INVESTIGATION INTO THE CHALLENGES ENCOUNTERED BY REGULATORY AFFAIRS PROFESSIONALS WORKING IN THE MEDTECH INDUSTRY

BY

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This project is submitted in part fulfillment of the QQI/NUI requirements for the award of Master of Science in Medical Technology Regulatory Affairs.

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Declaration

Title: Investigation into the Challenges Encountered by Regulatory Affairs Professionals working in Medtech Industry

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Declaration:

"I hereby declare that this project is entirely my own work and that it has not been submitted for any other academic award, or part thereof, at this or any other education establishment".

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ABSTRACT

This research focused on the challenges experienced by Regulatory Affairs professionals working in the Medtech industry. Initial brainstorming with regulatory colleagues who have greater than ten years' experience identified three main challenges:

1 Different Regulatory Frameworks in different regions (lack of regulatory harmonisation across geographies)
2 Evolving Regulatory Frameworks/Requirements for example European Medical Devices Regulation (MDR) and the In Vitro Diagnostics Regulation (IVDR)
3 Staying informed on changing government policies/status and the impact this has on the Medtech industry for example Brexit

A detailed literature review yielded sufficient information for Europe and the United States however information regarding China, Korea or Japan was not easily obtained. A survey was conducted via SurveyMonkey™ to Medtech Regulatory Affairs professionals located in Ireland which was designed to provide details on the following four research questions:

1 What is the main challenge experienced by Regulatory Affairs professionals in gaining regulatory approval in United States, Europe, China, Korea and Japan?
2 How are Regulatory Affairs professionals staying informed on changing and evolving global regulatory requirements?
3 How are the regulatory requirements communicated internally in companies by Regulatory Affairs professionals?
4 Are Regulatory Affairs professionals aware of changing government policies that impact the Medtech industry?

The survey identified that the main challenge experienced by Regulatory Affairs professional is the lack of regulatory harmonization across different geographies. The survey identified the tools and methods used by Regulatory Affairs professionals to stay informed on global regulatory requirements and changing and evolving regulatory requirements. The main method used by Regulatory Affairs professionals to communicate regulatory requirements is through project team meetings. This highlighted a tool that is possibly underutilised by Regulatory Affairs professionals, the regulatory strategy document. Regulatory Affairs professionals are not overly concerned by changing government policies. This research is useful as it provides insight into the challenges experienced by regulatory Affairs professionals working in the Medtech industry and supporting global jurisdictions.

Key Words: ‘Regulatory Affairs’, ‘Medtech Industry’, ‘Challenges’, ‘Regulatory Frameworks’

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1.1 Introduction

This research focuses on the challenges experienced by the Regulatory Affairs professional working in the Medtech industry. The challenges include; (1) the challenge of knowing and navigating the global regulatory frameworks and requirements, (2) the challenge of staying informed on the evolving regulatory frameworks and knowing how to comply with the revised requirements and (3) the challenge of the impact changing government status has on the Medtech industry.

Manufacturers of medical devices must comply with applicable regulations before selling their devices in specific regions. "Periods of regulatory change have continuously shaped the Medtech industry but, globally, the sector is currently experiencing regulatory change at an unprecedented pace." (Irish Medtech Association 2017) This research surveyed Regulatory Affairs professionals working in the Medtech industry in Ireland who support global jurisdictions. The Medtech industry in Ireland is an important, valuable sector, to ensure its continued success Irish companies need to be successful; part of this success is the speed in getting products to market. The expertise of the profession is to ensure the timely release of safe, compliant devices to the market which complies with the differing regulatory requirements worldwide.

"Ireland is one of Europe's largest Medtech hotspots and, as a globally recognised centre of excellence, is home to 300+ companies, employing 25,000 people. Thirteen of the world's top fifteen companies have operations here. Ireland also employs the highest number of Medtech personnel per capita in Europe." (IDA Ireland, 2017)

"The global medtech industry is expected to reach €475 billion in 2018, an annual growth of 5.5% over the next three years." (IMDA 2016) Ramakrishna (2015) notes that the driving factors behind the medical device market growth are: 1) longer life span with a growing ageing population, 2) higher quality of life and changing life styles; 3) public awareness, reference **Figure 1**.

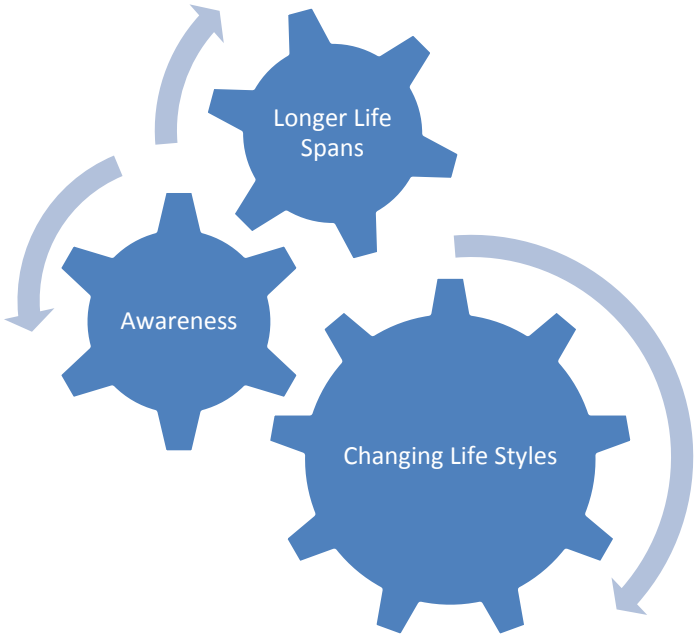

Figure 1: Drivers of growth for medical devices (Ramakrishna 2015 pg10)

The Regulatory Affairs professional has a critical role to play in ensuring safe, compliant medical devices which meet the global regulatory requirements are available to patients. In the WHO (2015) report on 'Systematic review of needs for medical devices for ageing populations' it notes that medical devices are needed for effective management of many chronic health conditions and, if selected and used appropriately, may be instrumental in addressing the priority health care needs of a population.

1.2 What is Medtech?

"Medical technology can be considered as any technology used to save lives in individuals suffering from a wide range of conditions. In its many forms, medical technology is already diagnosing, monitoring and treating virtually every disease or condition that affects us. Medical technology can be familiar, everyday objects such as sticking plasters, syringes or latex gloves. Alternatively, it could also be spectacles, wheelchairs and hearing aids. Meanwhile, at the high tech end of the scale, medical technology includes total body scanners, implantable devices such as heart valves and pacemakers, and replacement joints for knees and hips. In fact, there are more than 500,000 medical technologies currently available and they all share a common purpose: improving and extending peoples' lives." (Eucomed 2012a)

1.3 What is a Medical Device?

Medical devices are used in numerous applications throughout the healthcare industry and encompass a range of products including plasters, pressure relief mattresses, orthopaedic devices and cardio-thoracic medical device systems. To allow a manufacturer determine if their product is a device or not, and to ensure boundaries between various fields in the medical world (e.g. pharmaceuticals and medical devices), the regulatory frameworks in each of the regions clearly define the term medical device. (WHO 2003)
Examples of the various medical devices are provided in **Figure 2**.

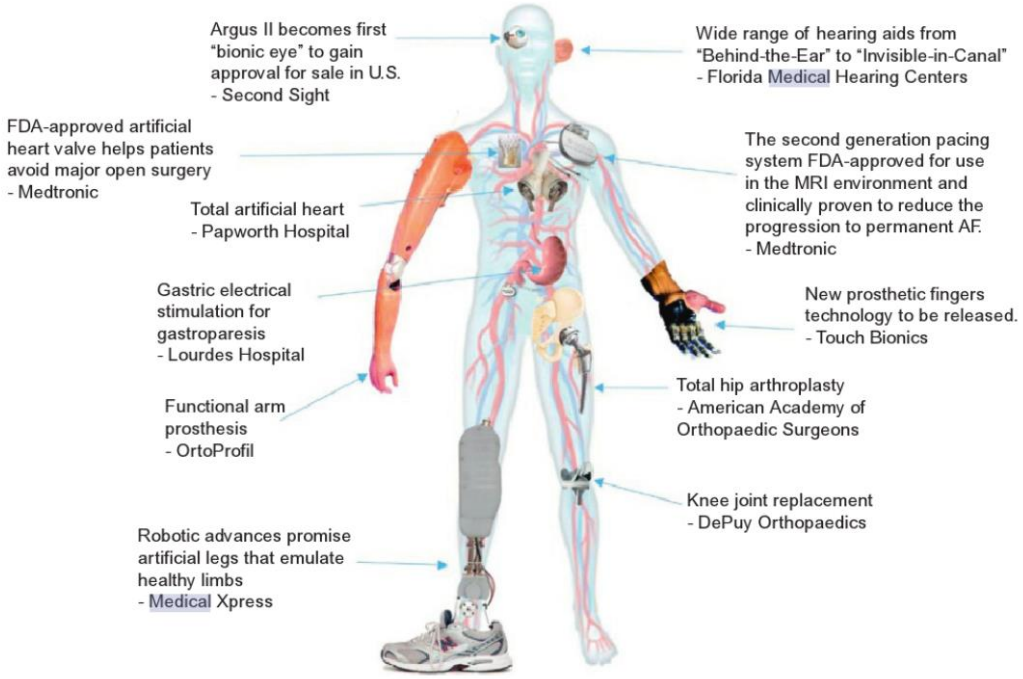

Figure 2: Examples of medical devices for the human body (Ramakrishna et al 2015 pg5)

Each region has its own definition for a medical device; this research is focused on United States, Europe, China and Korea and Japan. Although each of the definitions is slightly different, they are generally the same. The definitions for medical devices marketed in the regions discussed in this research are provided in **Table 1**.

"It is important to check in every jurisdiction whether a particular product falls under medical device regulations, because certain products may be considered to be medical devices in some jurisdiction but not in others. A medical device may be supported in its function by pharmacological, immunological or metabolic means but if these become the primary mode of

action, the product is no longer a medical device but instead it is regulated as a medicine." (Theisz 2015)

These definitions help companies identify if the product they are manufacturing is a medical device. If the company is manufacturing a medical device it must comply with the applicable regulations for the market in which the device will be sold. Three (US, EU and China) out of the five regions described in **Table 1** specifically state in the medical device definition that the device cannot achieve its primary mode of action via chemical, pharmacological or immunological means. These definitions distinguish a medical device versus a drug.

Table 1 : Medical Device Definitions

Region	**Medical Device Definition**
United States	"an instrument, apparatus, implement, machine, contrivance, 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." (FDA 2015b)
Europe	Article 1(2)a of Directive 93/42/EEC (European Council, 1993, p 3) gives the following definition: "medical device' means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: — diagnosis, prevention, monitoring, treatment or alleviation of disease, — diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap, — investigation, replacement or modification of the anatomy or of a physiological process, — control of conception,

Region	Medical Device Definition
	and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means" (European Council 1993)
China	"'Medical devices' as defined by these regulations refers to: any instrument, apparatus, appliance, material, or other article whether used alone or in combination, including the software necessary for its proper application. It does not achieve its principal action in or on the human body by means of pharmacology, immunology or metabolism, but which may be assisted in its function by such means; the use of which is to achieve the following intended objectives: 1. Diagnosis, prevention, monitoring, treatment or alleviation of disease; 2. Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap conditions; 3. Investigation, replacement or modification for anatomy or a physiological process; 4. Control of conception." (CFDA 2017)
Korea	"the term "medical device" means any instrument, machine, contrivance, material or similar article that is used on human beings or animals either alone or in combination with other devices and that falls under any of the following items provided below. However, drugs or quasi-drugs under the Pharmaceutical Affairs Act or, among the disabled-assistive-devices under Article 65 of the Act for Welfare of the Disabled, artificial limbs and orthotics shall be excluded: <Amended on April 11, 2007> 1. Articles used for the purpose of diagnosis, cure, alleviation, treatment, or prevention of illness; 2. Articles used for the purpose of diagnosis, cure or alleviation of or compensation for an injury or disability; 3. Articles used for the purpose of test, replacement, or modification of the structure or functions [of the body]; or 4. Articles used for the purpose of control of conception."(Medical Devices Act, Act No. 10326, May 27, 2010)
Japan	'A device is defined as an instrument or apparatus intended for use diagnosing, fittings and parts which are used in diagnosing, curing, or directly preventing diseases in humans or animals, or intended to affect the structure or functions of the bodies of humans or animals.'(Medical Device And Diagnostic Industry 2004)

1.4 The role of the Regulatory Affairs Professional in Medtech Industry

Regulatory Affairs is a profession within regulated industries, such as medical devices, in vitro diagnostics and pharmaceuticals. Regulatory Affairs professionals have responsibility for ensuring their companies comply with all of the regulations and laws where their products are marketed and sold. They work with agencies such as Notified Bodies (NB) in Europe, the Food and Drug Administration (FDA) in United States, the China Food and Drug Administration (CFDA) in China, the Ministry of Food and Drug Safety (MFDS) in Korea, and Pharmaceuticals and Medical Devices Agency (PMDA) in Japan to gain product approvals which are required prior to marketing and selling their devices in these regions. They advise their companies on the regulatory requirements and the regulatory environment that would affect approval and release of their products in the different regions.

Regulatory Affairs professionals are involved in the various stages of the product lifecycle, from the development to approval, distribution, marketing and post-market surveillance of the medical devices, see **Figure 3**.

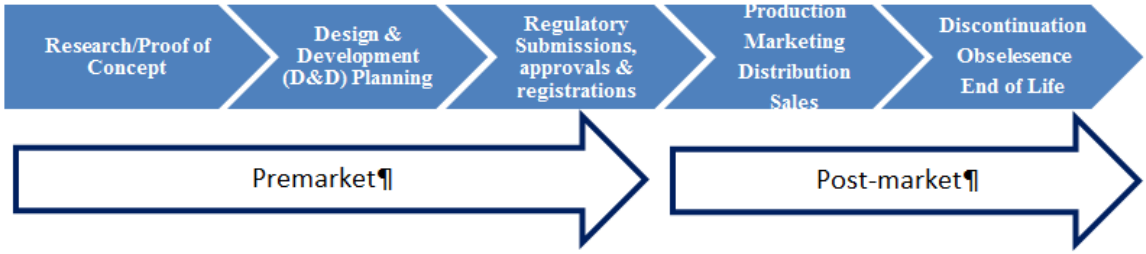

Figure 3: Typical Medical Device Life Cycle (Theisz, 2015 pg22)

The Regulatory Affairs function can be divided into two sections; pre-market and post-market approval and the responsibilities are described in **Table 2**.

Table 2: Regulatory Affairs Responsibilities Pre and Post Market

Pre-Market Approval – Regulatory Affairs Responsibilities	**Post-Market Approval – Regulatory Affairs Responsibilities**
• Regulatory Strategy • Submissions to gain market approval • Interpreting regulatory agency requirements • Liaising with regulatory bodies	• Regulatory Strategy for changes • Change Assessment • Submission activity as required by change assessment • File maintenance e.g. Design Dossier/Technical Files are required to be 'state of the art' in EU • Recertification/Certification Renewal • Audit Support • Post Market Surveillance

"There are differences between the regulatory systems and required documents for registration in different countries. There are around 60 - 65 countries which have implemented regulation for medical devices or will soon implement regulations." (Ramakrishna et al 2015, pg207). Ramakrishna et al (2015) gives the example of a device getting approval in the United States FDA and it may not enter the market in China until CFDA have approved it even though it has undertaken the most stringent procedures in the world mandated by US FDA." (Ramakrishna et al 2015 pg207)

The Regulatory Affairs professional needs to understand the requirements in each of the regions the business wants to market and sell products. This can be difficult because it can be difficult to source the requirements and in some regions there is a language difference. Information is available on the World Wide Web but whether this information is official or accurate has to be determined. Regulations are evolving and changing, the challenge of knowledge management, ensuring information is available and accessible when needed is a challenge.

"In business there's a saying: *Time is money*. The more time it takes for something to get done, the more money it costs. Companies that can figure out a way to compress the time it takes for something to happen can realize significant cost savings and also get their products into the market faster, beating the competition and increasing their market share." (NSAI 2016) For these reasons companies have a desire to get products to the market faster to facilitate faster market access companies need to engage the Regulatory Affairs function in critical business functions including organizational and corporate strategy, health technology assessment, legal issues and government affairs throughout the development process.

"Increasingly new products have a global reach, especially in new and emerging markets. The regulatory landscape in these regions can influence decision-making throughout development and therefore requires strategic regulatory consideration early in the development process and throughout the development process." (Page, 2014)

1.5 Challenges for Regulatory Affairs Professional in Medtech Industry

Initial brainstorming with colleagues working in Regulatory Affairs in the Medtech industry with greater than ten years regulatory experience identified three main challenges for the Regulatory Affairs professional to stay informed and be knowledgeable on:

1. Different Regulatory Frameworks in different regions (lack of regulatory harmonisation across geographies)
2. Evolving Regulatory Frameworks/Requirements for example European Medical Devices Regulation (MDR)
3. Staying informed on changing government policies/status and the impact this has on the Medtech industry for example Brexit

The literature review which will be discussed in detail in Chapter 2 reviews these challenges in detail.

1.6 Scope of Research

This research will investigate these challenges experienced by the Regulatory Affairs professionals working in medtech industry in Ireland supporting products that are internationally available. It is important for Regulatory Affairs professionals to understand the main challenges that are encountered when submitting devices for review and approval to regulatory agencies. It is important to understand the challenges involved in maintaining compliance of approved devices. This understanding will provide information to the

Regulatory Affairs professionals to allow better planning of submissions; it will provide a better understanding of the role of the Regulatory Affairs professional and the key contributions they can have to the business strategy. By understanding the challenges the Regulatory Affairs profession can bring awareness to the business on the regulatory restrictions during the product approval process and ensure this information is considered in the overall business strategy.

In the past the role of the Regulatory Affairs professional was more of a tactical role, managing the submission process, communicating to stakeholders and ensuring compliance with rules and policies. In the future the role will require strategic thinking. Wong and Tong (2013, pg7) stated that it "will be critical for the Regulatory Affairs professional to communicate across the organization into both commercial and clinical functions and serve as a strategic business partner that can help decipher the "noise" to guide informed decision making for commercial and clinical investment. Delivering in this expanded role will require flexible strategic thinking, complex stakeholder management and a firm understanding of the organization's goals and plans." The Regulatory Affairs professional will need to educate the business decision makers on the regulatory landscape, which markets will provide the fastest approval and start to generate revenue. Regulatory Affairs professionals will need to know how to navigate the regulatory frameworks to ensure efficient use of the research and development testing and validations and eliminate the need to carry out specific testing for each region.

1.7 Research Objective and Research Questions

The goal of this dissertation is to investigate the main challenges experienced by Regulatory Affairs professionals and to understand what tools and methods are used to communicate these challenges to the business and to understand how the Regulatory Affairs professional stays informed.

Research Objective	Investigate the challenges encountered by Regulatory Affairs professional working in Medtech Industry.

By understanding these challenges the Regulatory Affairs professional will have an opportunity to incorporate and mitigate against them by using a regulatory strategy and

ensuring this strategy addresses these issues and provides solutions that would otherwise lead to potential time delays in getting products to the market. **Table 3** details the research questions to be addressed.

Table 3: Research Questions

Number	Research Question
1	What is the main challenge experienced by Regulatory Affairs professional in gaining regulatory approval in United States, Europe, China, Korea and Japan?
2	How are Regulatory Affairs professionals staying informed on changing and evolving global regulatory requirements?
3	How are the regulatory requirements communicated internally in companies by Regulatory Affairs professionals?
4	Are Regulatory Affairs professionals aware of changing government policies that impact the Medtech industry?

This research will investigate whether the challenges identified in the literature are significant in the context of Regulatory Affairs professionals working in the medtech industry.

2 Chapter 2 Literature Review

2.1 Introduction

This chapter gives an overview of the literature searches which focused on the three main challenges encountered by Regulatory Affairs professionals working in the Medtech industry;(1) different regulatory frameworks in different regions (lack of regulatory harmonisation across geographies): United States, Europe, China, Korea and Japan, (2) evolving regulatory frameworks/requirements for example the new regulation for medical devices in Europe and (3) staying informed on changing government policies that impact the Medtech industry. The details of the review for each challenge are discussed in this chapter. The following search terms were used 'medical devices' 'regulation' 'challenges' to search the scientific databases (Pubmed, ProQuest Disseration UK & Ireland, Scopus, Embase). The literature search yielded sufficient information on the US and Europe but very little on Japan, China and Korea.

2.2 Challenge One: Lack of regulatory harmonization across geographies

To investigate the challenge of the lack of regulatory harmonization across geographies a review of the regulatory frameworks in United States, Europe, China, Korea and Japan was completed. These are not the only regions that have medical device regulations and requirements, regions such as Australia, Canada, and various other geographies have specific requirements. Due to time restraints it is not possible to cover all regions in this research. This research has focused on the US and EU, China, Korea and Japan. The top three markets for medical devices are US, EU and China. US has been included in this research as it is the largest market for medical devices "the current global market is valued at $228 billion, up from $164 in 2010 and projected to reach $440 billion by 2018. The US market value is 38% of the global total and China has become the third largest medical device market valued at $48 billion." (The Whitaker Institute 2015)

The EU was chosen as it is the second biggest medical device market. "The European medical technology market is estimated at roughly €100 billion. Based upon manufacturer prices the European medical technology market is estimated to make up 31% of the world market. It is the second largest medical technology market after the US (± 40%)." (MedTech

Europe 2015) Korea was included in this research because “South Korea has the highest healthcare expenditure of all the “Asian Tigers”, with an estimated 55% funded by the public sector.” (Wong and Tong 2013)

Japan has been chosen because ‘Japan is an economic powerhouse, and its medical device market is one of the biggest in the world. The Japanese medical device industry was valued at US$28.1 billion in 2016 and is projected to grow steadily through 2020, when it should reach over US$31.7 billion.’ (Emergo 2017a)

“According to the World Health Organization (WHO), medical device harmonization is a process to encourage convergence in regulatory practices related to ensuring the safety, effectiveness/performance, and quality of medical devices, promoting technological innovation, and facilitating international trade.” (Ramakrishna et al 2015)

To investigate the lack of harmonization across the geographies (US, EU, China, Korea and Japan) this research will present details on the classification of medical devices in each region and provide an overview of the regulatory pathways in each region. “The different regulatory authorities in each country recognize different classes of medical devices based on their design complexity, their use characteristics, and their potential safety hazard if misused. Each country defines these categories in different ways. But typically, they are regulated into class I, II (IIa, IIb), and III (or A, B, C, D) based on the risk level to patients, ranging from low risk to high risk, refer to **Table 4**.” (Ramakrishna et al 2015)

Table 4: Classification of Medical Devices (Ramakrishna et al 2015 pg22)

Country	**Classification**			
US	I	II		III
Europe	I	IIa	IIb	III
China	I	II	III	IV
Korea	I	II	III	IV
Japan	I	II	III	IV

2.2.1 Classification of Medical Devices in United States

"The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services. It consists of the Office of the Commissioner and four directorates overseeing the core functions of the agency: Medical Products and Tobacco, Foods and Veterinary Medicine, Global Regulatory Operations and Policy, and Operations. FDA is responsible for: protecting the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices." (FDA, 2015a)

Medical devices are regulated by the Food and Drug Administration (FDA). The FDA classifies medical devices based on the risks associated with the device. Devices are classified into one of three categories—Class I, Class II, and Class III, refer to **Table 5**. (FDA 2014)

Table 5: Classifying types of medical devices by level of risk in US (Ramakrishna et al 2015 pg27)

Risk to Patient		
Low Risk	Medium Risk	High Risk
Class I	Class II	Class III
Increasing Regulatory Controls		
General Controls Most exempt from 510(k) clearance	General Controls + Special Controls Usually requires 510(k) clearance	General Controls + Special Controls Premarket Approval (PMA)

"Class I includes devices with the lowest risk and Class III includes those with the highest risk. Class I devices present a low risk of harm to the user and are subject to general controls that are sufficient to protect the user. Most are exempt from the regulatory process." (FDA 2015c)

"Class II medium risk devices usually require 510(k) clearance, which determines whether the new device is substantially equivalent to an existing legally marketed device (predicate) device. Substantial equivalence means that the new device is at least as safe and effective as the predicate, that the device performs in a manner similar to that of the predicate in its

intended use, technological characteristics, and safety and effectiveness. If a device is determined to be substantially equivalent, a clinical trial is usually not required to prove its safety and effectiveness. Other requirements such as special controls may be imposed, such as those for labeling requirements and post-market surveillance." (FDA 2014, 2015a, 2016a and 2016b)

"Class III high risk devices, these are the the most stringent regulatory category for medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Due to the level of risk associated with Class III devices, FDA has determined that general and special controls alone are insufficient to assure the safety and effectiveness of class III devices. Therefore, these devices require a premarket approval (PMA) application under section 515 of the FD&C Act in order to obtain marketing clearance. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). An approved PMA is, in effect, a private license granting the applicant (or owner) permission to market the device. The PMA pathway typically requires significant clinical data to support the safety and effectiveness of the device, a quality system pre-approval audit is typically required prior to FDA granting the PMA approval." (FDA 2016c)

"Novel devices without a predicate are automatically classified as Class III, regardless of their risk profile. The *de novo* process was introduced by the FDA as a means to reclassify novel devices of low to moderate risk profiles." (FDA 2017a)

"An Humanitarian Device Exemption (HDE) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. HDEs are exempt from requirements to demonstrate effectiveness. Still, they must pose no unreasonable risks, or at least the probable benefits should outweigh the risks. And the device must be used at a facility with an Institutional Review Board. HDEs provide a powerful incentive for device manufacturers to develop devices that help diagnose or treat patients with rare conditions. Otherwise, a company's research and development costs would likely exceed the market returns for serving such small patient populations." (FDA 2015c)

In the FDA guidance ‘Medical Device Classification: Product Codes’ FDA discuss “unclassified device which is a pre-amendments device for which a classification regulation has not been promulgated. Unclassified devices require submission of a 510(k) premarket notification to CDRH. A not-classified device is a post-amendments device for which the Agency has not yet reviewed a marketing application or for which the Agency has not made a final decision on such a marketing application. A pre-amendments device is a device that was on the market prior to the enactment of the Medical Device Amendments to the FD&C Act on May 28, 1976.” (FDA 2013)

There are three classifications for medical devices in the US Class I, II, and III. “Regulatory control increases from Class I to Class III. The device classification regulation defines the regulatory requirements for a general device type. Most Class I devices are exempt from Premarket Notification 510(k); most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval.” (FDA 2015d) The FDA provides a special access route for Humanitarian Device Exemption as discussed above.

2.2.2 Regulatory Pathways for Medical Devices in United States

The regulatory pathways in the US include premarket notification, commonly known as the 510(k) process; most Class II devices require a 510(k) (FDA 2015d) and Premarket Approval (PMA) for the higher classification, Class III devices. “Premarket Notification, 510(k) is required when demonstrating substantial equivalence to a legally marketed device, when making significant modifications to a marketed device, and when a person required to register with FDA introduces a device for the first time. If a device requires the submission of a 510(k), it cannot be commercially distributed until the FDA authorizes it. A device is substantially equivalent (SE) if it has the same intended use and same technological characteristics as a legally marketed device, known as the predicate. A legally marketed device:

1. was legally marketed prior to May 28, 1976 ("preamendments device"), for which a PMA is not required, or
2. was reclassified from Class III to Class II or Class I, or
3. was found SE through the 510(k) process.

Applicants must compare their device to one or more similar legally marketed devices and support their SE claims. If the device is SE to a predicate, it is placed in the same class. If it is not SE, it becomes non-SE and is placed into Class III." (FDA 2015d)

"Premarket Approval (PMA) refers to the scientific and regulatory review necessary to evaluate the safety and effectiveness of Class III devices or devices that were found not substantially equivalent to a Class I or II predicate through the 510(k) process. PMA is the most involved process. To reasonably assure that a device is safe and effective, PMA requires valid scientific evidence that the probable benefits to health from the intended use of a device outweigh the probable risks, and that the device will significantly help a large portion of the target population. Sources of valid scientific evidence may include well controlled investigations, partially controlled studies, historical controls, well documented case histories by qualified experts, and robust human experience. Independence is an important concept for PMAs, meaning that each PMA should establish the safety and effectiveness of the device under review, and that data about one device cannot be used to support another." (FDA 2015d)

"Investigational Device Exemptions (IDE) allows an investigational device to be used in a clinical study to collect the safety and effectiveness data required for a Premarket Approval (PMA) application or a Premarket Notification (510(k)) submission to FDA. Clinical studies with devices of significant risk must be approved by both FDA and an Institutional Review Board (IRB) before the study can begin. Studies with devices posing non-significant risk must be approved by an IRB before the study can begin." (FDA 2015d)

"FDA De Novo Submissions for new devices. Entirely new devices are automatically considered to be Class III in the US. However, many new products are not high risk. This is why the FDA has the "*de novo"* process. You may consider filing a "*de novo*" submission if the FDA determines, through means such as a 513(g) or Pre-Submission, that your device is a "novel" with no existing classification or predicate device on the market. Within 120 days after your *de novo* submission, the FDA will determine if your device is Class I or II and may issue an entirely new product code and regulation number. If rejected, your device will remain Class III." (Emergo 2017d)

Table 6 compares the 510(k) and the PMA submission, the major difference is in relation to substantial equivalence.

Table 6: Summary Comparison of 510(k) and PMA (Ramakrishna et al 2015 pg96)

510(k) Submissions	PMA Submissions
• primarily for Class II devices • a Class I or II preamendment or legally marketed device (predicate) exists • third party review option is available for devices not requiring clinical data • documented proof of Substantial Equivalence to a predicate is required	• primarily for Class III devices • a Class I or II preamendment or legally marketed device (predicate) does not exist • device is life supporting and/or has potential risk to patient • documented safety and effectiveness data for the device is required

"The most comprehensive regulatory system comes from the US FDA. The US FDA's budget was approximately $2 billion, approximately $45 million of which was allocated to the Center for Devices & Radiological Health (CDR) activities in FY2009; the CDRH is in charge of medical devices." (Ramakrishna et al 2015) During the literature review it became obvious that FDA has the most comprehensive regulatory system. The FDA website provides detailed information and is an excellent resource available to the Regulatory Affairs professional.

2.2.3 Classification of Medical Devices in Europe

Overview of European Regulatory Framework:

To provide an understanding of the classification of medical devices in Europe it is first important to understand the existing regulatory framework and the key stakeholders for example Competent Authorities, Notified Bodies Authorised Representative. It is important to know that the regulatory framework in Europe is undergoing change. The changes to the regulatory framework (Medical Device Regulation) are discussed in detail in section 2.3. The existing regulatory framework for medical devices in Europe "is regulated by the following 3 directives:

- Council Directive 90/385/EEC on Active Implantable Medical Devices (AIMDD) (1990)
- Council Directive 93/42/EEC on Medical Devices (MDD) (1993)
- Council Directive 98/79/EC on In Vitro Diagnostic Medical Devices (IVDMD) (1998)" (European Commission 2017a)

The new regulatory framework replaces these three Directives and with two regulations:

- Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
- Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

Key Stakeholders:

"Each country within the EU and partner countries has a Competent Authority. The Competent Authority is a body within the government of the Member States that transposes the requirements of the Medical Device Directives into National Law. The Competent Authority is also responsible for specifying one or more Notified Bodies, to act as independent third party assessors of the manufacturer's compliance." (BSI 2014)

"The role of a Notified Body is to conduct a conformity assessment under the relevant EU Directives. The Notified Body conducts the conformity assessment against the relevant sections of the applicable Directive (MDD, AIMDD or IVDD). The conformity assessment usually involves an audit of the manufacturer's quality system and depending upon the particular classification of the device, a review of the relevant technical documentation provided by the manufacturer in support of the safety and performance claims for the device." (BSI 2017b)

"European Authorized Representative serves as a liaison between you and the national Competent Authorities (Ministries of Health). Additionally, your appointed representative will:

- Assist with certain device registrations, as required
- Be identified on your product labeling throughout Europe
- Make a current copy of your Technical File or CE Declaration of Conformity available for inspection by a Competent Authority, upon request
- Assist with Incident and Field Safety Corrective Action (FSCA) reporting, in cooperation with you and your distributors" (Emergo 2017e)

What is CE Marking?

"CE marking is the medical device manufacturer's claim that a product meets the essential requirements of all relevant European Directives and is a legal requirement to place a device on the market in the European Union." (BSI 2014) "A CE mark is a logo that is placed on medical devices by a manufacturer in order to indicate that their product conforms to the requirements of the directives. It indicates that the device works in accordance with the intended purpose and meets legislation relating to safety and performance. A product that bears a CE mark can be freely marketed anywhere in the European Union." (MHRA 2016)

"CE marking is the manufacturer's declaration that the medical device meets the appropriate regulatory requirements. To understand which requirements you need to meet, you must classify the device and identify the appropriate conformity assessment route for your product. This dictates the required activities to demonstrate conformity. We will review the route you chose to confirm its suitability, and work with you to execute the most efficient review process for the route selected. Our trusted review processes allow you to build reliability and confidence into your CE marking project planning." (BSI 2017c)

"Since 14 June 1998 no medical device covered by the MDD 93/42/EEC shall be placed on the market that does not carry a CE mark. 'Placing on the market' means making available in return for payment or free of charge of a device other than a device intended for clinical investigation, with a view toward distribution and/or use on the Community market, regardless of whether it is new or fully refurbished. The only devices not requiring a CE-mark are 'custom-made devices' and 'devices intended for clinical investigations', where the manufacturer must keep documentation in accordance with MDD Annex VIII. Custom-made device means any device specifically made in accordance with a duly qualified medical practitioner's written prescription which gives, under his responsibility, specific design characteristics and is intended for the sole use of a particular patient." (Medical Device Certification 2009)

Classification of Medical Devices:

This research focused on the general medical devices governed by the Directive 93/42/EEC. "General medical devices (Directive 93/42/EEC) and related accessories must be classified into one of four classes, which are based on the perceived risk of the device to the patient or user. The classification of a device determines the conformity assessment options that are applicable to the device, with higher risk devices undergoing higher levels of assessment." (HPRA 2009)

Table 7: Medical Device Classification and Corresponding Risk Profile in EU

Class	**Type**
I	Low Risk
IIa	Medium Risk
IIb	Higher Risk
III	Highest Risk

"The rules governing device classification are listed in Annex IX of Directive 93/42/EEC and are further elaborated on in the MEDDEV guidance 'MEDDEV 2.4/1 Guidelines for the Classification of Medical Devices'." (HPRA 2009) "There are eighteen rules outlined in Annex IX of the Directive and related Regulation that lay down the basic principles of classification. In MEDDEV 2.4/1, these rules are further explained and descriptive examples are provided. The eighteen rules are subdivided into four groups as follows, reference **Table 8**:" (HPRA 2009)

Table 8: Rule Categorization from MEDDEV 2.4/1 Guidelines for the Classification of Medical Devices

Rules	**Device**
Rules 1 – 4	Non-invasive Devices
Rules 5 – 8	Invasive Devices
Rules 9 – 12	Active Devices
Rules 13 – 18	Special rules e.g. devices containing tissue of animal origin, drug-device combinations Annex

Annex IX and MEDDEV 2.4/1outlines a number of key characteristics, that must be considered to correctly classify a device using the eighteen classification rules, these are; duration of contact, degree of invasiveness, whether or not the device is active, part of the body affected. (HPRA 2009)

Class I:

Class I medical device without a measuring function and supplied in non-sterile condition does not require the involvement of a Notified Body. "Manufacturers of low risk devices (Class I) are required only to self-declare to the Essential Requirements to a national "Competent Authority". The competent authorities oversee the regulation of medical devices on the market." (Sorenson & Drummond 2014)

"The devices must meet the essential requirements set out in Annex I of the Directive which apply to them, taking account of the intended purpose of the devices concerned. Devices must be designed and manufactured in such a way that, when used under normal conditions of use and for the purposes intended by the manufacturer, they will not compromise the clinical condition or the safety of patients or the safety and health of users or other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety. The devices must achieve the performance as intended by the manufacturer." (European Commission 2009)

"In the case of products placed on the market in sterile condition the manufacturer or his authorised representative must follow the procedure referred to in Annex II or V of the MDD. For devices with a measuring function the manufacturer or his authorised representative must follow one of the procedures referred to in Annex II, IV, V or VI of the MDD. This requires the intervention of a notified body. In all other cases the intervention of a Notified Body is not required for Class I devices." (European Commission 2009)

Class I (sterile or measuring), IIa, IIb and Class III:

"More moderate and high-risk devices (Class I sterile/measuring, IIa, IIb and III) require a combination of clinical and nonclinical data on the device being evaluated." (Sorenson & Drummond 2014)

The certification of Class I (sterile/measuring), IIa, IIb and III "usually includes the following steps:

- decision whether or not a product is a medical device and by which of the European Medical Devices Directives it is covered
- classification of the device(s) by the manufacturer
- contact to Notified Bodies, preliminary discussions and exchange of information, choice of the Notified Body
- answering of specific questions of the chosen Notified Body (usually by filling out a questionnaire provided by the Notified Body); confirmation of device classification by the Notified Body, time and cost estimation for different certification routes; choice of the certification route by the manufacturer
- formal application and certification contract
- submission of documents to the Notified Body
- evaluation of the submitted documents and report
- audit of the manufacturer's operations and if applicable and required also suppliers' and/or subcontractors' facilities including reporting
- decision about the certification and issuing of the relevant certificate(s), which are usually valid for five years
- surveillance audits
- full re-audit and issuing of a new certificate usually after five years" (Medical Device Certification 2009)

2.2.4 Regulatory Pathways for Medical Devices in Europe (Conformity Assessment)

Medical devices are classified in accordance with Annex IX of the MDD. The classification determines which conformity assessment procedure the manufacturer must follow in accordance with the Annexes II, III, IV, V, VI and VII of the MDD. (Medical Device Certification 2009)

Annex II – EC Declaration of Conformity (Full Quality Assurance System):
"Most comprehensive conformity assessment procedure referring to a full quality system including the design phase for new devices or changes of existing devices; Section 4 (Examination of the Design of the Product) applies only to class III devices; this Section is similar to Annex III - EC Type-Examination with the difference that in-house test results obtained by the manufacturer under his full quality management system may be used as the basis of certification; the manufacturer may choose the harmonized standard EN ISO 13485 in combination with the respective guidance standard as the basis of his quality system or use an equivalent quality system suitable to fulfil the requirements of the MDD." (Medical Device Certification 2009)

Annex III - EC Type Examination:
"A conformity assessment procedure for the product design which involves examination and third party testing of representative samples of the device and certification that the device meets the applicable essential requirements of the MDD; EC Type Examination is applicable only to class IIb and III devices." (Medical Device Certification 2009)

Annex IV - EC Verification:
"A conformity assessment procedure in which the Notified Body examines and tests every individual device or devices taken on a statistical basis, if the manufacturer manufactures homogeneous batches; the Notified Body releases individual devices or batches; EC Verification may be applied to class IIa, IIb and III devices." (Medical Device Certification 2009)

Annex V - EC Declaration of Conformity (Production Quality Assurance):

"A conformity assessment procedure for the quality system of the manufacturer excluding the design phase of new devices but including all other aspects of conformity with the MDD; this conformity assessment procedure is the most suitable procedure for sterile class IIa devices, if the manufacturer does not choose the Annex II as the basis of certification; it may also be applied to class IIb and III devices in combination with Annex III; the manufacturer may base his quality system on the harmonized standard EN ISO 13485." (Medical Device Certification 2009)

Annex VI - EC Declaration of Conformity (Product Quality Assurance):

"A conformity assessment procedure for the quality system for manufacturers of devices whose relevant properties can be assessed in final inspection; the manufacturer may base his quality system on the standard EN ISO 13485; this conformity assessment procedure is not suitable for devices involving special manufacturing processes requiring validation, like sterilization; Annex VI may not be used for the assessment of class III products." (Medical Device Certification 2009)

Annex VII - EC Declaration of Conformity:

"A conformity assessment procedure in which the manufacturer himself declares the compliance of his devices with the MDD; suitable for class I devices, and required for class IIa devices in combination with one of the Annexes IV, V, or VI." (Medical Device Certification 2009)

"Each conformity assessment procedure has a well-defined level of regulatory oversight that is directly proportionate with the device class it applies to. Where there are alternative conformity assessment procedures with an equivalent or higher level of regulatory scrutiny, the manufacturer may choose the one that it wants to use." (Theisz 2015)

2.2.5 Classification of Medical Devices in China

"Medical devices are classified according to the risk level associated with their intended use. In general, the risk level depends on the design of a medical device as well as its intended use. The Sate shall classify medical devices and administer them on the basis of the following classification:

- Class I medical devices are those for which safety and effectiveness can be ensured through routine administration.
- Class II medical devices are those for which further control is required to ensure their safety and effectiveness.
- Class III medical devices are those which are implanted into the human body or used for life support or sustenance or pose potential risk to the human body and thus must be strictly controlled in respect to safety and effectiveness

These class definitions are not the same as those used in the European Union; and the Class III classification is much broader than many manufacturers may be used to. There are many reasons for these classification differences in China. The two key reasons are

1. Historical reasons, i.e. some devices are classified as different classification or even as a drug even before medical device regulation came into being and hence the device may follow the old classification
2. Social reason, i.e. the SFDA may consider some device to have higher risk in China, e.g. after some adverse events." (Wong and Tong 2013)

2.2.6 Regulatory Pathways for Medical Devices in China

"In China, China Food & Drug Administration (CFDA) is the regulatory authority for food, drugs, and medical devices. Under CFDA, the department of Medical Device Supervision takes on the responsibility for regulating medical devices. The new regulation for the supervision and administration of medical devices (National Council Order No. 650) came into force as of October 1, 2014. The purpose of these regulations is to strengthen the supervision and administration of medical devices; to ensure their safety and effectiveness; and to protect human health, life, and safety. China has its own national standards (in the Chinese language), which follows the international standards closely, to regulate medical devices market." (Ramakrishna et al 2015)

"Each medical device or medical device family should have a Medical Device Registration Certificate before it can be placed on the market in China. The certificate is owned by the local manufacturer or the distributor and must be renewed every five years. The precise requirements for product registration vary depending on the device class but can include sample testing, clinical evaluation/investigation and site inspection. For every imported medical device, before registration, the applicant should write a product standard which follows China National Standard as the first step. The manufacturer can use an ISO/IEC standard as product standard, but the standards should be translated into Chinese. The applicant should arrange product testing by the national Testing Centre to ensure that product passes the test as per the China National Standard. Once State Food and Drug Administration (SFDA) Application Receiving Office has all the required information, the application is passed to the Medical Devices Evaluation Centre, then to the Department of Medical Devices, and then to the Director General of the SFDA for final approval. Finally, the result of the application and certificate of approval is sent back to the Application Receiving Office for collection by the applicant." (Wong and Tong 2013) The SFDA was restructured in March 2013 to become the CFDA.

2.2.7 Classification of Medical Device in Korea

"Medical devices are divided into four classes, Class I being lowest risk and Class IV being highest risk, a strict system of 2,139 classifications segments devices, including 64 IVD device reagents and 16 U-healthcare. If a product is not listed in the Korean system, the company should contact the Medical Device Evaluation Department of the KFDA and ask for a classification determination via the website or phone." (Wong and Tong 2013)
"Medical devices in Korea can be classified into 1 of 3 main types and four classes. The Product Types include new (novel) products, improved products and equivalent products:

- New (novel) product: a medical device that is not equivalent to an approved medical device in the purpose of use, working mechanism, or raw materials
- Improved product: a medical device that is equivalent to an approved medical device in the purpose of use, working mechanism or raw materials, but not equivalent in performance, test specifications, instructions for use
- Equivalent product: a medical device that is equivalent to an approved medical device in the purpose of use, working mechanism, raw materials, performance, test specification and instructions for use" (NAMSA 2014)

2.2.8 Regulatory Pathways for Medical Devices in Korea

"Under Korean regulations, a foreign manufacturer without an office in Korea cannot directly submit a device registration application to the KFDA; therefore, the company may allow its importer to do the registration. The foreign manufacturer also may hire an independent third party based in Korea to make the registration in its own name. All medical devices require the pre-market registration from the KFDA before they can be manufactured locally or imported into Korea. There are two types of pre-market license. One is the pre-market approval for Class II, III and IV devices and the other is the pre-market notification for Class I devices except those that have sterile and/or measurement function." (Wong and Tong 2013)

"The procedure for Class I devices is relatively simple, only notification is required, not approval. The applicant submits a standard notification to one of the six regional KFDAs depending on the applicant's residential district. This notification includes information on the product, its manufacturer or importer, its classification, purpose of use, instructions for use, raw materials and specifications, dimensional drawings, precautions and the labelling to be used. Once it is submitted, the regional KFDA will issue an acceptance letter, which is equivalent to a product license." (Wong and Tong 2013)

"Class II, III, and IV devices need to go through a full review and approval process, refer to **Figure 4**. Approval in the country of origin can speed up the process somewhat but is not sufficient for product registration in Korea. The two main requirements for a product license are a technical file and type testing." (Wong and Tong 2013)

"Companies need to designate a local license holder/distributor and have their products tested at the Korean Ministry of Food and Drug Safety (MFDS) designated labs in Korea. In most cases foreign test reports can be accepted for biocompatibility but they must be conducted under Good Laboratory Practices for them to be eligible. For manufacturers and distributors entering Korea for the first time, the MFDS inspects all products except Class I devices, and even some of those may be inspected. In the case of new (novel) products, clinical trial data will be required and/or clinical evaluation reports citing published clinical trials of equivalent devices.

The process for medical device approval in Korea involves two types of technical document review. A General Technical Document Review (TDR) is sufficient for devices that are considered to be substantially equivalent to previously approved products. A more detailed Safety and Efficacy Review (SER) is required for novel devices or devices with new performance, new structure, new purpose of use, or significant differences from previously approved devices that affect safety and effectiveness. Clinical study data are essential for SERs." (NAMSA 2014)

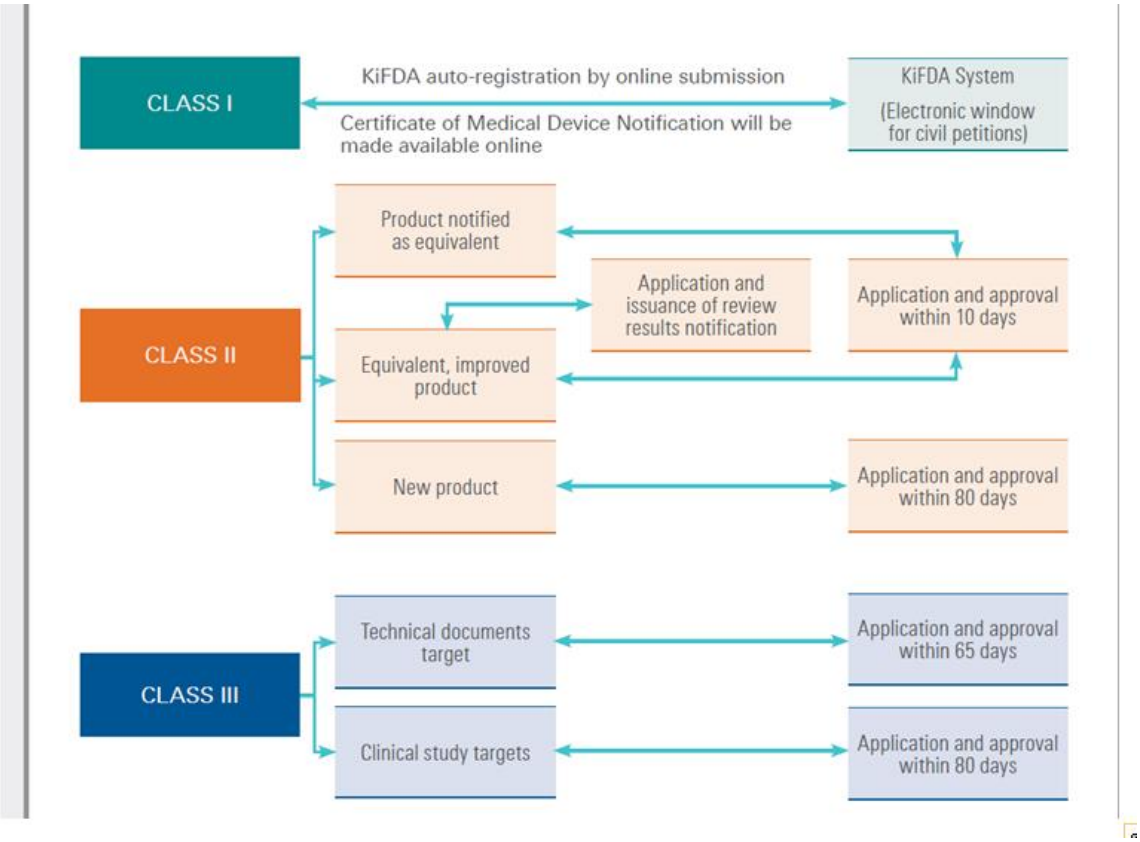

Figure 4: Korean Notification/Approval Process (NAMSA 2014)

2.2.9 Classification of Medical Devices in Japan

"In Japan, medical devices are classified mainly into four classes, on the basis of risk-based system following the Global Harmonization Task Force (GHTF) rule as shown in the **Table 9."** (Wong and Tong 2013)

Table 9: Overview of classification and pre-market regulation for medical devices (Wong and Tong 2013 pg393)

Category		**Risk-based classification**	**Technical stds. for certification**	**Type of regulation**	**Reviewed by**	**QMS**
General MD		Class I extremely low risk	NA	Self-declaration	MAH (report to PMDA)	*Some exception
Controlled MDs	Designated controlled medical devices	Class II low risk	Yes	3rd Part Certification	Registered Certification Body	Applied
	Other than above		No	Minister's Approval	PMDA and MHLW	
Specially Controlled MDS		Class III medium risk	NA			
		Class IV high risk				

"In Japan, the medical devices are divided into Class I, II, III and Class IV. Class I medical devices are defined as general medical devices extremely low risk in the human body. Approval of Class I medical devices is not required, but marketing notification is necessary. Class II medical devices are controlled medical devices designated by the Minister of Health, Labor, and Welfare, for which applicable certification standards are specified by the Minister low risk to the human body (certification by a registered certification body is required) or other controlled medical devices low risk to the human body. Class III medical devices are specially controlled medical devices medium risk to the human body. Class IV medical devices are specially controlled medical devices highly invasive to patients high risk to the human body. For Class III and Class IV medical devices, the Minister's approval for the product is required." (Ramakrishna et al 205)

2.2.10 Regulatory Pathways for Medical Devices in Japan

"Registration of medical devices in Japan is complicated, costly, and will generally take between 1-3 years depending on the device classification. In some cases, Japanese regulators require clinical trials in Japan to be conducted, and the costs of these trials can be very high. Product registration in Japan needs to be pursued carefully and only after determining that there is a strong market demand for your product." (Pacific Bridge Medical 2017)
"Ministry of Health, Labor, and Welfare (MHLW) – The MHLW is Japan's primary regulatory body for creating and implementing safety standards for medical devices and drugs. Within the MHLW, the Pharmaceutical and Food Safety Bureau is in charge of pharmaceutical and medical device regulatory policy. The MHLW's responsibilities in policies and administrative measures include:

- Final judgment on registration approval
- Product withdrawal from the market

Pharmaceutical Medical Devices Agency (PMDA) – The PMDA is an independent administrative agency that works with the MHLW to ensure the safety and quality of drugs and medical devices in Japan. The PMDA is the "technical arm" of the MHLW.
The PMDA's responsibilities in assisting the MHLW'S measures include:

- Approval review of medical devices
- QMS/GLP/GCP inspection
- Collection and analysis of Adverse Event Reports" (Pacific Bridge Medical 2017)

The Notification pathway, "Class I medical devices are categorized as 'General Medical Devices' by PAL. A marketing authorization holder (MAH) who intend to market a 'general medical device' is not required to obtain the minister's approval and is allowed to launch a medical device onto the Japanese market by submitting the marketing notification for the medical device to PMDA." (Wong and Tong 2013)

"The pre-market certification (third-party certification) pathway, Class II medical devices are called 'Controlled Medical Devices' in PAL. Among the controlled medical devices, medical devices to which there is the certification standard applicable are recognized as 'Designated Controlled Medical Devices'. To register and market a designated controlled medical device, the MAH needs to file pre-market certification application with a registered certification body

(third-party certification body) and obtain their certification. Application dossiers for pre-market certification have to be written in Japanese and the technical data and supporting information have to be submitted following the summary technical documentation (STED) format." (Wong and Tong 2013)

"The pre-market approval pathway, 'Class III and IV medical devices are defined as 'Highly Controlled Medical Device in PAL. When an MAH intends to launch a 'specially controlled medical device' onto the Japanese market, the minister's approval to market the medical device is required. The minister's approval is granted on the basis of the scientific review at the PMDA. Class II devices other than Specified Controlled Medical Devices are also subject to pre-market approval. In the case that no applicable certification standard has been established or that the product is deemed as new medical device, the MAH is required to submit an application to the PMDA to obtain the minister's approval for the product. Application dossier for pre-market approval has also to be written in Japanese and the technical data and supporting information have to be submitted following the STED format." (Wong and Tong 2013)

"If the manufacturing facilities are located outside of Japan, these foreign manufacturing facilities are required to obtain the Foreign Manufacturer Accreditation, these are valid for five years and are renewable." (Wong and Tong 2013)

"Japan represents an important market for medical device manufacturers. Even if authorities have started to simplify the regulatory process in the past years, it is still complex for foreign manufacturers to penetrate this market, especially since Japan still does not accept CE and FDA approvals. Having a clear understanding of the regulatory and market hurdles is key to decrease time and cost to market and avoid hazardous strategies." (Clarivate Analytics 2017)

2.2.11 Conclusion on Lack of regulatory harmonization across geographies

To understand the lack of regulatory harmonization across geographies, the classification and regulatory pathways for US, EU, China, Korea and Japan were studied. "Medical device regulations across the globe have significant variations" (Zhang et al 2016) each region has a risk based classification however a Class III in Europe may not be a Class III in the US for example a coronary guide wire is a Class III in Europe whereas in the US it's a Class II.

The literature review yielded lots of information for the US and EU "the US was the first country to legally define a 'medical device', and also was the first country to establish a medical device management procedure. As the second largest medical device manufacturers and consumers in the world, the EU also has a rich history of medical devices regulation. The US and EU have established relatively mature medical devices regulations, which have a key influence in the world." (Zhang et al 2016) Very little information is available on the other regions, China, Korea and Japan.

The impact of the lack of regulatory harmonisation to the Regulatory Affairs professional is the need to "adjust to the dynamic regulatory environment found in both the Asia-Pacific region and the broader global environment, the regulatory function should strive to operate as a centre of intelligence for the organization, proactively sensing signals of change in the external environment and disseminating the insights to the organization." (Wong and Tong 2013)

"Globalization impacts the role of the regulatory professional, in addition to learning global requirements, you also must be aware of different ways to interact with multiple global agencies. For example, certain cultures may have a different question-and-answering technique than we may have in the US, EU or Canada. Globalization has made the regulatory profession far more complex than it has been before. " (RAPS 2016a)

2.3 Challenge Two: Evolving regulatory frameworks

"The regulation of medical devices is a vast and rapidly evolving field" (WHO 2003). This section of thesis will briefly outline the evolving regulatory frameworks in United States, China, Japan, and Korea. Europe will be assessed in detail as a case study to examine the challenge of evolving regulatory frameworks for the Regulatory Affairs professional. Europe has been chosen as a case study as the regulatory framework recently changed with the introduction of the medical devices regulation in May 2017.

2.3.1 United States Evolving Regulatory Framework

"The long legal journey toward medical device regulation in United States began with the Pure Food and Drugs act of 1906. Medical devices were not included as no one envisioned how technology would grow increasingly complex and need to be regulated. The Medical Device Amendments of 1976 gave FDA authority to ensure the safety and effectiveness of a range of life-saving medical devices while also protecting the public from fraudulent devices. The Amendments:

- defined a medical device,
- established three device classes (I, II, and III),
- identified pathways to market,
- established Advisory Panels, and
- set clinical investigation requirements.

Subsequent legislation strengthened the FDA's regulatory authority:" (FDA 2015c) An overview of the major medical device legislation is provided in **Table 10**.

Table 10 : Major Medical Device Legislation in US (FDA 2015c)

Legislation	**Significance**
Safe Medical Devices Act of 1990	• established Quality System requirements supported postmarket surveillance allowed FDA discretion for PMAs brought to panel
FDA Modernization Act of 1997	• supported for early collaboration, expanded Class I and Class II exemptions • set the "least burdensome provision"* • supported dispute resolution • established evaluation of automatic Class III designation (giving the sponsor the opportunity to request lower classification due to a minimal risk device, known as "de novo" review) • mandated free and open participation by all interested persons
Medical Device User Fee and Modernization Act (MDUFMA) of 2002	• established a fee schedule for most types of device submissions to achieve shorter review times • requires FDA to include paediatric experts on the panel for a product intended for paediatric use
FDA Modernization Act of 2007	• reauthorized and expanded MDUFMA
The 21st Century Cures Act (Cures Act) 2016	• is designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently. (FDA 2017b)

The **least burdensome provision allows industry and FDA to consider the least burdensome appropriate means of evaluating a device's effectiveness when there's a reasonable likelihood of its approval. The intent is to help expedite the availability of new device technologies without compromising scientific integrity in the decision-making process or FDA's ability to protect the public health. This provision does **not** lower the standard for premarket clearance and approval.*

2.3.2 China Evolving Regulatory Framework

"The first medical device regulations in China were adopted in 2000 with State Council Order 276. Since then there have been many additions and improvements, culminating with a major overhaul introduced by State Council Order 650 in 2014. The newly revised regulations include significant changes to the product classification rules and the implementation of risk-based regulatory controls, aligning thus better with the major established markets." (Theisz 2015)

As noted by Ramakrishnan et al (2013) "medical device companies doing business in China should keep a close watch on the development of the draft rules and the actual enforcement of the revised regulation because the changes will have significant implications on their operations in China".

2.3.3 Korea Evolving Regulatory Framework

"Since 1997, medical devices have been regulated by the Korean Food and Drug Administration (KFDA), which is an independent agency under the supervision of the Ministry of Health and Welfare (MOHW). Previously, the governing law for medical devices was the Pharmaceutical Affairs Act, which also had mainly covered drugs since 1953. However, to better cover medical devices and speed international harmonization, the new Medical Device Act was announced on 29 May 2003. It went into implementation and full enforcement began on May 30, 2004 with the requirement that all medical devices to be sold in South Korea meet the requirements of the Korea Good Manufacturing Practices (KGMP), mostly identical with ISO 13485:2003 standard." (Wong and Tong 2013)

2.3.4 Japan Evolving Regulatory Framework

"On November 25, 2014, the Japanese government revised the Pharmaceutical Affairs Law (PAL) and implemented the new PMD Act ("Act on Securing Quality Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics"). The new PMD Act was based on previous ordinances implemented in the summer of 2014. Two of the main points of this revision are to increase safety measures for medical devices and introduce new cellular and tissue therapeutic product regulations." (Pacific Bridge Medical 2015)

"Many of the changes identified in the new PMD Act will help more foreign medical device companies get their products on the Japanese market sooner. It is important that foreign medical device manufacturers study these new regulations so they can use them to their advantage to succeed in the Japanese marketplace." (Pacific Bridge Medical 2015)

2.3.5 Europe Evolving Regulatory Framework

To understand the challenges of evolving regulatory frameworks for the Regulatory Affairs professional the research focused on the changing regulatory landscape in Europe. The existing regulatory framework for medical devices in Europe "is regulated by the following 3 directives:

- Council Directive 90/385/EEC on Active Implantable Medical Devices (AIMDD) (1990)
- Council Directive 93/42/EEC on Medical Devices (MDD) (1993)
- Council Directive 98/79/EC on In Vitro Diagnostic Medical Devices (IVDMD) (1998)" (European Commission 2017a)

"The directive is one of the legal instruments available to the European institutions for implementing European Union policies. It is a flexible instrument mainly used as a means to harmonize national laws. It requires EU countries to achieve a certain result but leaves them free to choose how to do so. The directive forms part of the EU's secondary law. It is therefore adopted by the EU institutions in accordance with the founding Treaties. Once adopted at EU level, it is then transposed by EU countries into their internal law for application." (EUR-Lex 2015a)

"On May 5, 2017 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC." (EUR-Lex 2017) Regulation 2017/745 is the new Medical Device Regulation (MDR).

"Regulations are legal acts defined by Article 288 of the Treaty on the Functioning of the European Union (TFEU). They have general application, are binding in their entirety and directly applicable in all European Union countries. The regulation forms part of the EU's

secondary law. It is adopted by the European institutions on the basis of founding treaties. It aims to ensure uniform application of the EU law in all EU countries." (EUR-Lex 2015b) "Article 120.3 of the Medical Device Regulation says, from the date the regulation is fully applicable – May 26, 2020, products may still be placed on the market or put into service as long as their certificates remain valid, they still comply with the legacy directives and there are no significant changes in the design and intended purpose of the product." (Medtech Insight 2017)

"Compared to the MDD, the MDR promotes a shift from the pre-approval stage (i.e., the path to CE Marking) to a life cycle approach. This approach is similar to the life-cycle view advocated by the US Food and Drug Administration and advanced by many international standards. The MDR concentrates the harmonization efforts between European Member States by means of a new regulatory body called the Medical Device Coordination Group (MDCG)." (Emergo 2017f)

2.3.6 Background on the regulations in EU

The revision of the European regulatory framework was prompted mainly by two scandals in Europe that led to a loss of reputation and trust in the European regulatory frameworks. "Problems with diverging interpretation of the current Directives as well as the incident concerning fraudulent production of the PIP silicone breast implants highlighted weaknesses in the legal system in place at the time and damaged the confidence of patients, consumers and healthcare professionals in the safety of medical devices. Such problems should not occur again and the safety of all medical devices available in the EU has to be strengthened. Moreover, revision of the legislation was necessary to consolidate the role of the EU as a global leader in the sector over the long-term and to take into account all technological and scientific developments in the sector.

The new regulations will ensure:

- a consistently high level of health and safety protection for EU citizens using these products
- the free and fair trade of the products throughout the EU
- that EU legislation is adapted to the significant technological and scientific progress occurring in this sector over the last 20 years." (European Commission 2017d)

“In 2009 surgeons in France began reporting an abnormally high rupture rate with PIP’s breast implants, and in 2010 the French medical safety agency (AFSSAPS) issued a recall of PIP implants. By March of 2010 PIP was in liquidation, and facilities inspection had revealed that the company was substituting unapproved industrial-grade silicone in their implants in place of approved medical-grade silicone (Keogh 2012), a substitution that could potentially cause increased health hazards in the event of rupture. A 2012 UK report on PIP implants, however, found that although PIP implants were more likely to rupture (about double other brands), the PIP silicone was not toxic or carcinogenic (Lancet 2012 MHRA; Keogh 2012). The French government recommended the removal of PIP implants and announced that the 30,000 French women who received PIP implants were entitled to have them removed at no cost (Horton 2012; O’Dowd 2011). In December 2011 a fraud lawsuit was filed against PIP by CNAM, France’s state health insurance fund, for the use of unapproved silicone. “(NAMSA 2015)

“In August 2010 DePuy recalled the ASR™ XL Acetabular System and DePuy ASR™ Hip Resurfacing System, used in some hip replacement surgeries. This recall was carried out because an unusually high proportion of patients with these implants required a revision (a second hip replacement operation) following implant of this product. Information from the National Joint Registry in England and Wales indicates that rates of revision surgery within 5 years after use of either of these products in hip surgery were higher than acceptable: 12% for ASR Hip Resurfacing System and 13% for ASR XL Acetabular System. These compare to revision rates of between 3% and 6%, which were previously recorded.’ (HSE 2016) ‘The controversy rose to scandal status recently when it was revealed that 650 French patients were fitted with hip prostheses with modification that had not been approved in the EU (Samuel 2013)” (NAMSA 2015)

The European Parliament issued, on June 11, 2010 a non-binding call to the European Commission (EC) to create solutions to prevent recurrence of events such as those leading to the recall of PIP implants in France. “The existing regulatory framework has demonstrated its merits but has also come under harsh criticism, in particular after the French health authorities found that a French manufacturer (Poly Implant Prothèse, PIP) had for several years apparently used industrial silicone instead of medical grade silicone for the manufacture of breast implants contrary to the approval issued by the notified body, causing harm to thousands of women around the world. In an internal market with 32 participating countries

and subject to constant technological and scientific progress, substantial divergences in the interpretation and application of the rules have emerged, thus undermining the main objectives of the Directives, i.e. the safety of medical devices and their free movement within the internal market. Moreover, regulatory gaps or uncertainties exist with regard to certain products (e.g. products manufactured utilising non-viable human tissues or cells; implantable or other invasive products for cosmetic purposes). This revision aims to overcome these flaws and gaps and to further strengthen patient safety. A robust, transparent and sustainable regulatory framework should be put in place that is 'fit for purpose'. This framework should be supportive of innovation and the competitiveness of the medical device industry and should allow rapid and cost-efficient market access for innovative medical devices, to the benefit of patients and healthcare professionals." (EUR-Lex 2012)

"The proposal of the revision of the European legislation for medical products points out that the manufacturers must take more responsibility regarding transparency and traceability of the medical devices placed on the European market. This is indicated by the nomination of "qualified person", the tightening of traceability of the suppliers and the implementation of the Unique Device Identifier number. Additional requirements on clinical evaluation and post market clinical follow-up underline these aspects. The instrument of unannounced factory and device inspections by Notified Bodies seems to be an attempt to force the manufacturer to implement the quality system in daily working routines and not only for the annual announced audit." (Schröttner and Neubauer 2013)

"Eucomed, the European medical technology industry association, recognises the need to modernise and strengthen the current medical devices legislation in Europe, in particular, by coupling more enhanced Member State engagement with better European science-based coordination and management of the regulatory system. The objective should be to achieve a smart and efficient legislative framework that is consistently implemented across the EU and guarantees patient safety, high quality and rapid access to the latest medical technologies. This legislative framework should at the same time encourage research and innovation and reduce administrative burden, in particular for SMEs, which are the backbone of the medical technology sector." (Eucomed 2011)

2.3.7 Requirements of the new European regulation

"The new regulation contains a number of improvements; stricter control of high-risk devices via a new pre-market scrutiny mechanism with the involvement of a pool of experts at EU level; reinforcement of the criteria for designation and process for oversight of Notified Bodies; inclusion of certain aesthetic devices which present the same characteristics and risk profile as medical devices; introduction of a new risk classification system for *in vitro* diagnostic medical devices in line with international guidance; improved transparency through the establishment of a comprehensive EU database on medical devices and of a device traceability system based on Unique Device Identification; the introduction of an "implant card" containing information about implanted medical devices for a patient; the reinforcement of the rules on clinical evidence, including an EU-wide coordinated procedure for authorization of multi-center clinical investigations; strengthening of post-market surveillance requirements for manufacturers; improved coordination mechanisms between EU countries in the fields of vigilance and market surveillance." (European Commission, 2017d) The new requirements on Notified Body scrutiny and the clinical requirements are discussed in further detail in the following paragraphs.

2.3.8 Notified Body Scrutiny in the new European Regulation

"In order for medical devices to access the market and reach patients and users, and to ensure that the product is safe and performing as designed, manufacturers must accomplish a conformity assessment and, with the exception of low risk class I devices, undergo an inspection and certification procedure carried out by Notified Bodies. Notified Bodies are independent third parties nominated and monitored by Member States authorities. They carry out pre- and post-market conformity assessment and certification of medical devices based on the requirements of the EU Directives." (Eucomed 2011) "To continue to guarantee a consistent approach to the quality of the work carried out by Notified Bodies as well as a high level of safety across the EU, a complete series of control and monitoring measures are needed: 1.Precise and mandatory requirements for the designation of Notified Bodies; 2. EU-wide mandatory accreditation standards for Notified Bodies, which include standards for competence, training, staffing, transparency and expertise of Notified Bodies; 3. Precise, binding, transparent measures for Competent Authorities to control and monitor the activities and performance of Notified Bodies; 4. Audits of Notified Bodies by joint teams composed of different national Competent Authorities and the European Commission; 5. EU-level

oversight of the way Member States designate and monitor their Notified Bodies." (Eucomed 2011)

As outlined in the European Commission press release in September 2012 one of the main elements of the new regulations would be stronger supervision of independent assessment bodies by national authorities. (European Commission 2012)

As a result there is greater scrutiny of Notified Bodies by the Competent Authorities. This has resulted in the reduction of the total number of Notified Bodies from over 80 in the recent past to less than 60 now. A Notified Body that is no longer accredited results in challenges for the manufacturer because device certification can lose its validity. The manufacturer must quickly recertify its devices with a new accredited Notified Body and ensure there is no disruption to the supply chain. (Emergo 2017b)

In the European Commission press release in June 2014, it outlines some of the main achievements of the joint action plan, eight Notified Bodies had corrective actions and in some cases limitations to their scope. (European Commission 2014) Furthermore joint voluntary audits were carried out where major shortcomings were identified, immediate corrective action was taken, including temporarily suspending or limiting the scope of activities of the notified body concerned. (European Commission 2014) "Notified Bodies will need to be designated under the Regulation and the process of designation will be coordinated at a European level. The designation process will start six months after the adoption of the Regulation and be phased through the transition period. Given the number of Notified Bodies likely to seek designation, and the resources available for the designation process, there will be a lengthy process to designate all the Notified Bodies across the EU." (BSI 2017e)
To ensure a seamless transition from the Directive to the Regulation the Regulatory Affairs professional needs to engage with their Notified Body and ensure they continue to meet their needs. The Regulatory Affairs professional needs to ensure there is no disruption to the supply chain. The risks include the Notified Body no longer have the designation to carry out conformity assessment or the Notified Body ceases to do business. These risks need to be communicated to the business within the company.

2.3.9 Clinical evaluation requirements in the new European Regulation

The new regulation introduces a scrutiny process for Class IIb and Class III implantable devices; this will "ensure robust evidence on patient safety and performance characteristics prior to market approval and is subject to accredited Notified Bodies' (NAMSA 2016) The scrutiny process will be carried out by an expert panel in parallel or post the Notified Body review, this has not yet been determined. In the past "many Notified Bodies lacked the expertise and experience to adequately evaluate the provided clinical evidence in view of patient safety and clinically relevant risk/benefit ratio." (NAMSA 2016)

"The new European Medical Devices Regulation was published in the Official Journal of the European Union on 5th May 2017. The Regulations will enter into force on May 25th 2017, marking the start of the transition period for manufacturers selling medical devices into Europe. The MDR, replaces the Medical Devices Directive (93/42/EEC) and Active Implantable Medical Devices Directive (90/385/EEC), and has a transition period of three years. Manufacturers have the duration of the transition period to update their technical documentation and processes to meet the new requirements. Article 120 of the Regulation states a number of transitional provisions, refer to **Figure 5**." (BSI 2017d)

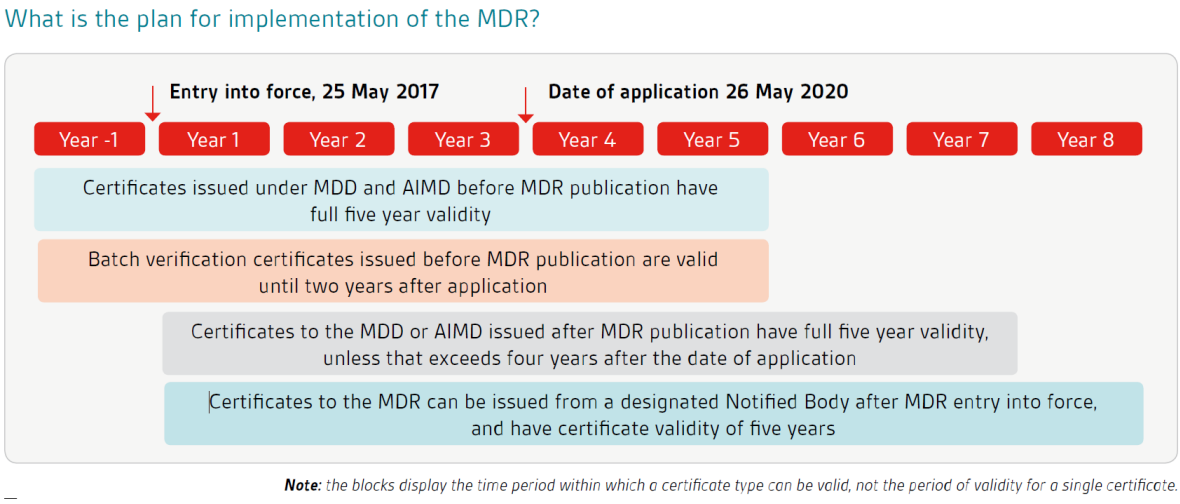

Figure 5: Medical Device Transition Period (BSI 2017d)

2.3.10 Medical Device Regulation Scope in the new European Regulation

"The scope of the MDR brings products without an intended medical purpose that are listed in Annex XVI within its scope. The Article also states that medical devise, their accessories and the products listed in Annex XVI will be referred to as 'devices'. In the definition of accessories, no exception is made for products without a medical purpose that will be considered medical devices and therefore their accessories will also fall within scope of the MDR. The definition of medical device is extended to include products for cleaning, disinfection and/or sterilization. The article also covers in-vitro diagnostics (IVD) in order to align the MDR and the In Vitro Diagnostic Device Regulation (IVDR)." (Emergo 2017f)
"Certain products for aesthetic purposes are brought under the Medical Devices Regulation. The specific products affected are listed in Annex XV of the Regulation. One of the challenges of addressing aesthetic products that are not considered to have a medical purpose is the characterization of benefit versus risk. The Commission is charged with adopting common specifications that address the application of risk management and clinical evaluation of safety of these products. The Regulation applies to aesthetic products from the date that these common specifications are adopted." (BSI 2017e)

"The Regulation extends the scope of the legislation beyond requirements on the manufacturer. The requirement remains for a manufacturer located outside the EU to have an authorised representative within the EU. Additional requirements have been added to cover the supply chain responsibilities of other economic operators, namely the distributor, in all cases, and the importer, where the manufacturer is located outside the EU. The key points in the definitions of these terms are:

- Manufacturer – produces or fully refurbishes a device, or has a device designed, manufactured or fully refurbished, and markets that device under their name or trademark;
- Authorised Representative – acts on the manufacturer's behalf in relation to specified elements of the manufacturer's obligations and is established within the EU with a written mandate from a manufacturer located outside the EU;
- Importer – places a device from outside the EU on the EU market and is established within the EU; and

- Distributor – makes a device available on the market, up until the point of putting it into service, but is not the manufacturer or the importer

The Regulation also requires the manufacturer to have sufficient financial coverage for their potential liabilities in the event of claims for compensation for damage caused by their devices." (BSI 2017e)

2.3.11 Unique Device Identification and EUDAMED Database in the new European Regulation

"The European Commission is responsible for the EUDAMED database, but users are responsible for their own content. There will be an extensive amount of information collected and transmitted electronically, as well as a mandate to use UDI. Class III medical device manufacturers must generate a summary of safety and clinical performance in language that can be understood by the intended patient (Article 32). The summary of safety and clinical performance will be assessed by the Notified Body who uploads it into EUDAMED. There it will be publically accessible." (Emergo 2017f) "EUDAMED will be the interface for registering economic operators and devices, obtaining a single registration number and communicating between the various parties under the Regulation, including submitting clinical investigation reports, vigilance reports and periodic safety update reports." (BSI 2017e)

"Unique Device Identification (UDI) will have to be implemented. The timing for this implementation is on a longer timescale than the transition for the Regulation and is phased according to the classification of the medical device. While the UDI requirements are similar to those in the USA, there are some differences in the classification of devices between the USA and the EU which might lead to the timescales for implementation diverging." (BSI 2017e)

2.3.12 Labelling Requirements in the new European Regulation

"Chapter 3 of the Regulation includes requirements regarding the information supplied with the device and covers labelling and instructions for use. Another addition by the Council is that there should be an indication on the label that the product is a medicals device, similar to the current identification of an IVD." (Emergo 2017f) "The patient also has to be provided with a physical card containing particular information, some of which will be batch specific:

- Identification of the device – device name, model, serial number, batch code or lot number and UDI; and
- Name, address and URL of the website of the manufacturer" (BSI 2017e)

2.3.13 Conformity Assessment in the new European Regulation

"Classification remains essentially the same under the MDR, but it is recommended to do a thorough assessment of all devices and not to rely on the current classification schemes. The definitions and basic principles have some minor changes. There are 22 classification rules (Annex VIII). Rule 3 now places substances in contact with cells, tissues or organs before administering in the body into Class III. Rule 4 also applies to invasive devices that comes into contact with injured mucous membranes. Rule 6 keeps the reusable surgical instruments in Class I, but at the same time these devices get a similar status as sterile or measuring devices, and Notified Body involvement is required; a new classification, Class Ir, applies to these devices as well. Additional classification changes under the MDR include the following:

- The MDR considers surgical meshes Class III
- A new rule is introduced – Rule 11 – for classification of software. Software can fall under any risk class
- Rule 18 states that non-viable tissue of human or animal cells will be considered Class III
- Rule 19 classifies nano-materials depending on their potential for internal exposure
- Rule 20 places devices intended for inhalation of medical substances in risk Class IIa or IIb
- Rule 21 places devices composed of substances absorbed or dispersed in different classes based on their level of internal exposure

- Rule 22 places active therapeutic devices with an integrated diagnostic function, which provides data on patient management in Class III (e.g. closed loop systems or automated external defibrillators)" (Emergo 2017f)

2.3.14 Technical Documentation requirements in the new European Regulation

"The Regulation defines additional detail for the content of the technical documentation – often referred to as the technical file, for each medical device or family and requires that the information is presented in a clear, organized, readily searchable and unequivocal way. The Regulation also reinforces the emphasis on the requirements driving a life cycle approach to the management of the medical device with the routine updating of the technical documentation including i) in the light of information gathered during post-market surveillance, ii) evolution in the state of the art, and iii) development of changes to standards or common specifications used to support CE-marking." (BSI 2017e)

2.3.15 Post-market Surveillance requirements in the new European Regulation

The Regulation contains significant changes in requirements in the post-market area, including Post-Market Surveillance (PMS) planning and implementation, vigilance reporting and handling field safety corrective actions. There are enhanced requirements for PMS plans, including conducting active post-market clinical follow-up (PMCF) when necessary, preparing periodic safety update reports (PSUR) for Class II and Class III devices and submitting or having these available for Notified Body Review at defined intervals depending on the device classification, and maintaining post-market surveillance reports (PMSRs) available for Class I devices. In regards to the requirements for vigilance, information previously contained in guidance has been included in the Regulation itself. The number of exemption rules that obviate the need to report events have been reduced. The timelines for reporting events that are considered serious public health threats or a death or unanticipated serious deterioration in health have remained unchanged at two and ten days respectively but the timeline for reporting all other events has been decreased from 30 days to 15 days. This reduces the time available to determine whether an event meets the reporting criteria and could lead to submissions of more follow-up reports to provide additional information. Taken together, these changes are likely to lead to an increase in the number of reports submitted. When conducting a Field Safety Corrective Action, the manufacturer has to inform the

Competent Authority before implementing the action, unless this would cause a delay with a consequent risk to health" (BSI 2017e)

2.3.16 Overall conclusion on evolving regulatory frameworks

"The Life Sciences sector is going through a period of unprecedented regulatory change **Figure 6**, affecting organisations involved in pharmaceuticals, medical devices, and in-vitro diagnostics. Driven by a need to strengthen the regulatory platform across the European Union (EU) that aims to better ensure patient safety, new regulations are seeking to harmonise and simplify the rules by improving transparency and product traceability, demanded by patients and the public." (Deloitte 2016)

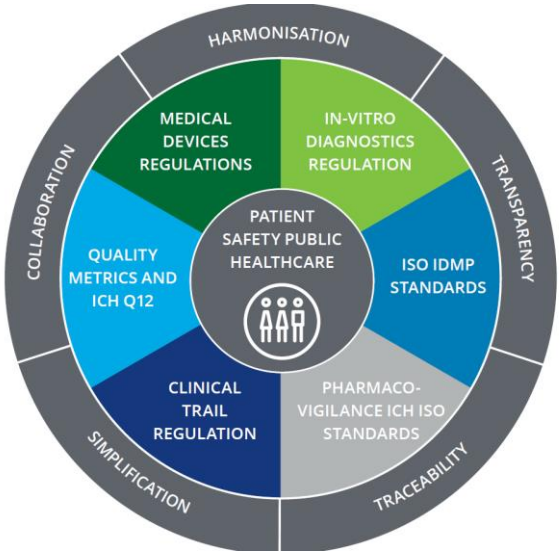

Figure 6: Change in Regulatory Landscape (Deloitte 2016)

The Regulatory Affairs professional has an important role in understanding and interpreting the requirements of the new medical device regulation. "By understanding where the key interest and points of debate are for a health authority (e.g. efficacy, safety, cost) the regulatory professional can help guide the direction of a clinical program or a commercial campaign toward those area most likely to satisfy a regulators priorities while still serving the organization's needs. Part of this role will include actively participating in the strategic business planning process to lend a perspective on feasibility and any prior precedent. It will be critical for the internal expert to communicate across the organization into both commercial and clinical functions and serve as a strategic business partner that can help decipher the 'noise' to guide informed decision making for commercial and clinical investment." (Wong and Tong 2013)

Evolving regulatory frameworks are burdensome to the Medtech industry, they impact existing approved products, for example, in the new MDR classification rules, the MDR considers surgical meshes as class III whereas the MDD considered them class IIb. This up-classification will require "robust clinical evidence on patient safety and performance characteristics prior to market approval and is subject to accredited notified bodies." (NAMSA 2016)

Evolving regulatory frameworks can impact products under development, for example the new MDR introduces the requirement that all implantable products require a patient implant card. (BSI 2017e) This new requirement can cause a delay in getting products to the market. The manufacture will need to ensure the implant card is developed and contains the required information; if the product is supplied globally translations will be required. These tasks take time and will delay the products speed to market.

2.4 Challenge Three: Changing Government Policies and the impact on Medtech Industry

"Changes in the work of the FDA have come rapidly in the past 20 years, shaped at least in part by political pressure, consumer activism, and industry involvement. Patient advocacy groups influenced a law to stimulate industry interest in developing so-called orphan drugs for rare diseases, and they played a role in the agency's development of accelerated techniques for drug approval, beginning with drugs for AIDS. Congress passed a law that simultaneously extended patent terms to account for time consumed by the drug approval process and facilitated the approval of generic human and animal drugs to offer a lower-cost alternative to brand name pharmaceuticals. Also, Congress instituted procedures for industry to reimburse the FDA for review of drugs and biologics to speed the agency's evaluations." (FDA 2009)

"The two sectors currently most affected by the regulatory environment in the U.S. are healthcare and financial services. New regulations are expensive in terms of compliance, as companies need to transform data tracking and gathering systems, reporting functions and, in some cases, their organizational structures." (Forbes 2014)

To explore the impact of new government regulations in detail Brexit was chosen as a case study to demonstrate the impact this has on the Medtech industry. Brexit is the common term

used to describe the United Kingdom's (UK) withdrawal from the European Union (EU). "On 29 March 2017 the UK notified the European Council of its intention to leave the EU, thus formally triggering Article 50 of the Treaty on European Union." (EUR-Lex 2017a) Article 50 states "any Member State may decide to withdraw from the Union in accordance with its own constitutional requirements." (EUR-Lex 2017b)

2.4.1 Impact of Brexit on Medtech Industry

Azambuja (2017) states Brexit is expected to have a significant impact on the medical devices industry. Brexit could result in uncertainty over key elements of the medical devices legislation, which includes manufacturers and authorized representatives, notified bodies, and data privacy issues in clinical investigations. (Azambuja 2017)

2.4.2 Brexit Timelines

"The negotiations on the orderly withdrawal of the UK from European Union must be completed within a period of two years from the moment Article 50 is triggered. If no agreement is reached within this period, the Treaties will cease to apply to the withdrawing Member State. The negotiations themselves will last approximately 18 months (early June 2017 – October/November 2018), reference **Figure 7**". (European Commission 2017e)

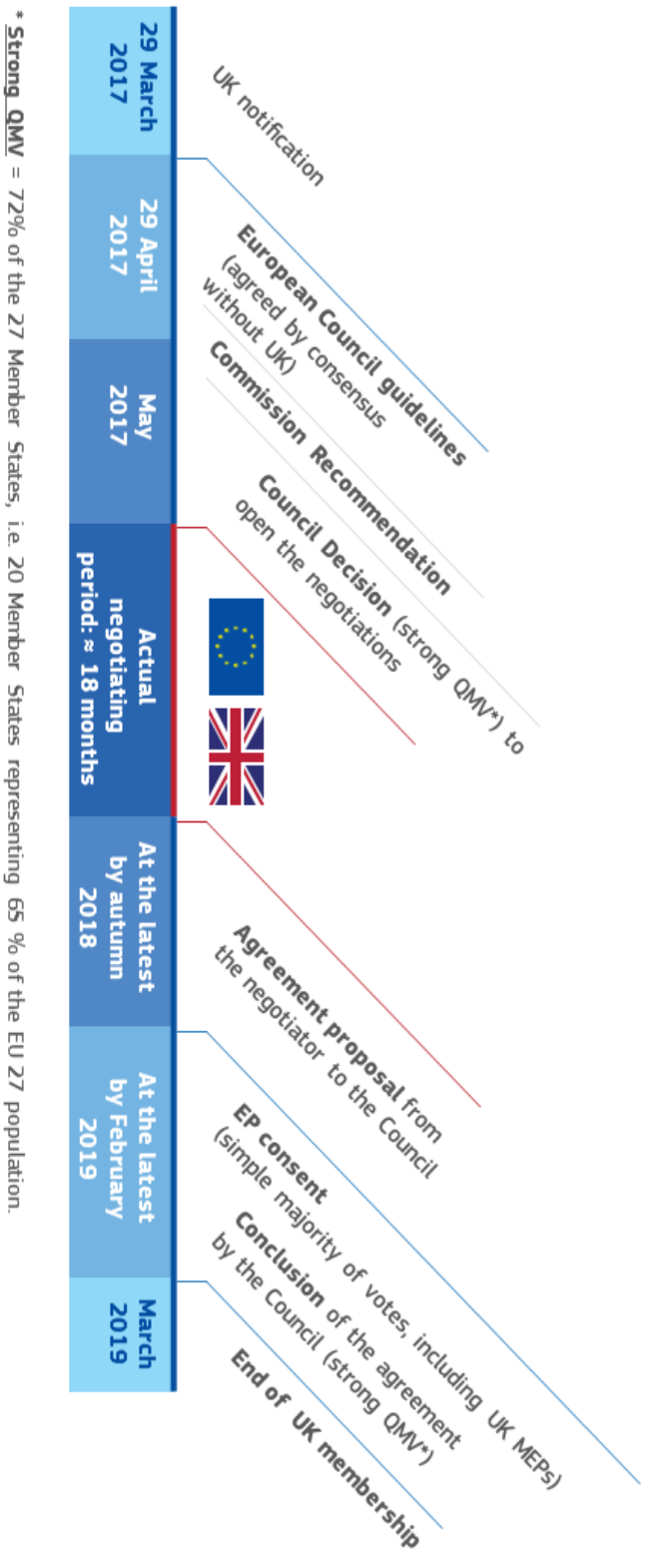

Figure 7: Brexit Timelines (European Commission, 2017e)

2.4.3 Impact of Brexit on Manufacturers

"Depending on the exact terms of the UK's withdrawal from the EU, UK medical device manufacturers will be required to appoint an Authorized Representative established within an EU Member state to permit the continued marketing of their products within the EU. Alternatively UK manufacturers may choose to establish a presence in an EU Member state and to transfer their responsibility as legal manufacturer to this new address in the EU Member state." (Azambuja 2017)

2.4.4 Impact of Brexit on Authorized Representative

"UK Authorized Representative may lose their right to be appointed as the point of contact for third country manufacturers with competent authorities in EU Member states. Manufacturers not established in the EU and currently working with UK based Authorized Representative may also be required to appoint an Authorized Representative established in an EU Member state to continue fulfilling the requirements of the Directives. Identification of experienced Authorized Representatives may be more challenging in the future due to the requirements of the new Regulations. With the new Regulations the Authorized Representative is jointly liable with the manufacturer for defective medical devices placed on the EU market. It is anticipated that some Authorized Representatives will cease their current activities due to their inability to undertake this potential liability." (Azambuja 2017)

2.4.5 Impact of Brexit on Notified Bodies

Assessing the conformity of medical devices and in vitro diagnostics products with the applicable Directive is the role of Notified Bodies. "Each country within the EU has a Competent Authority. The Competent Authority is a body within the government of the Member States that transposes the requirements of the Medical Device Directives into National Law. The Competent Authority is also responsible for specifying one or more Notified Bodies, to act as independent third party assessors of the manufacturer's compliance. The designation of these notified bodies by the UK competent authorities is based on the provisions of the relevant EU medical devices Directives. The role of a Notified Body is to conduct a conformity assessment under the relevant EU Directives. The Notified Body conducts the conformity assessment against the relevant sections of the applicable Directive (MDD, AIMDD or IVDD). The conformity assessment usually involves an audit of the manufacturer's quality system and depending upon the particular classification of the device,

a review of the relevant technical documentation provided by the manufacturer in support of the safety and performance claims for the device. The technical documentation is assessed against the essential requirements set out within the EU Directives and considers the relevant guidance set out by the EU. Once the Notified Body has determined a manufacturer has conformed to the relevant assessment criteria, it issues a CE certificate to show that the products assessed meet the requirements. The manufacturer signs a Declaration of Conformity and applies the CE mark (with or without the Notified Body number)." (BSI 2014) Notified Bodies play a critical role in the EU regulatory framework, enabling compliant products to reach the market and preventing non-compliant product from endangering consumers and other end users.

"Post-Brexit, there are four options for UK Notified Bodies:

- World Trade Organisation (WTO) rules – the UK falls back on WTO rules and UK Notified Bodies no longer have a role in regulated product conformity assessment across the EU/EEA. Product must be re-certified to enter the EU market from the UK, as with any other third country.
- Full recognition – UK Notified Bodies are still recognized in the EU/EEA and the UK plays a partial role in determining regulatory policy. This would be a similar option to that of non-EU EEA members such as Norway and Iceland.
- FTA with mutual recognition of regulated conformity assessment – UK Notified Bodies would meet UK requirements, which in turn would be deemed sufficient to meet EU requirements
- FTA with recognition of regulated conformity assessment – this is a 'hybrid' possibility of Options 2 and 3. In this option, in most areas mutual recognition of conformity assessment would apply, as in Option 3. For more complex products, where a Notified Body certificate is always required, UK Notified Bodies would be recognized as equivalent to EU Notified Bodies, as in Option 2: they would be able to apply the same standards (which are European and international standards) and to issue certificates stating that products meet EU laws. It would be similar to arrangements with Canada, Australia and Turkey. The areas to be chosen would reflect the importance of the sectors and would need to be negotiated specifically." (BSI 2017)

Manufacturers who utilise BSI as their Notified Body need to work closely with them to understand what the impact of Brexit will have. It will be important that that there is no disruption to product availability on the market.

2.4.6 Impact of Brexit on Clinical Investigations & Data Privacy

"The UK could become a 'third-country' for the purposes of the application of the Data Protection Directive. Article 25.1 of the Data Protection Directive prohibits the transfer of personal data outside the EU to countries that do not ensure an adequate level of data protection. The UK may be required to undergo an "adequacy assessment" carried out by the European Commission, for the purposes of the application of Data Protection Directive. Pending the decision of the European Commission, or in the case of a negative decision by the European Commission, UK companies will be required to comply with the requirements provided by the EU law for the transfer of personal data to third countries." (Azambuja 2017)

2.4.7 Impact of Brexit on EMA and MHRA

"With the UK deciding by referendum to leave the EU, the vote will have major implications for the regulation of medicines and medical devices across the entire continent. Not only will the European Medicines Agency (EMA) have to uproot its headquarters from London, but the UK's Medicines and Healthcare products Regulatory Agency (MHRA) will have to decide if they want to continue conducting drug manufacturing and clinical trial site inspections alongside EMA, and whether the UK will now have to develop its own drug approval system as UK pharmaceutical regulations are primarily determined at the EU level. As lawyers have pointed out: EU Directives, such as Directive 2001/83/EC governing medicinal products, require the UK to implement relevant legislation into national law. This is done by reference to the European Communities Act of 1972 and through the implementation of the Human Medicines Regulation of 2012. The UK's departure from the EU would mean these laws remain in place unless the UK government decided to change them. A number of questions remain to be answered, particularly on whether EMA would lose access to MHRA experts who, as the Financial Times points out, led the review of more drug applications than any other domestic EU regulator in 2014." (RAPS 2016b)

2.4.8 Overall conclusion on impact of Brexit to Regulatory Affairs professional

"There is a need for some kind of market acceptance arrangement for devices in both the UK and Europe. Where European Member States can work together and share efforts in market surveillance, the UK must somehow do all that on its own. With a majority of medical devices being imported into the UK, that is going to require a substantial investment in time and brains, while at the same time the MDR and IVDR will have to be implemented. Getting this process running smoothly will be essential to guarantee continuity of supply to British hospitals, while at the same time the possibility of tougher immigration rules will make it harder for the MHRA to attract qualified European workers to fill their ranks" (Emergo 2017g)

"Another problem involves access to Eudamed. Non-European countries do not have access to Eudamed unless they can establish special arrangements. Only very few people fully understand the value of the new Eudamed, so access to the database may be overlooked in the negotiations. Prime Minister May indicated that the UK will make no contributions to the EU, although some specific programs may be sponsored by the UK." (Emergo 2017g)

The impact of Brexit is still not fully understood. It will be important for companies that work with UK based Notified Bodies for example BSI to work closely with the Notified Body to ensure that post Brexit they will continue to exist and can continue to provide the necessary services to the manufacturer. The Regulatory Affairs professional will need to work closely with their UK based Notified Bodies and communicate any risk to product availability on the market to the company.

2.4.9 Overall conclusion on changing government policies and the impact on Medtech industry

The detailed review of the Brexit case study demonstrates the impact changing government regulations can have on the Medtech industry. "The regulatory environment is changing rapidly and professionals must be able to gauge how new developments will affect the future environment. New regulations with far-reaching ramifications have emerged in only the last few month; in January 2012, Chinese officials issued a set of rules to deal with the conflict of interest of healthcare government officials in connection with pharmaceuticals and device

manufactures, and released a new Five Year Plan for pharmaceutical and medical device industries." (Wong and Tong 2013)

3 Chapter 3: Methodology

3.1 Introduction

This chapter presents a detailed discussion on the potential research approaches, strategies, time horizons and data collection techniques and procedures. Based on the research objectives the options available to the researcher are considered and the advantages and disadvantages discussed. This chapter explores the methodology selected by the researcher and rationalizes why it is deemed the most appropriate.

3.2 Research Objective and Questions

The goal of this research is to understand the challenges experienced by Regulatory Affairs professionals and determine whether company size, years of regulatory experience, and organisation structure influence these challenges. The goal shall be addressed through answering the research questions in the **Table 11**.

Table 11: Research Questions

Number	Research Question
1	What is the main challenge experienced by Regulatory Affairs professional in gaining regulatory approval in United States, Europe, China, Korea and Japan?
2	How are Regulatory Affairs professionals staying informed on changing and evolving global regulatory requirements?
3	How are the regulatory requirements communicated internally in companies by Regulatory Affairs professionals?
4	Are Regulatory Affairs professionals aware of changing government policies that impact the Medtech sector?

3.3 Appropriate Research Methods

The research onion, **Figure 8**, was developed by Saunders et al. (2012). It illustrates the stages that must be covered when developing a research strategy. When viewed from the outside, each layer of the onion describes a more detailed stage of the research process (Saunders et al., 2012). The research onion provides an effective progression through which a research methodology can be designed. Its usefulness lies in its adaptability for almost any type of research methodology and can be used in a variety of contexts (Bryman, 2012).

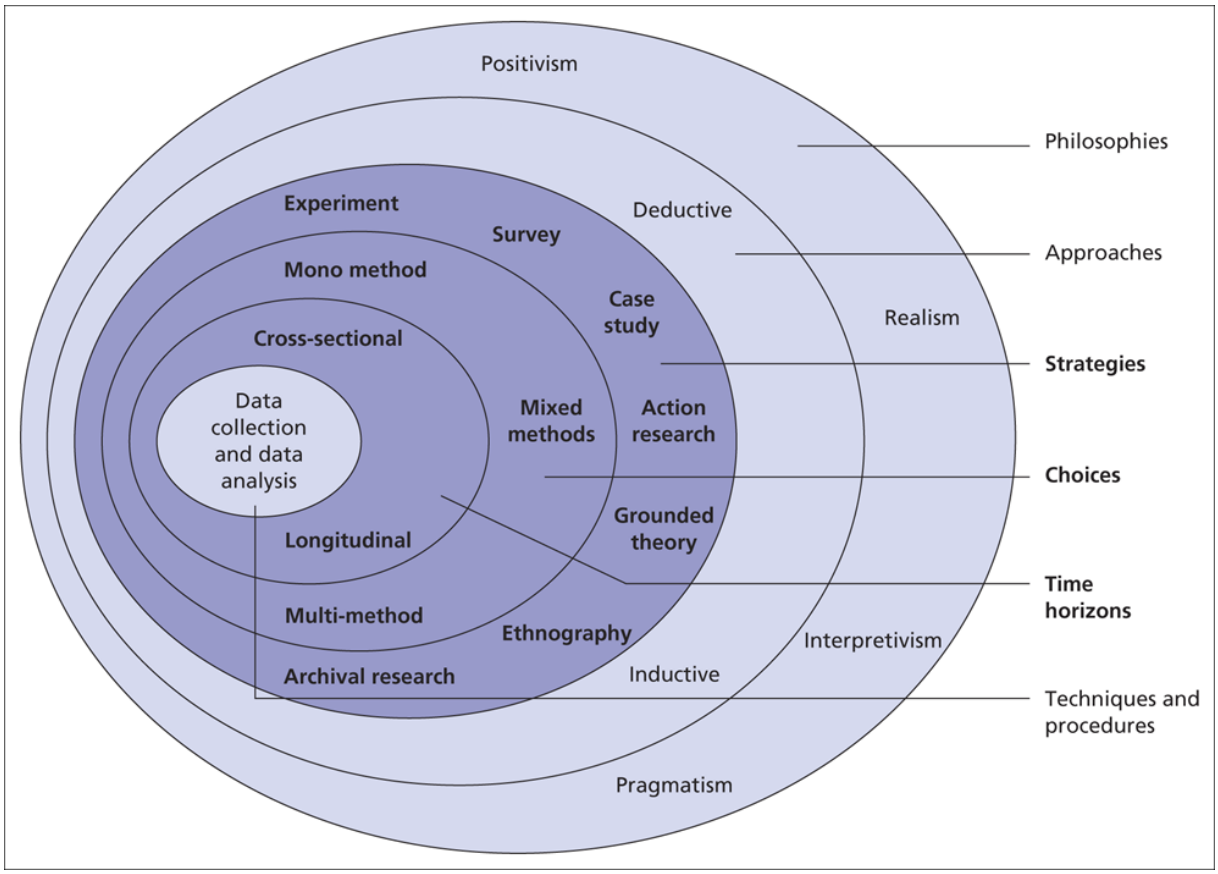

Figure 8: The research 'onion' (Saunder et al 2012)

3.4 Research Philosophy

According to Saunders et al. (2012) there are four research philosophies – positivism, realism, interpretivism and pragmatism. The philosophical approach taken influences the research approaches, methodological choice and research strategies selected (Saunders et al. 2012). The philosophy provides the justification for the research methodology. This research follows the pragmatic approach; this approach involves using the method which appears best suited to the research problem. Pragmatic researchers have the freedom to use any of the methods, techniques and procedures typically associated with quantitative or qualitative research. (Saunders et al. 2012)

3.5 Research Approaches

According to Saunders et al. (2012) selection of an appropriate research approach is critical as this facilitates the design of the research, taking potential constraints into consideration. In addition, it will help to define the most appropriate research strategies and choices in order to address the research question (Saunders et al. 2012).

Saunders et al. (2012) identifies three main research approaches which may be utilized i.e. deduction, abduction and induction. A deductive approach involves the testing of a proposed theory through collection of data in order to prove or disprove the theory. This is supported by Robson (2011) who notes that deductive logic is concerned with testing a pre-existing theory or concept. An inductive approach focuses on development of a theory following collection of data (Saunders et al. 2012). Robson (2011) notes the deductive and inductive approaches have been criticised as not being representative of actual research practice and that the abductive approach may be utilized as an alternative. According to Saunders et al. (2012), an abductive approach combines the inductive and deductive approaches - it involves data collection in order to explore an observed phenomenon; this data is utilized to develop a new or modified theory which is subsequently tested (Saunders et al. 2012). The research undertaken in this dissertation follows the pragmatic research philosophy. As this research is focused on identifying the main challenge experienced by the Regulatory Affairs professional, as opposed to proving or disproving a hypothesis, it can be argued that this research is inductive in nature.

3.6 Methodological Choice

The methodology choices outlined in the research onion include the mono method, the mixed method, and the multi-method (Saunders et al. 2012). The mono-method involves using one research approach for the study. The mixed-methods required the use of two or more methods of research, and usually refer to the use of both a qualitative and a quantitative methodology. In the multi-method, a wider selection of methods is used (Bryman, 2012). The main difference between the mixed and the multi-method is that the mixed-method involves a combined methodology that creates a single dataset (Flick, 2011). The multi-method approach is where the research is divided into separate segments, with each producing a specific dataset; each is then analysed using techniques derived from quantitative or qualitative methodologies (Feilzer, 2010). This research used the quantitative approach.

3.7 Qualitative Research

Qualitative research is associated with the inductive approach, typically involves collection of non-numerical data and is subjective from an ontological perspective as it is focused on an individual's or group's perspective of an event (Robson 2011). Depending on the research question, a qualitative approach may be more favourable than a quantitative approach if further understanding is sought regarding a particular concept or phenomenon (Creswell 2009). Bryman (2012) notes that opponents of qualitative research have argued that this approach is too subjective, is difficult to replicate, presents difficulty regarding generalization of findings and may lack transparency.

3.8 Quantitative Research

Quantitative research is typically aligned with the deductive approach, is objective from an ontological perspective and is focused on obtaining numerical data on which statistical analysis can be performed (Robson 2011). Bryman (2012) notes that certain limitations are associated with the quantitative approach, namely that it does not take into account that individuals interpret the same event or terminology differently. In addition, Bryman (2012) notes that it has been argued that quantitative analysis results in a static view which creates objective relationships between variables that may have actually been influenced by the individuals tested during the research. The quantitative approach can be most effectively used for situations where there are a large number of respondents available, where the data can be

effectively measured using quantitative techniques, and where statistical methods of analysis can be used (May, 2011).

3.9 Research Strategies

The research strategy is how the researcher intends to carry out the work (Saunders et al. 2012). The strategy can include a number of different approaches, such as experimental research, action research, case study research, interviews, surveys, or a systematic literature review. A survey is typically utilized for exploratory and descriptive research and facilitates gathering of data from a sizeable population (Saunders et al. 2012) and hence is considered a potentially appropriate strategy for investigating challenges experienced by Regulatory Affairs professionals. There are various methods available to conduct a survey or questionnaire as shown in **Figure 9**. Self-administered surveys are completed by the respondents and can be delivered over the internet, by post or hand-delivered. Interview administered surveys are directed by an interviewer either over the phone or face-to-face.

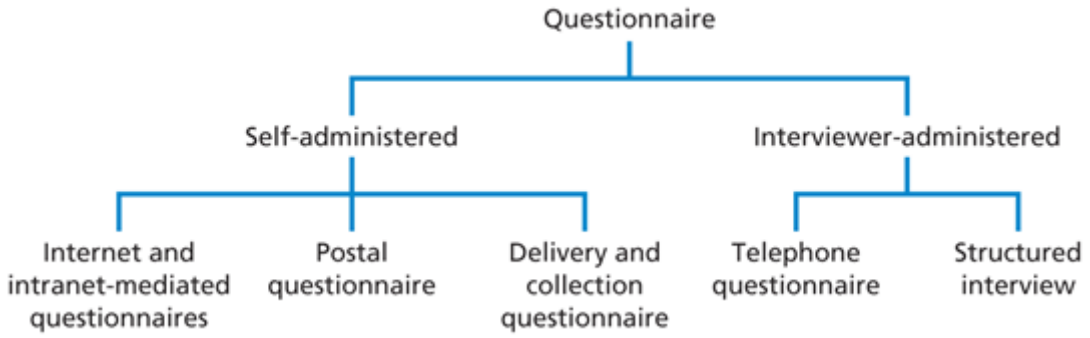

Figure 9: Types of Questionnaire (Suander et al 2012)

There are advantages associated with using web surveys. There are low costs involved and many software packages are available to support the design of a survey without training. The collection of data is in real time thus ensuring fast turnaround. The respondents are given the opportunity to complete the survey at their own convenience. A disadvantage common to all self-administered questionnaires is that an interviewer is not at hand to answer any questions or clarify any misunderstandings (Brace, 2013). The solution to mitigate this issue is to ensure that the survey questions are "clear, unambiguous and engaging" (Brace, 2013) and the planned pilot will verify the adequacy of the design before it is sent to all respondents.

Couper et al (2008) discusses the use of a web survey and the following advantages are identified, increased speed and efficiency, self-administered, computerised, and enables worldwide distribution. These characteristics support the use of a survey in this qualitative research as the respondents are located throughout Ireland and all have access to computers and the internet. Also a limited timeframe is available and interview administered questionnaires require time and resources beyond the scope of this dissertation and researcher.

Narrative inquiry is also proposed as a potential strategy for this exploratory research as it involves the researcher conducting a qualitative interview with a small sample of participants to gain an understanding of their perception of an event (Saunders et al. 2012). Creswell (2009) notes that narrative inquiry can take the form of one-to-one interviews, telephone interviews, focus groups and interviews via the internet and email. Although the technique of narrative inquiry would facilitate the researcher gaining a deep understanding of the participants' perception of challenges, it is also recognised that individuals interpret events differently based on their own experience. Therefore although narrative inquiry is a potential research strategy, the data collected may not be representative of the wider population. This view is supported by Creswell (2009) who states that data collected is 'filtered' through the perception of the interviewee and that the presence of the researcher may impact on data recorded.

An archival research strategy is one where the research is conducted from existing materials (Flick, 2011). As part of this research a systematic literature review was completed to identify common concepts in the challenges experienced by Regulatory Affairs professionals. These concepts were reviewed and a questionnaire was developed to determine if the concepts identified from the literature review are reflective of the working environment i.e. the Medtech sector in Ireland for Regulatory Affairs professionals.

Ethnography involves the close observation of people, examining their cultural interaction and their meaning (Bryman, 2012). In this research process, the observer conducts the research from the perspective of the people being observed, and aims to understand the differences of meaning and importance or behaviours from their perspective. Ethnographic research facilitates the researcher obtaining an insider's perspective as they are immersed in the daily activities of the participants under investigation (Robson 2011). As the researcher is a Regulatory Affairs professional with over ten years' experience this research strategy would

be an appropriate approach. However the basis of this strategy is to observe people and to complete a comprehensive study, the researcher would need to visit numerous companies, small to medium enterprises and large multinationals, and spend timing observing the regulatory professionals there is a time constraint to this research which eliminates this as a feasible option.

3.10 Time Horizon

Based on the research question, it is proposed that either a Cross-Sectional or Longitudinal Time Horizon would be acceptable. A Cross-Sectional Time Horizon is focused on a particular point in time, whereas Longitudinal research is focused on a particular phenomenon over a period of time (Saunders et al. 2012). The Cross-Sectional time horizon is dubbed the "snapshot" time collection, where the data is collected at a certain point (Flick, 2011). The Time Horizon selection is limited however by the time constraints for this research, and hence it is proposed that a Cross-Sectional research design would be more feasible.

Table 12: Summary of Research Approach

Methodology Layer per the Research Onion	**Research Approach**
Philosophy	Pragmatism
Approach	Induction
Methodological Choice	Quantitative
Strategy	Survey
Time Horizon	Cross-Section
Data Collection Tools	Questionnaire

3.11 Questionnaire Design

"The validity and reliability of the data you collect and the response rate you achieve depend largely on the design of your questions, the structure of your questionnaire, and the rigour of your pilot testing" (Saunders et al 2012, p 459). The design of the survey is very important and adequate time should be given to this part of the dissertation. The following lists of items are important to consider when designing the survey:

- Purpose of the survey
- Target audience
- Required sample size
- Type of questions to be incorporated
- Method of data collection
- Data analysis. How will the data be analysed?

3.12 Purpose of the Survey

A literature review was conducted into the challenges that impact the Regulatory Affairs professional during the process of gaining approval to market and sell devices in various regions. The three main challenges investigated were (1) different regulatory frameworks and requirements across geographies, (2) evolving regulatory frameworks and requirements and (3) the impact changing government policies has on the MedTech industry.

The purpose of the survey was to poll Regulatory Affairs professionals working in the MedTech sector in Ireland and confirm the main challenge. The survey sought to identify how Regulatory Affairs professionals are staying informed on different regulatory frameworks throughout the world and evolving regulatory frameworks. The survey sought to identify if companies are utilizing regulatory strategy and how they communicate regulatory requirements within their companies.

3.13 Target Audience

The survey focused on Regulatory Affairs professionals working in the MedTech sector in Ireland. The author used business contacts internally in her own organisation, students from the course MSc in Medical Technology Regulatory Affairs and contacts identified by the academic supervisor. The author requested these contacts to circulate the questionnaire to their colleagues as relevant. Contacts from small to medium enterprises and marge multinationals were identified.

3.14 Sample Size

An appropriate sample size is required to ensure accurate results. The variability in responses to a survey question starts to level off when there are more than 30, according to Hague, Hague & Morgan (2013) and shown in **Figure 10**. Therefor the survey will aim for over 30 responses.

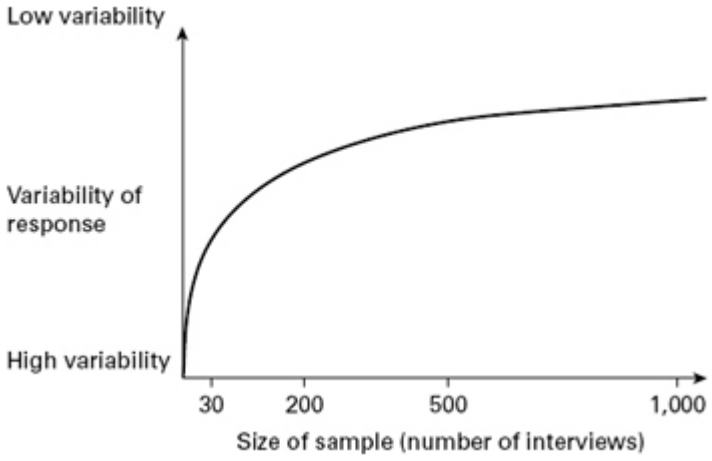

Figure 10: Variability of Response and Sample Size (Hague, Hauge, & Morgan 2013)

3.15 Type of Questions

The survey consisted of multiple choice questions where respondents select one or more options from a list of answers defined by the researcher. Likert Scale questions give respondents a range of options—for example, starting at "not at all important" scaling all the way up to "very important". Rating scales the respondent selects the number that most accurately represents their response. Open-ended questions require respondents to type their answer into a comment box. By using a range of questions types it is hoped that the people

participating in the survey didn't suffer survey fatigue and were therefore committed to completing the survey. The survey was designed to be engaging.

3.16 Method of data collection

Prior to distribution of the survey, a pilot study was conducted with four participants, they were asked to provide feedback to the questionnaire. Following completion of the pilot survey, some modifications were made to the survey questionnaire.

- Addition of an introductory question on the size of the company the participant works for and whether or not it is Irish owned, a multinational or other.
- Refined the number of challenges, there was duplication in the challenges listed. The survey now identifies three challenges and requests the participant to rank these from 1 to 3, where 3 is most challenging and 1 is least challenging.
- The questions have been grouped according to the challenge, this is to provide a better flow and make it logical and pleasing for the participant.
- Definitions were included for regulatory strategy and regulatory plan to ensure clarity
- Addition of questions specific to changing government policies, does the participants company track this information and does the participant spend time understanding this challenge and is it incorporated into the regulatory strategy.

The survey was created using SurveyMonkey^{TM} software in order to generate a questionnaire which accessible and efficient in data collection. Survey Monkey is available at www.surveymonkey.com and is used in academia and industry to support research efforts. Survey Monkey allows the survey link to be emailed to respondents. In doing so, respondents can forward the invitation email to relevant personnel within the industry thus increasing the response rate. The survey was distributed to all participants via email, the email included an explanation of the purpose of the survey and closing dates. The survey may therefore be classified as an internet-mediated self-completed survey. Follow up emails were also sent out to encourage a high response rate.

3.17 Data Analysis

The survey collected quantitative data, which in its raw format coveys very little meaning therefore it needs to be processed to make it useful (Saunders et al 2012). Chapter 4 of this dissertation provides graphs to show the relationships and trends within the data gathered as part of the survey.

Table 13 identifies the content of the survey questions and the rationale for each question. There are four research questions as identified in chapter one, each of these research questions was used as the basis for the questions used in the survey sent out to Regulatory Affairs professionals working in the Medtech industry in Ireland.

Table 13: Identification of how survey questions link to research questions

Research Question	Survey Question	Rationale for asking these question
	1. Name 2. Company	These questions have been asked to aid in the organisation of the data. As identified in the email to survey participants this information will not be used as it's confidential.
Question 1 What is the main challenge experienced by Regulatory Affairs professional in gaining regulatory approval in United States, Europe, China, Korea and Japan?	3. Company Identification e.g. Irish/ Multinational/Other	Questions 3, 4, 5, 6 and 7 in the survey are linked to identifying the main challenge experienced by Regulatory Affairs professionals. From a review of the literature, three areas were identified as being challenging for the Regulatory Affairs professional. Question seven has been posed to see if the Regulatory Affairs professionals working in the Medtech sector identify one main challenge.
	4. Type of company ▪ SME: Micro enterprise (<10 employees) ▪ SME: Small enterprise (<50 employees) ▪ Medium size enterprise (between 50 – 249 employees) ▪ Large enterprise (> 250 employees)	
	5. Years of experience working in Regulatory Affairs	
	6. Indicate the regions you/or your team have regulatory responsibility for: ▪ United States (US) ▪ Europe (EU) ▪ Both EU and US ▪ Regions outside the EU and US only ▪ Other	
	7. Challenges: ▪ Different regulatory frameworks in different regions (lack of regulatory harmonisation across geographies) ▪ Evolving regulatory frameworks e.g. MDR & IVDR ▪ Staying informed on changing	

Research Question	Survey Question	Rationale for asking these question
	government policies and the impact this has on the Medtech industry e.g. Brexit	
Question 2 How are Regulatory Affairs professionals staying informed on changing and evolving global regulatory requirements?	8. Association the Regulatory Affairs professional is a member of: ▪ Irish Medtech Association ▪ AdvaMed ▪ Medtech Europe ▪ IMDRF	Question eight and nine identify the associations Regulatory Affairs professionals have membership to.
	9. List any other associations you participate in	
Question 3 How are the regulatory requirements communicated internally in companies by Regulatory Affairs professionals?	10. Rank the tools/methods used for communicating regulatory requirements	Questions ten and eleven have been asked to identify how regulatory requirements are communicated internally in companies and to investigate if there is trend.
	11. Identify other tools/methods for communicating regulatory requirements	
Question 2 How are Regulatory Affairs professionals staying informed on changing and evolving global regulatory requirements?	12. Rank the methods for staying informed: ▪ External Training ▪ Internal Training ▪ Conferences ▪ Subscriptions to newsletters/websites ▪ Membership to reg. associations	Question twelve and thirteen have been asked to identify the training regulatory professionals engage in.
	13. Other methods for staying informed	
Question 3 How are the regulatory requirements communicated internally in companies by Regulatory Affairs professionals?	14. The stage of product life cycle teams typically first engage Regulatory Affairs	Questions fourteen, fifteen, sixteen have been asked to identify if there are trends in how regulatory requirements are communicated internally in companies.
	15. Rank the importance of alignment between Regulatory Affairs and R&D	
	16. Reporting structure: ▪ Managing Director/CEO ▪ Business Unit/Franchise/Division ▪ Quality Management ▪ Research & Development ▪ Regulatory Management	

Research Question	Survey Question	Rationale for asking these question
Question 4 Are Regulatory Affairs professionals aware of changing government policies that impact the Medtech sector?	17. Does your company have a government affairs department?	Questions seventeen, eighteen, nineteen and twenty all relate to government affairs. These questions have been posed to determine how important regulatory affairs professionals consider government affairs.
	18. How often do the government affair department publish information?	
	19. As a Regulatory Affairs professional how important is it to stay informed on government affairs?	
	20. When you develop a regulatory strategy for a product do you incorporate the impact government affairs changes could have on the regulatory strategy e.g. Brexit?	

3.18 Limitations

There are limitations associated with the use of surveys Bell (1996) observed that biases may occur, either in the lack of response from intended participants or in the nature and accuracy of the responses that are received. Other sources of error include intentional misreporting of behaviors by respondents to confound the survey results or to hide inappropriate behavior. Finally, respondents may have difficulty assessing their own behavior or have poor recall of the circumstances surrounding their behavior. The questionnaire data collection tool facilitates data collection from a large number of participants however it is limited by the fact that it does not facilitate in-depth investigation with respondents, as in the case of individual interviews or focus groups.

3.19 Conclusion

This chapter presented a detailed discussion on the philosophical approach taken and the available research approaches, strategies, time horizons and data collection techniques. This chapter explored the methodology selected by the researcher and rationalised why it is deemed the most appropriate. Lastly, this chapter outlined the execution of this methodology in relation to this research and presented the associated limitations.

4 Chapter 4 Analysis/Discussion

This section of the dissertation reviews the data returned from the survey. The results are presented and analysed in this chapter. The aim of the research was to investigate the research questions identified **Table 14**.

Table 14: Research Questions

Number	Research Question
1	What is the main challenge experienced by Regulatory Affairs professional in gaining regulatory approval in United States, Europe, China, Korea and Japan?
2	How are Regulatory Affairs professionals staying informed on changing and evolving global regulatory requirements?
3	How are the regulatory requirements communicated internally in companies by Regulatory Affairs professionals?
4	Are Regulatory Affairs professionals aware of changing government policies that impact the Medtech sector?

4.1 Data Analysis - Introduction to the Survey Results

Forty people completed the survey however five people started the survey but did not complete all the questions. These five respondents were removed from the analysis as partial answers were discarded. Therefore thirty-five completed responses were returned from respondents representing varying size companies within the Medtech industry in Ireland. The aim was to gain survey responses from more than 30 industry representatives to ensure reduced response variability. The company sizes represented are shown in **Figure 12**.

4.1.1 Results from Survey Questions One and Two

Questions one and two identified the respondents name and their company name. These questions were asked to aid in the organization of the data. As identified in the email to survey participants this information is confidential and is not detailed in the thesis.

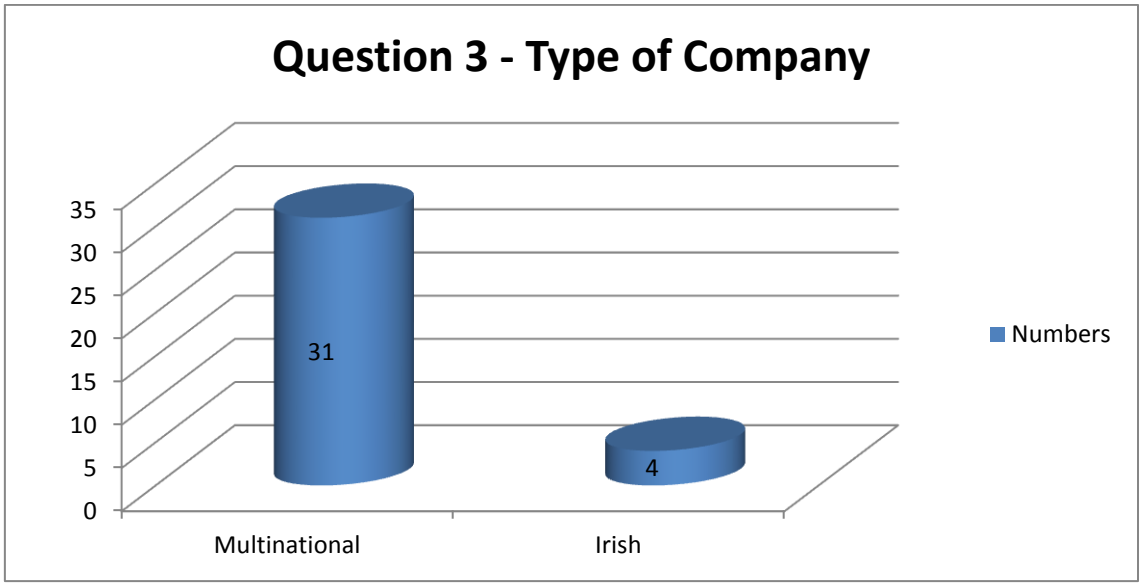

Figure 11: Survey Results Question 3 Type of Company

4.1.2 Results from Survey Question Three – Company Identification

The respondents to the survey were requested to identify their company as being Irish, Multinational or Other, reference **Figure 11**. The majority of the respondents, eighty-nine percent work for multinationals. The research focused on Regulatory Affairs professional working in the Medtech sector in Ireland. "Thirteen of the world's top fifteen companies have operations here. Ireland also employs the highest number of Medtech personnel per capita in Europe." (IDA Ireland 2017)

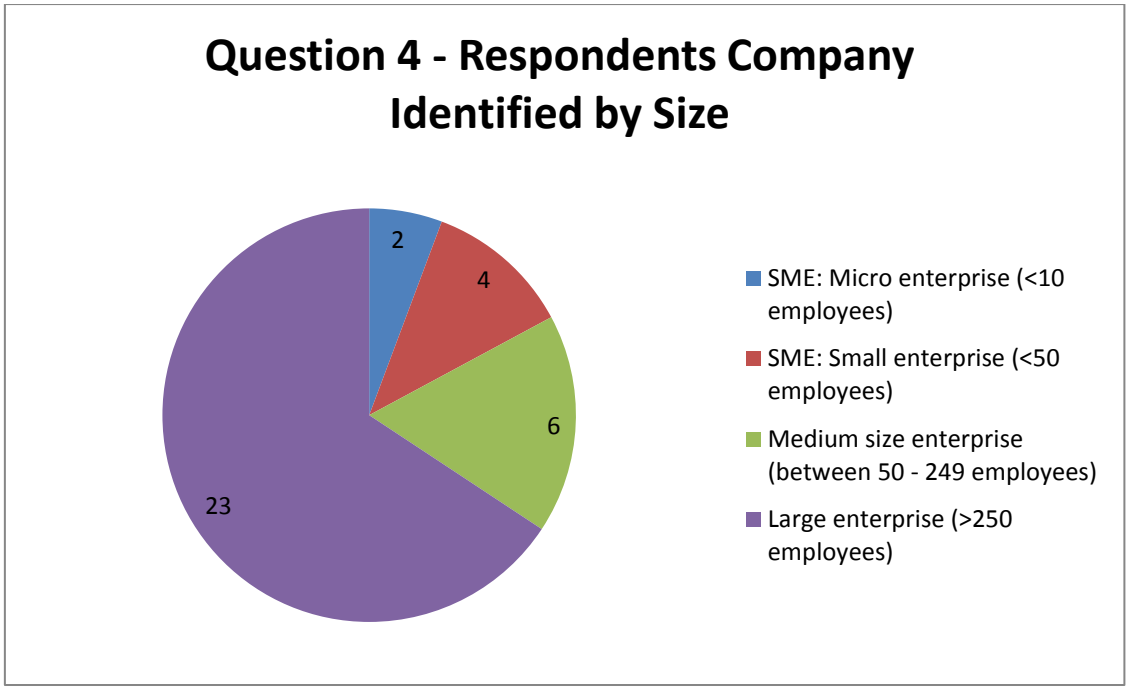

Figure 12: Survey Results Question 4 Company Size

4.1.3 Results from Survey Question Four – Type of Company

The majority of respondents work for multinationals, sixty-six percent of the respondents. The least represented are the micro enterprises with six percent of the respondents working in this size company. As outlined in the Irish Medtech report "Future skills need analysis for the medical technology sector in Ireland to 2020' Ireland is recognised as a global medtech hub with 18 of the world's top 25 medtech companies based here. As many as 60% of the 450+ medtech businesses in Ireland are home grown, and 80% are small and medium enterprises (SMEs)". (Irish Medtech Association 2017) The sample size in the survey is small however it is reflective of the industry representing the varying sized companies and representing both Multinational and Irish companies, see **Figure 12**.

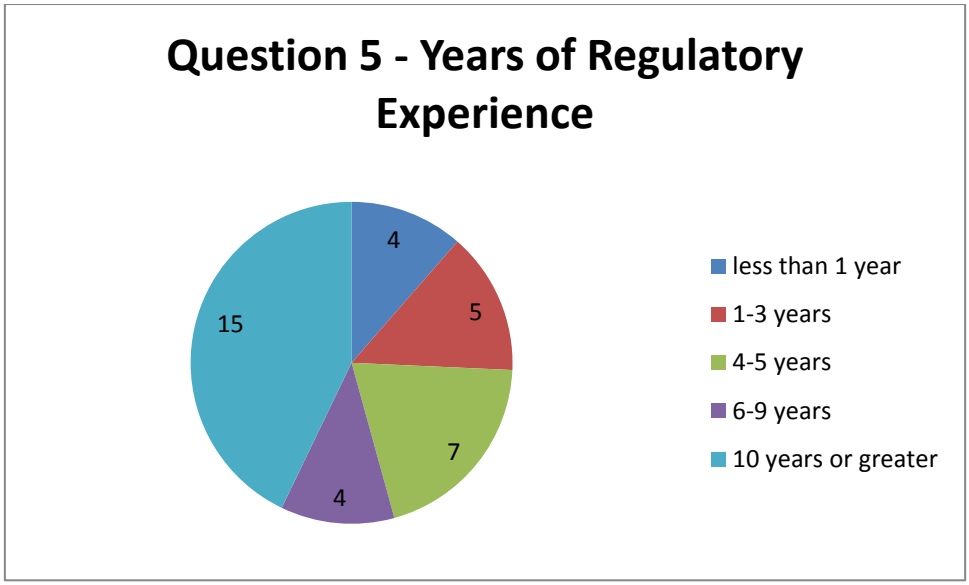

Figure 13: Survey Results Question 5 Years of Regulatory Experience

Forty-three percent of respondents have greater than ten year's regulatory experience. The respondents with greater than ten year's regulatory experience are spread across the four types of companies identified in the survey; SME: Micro enterprise (<10 employees), SME: Small enterprise (<50 employees), Medium size enterprise (between 50 – 249 employees) and Large enterprise (>250 employees). Eleven percent have less than one year of regulatory experience and work in the large enterprise and medium enterprise size companies. To demonstrate diversity in the responses, the Regulatory Affairs professionals were requested to identify their years of regulatory experience in question 5, the results are presented in **Figure 13**.

4.1.4 Results from Survey Question Six Regions of Regulatory Responsibility

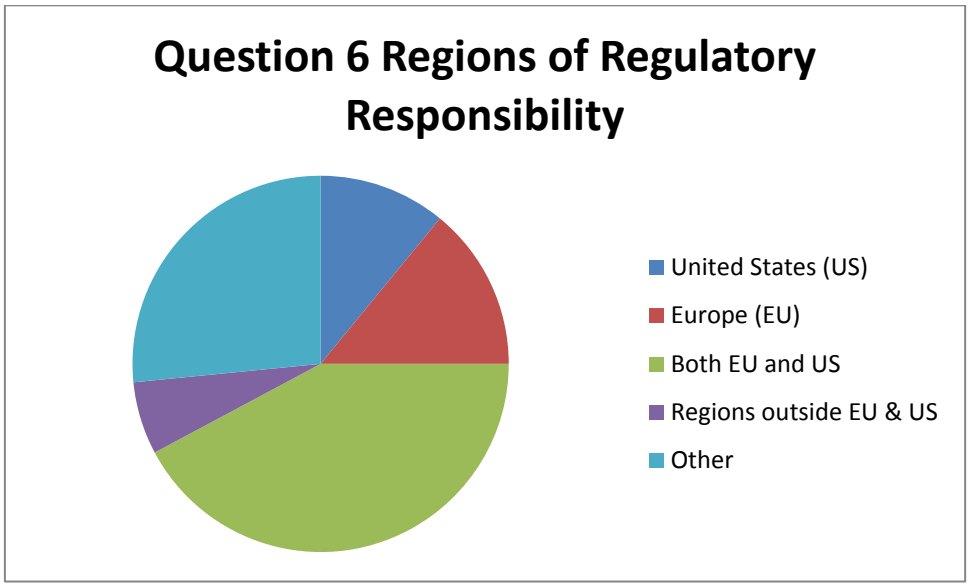

Figure 14: Survey Results – regions of Regulatory Responsibility

4.2 Research Question One - Main Challenge for Regulatory Affairs Professional

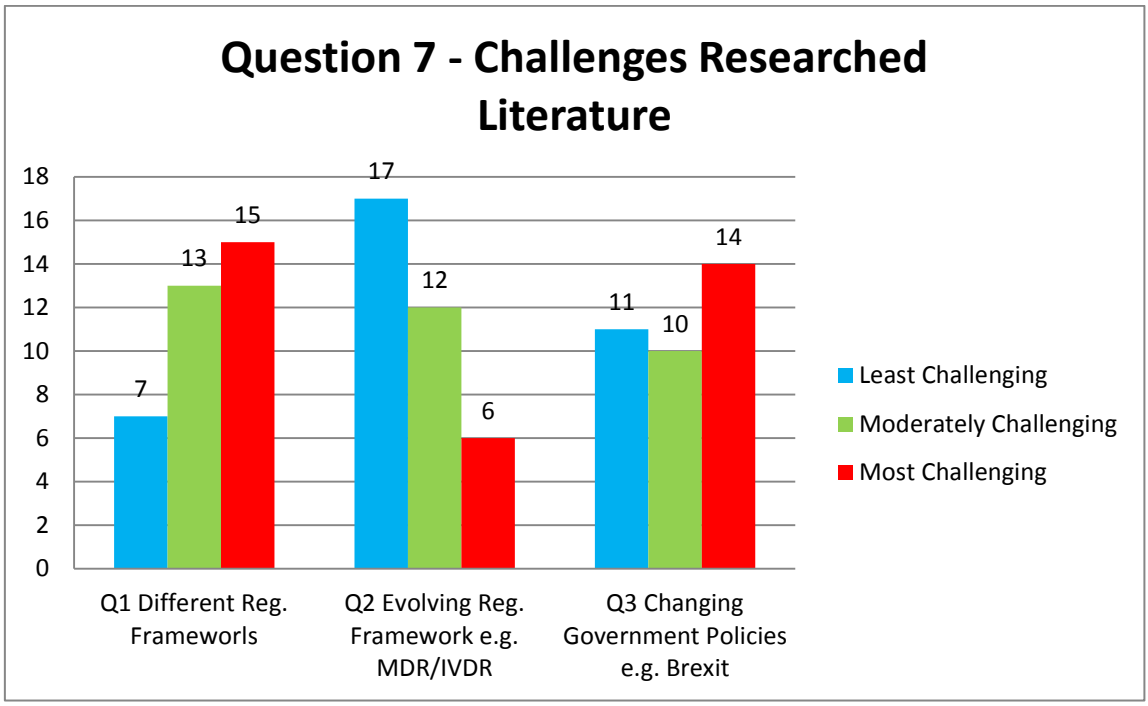

Figure 15: Survey Results - Question 7 Challenges

4.2.1 Results from Survey Question Seven - Challenges

The literature review investigated three challenging areas for Regulatory Affairs professional. In question seven of the survey respondents were asked to identify which of these they found the most challenging. Fifteen respondents identified question one which identified different regulatory frameworks in different regions (lack of regulatory harmonisation across geographies) as the most challenging area for Regulatory Affairs professionals. This is not surprising; the current regulatory landscape in Europe is changing with new regulations for medical devices and in vitro diagnostic products. FDA are continuously generating guidance documents and whilst not mandatory they do form the basis for review of submissions by FDA personnel therefore Regulatory Affairs professionals are obliged to follow them and stay informed. 'Marketing products in China as a foreign manufacturer is challenging due to the rapidly changing regulatory environment and lack of available information and documents published in English." (Lueddemann et al 2016)

During the search for literature there was plenty of information available on the US and EU but not too much information available on China, Korea or Japan. Zhang et al (2016) points out 'most regulatory research has focused on the US and EU medical device regulations with little written about the Chinese medical device regulations."

4.2.2 Conclusion of Research Question One

While attempts are being made to harmonize the global regulatory requirements, this is still an evolving and changing area. As identified by the survey results, global differing regulatory frameworks continues to be the main challenge identified by the Regulatory Affairs professionals.

4.3 Research Question Two - Staying Informed on Changing and Evolving Global Regulatory Requirements

Research question two posed the following question, how are Regulatory Affairs professionals staying informed on changing and evolving global regulatory requirements?

To address research question two the following questions were asked in the survey:

- Question 8 Association the Regulatory Affairs professional is a member of:
    - Irish Medtech Association
    - AdvaMed
    - Medtech Europe
    - IMDRF
- Question 9 List any other associations you participate in
- Question 12 Rank the methods for staying informed:
    - External Training
    - Internal Training
    - Conferences
    - Subscriptions to newsletters/websites
    - Membership to reg. associations
- Question 13 Other methods for staying informed

The survey requested respondents to identify the associations they have membership too. The response to this question provides insight into how Regulatory Affairs professionals are staying informed and knowledgeable on changing and evolving global regulatory requirements.

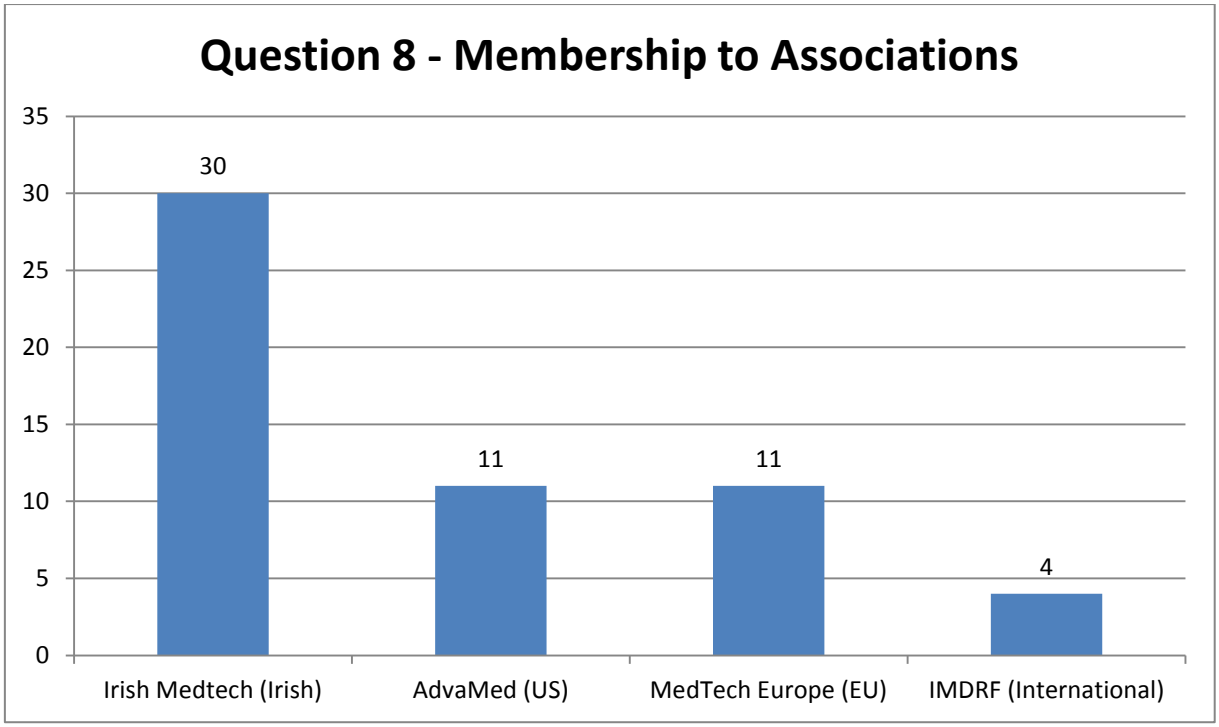

Figure 16: Survey Results Question 8 Membership to Associations

4.3.1 Results from Survey Question Eight – Associations (membership)

Respondents were asked in question eight of the survey to identify the associations they or a member of their team participate in. Eighty-three percent of respondents or a member of their team are members of Irish Medtech Association. The Irish Medtech Association is the business association within Ibec (Irish Business and Employers Confederation) representing the medical devices and diagnostics sector. Irish Medtech Association's broad focus is to promote and support an environment that encourages the sustainable development and profitable growth of our multinational and small to medium size medical device and diagnostic companies. (Irish Medtech Association 2017)

Thirty-one percent of respondents identified that they have membership with AdvaMed and Medtech Europe. AdvaMed, Advanced Medical Technology Association, is a trade association in the US that leads the effort to advance medical technology and act as the common voice for companies producing medical devices, diagnostic products and health information systems. Medtech Europe, is the European trade association representing the medical technology industries, it represents diagnostics and medical devices manufacturers operating in Europe. Eleven percent of respondents identified they or a member of their team participate in the IMDRF, International Medical Device Regulators Forum, is a voluntary group of medical device regulators from around the world who have come together to build

on the strong foundational work of the Global Harmonization Task Force on Medical Devices (GHTF) and aims to accelerate international medical device regulatory harmonization and convergence.

4.3.2 Results from Survey Question Nine – Other Association

Question nine was an open ended question requesting respondents to identify any other associations they participated in. Four respondents identified standards organizations such as NSAI, AAMI, ISO, IEC and ASTM. Two respondents identified TOPRA and RAPs and three respondents identified industry associations such as British In Vitro Diagnostic Association (BIVDA) and ABIMED / ABIMOD – Brazil, Canifarma – Mexico, KMDIA - Korea Medical Device Industry Association.

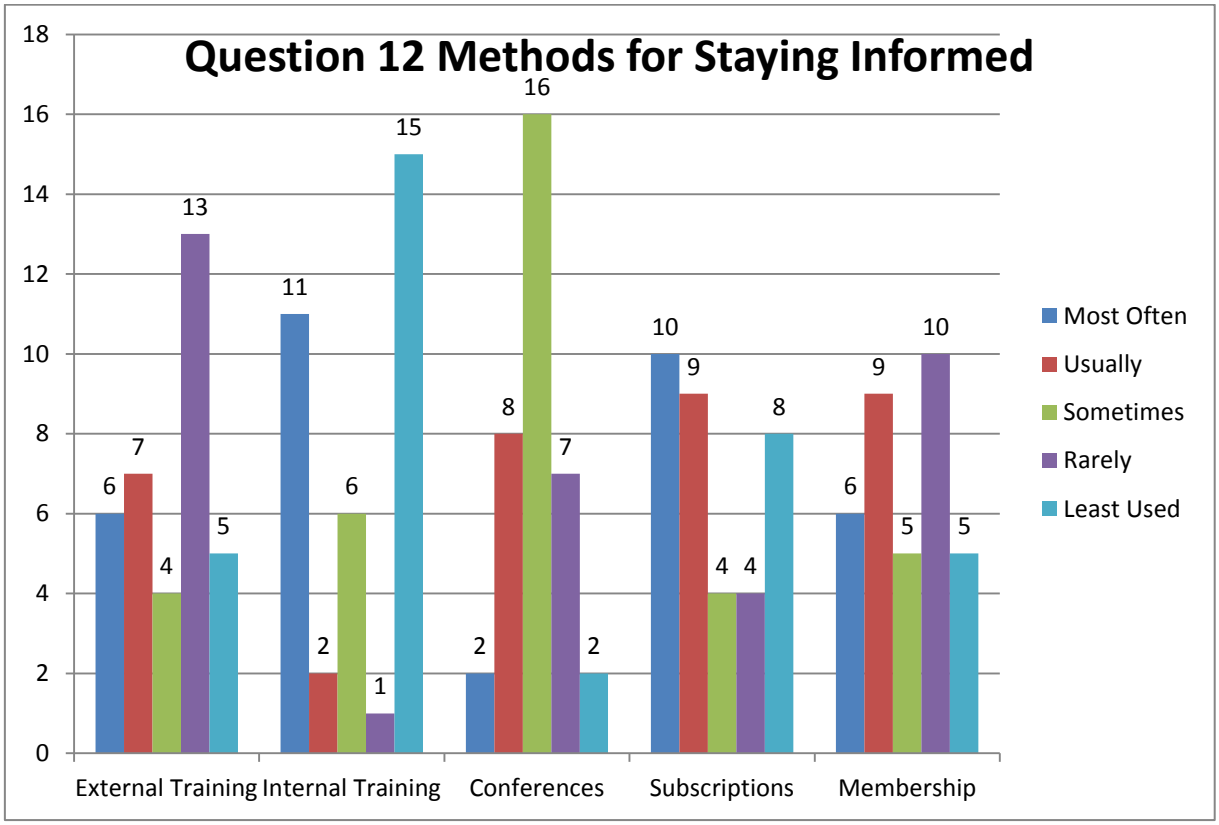

Figure 17: Survey Results Question 12 Methods of Staying Informed

4.3.3 Results from Survey Question Twelve – Methods for Staying Informed

The method used most often for staying informed on evolving regulatory requirements is internal training. This is not surprising as the majority of the respondents, sixty-six percent work in multinationals and this is an option available to them. Multinational companies typically have regulatory representatives in each of the regions they market and sell devices. Interestingly twenty-nine percent used subscriptions and membership to regulatory associations as a method for staying informed on evolving regulatory requirements.

4.3.4 Results from Survey Question Thirteen – Other Methods for Staying Informed

Question thirteen was an open-ended question asking respondents to identify any other means they use to stay informed on evolving regulatory requirements. A number of respondents indicated informal networking and one respondent identified podcasts and yet another identified the use of twitter and social media.

4.3.5 Conclusion of Research Question Two

Regulatory Affairs professionals are actively involved in various associations, as identified in **Figure 16**. In **Figure 17**, methods for staying informed, internal training is identified as the most often used method. The majority of respondents eighty-nine percent work for multinationals and therefore have access to experts that can deliver training internally.

4.4 Research Question Three - Communicating Regulatory Requirements

Research question three posed the following question, how are the regulatory requirements communicated internally in companies by Regulatory Affairs professionals? The three challenges investigated in the literature review:

1. challenge of knowing and navigating the global regulatory frameworks and requirements,
2. the challenge of staying informed on the evolving regulatory frameworks and knowing how to comply with the revised requirements,
3. the challenge of the impact of changing government status can impact the business

The RAPs (2017) report on 'Why Regulatory Professionals Need Business Training', points out that business acumen in regulatory professionals is extremely beneficial in a small or mid-sized company, where senior regulatory professionals are required to wear multiple hats and make broad-ranging business decisions. "Small Companies often have minimal capital, which makes getting it right the first time from a scientific, business and regulatory perspective imperative to the life of the firm." Regulatory Affairs professional need to know the regulatory frameworks and know what impact evolving regulatory frameworks have on product in development and to products on the market and they need to be able to communicate these requirements to the business.

To address research question three the following questions were asked in the survey:

- Question 10 Rank the tools/methods used for communicating regulatory requirements
- Question 11 Identify other tools/methods for communicating regulatory requirements
- Question 14 The stage of product life cycle teams typically first engage Regulatory Affairs
- Question 15 Rank the importance of alignment between Regulatory Affairs and R&D
- Question 16 Reporting structure:
    - Managing Director/CEO
    - Business Unit/Franchise/Division
    - Quality Management
    - Research & Development
    - Regulatory Management

These questions were posed to identify the methods used by Regulatory Affairs professional to communicate regulatory requirements, to understand when Regulatory Affairs are engaged in product life-cycle, to understand the importance of the alignment of research and development with Regulatory Affairs and to gain insight into the Regulatory Affairs reporting structures in companies.

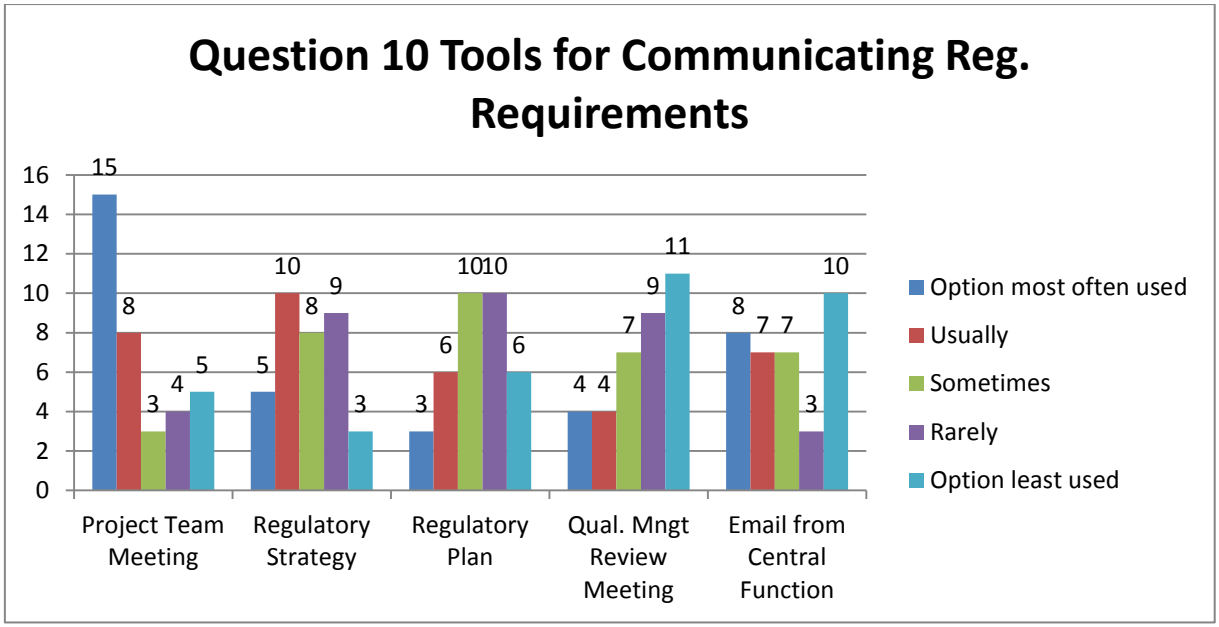

Figure 18: Survey Results Question 10 Communicating Regulatory Requirements Internally in Company

4.4.1 Results from Survey Question Ten - Rank the tools/methods used for communicating regulatory requirements

Question 10 of the survey asked respondents to rank the most often used tool and the least used tool from five options. Forty-three percent of respondents identified project team meetings as the most often used forum for communicating regulatory requirements. Twenty-nine percent identified either regulatory strategy or regulatory plan as the usual or sometimes utilised tool. During project team meetings the team will be focused on a specific goal, to get market approval to launch the product in Europe for example. The core team at the project team meeting will want to know the immediate regulatory requirements to achieve this goal but this does not take the overall regulatory strategy into consideration.

4.4.2 Results from Survey Question Eleven - Identify other tools/methods for communicating regulatory requirements

Question eleven of the survey was an open-ended question asking respondents to identify other tools and methods they use to communicate regulatory requirements. A number of respondents provided greater detail on using regulatory strategy and indicated that since the introduction of regulatory strategies it ensures teams understand the specific regulatory requirements for a project or to launch a product. The regulatory strategy ensures alignment with the business priorities and they are a method of ensuring regulatory engage with the

business on strategy and business goals. The strategy is also used to highlight differences in regulatory requirements between geographies and to include risk assessment for the project/ product. The risk assessment highlights specific regulatory risks for the project, the consequences of such risks and the mitigation plan. The regulatory strategy should be a live document so that changing regulations are captured and their possible impact recorded throughout the lifecycle of the project. The regulatory strategy also provides a historical record for the project and can be used for 'lessons learned' in future projects. Other methods respondents employ is to have regional regulatory folks present to the product specialists. This is a good way of developing relationships and engaging folks to drive discussion and ensure the non-regulatory individuals have a sufficient understating of the regulatory pathway when determining business strategy, timing of market launches and availability of product. The regulatory strategy will take a broad over view of the regions the business wants to market the products in and determine which regions it makes regulatory sense to gain approval in. A good regulatory strategy will detail the pre-market requirements and the post market requirements for example how often the manufacturer will be audited, what are the post market surveillance requirements. The importance of a "well executed strategy, one that facilitates the capture of emerging opportunities, produces enduringly good performance, is adaptable to changing business conditions and can withstand the competitive challenges from rival organizations" *(*Thompson et al 2012, p.4). A well-executed regulatory strategy has similar objectives. The regulatory strategy is an important document because it outlines the regulations and regulatory requirements that need to be adhered to throughout all the stages of a device life cycle; from the initial research and development phase to manufacturing and marketing of the device (Santalucia, 2012). Thus taking into account the emerging opportunities.

"The regulatory requirements differ globally, if the company plans to market the device globally, global regulatory requirements need to be considered. Furthermore the regulations are continuously increasing and it is important to stay up to date with the global requirements. For this reason the regulatory strategy needs to be a living document which is reviewed and updated through the evolution of the device." (Santalucia, 2012)

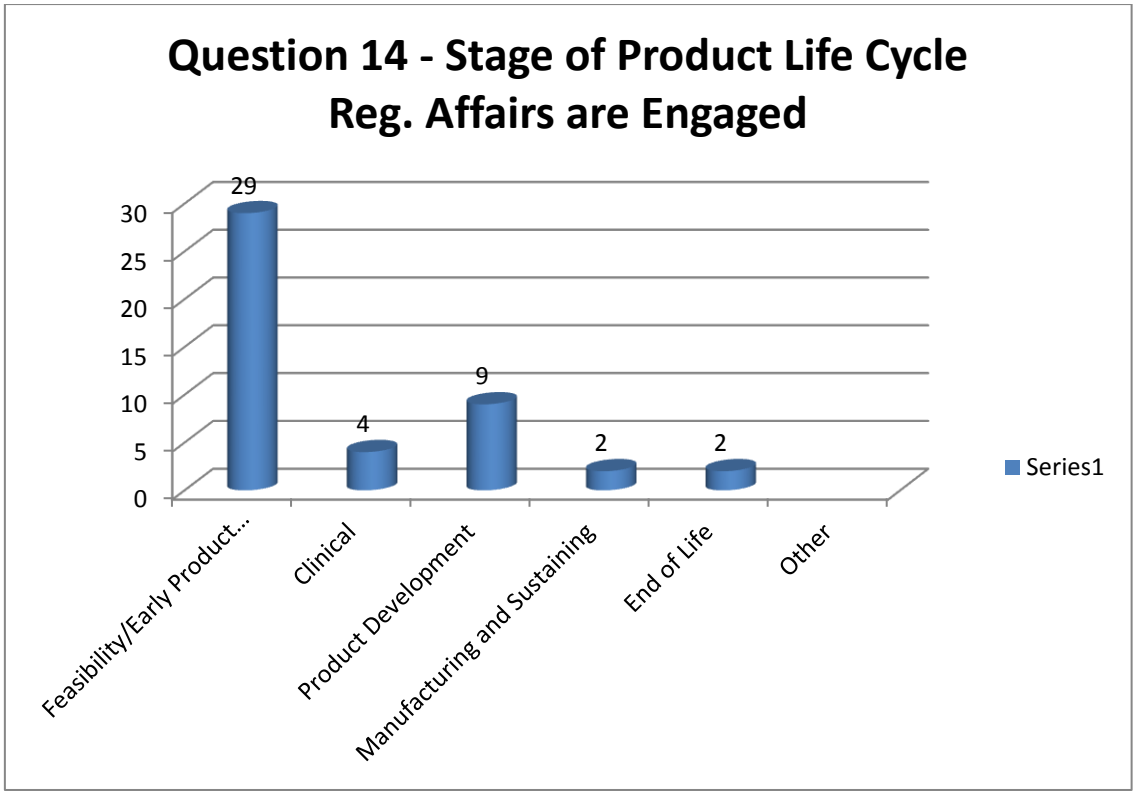

Figure 19: Survey Results Question 14 Alignment of Regulatory Affairs with R&D

4.4.3 Results from Survey Question Fourteen - The stage of product life cycle teams typically first engage Regulatory Affairs

The results from question fourteen align with the response to question fifteen. Regulatory Affairs are engaged in the feasibility/early product development phase of the product lifecycle. "Even at very early stages of development, a regulatory professional must understand the business implications of choices made. This is because the design of the nonclinical program facilitates the conduct of appropriate clinical studies at the appropriate target patients doses i.e. doses that are relevant for safety and efficacy and are in line with the business strategy. Regulatory decisions that transcend both business and regulatory is the design of the clinical program. The clinical program and the clinical study end points directly affect the product's label claims and ultimately the manner in which the product is marketed." (RAPS 2017)

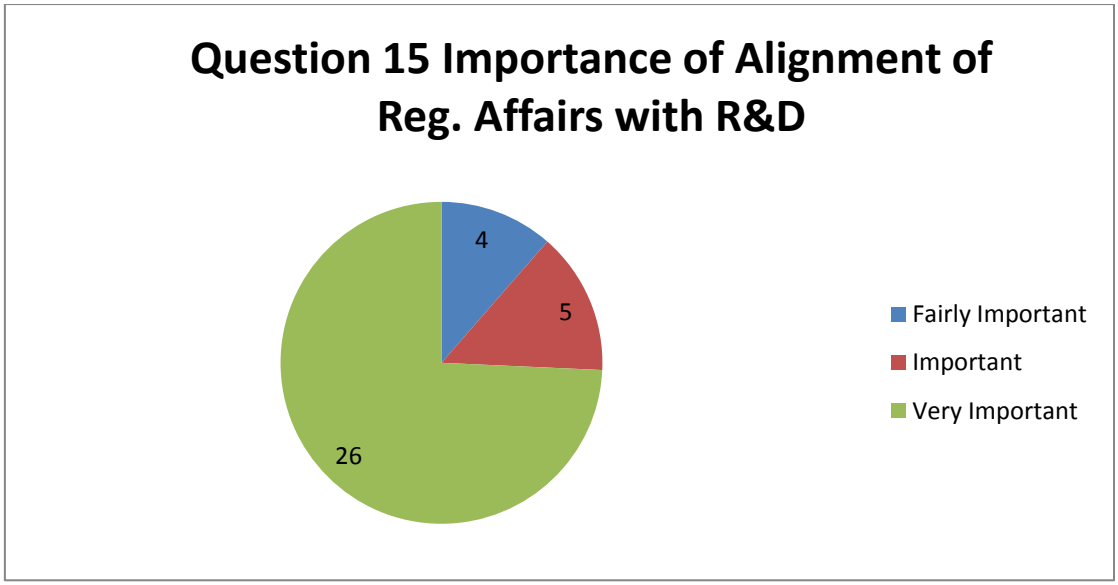

Figure 20: Survey Results Question 15 Product Life Cycle Phase Regulatory Affairs are Engaged

4.4.4 Results from Survey Question Fifteen - Rank the importance of alignment between Regulatory Affairs and R&D

Question fifteen requested respondents to rank the importance of the alignment of Regulatory Affairs with the research and development (R&D) function from fairly important to very important. Seventy-four percent of respondents identified the alignment of Regulatory Affairs with R&D as very important, reference **Figure 19**

4.4.5 Results from Survey Question Sixteen - Reporting structure

Another area that was reviewed as part of the survey was the reporting structure of the Regulatory Affairs function. Forty-three percent of respondents report to regulatory function, the next highest number is twenty-three percent who report into quality management, followed by twenty percent into the managing director/CEO of the company and fourteen percent into the business unit/franchise/division. A review of the data indicates that those respondents reporting into the regulatory function work for large and medium size enterprise whereas those respondents that report into the managing director/CEO are for the most part small and micro enterprises, reference **Figure 21**.

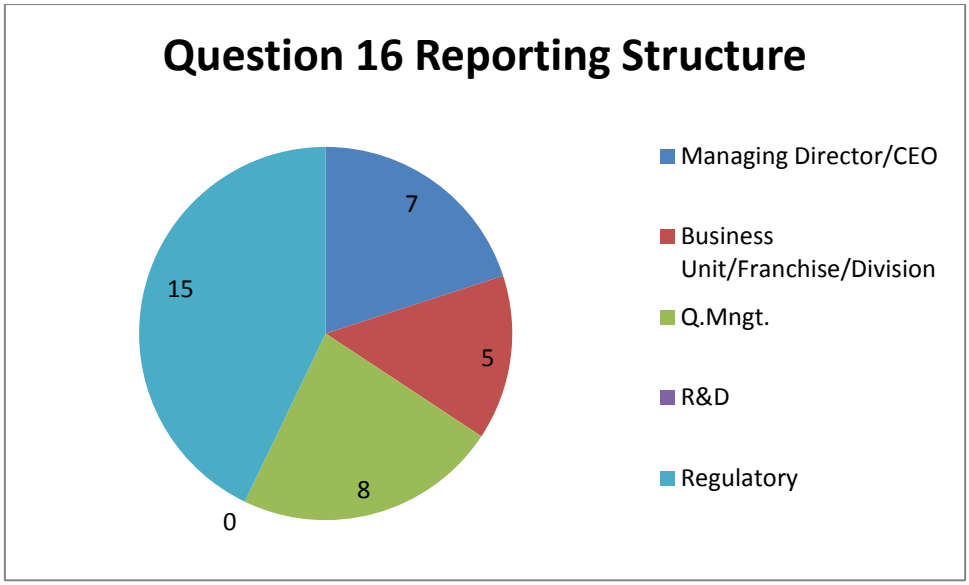

Figure 21: Survey Results Question 16 Regulatory Reporting Structure

4.4.6 Conclusion of Research Question Three

The questions in the survey have identified that regulatory strategy as a tool for communicating regulatory requirements is an underutilised tool. Regulatory Affairs professionals tend to communicate requirements as part of project team meetings which would suggest that as required they provide insight into the regional requirements. Regulatory strategy is used but it is not the predominant tool.

4.5 Research Question 4 - Government Affairs

Research question four posed the following question, Are Regulatory Affairs professionals aware of changing government policies that impact the Medtech sector? To gain an insight into Regulatory Affairs professionals' knowledge on government affairs Brexit was used as an example. Brexit is the common term used to describe the United Kingdom's withdrawal from the European Union. There are a lot of unknowns with Brexit as the negotiation process to withdraw just commenced in May 2017.

To address research question four the following questions were asked in the survey:

- Question 17 - Does your company have a government affairs department?
- Question 18 - How often do the government affair department publish information?
- Question 19 - As a Regulatory Affairs professional how important is it to stay informed on government affairs?
- Question 20 - When you develop a regulatory strategy for a product do you incorporate the impact government affairs changes could have on the regulatory strategy e.g. Brexit?

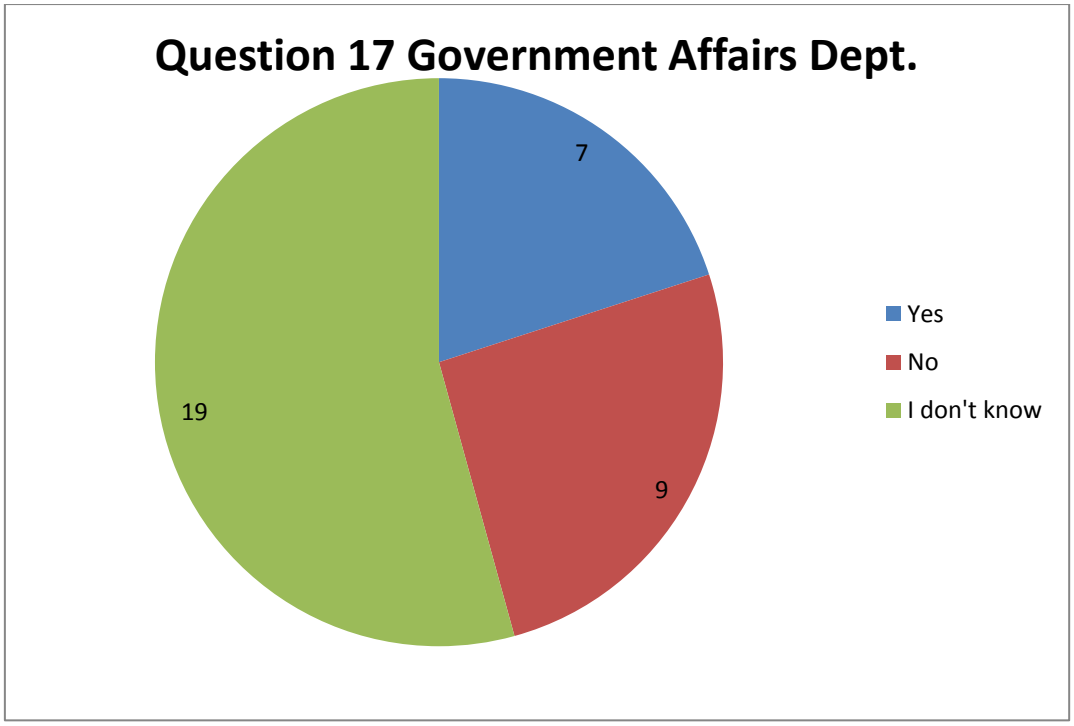

Figure 22: Survey Results Question 17 Existence of Government Affairs function in Company

4.5.1 Results from Survey Question Seventeen – Government Affairs Department

Only twenty percent of the respondents identified that their company has a government affairs department. These twenty percent work in multinational companies. Only one respondent identified that they always consider government affairs when developing a regulatory strategy.

4.5.2 Results from Survey Question Eighteen – Frequency of publication of material by Government Affairs Department

The majority of respondents identified this question as not applicable, for those who responded they indicated that publication is weekly or monthly.

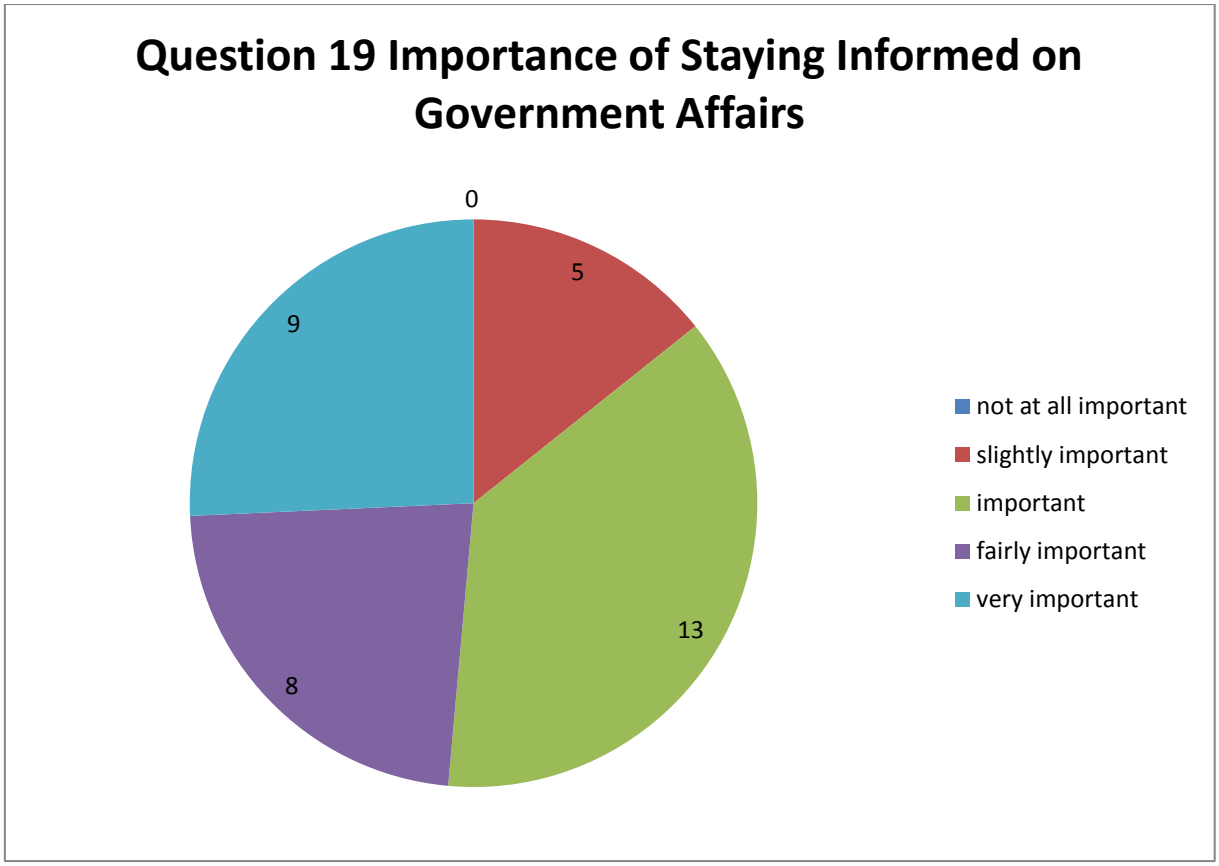

Figure 23: Survey Results Question 19 Importance of Staying Informed on Government Affairs

4.5.3 Results from Survey Question Nineteen – Importance of Staying Informed on Government Affairs

A little less than half of the respondents thirty-seven percent identified that staying informed on government affairs is important.

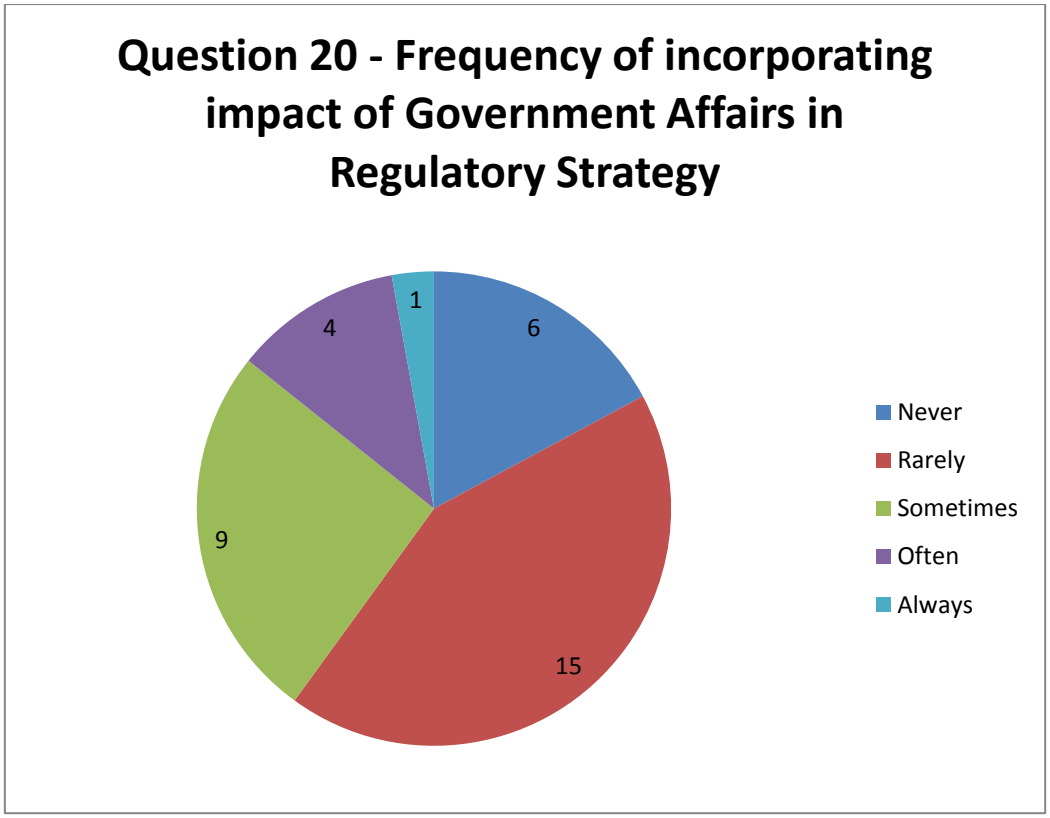

Figure 24: Survey Results Question 20 Frequency of Incorporating impact of Government Affairs in Regulatory Strategy

4.5.4 Results from Survey Question Twenty – Frequency of Incorporating Government Affairs into Regulatory Strategy

The highest percentage fifteen percent stated they rarely include government affairs in the regulatory strategy document. Only one percent stated they never include government affairs.

4.5.5 Conclusion of Research Question Four

The survey results indicate that in general most companies do not have a department that takes care of government affairs. The majority of the respondents indicate that they rarely incorporate government affairs into the regulatory strategy. This is reflective of how often government affairs impacts the regulatory strategy for pre-market approval of devices/products. Respondents indicated for the most part that it is important to stay informed on government affairs.

4.6 Data Analysis Conclusion

The results of the survey indicate that the main challenge identified by the respondents to the survey is lack of regulatory harmonisation across geographies. "According to the World Health Organization (WHO), medical device harmonisation is a process to encourage convergence in regulatory practices related to ensuring the safety, effectiveness/performance and quality of medical devices, promoting technological innovation, and facilitating international trade. The European Union is a good example of the harmonization of medical devices, from which the advantages and benefits can be sensed – it was estimated that the European GDP had increased up to 1.5% between 1987 and 1993 due to the promoted completion of a single set of Europe requirements and regulations." (Ramakrishna et al 2015) The results also suggest that the use of regulatory strategy as a tool to communicate regulatory requirements is underutilised. As indicated by a Regulatory Affairs director working in a multinational with over twenty years regulatory experience "for a strategic thinking company, Regulatory Affairs should be at the heart of discussions on how business moves forward in navigating the many challenges which lie ahead." The use of the regulatory strategy document is a useful tool that should be used by Regulatory Affairs professionals to map out the regulatory landscape. As noted by Theisz (2015) "the regulatory strategy is part of the wider market access strategy, which includes the clinical strategy that specifies what clinical trials are required, if any, in support of the regulatory submissions, and the reimbursement strategy in markets where the purchase of the device can be covered by health insurance or other payer systems."

5 Chapter 5 Conclusions/Recommendations

The aim of this research was to investigate the challenges encountered by Regulatory Affairs professionals working in the Medtech industry. Initial brainstorming identified three main challenges:

1. Different Regulatory Frameworks in different regions (lack of regulatory harmonisation across geographies)
2. Evolving Regulatory Frameworks/Requirements
3. Staying informed on changing government policies/status and the impact this has on the Medtech industry

A detailed literature review was completed to investigate the issues these challenges present to the Regulatory Affairs professional. The literature review yielded sufficient information for Europe and the United States however information regarding China, Korea or Japan was not easily obtained. From the information researched in the literature review a survey was compiled to address the following four research questions:

1. What is the main challenge experienced by Regulatory Affairs professional in gaining regulatory approval in United States, Europe, China, Korea and Japan?
2. How are Regulatory Affairs professionals staying informed on changing and evolving global regulatory requirements?
3. How are the regulatory requirements communicated internally in companies by Regulatory Affairs professionals?
4. Are Regulatory Affairs professionals aware of changing government policies that impact the Medtech industry?

An overview of findings for each research questions is presented in the next section of the thesis. By understanding the challenges that Regulatory Affairs professionals experiences it provides information to the Regulatory Affairs professional to allow better planning of submissions; it provides a better understanding of the role of the Regulatory Affairs professional and the key contributions they have to the business strategy.

5.1 Research Question One: Main challenge experienced by Regulatory Affairs professional

The survey identified that main challenge identified by Regulatory Affairs professional is different regulatory frameworks in different regions i.e. the lack of regulatory harmonisation

across geographies. There is no quick fix solution to this challenge however a tool that Regulatory Affairs professional could use is the regulatory strategy. By developing robust regulatory strategies the regulatory landscape can be mapped out and communicated to the business team. The regulatory strategy has to be developed in conjunction with the business goals.

There are a number of organizations across the globe working on harmonization; these include Global Harmonization Task Force (GHTF), International Medical device Regulatory Forum (IMDRF), Asian Harmonization Working Party (AHWP), Pan American Network for Drug Regulatory Harmonization (PANDRH) Pan African Harmonization Working Party on Medical Devices and Diagnostics (PAHWP) and societies which include Regulatory Affairs Professionals Society (RAPS) and Association of Southeast Asian Nations (ASEAN). (Ramakrishnan et al 2015) This demonstrates the complexity of harmonization, the need for seven different organizations looking at different regions. "According to the World Health Organization (WHO), medical device harmonization is a process to encourage convergence in regulatory practices related to ensuring the safety, effectiveness/performance, and quality of medical devices, promoting technological innovation, and facilitating international trade. (Ramakrishna et al 2015) "The European Union is a good example of the harmonization of medical devices" (Ramakrishna et al 2015) Organizations such as Asian Harmonization Working Party AHWP may incorporate a similar process for the countries they represent but for the foreseeable future Regulatory Affairs professionals will continue to experience the challenge of different regulatory frameworks in different regions.

5.2 Research Question Two: Staying informed on changing and evolving global regulatory requirements

To understand how the Regulatory Affairs professional stays informed on new requirements the survey completed as part of this research identified the associations the Regulatory Affairs professional has membership to and the methods the Regulatory Affairs professional uses for staying informed. Eighty-three percent of the respondents to the survey identified that they have membership to the Irish Medtech, which is the business association within Ibec representing the medical devices and diagnostics sector. The survey was sent to Regulatory Affairs professionals working in the Medtech sector in Ireland.

The method used most often for staying informed on evolving regulatory requirements is internal training. This is not surprising as the majority of the respondents, sixty-six percent work in multinationals and this is an option available to them. Multinational companies typically have regulatory representatives in each of the regions they market and sell devices. Interestingly twenty-nine percent used subscriptions and membership to regulatory associations as a method for staying informed on evolving regulatory requirements.

5.3 Research Question Three: Methods for communicating regulatory requirements internally in companies

The survey identified that regulatory strategy as a tool for communicating regulatory requirements is an underutilised tool. Regulatory Affairs professionals tend to communicate requirements as part of project team meetings which would suggest that as required they provide insight into the regional requirements. Regulatory strategy is used but it is not the predominant tool.

A small number of twenty-nine percent of respondents identified either regulatory strategy or regulatory plan as the usual or sometimes utilized tool. The Regulatory Affairs professional uses project team meetings to communicate regulatory requirements. Project team meetings typically focus on immediate goals for example product approval in Europe. The utilization of a regulatory strategy to communicate regulatory requirements ensures the Regulatory Affairs professional has a consistent format to communicate the ever evolving regulatory requirements and ensure the business is seeing the global strategy. A "well executed strategy, one that facilitates the capture of emerging opportunities, produces enduringly good performance, is adaptable to changing business conditions and can withstand the competitive challenges from rival organizations" (Thompson et al 2012, p.4)

5.4 Research Question Four: changing government policies/status and the impact this has on the Medtech industry

As identified by the survey only twenty percent of the respondents identified that their company has a government affairs department. A little less than half of the respondents thirty-seven percent identified that staying informed on government affairs is important. From these results it indicates that the government affairs are not a high priority. This is reflective of how often government affairs impacts the regulatory strategy for pre-market approval of devices/products.

There was limited information available on the EU and US and no information on China, Korea or Japan. FDA identifies political pressure, consumer activism, and industry involvement impact the work completed by the FDA. (FDA 2009)

To understand the impact of government status on the Medtech industry Brexit was used as a case study. Brexit the common term used to describe the United Kingdom's withdrawal from the European Union was identified as a case study. Brexit is very interesting as the United Kingdom is the first country to leave the European Union. This research has identified that the ideal scenario for the Regulatory Affairs professional and for the Medtech industry is to have harmonization; Brexit could disrupt the existing harmonization in Europe. From the survey results, only thirty-seven percent identified that staying informed on government affairs is important. Further research could be completed on the area of government affairs, in the survey only twenty percent of the respondents identified that their company had a government affairs department and the majority of these respondents work in multinational companies. "The two sectors currently most affected by the regulatory environment in the U.S. are healthcare and financial services. New regulations are expensive in terms of compliance, as companies need to transform data tracking and gathering systems, reporting functions and, in some cases, their organizational structures." (Forbes 2014) As Brexit unfolds the Regulatory Affairs professional will need to stay informed and engaged to ensure the business side of the industry understands the impact this government policy will have on the Medtech industry.

5.5 Limitations

All research has limitations. The survey has the limitation of the subjectivity by the researcher to develop the survey questionnaire, the sample accessed and the reliability of the returned responses. Thorough survey design and completion of a pilot run have been used to minimize the impact of such limitations. In addition respondents were asked to forward the survey to additional personnel to ensure a statistical valid sample size.

5.6 Future Work

The research presented in this dissertation offers opportunities for future research projects. Interviews could be carried out with Regulatory Affairs professional to identify ideas on solutions to the challenges of un-harmonized regulatory frameworks. It would be interesting

to understand how regulatory teams and regulatory individuals working in smaller companies are coping with knowledge management.

As Brexit unfolds it will be interesting to understand the impact this has to the European Union and the impact it has on the Medtech industry.

It will be interesting to follow the numerous organizations advocating global harmonization, the improvements and developments they will bring about in the future.

5.7 Social Media

Question thirteen of the survey was an open ended question requesting respondents to identify the methods used to stay informed on the regulatory environment. Two respondents identified social media as a means of staying informed. Most regulatory agencies have a presence on social media they have Twitter account, Facebook page and may use LinkedIn, Google+. They use social media to provide the latest news and information on for example standards, industry best practice, conferences, training. This is an area that Regulatory Affairs professionals need to engage with to ensure they are informed on the ever changing regulatory environment.

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Appendix 1: Acronyms

AHWP	Asian Harmonization Working Party
AIMD	Active Implantable Medical Device
ASEAN	Association of Southeast Asian Nations
BSI	British Standards Institution
CA	Competent Authority
CDRH	Center of Devices and Radiological Health
CE	Conformité Européenne
CFDA	China Food and Drug Administration
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FD&C	Food Drug & Cosmetics Act (US)
FDA	Food and Drug Administration (US)
FTA	Free Trade Area
GHTF	Global Harmonisation Task Force
HDE	Humanitarian Device Exemption (US)
HPRA	Health Products Regulatory Authority
IDA	Industry Development Authority
IEC	International Electrotechnical Commission
IMDRF	International Medical Device Regulatory Forum
IRB	Institutional Review Board
ISO	International Organization for Standardization
IVDD	In Vitro Diagnostic Directive
IVDR	In Vitro Diagnostics Regulation
KFDA	Korea Food and Drug Administration
MAH	Marketing Authorization Holder
MDD	Medical Devices Directive
MDR	Medical Device Regulation
MEDDEV	MEDICAL DEVICES : Guidance document
MFDS	Ministry of Food and Drug Safety (Korea)
MHLW	Ministry of Health Labor & Welfare (Japan)
MHRA	Medicines and Healthcare Products Regulatory Agency
NA	Not Applicable
NB	Notified Body
NSAI	National Standards Authority Ireland
PAHWP	Pan African Harmonization Working Party on Medical Devices and Diagnostics
PANDRH	Pan American Network for Drug Regulatory Harmonization
PMA	Premarket Approval
PMCF	Post-Market Clinical Follow-up
PMD	Pharmaceutical and Medical Device Act
PMDA	Pharmaceutical & Medical Devices Agency (Japan)
PMS	Post Market Surveillance
PSUR	Periodic Safety Update Reports
RAPS	Regulatory Affairs Professional Society
SE	Substantial Equivalence

SER	Safety and Efficacy Review
SFDA	State Food and Drug Administration
SME	Small to Medium Enterprises
STED	Summary Technical Documentation format
TDR	Technical Document Review
TFEU	Treaty on the functioning of the European Union
UK	United Kingdom
US	United States
WHO	World Health Organisation
WTO	World Trade Organisation

Appendix 2: Finished Survey

1. Welcome to My Survey

Thank you for participating in this survey. Please complete the information below which will be used for identification only. Note that this research guarantees respondent confidentiality and the survey results will not be integrated, analysed or reported in a way that will personally identify you.

* 1. Name:

* 2. Company:

* 3. Please tick the box below which best identifies your company?

- Irish
- Multinational
- Other

* 4. What type of company do you work for?

- SME: Micro enterprise (<10 employees)
- SME: Small enterprise (<50 employees)
- Medium size enterprise (between 50 - 249 employees)
- Large enterprise (>250 employees)

* 5. Please indicate how long you have worked in the role of regulatory affairs.

- less than 1 year
- 1-3 years
- 4-5 years
- 6-9 years
- 10 years or greater

* 6. Please indicate below the regions you/or your team have regulatory responsibility for (tick all that apply).

- [ ] United States (US)
- [ ] Europe (EU)
- [ ] Both EU and US
- [ ] Regions outside the EU and US only
- [ ] Other (please specify)

2. Key Challenges Identified from Literature Review

* 7. The literature review completed as part of the research has identified three challenging areas for the regulatory affairs professional to stay informed and be knowledgeable on. From the following list please rank the concepts from most challenging to least challenging where 3 is the most challenging and 1 is the least challenging to stay informed.

- [ ] Different Regulatory Frameworks in different regions (lack of regulatory harmonisation across geographies)
- [ ] Evolving Regulatory Frameworks/Requirements e.g. European Medical Devices Regulation (MDR) and In Vitro Diagnostics Regulation (IVDR)
- [ ] Staying informed on changing government policies and the impact this has on the MedTech industry e.g. Brexit

3. Evolving Regulatory Frameworks/Requirements

8. Do you or a member of your team participate in the following associations? (tick all that apply)

- [ ] Irish Medtech Association (formerly IMDA)
- [ ] Advanced Medical Technology Association (AdvaMed)
- [ ] MedTech Europe (formerly Eucomed)
- [ ] International Medical Devices Regulatory Forum (IMDRF)

9. Please list any other associations you and/or your team participate in.

* 10. Please rank the following tools/methods for communicating regulatory requirements within your company, where 1 is the option you use most often and 5 is option you least use.

	Project Team Meetings
	Regulatory Strategy - documents the overall activities to bring a new or modified product to market with the business strategy.
	Regulatory Plan - documents specific steps and actions required to meet regulatory strategy objectives. It contains specific elements required for the regulatory submission.
	Quality Management Review Meetings
	Email from a central function

11. What other tools/methods do you use in your company for communicating regulatory requirements? Please enter any comments in the box below. All feedback is appreciated.

* 12. Please rank the following methods for staying informed on the evolving regulatory environment and evolving government affairs, where 1 is the option you use most often and 5 is the option least used.

- [ ] External Training
- [ ] Internal Training
- [ ] Conferences
- [ ] Subscriptions to online newsletters, websites
- [ ] Membership to regulatory associations e.g. Irish Medtech Association (formerly IMDA), AdvaMed etc.

13. Please indicate what other methods you use for staying informed on the evolving regulatory environment.

4. Different Regulatory Frameworks

* 14. At what stage of the product life cycle do teams typically first engage the regulatory affairs function in your company?

- [ ] Feasibility/Early Product Development
- [ ] Clinical
- [ ] Product Development
- [ ] Manufacturing and Sustaining
- [ ] End of Life
- [ ] Other (please specify)

* 15. In your view rank how important the alignment of regulatory affairs with the R&D organisation is in your company?

Not at all important	Slightly Important	Important	Fairly Important	Very Important
☆	☆	☆	☆	☆

* 16. In your company what function does the regulatory group report to?

- ◯ Managing Director/CEO
- ◯ Business Unit/Franchise/Division
- ◯ Quality Management
- ◯ Research & Development
- ◯ Regulatory Management

Other (please specify)

5. Government Affairs

* 17. Does your company have a government affairs department?

- ◯ Yes
- ◯ No
- ◯ I don't know

* 18. How often do the government affairs department publish information?

- ◯ Weekly
- ◯ Monthly
- ◯ Quarterly
- ◯ Not applicable

* 19. In your role as a regulatory affairs professional, do you think it is important to stay informed on government affairs?

- ◯ Not at all important
- ◯ Slightly important
- ◯ Important
- ◯ Fairly Important
- ◯ Very Important

* 20. As a regulatory affairs professional, when you develop a regulatory strategy for a product do you incorporate the impact government affairs changes could have on the regulatory strategy e.g. Brexit?

- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Often
- ◯ Always

Appendix 3 Survey Email

Dear Regulatory Affairs Professionals,

I am conducting research on the challenges faced by Regulatory Affairs professional in relation to staying informed on:

(1) Different regulatory frameworks/requirements in different regions (lack of regulatory harmonization across geographies)
(2) Evolving regulatory frameworks/requirements e.g. European Medical Devices Regulation (MDR) & In Vitro Diagnostics Regulation (IVDR)
(3) Changing government policies e.g. Brexit

I would appreciate your support in completing a quick survey (20 questions) to gain industry insight into these challenges.

Your participation in the survey is completely voluntary and all of your responses will be kept confidential.

If you know anyone that works in Regulatory Affairs, please feel free to forward the survey to them.

Please click the link below to go to the survey (or copy and paste the link into your Internet browser).
https://www.surveymonkey.com/r/JLHLN6B

This research is being conducted as part of the MSc in Medical Technology Regulatory Affairs.

I appreciate you taking the time to complete the survey. Please do not hesitate to contact me if you have any questions.

Kind regards,
Claire O'Brien

Regulatory Affairs Manager

Appendix 4 Literature Protocol

Literature Protocol

Title:

Challenges encountered by Regulatory Affairs Professional in Medtech sector in Ireland

Contents

Purpose

The purpose of this thesis is to understand the challenges the regulatory affairs professionals' experiences working in the MedTech sector in Ireland.

It is important for regulatory affairs professionals to understand the main challenges that are encountered when submitting products for review and approval to regulatory agencies. This understanding will provide information to the regulatory affairs professionals to allow better planning of submissions; it will provide a better understanding of the role of the regulatory affairs professional and the key contributions they can have to the business strategy; it will provide an insight into knowledge management processes employed by regulatory affairs professionals in relation to different regulatory frameworks and evolving regulatory frameworks.

"Medical devices are serving an increasingly central role in clinical practice. Improving patients' health and quality of life"(Sorenson & Drummond 2014). As regulatory affairs professionals we want to ensure devices are available to patients. It is important that we understand the regulatory frameworks in the regions our company plans to market devices so we can ensure high quality submissions that contain all the required information to support a fast review and approval by the regulatory agency. We want to ensure that products reach the market in a timely manner and are available to the patients in need of these products.

'Knowledge management is one of the most significant challenges for regulatory functions within organizations. Proper capture of knowledge and centralization of information sources yield process efficiencies' (Kearney 2011) The US and Europe are two of the biggest markets for medical devices and they have different regulatory frameworks. (Kirisits and Redekop 2013) The US regulatory framework has not changed significantly in the last few years. The EU regulatory framework is undergoing substantial changes, additional clinical and post-market requirements, and more responsibility for the manufacturer regarding transparency of the medical devices placed on the European market. (Schröttner and Neubauer 2013) As the regulatory framework changes the regulatory affairs professional needs to develop their knowledge on the new requirements, this is knowledge management.

In Asia the regulatory requirements are increasing and for the well established markets for example China and Japan the requirements are evolving. The regulatory environment is always evolving and changing. As companies want to market their products globally the regulatory affairs professional must develop expertise and knowledge on how to get products through the review process with the regulatory

agency and post approval how to maintain the product on the market for example complying with post-market requirements.

Scope

The scope of the dissertation will include a review of the current challenges faced by regulatory affairs professionals working in the MedTech sector in Ireland. These challenges are encountered as they work through the regulatory pathways to gain market approval for their products in United States, Europe and Asia and Japan.

This research has focused on the US and EU regions as these markets are globally recognised by the medical device industry as important, Asia has been chosen as it is an emerging market and Japan has been chosen because 'Japan is an economic powerhouse, and its medical device market is one of the biggest in the world.'(Emergo 2017)

The thesis will review literature to identify the challenges encountered by regulatory affairs professionals.

A survey will be administered to identify what are the top challenges experienced by the regulatory affairs professionals working in the MedTech sector in Ireland and what are the tools and processes to minimize the impact of these challenges on speed to market.

Objectives

1. Identify the top challenges regulatory affairs professionals encounter.
2. What tools/processes do regulatory affairs professionals utilize to manage these challenges?
3. Identify how regulatory affairs teams are structured – do specialists have responsibility for Global RA or Region Specific RA?
4. How do regulatory affairs professionals stay informed on evolving regulatory frameworks/changing regulatory environment?
5. What processes/tools do regulatory affairs specialists use for knowledge management?

Methods

Search Terms:	'medical devices' 'regulation' 'challenges'
Period covered by Search:	Last 10 years
Literature Sources used to identify data:	Scientific Databases: • Pubmed • Google Scholar • ProQuest Dissertation UK + Ireland • Scopus • Embase
Database search details:	Details for each database are covered in Appendix A Literature Search Report. All searches will be performed through online databases.
Information from Networking:	**Thesis by Susan McMonagle:** Medical Device Software Regulatory Challenges in Europe and the United States (August 2014) **Thesis by Kevin Naughton:** A Study of Irish Medical Device Companies Best Practice New

Product Development Tools and Methodologies (September 2009)

Selection criteria:

The following criteria will be used to assess the suitability of material (articles, reports, etc.) for inclusion/exclusion in the analysis stage of this report:

Inclusion Criteria:

1. Article includes reference to regulatory challenges

2. Article include reference to medical devices regulation in Europe, US, Asia, Japan

3. Differences and challenges of regulatory frameworks

Exclusion Criteria:

1. Paper is not specific to regulatory challenges.

2. Pharmaceutical specific – this is not part of the scope of the thesis.

3. Paper is specific to a region/country not covered by the thesis

4. Paper is not available for download

Outputs:

All literature citations selected for inclusion will be listed in Appendix A.

Data selection process:

A flowchart describing how data were assessed for suitability for inclusion in the clinical evaluation is included overleaf – Figure 1: Citation Assessment Flowchart.

- The outputs of the Literature Search will be summarized and any deviations from the Search protocol will be noted. Following this method a summary identifying all outputs of the database search will be created.
- The screening and selection of the published literature will be conducted as detailed in Figure 1 and recorded in a report.
- Those data which were identified and subsequently excluded following closer review will be recorded and the rationale for exclusion noted.

Date of Search:	The dates of the respective searches will be listed in the report
Name of person conducting search:	Claire O'Brien Regulatory Affairs.

The flowchart in Figure 1 below visually outlines the process used in assessing citations retrieved from queries of online databases.

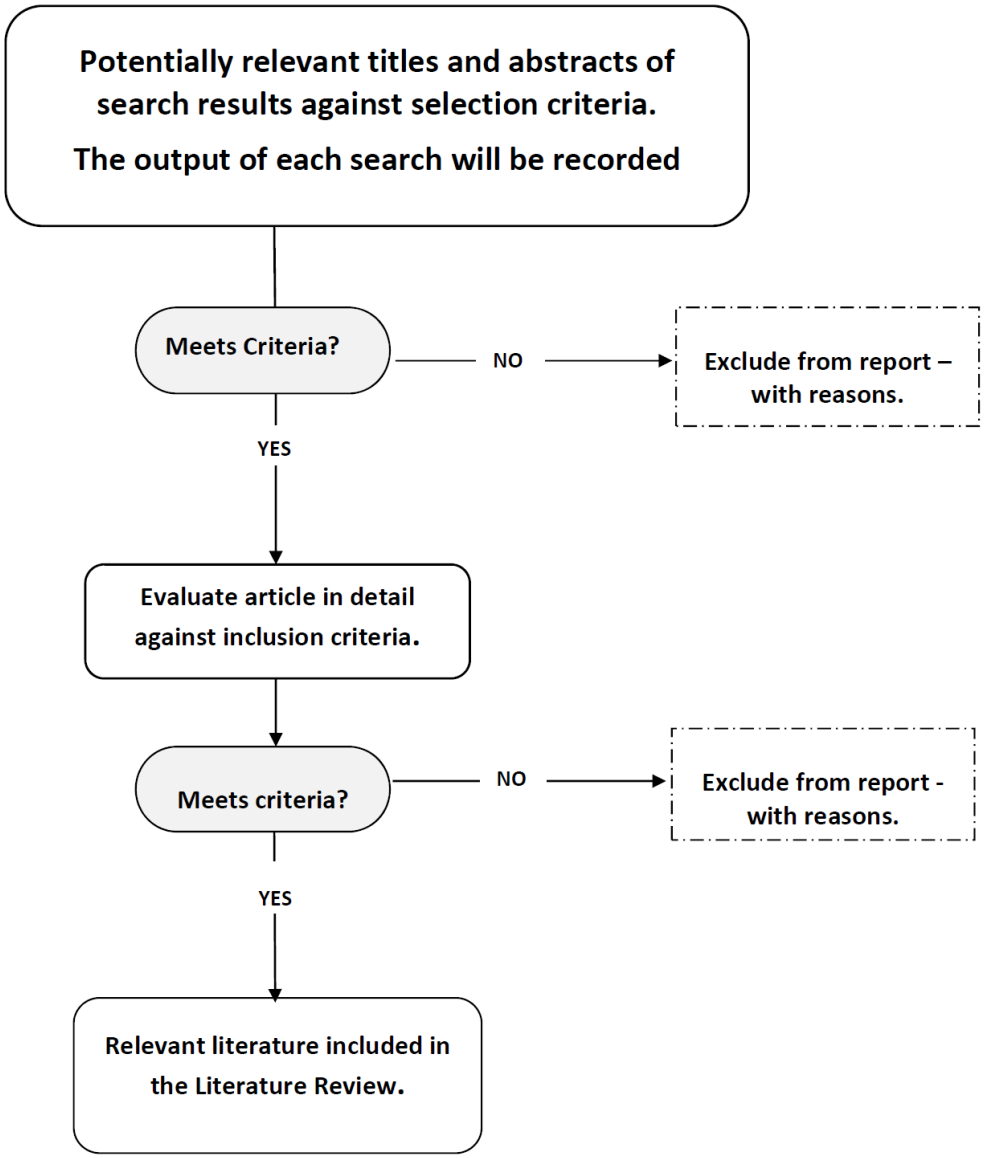

Figure 1 Citation Assessment Flowchart

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Sorenson, C. and Drummond, M., 2014.Improving Medical Device Regulation: The United States and Europe in Perspective. *The Millbank Quarterly* [online] Vol.92, No.1 (114-150)

Kirisits, A. and Ken Redekop, W. (2013). The Economic Evaluation of Medical Devices – Challenges Ahead. Erasmus University Rotterdam [online]

Appendices

Appendix A:

Literature Searches 2017.xlsx

PubMed Searches

Recent queries in pubmed				
Search	**Query**	**Items found**	**Time**	**Date**
#5	challenges Filters: published in the last 10 years Sort by: [relevance]	72	06:35:39	22-Jan-17
#4	Search medical device regulation challenges Sort by: [relevance]	88	06:35:26	22-Jan-17
#3	Search 'medical devices' 'regulation' 'challenges' Sort by: [relevance]	223	06:18:45	22-Jan-17
#2	Search medical devices regulatory affairs challenges Sort by: [relevance]	8	06:18:11	22-Jan-17
#1	Search 'medical devices' 'regulatory affairs' 'challenges' Sort by: [relevance]	0	06:18:11	22-Jan-17
Results	**Meets Criteria**	**Include**	**Exclude**	**Notes**
1: Sorenson C, Drummond M. Improving medical device regulation: the United States and Europe in perspective. Milbank Q. 2014 Mar;92(1):114-50. doi: 10.1111/1468-0009.12043. PubMed PMID: 24597558; PubMed Central PMCID:	Yes	Yes		Review
3: Kaushik A, Saini K, Anil B, Rambabu S. Harmonized Medical Device Regulation: Need, Challenges, and Risks of not Harmonizing the Regulation in Asia. J Young Pharm. 2010 Jan;2(1):101-6. doi: 10.4103/0975-1483.62221. PubMed PMID: 21331201; PubMed Central PMCID: PMC3035876.	Yes			Review
4: Avery M, Liu D. Bringing smart pills to market: FDA regulation of ingestible drug/device combination products. Food Drug Law J. 2011;66(3):329-52, i. PubMed PMID: 24505852.	No - pharmceutical specific			
6: Zhang S, Kriza C, Kolominsky-Rabas PL; National Leading-Edge Cluster Medical Technologies 'Medical Valley EMN'.. Assessing new developments in the pre-market regulatory process of medical devices in the People's Republic of China. Expert Rev Med Devices. 2014 Sep;11(5):527-35. doi: 10.1586/17434440.2014.932688. Review. PubMed PMID: 25060514.	Yes			couldn't download

9: Tyler RS. The goals of FDA regulation and the challenges of meeting them. Health Matrix Clevel. 2013;22(2):423-31. PubMed PMID: 23668096.	Yes			Review
15: Schröttner J, Neubauer R. Future Challenges for Medical Device Manufacturers Regarding the Revision of the European Legislation. Biomed Tech (Berl). 2013 Sep 7. pii: /j/bmte.2013.58.issue-s1-J/bmt-2013-4233/bmt-2013-4233.xml. doi: 10.1515/bmt-2013-4233. [Epub ahead of print] PubMed PMID: 24042885.	Yes			Review
16: Blake K. Postmarket surveillance of medical devices: current capabilities and future opportunities. J Interv Card Electrophysiol. 2013 Mar;36(2):119-27. doi: 10.1007/s10840-013-9778-6. PubMed PMID: 23479089.	Yes			Review
22: Levesque K, Coqueblin C, Guillot B; participants of round table n3 of Giens XXIX : Aubourg Lucie 4 Avouac Bernard 5 Carbonneil Cédric 6., Aubourg L, Avouac B, Carbonneil C, Cucherat M, Descamps-Mandine P, Hanoka S, Goldberg M, Josseran A, Parquin F, Pitel S, Ratignier C, Sechoy O, Szwarcenstein K, Tanti A, Teiger E, Thevenet N. Post-approval studies in France, challenges facing medical devices. Therapie. 2014 Jul-Aug;69(4):303-21. doi: 10.2515/therapie/2014051. English, French. PubMed PMID: 25230354.	Yes - post approval			couldn't access on
24: Silva AP, Tagliari PO. [Convergence of healthcare regulation in the Americas: history, development, and new challenges]. Rev Panam Salud Publica. 2016 May;39(5):281-287. Portuguese. PubMed PMID: 27706413.	Yes			Not in English
25: Fuchs S, Olberg B, Panteli D, Perleth M, Busse R. HTA of medical devices: Challenges and ideas for the future from a European perspective. Health Policy. 2016 Sep 14. pii: S0168-8510(16)30215-9. doi: 10.1016/j.healthpol.2016.08.010. [Epub ahead of print] PubMed PMID: 27751533.	Yes			Not applicable
27: Jarosławski S, Saberwal G. Case studies of innovative medical device companies from India: barriers and enablers to development. BMC Health Serv Res. 2013 May 30;13:199. doi: 10.1186/1472-6963-13-199. PubMed PMID: 23721110; PubMed Central PMCID: PMC3669049.	No - India specific			

30: Rotter RG. [The global harmonization task force : successes and challenges]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2009 Jun;52(6):601-4. doi: 10.1007/s00103-009-0858-9. German. PubMed PMID: 19418030.	Yes			In German
31: Sarpatwari A, Kesselheim AS. The 21st century cures act: Opportunities and challenges. Clin Pharmacol Ther. 2015 Dec;98(6):575-7. doi: 10.1002/cpt.208. PubMed PMID: 26264909.	Yes			Review
43: Howes K. Regulatory challenges for diagnostic development - a European perspective. Expert Opin Med Diagn. 2007 Oct;1(2):153-7. doi: 10.1517/17530059.1.2.153. PubMed PMID: 23489302.	Yes			Not easy too find
46: Rao SV, Califf RM, Kramer JM, Peterson ED, Gross TP, Pepine CJ, Williams DO, Donohoe D, Waksman R, Mehran R, Krucoff MW. Postmarket evaluation of breakthrough technologies. Am Heart J. 2008 Aug;156(2):201-8. doi: 10.1016/j.ahj.2008.01.036. PubMed PMID: 18657647.	Yes			Not easy too find
53: Vincent CJ, Niezen G, O'Kane AA, Stawarz K. Can standards and regulations keep up with health technology? JMIR Mhealth Uhealth. 2015 Jun 3;3(2):e64. doi: 10.2196/mhealth.3918. PubMed PMID: 26041730; PubMed Central PMCID: PMC4526895.	Yes			Review
66: Ganz RA. The impact of health care reform on innovation and new technology. Gastrointest Endosc Clin N Am. 2012 Jan;22(1):109-20. doi: 10.1016/j.giec.2011.08.006. Review. PubMed PMID: 22099717.	Yes			Can't download
69: Willis SL, Lewis AL. The interface of medical devices and pharmaceuticals: Part II. Med Device Technol. 2008 May-Jun;19(3):38-43. PubMed PMID: 18557409.	No			No access online

Appendix 5 Survey Results

5.1 Question 3 & 4 Type of Company & Company Size

Company Size	Type of Company
Large enterprise (>250 employees)	Multinational
Large enterprise (>250 employees)	Multinational
Large enterprise (>250 employees)	Multinational
Large enterprise (>250 employees)	Multinational
Large enterprise (>250 employees)	Multinational
Large enterprise (>250 employees)	Multinational
Large enterprise (>250 employees)	Multinational
Large enterprise (>250 employees)	Multinational
Large enterprise (>250 employees)	Multinational
Large enterprise (>250 employees)	Multinational
Large enterprise (>250 employees)	Multinational
SME: Small enterprise (<50 employees)	Irish
Large enterprise (>250 employees)	Multinational
Large enterprise (>250 employees)	Multinational
SME: Micro enterprise (<10 employees)	Multinational
SME: Micro enterprise (<10 employees)	Irish
Large enterprise (>250 employees)	Irish
Large enterprise (>250 employees)	Multinational
SME: Small enterprise (<50 employees)	Irish
Large enterprise (>250 employees)	Multinational
Medium size enterprise (between 50 - 249 employees)	Multinational
Large enterprise (>250 employees)	Multinational
Medium size enterprise (between 50 - 249 employees)	Multinational
Medium size enterprise (between 50 - 249 employees)	Irish
Medium size enterprise (between 50 - 249 employees)	Multinational
SME: Small enterprise (<50 employees)	Irish
Large enterprise (>250 employees)	Multinational
Medium size enterprise (between 50 - 249 employees)	Irish
Medium size enterprise (between 50 - 249 employees)	Irish
SME: Small enterprise (<50 employees)	Multinational
Large enterprise (>250 employees)	Multinational
Large enterprise (>250 employees)	Multinational
Large enterprise (>250 employees)	Multinational
Large enterprise (>250 employees)	Multinational
Large enterprise (>250 employees)	Multinational

Company Size	Number of Respondents
SME: Micro enterprise (<10 employees)	2
SME: Small enterprise (<50 employees)	4
Medium size enterprise (between 50 - 249 employees)	6
Large enterprise (>250 employees)	23
Total	36

Type of Company	Numbers
Multinational	31
Irish	4

5.2 Question 5 Years of Regulatory Experience

Years of Experienc	Company Size
10 years or greater	Large enterprise (>250 employees)
1-3 years	Large enterprise (>250 employees)
less than 1 year	Large enterprise (>250 employees)
1-3 years	Large enterprise (>250 employees)
10 years or greater	Large enterprise (>250 employees)
less than 1 year	Large enterprise (>250 employees)
4-5 years	Large enterprise (>250 employees)
10 years or greater	Large enterprise (>250 employees)
4-5 years	Large enterprise (>250 employees)
6-9 years	Large enterprise (>250 employees)
10 years or greater	Large enterprise (>250 employees)
10 years or greater	SME: Small enterprise (<50 employees)
10 years or greater	Large enterprise (>250 employees)
10 years or greater	Large enterprise (>250 employees)
10 years or greater	SME: Micro enterprise (<10 employees)
10 years or greater	SME: Micro enterprise (<10 employees)
1-3 years	Large enterprise (>250 employees)
1-3 years	Large enterprise (>250 employees)
10 years or greater	SME: Small enterprise (<50 employees)
6-9 years	Large enterprise (>250 employees)
10 years or greater	Medium size enterprise (between 50 - 249 employees)
10 years or greater	Large enterprise (>250 employees)
4-5 years	Medium size enterprise (between 50 - 249 employees)
4-5 years	Medium size enterprise (between 50 - 249 employees)
1-3 years	Large enterprise (>250 employees)
less than 1 year	Medium size enterprise (between 50 - 249 employees)
4-5 years	SME: Small enterprise (<50 employees)
4-5 years	Medium size enterprise (between 50 - 249 employees)
10 years or greater	Medium size enterprise (between 50 - 249 employees)
10 years or greater	SME: Small enterprise (<50 employees)
4-5 years	Large enterprise (>250 employees)
less than 1 year	Large enterprise (>250 employees)
6-9 years	Large enterprise (>250 employees)
6-9 years	Large enterprise (>250 employees)

Years of Regulatory Experience	Numbers
less than 1 year	4
1-3 years	5
4-5 years	7
6-9 years	4
10 years or greater	15
Total	**35**

5.3 Question 6 Regions of Regulatory Responsibility

Please indicate below the regions you/or your team have regulatory responsibility for (tick all that apply).					
United States (US)	Europe (EU)	Both EU and US	Regions outside the EU and US only	Rest of the World	Other (please specify)
United States (US)	Europe (EU)	Both EU and US			Int'l
		Both EU and US			
United States (US)		Both EU and US			
United States (US)	Europe (EU)	Both EU and US			international
		Both EU and US			also support international countries
		Both EU and US			
		Both EU and US			
		Both EU and US			International
		Both EU and US			
		Both EU and US			Notification of change to Japan and International regions
		Both EU and US	Regions outside the EU and US only		
United States (US)	Europe (EU)	Both EU and US			
		Both EU and US			Japan and International
			Regions outside the EU and US only		
United States (US)	Europe (EU)	Both EU and US			Global - Alsa, Middle East etc
		Both EU and US			
		Both EU and US			Note that the company is not a legal manufacturer
		Both EU and US			International
United States (US)	Europe (EU)				Korea, Australia
		Both EU and US			Canada, Latia America & ROW markets
		Both EU and US			Worldwide
United States (US)	Europe (EU)	Both EU and US	Regions outside the EU and US only		
					All of above, i.e. Eu, US and RoW
		Both EU and US			
					Technically no responsibilities (supplier)
	Europe (EU)				
	Europe (EU)				
		Both EU and US			RA dept of Technopath Clinical diagnostics have responsibility for all global regions
		Both EU and US			Asia, Middle East, Africa; worldwide really.
		Both EU and US			
		Both EU and US			
	Europe (EU)				RA for European manufacturer
		Both EU and US			
		Both EU and US			
			Regions outside the EU and US only		

United States (US)	7
Europe (EU)	9
Both EU and US	27
Regions outside EU &	4
Other	17

5.4 Question 7 Challenges Researched in Literature

Different Regulatory Frameworks in different regions (lack of regulatory harmonisation across geographies)	Evolving Regulatory Frameworks/Requirements e.g. European Medical Devices Regulation (MDR) and In Vitro Diagnostics Regulation (IVDR)	Staying informed on changing government policies and the impact this has on the MedTech industry e.g. Brexit
2	3	1
3	1	2
3	2	1
2	1	3
3	2	1
2	3	1
1	2	3
2	3	1
2	1	3
3	2	1
3	1	2
2	1	3
3	1	2
2	3	1
3	1	2
2	3	1
3	1	2
3	1	2
1	2	3
3	2	1
3	2	1
3	1	2
1	2	3
1	2	3
1	2	3
1	2	3
2	3	1
2	1	3
2	1	3
2	1	3
3	1	2
1	2	3
3	1	2
3	1	2
2	1	3

	Rank	Q1 Different Reg. Frameworks	Q2 Evolving Reg. Framework e.g. MDR/IVDR	Q3 Changing Government Policies e.g. Brexit
Least	1	7	17	11
Medium	2	13	12	10
Most	3	15	6	14

5.5 Question 8 & 9 Membership to Associations

					Please list any other associations you and/or your team participate in.
					Open-Ended Response
Irish Medtech Association (formerly IMDA)	Advanced Medical Technology Association (AdvaMed)	MedTech Europe (formerly Eucomed)	International Medical Devices Regulatory Forum (IMDRF)	None	Notified Body Task Force (NBTF)
Irish Medtech Association (formerly IMDA)					
Irish Medtech Association (formerly IMDA)					
Irish Medtech Association (formerly IMDA)	Advanced Medical Technology Association (AdvaMed)				
Irish Medtech Association (formerly IMDA)	Advanced Medical Technology Association (AdvaMed)	MedTech Europe (formerly Eucomed)			NSAI and Standards development
Irish Medtech Association (formerly IMDA)		MedTech Europe (formerly Eucomed)			
Irish Medtech Association (formerly IMDA)					
Irish Medtech Association (formerly IMDA)	Advanced Medical Technology Association (AdvaMed)	MedTech Europe (formerly Eucomed)			
Irish Medtech Association (formerly IMDA)			International Medical Devices Regulatory Forum (IMDRF)		
Irish Medtech Association (formerly IMDA)	Advanced Medical Technology Association (AdvaMed)				Standard Technical Commitees
Irish Medtech Association (formerly IMDA)	Advanced Medical Technology Association (AdvaMed)	MedTech Europe (formerly Eucomed)	International Medical Devices Regulatory Forum (IMDRF)		
Irish Medtech Association (formerly IMDA)		MedTech Europe (formerly Eucomed)			
Irish Medtech Association (formerly IMDA)					
					ABIMED / ABIMOD - Brazil Canifarma - Mexico KMDIA - Korea Medical Device Industry Associations
Irish Medtech Association (formerly IMDA)					
Irish Medtech Association (formerly IMDA)					TOPRA
Irish Medtech Association (formerly IMDA)					N/A
Irish Medtech Association (formerly IMDA)	Advanced Medical Technology Association (AdvaMed)	MedTech Europe (formerly Eucomed)	International Medical Devices Regulatory Forum (IMDRF)		RAPS
	(AdvaMed)				
Irish Medtech Association (formerly IMDA)					
Irish Medtech Association (formerly IMDA)					None currently
Irish Medtech Association (formerly IMDA)					N/A
Irish Medtech Association (formerly IMDA)					
Irish Medtech Association (formerly IMDA)		MedTech Europe (formerly Eucomed)			
					BIVDA
Irish Medtech Association (formerly IMDA)	Advanced Medical Technology Association (AdvaMed)	MedTech Europe (formerly Eucomed)			None
Irish Medtech Association (formerly IMDA)					Peripheral involvement in standards (via NSAI).
Irish Medtech Association (formerly IMDA)					
Irish Medtech Association (formerly IMDA)		MedTech Europe (formerly Eucomed)			

Irish Medtech Association (formerly IMDA)	Advanced Medical Technology Association (AdvaMed)				Irish Medtech QA/RA forum
Irish Medtech Association (formerly IMDA)					
Irish Medtech Association (formerly IMDA)					we participate in various standards development organisation such as NSAI, AAMI, ISO, IEC, ASTM. This helps us keep up to date on changing standard requirements
Irish Medtech Association (formerly IMDA)	Advanced Medical Technology Association (AdvaMed)	MedTech Europe (formerly Eucomed)			
Irish Medtech (Irish)	**AdvaMed (US)**	**MedTech Europe (EU)**	**IMDRF (International)**		
30	11	11	4		14

5.6 Question 10 & 11 Tools/Methods used to Communicate Regulatory Requirements

						What other tools/methods do you use in your company for communicating regulatory requirements? Please enter any comments in the box below. All feedback is appreciated.
Regulatory Strategy - documents the overall activities to bring a new or modified product to market with the business strategy.	Regulatory Plan - documents specific steps and actions required to meet regulatory strategy objectives. It contains specific elements required for the regulatory submission.	Quality Management Review Meetings	Email from a central function			Open-Ended Response
4	5	2	1			QMP Projects, RA Internal Meetings
4	5	3	2			Fusion site,
3	4	5	1			Sharepoints/Fusion pages
3	2	4	5			Word of mouth/ others (different franchise) experience at reg team meeting
2	3	5	4			are usually involved in the Technical committee at some level so the person representing that standard would typically inform the wider audience and functions of its status and impact to the business. also the Standards management system within
1	2	3	5			
3	4	5	2			
3	4	5	2			
2	5	4	3			
4	3	2	1			attached to change requests and contains a global assessment for all regions
4	5	1	3			news articles, database searches
5	4	3	2			informal updates and one-on-one meetings
4	3	5	1			

1	2	3	5			1) The Product Specialists at the sites are the voice of International Regulatory Affairs in the Regions at Project Meetings (as the Regions cannot attend Project Team Meetings). It is important that the Product Specialists understand the basis Regulatory requirements in the Regions. We have the Regions present periodically (3 times a year) to the Product Specialists at the sites to keep the sites informed on regulatory requirements 2) Communication sessions between Functions at the Manufacturing Sites and Regulatory Affairs in the Regions
1	5	4	3			
2	3	1	5			at various timepoints.
5	4	3	2			
2	3	4	5			RSS feed to Gray Sheet
3	4	2	1			Intranet
1	2	5	3			
4	3	5	2			Weekly Management Meetings
2	1	4	5			Monthly Regulatory Intelligence Meetings
4	3	5	1			outside formal meetings
3	2	4	5			communicate via presentations the regulatory requirments for a project. Changes in Regulations are also reviewed by a multi-site team to assess the
5	1	2	4			slides/other documents. Quality conference with Quality & RA Leaders from various
2	4	5	3			None
4	5	3	1			Global Alere Regulatory Forums GRID (Global Regulatory Information Database)
4	3	1	2			conferences and meetings
2	3	5	4			(Document Control Request) review, which is not ideal but better than releasing a device not approved or which does not meet the requisite regulatory requirments.
3	2	4	1			
2	4	3	5			communicate the high-level regulatory strategy to gain the required approvals to market products is the regulatory strategy . It provides key timelines and deliverables to the project manager and is utilized in the product development lifecycle as it is a live document . The strategy is also used to

3	4	1	5			Process controls for key activities like Validation, Design Control etc.
2	4	5	3			exercise at the start of the project as you're providing information to the Team on regulatory requirements thereby setting
1	3	4	5			regulatory strategies. Since their introduction they have helped ensure that teams understand the specific regulatory requirements for the project/ product. They ensure alignment with the business strategy/business goals, as regulatory need to engage with the business to understand business priorities. The strategy is also used to highlight differences in regulatory requirements between geographies and to include risk assessment for the project/ product. The risk assessment highlights specific regulatory risks for the project, the consequences of such risks and the mitigation plan. Getting such a document approved by the impacted functions ensure that everyone is aware of the submission plan and reasons for the strategy. It should
2	1	4	3			Pacific Bridge Medical, Radar (Emergo) consultant publications for APAC, tuv/Bsi

5.7 Question 12 & 13 Methods of Staying Informed

4	1	2	3	5	Reliant on information shared from those in my regulatory group who attend conferences, or from Senior members of the group i.e forums.
4	5	3	1	2	Regulatory Contacts
4	3	5	1	2	
5	3	4	1	2	
2	3	4	1	5	Membership RAPS, FDA Newsletter, LinkedIn etc
2	5	4	3	1	Consultants, colleagues
2	1	3	4	5	Internal information sharing meetings
1	5	3	2	4	Podcasts on various subjects
1	4	3	2	5	None
1	5	3	4	2	Feedback from Management
4	5	3	1	2	
3	5	1	2	4	Generally through networking with former colleagues, and subscribing to web-sites such as FDA, HPRA, NSAI. We also have a Regulatory Agent we use in the US and also for Malaysia who have a worldwide presence, and who are helpful in answering general regulatory queries.
4	5	3	1	2	
4	1	2	5	3	We in Boston Scientific have various RA Fora which are used to discuss a wide variety of regulatory topics.
2	1	3	5	4	Social Media
1	2	3	5	4	
4	5	3	2	1	One method we are considering is the use of social media. Most regulatory agencies/ associations have a strong presence on twitter and therefore provide access to immediate information. How this is built into the business plan for staying informed has still to be established.
3	5	2	1	4	

Please rank the following methods for staying informed on the evolving regulatory environment and evolving government affairs, where 1 is the option you use most often and 5 is the option least used.					**Please indicate what other methods you use for staying informed on the evolving regulatory environment.**
External Training	Internal Training	Conferences	Subscriptions to online newsletters, websites	Membership to regulatory associations e.g. Irish Medtech Association (formerly IMDA), AdvaMed etc.	Open-Ended Response
4	3	2	5	1	Networking with peers
3	1	2	5	4	
4	5	3	2	1	
1	2	3	5	4	
4	3	1	5	2	Feedback from various agencies through either working through getting a product approved, or having meetings with the agencies. eg we have annual account meetings with our Notified Bodies and we would discuss such topics.
2	1	5	4	3	
5	3	2	4	1	
5	1	4	2	3	websites - FDA.gov, HPRA etc
5	1	3	2	4	
2	1	4	3	5	Global Regulatory intranet and forums where hot topics are discussed and experiences shared
5	1	4	3	2	
4	5	2	1	3	Peer discussions
2	1	3	5	4	
4	5	3	2	1	Use of informal networks (ex-colleagues etc.)
4	5	3	1	2	
3	5	2	1	4	CPD, my own initiative, fellow regulatory professionals
1	5	4	2	3	

5.8 Question 14 Stage of Product Life Cycle Regulatory Affairs are Engaged

At what stage of the product life cycle do teams typically first engage the regulatory affairs function in your company?					
Feasibility/Early Product Development	Clinical	Product Development	Manufacturing and Sustaining	End of Life	Other (please specify)
Feasibility/Early Product Development					
Feasibility/Early Product Development		Product Development			
	Clinical	Product Development			
	Clinical				
		Product Development			
		Product Development			
Feasibility/Early Product Development					
		Product Development			
Feasibility/Early Product Development	Clinical	Product Development	Manufacturing and Sustaining	End of Life	
Feasibility/Early Product Development					
Feasibility/Early Product Development					
Feasibility/Early Product Development					Concept
Feasibility/Early Product Development					
Feasibility/Early Product Development					
Feasibility/Early Product Development					
Feasibility/Early Product Development					
Feasibility/Early Product Development					
Feasibility/Early Product Development					
Feasibility/Early Product Development					
Feasibility/Early Product Development					
Feasibility/Early Product Development					
Feasibility/Early Product Development					
Feasibility/Early Product Development					
Feasibility/Early Product Development		Product Development			

Feasibility/Early Product Development					
Feasibility/Early Product Development					
Feasibility/Early Product Development					
Feasibility/Early Product Development					
Feasibility/Early Product Development		Product Development			
Feasibility/Early Product Development					
Feasibility/Early Product Development					
Feasibility/Early Product Development					
Feasibility/Early Product Development					
	Clinical	Product Development	Manufacturing and Sustaining	End of Life	
Feasibility/Early Product Development					
29	4	9	2	2	1

5.9 Question 15 Importance of Alignment between Regulatory Affairs & Research & Development

In your view rank how important the alignment of regulatory affairs with the R&D organisation is in			
	Fairly Important	Important	Very Important
Fairly Important	1		
Important		1	
Very Important			1
Very Important			1
Very Important			1
Fairly Important	1		
Very Important			1
Very Important			1
Important		1	
Very Important			1
Very Important			1
Very Important			1
Very Important			1
Very Important			1
Very Important			1
Very Important			1
Very Important			1
Very Important			1
Very Important			1
Very Important			1
Important		1	
Very Important			1
Very Important			1
Very Important			1
Very Important			1
Very Important			1
Very Important			1
Important		1	
Very Important			1
Very Important			1
Fairly Important	1		
Fairly Important	1		
Very Important			1
Important		1	
	4	5	26

5.10 Question 16 Reporting Structure

In your company what function does the regulatory group report to?				
Response	BU/Franchise/Division	Reg Mngt	Managing Director/CEO	Quality Mngt.
Business Unit/Franchise/Division	1			
Regulatory Management		1		
Regulatory Management		1		
Regulatory Management		1		
Regulatory Management		1		
Regulatory Management		1		
Regulatory Management		1		
Regulatory Management		1		
Regulatory Management		1		
Business Unit/Franchise/Division	1			
Regulatory Management		1		
Managing Director/CEO			1	
Business Unit/Franchise/Division	1			
Managing Director/CEO			1	
Managing Director/CEO			1	
Managing Director/CEO			1	
Quality Management				1
Regulatory Management		1		
Quality Management				1
Quality Management				1
Managing Director/CEO			1	
Quality Management				1
Quality Management				1
Regulatory Management		1		
Business Unit/Franchise/Division	1			
Quality Management				1
Regulatory Management		1		
Managing Director/CEO			1	
Quality Management				1
Managing Director/CEO			1	
Regulatory Management		1		
Quality Management				1
Regulatory Management		1		
Business Unit/Franchise/Division	1			
Regulatory Management		1		

5.11 Question 17, 18, 19 & 20 Government Affairs

Does your company have a government affairs department?	How often do the government affairs department publish information?	In your role as a regulatory affairs professional, do you think it is important to stay informed on government affairs?	As a regulatory affairs professional, when you develop a regulatory strategy for a product do you incorporate the impact government affairs changes could have on the regulatory strategy e.g. Brexit?
Response	Response	Response	Response
Yes	Weekly	Slightly important	Rarely
I don't know	Not applicable	Important	Sometimes
Yes	Weekly	Fairly Important	Rarely
I don't know	Not applicable	Important	Rarely
No	Not applicable	Very Important	Never
Yes	Monthly	Important	Rarely
No	Not applicable	Very Important	Often
I don't know	Weekly	Fairly Important	Never
I don't know	Not applicable	Fairly Important	Rarely
No	Not applicable	Important	Sometimes
Yes	Weekly	Important	Rarely
No	Not applicable	Fairly Important	Sometimes
Yes	Not applicable	Important	Rarely
No	Not applicable	Very Important	Rarely
No	Not applicable	Fairly Important	Often
No	Not applicable	Fairly Important	Always
No	Not applicable	Fairly Important	Rarely
Yes	Quarterly	Slightly important	Sometimes
No	Not applicable	Important	Sometimes
I don't know	Not applicable	Important	Sometimes
No	Not applicable	Fairly Important	Often
No	Not applicable	Important	Often
No	Not applicable	Important	Sometimes
I don't know	Not applicable	Slightly important	Rarely
No	Not applicable	Very Important	Sometimes
No	Not applicable	Slightly important	Never
No	Not applicable	Very Important	Never
No	Not applicable	Very Important	Never
No	Not applicable	Important	Rarely
No	Not applicable	Slightly important	Sometimes
I don't know	Not applicable	Important	Rarely
No	Not applicable	Very Important	Rarely
Yes	Monthly	Very Important	Never
I don't know	Not applicable	Very Important	Rarely
I don't know	Not applicable	Important	Rarely