health authorities, then the manufacturers of the devices are allowed to continue selling their devices in the market under the conventional monitoring process as per the medical device regulations in the EU and the US.

10.Withdraw the device from the market: In the point 10, if the new or existing risks are judged not acceptable by the health authorities, then the manufacturers of the identified medical devices are urged to withdraw their devices from the market.

6.3 Limitation of the research and suggestion of further research

The limitation of the research can be attributed to the lack of access to the sales data of each selected manufacturer for this research. The sales data can help to have accurate comparison of all the hip implants performance of each manufacturer. Additionally, the data of hip implants that were used is limited to several codes with PMA class III devices. There are several hip implants that are cleared as class II in the US market that should be taken in consideration. These several hip implants are classified as class III in the EU. These class II devices were left out of this research due to the consistency of risk classification of class III selection in the EU and the US of hip implants. The hip implants that were used for this research are consisted of different parts: acetabular component, plastic liner, femoral head and femoral stem as it shows in Figure. 12.

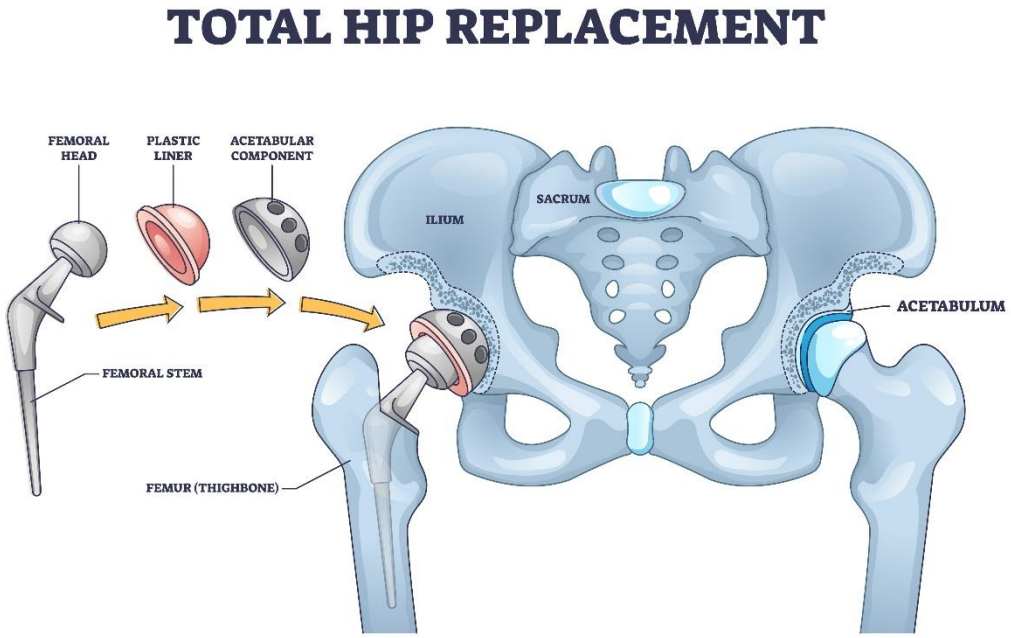

Figure 12. Example of hip implants used in total hip replacement (Source: Adobe Stock, education licence, 2023).

Further studies that will add a value to the vigilance of the MDR and medical device reporting of the FDA is the study of complaints in different social media platforms. There are plenty of hidden complaints in social media platforms. Social media platform might contain hidden complaints are Facebook, TikTok, YouTube, Twitter etc.

7 Conclusion

State of the art is seen to represent the best practice to ensure the intended use and the safety of the medical devices. State of the art continue to be a myth in the lack of clear definition of what actually is state of the art. A clear definition of state of the art is required with guidance on how to ensure its interpretation. The implementation of ISO 14971:2019 is different in both the US FDA and the EU MDR. The EU MDR is stricter than the US FDA as it requires the manufacturer of medical devices to remove or reduce risks as far as possible. Assessing risk as acceptable is not enough to show the safety of the hip implants in the EU. In the US, FDA does not force the manufacturer of medical devices to reduce acceptable risks any further.

The existing medical device risk management process in both the US and the EU do not involve all patients that use medical devices. The involvement is limited to those patients that are part of clinical trial or clinical follow up. Involving patients in medical devices as enabler not as consumer is a must. The safety of the medical devices in not fully reliable. The reason is that many complaints were not taken in consideration as they are not communicated either to competent authorities in the EU or to the FDA in the US. In the US patients can use the MedWatch form to communicate medical devices problems to the FDA. In return FDA will urge the manufacturers of medical device to conduct appropriate investigation using the MedWatch form. However, in the EU patients do not have any form to use that will enable them to communicate medical devices problems to competent authorities or notified bodies. The only form that exists in the EU for reporting medical devices problems is MIR and this form is designed to be used only by the manufacturer of medical devices.

It can be concluded that the FDA MedWatch is robust than the EU Vigilance reporting mechanism. However, both mechanisms lack a clear reliable risk acceptability traceability in term of medical device experiences. The reporting mechanism of adverse events or medical device problems require the involvement of the patients. Involvement of the patients will ensure that all

medical devices issues are reported to health authorities. To facilitate the patients' involvement in reporting medical devices problems will require new guidance for patients and training of the patients on how to report medical device problems. The training can be offered to patients using online video training. The involvement of the patient will help to reduce the adverse event without identified device or use problem and insufficient information revealed in section 5.1 Device problems using product codes NXT, KWA and MRA. Additionally, it is highly recommended that the reports of MedWatch and MIR to be shared with patients too not only with the FDA, competent authorities and notified bodies. Capturing all the medical devices problems will certainly help the manufacturers to update their risk management files with accurate information and take appropriate actions to reduce risks as needed, and eventually enhance patient safety by marketing controlled safe medical devices. The provided DFMEA in the appendix 1 can be used as tool to embrace the inherent safety by design that is required by both the US and the EU medical device regulations.

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DFMEA example

	Risk Analysis (as per ISO 14971:2019 clause 5)			Risk Estimation & Evaluation (as per ISO 14971:2019 clauses 5.5, 6)			Risk Control / Mitigation (as per ISO 14971:2019 clause 7.1)		Risk Control Verification (as per ISO 14971:2019 clause 7.2)		Residual Risk Estimation & Evaluation (as per ISO 14971:2019 clause 7.3)			(as per ISO 14971:2019 clauses 7.4 and 8)	(as per ISO 14971:2019 clause 7.5)	Periodic review (as per ISO 14971:2019 clauses 9 and 10)
Risk ID	Hazard (Known and foreseeable sources of harm)	Hazardous situation (How the patient is exposed to the hazard)	Harm (Physical injury or damage to health)	S Severity of the harm	P Probability of harm occurring	S x P Risk acceptability	Inherently safe design and manufacture	Information for safety (warnings, precautions, contraindications) and training of users	Risk control implementation verified (Y/N)	Validation of the effectiveness of risk control (proof)	S Severity of the harm	P Probability of harm occurring	S x P Risk acceptability	Benefit-Risk analysis	New risks arising from risk control? Existing risks affected?	DFMEA living document needed to be reviewed and updated as needed: for Example once a year
R1	Crack	List potential scenarios where the crack of the hip implant can happen	List here physical injury or damage to health. Example: tissue damage, infection	4	4	16	Reliable long-life Biocompatible material resistant to crack with the appropriate weight and appropriate design specifications	Instructions for use and trainings of surgeons	Y	Design verification and/or design validation, testing records	4	2	8	Acceptable	None	Review the risk R1 to ensure the effectiveness of the risk control measures from the experience of the device in the market
R2	Degraded	List potential scenarios where the Degradation can happen	List here physical injury or damage to health. Example: tissue damage, infection	4	4	16	Reliable long-life Biocompatible material resistant to degradation with appropriate weight and appropriate design specifications	Instructions for use and trainings of surgeons	Y	Design verification and/or design validation, testing records	4	2	8	Acceptable	None	Review the risk R2 to ensure the effectiveness of the risk control measures from the experience of the device in the market
R3	Fracture	List potential scenarios where the fracture of the hip implant can happen	List here physical injury or damage to health. Example: tissue damage, infection	4	4	16	Reliable long-life Biocompatible material resistant to fracture with appropriate weight, and appropriate design specifications	Instructions for use and trainings of surgeons	Y	Design verification and/or design validation, testing records	4	1	4	Acceptable	None	Review the risk R3 to ensure the effectiveness of the risk control measures from the experience of the device in the market
R4	Noise	List potential scenarios where the noise can happen	List here physical injury or damage to health. Example: tissue damage, infection	5	4	20	Reliable long-life Biocompatible material without introducing any noise due to frictions with appropriate weight and appropriate design specifications	Instructions for use and trainings of surgeons	Y	Design verification and/or design validation, testing records	5	1	5	Acceptable	None	Review the risk R4 to ensure the effectiveness of the risk control measures from the experience of the device in the market
R5	Loose	List potential scenarios where the loose of the hip implant can happen	List here physical injury or damage to health. Example: tissue damage, infection	4	4	16	Reliable long-life Biocompatible material with appropriate weight and appropriate design specifications	Instructions for use and trainings of surgeons	Y	Design verification and/or design validation, testing records	4	1	4	Acceptable	None	Review the risk R5 to ensure the effectiveness of the risk control measures from the experience of the device in the market
R6	Other hazard	List potential scenarios where the other hazard of the hip implant can happen	List here physical injury or damage to health.	5	4	20	Reliable long-life Biocompatible material resistant to degradation with appropriate design specifications	Instructions for use and trainings of surgeons	Y	Design verification and/or design validation, testing records	5	1	5	Acceptable	None	Review the risk R6 to ensure the effectiveness of the risk control measures from the experience of the device in the market

Risk Estimation following ISO 14971:2019, clause 5.5.

Severity (S)

Severity Score	Severity Category	Patient Safety Description
5	Catastrophic	• Potential of multiple deaths or serious injuries • Results in patient death
4	Critical	• Potential of death • Results in permanent impairment or life-threatening injury • Major injury requiring hospitalization or extension of hospital stay and it is irreversible
3	Serious	• Results in injury or impairment requiring medical intervention
2	Minor	• Results in temporary injury or impairment not requiring medical intervention • Short-term pain or minor injury, not requiring medical attention
1	Negligible	• No potential of injury • Inconvenience or temporary discomfort

Probability of Occurrence (P) following ISO/TR 24971:2020 section 5.5.2.

The probability of occurrence criteria		**Probability range**
Very High	Likely to occur very frequently	Equal or greater than 1 /10000
High	Likely to occur repeatedly	less than 1/10000 and equal or greater than 1/100000
Moderate	Likely to occur sometime	less than 1/100000 and equal or greater than 1/1000000
Low	Not likely to occur, but possible	less than 1/1000000 and equal or greater than 1/10000000
Very Low	Not likely to occur	Equal or greater than 1/100000000

Risk Evaluation following ISO 14971:2019, clauses 6 and 8.

Risk Acceptability Matrix

Probability of Occurrence		**Severity**				
Numerical attributes	**Probability criteria**	**5**	**4**	**3**	**2**	**1**
		Very High	**High**	**Moderate**	**Low**	**Very Low**
5	**Very High**	25	20	15	10	5
4	**High**	20	16	12	8	4
3	**Moderate**	15	12	9	6	3
2	**Low**	10	8	6	4	2
1	**Very Low**	5	4	3	2	1