Multiregional Medical Device Registration
by
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Title: Multiregional Medical Device Registration

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<u>Declaration:</u>

"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".

Martha Julie Folan.

Abstract:

The landscape of multiregional medical device registration is an area with highly variable regulations, varying regulator application and expectations, alongside swift changes in some regions.

Accessing international medical device markets is a key growth strategy from a business perspective and an important component for the commercialisation of medical device portfolios.

This dissertation outlines medical device registration requirements for specific regions of business growth, outside the European approval system and USA FDA clearances. Those requirements are embedded as an input into a design control process and a proposed Global Registration Dossier, to ensure delivery of all regional requirements to support regional submissions. The optimal proposed dossier will be the result of, a mapping exercise of the main regulatory submission formats that are currently used, in addition to registration benchmarking in conjunction with the literature review.

The proposed Global Registration Dossier format will support a business, to deliver information that meets global registration requirements and enable timely access to this essential information. This will reduce delays in submitting devices to the appropriate regulatory agencies in the differing regions and in turn have a positive impact on the business, by means of faster approval times.

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1.1 Global medical device registration:

Unlike most industries, strict regulatory oversight exists in the medical device industry primarily to mitigate against potential risks to human health (O' Dwyer & Cormician, 2017). Globally, regulation and registration processes dictate that medical device manufacturers demonstrate the safety, performance and efficacy of their products prior to being granted market access. For medical device companies, gaining and maintaining regulatory compliance is essential and synonymous with market access and ongoing trade viability, but it is also expensive, time-consuming and risky (Engberg & Altman, 2015). It is vital that medical device companies learn how to manage regulatory and innovation demands simultaneously, for the sake of their businesses and the patients they serve (O'Dwyer & Cormician, 2017).

Wong and Kaiyu (2013) discuss that historically, the role of the regulatory affairs function within medical device companies has been more tactical than strategic. While this tactical focus has served the industry well in the past, regulatory authorities around the world are raising the bar for market access. "Regulatory reforms as well as the increased availability of real-world safety and efficacy data continue to alter the path to approval and the underlying investment case for medical devices. Globalization will also play a key role in shifting regulatory requirements. New regulatory frameworks are evolving and regional partnerships will be the main driver of harmonization going forward, especially in the Asia-Pacific" (Wong & Kaiyu, 2013).

This dissertation will outline medical device registration requirements for specific regions of business growth, outside the European approval system and USA FDA clearances. These Countries have been chosen as target business markets because accessing medical device markets outside both (EU & USA) jurisdictions is a key growth strategy from a business perspective and an important component for the overall regulatory strategy of medical device portfolios.

In Vitro Diagnostic (IVD) products and reimbursement strategies for medical devices are not within the scope of this dissertation due the differing regulatory

requirements for IVD products and the complexities of reimbursement applications.

1.2 Background:

Substantial business growth opportunities lie outside of the US and Europe in the medical device industry. As per the U.S. Department of Commerce, the USA, Japan, and Europe are the largest markets but are reaching saturation point with annual growth rates of between 3% and 5% (marketrealist, 2015). Asia's healthcare landscape is changing in parallel with its burgeoning middle class. China, India and ASEAN's middle classes are expected to grow by around 100 million people in the next ten years. India's next five-year plan is poised to increase the healthcare expenditure to 3% of GDP and to 5% by 2020. In 2013, Wong and Kaiyu estimated the Indian medical device industry to be approximately US$ 3.0 billion and the medical equipment industry is around half a billion, and is growing at a rate of over 15%. Asia's demand for healthcare will continue to grow with more people able to afford the care (Pacific Bridge Medical, 2017). As per the same source, US medical devices constitute 30% of devices that are imported into Brazil.

China's economic growth is slowing down, but the medical device industry is still on the rise. The Chinese medical device industry was valued at US$18.8 billion in 2016 and is projected to grow modestly through 2019, when it should reach over US$24 billion (Emergo, 2017). The South Korea device market is ranked third largest medical device market in Asia Pacific counties, behind Japan and China and while its market is slowing down it will still outperform mature markets such as New Zealand and Australia (Cision, 2016).

In Latin America, the Countries, Brazil, Mexico, Columbia, Chile and Argentina when combined, represent the third largest economy in the world with a healthcare expenditure comparable to China and India (Emergo, 2015).

Saudi Arabia, in the Middle East has the most established regulatory framework with the largest and most technologically advanced health care system in the Gulf Corporation Council and other states are jockeying to bring their systems to a comparable or higher level (Howard, 2014). Hong Kong is a prosperous economy and acts as a hub for trade throughout Asia.   Likewise, in Australia the medical device market is one of the wealthiest healthcare markets in Asia-Pacific,

Australia's spending on health is at par with European markets such as Finland, Norway and the United Kingdom. Like so many other developed countries in the world, increased life expectancy, income and demands for a higher quality of life are driving an increase in health expenditure (Wong and Kaiyu, 2013). Turkey is the 16th largest economy in the world and the 6th largest in Europe with a robust economic growth at an average annual GDP growth of 6.7% between 2010 and 2016 (Demir, 2017).

1.3 Research objective and research questions:

Due to the trajectory of market growth and the subsequent business opportunities in emerging markets, a proposed Global Registration Dossier will support a business, in enabling different regions to have available and access essential information to submit registrations in a timely manner, facilitating commercial availability of product in the region. The aim of the dissertation is to collate registration requirements for the market regions outlined in table 1, so as to embed those requirements into a design control process, to ensure delivery of regional requirements to support regional submissions. These countries have been chosen for their market growth potential.

Australia	Egypt	Russia
Argentina	Hong Kong	Saudi Arabia
Brazil	India	Singapore
Canada	Japan	South Korea
China	Malaysia	Taiwan
Columbia	Mexico	Turkey

Table 1. Countries in the scope of dissertation.

Using these global regulatory registration requirements as an input, this thesis will outline how they are considered in existing design control and development processes of a product. In addition, understanding these requirements will assist

in identifying where a company can reduce registration time in some markets once the device is available for first commercialisation. Elements of the dissertation will include the registration requirements as a foundation to propose a Global Registration Dossier format for medical devices that will facilitate worldwide submissions.

Section 2, reviews the literature with respect to the registration requirements in the identified regions. It outlines the current influences and challenges that medical device manufacturers face, in the registration of medical devices in a global environment.

Section 3 outlines the methodology of this dissertation. The findings from the literature and benchmarking are discussed in Section 4, which proposes a Global Registration Dossier format and provides the context to the role it plays in New Product Introduction/Design Control process.

Chapter 2 Literature Review:

2.1 Introduction

Multiregional registration of medical device products is varied and complex for many manufacturers regardless of company size from start up to multinational. Regulatory requirements range from comprehensive reviews by regulatory agencies with well-established regulatory frameworks to voluntary or no requirements in some emerging economies. The principle objective of medical device regulation is to protect patients and enhance the medical care of the country (Tamura & Kutsumi, 2014). Additional influences in the regulatory sphere are the voluntary agencies such as International Medical Device Regulatory Forum (IMDRF) and its affiliate organizations such as the Asian Harmonization Working Party (AHWP), the Pan American Health Organization (PAHO) and the Asia Pacific Economic Cooperation (APEC), whose aims include international medical device regulatory harmonization and convergence. This chapter explores an overview of the regulations and a summary of main points for registration in specific countries and the challenges faced which are identified in the literature. The literature protocol is outlined in section 3. These regions have been chosen due to potentially lucrative sales and reimbursement markets.

This section is not intended to be a registration manual, but rather provide an overview for the regulations and regulatory agencies. It provides a context for the differences between regions and the differing registration requirements. To facilitate this context, the discussion is around countries outside of the United States and Europe. However, these regions will be referred to, as typically these approvals support the first markets into which the products are launched. This section will also consider the efforts of global harmonization of medical device approval.

2.2 Overview of the Regulations

2.2.1 Australia:

2.2.1.1 Regulator:

Therapeutic Goods Administration (TGA) is a division of the   Australian Government's Department of Health and Aging.

2.2.1.2 Regulation:

Therapeutic Goods (medical devices) Regulations 2002.

2.2.1.3 Device Classification:

Risk based classification system based on rules and the intended purpose of the device. Class I lowest risk to Class III higher risk device.

2.2.1.4 Representation in country:

Appointment of an Australian Sponsor on

behalf of the manufacturer is mandatory (ARGMD, tga.gov 2011).

2.2.1.5 Overview of how to register:

The appointed Sponsor on behalf of the manufacturer will submit 'Manufacturer's Evidence' for all devices except Class I non-sterile devices. Manufacturer's evidence is the substantive evidence that the manufacturer's Quality Management System supports the scope of manufacture. Manufacturers evidence may consist of either conformity assessment certificates issued by TGA, EC Certificates to the European Medical Device Directives or Mutual Recognition Agreements (MRA) certificates issued by a European Notified Body. One of the above conformity assessment certificates must be accepted by TGA prior to commencing product registration. Australia has a bilateral Mutual Recognition Agreement (MRA) with the EU in relation to Conformity Assessment.   This means on principle both jurisdictions recognise the conformity assessment procedures and assessment bodies in the other jurisdiction for the purposes of product assessment (ARGMD, tga.gov, 2011).   It is to be noted that TGA have suspended MRA for class III products until such a time that 'confidence building' measures have been completed (TUV.SUD, 2012). Anecdotally these 'confidence building' measures will most likely be reviewed after the implementation of the new Medical Device Regulation in Europe. This

reduces some of the review burden but does not eliminate it. The level of review during device submissions is dependent on the classification of the device. Class III review entails a mandatory level two audit which includes an in-depth review of the product clinical evaluation report.

The TGA will either approve or reject the application. If approved, an Australian Register of Therapeutic Goods (ARTG) listing number will be issued (ARTG Certificate of Inclusion) and the listing will be included on the ARTG database on the TGA website (tga.gov.au).

2.2.1.6 Primary documents required:

Australian Declaration of Conformity, Australian Essential Principles, labels, product brochures, Instructions for Use. For Class III devices in addition to the initial review, a mandatory Level 2 audit entails TGA requesting the device Clinical Evaluation Report and risk management documents (ARGMD, 2017).

2.2.2 Argentina:

2.2.2.1 Regulator:

Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (National Administration of Drugs, Food and Medical Technology) ANMAT (anmat, 2017).

2.2.2.2 Regulation:

ANMAT Provision 727-2013 (Emergo, 2013).

2.2.2.3 Device Classification:

Risk based classification (I, II, III, VI) with class I a low risk and class IV high risk device.

2.2.2.4 Representation in Country:

Local Authorised Representative (LAR) required.

2.2.2.5 Overview of how to register:

Imported medical products need to be registered with ANMAT through an authorized medical importer. The product registration process may take from 4 to 12 months (Emergo, 2013).

Documentation required may vary according to product and can also depend on what the ANMAT evaluator requires on a case by case basis. In general, the following documents are required:

- Letter or Certificate of Representation/Distribution in Spanish with an apostille,
- Users or Technical manual (in Spanish),
- Essential Principles,
- Brochures and labels (Merit Medical, 2016).

Additional documents that may be required are: electrical safety certification, manufacturing flowchart process and description; sterilization methods and parameters; scientific or clinical evidence report and Certificate of Foreign Government (CFG) (export.gov, 2016).

2.2.2.6 Primary documents required:

Submission dossier and labels must be provided in Spanish. Approval once granted is valid for five years.

2.2.3. Brazil

2.2.3.1 Regulator:

Agência Nacional de Vigilância Sanitária (National Sanitary Surveillance Agency) ANVISA.

2.2.3.2 Regulation:

Brazilian Ministry of Health, under Article 12 of Law No. 6360 of September 23, 1976, published in the Official Gazette of September 24, 1976(Pedrosa, 2014).

2.2.3.3 Device Classification:

Risk based classification with Class I low risk devices and class IV high risk devices. Medical devices are classified using the classification rules in Annex II of Resolution RDC No. 185/2001 Registration of medical devices (Pedrosa, 2014).

2.2.3.4 Representation in Country:

Foreign manufacturers need to appoint a Brazil Registration Holder (BRH) if there is no company representative in the Country.

2.2.3.5 Overview of how to register:

Manufactures require a Marketing Authorisation from ANVISA prior to placing products on the market.

Prior to importing the manufacturing site must undergo an audit to ensure it complies to BGMP (Brazil Good Manufacturing Practices) by ANVISA for higher class (Class III and IV) devices (Theisz, 2015). A period of 2-3 years should be allowed for the completion of the BGMP audit or 1 year through the Medical Device Single Audit procedure (MDSAP) procedure. Resolution No. 15/2014 introduced and exemption from GMP certification for class I and II devices. Higher risk devices require the *registro* submission route and lower risk devices require the abbreviated *cadastro* submission route. In addition, electrical devices and devices with a measuring function must also obtain National Institute of Metrology, Quality and Technology (INMETRO) certification prior to registration with ANVISA, which involves testing and certification by organisations accredited by INMETRO (Theisz, 2015). The INMETRO certificate allows the manufacture to affix an INMETRO certification mark on its products. *Cadastro* no longer are subject to expiry(Merit Medical, 2016). There is a necessity to maintain a local Technical file in Portuguese which must be in place by August 2018 and which ANVISA may review at any time (Merit, 2016). *Registro's* are valid for five years and require annual factory inspections.

2.2.3.6 Primary documents required:

Cadastro and *Registro* application must follow the content and format defined in Resolutions RDC No 185/2001 for medical devices (Theisz, 2015).

2.2.4 Canada

2.2.4.1 Regulator:

Health Canada

2.2.4.2 Regulation:

Canadian Medical Device Regulation

2.2.4.3 Device Classification:

Four risk classifications I, II, III and IV, with class I, the lowest risk category and class IV the highest risk (Canada.ca, 2017).

2.2.4.4 Representation in Country:

Not Required

2.2.4.5 Overview of how to register:

Class I devices are regulated by the Medical Device Establishment licence (MDEL) which is held by the manufacturer or distributor. While a licence is not required, the licence holder must have evidence that a device complies to the safety and efficacy principles as per sections 10-20 of the regulation. Licence holders can have this information requested at any time. Class II, III and IV require a Canadian product Medical Device Licence (MDL) and ISO13485 Quality Management System (QMS) accreditation. The company's ISO 13485 QMS must also be CMDCAS (Canadian Medical Device Conformity Assessment Scheme) certified. There is no expiry on the licence but an annual confirmation that the information that Health Canada have on file for the device is required and if not completed the licence is cancelled (Canada.ca, 2017).

On January 1st, 2019 Health Canada will only accept Medical Device Single Audit Program (MDSAP) certificates (Health Canada, 2015) MDSAP is discussed in more detail in section 2.4.3.

2.2.4.6 Primary documents required:

For Class II devices submit a Medical Device Licence application with CMDCAS ISO13485 certification, Declaration of Conformity and device Instructions for Use.

For Class III and IV the application will require Quality Plan, Risk Management documents, device information and for Class IV Clinical evidence data.

2.2.5 China

2.2.5.1 Regulator:

China Food and Drug Administration (CFDA).

2.2.5.2 Regulation:

Regulations for the Supervision and Administration of Medical Devices (SC [2014] Decree No 650) (CFDA.Gov, 2017 & Lueddemann *et al*, 2016).

2.2.5.3 Device Classification:

Risk based classification system with class I lower risk product and class III high risk devices (Ramakrishna *et al*, 2015). Classification is determined based on the application code and the generic product name. CFDA decree No.15, The Rules for Classification of Medical Devices, January 1, 2016 outlines classification rule (CFDA.gov, 2017).

2.2.5.4 Representation in Country:

Companies outside China must designate an agent located in China who will coordinate your CFDA device registration (Lueddemann *et al*, 2016).

There are three distinct types of agent required. These roles can be performed by three separate entities or a single entity. The three types of agent and their key responsibilities are listed below:

- Registration Agent: The company that registers the product is the registration agent.

- After Sales Agent: The after sales agent provides technical service and support for the medical device product. The business scope described in the business license of the local legal Chinese entity must include a provision stating that the after sales agent will provide such services.

- Legal Agent: The legal agent's key responsibilities include: a) reporting any adverse events regarding the medical device that occur inside or outside China to the CFDA; and b) handling any recall issues as they arise, as well as other regulatory matters.

A device manufacturer also may set up its own legal structure in China, called a Wholly Foreign Owned Enterprise (WFOE), and thus act as its own China agent(s) (Folan & O'Connor, 2017).

2.2.5.5 Overview of how to register:

Having CE Mark (EU) approval, demonstrated in the form of a Certificate of Free Sale (CFS) or USA FDA approval in the form of a Certificate of Foreign Government (CFG) is required. In addition, a notarised copy of the manufacturing facilities ISO 13485 Certificate is also required to satisfy the requirement for proof of qualification of the manufacturer.

The "Product Technical Standard document" is prepared according to CFDA [2014] No. 9 (Lueddemann *et al* ,2016). Review the Chinese Medical Device Evaluation Centre websites to ensure compliance with the Technical Review Guidelines and consult the China company agent to ensure you have included sufficient detail to conduct the 'type testing' to be performed in state approved Test Labs in China. Devices are sent for testing to a CFDA authorized Medical Device Evaluation Centre, ensuring that the chosen centre has the requisite

technology certification to perform all the required testing on your device (Zhang *et al*, 2016).

Primary documents required:

For Class I devices an application filing with CDFA is appropriate. For class II and III devices the STED format registration dossier is required for CMDE technical review. For both class II and III classifications type testing reports from a China accredited lab are required and unless exempt, China clinical trials. The registration package includes the following: Testing reports, Agent authorization letter, Certificate of Free Sale, Clinical Evaluation report and all the product technical documents (Lueddemann *et al*, 2016). All documents must be in Simplified Chinese when submitted to CFDA for review. The submission fee is required as part of the application process to CFDA (Zhang *et al*, 2016). Following a successful review, the CFDA issues a registration certificate and publishes it on the CFDA website. Certificates are valid for 5 years. Once the certificate is issued the device may be made available commercially (Emergo, 2016).

2.2.6 Columbia:

2.2.6.1 Regulator:

Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA)(invima.gov.co).

2.2.6.2 Regulation:

4725 Decree of 2005 (IMDRF, 2016).

2.2.6.3 Device Classification:

Class I, Class IIa, Class IIb or Class III.

2.2.6.4 Representation in Country:

Legal Representative if there is no in-country presence.

2.2.6.5 Overview of how to register:

Provide a Certificate of Free Sale (CFS) or Certificate to Foreign Government (CFG) to demonstrate that your device can be legally sold in your home market or Australia, Canada, Japan or the US.

For Classes IIa, IIb, and III, provide test reports. Provide clinical data for Class

IIb and III devices. INVIMA automatically approves Class I and IIa applications, so the company may begin selling right away (Merit Medical, 2016). The agency will still review the application and manufacturers must respond to any additional information requests within 30 days. Failure to comply will result in approval being revoked.

For Class IIb and Class III devices, INVIMA must review and approve the application prior to commencing commercialisation; the review could take 4-6 months. During this review, INVIMA may ask follow-up questions or request additional information. Once approved, INVIMA will issue the registration certificate (Merit Medical, 2016). The company may begin marketing the device in Colombia. Registrations are valid for 10 years. For Class I and IIa devices, once INVIMA receives the application for renewal, the registration will be automatically renewed. For Class IIb and III devices, application renewals are due to INVIMA three (3) months before the expiration of the registration certificate (Emergo, 2016).

2.2.6.6 Primary documents required:

Certificate of Free Sales (CFS) or Certificate of Foreign Government (CFG) QMS Certification, registration application dossier including detailed device information and test reports. Documents must be submitted in Spanish (IMDRF, 2016).

2.2.7 Egypt:

2.2.7.1 Regulator:

Central Administration of Pharmaceutical Affairs (CAPA), and Drug Policy and Planning Centre (DPPC) divisions of the Egyptian Ministry of Health.

2.2.7.2 Regulation:

Egyptian Regulation for Medical Devices (eda.mohp.gov.eg., 2017).

2.2.7.3 Device Classification:

Class I, IIa, IIb and III Risk based classification aligned with Europe.

2.2.7.4 Representation in Country:

If there is no in country representative, an authorized representative, Egypt Registration Holder, needs to be appointed.

2.2.7.5 Overview of how to register:

DPPC is responsible for reviewing and approving Class I, IIa and IIb medical devices. These products can be sold while registration is under review. Class III medical devices are registered at CAPA and can be sold only after receiving approval. The process involves emailing for an appointment with the registration department who will subsequently send an appointment within 5 days. The appoint can be 2-3 months out and at this appointment the file is submitted. An approval timeline of 4 to 6 months can be expected (eda.mohp.gov.eg., 2017). A 'Letter of Exemption' enables sales during the registration process (Merit Medical, 2016).

2.2.7.6 Primary documents required:

Clinical data, test reports and other data to support the safety and efficacy of the device, as required (Emergo, 2017). Due to misbranding incidences in 2016 specific requirements have been introduced such as;

- The device 'Country of Origin' information is required on every level of labeling.
- Particular requirements are requested on the Declaration of Conformity (eda.mohp.gov.eg., 2017).
- Statement letters are requested from the manufacturers and
- Samples can be requested for product testing.

2.2.8 Hong Kong:

2.2.8.1 Regulator:

Medical Device Control Office (MDCO), Department of Health Hong Kong.

2.2.8.2 Regulation:

Voluntary Listing since 2004. Hong Kong currently has no mandatory registration for medical devices, but manufacturers and importers can opt for voluntary registration of Class II, III, and IV devices under the Medical Device Administrative Control System (MDACS) (mdco.gov.hk, 2017). The government intends to make the MDACS a mandatory system soon (Pacific

Bridge Medical, 2016). At time of dissertation submission (2017) this is expected in the next 1-2 years.

2.2.8.3 Device Classification:

A listing of device classifications from class I to class IV.

2.2.8.4 Representation in Country:

A Local Representative Person (LPR) is mandatory. The LRP must be either the manufacturer of the device or accredited by the manufacturer to perform the duties of the LRP (TUV-SUD, 2016).

2.2.8.5 Overview of how to register:

Voluntary registration. Class I are exempt. Class II, III and IV require reference country approvals (Europe, United States, Japan, Australia and Canada) (mdco.gov.hk, 2017).

2.2.8.6 Primary documents required:

Essential Principles, risk documents, product brochures and labelling. The licence when issued is valid for five years and should be renewed six months in advance of expiration (Pacific Bridge Medical, 2016).

2.2.9 India:

2.2.9.1 Regulator:

Ministry of Health and Family Welfare and the Central Drugs Standards Control Organization (CDSCO)/Drug Controller General of India (DCGI).

2.2.9.2 Regulation:

Drug Regulations under Drug and Cosmetics Act of 1940 and Drugs and Cosmetics rule 1945 (cdsco.nic.in).

New legislation the "Medical Device Rules 2017" by the Ministry's Central Drugs Standard Control Organization (CDSCO), will replace India's longstanding Drugs and Cosmetics Act and will become effective Jan 1[st,] 2018 (Raps.org, 2017).

2.2.9.3 Device Classification:

Limited number of devices require registration and are on a list of Notified Medical Devices.

2.2.9.4 Representation in Country:

India Authorised Agent to be appointed if there is no in country presence.

2.2.9.5 Overview of how to register:

If the device being registered is on the notified devices list compile a device application that includes the company providing Power of Attorney to the Indian Agent, assembling 'Schedule D1, a Plant Master File' and 'Schedule D2 a manufacturing 'Site Master File' along with Form 40, file application with CDSCO fees (cidco.nih.in, 2013). CDSCO will issue a registration Certificate (Form 41) which is valid for three years. Once your distributor is identified you can apply for import licence which will be issued in the name of your identified distributor (Emergo, 2016).

2.2.9.6 Primary documents required:

Application as per Form 40, Schedule D1, Plant Master File, Schedule D2, Site Master File, ISO13485 Certification, proof of approval in reference countries and proof of approval in home country (cidco.nih.in, 2013).

2.2.10 Japan:

2.2.10.1 Regulator:

Pharmaceutical and Medical Devices Agency (PMDA) is part of the Ministry of Health Labour and Welfare (MHLW).

2.2.10.2 Regulation:

Pharmaceutical and Medical Device Law (PMD Law) 2014.

2.2.10.3 Device Classification:

Risk based classification system, Class I low risk, to Class IV high risk devices (Ramakrishna *et al*, 2015).

2.2.10.4 Representation in Country:

Marketing Authorization Holder (MAH) or Designated Marketing Authorization Holder (DMAH).

2.2.10.5 Overview of how to register:

Class I are low risk and are Notified to PMDA, Class II (low/medium risk) are 'specified controlled' and require pre-market Certification or *Ninsho*. Third party certification is used for *Ninsho* services. A *Ninsho* pathway followed where a JIS (Japanese Industrial Standard) exists. If there is no JIS for the device then the

Shonin approval route is to be followed. Class II Controlled are medium risk devices (Altenstetter, 2014). Highly controlled devices Class III (medium/high risk) and Class IV are high risk devices. Pre-Market Approval (PMA or *Shonin)* is required for Controlled Class II, Class III and Class IV devices (Altenstetter, 2014). Foreign manufacturers must register their manufacturing facilities with the Ministry of Health, Labour and Welfare (MHLW) though the Pharmaceutical s and Medical Devices Agency(PMDA). This is referred to as a Foreign Manufacturer Registration and this is valid for five years (TUV.SU, 2016). To register a medical device the application of a Quality Management System (QMS) Conformity Assessment must be submitted in conjuction with the Premarket Approval submission. The registered manufacturers sites will be listed on Japans Quality Management System (Japan Ordinance #169) (Altenstetter, 2014). In addition, a warehouse manufacturer is appointed, this is a registered entity that receive incoming product shipments and is named on the device registration application (TUV SUD, 2016).

2.2.10.6 Primary documents required:

A submission file is submitted that is not unlike the STED format. In addition, the following information is included, JMDN Code and device classification, details of use in foreign countries. If the device is a novel product and has no predicate already registered in Japan, clinical data is required. Foreign clinical trial data can be used for Japan PMA submission if PMDA accepts the extrapolation of foreign clinical trial considering the following points, racial differences between Japanese or Asian subjects and other patient populations, existing surgical techniques in Japan and the design of the foreign clinical trial.

2.2.11 Malaysia

2.2.11.1 Regulator:

Medical Device Authority (MDA) under the Ministry of Health, Malaysia

2.2.11.2 Regulation:

Medical Device Act 2012 (Act 737) and Medical Device Regulations 2012. (TUV.SUD, 2016). End of voluntary registration and enforcement of Mandatory registration effective July 1[st,] 2016.

2.2.11.3 Device Classification:

Medical devices in Malaysia are classified according to rules listed in Medical Device Regulations 2012, Appendix 1 of Schedule 1. Medical devices are classified as Class A (low risk), Class B (low to moderate risk), Class C (moderate to high risk), and Class D (highest risk) (mdb.gov.my, 2017).

2.2.11.4 Representation in Country:

Authorised Representative (AR) required (mdb.gov.my, 2017).

2.2.11.5 Overview of how to register:

While the MDA ultimately approves or rejects medical device applications, a third-party review by a Conformity Assessment Body (CAB) is also required. Act 737 has delegated conformity assessment duties to the CABs (TUV SUD, 2016).

Registered CABs conduct conformity assessments for classification B to D to ensure compliance to Malaysian medical device regulatory requirements and are listed on the MDA Website (mdb.gov.my, 2017). Upon successful review, the CAB issues a certificate that becomes part of the medical device registration application (mdb.gov.my, 2017). If a device has been approved in one of the recognized reference markets (US, Europe, Australia, Japan, and/or Canada), the manufacturer can utilize this approval and complete an abridged CAB review. This simplified process provides CAB review based on a verification of evidence based compliance in one of the reference markets. When the registration fee has been paid and the application is approved, the MDA issues a Certificate of Registration. Once registered, a medical device listing is valid for five years (Emergo, 2017).

2.2.11.6 Primary documents required:

An application for medical device registration is submitted online by the Authorized Representative using the MDA Medical Device Centralized Online Application System called MEDCAST, (TUV SUD, 2016). The application includes the following:

Common Submission Dossier Template (CSDT) for device classification B to D. All documents are submitted in electronic format. Official certificates must be accompanied by a Certified True Copy statement (Emergo, 2017).

2.2.12 Mexico:

2.2.12.1 Regulator:

COFEPRIS –Federal Commission for Protection Against Sanitary Risks (cofepros.gov.mx, 2017).

2.2.12.2 Regulation:

Registrations: LGS (General Law of Health) –RIS (Rule for Health Supplies) and GMP: RIS Art 180, Normative NOM 241-SSA1-2012.

2.2.12.3 Device Classification:

Risk based 3 tier classifications, Class I is low risk with Class III high risk medical devices.

COFEPRIS also provides a list of products considered Class I Low Risk, which are still regulated but have faster review and approval times (Emergo, 2017).

2.2.12.4 Representation in Country:

Appoint a Mexican Registration Holder if no presence in country.

2.2.12.5 Overview of how to register:

Class I Low Risk devices require an application with basic company and device information to COFEPRIS, these have a very fast turnaround time. There are alternate paths for approval of devices;

- Authorized Third Party (ATP) where a third-party Conformity Assessment Body (CAB) approved by COFEPRIS. The ATP process takes between 3 to 4 months.
- Equivalence Process which levers off either US or Canadian approval and takes between 8 and 10 months.
- Standard process involves a full submission review by COFEPRIS and takes up to 18 months (Merit Medical LATAM, 2016).

Registration certificates if approved are valid for five years.

2.2.12.5 Primary documents required:

If the country of origin is either USA or Canada, a Certificate of Foreign Government (CFG) and Establishment Investigation Record (EIR) or CMDCAS Inspection Report and Canadian Medical Device Licence respectively are

required. Technical Document summary document, labels and certificate of Analysis (COA) in addition of Letter of Authorization (LOA). These documents are used to support the dossier for submission (Merit Medical LATAM, 2016).

2.2.13 Russia:

2.2.13.1 Regulator:

Federal Service for Surveillance in Healthcare (Roszdravnadzor (RZDN)).

2.2.13.2 Regulation:

Resolution (Decree) #1416 Approval of Regulation of the State Registration of Medical Devices (roszdravnadzor.ru, 2017 & Stepanov, 2017).

2.2.13.4 Device Classification:

Risk based classification aligned with Europe, four classes, I, IIa, IIb and III with Class I being low risk and Class III highest risk (Kalachev, 2017).

2.2.13.5 Representation in Country:

Authorised Manufacturers Representative (AMR)

2.2.13.6 Overview of how to register:

There are several cycles in the Russian Registration process, including the requirements for product testing irrespective of any regulatory approvals in other jurisdictions. Resolution No. 4043, dated 27/4/2017, chapter III, contains an exhaustive checklist of requirements which may be checked during inspections (Stepanov, 2017).

Stage 1, the manufacturer prepares a submission dossier including technical, toxicological data and organises product samples and these are provided to the RZDN. The RZDN will then provide this submission to an 'expertise centre'. The expertise centre will review the information and can request additional information during this review. When the information has been reviewed the expertise centre will provide their opinion to RZDN which is either to reject the application or proceed to the next step, which is the clinical evidence review or clinical trial. Once permission is provided to continue to the clinical trial the registration process is stopped until this stage is complete. Upon successful completion of the clinical trial the registration process is restarted and an additional submission file is submitted to RZDN (Merit Medical, 2016). Again, this is reviewed with the expertise centre and there may be additional information

required. The expertise centre will provide its recommendation to RZDN to either approve or reject the submission. If approved the RZDN issues a Registration Certificate. This does not expire unless the manufacturer makes changes to the device, changes their manufacturing address or changes their contact details. The Registration is published on the database of the RZDN website.

2.2.13.7 Primary documents required:

Biological testing including- Toxicology testing and all Design Verification/Design Validation technical reports (roszdravnadzor.ru, 2017).

2.2.14 Saudi Arabia:

2.2.14.1 Regulator:

Saudi Arabian Food and Drug authority (SFDA).

2.2.14.2 Regulation:

Medical Devices Interim Regulation (MDIR) & Implementing Rules 1-8 (sfda.gov.sa, 2017).

2.2.14.3 Device Classification:

Class I (low risk) Class IIa, IIb and Class III (high risk).

2.2.14.4 Representation in Country:

Local Authorised Representative required (MDS-IR6, 2017).

2.2.14.5 Overview of how to register:

Medical Devices National Registry (MDNR) for establishment registration (MDEL) and medical device listing

Medical Device Market Authorization (MDMA).

–Authorized Representative (AR) needs to be appointment & AR Agreement needed for obtaining Authorized Representative license.

–Device must have prior authorization in one of the IMDRF markets (Australia, Canada, USA, Europe and/or Japan).

All marketing material must be approved by SFDA before use in Kingdom of Saudi Arabia by the Authorized Representative (MDS-IR6, 2017).

2.2.14.6 Primary documents required:

Safety data, including information on intended use, warnings, precautions and potential adverse events (Howard, 2014).

2.2.15 Singapore:

2.2.15.1 Regulator:

Medical Device Branch under the Health Sciences Authority (HSA).

2.2.15.2 Regulation:

Health Products Act 2007 and Health Products (Medical Devices) Regulations 2010 (Ramakrishna *et al*, 2015).

2.2.15.3 Device Classification:

Device classification in Singapore is based on a four-tier system (Class A, B, C, and D), with Class A assigned to the lowest-risk products and Class D assigned to the highest-risk products (Ramakrishna *et al*, 2015). Device Classification is determined by referencing the Health Sciences Authority's GN-13: *Guidance on the Risk Classification of General Medical Devices* (HSA.gov.sg, 2017).

2.2.15.4 Representation in Country:

In Country Registrant must be appointed.

2.2.15.5 Overview of how to register:

Class A, non-sterile devices are exempt from registration, however they must still conform to the Essential Principles for Safety and Performance for medical devices (HSA.gov, GN-02, 2015). All other device classifications require mandatory registration. Singapore utilises an electronic system and multiple registration pathways are available dependant on device classification.

Class A sterile devices are registered upon submission of application dossier via the Medical Device Information and Communication System (MEDICS). After review of the dossier if no additional questions are outstanding the regulatory decision is listed on the SMDR. For a successful registration, this process takes approximately one month.

 There are 4 evaluation routes for Class B Medical Devices (HSA.gov GN-15, 2014):

1. Full Evaluation Route – A medical device that has not obtained any prior approval from any of HSA's reference regulatory agencies at the point of application will be subject to the full evaluation route.

2. Abridged Evaluation Route – To qualify, a medical device must have obtained at least one regulatory agency approval for a labelled use identical to the one intended for marketing in Singapore at the time of submission.

3. Expedited Class B Registration (EBR) Evaluation Route

   To qualify for Expedited registration, at the time of the submission the medical device must have the following approval from at least one of HSA's independent reference regulatory agencies, for a labelled use identical to the one intended for marketing in Singapore and marketed for at least three years in the above independent reference regulatory agency's jurisdiction and no safety issues globally with the use of the device.

4. Immediate Class B Registration (IBR) Evaluation Route

   To qualify for the IBR evaluation route, at the time of the submission the medical device must have approval from at least two of HSA's independent reference regulatory agencies for a labelled use identical to the one intended for marketing in Singapore and marketed for at least three years in two of the above independent reference regulatory agencies (IMDRF Members) jurisdiction and no safety issues globally in the past three years. In addition, there must be no regulatory agency rejection or withdrawal of device submission in any of the reference country. Process for Evaluation Routes (1-3) Above: is the submission of application via MEDICS, verification of the application, regulatory review and if accepted listing on SMDR for successful registration (HSA.gov GN-15, 2014) .

Process for the IBR Evaluation Route: Class C & D Medical Devices. There are 3 evaluation routes for Class C & D Medical devices:

1. Full Evaluation Route (qualifications as defined above for Class B).

2. Abridged Evaluation Route (qualifications as defined above for Class B).

3. Expedited Evaluation Route:
   - Expedited Class C Registration (ECR) – the same requirements as per Class B.
   - Expedited Class D Registration (EDR) – the same requirements as per Class B (HSA.gov GN-15, 2014).

There are several devices that do not qualify for the Expedited registration.

A successful regulatory decision will result in a listing on SMDR (Pacific Bridge Medical, 2017).

2.2.15.6 Primary documents required:

The HSA submission dossier, or technical file, is based on the ASEAN CSDT (Common Submission Dossier Format). The information required in the submission depends on your device classification and the selected evaluation route. The manufacturer must also prepare a Declaration of Conformity to the Essential Principles. Once approved, the product is listed in the Singapore Medical Device Register (SMDR) database.

2.2.16 South Korea:

2.2.16.1 Regulator:

Ministry of Food and Drug Safety (MFDS)

2.2.16.2 Regulation:

Medical Devices Act (mfds.gov.kr, 2017).

2.2.16.3 Device Classification:

Risk classification system with Class I lower risk and Class IV high risk Also devices can be classified into one of three main types; New (novel) product, Improved product or an Equivalent product. Medical devices are classified as per the, Regulations for Product Classification of Medical Device and Class by Product [Ministry of Food & Drug Safety Notification No, 2009-41(Jun 2009 Amended)] (mfds.gov.kr, 2017).

2.2.16.4 Representation in Country:

Manufacturers require a Korea license Holder (KLH) or a Korea In-Country caretaker (ICC) if there is no in Country representative.

2.2.16.5 Overview of how to register:

Since January 2016, Korea License Holder applies to Ministry of Food and Drug Safety (MFDS) for a Korea Good Manufacturing Practice (KGMP) Certificate. KGMP approval is required for all Class II, III and IV devices. KGMP certification/ audit needs are based on a combination of: Importer-Legal Manufacturer-manufacturing site-KGMP Product group (Merit, 2016). There are 26 KGMP product categories. Certification must be obtained prior to submitting a Medical Device application (Folan & O'Connor, 2017). A device registration

package in STED format is required for a class IV only, STED is not mandatory for other classifications as yet (mfds.gov.kr, 2017). A Business License and import license is required prior to importing devices.

2.2.16.6 Primary documents required:

Device Registration Package in STED format, as per Ministry of Food and Drug (MFDS) Notification 2013-181, Notification of Partial Amendments to the Regulations for Approval, Notification, and Review of Medical Devices required for Class IV device since January 2014 (mfds news, 2013). In addition, clinical reports are accepted where the clinical investigation is conducted with the exact device as per the final regulation. There are currently 63 product families that require a clinical investigation.

2.2.17 Taiwan:

2.2.17.1 Regulator:

Taiwan Food and Drug Administration (TFDA).

2.2.17.2 Regulation:

Pharmaceuticals Affairs Act (fda.gov.tw, 2017).

2.2.17.3 Device Classification:

Risk based classification system with class I lower class device and class III higher risk devices (fda.gov.tw, 2015).

2.2.17.4 Representation in Country:

Manufacturer without an office in Taiwan must appoint an in-Country representative.

2.2.17.5 Overview of how to register: Premarket approval is required for all

classes of medical device prior to Taiwanese market entry. The following are important documents for medical devices in Taiwan, Regulations Governing Management of Medical Devices, Guidelines for Registration of Medical Device and How to apply for Medical Device Licence in Taiwan (fda.gov.tw, 2015). Class II and III devices require 'home' approval in their own jurisdiction first. Prior to a medical device becoming available in Taiwan Quality System Documentation (QSD) registration for the manufacturing facility is required in addition to a medical device registration. QSD is waived for class I (non-sterile) devices. QSD requirements are easier to meet once you have home approval as there is a simplified mode if the manufacture has US FDA Clearance and EU CE

Marking on devices. Prior to importation of any classification of device the TFDA issues a "medical device permit licence" upon registration approval (fda.gov.tw, 2014). There is a technical Cooperation Program in place between Europe and Taiwan, so an EU Manufacturing location can waive the QSD requirements once an ISO13485 audit is conducted by an approved 3rd party Conformity Assessment Body (CAB) and the requirements for TFDA are included, the manufacturer does not need to complete the QSD (tuv-sud).

2.2.17.6 Primary documents required:

For class II and III medical devices the Summary Technical Documentation (STED) format for submissions is required and in addition the following must be included; QSD Registration certificate, Certificate of Foreign Government (CFG), a Letter of Authorisation, pre-clinical test reports, which can be waived if both US CFG and European Certificate of Free Sale (CFS) are available. Upon TFDA approval the medical device product licence is issued and is valid for five years.

2.2.18 Turkey:

2.2.18.1 Regulator:

Turkish Ministry of Health (Sağlık Bakanlığı)

2.2.18.2

Regulation: Leverage off MDD 93/42/EEC & Turkish Pharmaceutical regulation.

2.2.18.3 Device Classification:

Risk based classification aligned with Europe (EC/93/42/EEC) which are Class I, IIa, IIb & III with Class I lower risk and Class III highest risk device.

2.2.18.4 Representation in Country:

Appoint Turkish Registration Holder if no in country representation.

2.2.18.5 Overview of how to register:

The Turkish representative applies for access to the Product Tracking System (UTS). Medical Device National Databank UTS replaced TITUBB on June 12th, 2017 (Demir, 2017). Approved product certificates on the former system TITUBB have been transferred to UTS. Products that were in draft are subject to the additional requirements of UTS and companies are required to provide the additional submission data (Demir, 2017).

The Declaration of Conformity, CE Certificate, Design Examination certificate and the Turkish Label and Instructions for Use have always been required and are submitted on the database to start the registration process. The additional information now required as part of UTS include labelling of device being MRI Compatible, containing latex, containing ionized radiation, single use, limited usage, calibration and sterilisation (Demir, 2017). Medical devices that require calibration, maintenance, reparation will be tracked on a serial number basis. All other products are planned to be tracked on either serial number or lot number basis. The UTS system supports tracking linear barcodes and 2D barcodes and it is planned to access the barcode standards implemented by the company (Demir, 2017). Apostilled CE Certificates are sent directly to the Ministry of Health. Once the review is completed approval to sell devices is granted.

2.2.18.6 Primary documents required:

Declaration of Conformity, CE Certificate, Design Examination certificate and the Turkish Label and Instructions for use. Apostilled CE Certificates in Country of Origin.

2.3 Considerations in Registering medical devices

Table 2, summarizes key elements of Regulator, Regulation, Classification and if representation is required in the jurisdiction for each country. A list of the Regulatory agency web sites for these countries is located in Appendix 1. Canada is the only Country that does not require in-country representation as a pre-requisite in registering medical devices. In all other jurisdictions if the manufacturer does not have a presence locally in the jurisdiction a legal or authorized representative must be appointed prior to registration or distribution of medical devices.

Currently the listing of information contained within each of the country section is correct at the time of writing, however there are proposed changes on the horizon and these will be outlined in section 2.4.

Table 3, summarises the device classifications in each country discussed and the approximate approval timelines associated with each classification. The table also includes the period of validity for the approval of each device.

Country	Regulator	Regulation	Device Classification	In Country Representation
Australia	Therapeutic Goods Administration (TGA)	Therapeutic Goods (medical devices) Regulations 2002	Class I, IIa, IIb & III	Australian Sponsor mandatory
Argentina	Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT)	ANMAT Provision 727-2013	Class I, II, III, VI	Local Authorised Representative (AAR)
Brazil	Agência Nacional de Vigilância Sanitária (National Sanitary Surveillance Agency) ANVISA	Brazilian Ministry of Health, under Article 12 of Law No. 6360 of September 23, 1976	Class I, II, III, VI	Brazil Registration Holder (BRH)
Canada	Health Canada	Canadian Medical Device Regulation	Class I, II, III, VI	Not Required
China	China Food and Drug Administration (CFDA)	Regulations for the Supervision and Administration of Medical Devices (SC [2014] Decree No 650).	Class I,II &III	Representation required if no in-Country Presence
Columbia	Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA).	4725 Decree of 2005	Class I, IIa, IIb & III	Legal representative if no in-Country Presence
Egypt	Central Administration of Pharmaceutical Affairs (CAPA), and Drug Policy and Planning Centre (DPPC) divisions of the Egyptian Ministry of Health.	Egyptian Regulation for Medical Devices	Class I, IIa, IIb & III	Authorised representative if no in-Country representative
Hong Kong	Medical Device Control Office (MDCO), Department of Health Hong Kong.	Voluntary Listing since 2004 (Medical Device Administrative Control System (MDACS) is expected to be Mandatory circa 2018-2019)	Class I, II, III, VI	Local Representative required
India	Ministry of Health and Family Welfare and the Central Drugs Standards Control Organization (CDSCO)	Drug Regulations under Drug and Cosmetics Act of 1940 and Drugs and Cosmetics rule 1945. New legislation the Medical Device Rules 2017 will become effective Jan 1st, 2018.	Notified list system	India Authorized Agent if no in-Country representative.
Japan	Pharmaceutical and Medical Devices Agency (PMDA) is part of the Ministry of Health Labour and Welfare (MHLW).	Pharmaceutical and Medical Device Law (PMD Law) 2014	Class I, II, III, VI	Marketing Authorization Holder (MAH) or Designated Marketing Authorization Holder
Malaysia	Medical Device Authority (MDA) under the Ministry of Health, Malaysia	Medical Device Act 2012 (Act 737) and Medical Device Regulations 2012. End of voluntary registration and enforcement of Mandatory registration effective July 1st, 2016.	Class A,B,C & D	Authorised Representative (AR) required
Mexico	COFEPRIS –Federal Commission for Protection Against Sanitary Risks	Registrations: LGS (General Law of Health) –RIS (Rule for Health Supplies) and GMP: RIS Art 180, Normative NOM 241-SSA1-2012.	Class I,II &III	Mexican Registration Holder if no in-Country presence.
Russia	Federal Service for Surveillance in Healthcare (Roszdravnadzor (RZDN))	Resolution (Decree)#1416 Approval of regulation of the State Registration of Medical Devices	Class I, IIa, IIb & III	Authorised Manufacturers Representative (AMR)
Saudi Arabia	Saudi Arabian Food and Drug authority (SFDA)	Medical Devices Interim Regulation (MDIR) & Implementing Rules 1-8	Class I, II &III	Local Authorised Representative required
Singapore	Medical Device Branch under the Health Sciences Authority (HSA).	Health Products Act 2007 and Health Products (Medical Devices) Regulations 2010.	Class A,B,C & D	In Country Registrant must be appointed
South Korea	Ministry of Food and Drug Safety (MFDS)	Medical Devices Act	Class I, II, III, VI	Korea license Holder (KLH)
Taiwan	Taiwan Food and Drug Administration (TFDA)	Pharmaceuticals Affairs Act	Class I, II &III	An in-Country representative must be
Turkey	Turkish Ministry of Health (Sağlık Bakanlığı)	Leverage off MDD 93/42/EEC & Turkish Pharmaceutical Database upload for registrations: Medical Device National Databank (TITUBB).	Class I, IIa, IIb & III	Appoint Turkish Registration Holder if no in-Country representation.

Table 2. Summary table of the countries regulatory information,

[source: compiled by dissertation author].

Country	Device Classification	Approval Timeline	Validity of Registration post approval
Australia	Class I (low risk)	Automatic inclusion	no expiry
	Class Is/m (low risk)	6-8 weeks	no expiry
	Class IIa (medium risk)	6-8 weeks	no expiry
	Class IIb (medium risk)	6-8 weeks	no expiry
	Class III (high risk)	12 months	no expiry
Argentina	Class I (low risk)	4-6 months	5 years
	Class II (medium risk)	8-12 months	5 years
	Class III (high risk)	8-12 months	5 years
	Class IV (highest risk)	8-12 months	5 years
Brazil	Class I (low risk)	3-4 months	5 years
	Class II (medium risk)	3-4 months	5 years
	Class III (high risk)	6-8 months	5 years
	Class IV (highest risk)	6-8 months	5 years
Canada	Class I (low risk)	Exempt from licencing	1 year-annual registration fee per licence
	Class II (medium risk)	2-4 weeks	1 year-annual registration fee per licence
	Class III (high risk)	4-5 months	1 year-annual registration fee per licence
	Class IV (highest risk)	6-8 months	1 year-annual registration fee per licence
China	Class I (low risk)	Filing on site	does not expire
	Class II (medium risk)	12-18 months	5 years
	Class III (high risk)	14-18 months	5 years
Columbia	Class I (low risk)	1-2 months	10 years
	Class IIa (medium risk)	1-2 months	10 years
	Class IIb (medium risk)	2-3 months	10 years
	Class III (high risk)	4-6 months	10 years
Egypt	Class I (low risk)	4-6 months	10 years
	Class IIa (medium risk)	4-6 months	10 years
	Class IIb (medium risk)	4-6 months	10 years
	Class III (high risk)	4-6 months	10 years
Hong Kong	Class I (low risk)	Exempt from licencing	n/a
	Class IIa (medium risk)	6-9 months	5 years
	Class IIb (medium risk)	6-12 months	5 years
	Class III (high risk)	12-15 months	5 years

Country	Device Classification	Approval Timeline	Validity of Registration post approval
India	Notified list of devices	9 months	3 years
Japan	Class I (low risk)	1 week	Does not expire-subject to QMS inspection every 5 years
	Class II (medium risk)	6 months	Does not expire-subject to QMS inspection every 5 years
	Class II (high risk)	12 months	Does not expire-subject to QMS inspection every 5 years
	Class III (high risk)	12 months	Does not expire-subject to QMS inspection every 5 years
	Class IV (high risk)	18 months	Does not expire-subject to QMS inspection every 5 years
Malaysia	Class A (low risk)	12 months	5 years
	Class B (low to moderate risk)	12-24 months	5 years
	Class C (moderate to high risk)	12-24 months	5 years
	Class D(highest risk)	12-24 months	5 years
Mexico	Class I (low risk)	2-3mths or 8-10mths pathway dependant	5 years
	Class II (medium risk)	2-3mths or 8-10mths pathway dependant	5 years
	Class III (high risk)	2-3mths or 8-10mths pathway dependant	5 years
Russia	Class I (low risk)	6-8 months	Does not expire
	Class IIa (medium risk)	10-12 months	Does not expire
	Class IIb (medium risk)	10-12 months	Does not expire
	Class III (high risk)	10-12 months	Does not expire
Saudi Arabia	Class I (low risk)	2-6 months	3 years
	Class IIa (medium risk)	2-6 months	Variable validity by MDMA-Maximum is 3 years
	Class IIb (medium risk)	2-6 months	Variable validity by MDMA-Maximum is 3 years
	Class III (high risk)	2-6 months	Variable validity by MDMA-Maximum is 3 years

Singapore			
	Class A (low risk)	1 month	
	Class B (low to moderate risk)	2-6 months pathway dependant	
	Class C (moderate to high risk)	4-8 months pathway dependant	
	Class D(highest risk)	6-11 months pathway dependant	
South Korea		effective upon listing on MFDS	
	Class I (low risk)	website	Does not expire
	Class II (medium risk)	3-4 months	Does not expire
	Class III (high risk)	5-6 months	Does not expire
	Class IV (highest risk)	7-10 months	Does not expire
Taiwan	Class I (non sterile)	Immediate approval	5 years
	Class I (Sterile)	1-3 months	5 years
	Class II (medium risk)	9-12 months	5 years
	Class III (high risk)	12-18 months	5 years
Turkey	Class I (low risk)	2 weeks approx	Does not expire
	Class IIa (medium risk)	2 weeks approx	Does not expire
	Class IIb (medium risk)	2 weeks approx	Does not expire
	Class III (high risk)	2 weeks approx	Does not expire

Table 3. Approval timelines for each country. These timelines are approximates based on real time data provided by Merit Medical Regional Regulatory personnel (Merit, 2016) [data compiled by dissertation author].

2.4 Upcoming changes in registering devices:

2.4.1 Thiesz (2015) succinctly describes the registration of devices as involving the compilation and submission of documentation required for marketing applications to the relevant regulatory agencies and any administrative activities related to the registration. During this stage, regulatory professionals interface with the relevant authorities (regulatory agency or legal representative) and coordinate efforts within their own organisations to address questions or deficiencies raised during the review process until the marketing approval of the device is obtained. Upon review of this statement it is correct to a point. This is the process in registering a device but it is not the entire picture. Wong and Kaiyu (2013) discuss that a regulatory professional will continue to 'execute tactical requirements' and will also own strategic relationships with regulators…and 'will have a fluent understanding of the organization's strategy and active participation in product development and commercialization, making them a more robust business partner to the clinical and commercial functions'. By developing as a strategic business partner regulatory personnel can offer their knowledge of regulations and the fluid registration requirements in a more

interactive way, to support and add value to the business with options long before commencing the actual registration process, thereby becoming a strategic partner. In developing a global regulatory strategy timing is key. The timing of the initial approval (CE Mark or FDA), the timing of the product launch and the timing of commencement of global registrations are all part of this.

2.4.2 In China, regulatory professionals are aware that FDA approval or CE Mark is required prior to commencing registration. Local Chinese testing of medical devices is a key step in the approval process in China. CFDA has charged companies thousands of dollars for mandatory 'in-country' testing of devices in CFDA approved laboratories. Recently, the Chinese Food and Drug Administration (CFDA) have eliminated testing fees for medical devices at several testing centres, effective since April 1, 2017. Where previously a business could plan for approval times of up to 18 months, regulatory approval timelines are now more unpredictable with longer approval times associated with submissions. The good news is foreign device companies can save significant amounts of money with the waiving of these testing fees. The bad news, is with less cash going to the testing centres, there have been more delays and testing times have been elongated (Pacific Bridge Medical, 2017). From a business perspective, the market in China is also larger than some other countries and is also expected to increase at a higher rate for higher classification devices. For this reason, it is important to gain as much of the available market segment in China as soon as possible and ensure that a competitor's device is not established in the market place, prior to launching the company's product in the market (Folan & O'Connor, 2017). The decision becomes a business strategy, not just a regulatory decision. The business must decide to, wait, utilise a free testing lab and lose market segment or push ahead and pay testing fees in a different accredited lab and potentially gain an earlier launch date. It comes down to the device, its classification, the novelty of the device and balancing costs within the business.

2.4.3 In the case of a company registering a device for the first time in South Korea a company is required to undergo a Good Manufacturing Practice audit and obtain Korea Good Manufacturing Practices (KGMP) certification in Korea. Likewise, in Brazil for class III and IV devices a company must undergo audit

and receive BGMP certificate in Brazil prior to initiating registration of devices. In both Korea and Brazil this certification process can be started in the very early stages of a product development. In Korea, it can take up between four to six months to have the on-site audit. Currently for Brazil there is an inspection backlog of several years which delays BGMP certification and thus medical device registration (Bauer, 2017). On the horizon for Brazil ANVISA will utilise the MDSAP certification as basis for the issuance of BGMP certificate supporting faster medical device registration at ANVISA (Bauer, 2017).

Health Canada is transitioning from CMDCAS to MDSAP and will only accept MDSAP certificate from Jan 1st, 2019, therefore a company wanting to continue registration and supply of medical devices into Canada, are required to be certified to MDSAP prior to the Jan 2019 date.

2.4.4 Hong Kong currently has voluntary registration. This has been a good strategy for companies who have used the registration process, as health care facilities and professionals were more likely to used registered devices. In addition, for a company to compete for tenders it is required that the device be registered (Merit, 2016). Recently the Department of Health advised that products registered under the voluntary system will be transferred directly to the regulation list without another dossier submission. If the company is not on the voluntary list and mandatory registration is initiated, there will be a long line of companies trying to register their products at the same time, and this may impact sales in Hong Kong (Pacific Bridge Medical, 2016).

2.4.5 The Indian Ministry of Health recently (June 2017) published a notification to its impending Medical Device Directive which was announced in 2017 and has an implementation date of 2018, "significant changes to the medical device regulations include;

1. Device licenses will no longer expire. The manufacturer will need to pay the renewal fee every 5 years to continue marketing the product.

2. Device registration approval for imported devices will take an estimated maximum of 9 months. Registration will automatically imply import license and will eliminate a three month wait for an import license. If the

Ministry of Health fails to complete a regulatory process in a pre-determined amount of time, then the license will be "deemed" to be approved" (Pacific Bridge Medical, 2017).

Another layer of complexity in India is in mid-February 2017, "India's National Pharmaceutical Pricing Authority (NPAA) fixed the price of drug eluting stents at $450 and bare metal stents at $110 USD. The NPAA may look to regulate the prices of 14 other medical devices that also have high price mark-ups. These devices range from artificial heart valves to consumables such as catheters and syringes". The NPAA are attempting to deal with the high cost of medical devices and has requested medical device manufacturers, to track and log details about costs associated with production (Pacific Bridge Medical, 2017).

2.4.6 In Turkey, a draft guideline of the Turkish Good manufacturing practices guidance, which is to be applied in the manufacturing sites of medical device companies was released in June 2017. Upcoming Turkish REACH and RoHS 2 are expected to be published by the end of 2017 (Demir, 2017).

An important element for the registration of devices is the continuous development of the regulatory professional as a strategic minded individual particularly in the regions. With primary access to regulators and a keen understanding of the levers that guide their submission expectations, review and lines of inquiry, the regulatory professional is in a unique position to add value to the organization. By understanding where the key interests 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 areas most likely to satisfy a regulators priority while still serving the organization's needs.

2.5 Harmonization the key players and the drivers of change

The global market for medical devices is huge and it will continue showing a significant growth in the future (Ramakrishna *et al*, 2015). It is evident that each country or region have their own regulation or interpretation of regulation for medical devices however according to (Tamura & Kutsumi, 2014) approaches have been made to discuss the global convergence of medical device regulations

despite these different situations. Ramakrishna *et al*, also discusses the differences between the different markets, and state that manufacturers must clarify their target markets and comply with the regulations accordingly. They (Ramakrishna *et al*, 2015) use the example of a medical device entering the Chinese market, while the device has undergone stringent review procedures with the US FDA, it may not enter the China market without undergoing China FDA (CFDA) review and approval. From the review of the countries in section 2.2, it is evident that there are differences in regulations, registration requirements, and review processes which manufacturers must comply with, in order to enable the registration and commercialisation of devices in these countries.

The need for global harmonisation of medical devices is real and includes the following reasons;

1. minimize regulatory barriers;
2. facilitate trade between different countries; and
3. reduce the cost of implementing regulations for government and industry (Ramakrishna *et al*, 2015).

2.5.1 International Medical Device Regulators Forum (IMDRF):

Europe, the United States, Australia, Canada and Japan have well established mature regulations and regulatory processes for healthcare products. Product approvals issued by the regulatory agencies in these countries are widely recognised and according to Theisz (2015) would usually enable the obtaining of marketing approvals in many countries in the emerging markets of Latin America and Asia Pacific.

The Global Harmonization Task Force (GHTF) was established in 1992 and was a voluntary harmonization effort incorporating regulators and industry from Europe, Japan, Canada and Australia. GHTF members felt a new operating model was necessary to achieve the original objectives of the force and meet the increasing challenges of globalization and emerging technologies (IMDRF.org, 2013). The GHTF was replaced in 2012 by the International Medical Device Regulators Forum (IMDRF). Representatives from the five founding members of the GHTF proposed participation from Brazil, Russia, China and India as committee members to the new forum, to discuss true globalisation because of

their population and economic influence (Tamura & Kutsumi, 2014). In 2012, the new forum included Australia, Brazil, Canada, the European Union, Japan and the United States. China officially joined in 2013 and Singapore has joined more recently (IMDRF.org).

2.5.2 Association of Southeast Asian Nations (ASEAN):

The Association of Southeast Asian Nations, or ASEAN, was established on 8th August 1967 in Bangkok, Thailand, with the signing of the ASEAN Declaration (Bangkok Declaration), by the founding members of ASEAN, namely Indonesia, Malaysia, Philippines, Singapore and Thailand (ASEAN.org). There are currently ten-member states. Aims of the association include accelerating economic growth, aid each other with training and research facilities in the educational, professional, technical and administrative spheres; and to maintain close and beneficial cooperation with existing international and regional organisations with similar aims and purposes (ASEAN.org).

2.5.3 Pan American Health Organisation (PAHO):

The Pan American Health Organisation (PAHO) is a regional working group and is an affiliate of the World Health Organisation (WHO). PAHO was established in 2012 and has 16 active participants. These participants include Argentina, Columbia, Mexico and Brazil. One of the aims of the organisation is to improve the safety and technical efficacy of medical devices within the region (Lamph, 2012). An objective of the group is to strengthen the regulation capacity of medical devices within the Americas. In 2016 among other subjects, PAHO also discussed:

1. IMDRF Working Group "Table of Contents" and the possibility to create a mirror working group for the region.

2. Opportunities for knowledge sharing of the Regional Working Group.

3. Definition of the 2017 working plan (Orofino, 2016).

2.5.4 Asian Harmonization Working Party (AHWP):

Established as a voluntary organization, the Asian Harmonization Working Party (AHPW), "Its goals are to study and recommend ways to harmonize medical device regulations in the Asian and other regions and to work in coordination with the Global Harmonization Task Force (now IMDRF), Asia Pacific Economic Cooperation (APEC) and other related international organizations aiming to establish harmonized requirements, procedures and standards" (AHWP). Membership includes China, Hong Kong, India, Malaysia, Saudi Arabia, Singapore and South Korea. The Asian Harmonisation Working Party (AHWP) has developed a playbook, which is a guide to other member jurisdictions that are developing their medical device regulatory framework.

Table 4, summarizes the working party organizations and their full list of member Countries;

Organisation	Member Countries on June 1st 2017
International Medical Device Regulators Forum (IMDRF)	Australia, Brazil, Canada, China, Europe, Japan, Russia, Singapore, and the United States of America
Association of Southeast Asian Nations (ASEAN)	Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Thailand, Vietnam
Asian Harmonisation Working Party (AHWP)	Abu Dhabi, Brunei Darussalam, Cambodia, Chile, Chinese Taipei, Hong Kong SAR, China, India, Indonesia, Jordan, Kazakhstan, Kingdom of Saudi Arabia, Republic of Korea, Laos, Malaysia, Mongolia, Myanmar, Pakistan, People's Republic of China, Philippines, Singapore, South Africa, State of Kuwait, Tanzania, Thailand, Vietnam, Yemen
Pan American Health Organisation (PAHO)	Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Canada, Chile, Columbia, Costa Rica, Cuba, Dominica, Dominican Republic, Ecuador,

El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, Saint Lucia, St Vincent, St Kitts, Suriname, Trinidad and Tobago, USA, Uruguay, Venezuela

Table 4. Membership of the influential organizations on June 1st, 2017. [Source: compiled by dissertation author].

Wong & Kaiyu (2013) discuss that large-scale initiative (harmonization in Asia) will require an unprecedented level of cooperation across national health authorities. The authors Wong & Kaiyu (2013) agree with Theisz (2015), in the concept that if harmonization of regulations and registration requirements in the various regions is successful, "the harmonization will eliminate some of the unknowns in the regulatory environment, but getting there will challenge manufacturers that must reconcile the harmonized promise of tomorrow against the fragmented regulatory landscape of the near term".

Figure 1, is a graphical illustration of the interconnections between the harmonisation groups in the different regions apart from Egypt and Turkey. Egypt and Turkey are not members of these associations.

Figure 1, outlines the complexity and overlap of the Harmonisation groups
[updated and adapted from original slide by Brandwood Biomedical].

2.6 Additional influences

In parallel to the previously mentioned working groups there are many influences that require consideration for device manufacturers in the global arena. While a primary objective of all parties is to reduce the regulatory burden in making life saving medical devices available in the different regions, one would question the evidence to support, if indeed there is an overall global strategy for the convergence of regulation and registration requirements.

2.6.1 Medical Device Regulation (MDR)

One of the most important influences in the coming years for medical device manufacturers is the recently released Medical Device Regulation (MDR) in Europe. The European Parliament sitting on 5th April 2017 adopted the MDR, with a transitional period ending May 2020. The Medical Device Regulation will replace the existing three European Directives (for Medical Devices, In Vitro

Diagnostic Directive and the Active Implantable Directive) with two Regulations (Ramakrishna *et al*, 2015). While the scope of this dissertation is not the European requirements and will not discuss the MDR in detail its influence however will ripple out into many jurisdictions where a country's registration processes, either fully or partially leverages the European regulatory framework. Many regions adopted parts, or the full European model in its regulations as it had been considered a 'best practice' regulatory model which has been adapted into so many markets around the world" (Brandwood, 2017). According to Brandwood, elements of the European model especially around risk based classification, Essential Principles and Conformity Assessment procedures are essentially derivatives of the former European Directives. Not only is the implementation of MDR a mammoth task for device manufactures to coordinate and implement, but the more stringent requirements may send waves of disjoint into the review processes of the countries that lever off European requirements. To postulate, it may have positive impact in countries as the MDR Conformity Assessments to the Essential Requirements and Clinical evidence become more stringent. It may also allow for the emergence of Mutual Recognition Agreements (MRA) between countries, like Australia, based on the fact that tighter controls will bring with it more confidence in the European system. Additional considerations with the MDR for global device manufacturers is the impact of possible reclassification of devices and updates to labelling particularly. If labelling is revised this may trigger device amendments to registrations in some jurisdictions. As the MDR is only commencing its transition phase there is currently very little literature on the possible impact of the MDR. Countries in the APEC and ASEAN regions are watching the changes in Europe with keen interest, many AHWP member jurisdictions rely on European Conformity Assessment procedures to abridge local regulatory requirements e.g. Taiwan and Saudi Arabia.

2.6.2 ASEAN Medical Device Directive (AMDD):

The ASEAN Medical Device Directive (AMDD), not as high profile as the newsworthy MDR in Europe but none the less for global manufacturers who scan the horizon, it is firmly on their radar. The AMDD was initially announced in

2012 by the ASEAN Medical Device Product Working Group and they released a draft of the ASEAN Medical Device Directive. Upon review, the AMDD is aligned with the European Medical Device Directive 93/42/EEC and it is a high level non-binding document that lays out uniform rules for product pre-market registration and post market surveillance. Theisz (2015) discusses that ASEAN countries had expressed their commitment to implement the AMDD before the end of 2015. The Asian Harmonisation Working Party (AHWP) developed a play book to guide member economies in the development of their regulatory framework (AHPW.org). In January 1, 2012, Singapore Health Science Authority (HSA) rolled out a state of the art regulatory system for medical devices making it the first nation to adopt the AMDD. As of March 2017, the AMDD remains a work very much in progress "although Singaporean and Malaysian governments have made the most progress in terms of implementing the directive" (Emergo, 2017). To date Singapore has implemented the AMDD, Malaysia plans to ratify the ASEAN Medical Device Directive (AMDD) in mid-2017 and Malaysia's registration regulation requiring CSDT was implemented on July 1st, 2017 (Emergo, 2017). Anecdotally, some countries tried to implement AMDD but were unsuccessful due to lack of resources or inadequate expectations within their government departments to enforce the implementation.

2.6.3 Medical Device Single Audit Program (MDSAP):

The Medical Device Single Audit Program (MDSAP) is an initiative that started in 2014 by the IMDRF and was developed to enable "appropriate regulatory oversight of manufacturers quality management systems while minimizing regulatory burden on industry and promote globally …a greater alignment of regulatory approaches and technical requirements based on international standards and best practices" (US fda.gov, 2017). The International partners participating in MDSAP are the regulatory agencies in Australia (TGA), Brazil (ANVISA), Canada (Health Canada), Japan (MHLW & PMDA) and the World Health Organization (WHO) with the European Union (EU) being official observers. MDSAP is a program that allows medical device manufactures to be audited once for compliance with the regulatory requirements of up to five different medical device markets.

In Brazil, ANVISA uses the reports as an input into their premarket and post market assessment procedures. In RDC 15/2014 and RE 2.347/2015 ANVISA may use MDSAP audits in lieu of a premarket inspection to grant the ANVISA Good Manufacturing Practices (GMP) certificate to manufacturers who intend to put class III or IV devices on the Brazilian Market (FDA.gov, 2017). Currently there are delays up to three years in ANVISA conducting BGMP audit. TGA in Australia will take MDSAP into consideration when determining if a manufacturer has demonstrated compliance with an Australian Conformity Assessment Procedure, or take into account when considering issuing a TGA Conformity Assessment Certificates (Conformity Assessment Certificates are required by manufacturers for devices that incorporate a medicinal substance or material of animal origin). Health Canada will operate its current CMDCAS and MDSAP programs in parallel for class II, III or IV devices. However, from January 1st, 2019, Health Canada will only accept MDSAP certificates. Japan (MHLW and PMDA) will trial the use of MDSAP audit reports when submitting premarket or periodical post market QMS inspection applications, to exempt a manufacturing site from an onsite inspection and/ or to allow a MAH to substitute part of the documents required for the inspection with the report (fda.gov, 2017).

MDSAP notes the Quality Management Systems standard, ISO13485:2012 *Medical devices - Quality management systems - Requirements for regulatory purposes* (ISO 13485:2003), is the internationally recognised standard for a comprehensive management system for the design and manufacture of medical devices. It is seen as the first step towards achieving compliance with European, Canadian and other regulatory requirements for medical device manufacturers (NSAI.ie, 2017). At the time of writing the ISO13485:2016 version while published on March 1st, 2016, has not been harmonised in Europe. Once it is published in the Official Journal of Harmonised standards (July 2017) it becomes the harmonised standard. However, this standard began a three-year transition period when it was published in 2016, (NSAI, 2017) which for device manufactures means their ISO13486 certification to the 2012 version of the standard ends in 2019. This transition date of 2019 is being also forced by MDSAP. The MDSAP audit model was revised to consider ISO13485:2016 and with Health Canada's transition from CMDCAS to MDSAP by January 1st, 2019

(MDSAP FAQ, 2017) it will force manufacturers who want to continue the supply of devices into Canada from January 2019, to adopt ISO13485:2016 earlier than they may have planned for.

2.6.4 Summary of Influences;

The merging of all these influences mean many things for medical device manufacturers. It means a product regulatory strategy is no longer a standalone regulatory document, it becomes a business/regulatory strategy document. It outlines timing of product launches and scheduled global registrations become more strategic decisions around the management of resources, updating QMS systems in parallel with juggling the day to day support of a business. Figure 2 is a graphical representation of these influencing activities. These are in addition to the ongoing regulatory activities such as, registration of medical devices, device change control activities during product life cycle and post market obligations (complaints, vigilance and recall activity) which a medical device manufacturer must meet in countries, where devices are registered. Medical devices are designed to maintain the health and safety of people; therefore, medical devices are undergoing rigorous management by competent health authorities in all countries. In recent years, Asian countries have been reforming their regulations and standards for medical devices with substantial changes (Yi-Hui *et al*, 2016).
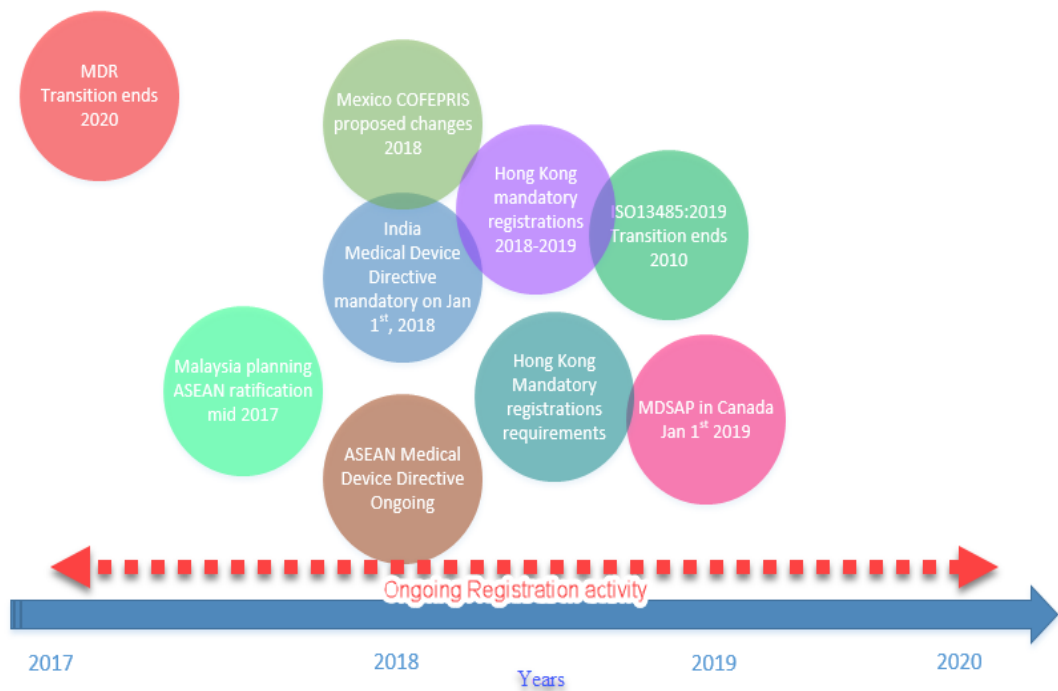
Figure 2, Influencing activities for a medical device company.
[graphic compiled by dissertation author].

2.7 Registration Submission Formats:

2.7.1 As more IMDRF, APEC, PAHO and AHWP members develop and revise regulatory requirements, the development of global design inputs/design outputs to support the compilation of a global submission dossier continues to be a challenge for manufacturers, particularly those in the global arena. As part of the overview of registrations in the countries outlined within this dissertation the document submission formats of STED and CSDT were noted as the expected registration format in some jurisdictions. The STED format is the Summary Technical Document. This format was created by the Global Harmonization Task Force (GHTF), the precursor organization to the current International Medical Device Regulators Forum (IMDRF), to globally standardize medical device regulatory submissions (Emergo, 2016). Part of the difficulty for medical device manufacturers is the need to re-create the same submission packages multiple times for country registrations with the addition of local requirements.

The ASEAN Medical Device Directive (AMDD) has included the Common Submission Dossier Template (CSDT) as the format of premarket submissions for ASEAN regions once the AMDD Directive is implemented (AHWP/WG1a/F004:2013). The Common Submission Dossier Template (CSDT) is based on the STED format and those STED requirements are incorporated as a subset of CSDT. From the ASEAN, Medical Device Working Party CSDT document the introduction section describes "Essentially, the CSDT contains elements of the Summary Technical for demonstrating conformity to the Essential Principles of Safety and Performance of Medical Devices".

The AHWP released a comparison document in 2013 illustrating (STED) [GHTF SG1/N011R17] the differences between both the STED and CSTD formats. AHPW acknowledges that eliminating differences between jurisdictions "decreases the cost of gaining regulatory compliance and allows patients earlier access to new technologies and treatments" (GHTF SG1/N011R17, 2013). The STED and ASEAN CSDT format has been available for some time for medical devices. However, there is the temptation of each county having its own interpretation of requirements and this can be seen in the ASEAN CSDT with Malaysia, Singapore and ASEAN each having issued their own version of a guidance document on how to compile a CSDT.

2.7.2 Further IMDRF developments in 2014, led to the launch the IMDRF Table of Contents (ToC) submission template again with a different format to STED (which its predecessor the GHTF introduced). In the 'Purpose' section of the Non-In Vitro Diagnostic Device Market Authorization Table of Contents (nlVD MA ToC) the IMDRF state this is "To create a comprehensive submission structure that can be used as a harmonized international electronic submission format while minimizing regional divergences and indicating where regional variation exists".
The primary aim of these working parties is to ease the regulatory burden and aid the convergence of regulatory requirements. Unfortunately, the burden for industry appears to be increasing and diverging further way from true harmonization without a long term global strategic plan by these working groups.

As evident from the outline of the registration requirements outlined above there is a tendency for each jurisdiction to add local supplementary requirements, which means if manufacturers use the STED, CSTD or the Table of Contents (ToC) formats, those manufacturers still need to be prepared to adjust dossiers for each separate market.

2.7.3 Theisz (2015) restates an interesting thought for manufacturers regarding the compilation of a registration dossier format.

Product specific documents that are mandatory in terms of the European Directives are referred to as a Design Dossier for Class III medical devices and technical documentation for the other classifications (class I, IIa and IIb). These documents represent a subset from the Quality Management System ISO13485 *Medical Devices-Quality Management Systems: Requirements for Regulatory Purposes*. [Note: there are elements of MDD93/42/EEC Annex II compliance that are not covered by ISO13485. Annex ZB of ISO13485 highlight those sections not covered]. He continues to discuss that early guidance on technical documentation mentions generating a 'Technical File' which manufacturers have interpreted to be a separate document that was to be submitted to Notified Bodies for review. In 1999 NB Med (the Notified Bodies coordination group) guidance issued further clarification and replaced the term "technical file document" with "technical documentation" clarifying that a product documentation system rather than a standalone document or 'Technical File' had to be generated and maintained.

The discussion continues with the US FDA requirements regarding Design Controls as per 21 CFR Part 820, which are a mandatory part of the Quality System Regulation (QSR) and is applicable to most medical devices which are to be marketed in the USA. Practically all sections of the Design Control requirements specify information that should be recorded as part of the approved design and development plan and this format is called a Design History File (DHF) a term specific to US regulations. The DHF is not a requirement as per the ISO13485 Quality Management Systems standard, however the requirements for a manufacturer to produce specific device documentation in both jurisdictions do overlap.

Mandatory device or quality systems documentation is not specific to Europe (ISO13485) or US FDA (QSR part 820).   It is also mandatory in many of the jurisdictions discussed within the scope of this dissertation. Product and Quality Management Systems information is mandated by Australia's TGA through the Therapeutic Goods (Medical Devices) Regulations 2002, Schedule 3 §1.4 (5), §2.3 (3). Canada mandates information through its Medical Device Regulation SOR/98-282 section 32 Application for a medical device. Likewise, Japan mandates information through its Pharmaceutical and Medical Device (PMD) Act in November 2014.

While the term Design History File (DHF) may be intrinsically identified with the USA Food and Drugs Administration (FDA), Theisz (2015) uses the term in a broader context, of device information that a device manufacturer compiles as part of the design and development process for that product. He proposes that device manufacturers utilise the Design History File as the basis of the STED submission format as the STED format is a subset of the Design History File. Figure 3, outlines how both the DHF document requirements are mapped to the STED submission format.
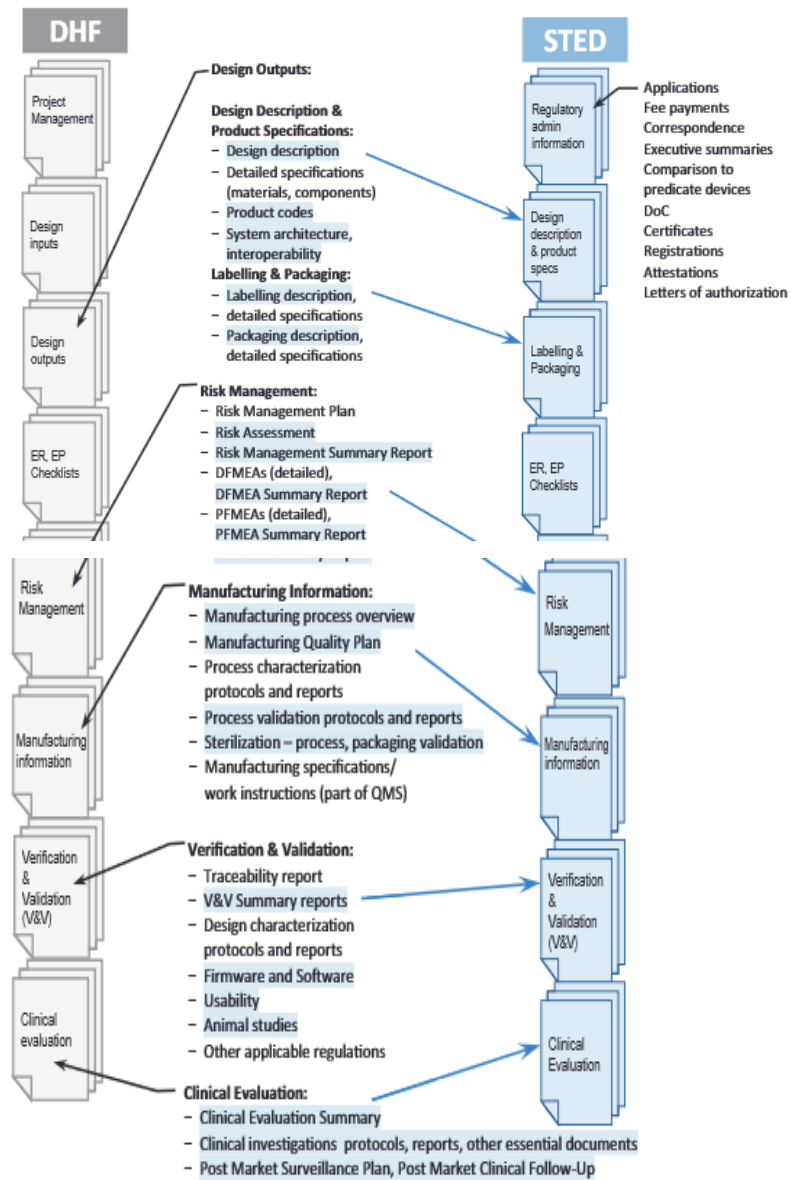
Figure 3, The STED (blue shading) is a sub set of the DHF.
(Source: Theisz, 2015, image reproduced with kind permission from Pan Stanford Publishing).

Like the premise of this dissertation, Theisz supports "that generating separate sets of documentation packages for each jurisdiction is laborious and difficult to maintain, incurring high administrative overheads", Industry would prefer a standardised format for submission dossiers in multiple jurisdictions. Wong and Kaiyu (2013) utilise a simple costing exercise to illustrate how delays to the market can cost a business revenue. Using a rough calculation, assume a product will achieve a forecast of $30 million per year of peak sales. This is translated to

sales of over $82,000 per day. "The company would lose a million dollars for each 12 days of delay!". Or alternately faster launch makes almost $2.5 million extra per month (Wong & Kaiyu, 2013). There are several areas through the development process that can cause delays, but a more efficient system of compiling documents can reduce inefficacies and in turn reduce time to registration, which will have a positive impact on the bottom line.

As part of the benchmarking exercise discussed in section 4, anecdotally the companies contacted were asked if it was common practice to take documents directly from a product DHF and submit without any additional editorials for regulatory submissions. From the smaller company to the advanced regulatory systems of the multinational the answer was 'no', primarily because regulatory personnel would not use documents, with descriptions, overviews etc., where they are not written to a level of quality that they could be used directly in a regulatory submission. To use documents directly from a Design History file with minimal editing is a regulatory departments utopia, however in practice it would take a company many years of training, time and commitment across multiple departments to achieve that state.

Theisz has used the STED format as it was the most widely used for submissions for his DHF /STED structure. From the literature review, it has been observed that since 2015 the submission formats have progressed to CSTD and IMDRF Table of Contents (ToC) in parallel with STED. It is to be acknowledged however that with a change in work methods using DHF documents with another format other than STED, the DHF may be utilised as an integral input to a global regulatory submission dossier which will be explored in section 4.

Chapter 3: Methodology

3.1 Literature Search

The scope of the literature search included a search of regulatory association and agency databases as well as scientific databases for the period, 2012 to 2017. It is expected that this would provide sufficient coverage of new literature and emerging requirements that might have arisen during the time since the strengthening of regulation requirements circa 2012 after the medical device PIP (Poly Implant Prothèse) company implant controversy in Europe. One cause of this controversy was the use of low grade agricultural silicone in its artificial breast implants and these were approved by a Notified Body (Ramakrishna *et al*, 2015). The secondary scandal was an Eastern European Notified Body that approved a known, unsafe design, of a 'metal on metal' hip implant (Cohen, 2012).

Due to the pace of regulation and registration changes for medical devices in the regions outlined the literature search was completed up to July 1st, 2017 and new information will not be included after this date.

3.2 Methods:

Search Terms: Registration of medical devices in Asia /Asia-Pacific

Registration of medical devices in Japan

Registration of medical devices in Latin America

Registration of medical devices in Russia/CIS

Registration of medical devices in Middle East

Registration of medical devices in China

Global Regulatory Affairs

Regulatory strategies

Elements of Management Systems

Management of Global regulatory systems

Period covered by Search: 1st January 2012 to 1st July 2017

**Literature Sources used
to identify data**:   Scientific Databases:

- NUIG James Hardiman Library databases

- Yeats Library IT Sligo databases

- Bibliographies of articles retrieved

  Library Resources:

- James Hardiman Library, NUI Galway
- Yeats Library, IT Sligo
- Company Library
- Websites of Regulators
- Asia Harmonization Working Party [Asia Harmonization Working Party](#)
- International Medical Devices Regulators Forum http://www.imdrf.org/
- Asia- Pacific Economic Cooperation http://publications.apec.org/
- Association of South East Asian Nations http://asean.org/

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

Inclusion Criteria:

1. Paper discussed regional registration process.
2. Paper discussed IT infrastructure and information sharing online.
3. Paper discussed communication solutions.

Exclusion Criteria: 1. Paper described nonspecific technical or clinical study devices, veterinary devices and In Vitro diagnostic (IVD) devices.

2. Paper contained unsubstantiated opinions
3. Paper contained insufficient information to undertake an analysis.
4. Full text of paper is available only in a language for which an English translation is not readily available.

3.2 Benchmarking [questions and method]

The research question posed was "what is the best practice for international product registrations". The research objective was to take a cross section of successful Irish based medical device companies and find out what are the primary drivers behind their product portfolio registration processes in terms of methodologies and tools and use this to benchmark against the macro environment. These findings, along with the literature review theories, are discussed, and used to conclude what methodologies medical device companies could use to reduce the burden of multiple variations in their international product registrations in order to deliver products to the market in a timely manner and as cost effective as possible. Accessing medical device markets outside of the US and Europe is a critical growth opportunity from a business perspective and an important component for the regulatory strategy of the product launch plan.

3.2.1 Method;

This methodology followed a multi-phase mixed method approach to collecting data.

In the initial phase, informal discussions with the company's international regulatory personnel shared regional issues that when information outside of what is detailed in the STED/FDA submission formats (such as material safety data sheets, materials testing, sterility testing after sterilisation) is required for other country registrations, this is not readily available. This places additional burdens on regulatory and support function resources, in terms of unplanned time and cost. While this information is being compiled or generated the regional regulatory group endure delays in product registrations.

Also as part of the initial phase, a preliminary literature review was conducted. It became apparent that there is a lack of peer reviewed articles on registration

requirements in some emerging markets that are current. Regulations and registration requirements change swiftly, therefore there is difficulty in identifying literature that is accurate at the time of dissertation. Most literature in the field of regulatory affairs and the registration of medical devices in emerging countries is limited. The majority of literature available is centred around established regulatory frameworks such as Europe, the United States and Japan. In 2015, a literature search was conducted by Rey-Ares *et al*, to access, describe and compare requirements of medical devices in Latin America countries, specifically, Argentina, Brazil, Colombia and Mexico. They concluded that there is "scarce information on the processes and requirements to achieve coverage for medical devices in these Countries". Likewise, for Egypt and Saudi Arabia, a systematic review of polices and regulations was carried out (Gad *et al*, 2016) and they concluded despite the significant medical device market size information including regulations and market access "is highly deficient".

The second phase was to review submission formats discussed in the literature which are the STED format, the CSDT format and the IMDRF Table of Contents (ToC). An element of the Global Registration Dossier bench marking exercise was to conduct a comparison between the three formats. As there was no comparison document available in the literature, this exercise was conducted as part of the dissertation. This comparison mapping is outlined in Appendix 2. This exercise both confirmed that the existing formats of STED and CSTD were included in the Table of Contents format and provided the basis for an optimal documentation format which includes the critical elements of a medical device registration for all regions.

In the third phase, a number of medical device companies were identified across all categories, small (<50 employees), medium (51-249 employees) and large (> 250 employees) (O'Dwyer & Cormician, 2017), that had a regulatory function based in Ireland. A selection of ten companies were contacted with personalized requests for participation and the questions were emailed to participants. The primary method to obtain information was to have a telephone interview or face to face interview. If this was not convenient or possible due to location, it was requested that the questions be answered online via email correspondence. Specific personnel in regulatory functions were contacted because according to

Sauermann and Roach (2013) "personalization increases the odds of responding by as much as 48%".

3.2.2. Design of Questions:

The questions were designed to be leading to acquire the knowledge of how the different companies manage their international registration activity.

The themes that ran through the questionnaire were based on a company's;

- o   Management of registrations and
- o   Communications

Chapter 4: Findings Results/ Discussions

4.1 Introduction

Section 4 will converge, all of the overall registration requirements outlined in section 1, the findings in the literature in section 2, a discussion of the outcome of the benchmarking in section 4 and how these elements will combine to outline a Global Registration Dossier format. To support this work, the convergence of discussions need to be in the context of regulatory requirements, specifically requirements that are outlined in ISO13485: 2016 *Medical Devices-Quality Management Systems- Requirements for regulatory purposes.*

4.2 Findings from Companies

Ten medical device companies were identified, small medium and large (O'Dwyer & Cormician, 2017) that had a regulatory function based in Ireland. The companies were selected and contacted with personalized requests for participation. The primary method to obtain information was to have a telephone interview or face to face interview as this methodology provides the opportunity to ask more clarification questions during the interview. If this was not convenient or possible due to location of the company, it was requested that the questions be answered online via email correspondence. Prior to the meeting or calls the questions were emailed to participants to provide sufficient time to consider responses. From the ten companies contacted, eight companies participated which is an 80 percent (80%) response rate. From these eight companies three agreed to a face to face meeting. The remaining companies responded to the questions via email. Figure 4 illustrates the breakdown of responses. The face to face interviews elicited more information, as expected. A mixture of small and medium companies were chosen to interview, as smaller companies may have more resource constraints and potentially could be more innovative with work methodologies, than a larger company with developed systems.

From the eight companies that responded, six are large medical device manufacturers.
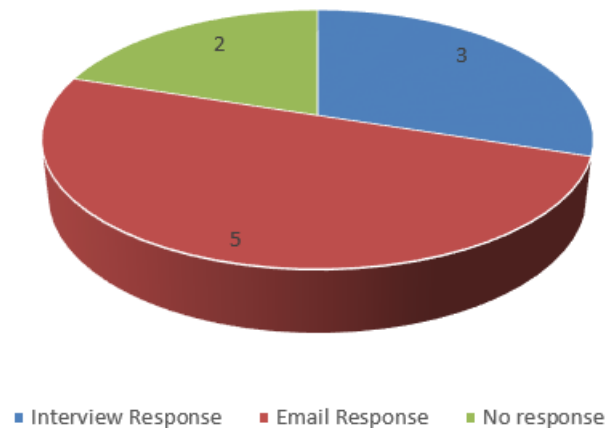
Breakdown of Survey Responses

Figure 4, Breakdown of survey responses from companies.

4.2.1 The Questions posed to the regulatory personnel regarding their companies are outlined in table 5 and shall be discussed in the following section;

1) Can you tell me how your organization manages their RA International Group?

2) I would like to understand your companies process of how a product gets from the CE Marked & FDA Cleared status to registered in the regions. [e.g. is it determined up front in a Regulatory Strategy, who decides where to register products].

3) How is communication between the regions managed for product changes and registration approvals?

4) In our company RA in the regions are very much in regional Silo's working with their Sales counterparts, with little contact with the manufacturing facilities. Do you think that works or how do you think that we can improve communication?

5) If applicable to your company, do the RA group share RA/QMS registration information or registrations electronically. If so how do they do this (e.g. electronic system, email, iCloud, other)?

6) Are there metrics around registrations that you are aware of? [time to market planned, priority of registrations, and who decides these].

7)   What kind of document control system does your company have (Fully electronic or centralized Document Control, paper based and electronic)?

8)   What are the top three difficulties (or most common pain points) you have with product registrations outside of EU and USA.

Table 5. Survey Questions

The findings from the responses were as follows;

4.2.2. **Q1. Can you tell me how your organization manages their RA International Group?**

Findings show that the larger Multinational Corporations (MNC) have separate business units at the manufacturing facilities, for example Cardiology, Electrophysiology, Pulmonary manufacturing divisions and these divisions co-ordinate with their international regulatory group. Due to the size of the businesses, these corporations have their International regulatory teams based in the regions (e.g. Asia-Pacific, Japan). The regions manage their own registrations. As an example, two of the larger corporations have a fully resourced regulatory team based in China that deal specifically with the Chinese market. The medium sized companies mainly use distributors or appoint agents to represent them in the various countries and their international registrations are coordinated by the regulatory personnel based in the manufacturing facility. As resources are more constrained in the small and medium organization the international registrations are "handled with all other responsibilities, internal registrations being just one aspect" of the regulatory professional's job according to one RA specialist in a medium sized company.

4.2.3 Q2. I would like to understand your companies process of how a product gets from the CE Marked & FDA Cleared status to registered in the regions. [e.g. is it determined up front in a regulatory strategy, who decides where to register products].

Five out of the eight companies, have a regulatory plan or regulatory strategy in place and this is how registrations outside of the EU and USA are managed. One

of these five larger corporations, use a regulatory plan for new product introduction projects, however its major growth comes from acquisitions. "Following an acquisition of particularly large company, can pose a severe burden on international teams, as marketing want to transfer all the products to the company's distributors or sell directly in country. In these situations, we work closely with marketing and generally try and use the marketing strategy to determine the regulatory strategy".

The other three responses included an SME company which levers off the EU approval and/or 510k clearances and carries out registrations in the countries that recognize these approvals initially. From there the sales group list by Country priority where the product is to be registered. This listing is reviewed for both status and priority on a quarterly basis. This SME does not have regulatory personnel in the regions and deals primarily with distributors. The second large company operates a different model of operation. It is a contract manufacturer and does not have regulatory plan for device it manufactures. This manufacturer operates with its customer to deliver a regulatory package in a particular format, STED as an example which they will compile, for the customer if contracted to do so, but they will have no visibility on the customers regulatory strategy or plan. They also do not have a regulatory plan of their own, they will contract with the legal manufacturer and deliver what their customer requests.

The third company, a large company, notifies its International group once CE Marking, FDA approvals/clearances are complete and wait for the international group to come back with their regional plans.

From the information obtained it became apparent, the primary model used is once CE mark and FDA clearances are obtained, the international regulatory teams are notified from the business unit and the only communication back from the international group is a notification that the product is approved and can be shipped. This simplistic model works as each region usually has its own registration plan, particularly if the company has a global presence and has multiple products. The disadvantage with this approach is that once the business unit make this notification the communication stops, until the international group(s) come back with the approval. One interviewee mentioned the 'lack of control' in that, the registration fell into a black hole and there was no visibility on registration status from the regions unless it was followed up. One company

stood out regarding information distribution, while it utilizes an electronic document control system and European submissions are in STED format, the interesting methodology is it pushes notifications out to the regions persistently in the latter phase of the design and development process. As an example, most companies will notify regulatory personal when the FDA clearance, the CE Mark and possibly the Canadian licenses become available. This one company notifies the international personnel upon successful product and process validation testing in order that the registration process can commence in countries with no regulatory requirements. This extra level of communication also means that, now international regulatory personnel have the opportunity to have type testing units built for testing being conducted in China or Russia, if the business decision has been identified in the regulatory plan. In addition, countries such as Japan can start assembling their submission dossiers, if a product is a priority registration, once successful product and process validation is complete. In all other companies, a common denominator is personnel in the regions reach into manufacturing sites either electronically or via a regulatory contact and they pull the information such as approval dates, status of projects from the manufacturing site of the product that will undergo registration post EU/US approval.

4.2.4 Q3. How is communication between the regions managed for product changes and registration approvals?

Outside of email communication with direct regions and business units, contact is between specific contact points including sales groups in the regions. Interestingly only three respondents out of eight, mentioned a change notification process, assessment of product changes or product changes being managed through a Quality department. Two of these companies send a change notification out to the international teams and draft a regulatory plan depending on the responses received back.

4.2.5 Q4. In our company RA in the regions are very much in regional Silo's working with their Sales counterparts with little contact with the manufacturing facilities, do you think that works or how do you think that we can improve communication?

Communication between manufacturing sites and the regions across all companies appear to be siloed for most of the larger corporations. Outside of email communication with direct regions and business units, contact is between specific contact points including sales groups in the regions. In some companies, regulatory and quality teams are resourced in the regions, but the challenge of communication is difficult to surmount. Only one respondent mentioned "this was the case in the past, but things have improved over the past number of years", unfortunately does not provide the detail on how it has improved, this was the most positive response. Two responded that either the company was too small to have this issue, or it was single point contact between RA and external contact. RA communication by its nature veers towards silos but two companies mention 'this [communication] needs to be developed'.

The shortcoming is it can be difficult to see the big picture of the direction the company is moving in, as most business exposure is to regional activity. More communication between different regions and manufacturing sites has the advantages of sharing knowledge, work practices and being part of a global team.

4.2.6 Q5. If applicable to your company, do the RA group share RA/QMS registration information or registrations electronically, if so how do they do this (e.g. electronic system, email, Cloud based technology, other)?

Continuing with the communication theme, most companies are not aware of how international groups share or if they share information. From the manufacturing sites information is primarily transferred though email, *dropbox* or *onedrive* tools.

4.2.7 Q6. Are there metrics around registrations that you are aware of? [time to market planned, priority of registrations, and who decides these].

Regarding metrics, only three companies (all multinationals) have metrics of between 5 to 10 working days for assessment of change, which is surprising as depending on the change this can prompt a re-registration in some jurisdictions. For registration planning five companies had planned registration dates with estimated approval dates. The majority of these are documented between the regulatory plan/strategy or in the device project files. The emphasis is on European, US and Canadian approvals. One MNC regulatory group 'contracts' product submission dates and approval dates with senior regulatory management. These priority regions and devices are tracked by senior management in the business units.

Another multinational measures metrics and reports them as part of an International Management Review. Metrics measured include initial regulatory requests, renewals and tender queries received into the 'international mailbox'. This company measures average days to closure of request and target a 10-working day closure time. This company started with a base level of 20 working days and introduced some 'lean processes' and now achieve a 10-day close out of requests consistently, unless some lengthy legalization of documents is required.

4.2.8 Q7. What kind of document control system does your company have (Fully electronic or centralized Document Control, paper based and electronic)?

Across all companies only one company had a fully integrated electronic system (document controls and regulatory systems) Agile, is customized by external consultants for the company. This system is rolled out to the regions. Four other companies have fully electronic and integrated document control systems and the remaining are a blend of paper based and partially electronic document control systems. Three companies have a system called 'Agile'. One company previously mentioned has it customized to their requirements, the other two companies use it as a document control repository. The other system mentioned in the response is Adaptiv.

4.2.9 Q8. What are the top three difficulties (or most common pain points) you have with product registrations outside of EU and USA.

Interviewees were asked for the top three most common difficulties or 'pain points', associated with registering medical devices in a global environment, (not all companies provided three examples);

- Five respondents had difficulties with navigating and understanding market requirements and obtaining information (standards & local requirements) to support registrations.
- Jointly with three respondents each are lack of regulatory resources, to support the international registrations and language requirements (for translation and labelling).
- Two respondents, had difficulty in their company's reliance on distributors. The companies had no prior visibility to distributor requests to register products thus making planning more difficult.
- One company had difficulties with obtaining materials information, another issue is ensuring the data is current always prior to sending to regional regulatory personnel and translation timelines/cost.
- One company cited accessing information from acquisitions.

It is almost reassuring that all companies to some extent face similar challenges when registering medical devices on a global scale. Wong and Kaiyu (2013) support these findings, in countries that do regulate medical devices, the regulatory landscape is highly variable and continuously changing, resulting in greater challenges associated with transparency, language barriers, and costs. "Regulatory reviews consist of technical and administrative components which can vary significantly between countries, even in the same region. Time frames for approval and the complexity of the approval process vary widely".

4.3 Registration System/Dossier Overview

4.3.1 Background to Design Control and New Product Introduction process:

From the benchmarking five out of the eight companies, had a regulatory plan or regulatory strategy in place and this is how registrations were typically captured and planned though the research and development (R&D) process, through to product launch.

As a very brief background, in general the New Product Introduction (NPI) process is a system that ensures planning and controls are in place, design inputs and design outputs are identified, verification and validations are completed and design reviews are conducted. There are usually specific activities assigned to each phase, but this is not a linear process and some activities may overlap. The multifunctional team (R&D, quality, engineering, regulatory affairs, supply chain, manufacturing and many others depending on the organization), can close or exit that stage of the project, once the activities from that stage are completed and progress onto the next phase of development after the formal review. Figure 5, outlines a simplistic Design control flowchart that outlines the different phases. Phase 1 is typically Research and Planning phase. The product concept is defined and documented into an initial plan. This is where the Design Inputs are considered such as engineering requirements, marketing requirements and the regulatory requirements. This is also when the specific country requirements from the country review in section 2, are provided to the design team as design inputs into the process. Activities that are associated with this Phase 2 the Design phase, are the tasks associated with the design of the device and establishment of the process. Device drawings and prototypes are developed during this phase. Phase 3 is Verification and Validation. These activities and the documents that are an output from this phase (e.g. Sterilization validation, packaging validation and labelling requirements, device validation reports) will support regulatory submissions globally. Phase 4 is when the device is in production and built to an approved process under the Quality Management System (a company may address multiple requirements under its QMS, ISO13485, FDA QSR 820, Ministerial Ordinance 169).
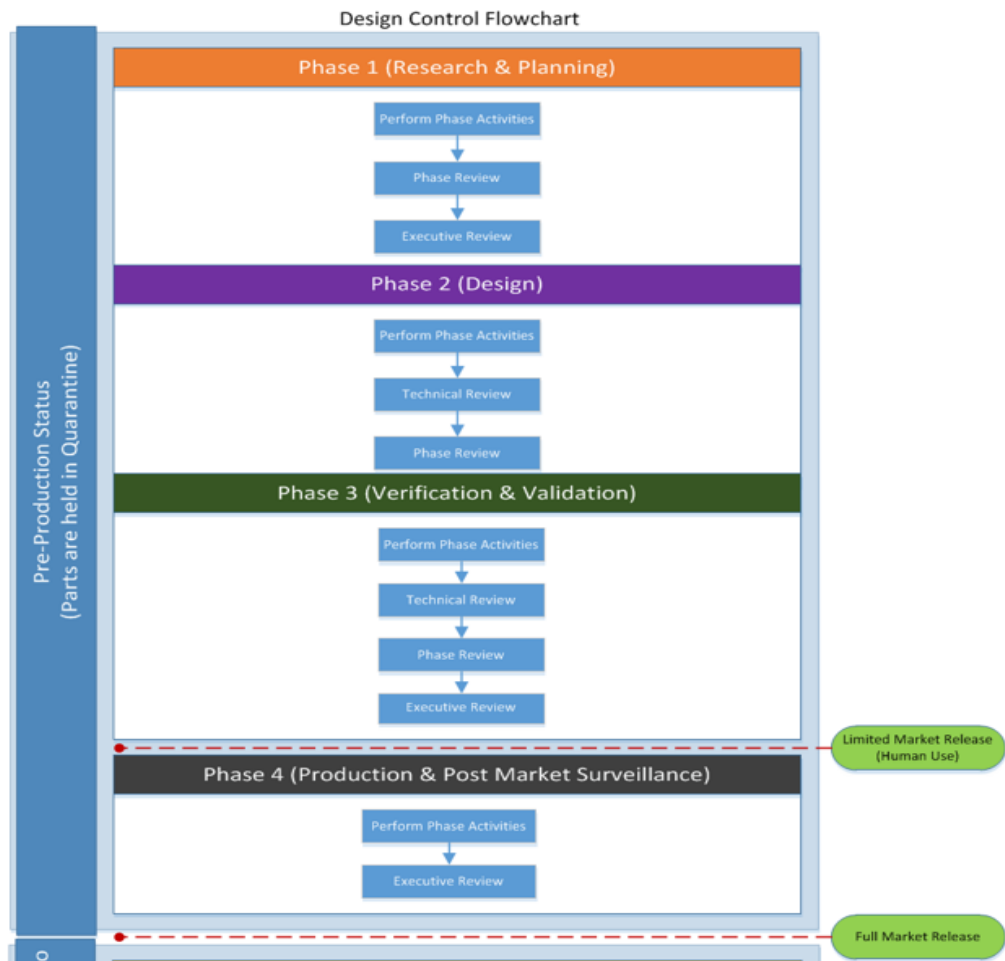
Figure 5, New Product Development/Design Control Process

Under ISO 13485:2016, "applicable regulatory requirements related to the product", section 7.2.1, Determination of requirements related to the product must be considered and under section 7.2.2. Review of requirements related to product "applicable regulatory requirements are met" (ISO/TC 210, 2017). The intent outlined in the ISO Handbook 13485 is the emphasises on the importance of relevant requirements as the basis of new product realization….Product requirements can cover additional factors such as, "regulatory requirements including applicable medical device licensing or facility registrations in the countries or regions where the product is placed on the market", the intended use, performance expectations and delivery schedules (ISO/TC, 2017).

Once initial regulatory approvals, traditionally CE Marking and/or FDA clearances are received, the product can then be released to Europe, USA and to countries with no regulatory requirements.

4.3.2 Regulatory Strategy:

The regulatory strategy is critical as this is the communication tool that regulatory personnel use to feedback specific requirements or design inputs to the project team in Phase 1. Examples of this are South Korea needs sterility testing of the product after sterilization, biocompatibility testing on the actual processed product materials (as opposed to testing on the base constituent materials), or China where devices require a Product Technical Specification for the CFDA type testing labs. The chosen testing centers will test all specification items listed in the device Product Technical Specifications. For each specification item, testing centers will utilize the testing method described by the manufacturer in the Product Technical Specifications.

Where there are upcoming changes that will influence information (or design inputs) on the regulatory strategy. In December 2016 CFDA announced a draft policy change which will allow for direct approval of some types of submission by CDE or CMDE without further review. The scope or medical devices include, Clinical trial approval or class III devices either local or imported. Approval of a technical change for class III and any imported device and license renewal of local class III device and any imported device. Under current procedures after the technical review process is finished by CDE ORCMDE these submissions are forwarded to CDA for administrative approval and license issuing. This new approval will allow CDE or CMDE issue approvals directly which can take a month or so off the approval times. The new policy was planned to be effective from July 1st, 2017 (Brandwood, 2017).

Asia Actual (2015) suggest four product development decisions that will impact sales in Asia as they assume that medical device manufacturers typically launch new products in Asia only after establishing success in US and Europe. Typically, decisions made during the product development process have significant impact on regulatory costs, time to market and time to revenue in Asian markets. These suggestions are;

- Incorporate Asian requirements into product testing, while most CE Marking, test reports are sufficient. As previously discussed South Korea require some additional requirements that include additional time points in sterility testing and includes Certification Body (CB) scheme certification

for electrical safety certification. China as also discussed will require test certificates for type testing from one of the local CFDA certified test laboratories.

- The second point is to design the Clinical trial if it is applicable, to include Asian Requirements. Whole clinical trials in support of FDA Clearances or CE Marking are typically acceptable. Additional information may be required such as; CSCSO in India will generally accept clinical data from outside India (except for drug-eluting stents, etc.), but may want to see ethnicity data. Again, Chinese registration of Class II and III devices will require a limited local clinical trial data. Pharmaceutical and Medical Devices Agency (PMDA) in Japan offers a Clinical Trial Consultation just for this purpose. One may also consider the 'Harmonization by Doing' program in Japan, which is designed to reduce the cost and time to register novel devices significantly by shifting 25% of a patient sample from a US clinical trial to Japan (Asia Actual, 2015).

- Selecting a fully recognized Notified Body, to avoid redundant Quality Management Systems Audit inspections, examples such as the Australian government has a mutual recognition treaty with the European Union whereby medical devices with CE Mark avoid local conformity assessment, greatly accelerating market listing in Australia.

However, since the 2012 PIP company silicone impact scandal in Europe (Ramakrishna *et al*, 2015), the Australian government has begun to deny recognition of certain Notified Bodies. Therapeutic Goods Administration (TGA) is "currently undertaking 'confidence building' activities in liaison with European regulatory authorities" (TGA.gov.au, 2014).

In Japan, if a device qualifies for Pre-Market Certification (most Class II and some Class III devices), conformity assessment will be performed by a private Registered Certification Body. Seven of the fourteen RCBs also provide CE Mark in Europe. A similar situation applies to most class II devices in Korea. In Malaysia's new and evolving regulatory system, all devices must undergo local conformity assessment, though the assessment for devices with reference country approval is greatly expedited. In these cases, manufacturers may request synergies if their Notified

Body is also their RCB in Japan or Third-Party Reviewer in Malaysia and South Korea (Asia Actual, 2015).

4.3.3 Through the benchmarking responses, one company uses this regulatory strategy tool very well and utilizes the stage gate process exits. At each stage gate of the process, prior to the stage exit meeting, this regulatory strategy is pushed out to the regions. At the start of the project the detail may be vague as registration dates are based on launch dates and approval dates but as the project develops timelines become fixed. At each stage gate review the strategy document becomes more refined and granular in detail.

A drawback this company finds is, once the approved dossiers are sent out to the regions, there is very little communication until the products start being approved. This 'loss of control' can be frustrating to the design team therefore the communication must become more consistently a two-way conversation. This simple but effective strategy is proposed to be used at the start of each design phase. The manufacturing site pushes out status notifications of the project to the International group, who respond by updating the regulatory strategy with any change in the regional plans for registration. Towards the end of stage 3, upon successful device and process validation, additional notifications are pushed out to the International group, in order that countries that have no regulations can commence with product supply. Also, countries such as Japan can start compiling their registration submissions. Regulatory personnel in the regions must reach back in to the manufacturing sites and provide updates to the status of the registration of the product in their regions so the project team continue to have visibility and the communication flow becomes more natural and does not become a 'black hole' on either side.

Another key use for the regulatory strategy document is for making business decisions. For countries like South Korea or countries that require additional testing as part of the development process, use the strategy document at an early stage gate exit (e.g. Stage Gate 2), to make the decision for either the R&D team carry out the testing, or the company pay a local test lab in the region to test in parallel. The decision for the team and business, will be down to cost and timelines, but now the requirement has been considered early in the process, not as an afterthought once the product has launched.

This proposed Global Submission Dossier outline will incorporate elements from the benchmarking exercises.

4.4 Submission Format

4.4.1 The comparative analysis of technical documentation formats in Appendix 2 illustrates an outline of the STED, CSDT and the IMDRF Table of Content (ToC) formats mapped against each other. This exercise was conducted in order to consider which of these formats or amalgamation of the formats could be used to propose an optimal format for a Global Registration Dossier and to verify that the registration requirements for countries that utilise the STED and CSDT submission formats are included. The most common formats used are the STED and CSDT. While the IMDRF Table of Contents (ToC) format appears not to be gaining traction in the regions it has some positive points regarding construction and level of detail. The IMDRF ToC format is intended for structuring electronic submissions however the format lends itself to a comprehensive global registration dossier when populated with STED and CSDT detail in the required sections of the ToC format. From an informal poll within the authors current company among regional regulatory personnel based in Asia, Europe Middle East and Africa (EMEA), Japan, North America, these regions do not have IMDRF ToC format on their radar however Brazil is in pilot stage with ToC. At a recent (2017) ANVISA seminar the audience were informed that it will take a year to implement but it will not replace the current ANVISA dossier for registration but will be an alternative pathway for medical device registrations in the future. Asian countries Malaysia and Singapore have implemented ASEAN CSDT and many other countries in the region are phasing over the CSDT format. The IMDRF ToC pilot stage ended in September 2016. At this time, there has been no update regarding the endorsement of ToC, which was to commence in January 2017 (IMDR/RPS WG/N26Final:2015).

4.4.2 IMDRF have issued a comparison document to illustrate how STED and CSTD document formats are aligned and how they are mapped against each other. There had been no comparison document available that outlined the

mapping of the three document formats (STED, CSTD and ToC), therefore the document in Appendix 2, has been developed as part of this dissertation to compare the two most commonly used formats with the newer Table of Contents format.

From that comparative exercise (Appendix 2) the IMDRF Table of Contents (ToC) is the format that has been chosen as the optimal for the Global Registration Dossier. It has the most comprehensive table of contents and all International registration requirements can be accommodated within it. The CSDT requirements are a subset of ToC, similar to the STED requirements being a subset of CSDT. Wong and Kaiyu (2013) concur with this observation that the "CSDT Documentation largely aligns with STED, with some key differences such as the Device Description section, which contains the following additional items: potential adverse effects and alternative therapies". They further discuss the benefits of the alignment between the CSDT and STED is that when adopted by ASEAN member countries, 80– 90% of the documentation submitted Food and Drug Administration can also be used to complete the submissions for the local ASEAN market, thereby reducing time in preparing the submission dossier. This alignment also provides regulators of member countries with a level of confidence that products which have been approved in countries where the STED has been adopted, product conforms to the same standards as the ASEAN Member countries.

4.4.3 Folder structure to support Table of Contents (ToC)

The Table of Contents (ToC) structure has seven chapters in total each of which is allocated specific information. ToC has three additional chapters that are not part of the STED or CSDT formats and these are Chapter 1, Regional Administration, Chapter 6A and 6B, Quality Management Systems for Procedures and Devices respectively. Chapters 6A and 6B are written in terms of ISO13485 (2003) the Quality Management System. The current ISO13485 harmonised standard is 2012 and ISO13485:2016 is in transition, however it is the ISO13485(2003) documented in this version outlined in the IMDRF document. The final released version of the ToC format may make provision for the most recent ISO13485 standard. It is proposed that the ToC format is the

most comprehensive format for a Global Registration dossier with a proposed additional folder outside the documented IMDRF structure. Upon review of the mapping document in Appendix 2, a gap was identified in the ToC format. While it is a very suitable format that considers most of the data required for registration in emerging markets, to work as a Global Registration Dossier, the element missing is the specific Country information, such as licences, Declarations of Conformity, Essential Principles specific to each Country, particularly those outside of the IMDRF. The additional proposed chapter that is included, is Chapter 7, titled 'Regions' and will be discussed as part of this section. Figure 6 is an outline of the IMDRF format from Chapter 1 thought to 6B. The overview chapters also contain the addition of the proposed Chapter 7.
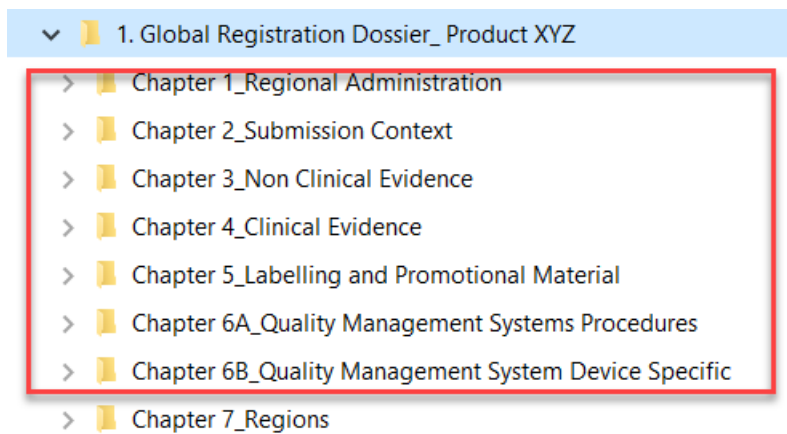
Figure 6, Overview of the format of Global Registration Dossier using ToC.

In the following sections, each Chapter will be described with an overview of the information to be contained within. Note that the IMDRF Final Document (2014) nIVD Marketing Authorisation (MA) TOC) outlines particular regional content for CFDA, HC, USFDA, TGA, ANVISA, EU, Japan and Russia in applicable sections for that jurisdiction.

4.4.4 Chapter 1 outlines the Regional Administrative section. Figure 7 is an exploded illustration with sub folders of the contents as per the ToC. Within this section many key registration documents will be organised. Documents which form the basis of registration requirements for example the Certificates of Free Sale, EC certificates, Quality Management Certificates can be stored in this

location. US FDA information (device listing, user fees, Class III summary) information is also included in this format. Manufacturing facility and Sterilisation facility information is required in many regions particularly Japan and India where submissions go to the detail of floor plans and of the manufacturing facility and Sterilisation facilities in Japan. Audit Reports and Quality Manuals are all typical documentation requested as part of global registration.

Figure 7, Chapter 1 the Submission Context.

4.4.5 Chapter 2 is where the product information starts being complied. Figure 8 provides an overview to the structure of this section.

Figure 8, content of chapter 2.

Chapter 2 provides the General summary of submission, e.g. the statement of device description. The comprehensive device description and principle of operation provides an in-depth description of, the intended use and patient population, principle of operation etc and the product specifications, where the device is already registered (this is also specific section of the CSDT), device indications for use, alternate therapies, variants, and accessories. The ToC accommodates in Ch2.2.4. Engineering or product drawings, prints, photographs of the deice and methods of sterilisation (the sterilisation report is not filed in this section) are maintained here. In addition, the ToC format requires information such as device vigilance, recalls and Field safety actions for the jurisdictions that the device is registered in. This information is to be maintained and updated as RA personnel require and utilise the information.

4.4.6 Chapter 3, Non-Clinical Evidence. This chapter provides particular focus on Design verification and Design Validation activity and includes the maintenance of with Verification and Validation device reports. Figure 9, outlines the main headings of the chapter.

- Chapter 3_Non Clinical Evidence
  - 3.1 Chapter Table of Contents
  - 3.2 Risk Management
    - 3.2.1 Risk Management Plan
    - 3.2.2 Risk Reports
    - 3.2.3 Usability and Human Factors
  - 3.3 Essential Principles (EP) Checklist
  - 3.4 Standards
    - 3.4.1 List of Standards
    - 3.4.2 Declaration and or Certification of Confomity
  - 3.5 Non Clinical Studies
    - 3.5.01 Physical and Mechanical Characterization
    - 3.5.02 Chemical_Material Characterization
    - 3.5.03 Electrical Systems safety_Mechanical and Environmental protection_Electromagnetic Compatibility
    - 3.5.04 Radiation Safety
    - 3.5.05 Software_Firmware
      - 3.5.5.01 Software_Firmware Description
      - 3.5.5.02 Hazard Analysis
      - 3.5.5.03 Software Requirement Specification
      - 3.5.5.04 Architecture Design Chart
      - 3.5.5.05 Software Design Specification
      - 3.5.5.06 Traceability Anaysis
      - 3.5.5.07 Software Development Environment Description
      - 3.5.5.08 Software Verification and Validation

- 3.5.06 Biocompatibility and Toxicology Evaulation
- 3.5.07 Non Material Mediated Pyrogenicity
  - 3.5.7.1 Electrical Safety Reports
  - 3.5.7.2 ElectroMagnetic Compatibility (EMC) Testing
- 3.5.08 Safety of Materials of Biological Origin
  - 3.5.8.1 Sterilsation Adoption Memos
  - 3.5.8.2 Sterlisation protocol & Report
  - 3.5.8.3 Residual Report
  - 3.5.8.4 Revaldiation Reports
- 3.5.09 Sterilization Validation
- 3.5.10 Animal Testing
- 3.5.11 Usability_ Human Factors
- 3.6 Non clinical biblography
- 3.7 Expiration Period and Package Validation
- 3.8 Other non-clinical Evidence

Figure 9, provides an overview of chapter 3

Chapter 3 involves a comprehensive listing of all the test protocols and reports that are required to establish conformity to the essential principles checklist of the device in question. Some sections will not apply depending on the device. Device Risk Management documents, Essential Principles and non-clinical testing is included under chapter 3.

Test summaries, protocols, reports, raw data for each of the applicable test reports are organised in this section. If applicable software requirements and design specification alongside verification and validation are addressed. Electrical safety testing and Electromagnetic Compatibility (EMC) requirements are considered. Biocompatibility testing, tissues of biological origin, sterilisation, residual toxicity, reprocessing if applicable to the device, animal testing etc are all allocated locations.

4.4.7 Chapter 4 Clinical Evidence

Figure 10 outlines the Clinical Evidence requirement of the device.

Figure 10, Clinical Evidence Overview

Chapter 4 is divided between clinical Evaluation via literature route and the clinical trials. It is a comprehensive format for registrations and includes the trial synopsis, device specific trials, Trial data, consent forms, IRB reviews, study description and statistical data. All clinical labelling is maintained in this section also.

4.4.8 Chapter 5 outlines the products Labelling and promotional material

Figure 11 depicts the outline of the structure of this section.

Figure 11, Overview of chapter 5, Labelling and Promotional material

The device labelling and Instructions for use (IFU) are maintained in this section. There are many differing labelling and IFU requirements outside of just translating the English version. China, Japan, Korea and Brazil amongst others require the licence number to be printed on the label in addition to it been provided in the local language. China requires simple Chinese, Japan require Japanese and Brazil require Brazilian Portuguese. TGA require the sponsor contact information (this can be a separate label). Hong Kong require device listing number (HK MD No###). eLabelling, patient labelling, physician labelling are also specific sections in this format.

4.4.9 Chapter 6A and 6B

Figure 12 outlines section 6A and 6B

Chapter 6A_Quality Management Systems Procedures
> 6A.1 Cover letter
> 6A.2 Table of Contents
> 6A.3 Administrative
>> 6A.3.1 Product Descriptive Information
>> 6A.3.2 General Manufacturing Information
>> 6A.3.3. Required Forms
> 6A.4 Quality Management System Procedures
> 6A.5 Management Responsbilities Procedures
> 6A.6 Resource Management pocedures
> 6A.7 Product Realisation procedures
>> 6A.7.1 Design and Development Procedures
>> 6A.7.2 Purchasing Procedures
>> 6A.7.3 Production and service controls procedures
>> 6A.7.4 Contol of monitoring and measuring devices procedures
> 6A.8 QMS Measurement analsysis and improvement procedures
> 6A.9 Other QMS procedures information
Chapter 6B_Quality Management System Device Specific
> 6B.1 Table of Contents
> 6B.2 QMS Information
> 6B.3 Management Responsibilities info
> 6B.4 Resource Management information
> 6B.5 Device Specific Quality Plan
> 6B.6 Product Realisation information
>> 6B.6.1 Design and development information
>> 6B.6.2 Purchasing information
>> 6B.6.3 Production and service controls information
>> 6B.6.4 Control of monitoring and measuring devices information
> 6B.7 QMS analysis and improvement information
> 6B.8 Other device specific QMS information

Figure 12, Overview of Quality Management and Quality Device information.

Figure 12 is set out as per the language in ISO 13485;2003, *Medical devices -- Quality management systems -- Requirements for regulatory purposes*, therefore the documents from the quality system and that are generated for the product are maintained in this section.

4.4.10 Chapter 7 Regions

This is the proposed additional chapter, for the regions. All country folders will be set up with similar format and outside of the submissions, regulator questions and responses and any other country specific information for the device can be held here. Figure 13 below outlines a proposed format for these folders.
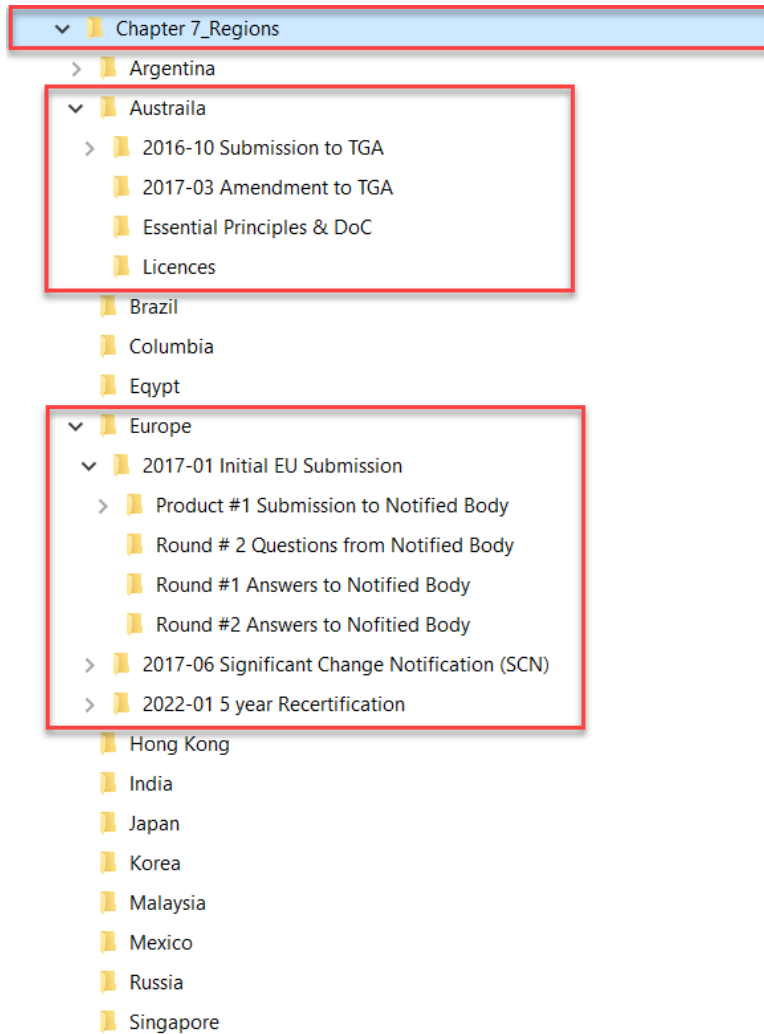
Figure 13, proposed regions folder.

From the two exploded view folders, Australia and Europe used as the example with similar sub folders such as certificates/licences/renewal information and submissions, dated with a year and month format. This will make it easy to identify how recent a submission is in any of the countries. Again, folders are split into submission, if amendments are made to licences or certification and what those are. By providing this additional chapter, it provides transparency to

both the manufacturing site and regional regulatory personnel to see dates submissions were made on, provides ease of location for certificates and licences used in country registrations, particularly those that utilise IMDFR Reference country approvals for expedited or abbreviated registration pathways.

In Figure 3, section 2.4, it was discussed that while Theisz (2015), mapped the DHF to the STED format, in most companies utilising the Design History File as the primary source for regulatory submissions, was not immediately feasible. However, building on this thought and using a multi phased approach a company could lever off this methodology. It is the ideal benchmark for a company to aim for, through a strategic and multiphase leaning of the registration process and training.

The nirvana for regulatory teams would be to utilise a fully integrated electronic document system that stored the product information and quality systems information. In an ideal world, the documents that the multifunctional teams generate, to a level of quality that they can be placed directly into a ToC format for each device as it goes through the design control process and subsequently taken directly out of these folders to be used in global regulatory submissions. From this location, everyone can access all supporting information and it is transparent to all functions.

While this may seem like nirvana, in reality smaller companies may not be a position to implement a fully electronic document system. However, the ToC format can still be utilised in its very basic form as the methodology in setting up device design files, it then does not matter if the company has one product or one hundred products. The re-creation of many iterations of submission files can be reduced for any size company. Not all of the sections of the ToC will be applicable for every device. Likewise, some of the additional information required in Chapter 1, the regional Administration section will be applicable, it can be used depending on the target markets the company chooses to launch products in.

For larger companies that do not have a fully integrated electronic document system, an interim solution is to introduce this ToC format, and it can be shared across regions in cloud based technology such as one drive. A full cost benefit

analysis would need to be engineered to customise a fully integrated electronic system.

"The Best Value Future State Solution (BFSS) is the solution that results in the most beneficial redesign item as viewed by the items stakeholders. It is the best combination of desired cost, implementation cycle time, risk and results" (Harrington *et al*, 1997).

Chapter 5 Conclusions:

5.1 The aim of the dissertation was to collate registration requirements for specific markets and to embed those requirements into a design control process, to ensure delivery of regional requirements and to support global medical device submissions. Using these global regulatory registration requirements as an input, they are considered in existing design control and development processes of a product by utilising the requirements in ISO13485:2016 Quality Management Systems.

In understanding regulatory and registration requirements, this will assist medical device manufacturers identify where a company can reduce registration time in some markets once it is available for commercialisation. By being aware of the fluidity of these requirements, particularly in the Asia Pacific regions a business strategy in parallel with regulatory strategy can provide the business with optimum solutions.

A gap in the literature has been identified for some countries, which makes it difficult for manufacturers to access accurate information, particularly countries such as Argentina and Columbia where there is no English translation of the requirements. This dissertation may assist with some updated general registration information.

An objective of this dissertation was to propose a Global Registration Dossier format for medical devices that will facilitate worldwide submissions. This has been achieved by the benchmarking process which entailed mapping the existing harmonisation groups (IMDRF and ASEAN) document formats (STED and (CSDT), in parallel with the mapping of the Table of contents format. With the additional proposed section included for the regional submissions, the Table of Contents structure is an optimal format that considers all the global requirements. The Utopic state is when regulatory personnel can pull directly from a products Design History file with minimum editing and word crafting. A company can grow and mature into developing phases of implementation from basic folder structures in a regulatory department, into training and awareness across all the functions that generate the device Design History File containing documents that are submission ready. By championing a multi phased project of development and training across multi functions who generate medical device data as part of

the research and development process or a manufacturing process, can over a number of years build a consistent system, where the future state is to generate a document as part of the DHF. This DHF will be stored on a fully integrated database where regulatory specialists can pull documents straight from the required format into their submission.

There will always be a need for the RA professional to provide the narrative for device submissions, but well written, structured test reports will facilitate a timely review and approval.

Exploiting the timing of the implementation of the European Medical Device Regulation is the perfect timing to consider a Global Registration Dossier format particularly for manufacturers that are required to reformat or reclassify devices.

5.2 Additional work:

Additional work needs to be completed, to implement a fully integrated electronic system. A project scope and costing for the project would be required initially. From there a company can determine the Best Value Future State Solution for them.

In the long term, a multi phased project of training and awareness across the many functions, that contribute documents to a design History File should be undertaken. Any size company, outside of financial constraints of implementing a fully electronic integrated system, can utilise cloud based technology can lean the design control process and regulatory process to deliver safe, well designed, and effective medical devices to the market.

As an interim solution, this dossier format can be used for companies on a cloud based platform to share registration data across regions or as the starting point of developing their own systems.

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Glossary of Terms

AHWP: Asian Harmonization Working Party

ARGMD: Australian regulatory guidelines for medical devices

AMMD: ASEAN Medical Device Directive the Association of Southeast Asian Nations (ASEAN) signed a formal agreement that harmonized medical device regulations. This agreement, formally called the ASEAN Medical Device Directive (AMDD), provides a more straightforward path to the market for medical device manufacturers (Pacific Bridge Medical, 2016).

Apostilled: An Apostille is a certificate issued by the Department of Foreign Affairs verifying the genuineness of the signature and/or seal of a public officer e.g. a Notary Public, on a public document and the capacity in which he or she has acted (notarypublic.ie, 2017).

APEC: Asia Pacific Economic Cooperation; Asia-Pacific Economic Cooperation (APEC) is a forum for 21 Pacific Rim member economies that promotes free trade throughout the Asia-Pacific region (apec.org, 2017).

ASEAN: Association of Southeast Asian Nations; The Association of Southeast Asian Nations (more commonly known as ASEAN) is a political and economic organization aimed primarily at promoting economic growth and regional stability among its members (ASEAN.ORG).

CFG: Certificate of Foreign Government: Certificate to Foreign Government (CFG) A Certificate to Foreign Government is issued for legally marketed devices in the United States that are in compliance with the requirements of the Federal Food, Drug, and Cosmetic Act (FD&C). Eligibility Note: Are cleared or approved by FDA for marketing in the U.S. (fda.gov).

CFS: Certificate of Free Sales are documents used in the registration of renewal of the registration of device products in third counties (i.e. Countries outside the

European Economic Area) or to accompany a shipment of that product (HPRA.ie).

CMDCAS: Canadian Medical Device Conformity Assessment Scheme; (CMDCAS) is a system designed to implement Canadian regulations requiring come medical devices be designed and manufactured under a registered quality management system (QMS).

CSDT: Common Submission Dossier Template, ASEAN Medical Device Directive, submission format.

Clinical Evaluation: The assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as the manufacture intended. (IMDRF, 2012).

DoC: Declaration of Conformity, as part of the conformity assessment procedures, the manufacturer of a medical device is required to make a declaration of Conformity which declared the device complies with; the applicable provisions of the essential principles, the classification rules and an appropriate conformity assessment procedure (tga.gov.au).

Essential Principles (EP): (or Essential Requirements (ERs) in Europe), are the requirements for safety and performance specified in Country Regulations. EP/ERs are divided into Part I (i.e., – general requirements) and Part II (i.e., – requirements for design and construction). Evidence of conformity must be provided for all general requirements in Part 1 for all devices—regardless of risk classification, design or construction. The Design and construction requirements in Part 2 may be not applicable, depending upon your device (medical device academy, 2013).

Gulf Cooperation Council (GCC), political and economic alliance of six Middle Eastern countries—Saudi Arabia, Kuwait, the United Arab Emirates, Qatar, Bahrain, and Oman. The GCC was established in Riyadh, Saudi Arabia, in May 1981.

IMDRF: International Medical Device Regulators Forum

MDR: Medical Device Regulation

MRA: Mutual Recognition Agreement, A mutual recognition agreement (MRA) is an international agreement by which two or more countries agree to recognize one another's conformity assessments. A mutual recognition arrangement is an international arrangement based on such an agreement.

PAHO: Pan American Health Organization

STED: Summary Technical Documentation Summary Technical Documentation (STED) was developed to drive more standardization of medical device regulatory submissions across markets. STED is recognized by US, European, Canadian, Australian and Japanese regulators, as well as in other markets (Emergo, 2016).

ToC: Table of Contents format, IMDRF Proposed submission format.

Appendix 1: Websites of Regulatory Agencies

Australia TGA: https://www.tga.gov.au/industry

Argentina ANMAT: http://www.anmat.gov.ar/ (Spanish).

Brazil ANVISA: http://portal.anvisa.gov.br/contact-us

Canada HC: https://www.canada.ca/en.htm (English site).

China CFDA: http://eng.sfda.gov.cn/WS03/CL0758/ (English site).

Columbia INVIMA: https://www.invima.gov.co/

Egypt: http://www.eda.mohp.gov.eg/Articles.aspx?id=46

Hong Kong MDCO: http://www.mdco.gov.hk/english/mdacs/mdacs.html

India CDSCO: http://cdsco.nic.in/forms/list.aspx?lid=1580&Id=1

Japan PMDA: https://www.pmda.go.jp/english/# and
MHLW http://www.mhlw.go.jp/english/

Malaysia: https://www.mdb.gov.my/mdb/ (English version of site).

Mexico COFRPRIS: http://www.cofepris.gob.mx/Paginas/Idiomas/Ingles.aspx

Russia: http://www.roszdravnadzor.ru/en (English version of site).

Saudi Arabia: https://mdma.sfda.gov.sa/

Singapore: http://www.hsa.gov.sg/content/hsa/en.html

South Korea: http://www.mfds.go.kr/eng/index.do?nMenuCode=137

Taiwan: https://www.fda.gov.tw/EN/lawContent.aspx?cid=5063&id=1440

Turkey: http://www.titck.gov.tr/TibbiCihaz (English Version of site).

Appendix 2: STED_CSDT and Table of Contents (ToC) Mapping

	ToC Non IVD	STED Content as per AHWP WG1a/F004:2013	CSDT Format as per AHWP WG1a/F004:2013
CHAPTER 1 – REGIONAL ADMINISTRATIVE			
CH1.01	Cover Letter		
CH1.02	Submission Table of Contents		
CH1.03	List of Terms/Acronyms		
CH1.04	Application Form/Administrative Information		
CH1.05	Listing of Device(s)		
CH1.06	Quality Management System, Full Quality System or Other Regulatory Certificates		
CH1.07	Free Sale Certificate		
CH1.08	User Fees		
CH1.09	Pre-Submission Correspondence and Previous Regulator Interactions		
CH1.10	Acceptance for Review Checklist		
CH1.11	Statements/Certifications/Declarations of Conformity		
CH1.11.1	Performance and Voluntary Standard		
CH1.11.2	Environmental Assessment		
CH1.11.3	Clinical Trial Certifications		
CH1.11.4	Indications for Use Statement with Rx and/or OTC designation Enclosure		
CH1.11.5	Truthful and Accurate Statement		
CH1.11.6	USFDA Class III Summary and Certification		
CH1.11.7	Declaration of Conformity	13.0 Declaration of Conformity	
CH1.12	Letters of Reference for Master Files		
CH1.13	Letter of Authorization		
CH1.14	Other Regional Administrative Information		
CHAPTER 2 – SUBMISSION CONTEXT			
CH2.1	Chapter Table of Contents	No content at this level	No content at this level
CH2.2	General Summary of Submission	no requirement	3.0 Executive Summary
CH2.3	Summary and Certifications for Premarket Submissions		
CH2.4	Device Description	6. 1 Design Description and Product Specifications including variants 6.2 Product Specifications	4.2 Device Description
CH2.4.1	Comprehensive Device Description and Principle of Operation	6.1 Design Description and Product Specifications including variants	4.2.1 Device Description & features
CH2.4.2	Description of Device Packaging		4.4 Device Labelling
CH2.4.3	History of Development	8.1 Device Design 8.3 Design and Manufacture	4.4 Manufactuing information
CH2.4.4	Reference and Comparison to Similar and/or Previous Generations of the Device	6.3 Reference to similar and previous generations of the device	n\a
CH2.4.5	Substantial Equivalence Discussion[510k specific]		
CH2.5	Indications for Use and/or Intended Use and Contraindications	6.1 Design Description and Product Specifications including variants 6.2 Product Specifications 7.0 Labelling [*point 4.2.4 IFU*]	4.2 Device Description 4.2.2 Intended Use 4.2.3 Indications 4.2.4 Instructions for Use 4.2.5 Contraindications 4.2.6 Warnings 4.2.7 Precautions 4.2.8 Potential Adverse Events 4.2.9 Alternate therapy
CH2.5.1	Intended Use; Intended Purpose; Intended User; Indications for Use		4.2.2 Intended Use 4.2.3 Indications 4.2.4 Instructions for Use
CH2.5.2	Intended Environment/Setting for use		4.2.3 Indications
CH2.5.3	Pediatric Use		4.2.2 Intended Use [USA Specific]
CH2.5.4	Contraindications For Use		4.2.5 Contraindications 4.2.6 Warnings 4.2.7 Precautions
CH2.6	Global Market History	1.1 Marketing History 8.1 Clinical Evaulation Summary 8.3 Post Market Surveillence	3.0 Executive Summary (Summary of RA Approvals Global)
CH2.6.1	Global Market History	1.1 Marketing History	3.0 Executive Summary (Summary of RA Approvals Global)
CH2.6.2	Global Incident Reports and Recalls		3.0 Executive Summary
CH2.6.3	Sales, Incident and Recall Rates		3.0 Executive Summary
CH2.6.4	Evaluation/Inspection Reports [TGA Specific]	No content at this level	No content at this level
CH2.7	Other Submission Context Information	8.1 Device Design 8.2 Manufacturing Process 8.3 Design and Manufacture	4.6 Manufacturer Information 4.6.1 Manufacturing Process 4.2.9 Alternate Therapies
CHAPTER 3 – NON-CLINICAL EVIDENCE			
CH3.1	Chapter Table of Contents	No content at this level	No content at this level
CH3.2	Risk Management	10.0 Risk Analysis and Control Summary	4.5 Risk Analysis 4.5.1 Results of Risk Analysis

CH3.3	Essential Principles (EP) Checklist	9.0. ER/EP Checklists	4.1 Relevant Essential Principles and method used to Demonstrate Confomity
CH3.4	Standards	11.0 Verification &Validation Summary and Reports	4.3 Summary of Design and Validation Documents
CH3.4.1	List of Standards	11.0 V&V Summary Reports	4.3 Summary of Design and Validation Documents
CH3.4.2	Declaration and/or Certification of Conformity	13.0 Declaration of Conformity	
CH3.5	Non-clinical Studies	11.0 Verification &Validation Summary and Reports	4.2.11 Other relevant specifications 4.3 Summary of Design and Validation Documents
CH3.5.01	Physical and Mechanical Characterization	11.0 Verification &Validation Summary and Reports	4.2.10 Materials 4.2.12 Other Descriptive information 4.3 Summary of Design and Validation Documents
CH3.5.01.1	[Study description, study identifier, date of initiation]	11.0 Verification &Validation Summary and Reports	
CH3.5.01.1.1	Summary	No content at this level	No content at this level
CH3.5.01.1.2	Full Report	No content at this level	No content at this level
CH3.5.01.1.3	Statistical Data	11.0 Verification &Validation Summary and Reports	
CH3.5.02	Chemical/Mechanical Characterization	11.0 Verification &Validation Summary and Reports	4.2.11 Other relavant specifications
CH3.5.02.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH3.5.02.1.1	Summary	No content at this level	No content at this level
CH3.5.02.1.2	Full Report	No content at this level	No content at this level
CH3.5.02.1.3	Statistical Data	11.0 Verification &Validation Summary and Reports	
CH3.5.03	Electrical Systems: Safety, Mechanical and Environmental Protection, and Electromagnetic Compatibility	11.0 Verification &Validation Summary and Reports	4.2.11 Other relevant specifications
CH3.5.03.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH3.5.03.1.1	Summary	No content at this level	No content at this level
CH3.5.03.1.2	Full Report	No content at this level	No content at this level
CH3.5.03.1.3	Statistical Data	No content at this level	No content at this level
CH3.5.04	Radiation Safety	11.0 Verification &Validation Summary and Reports	4.2.11 Other relavant specifications
CH3.5.04.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH3.5.04.1.1	Summary	No content at this level	No content at this level
CH3.5.04.1.2	Full Report	No content at this level	No content at this level
CH3.5.05	Software/Firmware	4.7 Firmware and Software (if applicple) 11.6 Software Verification and Validation	4.2.11 Other relevant specifications 4.3.1.1 Software validation
CH3.5.05.01	Software/Firmware Description	4.7 Firmware and Software (if applicple) 11.6 Software Verification and Validation	4.3.1.1 Software validation
CH3.5.05.02	Hazard Analysis	No content at this level	No content at this level
CH3.5.05.03	Software Requirement Specification	No content at this level	No content at this level
CH3.5.05.04	Architecture Design Chart	No content at this level	No content at this level
CH3.5.05.05	Software Design Specification	No content at this level	No content at this level
CH3.5.05.06	Traceability Analysis	No content at this level	No content at this level
CH3.5.05.07	Software Development Environment Description	No content at this level	No content at this level
CH3.5.05.08	Software Verification and Validation	No content at this level	No content at this level
CH3.5.05.08.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH3.5.05.08.1.1	Summary	No content at this level	No content at this level
CH3.5.05.08.1.2	Full Report	No content at this level	No content at this level
CH3.5.05.08.1.3	Statistical Data	No content at this level	No content at this level
CH3.5.05.09	Revision Level History	No content at this level	No content at this level
CH3.5.05.10	Unresolved Anomalies (Bugs or Defects)	No content at this level	No content at this level
CH3.5.06	Biocompatibility and Toxicology Evaluation	11.0 Verification &Validation Summary and Reports 11.4 Biocompatiblity	4.2.10 Materials 4.2.12 Other Descriptive information
CH3.5.06.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH3.5.06.1.1	Summary	No content at this level	No content at this level
CH3.5.06.1.2	Full Report	No content at this level	No content at this level
CH3.5.06.1.3	Statistical Data	No content at this level	No content at this level
CH3.5.07	Non-Material-Mediated Pyrogenicity	11.0 Verification &Validation Summary and Reports	
CH3.5.07.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH3.5.07.1.1	Summary	No content at this level	No content at this level
CH3.5.07.1.2	Full Report	No content at this level	No content at this level
CH3.5.07.1.3	Statistical Data	No content at this level	No content at this level

CH3.5.08	Safety of Materials of Biological Origin (human/animal)	11.0 Verification &Validation Summary and Reports 11.4 Biological Safety	4.3.1.2 Devices containing Biological Material
CH3.5.08.1	Certificates		
CH3.5.08.2	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH3.5.08.2.1	Summary	No content at this level	No content at this level
CH3.5.08.2.2	Full Report	No content at this level	No content at this level
CH3.5.08.2.3	Statistical Data	No content at this level	No content at this level
CH3.5.09	Sterilization Validation	11.5 Sterilisation	
CH3.5.09.1	End-User Sterilization	11.5 Sterilisation	
CH3.5.09.1.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH3.5.09.1.1.1	Summary	No content at this level	No content at this level
CH3.5.09.1.1.2	Full Report	No content at this level	No content at this level
CH3.5.09.1.1.3	Statistical Data	No content at this level	No content at this level
CH3.5.09.2	Manufacturer Sterilization		
CH3.5.09.2.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH3.5.09.2.1.1	Summary	No content at this level	No content at this level
CH3.5.09.2.1.2	Full Report	No content at this level	No content at this level
CH3.5.09.2.1.3	Statistical Data	No content at this level	No content at this level
CH3.5.09.3	Residual Toxicity		
CH3.5.09.3.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH3.5.09.3.1.1	Summary	No content at this level	No content at this level
CH3.5.09.3.1.2	Full Report	No content at this level	No content at this level
CH3.5.09.3.1.3	Statistical Data	No content at this level	No content at this level
CH3.5.09.4	Cleaning and Disinfection Validation		
CH3.5.09.4.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH3.5.09.4.1.1	Summary	No content at this level	No content at this level
CH3.5.09.4.1.2	Full Report	No content at this level	No content at this level
CH3.5.09.4.1.3	Statistical Data	No content at this level	No content at this level
CH3.5.09.5	Reprocessing of Single Use Devices Validation Data		
CH3.5.09.5.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH3.5.09.5.1.1	Summary	No content at this level	No content at this level
CH3.5.09.5.1.2	Full Report	No content at this level	No content at this level
CH3.5.09.5.1.3	Statistical Data	No content at this level	No content at this level
CH3.5.10	Animal Testing	11.7 Animal Testing	4.2.11 Other relavant specifications 4.3.1 PreClnical Studies
CH3.5.10.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH3.5.10.1.1	Summary	No content at this level	No content at this level
CH3.5.10.1.2	Full Report	No content at this level	No content at this level
CH3.5.10.1.3	Statistical Data	No content at this level	No content at this level
CH3.5.11	Usability/Human Factors	7.5 Usability	4.2.11 Other relavant specifications
CH3.5.11.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH3.5.11.1.1	Summary	No content at this level	No content at this level
CH3.5.11.1.2	Full Report	No content at this level	No content at this level
CH3.5.11.1.3	Statistical Data	No content at this level	No content at this level
CH3.6	Non-clinical Bibliography		4.2.11 Other relavant specifications
CH3.7	Expiration Period and Package Validation	6.4.2 Sterile packaging Validation 11.0 V&V Summary Reports	4.3 Summary of Design and Validation Documents
CH3.7.1	Product Stability	11.0 Verification &Validation Summary and Reports	4.2 Device Description 4.3 Summary of Design and Validation Documents
CH3.7.1.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH3.7.1.1.1	Summary	No content at this level	No content at this level
CH3.7.1.1.2	Full Report	No content at this level	No content at this level
CH3.7.1.1.3	Statistical Data	No content at this level	No content at this level
CH3.7.2	Package Validation	11.0 Verification &Validation Summary and Reports	4.3 Summary of Design and Validation Documents
CH3.7.2.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH3.7.2.1.1	Summary	No content at this level	No content at this level
CH3.7.2.1.2	Full Report	No content at this level	No content at this level
CH3.7.2.1.3	Statistical Data	No content at this level	No content at this level
CH3.8	Other non-clinical Evidence	11.0 Verification &Validation Summary and Reports 11.3 Medicinal Substances	4.3 Summary of Design and Validation Documents [CSDT has no specific requirement regarding medicinal substances] 4.2.11 Other relavant specifications
CH3.8.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level

CH3.8.1.1	Summary	No content at this level	No content at this level
CH3.8.1.2	Full Report	No content at this level	No content at this level
CH3.8.1.3	Statistical Data	No content at this level	No content at this level
CHAPTER 4 – CLINICAL EVIDENCE			
CH4.1	Chapter Table of Contents	No content at this level	No content at this level
CH4.2	Overall Clinical Evidence Summary	11.8 Clinical Evidence	4.3.2 Clinical Evidence
CH4.2.1	Clinical Evaluation Report		4.3.2 Clinical Evidence
CH4.2.2	Device Specific Clinical Trials	8.2 Clinical Investigations Protocols and Reports	
CH4.2.2.1	[Trial description, protocol #, date of initiation]	No content at this level	No content at this level
CH4.2.2.1.1	Clinical Trial Synopsis	No content at this level	No content at this level
CH4.2.2.1.2	Clinical Trial Report	No content at this level	No content at this level
CH4.2.2.1.3	Clinical Trial Data	No content at this level	No content at this level
CH4.2.3	Clinical Literature Review and Other Reasonable Known Information	11.8 Clinial Evaulation Summary	
CH4.3	IRB Approved Informed Consent Forms	8.2 Clinical Investigations Protocols and Reports	
CH4.4	Investigators Sites and IRB Contact Information	No content at this level	No content at this level
CH4.5	Other Clinical Evidence	11.8 Clinical Evaulation Summary 8.3 Post Market Surveillance	4.3.1 PreClnical Studies 4.3.2.1 Use of Existing Bibliography 4.4 Device Labelling [labelling]
CH4.5.1	[Study description, study identifier, date of initiation]	No content at this level	No content at this level
CH4.5.1.1	Summary	No content at this level	No content at this level
CH4.5.1.2	Full Report	No content at this level	No content at this level
CH4.5.1.3	Statistical Data	No content at this level	No content at this level
CHAPTER 5 – LABELLING AND PROMOTIONAL MATERIAL			
CH5.01	Chapter Table of Contents	No content at this level	No content at this level
CH5.02	Product/Package Labels	7.0Labelling and Packaging	4.4 Device Lablling
CH5.03	Package Insert/Instructions for Use	7.0Labelling and Packaging	4.2.4 Instructions of Use
CH5.04	e-labelling	7.0Labelling and Packaging	4.4 Device Lablling
CH5.05	Physician Labelling	7.0Labelling and Packaging	4.4 Device Lablling
CH5.06	Patient Labelling	7.0Labelling and Packaging	4.4 Device Lablling
CH5.07	Technical/Operators Manual	7.0Labelling and Packaging	4.4 Device Lablling
CH5.08	Patient File Stickers/Cards and Implant Registration Cards	7.0Labelling and Packaging	4.4 Device Lablling
CH5.09	Product Brochures	7.0Labelling and Packaging	4.2 Device Description
CH5.10	Other Labelling and Promotional Material	7.0Labelling and Packaging	4.4.1. samples of labels 4.4.2 IFU Training materials and instructions for Installation and Maintainence
CHAPTER 6A – QUALITY MANAGEMENT SYSTEM PROCEDURES			
CH6A.1	Cover Letter		
CH6A.2	Chapter Table of Contents		
CH6A.3	Administrative		
CH6A.3.1	Product Descriptive Information		
CH6A.3.2	General Manufacturing Information		
CH6A.3.3	Required Forms		
CH6A.4	Quality management system procedures		
CH6A.5	Management responsibilities procedures		
CH6A.6	Resource management procedures		
CH6A.7	Product realization procedures	8.3 Design & Manufacturing sites 8.1 Device Design	
CH6A.7.1	Design and development procedures		
CH6A.7.2	Purchasing procedures		
CH6A.7.3	Production and service controls procedures		
CH6A.7.4	Control of monitoring and measuring devices procedures		
CH6A.8	QMS measurement, analysis and improvement procedures		
CH6A.9	Other Quality System Procedures Information		
CHAPTER 6B – QUALITY MANAGEMENT SYSTEM DEVICE SPECIFIC			
CH6B.1	Chapter Table of Contents		
CH6B.2	Quality management system information	1. Project Management: D&D Project Plan and Milestones Reviews (DHF) 6.2.Manufacturing Quality Plan	
CH6B.3	Management responsibilities information		
CH6B.4	Resource management information		
CH6B.5	Device Specific Quality Plan		
CH6B.6	Product realization information	8.2 Manufacturing Process	4.6.1 Manufactuing process
CH6B.7	QMS measurement, analysis and improvement information		
CH6B.8	Other Device Specific Quality Management System Information		

*No content at this level indicate the STED & CSTD do not go to the level of placeholder for protocols and reports