A FIVE YEAR (2013-2017) RETROSPECTIVE STUDY ON THE DATA OF LABORATORY TESTING FOR BIOCOMPATIBILITY OF MEDICAL DEVICE IMPLANT REGISTERED WITH MALAYSIA MEDICAL DEVICE AUTHORITY

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by

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LIST OF SYMBOLS

H_A	Alternate hypothesis
df	Degrees of Freedom
=	Equal
≠	*Not equal*
H_0	Null hypothesis
%	Percentage
Σ	Sum up
f	Frequency
r	Response
>	greater-than sign
≤	less than or equal
∑	Total
N	total number

LIST OF ABBREVIATIONS

AMDI	Advanced Medical and Dental Institute
ASEAN	Association of Southeast Asian Nations
BSD	Biological safety Data
CAB	Conformity Assessment Body
CE	CE marking
CSDT	Common Submission of Dossier Template
DOC	Declaration of Conformity
EU	European Union countries
GHTF	Global Harmonisation Task Force
GMDN	Global Medical Device Nomenclature
HS	Harmonized system code
IMDRF	International Medical Device Regulators Forum
IPS	Institut Pengajian Siswazah
ISO	International Organization for Standardization
ISO/IEC	International Organization for Standardization and the International Electrotechnical Commission
MDA	Medical Device Authority, Ministry of Health Malaysia
MDCD	Medical Device Control Division of Malaysia
MDR	Medical Device Regulation
MeDC@St	Medical Device Centralised Online Application System
MHLW	Ministry of Health, Labour and Welfare
NANDO	New Approach Notified and Designated Organisation
OECD	Organisation for Economic Co-operation and Development
PAL	Pharmaceutical Administration Law
PMSV	Post Market Surveillance and Vigilance
QMS	Quality Management System
TGA	Therapeutic Goods Administration
UDI	Unique Device Identification
UMDNS	Universal Medical Device Nomenclature System
US FDA	Food and Drug Administration of United States
USA	United States of America
USM	Universiti Sains Malaysia
WHO	World Health Organisation

LIST OF APPENDICES

SATU KAJIAN LIMA TAHUN (2013-2017) SECARA RETROSPEKTIF KE ATAS DATA PENGUJIAN MAKMAL UNTUK BIOSERASI IMPLAN PERANTI PERUBATAN YANG DIDAFTAR DENGAN PIHAK BERKUASA PERANTI PERUBATAN MALAYSIA

ABSTRAK

Pihak Berkuasa Peranti Perubatan (MDA) telah mewajibkan pendaftaran peranti perubatan implant menerusi sistem MeDC@St sejak tahun 2013, yang memerlukan pendaftar untuk mendeposit data bioserasi praklinikal. Sejumlah 11,956 permohonan peranti perubatan telah didaftar antara tahun 2013 sehingga 2017, dan pada tempoh masa yang sama, MDA telah menerima lebih kurang 3000 laporan insiden negatif pasca-pasaran. Hal ini menunjukkan terdapat keperluan kritikal untuk menyemak semula data bioserasi praklinikal yang telah dideposit oleh pendaftar adalah mencukupi, menepati kaedah ujian ISO10993 dan mematuhi jaminan kualiti antarabangsa ISO/IEC17025 atau *OECD Principles of Good Laboratory Practice* (OECD-GLP). Kajian ini menfokus ke atas peranti perubatan implan yang memerlukan kebanyakan data bioserasi. Borang pengumpulan data yang mencerminkan halaman kemasukan data MeDC@St telah disediakan untuk pengambilan maklumat yang telah dideposit semasa pendaftaran antara Julai 2013 sehingga Disember 2017 secara manual, yang berjumlah 1925 pendaftaran dengan setiap satu pendaftaran boleh melebihi 100 halaman. Data yang dikumpul terdiri daripada frekeunsi jenis ordinal dan kategori bukan parametrik jenis nominal yang dianalisis secara statistik deskriptif diikuti dengan inferens menggunakan Kruskal-Wallis untuk perbandingan sehala. Kajian ini mendapati 61% and 44% daripada

pendaftaran mempunyai tahap kecukupan data bioserasi pada paras yang rendah untuk peranti perubatan implan bagi data biokeselamatan dari kedua-dua kategori risiko tahap satu (BSD1) dan dua (BSD 2). Kajian juga mendapati kebanyakan data bioserasi pendaftaran menunjukkan pematuhan terhadap kaedah ujian ISO10993 adalah pada paras yang rendah bagi kedua-dua BSD 1 (81.6%) dan BSD 2 (68.9%). Selanjutnya, kebanyakan data bioserasi tidak menyatakan pematuhan terhadap jaminan kualiti ISO/IEC17025 atau OECD-GLP bagi kedua-dua BSD 1 (84.0%) dan BSD 2 (72.0%). Pengeluar peranti perubatan implan, kelulusan pra-pasaran oleh pihak berkuasa dan badan penilai pematuhan daripada kalangan negara *Global Harmonisation Task Force* (status GHTF) mempunyai kehadiran yang kukuh di pasaran Malaysia untuk peranti perubatan implan dengan 1704 (88.5%) pendaftaran. Walaubagaimanapun, status GHTF tidak signifikan (P>0.05) dalam menyumbang pengaruh positif di mana kebanyakan pendaftaran mendeposit data bioserasi yang rendah kecukupan, tidak menepati kaedah ujian ISO 10993 dan tiada kenyataan jaminan kualiti. Secara keseluruhan, kajian ini menyimpulkan tidak boleh bergantung kepada status GHTF pedaftar dan mustahak untuk sistem atas talian MeDC@St dinaiktaraf bagi memastikan kemasukan data diselaraskan dengan senarai data bioserasi sebagaimana diperlukan oleh ISO10993-1 berdasarkan tahap risiko, menetapkan jenis-jenis kaedah ujian bioserasi mengikut ISO10993 dan pra-syarat deklarasi pematuhan laporan bioserasi terhadap jaminan kualiti ISO/IEC 17025 atau OECD-GLP.

A FIVE YEAR (2013-2017) RETROSPECTIVE STUDY ON THE DATA OF LABORATORY TESTING FOR BIOCOMPATIBILITY OF MEDICAL DEVICE IMPLANT REGISTERED WITH MALAYSIA MEDICAL DEVICE AUTHORITY

ABSTRACT

The Malaysia Medical Device Authority (MDA) since 2013 mandates registration of implantable medical device via MeDC@St online system which requires registrant to deposit preclinical biocompatibility data. A total of 11,956 medical devices are registered between 2013 to 2017, during the same period MDA received approximately 3000 negative post-market incidents reports. Shows critical need to review whether the preclinical biocompatibility data deposited by registrant were of adequate, complied with the ISO10993 test methods and adhered to international quality assurance of ISO/IEC17025 or OECD Principles of Good Laboratory Practice (OECD-GLP). The study focused on the implantable medical devices which require most number of biocompatibility data. Data collection form reflecting the MeDC@St data entry pages is prepared to manually retrieve the deposited information for registration between July 2013 to December 2017, amounting to 1925 registration with some exceeds 100 pages content per registration. The collected data has ordinal type frequency with non-parametric categories of nominal type that is analysed descriptively followed by inferential statistics using Kruskal-Wallis for one way comparison. The study found that 61% and 44% of the registration had low level adequacy of biocompatibility data for the implantable medical devices under the risk category of biological safety data risk level one (BSD1)

and two (BSD 2), respectively. The study also found the biocompatibility data compliance with ISO 10993 test methods for the majority of the registrations are low for both BSD1 (81.6%) and BSD2 (68.9%). Further the majority of the deposited biocompatibility data did not state adherence to either ISO/IEC17025 or OECD-GLP for both BSD1 (84.0%) and BSD2 (72.0%). The manufacturers, pre-market approval authorities and conformity assessment bodies (CAB) from the countries of Global Harmonisation Task Force (GHTF status) has strong presence in Malaysia for the implantable medical device with 1704 (88.5%) of the registrations. However, the GHTF status did not significantly ($P>0.05$) contribute positive influence whereby majority of the registration deposited biocompatibility data has low level of adequacy, non-compliance with ISO10993 and no statement of quality assurance adherence. Overall, the study concludes GHTF status of the registrant cannot be relied and importantly the MeDC@St online system need to be upgraded to ensure the registration data entry are aligned with the list of biocompatibility data as required by the ISO10993-1 risk levels, specify the types of ISO10993 biocompatibility test methods and prerequisite the declaration on the biocompatibility report quality assurance adherence to either ISO/IEC 17025 or OECD-GLP.

CHAPTER 1

INTRODUCTION

1.1 General

The term “medical devices” covers a wide range of equipment ranging from simple tongue depressors to Magnetic Resonance Imaging (MRI) machines. The definition of Malaysian Medical device is adopted from the Global Harmonisation Task Force (GHTF). It is defined as any instrument, apparatus, implement, machine, appliance, implant, in-vitro reagent or calibrator, software, material or other similar or related article used by human beings for diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disease (include prevention), life support, part to support the anatomy, disinfection of medical device and control of conception, apart from pharmacological, immunological or metabolic means (G.O.M, 2012d; MDA, 2014d; WHO, 2003). The same meaning is used by ASEAN (The ASEAN Secretariat, 2015). Besides, other similar or related product also can be considered as a medical device if it poses any issues to public health or public risk, with the gazettement of order (G.O.M, 2012e).

All medical devices carry a certain degree of risk where they could potentially cause problems under specific circumstances. Therefore, governments have to put in place policies to address the issue related to the safety and performance of the device. In developing countries such as Malaysia, the formation of a regulatory body for the medical device is essential. This is because a regulatory body could function to regulate the medical devices with assurance to be safe, effective, and quality before their placement in the market.

The current regulatory approach on the safety of the device is by estimating the potential of a device to become a hazard linked to safety problems and harm. The estimation used in this approach is referred to as the risk assessment. In Malaysia, governmental risk assessment for a medical device is based on 16 and 7 medical device specialty panels specific for general medical devices and IVD medical devices, respectively. The risk assessment is categorised into 4 classes known as A, B, C, and D, with Risk class A to be the lowest risk while class D to be the high-risk devices in Malaysia (MDA, 2014e, 2020b). As the associated risk (i.e. class) of the device increased to provide more benefits to the patient, the amount of testing that is required to establish safety and efficacy would also increase (European Commission, 2010; GHTF, 2006a, 2006b; MDA, 2014e). It is noteworthy that this risk classification may differ from one region to another region. As an example, European countries use I, IIa, IIB, and III, while in the US region, I, II, and III are used. However, the principle of classification adopted globally is basically the same.

An implantable medical device is considered one of the high-risk devices that is used to sustain, to support life and to present the potential unreasonable risk of illness or injury. Some examples of implantable medical devices that are classified as high risk include the breast implants, the heart valve implants (either animal tissue or mechanical valve), the implantable defibrillators and the pacemakers. These implants are usually manufactured through the deep drawn and the shallow drawn manufacturing processes. Apart from that, other devices can range from simple and low-risk devices such as the tongue depressors, gloves, patient bed and blood pressure Set, while the PCR test kit used for the detection of COVID-19 and Glucometers are set to be moderate risk class device.

Even though each device has its own potential risk, all the medical devices are proven to improve the quality of life. Health care providers use the medical devices for the benefit of patients such as to diagnose and to treat the illness of the patients. This indirectly helps the patients to overcome sickness or disease and improve their quality of life. Apart from that, for the patients suffering from a leaking (regurgitant) mitral valve or those with a narrowed (stenotic) mitral valve, the receiving of the implantable heart valve replacement may result in better preservation of heart function, long-term survival and usually eliminates the need for long-term use of blood thinners (anticoagulants). Besides, other devices such as the pacemakers can help the patients in their long-term survival.

The new and innovative medical devices lead the medical device industry to become one of the significant economic impact sectors and the improvement of the quality of life of the patients. Medical issues including the rising Global pandemic cases on COVID 19, the growing prevalence of chronic conditions, the growth in the complication of surgical procedures, infection prevention and the rising of geriatric population are projected to boost the global medical device market. In 2015, the global medical device sales had reached roughly US$371 billion and were estimated to increase to $800 billion in 2030 (Roger van den Heuvel et al., 2018). The Malaysian medical device trade industry is worth USD$2.47 billion with the import that worth USD$7250 million in 2018. A report from MIDA showed that Malaysia is up and becoming a global medical device manufacturing hub, with its medical device industry that comprises of over 200 manufacturers with the implemented investments of RM14.2 billion (MIDA, 2019).

To continue to boost the economy of the medical devices industry, the medical device manufacturers and the regulatory bodies must ensure the placement of the safe

medical devices in the local or global market. Therefore, the pre-market control mechanism by the regulatory body is essential to ensure that the manufacturers have the ability to demonstrate the safety assurance to the regulatory body *via* quality data or test report. This pre-market control mechanism for a medical device is also known as medical device registration. The government of Malaysia mandate the regulatory via the ACT 737 Section 5 that stated that no one could import, exported or placed medical devices locally unless it registered. The failure to comply with the requirements can lead to a fine of not exceeding two hundred thousand ringgit or imprisonment for a term of up to three years or both (G.O.M, 2012e). Apart from that, ACT 738 also forms an authority known as the Malaysian Medical Device Authority (MDA) to regulate these medical devices in Malaysia.

The medical device registration in Malaysia requires the registrants to submit medical device information and technical documentation. A secured online system was developed by MDA, namely the Medical Device Centralised Online Application (MeDC@St) to ease the submission of the medical device technical documentation. The technical documentation submission via the MeDC@St system can consists of a variety of the information but mainly related to the quality data, pre-clinical safety efficacy, clinical safety and efficacy.

Pre-clinical refers to the physical/chemical information that is fit for the characteristics and the properties of the material such as the physical, electrical, toxicological, chemical, morphological and mechanical properties performed by the manufacturers at the initial stage on the biological safety assessments (ISO, 2005). In the event in which the data is the same as the existing device with the same characterisation, the manufacturer can just perform a toxicological risk assessment and submit the data. However, if the characterisation is different, the manufacturer is

required to perform the pre-clinical safety efficacy of biocompatibility testing based on Annex A from ISO 10993-1.

Biocompatibility refers to the interaction between a medical device with the tissues and the physiological systems of the patients treated with the device. Evaluation of biocompatibility is part of the overall safety assessment of a device. By definition, biocompatibility is a measurement of how compatible a device is with a biological system. The purpose of performing the biocompatibility testing is to identify the fitness of a device for human use, to determine the usefulness of the device and to check for any potential harmful physiological effects.

A biocompatibility test is required to be performed by the manufacturer or the product owner if the medical device did not show any same characterisation with the existing device in the market. Annex A from ISO 10993-1 mentions that all the biocompatibility tests must be performed for the medical device and is based on the duration of the device to remain in the body. The test requirements in the matrix format consist of the cytotoxicity, sensitisation, irritation, acute toxicity, subchronic toxicity, genotoxicity, implantation and hemocompatibility.

Apart from the quality data and the pre-clinical biocompatibility requirements, clinical evidence is becoming another essential on the medical device safety. This includes the clinical evidence submitted by the registrant based on the essential principle for clinical evaluation. The manufacturer may submit clinical evidence such as a systematic review of existing bibliography, clinical experience with the same or similar devices and clinical investigation. However, a clinical investigation report is needed for higher risk class devices or for devices where there is little or no clinical experience. The ICH GCP International Standard may apply to clinical investigations

based on the nature, consideration and the requirements of national regulations. However, the GCP does not apply to IVD medical devices.

Even though the test is required to ensure device safety, the manufacturing facility and the testing facility are also required to fulfil a certain requirement. This is as an additional assurance to ensure that the manufactured device and testing facility which conduct the test met certain standards and produce quality products that are independent of the operational conduct for the medical device. The medical device manufacturing facility must adhere to the requirement of ISO 13485, while the pre-clinical testing facility must adhere to the OECD GLP and ISO 17025 quality assurance (E and Ramphal, 2014; Vargova and Erban, 1988; Khodabocus and Balgobin, 2011). The ISO 13485 is a stand-alone Quality Management System (QMS) standard that was derived from the internationally accepted and recognised ISO 9000 quality management standard series. The ISO 13485 is implemented and maintained to regulate medical device effectiveness and their processes in the manufacturing environment. This process is to ensure the safety for their intended purpose during the consistent design, development, production, installation and delivery of medical devices.

The OECD Principles of Good Laboratory Practices (Baldeshwiler, 2003) is used as a regulatory control mechanism to assure the quality and the integrity of non-clinical health and environmental safety studies regulated under the law. Such testing, for most of the part, is complex and variable. Thus, the OECD Principles of Good Laboratory Practice are specifically designed as a set of principles to be applied to individual studies to accommodate the complexity and variability of such studies.

While ISO/IEC 17025 is a voluntary standard to be applied to testing laboratory facilities conducting the individual assays to make sure that the testing followed the

established methodology with little variability. The focus of the quality is on the on-going operation of the laboratory itself and may be applied to any testing laboratory in any scientific discipline, instead of the specific conduct of a test. The requirement on this 2 quality assurance has essence in the ISO 10993 documents (ISO, 2009, 2018), apart from the mandatory requirement of GLP compliance for all biocompatibility test reports are included in FDA PMA or 510(k) submissions (US FDA, 2016b).

The OECD GLP is a standard published by the OECD and enforced by the regulatory agency in the OECD member states to the assure quality and integrity of non-clinical health safety data. It consists of a set of principles that covers the planning until the archiving of each safety study. The overall responsibility for all phases for the study is under the study director appointed for the study. Whereas, ISO/IEC 17025 is a standard published by the ISO that is voluntary implemented by laboratories with its enforcement is dependent on the particular country and regulatory agency. The ISO/IEC 17025 standard covers wider laboratories of both testing and calibration, occasionally include non-clinical safety testing laboratories. The testing is focuses based on customer requirements, quality control, proficiency testing and ongoing quality improvement that is more suitable for routine testing using a same standardised method with very little flexibility to modify. While, the OECD-GLP suites better for individually designed study because it allows the study director to make modification of the existing standard method, which must be declared, if it is required to correctly evaluate safety of a product particularly of new invention.

As mentioned before, MDA established the MedC@St system in 2013to handle the registration (MDA, 2013a, 2018d). The initial online registration system developed was without any detailed knowledge on the quality data (physical/chemical/material characterisation), the performance data and the safety data (biocompatibility) to be

submitted by the manufacturers to gain approval. The manufacturers, however, were given a transition period until 2016 to register for their products. The initial situation was challenging due to the complex nature of medical devices ranging from IVD to implants that are constantly adapting to new technologies. In consideration of the constraints in human resources, technical expertise and experience, it was not feasible for MDA to conduct a technical review on the submitted biocompatibility data. Therefore, the priority is still to register a medical device product so that MDA can continue to monitor the product performance and safety in the market.

The accumulated application data from 2013 to 2017 in the MeDC@St system database recorded more than 30,000 number of Medical Device application and more than 10,000 application were granted registration under the MDA since 2013 (MDA, 2018b, 2018c). During the same duration of 2013 to 2017, there have been more than 3000 cases of negative post-market incidents reported to MDA (MDA, 2018b, 2018c).

1.2 Problem statement

There is a critical need to study the adequacy of the biocompatibility reports submitted to MedC@St and the compliance with assured validity for the implant risk class. This is to ensure that the future submission of the biocompatibility data derived from the test reports meets the International Standards of ISO 10993. ISO/IEC 17025 and OECD GLP. Subsequently, this will allow only safe medical device products to be registered and will reduce or prevent any negative post-market incidence.

1.3 Objectives

1.3.1 General Objective

To investigate the adequacy of the biocompatibility reports submitted to MedC@St, compliance with International Standards of ISO 10993 and validity assurance (ISO/IEC 17025 and OECD GLP) of the registered medical device implants between the year 2013 to 2017.

1.3.2 Specific Objective

a. To profile the background of implantable medical device registrants in term of prior knowledge and experience related to biocompatibility.

b. To determine the adequacy level of biocompatibility data matching with the risk level as required by the biological safety evaluation data (BSD) requirement of ISO 10993-1 that is essential to ensure all aspects of product risk are considered prior approval.

c. To determine the compliance of the biocompatibility data, matching with the test guidelines prescribed by the ISO 10993-1 for the critical and correct judgment of product hazard prior approval.

d. To determine the Quality Assurance (ISO/IEC 17025 and OECD GLP) of the biocompatibility data uploaded by the implantable medical devices registrants to assure the validity of the biocompatibility report.

e. To analyse the registrant background information that influence adequacy level of biocompatibility data, compliance with ISO 10993 test method, quality assurance adherence, thus is important to improve the existing MedC@St system.

1.4 Research Hypothesis

The hypothesis for each parameter of information from the implant application is described in table 1.1, whereby the study seeks to analyse statistically whether there is any significant difference between the year 2013 to 2017.

Table 1.1 Hypothesis for each objective

Objective	Registration Parameters	Hypothesis for Statistical Analysis
a	Registrant Background Information • Role of establishment • Implant market • Implant risk class • Implant category • Manufacturer country • Manufacturer GHTF status • Pre-Market Approval from GHTF countries • Implant prior approval • Conformity Assessment Body (CAB) that conduct Conformity Assessment	H_0: The % of biocompatibility data for a specific registrant background information is not significantly different ($P > 0.05$) same across the five years (2013 to 2017) [$\mu_{2013} = \mu_{2014} = \mu_{2015} = \mu_{2016} = \mu_{2017}$] H_a: The % of biocompatibility data for a specific registrant background information is significantly different ($P < 0.05$) across the five years [$\mu_{2013} \neq \mu_{2014} \neq \mu_{2015} \neq \mu_{2016} \neq \mu_{2017}$]
b	Adequacy of biocompatibility data	H_0: The % of biocompatibility data for the selected biological safety data (BSD 1 or BSD 2) is not significantly different ($P > 0.05$) across the five years (2013 to 2017) [$\mu_{2013} = \mu_{2014} = \mu_{2015} = \mu_{2016} = \mu_{2017}$] H_a: The % of biocompatibility data for the selected biological safety data (BSD 1 or BSD 2) is significantly different ($P < 0.05$) across the five years (2013 - 2017) [$\mu_{2013} \neq \mu_{2014} \neq \mu_{2015} \neq \mu_{2016} \neq \mu_{2017}$]
c	Compliance of the test method with the ISO 10993	H_0: The % of biocompatibility data for the selected level of test method compliance with the ISO 10993-1 is not significantly different ($P > 0.05$) across the five years (2013 - 2017) [$\mu_{2013} = \mu_{2014} = \mu_{2015} = \mu_{2016} = \mu_{2017}$] H_a: The % of biocompatibility data for the selected level of test method compliance with the ISO 10993-1 is significantly different ($P < 0.05$) across the five years (2013 - 2017) [$\mu_{2013} \neq \mu_{2014} \neq \mu_{2015} \neq \mu_{2016} \neq \mu_{2017}$]

Table 1.1 Continue

d	Quality Assurance adherence (ISO/IEC 17025 and OECD GLP)	H_0: The % of biocompatibility data obtained from the testing conducted adhere to the selected quality assurance system (OECD GLP or ISO/IEC 17025) is not significantly different ($P > 0.05$) across the five years (2013 - 2017) [$\mu_{2013} = \mu_{2014} = \mu_{2015} = \mu_{2016} = \mu_{2017}$] H_a: The % of biocompatibility data obtained from the testing conducted adhere to the selected quality assurance system (ISO/IEC 17025 or OECD GLP) is significantly different ($P < 0.05$) across the five years (2013 - 2017) [$\mu_{2013} \neq \mu_{2014} \neq \mu_{2015} \neq \mu_{2016} \neq \mu_{2017}$]
e	Influence of Registrant Background Information on the adequacy of biocompatibility data, compliance on test method prescribed by the ISO 10993-1 and quality assurance adherence	H_0: The % of biocompatibility data of the year 2013 to 2017 registration for the adequacy with selected BSD, compliance of test method with the ISO 10993-1 and quality assurance adherence to OECD GLP or ISO/IEC 17025 is not influenced by the selected registrant background information H_a: The % of biocompatibility data of the 2013-2017 registration for the adequacy with selected BSD, compliance of test method with the ISO 10993-1 and quality assurance adherence to OECD GLP or ISO/IEC 17025 is influenced by the selected registrant background information

CHAPTER 2

LITERATURE REVIEW

2.1 Medical device

Medical device are defined by the Malaysian Medical Device Authority as implements, *in vitro* reagents, machine, implants, apparatuses, software, material or other analogous products that are meant for the use in the treatment, diagnosis, cure, prevention, the mitigation of disease, the control of conception, life support, sustenance and medical device disinfectant in humans. They are usually listed in the Malaysian published Gazette by order or any addenda to these (G.O.M, 2012e).

Medical device can be further divided into subgroups in some countries. In Europe, the medical device are divided into three different groups, including the general medical device, in vitro diagnostic device (IVD) and active implantable medical device (AIMD) (Jefferys, 2001). These groups are recognised and used by other countries as well. However, in Malaysia, the medical device groups are divided into 2 main groups, the general medical device and the in vitro diagnostic device (IVD) groups only. The implantable medical device group was incorporated into the general medical device group (G.O.M, 2012d; MDA, 2014e)

2.2 Implantable medical device

The implantable medical device is defined as the medical device that is either totally or partly introduced *via* surgically or medically method into the human body. It is also intended to remain in the body after the procedure. Jiang and Zhou (YEAR) described that 8% to 10% of the American population and 5% to 6% of the industrialised countries populations have experienced having an implantable medical device for rebuilding their body functions, expanding longevity and achieving a better

quality of life. Examples of implantable device include the cardiac pacemakers, implantable cardiac defibrillators (ICDs), hip implants, coronary stents, implantable insulin pumps and intraocular lenses (Joung, 2013). Based on ACT 737, the implantable medical device are considered to be one of the high-risk device globally. In Malaysia, most of the implantable medical device are invasive and fall into class D category. However, some medical device fall into the moderate risk group and are in class B and C categories (G.O.M, 2012d).

2.3 Economic importance of medical device

The medical device has the potential to become economically important globally, including in Malaysia. The impact is to assist patients to improve their quality of life while helping the health care providers to treat and diagnose patients. Rising Medical issues including the rising Global pandemic cases on COVID 19, the growing prevalence of chronic conditions, the growth in the complication of surgical procedures, infection prevention and the rising of geriatric population are projected to boost the global medical device market.

In 2015, the global medical device sales had reached roughly USD 371 billion and were estimated to increase to USD 795 billion in 2030, as shown in Figure 2.1. The United States (U.S.) expected continues to dominate the global market with the profits crossing of USD 300 billion in the year 2030. This is followed by China and India with USD 40 billion profits, France and Germany are expected to cross US$50 billion, next with Japan and UK below the USD 50 billion profits (Roger van den Heuvel et al., 2018). A similar scenario can also be reflected in Malaysia that shown that the Malaysian

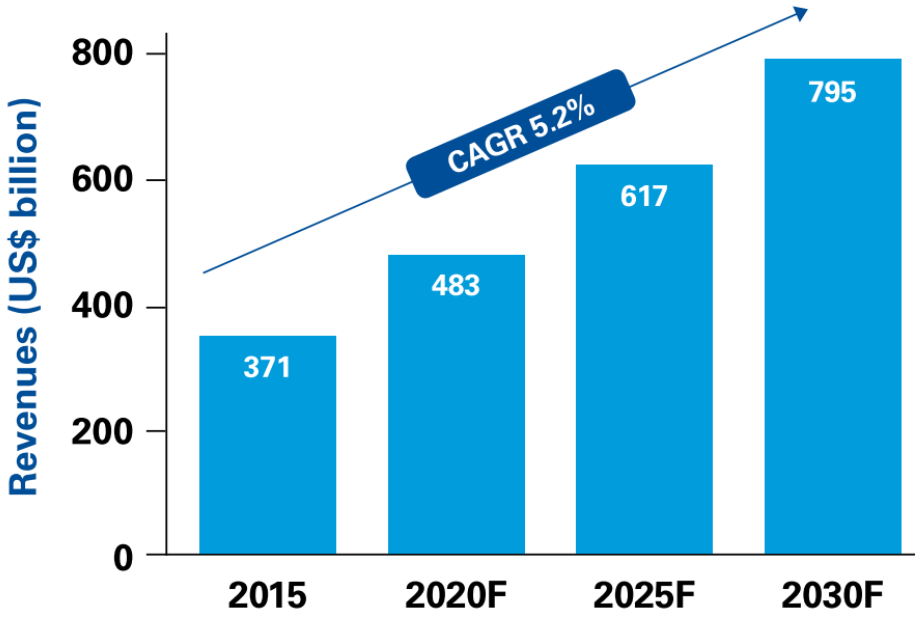

Figure 2.1 Global medical device sales forecast from 2015 to 2030

Source: Roger van den Heuvel et al., 2018

medical device trade industry is worth USD$2.47 billion with the import that worth USD$7250 million in 2018. A report from MIDA showed that Malaysia is up and becoming a global medical device manufacturing hub, with its medical device industry that comprises of over 200 manufacturers with the implemented investments of RM14.2 billion (MIDA, 2019).

U.S. products represented 24.6 % of the import market, therefore making the U.S. the highest exporting country of medical device to Malaysia within the same year. There is a 45% increase in imports from the U.S. for the year 2017 and 2018. The export is followed by Singapore as the second-largest exporter of medical device with a market share of 17.3%. Next is from Germany at 10.8 %, Japan at 9.9 %, China at 7.9 %, Belgium at 3 % and finally South Korea at 2.6 % (International Trade Administration, 2019). However, the type of imports and export medical device differ significantly. Under the Eleventh Malaysia Plan, the Malaysian government has identified the medical device as one of the high potential growth sectors (MITI, 2017). Over 90% of the medical device manufactured in Malaysia are exported to other countries (Matrade, 2019).

The global medical device industry is worth a value of USD 425.5 Billion in 2018 and is expected to reach USD 612.7 billion by 2025 (Fortune Business Insights, 2019). In Malaysia, the export sales for the medical device was exceeding RM 20 billion as of November 2018 (Matrade, 2019).

However, in 2019, the medical device such as the glove alone were projected for the export revenue worth a total of RM19.88 billion (Povera, 2019) and are expected to grow to RM28.8 billion in 2020 (MIDA, 2018). This, clearly show the economic impacts of the medical device on the global market as well as for the Malaysian market.

2.4 The danger of the faulty medical device

Even though the use of the medical device can improve the quality of life and plays a major role in boosting the global and local economy, however, the danger of faulty device is still the deciding factor. A faulty or defective device may result in inaccurate patient results that may cause suffering from pain or permanent impairment and may lead to misdiagnosis, delays in treatment, injuries, adverse events, or even death. Medical device danger is the unexpected events that may occur during or after the patient use of a medical device.

The use of pacemakers, breast implants, contraceptives and artificial hips are among the incidents that had caused injuries before and resulted in the needs for follow-up operations or death in some cases. For instance, implants had not been tested in patients before being allowed to place them in the market. The regulators in the UK received 62,000 "adverse incident" reports linked to medical device between the year 2015 and 2018 with a third of the incidents had serious repercussions for the patient while 1,004 cases resulted in death (The Guardian, 2019).

In the US, The New York Times has reported nearly 80,000 deaths as of 2018 caused by the medical device mesh, that hold the pelvic organs when the muscle becomes weak. This is together with 2 million injuries caused by faulty medical device (The Editorial Board, 2019). Apart from that, the literature search using ICIJ public research tool indicates that there are an estimated 70,000 recalls and safety notices from 11 countries (The Associated Press, 2018). According to AP News, there are 103,104 hip prosthesis injuries recorded by the US's FDA from the year 2008 to 2017. The number of other medical device injuries as reported to the US's FDA for the past 10 years to up to 2017 is summarised in Figure 2.2.

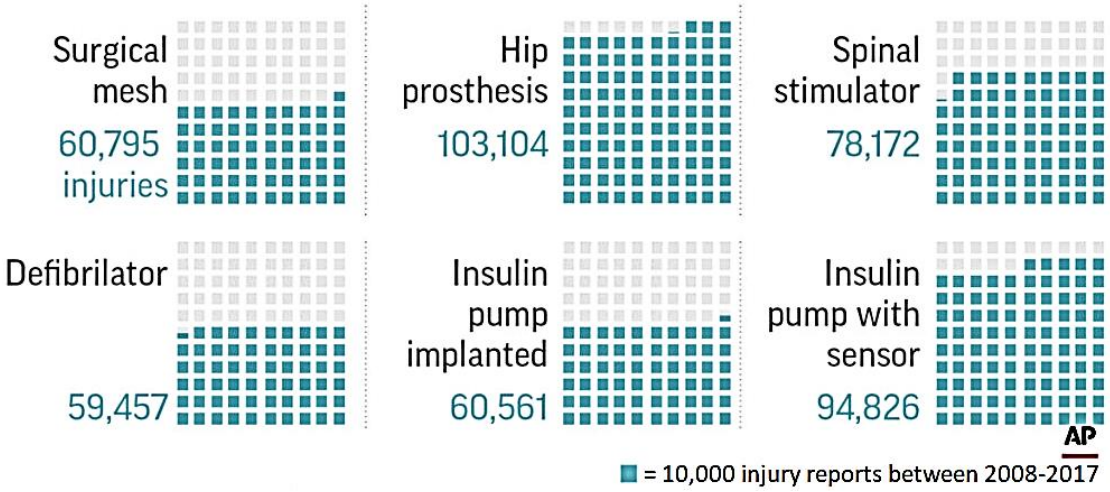

Figure 2.2 Injuries report data for the past 10 years up to 2017. Source AP News with the source from US FDA

Source: Mitch Weiss, 2018

In addition, the most notorious faulty medical device incident in the early year 2000 was the PIP scandal that involve the ruptured Poly Implant Prothèse (PIP) breast implants with an estimated of 300,000 women from 65 countries around the world affected by the faulty PIP implants. An estimated 600,000 implants were produced by the company as shown in Figure 2.3 and 2.4. The PIP implants had been placed within the market for more than 15 years but the production process and used materials used were being purposely changed without any control, thus resulted in poor quality production of capsules filled with non-certified silicone gel implants (Molitor et al., 2015). This controversy occurred possibly due to the liberality and flexibility of current medical device legal and regulatory framework. Apart from that, In the US, The New York Times has reported nearly 80,000 deaths as of 2018 as shown in Figure 2.5. Apart from that, the health problem caused by the medical device mesh, that hold the pelvic organs when the muscle becomes weak (Figure 2.6), was together with 2 million injuries caused by the faulty medical device (The Editorial Board, 2019). Besides, 1400 was killed by the faulty medical device (Figure 2.7).

The report from the Malaysian Medical device authority shows 1541 post-market issues with 335 incidences that involves 3 death and 70 serious injuries (MDA, 2018b). The number of post-market cases increases to 1642 in 2017 with 452 medical device reported as failure to function (MDA, 2018c). The findings raise concerns on the level of scrutiny the device are undergoing before and after they are in the market. Therefore, the medical device regulatory framework must be implemented in all countries globally, including in Malaysia.

MONDAY, APRIL 8, 2013 // THETELEGRAPH.COM.AU 21

Health risk for women

Call to remove implants

LONDON
JO McFARLANE

LEADING doctors have called for the UK government to remove PIP breast implants fitted to 50,000 women after research that showed their shells were faulty.

The casings are more likely to degrade than those used in others, leaving women given PIPs at risk of silicone leaking into their bodies, the research showed.

The doctors who conducted the research said all PIPs should be removed.

"If you have problems with the outer shell of an implant then it will act like a sieve and the silicone will leak out," Nigel Mercer, former president of the British Association of Aesthetic Plastic Surgeons, said.

"The batch testing for these implants was useless so we don't know which women could be most at risk.

"It's a lottery. I'd say to women: Have them out."

The scandal over French-manufactured PIP implants erupted in 2011 when it was shown they were more than twice as likely to rupture than other implants and were filled with industrial-grade silicone used in mattress production.

Women whose implants burst have complained of swollen lymph nodes, lumps and pains in their breasts. Despite French authorities agreeing to remove the implants from all women fitted with them, officials in the UK have continued to insist there is insufficient evidence to recommend removal.

Instead, the NHS will pay for women to have them removed only if specialists believe there is a clinical need and if the private clinics that fitted them refuse to remove them.

The NHS will not pay to have them replaced. But the latest research has fuelled further calls for the government to introduce a blanket policy to remove all PIPs.

About 95 per cent of women with PIPs had them fitted by a private clinic, while a minority were done on the NHS, mostly for breast reconstruction after cancer.

Figure 2.3 Newspaper article on "Health Risk for Women Call to remove Implants"

Source: Reported by Jo McFarlane on 8 April 2013 and published in The Telegraph

DAILY MIRROR

Don't wait to get help over PIP implant fears

COMPO DEADLINE

Lawyers urge Ulster women affected by surgery scandal to seek damages

"We have already processed thousands of claims in the UK"

Figure 2.4 Newspaper article on "Don't wait to get help over PIP implant fears; Lawyers urge Ulster women affected by surgery scandal to seek damages by Maurice Fitzmaurice"

Source: published on The Free Library By FARLEX on 1 November 2014

The New York Times

Opinion

80,000 Deaths. 2 Million Injuries. It's Time for a Reckoning on Medical Devices.

Patients suffer as the F.D.A. fails to adequately screen or monitor products.

By The Editorial Board

The editorial board represents the opinions of the board, its editor and the publisher.
It is separate from the newsroom and the Op-Ed section.

May 4, 2019

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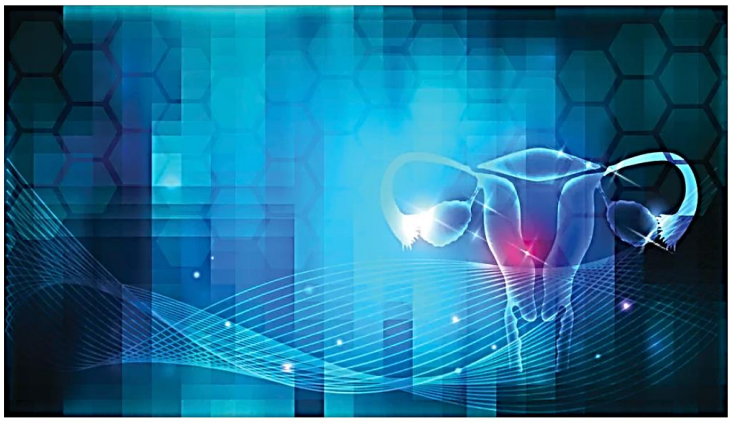
Figure 2.5 Newspaper article on 80,000 Deaths and 2 Million Injuries. "It's Time for a Reckoning on Medical Device"

Source: The Editorial Board on 4 May 2019 published in The New York Times

The Washington Post
Democracy Dies in Darkness

Health & Science

Vaginal mesh has caused health problems in many women, even as some surgeons vouch for its safety and efficacy



(iStock)

By **Susan Berger**

Jan. 20, 2019 at 9:00 p.m. GMT+8

Regina Stepherson needed surgery for rectocele, a prolapse of the wall between the rectum and the vagina. Her surgeons said that her bladder also needed to be lifted and did so with vaginal mesh, a surgical mesh used to reinforce the bladder.

Following the surgery in 2010, Stepherson, then 48. said she suffered debilitating symptoms for two years. An active woman who rode horses, Stepherson said she had constant pain, trouble walking, fevers off and on, weight loss, nausea and lethargy after the surgery. She spent days sitting on the couch, she said.

Figure 2.6 Newspaper article on Vaginal mesh has caused health problems in many women, even as some surgeons vouch for its safety and efficacy

Source: Reported by Susan Berger on 20 January 2019 and published in The Washington Post

1,400 killed and injured by faulty medical kit

By **Rachel Ellis**

ALMOST 1,400 patients were killed or seriously injured by faulty medical equipment last year – a rise of more than 100 per cent in just three years.

In one case, a patient died after becoming trapped down the side of a bed rail that was not fitted properly.

And in another, a diabetic patient died and several others went into hypoglycaemic comas after blood-glucose meters gave falsely high readings, leading patients to give themselves an insulin overdose.

According to figures from the Government's Medicines and Healthcare Products Regulatory Agency (MHRA), dangerous medical equipment resulted in 184 deaths and 1,197 serious injuries in England in 2006.

This compares with 176 deaths and 440 serious injuries in 2003. And experts fear these alarming figures are just the 'tip of the iceberg'.

Last year concerns about devices including ear thermometers, home testing kits, artificial limbs and implants led to 73 alerts being issued, 1,000 products being modified and some being banned from sale. Most faulty equipment is reported by doctors, nurses, hospitals and manufacturers. But from tomorrow, patients in England will also be invited to send in complaints.

Last night Dr Susanne Ludgate, Clinical Director at the MHRA, said: 'More and more medical devices are being used at home for a number of reasons – people are being discharged from hospital earlier, people want to take control of their own conditions and have, for example, dialysis at home, and there are more devices available to buy over the counter.

'This means there is more potential for things to go wrong. We can ensure a problem is addressed properly and potentially save patients from serious injury or even death.'

Last night Shadow Health Secretary Andrew Lansley said: 'This week sees the tenth anniversary of Tony Blair's "24 hours to save the NHS" pledge. I find it hard to believe that an increase in faulty medical equipment is what he had in mind as a legacy.'

Figure 2.7 Newspaper article on 1,400 killed and injured by medical kit

Source: Reported by Rachel Ellis on 28 April 2007 published in Daily Mail

2.5 History of medical device control

Medical device can be used to promote health quality and is becoming one of the most crucial health sectors globally. However, there is still a lot of unsafe medical device available in the market due to the lack of pre-market control to assess the safety, effectiveness, and quality of medical device. Therefore, the leading medical device countries in the world such as the US (Sorenson and Drummond, 2014) had initialised the regulatory framework to enable the safest patient access, high-quality medical device and avoiding the access to unsafe products. The framework was followed by other countries, but the standard and terms may not be uniformed. Even though a different term is used, but the functions such as pre-market, placing on market and post-market are quite similar (WHO, 2003). In addition, the risk management philosophy is applied even though the systems of pre-market review are the same. The medical device must satisfy the safety and performance, quality and labelling requirements.

A task force group known as the Global Harmonisation Task Force (GHTF) was founded in 1992 by the governments and industry representatives from Japan, Canada, Australia, the European Union, and the United States of America to harmonise national standards, to minimise regulatory barriers, facilitate trade and to improve access to new technologies. The role of this group was later taken over by IMDRF (IMDRF, 2011).

In Malaysia, the Medical Device Authority of Ministry of Health (MDA) was formed in the May of 2012 (G.O.M, 2012b). This organisation plays the roles to ensure the safety, quality and the effectiveness of the medical device in Malaysia (G.O.M, 2012f; MDA, 2020a). The regulatory framework in Malaysia was in line with the regulatory requirement stipulated from GHTF documentation and was created to fit