REGULATORY REQUIREMENTS FOR MEDICAL DEVICES IN SOUTHEAST ASIA AND CHINA

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List of Abbreviations

ACCSQ	ASEAN Consultative Committee for Standards and Quality
ACRA	Accounting and Corporate Regulatory Authority, Singapore
AHWP	Asian Harmonisation Working Party
AMDD	ASEAN Medical Device Directive
ASC	Announcement of Standard Conformity, Vietnam
ASEAN	Association of Southeast Asian Nations
AQS	Announcement of Quality Standards, Vietnam
AQSIQ	General Administration of Quality, Supervision, Inspection and Quarantine, China
BFAD	Bureau of Food and Drugs, Philippines
BHDT	Bureau of Health Devices and Technology, Philippines
CAB	Conformity Assessment Body
CCC	China Compulsory Certification
CMDR	Centre for Medical Device Registration, Singapore
CNCA	China National Certification and Accreditation Administration
CQC	China Quality Certification Centre
PRC	Certificate of Product Registration, Philippines
CSDT	Common Submission Dossier Template
DirJen POM	Directorate of Regulation for Production and Distribution of Medical Equipment, Indonesia
DMEHW	Department of Medical Equipment and Health Works, Vietnam
DoC	Declaration of Conformity
ECRI	Emergency Care Research Institute
EP	Essential Principles
EU	European Union
FSC	Certificate of Free Sale
GDP	Gross Domestic Product
GDPMDS	Good Distribution Practices for Medical Devices, Singapore
GHTF	Global Harmonisation Task Force
GMP	Good Manufactuing Practice
HIV	Human Immunodeficiency Virus
Hongkong SAR	Hongkong Special Administrative Region
HSA	Health Sciences Authority, Singapore
IEC	International Electrotechnical Commission
ISO	International Organisation for Standardisation
IVD	In vitro diagnostic
LTO	License to Operate, Philippines
LRP	Local Responsible Person, Hong Kong
MDACS	Medical Device Administrative Control System, Hong Kong
MDB	Medical Devices Bureau, Malaysia
MDCD	Medical Device Control Division, Thailand

MDCO	Medical Device Control Office, Hong Kong
MDPWG	Medical Devices Product Working Group (ASEAN)
MEDICS	Medical Device Information and Communication System, Singapore
MeDVER	Voluntary Registration Scheme for Establishments Dealing with Medical Devices, Malaysia
MHRA	Medicines and Healthcare products Regulatory Agency, UK
MoH	Ministry of Health, Vietnam
MOST	Ministry of Science and Technology, Vietnam
n.a.	not applicable
PKRT	Guidelines for Assessment of Medical Devices and Household Health Supplies, Indonesia
RA	Regulatory Authority
RMS	Risk Management System
RSAMD	Regulations for the Supervision and Administration of Medical Devices
SFDA	State Food and Drug Administration, China
SMDR	Singapore Medical Device Register
STED	Summary Technical Documentation
TFDA	Thai Food and Drug Administration
TGA	Therapeutic Goods Administration, Australia
UK	United Kingdom
USA	United States of America
US FDA	Food and Drug Administration, USA
QMS	Quality Management System

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1 Medical Devices in the Observed Asian Countries

Asia is the world's largest continent and, with approximately 4 billion people, it hosts 60 % of the world's current human population. Due to its vast size it comprises a huge range of differing cultures, environments, historical ties and governmental systems. Economically, it is the fastest growing region in the world.

The most frequently used measure for the overall size of an economy is the gross domestic product (GDP) which corresponds to the total monetary value of all production activity in a certain geographical area. Economic growth is generally measured as the rate of change in GDP over a certain period of time[1].

While the global GDP contracted by 1 % (real growth rate) in 2009 due to the financial crisis, Asia's GDP still grew at an estimated rate of 3.4 % and is expected to grow further in 2010 making a substantial contribution to the worldwide economic recovery[2].

China is one of the driving forces behind economic growth in Asia. Since opening its economy to the West in the late 1970s China has experienced a rapid economic growth with an estimated GDP of 8.789 trillion US $ in 2009 making it the world's second largest economy after the United States of America and recording an 8.2 % GDP increase in 2009[3]. But besides China, other newly industrialized and developing countries, especially in Southeast Asia, will play a central role in the highly dynamic economic development of the region in the future. For these countries the Asian Development Bank estimates a combined GDP growth of 3.9 % in 2009 and 6.4 % in 2010[3].

Southeast Asia forms a subregion of Asia which consists of countries geographically south of China, east of India and north of Australia. Ten countries of this subregion are members of the Association of Southeast Asian Nations (ASEAN), a political and economic grouping which was founded in 1967 to promote mutual economic development and competitiveness. The group's overall plan is to form a unified manufacturing and trading base similar to the European Union by eliminating trade and investment barriers within the region and harmonizing industry regulations. The current member countries are:

- Indonesia,
- Singapore,
- Malaysia,
- the Philippines,
- Thailand,
- Brunei,
- Cambodia,
- Vietnam,
- Laos,
- and Myanmar.

Combined, these ASEAN countries have a population of about 600 million people and a GDP of about 2.6 trillion dollars. By comparison, the European Union has 500 million people and a 14.7 trillion dollar GDP.

Economically and politically, the status of these countries is extremely diverse: There are four constitutional monarchies (Malaysia, Thailand, Brunei, Cambodia), as well as three presidential (Indonesia, Singapore, the Philippines) and two socialist republics (Vietnam, Laos). Myanmar is ruled by a military junta. Economically, Indonesia, the Philippines, Malaysia and Thailand are all counted among the newly industrialized countries, Indonesia being the largest economy in the region. Singapore and Brunei already have advanced, high-income economies, while Cambodia, Vietnam, Laos and Myanmar are usually classified as developing countries.

Towards the economic and social development of its member states the advancement of healthcare is one of the central issues for ASEAN which it plans to modernize and integrate across the region. The ultimate goal is an ASEAN healthcare market with harmonized standards and registration including an operable post market surveillance mechanism and effective mutual recognition agreements. This "healthcare integration roadmap" includes, among other projects, the harmonization of medical device regulation. To this end the Medical Devices Product Working Group (MDPWG) was founded in 2004 as a subgroup of the already existing ASEAN Consultative Committee for Standards and Quality (ACCSQ)[4]. The ACCSQ has been working on the removal of technical barriers to trade among the ASEAN members since 1992.

The aim of the MDPWG is to implement specific measures to facilitate the integration of the medical devices sector. These measures, among others, include the following:

- development of a common submission dossier template (CSDT) for product approval
- formalization of a post-marketing alert system for defective or unsafe medical devices
- evaluation of the feasibility of an abridged approval process for medical devices that have already been approved in benchmarked countries, such as the EU or the USA.
- evaluation of the feasibility of adopting a common approval process in all ASEAN member countries

The MDPWG is working on an overall harmonized regulation, the ASEAN Medical Device Directive (AMDD) which is based on the European Medical Device Directive and previous experiences with the ASEAN Cosmetics Directive[5]. It lays out the basic requirements for the safety and performance of medical devices, the classification system, a Common Submission Dossier Template for medical devices (CSDT) and an ASEAN-wide post-marketing alert system. It will not be a law in the ASEAN countries but all member states will be required to pass laws with the same provisions.

All ASEAN member states are also members of the Asian Harmonisation Working Party (AHWP) which was established in 1996 by regulatory affairs professionals with the goal of promoting harmonization of medical device regulation in Asia[6]. Apart from the ASEAN states several other Asian and non-Asian countries are also members. Among them are China, Hong Kong SAR, India,

Taiwan and South Korea, but also South Africa, Chile and some Arabic states, such as Abu Dhabi and Saudi Arabia. Since 2006 the AHWP is an official liaison body of the Global Harmonisation Task Force (GHTF), an organisation working towards global harmonization of medical device regulation. The AHWP developed the common submission dossier template (CSDT) which will be included as a part of the AMDD. Additionally, the AHWP also aims at establishing the Safety Alert Dissemination System (SADS), an adverse event reporting database for medical devices which is intended to facilitate sharing of information on adverse events among the member economies.

The efforts towards regulatory integration are still under discussion and at this point in time requirements for the registration of medical devices in the ASEAN member states are still diverse. But with growing prosperity and an increasingly ageing population, public and private healthcare spending will increase not only in the ASEAN countries, but across all Asia generating a growing demand in medical devices. Combined with the large populations of Asian countries this is an attractive outlook for medical device markets.

This master thesis will describe the current regulatory requirements for the registration of medical devices in the ASEAN member states, as well as China and Hong Kong SAR. China aims to provide safe, effective and low-cost public health and basic medical care to rural and urban citizens by 2020 with its Healthy China 2020 plan. Taken together with the huge population and dynamic economic growth this will offer immense opportunities for the medical device market. Although Hong Kong is part of China, as a special administrative region it has its own medical device regulations separate from China. It is already among the most advanced medical markets in the region and is expected to strongly influence China.

2 Global Harmonisation Task Force

Many ASEAN countries are currently trying to model their medical device regulations on the guidelines prepared by the Global Harmonisation Task Force (GHTF). The draft ASEAN Medical Device Directive as well is generally based on the guidelines of the GHTF.

2.1 Goals and Organisation

The Global Harmonization Task Force (GHTF) was established in 1993 as a voluntary international group of medical device regulatory authorities and medical device trade associations from the European Union (EU), the United States of America (USA), Canada, Japan and Australia, grouped into three geographical areas, namely Europe, North America and Asia-Pacific.

The mission statement, quoted from the GHTF web site, reads as follows[7]:

The purpose of the GHTF is to encourage convergence in regulatory practices related to ensuring the safety, effectiveness/performance and quality of medical devices, promoting technological innovation and facilitating international trade, and the primary way in which this is accomplished is via the publication and dissemination of harmonized guidance documents on basic regulatory practices. These documents, which are developed by five different GHTF Study Groups, can then be adopted/implemented by member national regulatory authorities.

The GHTF also serves as an information exchange forum through which countries with medical device regulatory systems under development can benefit from the experience of those with existing systems and/or pattern their practices upon those of GHTF founding members.

The GHTF carries out its activities through the Steering Committee, the GHTF Chair and the Study Groups:

The Steering Committee is composed of representatives from the Founding Members. It consists of up to eight members from each of the Founding Members' regions. Of each eight members, up to four may be from the regulatory sector and up to four from the industry sector. Its role is to provide policy and strategic direction in order to ensure that GHTF work continues to fulfil its goals and objectives. It is responsible for the assignment and oversight of new work items, adoption and monitoring of GHTF guidance documents and the authorization and promotion of GHTF training events.

The GHTF Chair is responsible for providing general management of all work of the GHTF and the Steering Committee. Chairmanship rotates between the national regulatory authorities of the three geographic areas with a term of office of three years.

Study Groups may be formed at any time by the Steering Committee. Currently, there are five Study Groups in the GHTF, each with a different topic. Recommended members include one participant from each region with founding member status as well as appropriate numbers from regulatory agencies and industry technical experts.

New work items are either proposed by one of the Study Groups or directly by the Steering Committee. At stage 1 the project must be approved by the Steering Committee before any work is initiated. At stage 2 the responsible Study Group will develop a Working Draft which will then be distributed among relevant experts from the member's national regulatory authorities or industry associations. External experts may be involved as well (stage 3). When consensus on the Working Draft document is reached, it will be reviewed by the Steering Committee (stage 4) before being posted on the GHTF website by the Chair as Proposed Document for six months (stage 5). During this time interested parties are encouraged to comment on the document. Once consensus is reached within a Study Group that its work on a document is complete, the document will be forwarded as Final Document to the Steering Committee for review (stage 6). Once endorsement of a Final Document is obtained it will be made available on the GHTF website in electronic format (stage 7).

All GHTF documents are reviewed and revised every three years or on an as-need basis.

2.2 Study Groups

2.2.1 Study Group 1: Premarket Evaluation[8]

Study Group 1 is concerned with the comparison of current medical device regulatory systems around the world with a focus on the premarket evaluation. The Study Group identifies principles suitable for harmonization and develops harmonized guidelines. Key terms such as "medical device" and "manufacturer" and the essential principles of safety and performance are defined in these documents. The Study Group has also published guidelines concerning the principles of classification and conformity assessment and is responsible for developing a standardized format for pre-market submissions and harmonized product labelling requirements. As of January 2010 ten Final Documents have been published by Study Group 1.

2.2.2 Study Group 2: Postmarket Surveillance/Vigilance[9]

Study Group 2 reviews current adverse event reporting, post-market surveillance and other forms of vigilance for medical devices and performs an analysis of different requirements amongst countries with developed device regulatory systems. The aim is to define requirements for a common medical device vigilance system and to provide an international protocol to define and facilitate the transmission of vigilance information on a global basis. Study Group 2 has currently published eight Final Documents.

2.2.3 Study Group 3: Quality Systems[10]

Study Group 3 is responsible for examining and harmonizing current quality system requirements. Three Final Documents are available covering the implementation and integration of a risk management system within the quality management system, process validation and the control of products and services obtained from suppliers.

2.2.4 Study Group 4: Auditing[11]

Study Group 4 examines current quality systems auditing practices and develops harmonized guidelines on audit practices and techniques. The four published Final Documents give guidance regarding training requirements for auditors, regulatory auditing strategy and reports.

2.2.5 Study Group 5: Clinical Safety/Performance[12]

Study Group 5 promotes harmonisation regarding requirements for evidence of the clinical safety and performance of medical devices. The group concentrates on establishing harmonized definitions for commonly used terms (clinical investigation, clinical data, clinical evaluation and clinical evidence) as well as developing harmonized guidance on the content and format for clinical investigation reports and on how to conduct and document a clinical evaluation. Two Final Documents are currently published by the Study Group.

For most Study Groups further documents are currently under development or posted for discussion on the GHTF web site.

The existing Study Groups can be supplemented by the formation of Adhoc Working Groups which develop guidelines or the position of the GHTF concerning certain subjects over a limited time frame. Currently, different Adhoc Working Groups are concerned with combination products, software, training partnerships, unambiguous identification and the global regulatory model[13].

The guidelines of the GHTF are not legally binding and regulatory authorities are not obligated to implement them on a national level. Nevertheless, they are accepted as good regulatory practice and may be adapted to national requirements before implementation.

2.3 Global Harmonized Medical Device Regulation Model

The guidance documents created by the GHTF Study Groups are intended as building blocks for a harmonized medical device regulatory model[14]. The fundamental key elements are

- risk-based premarket controls,
- a system of post-market vigilance and surveillance,
- a quality management and risk management process encompassing the life cycle
- and a regulatory audit process to periodically assess conformity.

Other important elements of the model are

- harmonized definitions,
- registration of manufacturers and listing of medical devices,
- applying clinical evaluation and clinical evidence during the life cycle,
- labelling
- and communications to users of medical devices.

The model can be applied to centralized regulatory systems, where a national regulatory authority (RA) is responsible for device regulatory activities, or decentralized regulatory systems, where third-party Conformity Assessment Bodies (CAB) are used. Advertising, import/export procedures and methods of regulatory enforcement are not covered by the GHTF.

2.3.1 Definition of the term Medical Device

The GHTF proposes the following harmonized definition of a medical device[15]:

"Medical device" means any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article:

a) intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of:

diagnosis, prevention, monitoring, treatment or alleviation of disease,

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

investigation, replacement, modification, or support of the anatomy or of a physiological process,

supporting or sustaining life,

control of conception,

disinfection of medical devices,

providing information for medical or diagnostic purposes by means of in vitro examination of specimens derived from the human body;

and

b) which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means.

This definition encompasses the terms *medical device* as well as *in vitro diagnostic (IVD) medical device.* The ASEAN Medical Device Products Working Group (MDPWG) has adopted this definition.

2.3.2 Classification of Medical Devices

Medical device classification is carried out to recognise differing degrees of inherent risk to patients, users and other persons. The principles of classification of general medical devices[16] and IVD medical devices[17] are treated in two separate documents by the GHTF due to the differing requirements of these product classes. For both types of products a four class system is proposed where the actual classification of a device depends on the claims made by the manufacturer and on its intended use (see table 2.1).

For general medical devices the classification is based on a set of 16 predetermined rules covering the following aspects:

- whether the device is intended for long term or short term use,
- whether it involves the use of associated pharmaceuticals and chemicals,
- whether it is invasive in normal bodily orifices or via surgical insertion
- and whether it operates by the exchange of energy with the body.

For IVD medical devices seven rules are proposed using the following main criteria:

- the intended use and indication for use of the IVD medical device (specific disorder, condition or risk factor for which the test is intended)
- the technical, scientific or medical expertise of the intended user (testing laboratories or self testing)
- the importance of the information to the diagnosis (sole determinant or one of several), taking into consideration the natural history of the disease or disorder including presenting signs and symptoms which may guide a physician
- the impact of the result to the individual and/or to the public health.

Classification of a medical device is the manufacturer's responsibility. It has to be done carefully, because the risk class establishes the correct conformity requirements: increasing risk equals increasing levels of regulatory requirements and conformity assessment procedures become more demanding for higher risk classes. An incorrect classification would therefore lead to a conformity assessment procedure which is not applicable to the particular device.

Table 2.1: proposed general classification system for medical devices and IVD medical devices

	Medical Devices		**IVD Medical Devices**	
Class	**Risk level**	**Device examples**	**Risk level**	**Device examples**
A	Low risk	Surgical retractors, tongue depressors	Low individual risk and low public health risk	Clinical chemistry analyser, prepared selective culture media
B	Low-moderate risk	Hypodermic needles, suction equipment	Moderate individual risk and/or low public health risk	Pregnancy self testing, urine test stripes
C	Moderate-high risk	Lung ventilator, bone fixation plate	High individual risk and/or moderate public health risk	Blood glucose self testing, HLA typing
D	High risk	Heart valves, implantable defibrillator	High individual risk and high public health risk	HIV Blood donor screening, HIV blood diagnostic

2.3.3 Essential Principles of Conformity and Conformity Assessment

The GHTF medical device regulatory framework requires medical devices to meet certain essential principles regarding safety and performance before they can be placed on the market. The basic framework for these *Essential Principles* is described in one document for both general medical devices and IVD medical devices[18]. Similar to medicinal products the underlying principle for evaluating, whether a medical device meets the essential requirements, is based upon a benefit risk assessment.

The guideline lists six general requirements of safety and performance that apply to all medical devices. As the first priority devices need to be designed and manufactured so that they will achieve the intended purpose without posing a danger to the safety of patients, users and other persons. The manufacturer is required to identify known or foreseeable dangers associated with the use of the medical device and to assess the inherent risk arising from the intended use and foreseeable misuse. The device, its labelling and packaging should be designed to minimise all identified hazards during the complete life cycle of the product. Finally, any undesirable effect must be outweighed by the benefits achieved by the device.

Apart from the general requirements a comprehensive list of design and manufacturing requirements is provided which are not applicable for every medical device. It is the responsibility of the manufacturer to decide which are relevant to his particular product and to provide reasons for the exclusion of the others. The following aspects are covered:

- chemical, physical and biological properties
- infection and microbial contamination
- manufacturing and environmental properties
- devices with a diagnostic or measuring function
- protection against radiation
- requirements for medical devices connected to or equipped with an energy source
- protection against mechanical risks
- protection against the risks posed to the patient by supplied energy or substances
- protection against the risks posed to the patient for devices for self-testing or self-administration
- information supplied by the manufacturer
- performance evaluation including, where appropriate, clinical evaluation

The evidence and possible procedures that may be used by the manufacturer to demonstrate compliance with the relevant *Essential Principles* and the process by which a Regulatory Authority or Conformity Assessment Body may confirm that the procedures are properly applied by the manufacturer are covered in two Final Documents of the GHTF: one for general medical devices[19],

one for IVD medical devices[20]. The conclusions drawn are nearly identical for both product types: The responsibility for the assessment lies with the manufacturer but a review of the process and the conclusions is conducted either by the Competent Regulatory Authority (RA) or a Conformity Assessment Body (CAB). The degree of involvement of the a RA or CAB is dependent on the risk class of the concerned medical device and increases with higher risk.

Both guidance documents propose five conformity assessment elements which are applicable to all four device classes:

- a quality management system (QMS)
- a system for post-market surveillance
- a summary technical documentation
- a declaration of conformity
- the registration of medical device manufacturers and their medical devices with the competent Regulatory Authority

An established and effectively implemented quality management system serves as evidence of the ability to produce medical devices that consistently meet the relevant requirements. The quality management system can be based on international standards, such as ISO 9001 as a general management standard and ISO 13485, which imposes special requirements to ensure the safety and efficacy of medical devices. Accordingly, within many countries, for example Canada or Singapore, obtaining this certification is a legal requirement under laws relating to medical devices. Within the GHTF regulatory system the application of standards remains voluntary and manufacturers may choose freely how compliance with the *Essential Principles* is achieved. Still, the use of international standards is strongly encouraged by the GHTF, as they are generally presumed to conform to the corresponding *Essential Principles* and to support global convergence in regulatory systems[21].

Certain requirements of a QMS have been discussed in Study Group 3 and guidance documents on the following topics have been published:

- Products and services obtained by suppliers are expected to be subject to control by the medical device manufacturer. The type and extent of controls have to be documented within the existing QMS[22].
- Process validation is a central requirement within a QMS. As medical devices differ widely in their nature and manufacture, only general guidance on how to plan and conduct process validation and how to reach a decision whether validation of a particular process is necessary are provided in the corresponding document[23]. Software validation is not covered by GHTF documents.
- Based on the *Essential Principles* manufacturers are expected to implement processes for addressing device related risks. This requirement can be met by a stand-alone risk management system (RMS), but for the obvious reasons of cost saving and higher

effectiveness it seems advantageous to integrate QMS and RMS. General guidance for manufacturers relating to this possibility is given[24].

The degree of assessment of the QMS by the RA or CAB depends on the risk class of the device. In the case of Class C and D devices a full QMS including design and development needs to be in place and be verified by the RA or CAB either by accepting existing relevant certification of the manufacturer or by carrying out an on-site audit of the facilities in question. For Class A and B devices a QMS is also a prerequisite but design and development activities do not necessarily have to be included. Manufacturers of Class A devices are normally not subject to premarket on-site auditing.

Detailed guidance on auditing practice is provided in the documents prepared by Study Group 4. They are mainly intended for auditing organizations covering auditing strategies[25] and the conducting[26] and documentation[27] of audits of quality management systems. The follow-up of corrections, corrective, preventive and improvement actions are also treated, as well as training requirements for auditors[28] and the competence criteria that should be met by an audit team.

The post-marketing surveillance system is expected to be part of the QMS and will be subject to review by the RA or CAB. It has to include complaint handling, vigilance reporting and corrective and preventive action according to guidance documents by Study Group 2. The procedures to be established and maintained will be described in chapter *2.3.5 Post-marketing Surveillance* of this thesis.

The technical documentation provides the evidence used in the conformity assessment procedure. A subset of this data, the Summary Technical Documentation (STED), is required to be held at the manufacturer for inspection purposes in case of Class A or B devices or to be submitted to the RA or CAB prior to marketing for Class C and D devices. The extent of evidence to be presented depends on the risk class of the concerned device. The general format and contents of the STED will be described in chapter *2.3.4 Summary Technical Documentation*.

Additionally, the manufacturer has to draw up a "Declaration of Conformity" (DoC), attesting that the respective medical device complies with the relevant *Essential Principles*. This declaration is expected to contain the following information:

- attestation of compliance with the applicable *Essential Principles*, of classification according to classification rules and of compliance with all applicable conformity assessment elements
- sufficient identification of the device to which the DoC applies
- the Global Medical Device Nomenclature (GMDN) code and term for the device
- the risk class of the device
- identification of the applied conformity assessment elements
- date of validity
- name and address of the device manufacturer

- name, position and signature of the responsible person authorised to complete the DoC on behalf of the manufacturer

Finally, the registration of manufacturers and their medical devices at the RA is the most basic level of regulatory control to simplify identification of devices and locating the responsible manufacturer. To fulfil this obligation the RA's responsibility lies in maintaining the corresponding register, while the manufacturer (or its local distributor or its Authorised Representative) provides the information required by the RA for this purpose.

During the conformity assessment procedure manufacturer and RA or CAB, respectively have different responsibilities which are dependent on the risk class of the device (see table 2.2). Where alternative approaches of a conformity assessment element are possible the manufacturer may choose the route he deems to be most appropriate. Depending on the form of implementation of the regulatory model, the responsibilities of RA and CABs may differ on a national level: In a centralized system, like the one used in the USA, the national competent authority is responsible for all activities, while in a decentralized system some obligations may be transferred to third-party CABs, like for example in the EU,where private third-party CABs are responsible for premarket activities. In the GHTF regulatory model all activities mentioned in table 2.2 can fall under the responsibility of either the national RA or a CAB, except for the registration, which is to be performed centrally by the national RA. This is deemed to be necessary, as a decentralized registration system is not suitable to the task of maintaining one central source of information[29].

While verification that a suitable adverse event procedure is in place can be performed by a CAB, it should be noted that the subsequent post-market surveillance, namely the establishment and maintenance of a national vigilance database and the evaluation of vigilance reports, have to be performed centrally by the RA. Regarding the audit process, the RA will establish audit requirements including the frequency of auditing, but the actual auditing may be performed by CABs which are appointed by the national RA.

In justified cases the conformity assessment procedures may be adapted by an RA or CAB:

A manufacturer may be exempted from a complete premarket submission and auditing can be limited in scope, if, among others, the device incorporates well-established technology, the device is an updated version of a compliant device without substantial changes or international standards applicable to the device are available and have been used by the manufacturer.

A more detailed premarket submission or a more in-depth audit may be required for medical devices that incorporate innovative technology, existing devices with a new intended use or device types that raise specific public health concerns.

Table 2.2: conformity assessment elements and responsibilities of manufacturer and RA or CAB, respectively (source: GHTF Final Documents GHTF/SG1/N40:2006, GHTF/SG1/N046:2008 and presentation by M. Gropp on the GHTF Regulatory Model at the 12th GHTF Conference[29]). Although the responsibilities are the same for Class C and Class D devices, it should be noted that a Class D STED will contain much more detailed information with respect to clinical and performance data, quality control and release.

	Responsibility Manufacturer				**Responsibility RA/CAB**			
	Risk Class				**Risk Class**			
Conformity Assessment Element	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
QMS	full QMS **or** QMS without design and development control	full QMS **or** QMS without design and development control	full QMS	full QMS	no general requirement of a premarket audit, except in special cases (assurance of sterility or measuring functions)	verify that a current and appropriate QMS is in place by reviewing certification or perform premarket audit	verify that a current and appropriate QMS is in place by reviewing certification or perform premarket audit	verify that a current and appropriate QMS is in place by reviewing certification or perform premarket audit
Post Market Surveillance	adverse event reporting procedure according to GHTF Study Group 2 guidance	adverse event reporting procedure according to GHTF Study Group 2 guidance	adverse event reporting procedure according to GHTF Study Group 2 guidance	adverse event reporting procedure according to GHTF Study Group 2 guidance	post-market audit possible in case of specific safety concerns	verify that an appropriate adverse event reporting procedure is maintained as part of QMS	verify that an appropriate adverse event reporting procedure is maintained as part of QMS	verify that an appropriate adverse event reporting procedure is maintained as part of QMS
Technical Documentation	compilation of STED upon request	compilation of STED upon request	compilation of STED and submission for review	compilation of STED and submission for review	premarket submission of STED normally not required	premarket submission of STED normally not required	premarket review of STED	premarket review of STED
Declaration of Conformity	preparation and maintenance	preparation, maintenance and submission	preparation, maintenance and submission	preparation, maintenance and submission	submission not requested, but to be kept on file at the manufacturer	review and verification	review and verification	review and verification
Registration	provide registration requirements	provide registration requirements	provide registration requirements	provide registration requirements	**RA** maintains register and verifies as appropriate	**RA** maintains register and verifies as appropriate	**RA** maintains register and verifies as appropriate	**RA** maintains register and verifies as appropriate

2.3.4 Summary Technical Documentation

As detailed in chapter 2.3.3 a technical documentation of the medical device has to be held by the manufacturer as part of the conformity assessment procedure. In many cases it is made up of an extensive collection of documents which are subject to control by the QMS. The manner by which this control is achieved should be described in the relevant Standard Operating Procedures (SOP). If changes are made during the life cycle, they need to be integrated into the documentation.

To allow for an efficient review by a RA or CAB a summary of the technical documentation needs to be compiled which provides an overview of the medical device. The GHTF proposes a harmonised format for the summary technical documentation (STED) for general medical devices in which this information should be presented[30]. The extent of information contained in the summary depends on the classification and complexity of the device and may include abstracts, summaries or existing controlled documents, as appropriate, as well as an *Essential Principles* checklist (EP checklist). For IVD medical devices a guidance document describing the STED is still in the proposal stage, but it basically suggests a similar structure for IVD medical devices taking into consideration the special requirements of this type of product. As the document has not been finalized yet, only the STED for general medical devices will be described here.

According to the GHTF guidance the STED should contain the following sections

- ***Device Description and Product Specification, including Variants and Accessories***

  A general description including the intended use, the intended patient population and medical condition should be provided here. The risk class together with the relevant classification rule should be presented and accessories, which are intended to be used in combination with the device are described. The product specification that will be available to the end user and a marketing history of the device and similar devices are also part of this section.

- ***Labelling***

  A complete set of labelling, including labels on the device and its packaging, instruction for use and promotional material, should be presented in this section. The required content of the labelling is detailed in another guidance document by GHTF Study Group 1[31].

- ***Design and Manufacturing Information***

  Design and manufacturing sites should be identified and a short description of the design and the manufacturing process, usually in the form of a flow chart, provided.

- ***Essential Principles Checklist***

  The *Essential Principles* checklist provides a tabular overview of the *Essential Principles*. The applicable requirements should be identified together with the employed method of demonstrating conformity and a reference of the controlled document that proves conformity. A justification should be given if certain requirements are deemed not to be applicable. The following methods to demonstrate conformity may be used:

- conformity with recognised standards
- conformity with commonly accepted industry test methods
- conformity with in-house test methods
- the evaluation of pre-clinical and clinical evidence
- comparison to similar devices already on the market

- ***Risk Analysis and Control Summary***

  The risks identified during risk analysis and the measures taken to control them should be summarized in this section.

- ***Product Verification and Validation***

  A summary of the results of verification and validation studies which demonstrate conformity with the *Essential Principles* should be presented in this section. Generally, information on engineering tests, laboratory tests, simulated use testing, animal tests demonstrating feasibility or proof of concept and any relevant published literature would be covered. Additional information can be provided if applicable on the following topics:

  - biocompatibility
  - medicinal substances incorporated into the device
  - biological safety of devices incorporating animal or human cells, tissues or their derivatives
  - sterilisation
  - software verification and validation
  - animal studies providing evidence of safety and performance
  - clinical evidence.

  The degree of details provided will be dependent on the risk class of the medical device concerned. Detailed information meaning that not only data summaries and test conclusions will be presented, but that test design, complete test and study protocols and methods of data analysis will also be included. Regarding the evaluation of clinical data to provide clinical evidence, guidance documents from Study Group 5 of the GHTF are available[32,33]. All elements contained in the Clinical Evaluation Report that are described there need to be addressed.

It should be noted that the Declaration of Conformity is not an official part of the STED. Nevertheless, it may be annexed to it, as soon as the conformity assessment procedure has been completed.

2.3.5 Post-marketing Surveillance

A post-marketing surveillance system enables the manufacturer to gain and review experience about a medical device which is already marketed. As one of the conformity assessment elements described in chapter 2.3.3, a manufacturer is required to implement such a system, which usually forms a part of the overall quality management system.

The post-market surveillance system requires manufacturers to

- systematically review experiences gained after the device is marketed
- implement adequate corrective action
- and notify the concerned RA of adverse events and near events.

Information about adverse events can originate from various sources, like for example expert user groups, customer surveys, customer complaints and warranty claims, service and repair information or literature reviews.

Guidance on the type of adverse events associated with medical devices and which should be reported to the concerned RA is provided by Study Group 2 of the GHTF[34]. It also gives instructions on the time frame for reporting and the content of adverse event reports but is restricted to general medical devices. Guidelines for IVD medical devices are still under discussion.

Figure 2.1 illustrates the GHTF Medical Device Regulatory Model in the form of a flow chart. The backbone of the flow chart is formed by the fundamental GHTF Model processes. The final guidance documents proposed by the GHTF Study Groups are indicated at the corresponding steps of the process.

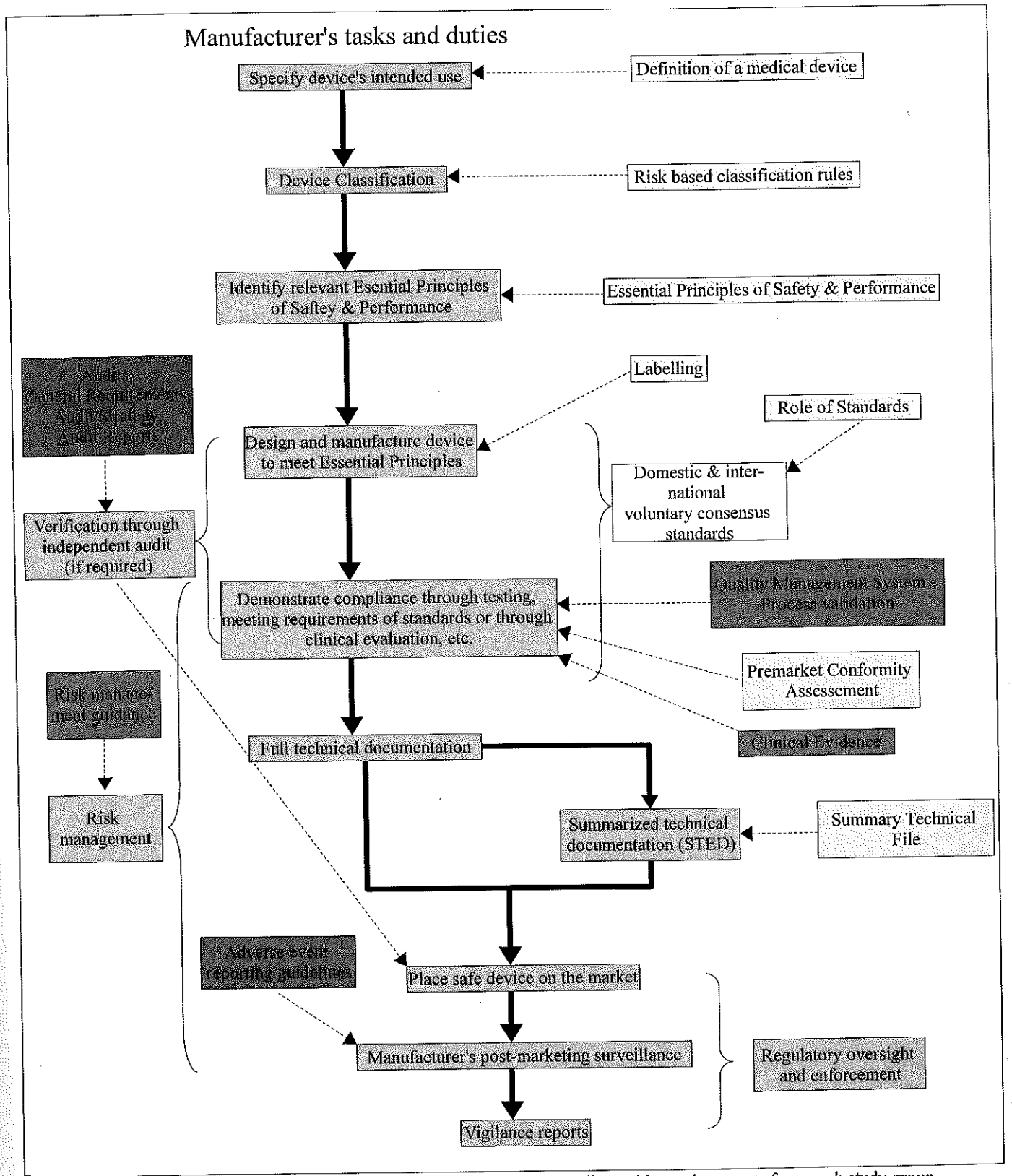

Figure 2.1 : Flow chart of the GHTF Model processes with corresponding guidance documents from each study group (adapted from: Final Document GHTF(AHWG(PD1)/N1R5)

GHTF Model Processes
GHTF Documents, Study Group 1
GHTF Documents, Study Group 2
GHTF Documents, Study Group 3
GHTF Documents, Study Group 4
GHTF Documents, Study Group 5

3 Regulatory Requirements for Medical Devices in Selected Asian Countries

3.1 Singapore

3.1.1 General Information

The Republic of Singapore is an island city-state located at the southern tip of the Malay Peninsula. Although it is the smallest nation in Southeast Asia, it is ASEAN's wealthiest and most developed member with an estimated GDP of $ 235.7 billion in 2009[2]. In terms of 2009's estimated GDP per capita, about $ 50,000, Singapore is the 8th wealthiest country in the world.

In 2009 the Singapore medical device market was valued at $ 216 million, similar to that of Bulgaria. In per capita terms, with a total of $ 45, the market is similar to that of South Korea and Hong Kong[35].

3.1.2 Regulation

Singapore's medical regulatory body is the Health Sciences Authority (HSA). Regulation of health products, i.e. medicinal products, innovative therapeutics, medical devices and health-related products, is ensured by the Health Products Regulation Group within the HSA. In this subgroup the Centre for Medical Device Registration (CMDR) conducts registration, certification and inspection for medical devices[36].

Until recently, only contact lens care products, radiation emitting devices and condoms came under statutory control through certain provisions in the *Medicines Act* and *Radiation Protection Act*. Since the implementation of the *Voluntary Product Registration Scheme* in 2002, Singapore has had a voluntary medical device registration system for higher risk devices under which a range of assessment and monitoring activities have been carried out by the CMDR to ensure medical devices available in Singapore are of an acceptable standard.

The Health Products Act[37], which was passed in February 2007, serves to regulate *the manufacture, import, supply, presentation and advertisement of health products and of active ingredients used in the manufacture of health products*[38] covering various types of health products such as medicinal products, medical devices or cosmetics. Implementation of the Health Products Act for the regulation of medical devices is currently phased in using three stages:

In phase 1, which started in November 2007, medical device firms were required to report product defects and adverse events to the HSA, notify the HSA prior to initiation of product recalls and to keep records of complaints and product distribution. Additionally, false or misleading advertisements and promotions of medical devices were prohibited.

In November 2008 the HSA began to license parties dealing in medical devices, including manufacturers and distributors, and started accepting registration applications for all medical devices, although this was not a legal requirement at that point in time, but was thought to serve as

familiarization for all parties involved with the process and its requirements (phase 2).

Since the last phase of implementation, which started with the second quarter of 2010, the unlicensed manufacturing, importation and wholesaling of medical device has been prohibited, as well as sale of unregistered Class B, C and D medical devices (classification according to GHTF, please refer also to the next chapter). By the second quarter of 2011, the sale of unregistered Class A medical devices will also be prohibited, making it an obligation to register all types of medical devices in Singapore by then.

3.1.3 Definition and Classification

The term medical device is defined in the first schedule of the Health Products Act. It is a verbatim adoption of the GHTF definition as detailed in *chapter 2.3.1*. Risk classes and classification rules for general medical devices[39] and IVD medical devices[40] were also adopted word for word (please refer to *chapter 2.3.2*).

3.1.4 Product Registration

Companies dealing with medical devices in Singapore have to apply for one of the following licenses, the type of which depends on the activities to be performed:

- Companies manufacturing medical devices in Singapore are obligated to apply for a manufacturer's license. To obtain a license the company needs to be certified to ISO 13485 standard.
- Companies importing medical devices into Singapore have to apply for an importer's license and are required to comply with the Good Distribution Practices for Medical Devices (GDPMDS) to ensure that products are consistently stored and handled under defined conditions as stipulated by the product registration or product specifications. The requirements of GDPMDS are detailed in a technical specification document by the HSA[41].
- Wholesalers wishing to supply medical devices have to apply for a wholesaler's license in Singapore. Like importers, wholesalers have to comply with GDPMDS.

Certification to ISO 13485 or GDPMDS is not performed by the HSA, but by certification bodies which are accredited by the Singapore Accreditation Council.

To register a medical device with the HSA the party applying for product registration, the so-called registrant, must be a Singaporean company registered with the Accounting and Corporate Regulatory Authority (ACRA). The registrant needs to enrol with the HSA in order to have access to the online Medical Device Information and Communication System (MEDICS) which is the only means by which product registration applications can be submitted. The product owner is defined as the manufacturer or the company selling the device and must issue a Letter of Authorisation to the registrant for each product application submitted.

The registration process is dependent on the risk class of the medical device concerned. Due to the low risk associated with the use of some class A devices, such as bandages, surgical brushes, tongue depressors or stethoscopes, these are exempted from product registration. The exemption is valid

solely for the intended purpose as detailed in the respective guidance document and also restricts any claim in advertising to those that are listed for the specific device[42]. Exemption from product registration does not entail exemption from the duties of manufacturers, importers or wholesalers dealing with these medical devices.

For all other class A devices only the following data needs to be included in an application for registration:

- name, address and contact information for all authorised importers
- copies in English of
    - labels (on the medical device and its packaging for all components)
    - instructions for use (if applicable)
    - patient information leaflet (if applicable)
    - promotional material
- sterilisation validation report (for sterile medical devices)
- certification on medical device metrology (for medical device with measuring function)
- certification to electrical safety standards, e.g. IEC 60601 (for active medical devices)

Certification to electrical safety standards or medical device metrology is to be performed by ISO-certified testing institutes. For class A IVD medical devices containing materials of animal, human, microbial and/or recombinant origin these must be listed as well as their immediate source.

After submission the HSA will determine if the device is classified correctly and whether the intended use and product claims are justified by the design of the device. After completing the review the device will be listed on the Singapore Medical Device Register (SMDR) which is publicly available online[43]. Product owners are required to keep complete distribution and complaint records and notify the HSA of product recalls and adverse events.

For class B, C and D medical devices a dossier in the Common Submission Dossier Template (CSDT) format[44] in English language has to be submitted online via MEDICS. In case of specific issues with the dossier or application a pre-submission consultation with the HSA can be arranged. The advice given by the HSA at such meetings is not legally binding. After submission the application undergoes a screening process to ensure correct classification, format and completeness. The screening process will usually be completed within 20 days. If any issues are raised during this process the registrant has to reply within a time frame of 30 days, otherwise the application will be rejected. Once all issues are clarified the dossier will be accepted for evaluation. During the review process additional information may be requested by the HSA at any time which has to be provided by the registrant within 30 days. The complete evaluation time is dependent on the risk class of the device and will take from 60 days for class B devices to 270 days for class D devices without clock stop time due to a request for additional information. If the HSA deems the device to be registrable the registrant may submit an application to list the device on the SMDR which will take another 20 days. It should be noted that pre-market review of the dossier and the conformity assessment is to be conducted exclusively by the HSA, the involvement of Conformity Assessment Bodies in this procedure is not foreseen in the Singaporean legislation.

The contents of the CSDT are detailed in two separate guidance documents for general medical devices[45] and IVD medical devices[46]. Both documents are currently listed as draft documents, because the CSDT document of the AHWP is itself still at a draft stage, but in practice all three guidances are already followed by registrants. Class B, C or D devices already having marketing approval in one of the GHTF founding members (EU, USA, Japan, Australia or Canada) qualify for an abridged application, which allows for the submission of summary data sets in certain sections of the submission document instead of detailed information (see table 3.1 and 3.2). For an abridged application all aspects of the quality of the medical device including packaging, labelling and intended purpose/indications for use have to be the same as the ones approved by the reference agency.

The Singaporean *Essential Requirements of Safety and Performance* are identical with the GHTF's requirements. The application of international standards, such as the International Organisation for Standardisation (ISO) or the International Electrotechnical Commission (IEC), to establish compliance with the *Essential Requirements* is recommended but not obligatory[47]. An *Essential Principles* checklist is part of section 4.1.1 of the CSDT (see table 3.1 and 3.2).

In comparison with the STED of the GHTF the CSDT is very similar but not exactly the same. The CSDT's device description contains several additional items, for example device counterindications, potential adverse effects and alternative therapies. Actual samples of the labelling to be used on the device and its packaging materials must be included as well as all existing instructions for the device (instructions for use, training, installation and maintenance). An executive summary of the whole dossier is also required.

In addition to the dossier a Declaration of Conformity as well as name, address and contact information for all authorised importers and wholesalers of the device have to be provided.

After completing the product registration an annual fee has to be paid to keep the medical device in the SMDR and to maintain the product registration.

Changes to a registered medical device must be notified to the HSA via an online change notification form and approved by the agency before the changed device can be sold in Singapore. Guidance as to which kinds of changes need to be notified and approved and which documents are needed for a notification are given in a guidance document which is currently available in a draft version only[48].

Table 3.1: CSDT requirements for general medical devices. Required indicates that the section has to be provided as described in the corresponding guidance document. Summary indicates that a summary of the studies undertaken can be provided. Detailed information indicates that full study reports have to be provided.

<table>
<tr><th colspan="2" rowspan="2">CSDT Section</th><th colspan="3">abridged dossiers</th><th colspan="2">full dossiers</th></tr>
<tr><th>Class B</th><th>Class C</th><th>Class D</th><th>Class B</th><th>Class C & D</th></tr>
<tr><td>3.0</td><td>executive summary</td><td colspan="5" rowspan="3">required</td></tr>
<tr><td>4.1.1</td><td>essential principles and evidence of conformity</td></tr>
<tr><td>4.2</td><td>device description</td></tr>
<tr><td>4.3</td><td colspan="6">summary of design verification and validation documents</td></tr>
<tr><td></td><td>sterilisation valdiation</td><td colspan="3" rowspan="4">summary</td><td colspan="2" rowspan="4">detailed information</td></tr>
<tr><td></td><td>shelf life data</td></tr>
<tr><td></td><td>projected useful life</td></tr>
<tr><td></td><td>metrological requirements</td></tr>
<tr><td>4.3.1</td><td colspan="6">pre-clinical studies</td></tr>
<tr><td></td><td>all pre-clinical studies as appropriate</td><td colspan="3">summary</td><td colspan="2" rowspan="2">detailed information</td></tr>
<tr><td></td><td>biological safety (for devices containing biological materials)</td><td colspan="3">detailed information</td></tr>
<tr><td>4.3.2</td><td colspan="6">clinical evidence</td></tr>
<tr><td></td><td>clincial evaluation report</td><td>may be required</td><td colspan="2">required</td><td>may be required</td><td>required</td></tr>
<tr><td></td><td>copies of studies referenced in the report</td><td colspan="3">not required</td><td colspan="2" rowspan="2"></td></tr>
<tr><td>4.4</td><td>device labelling</td><td colspan="3">required</td></tr>
<tr><td>4.5</td><td>risk analysis</td><td>may be required</td><td colspan="2">required</td><td colspan="2">required</td></tr>
<tr><td>4.6</td><td>manufacturer information</td><td colspan="3">required</td><td colspan="2">required</td></tr>
</table>

Table 3.2: CSDT requirements for IVD medical devices. *Required* indicates that the section has to be provided as described in the corresponding guidance. *Summary* indicates that a summary of the studies undertaken can be provided. *Detailed information* indicates that full study reports are to be provided.

<table>
<tr><th colspan="2" rowspan="2">CSDT Section</th><th colspan="3">abridged dossiers</th><th colspan="2">full dossiers</th></tr>
<tr><th>Class B</th><th>Class C</th><th>Class D</th><th>Class B</th><th>Class C & D</th></tr>
<tr><td>3.0</td><td>executive summary</td><td colspan="5" rowspan="3">required</td></tr>
<tr><td>4.1.1</td><td>essential principles and evidence of conformity</td></tr>
<tr><td>4.2</td><td>device description</td></tr>
<tr><td>4.3.1</td><td colspan="6">summary of design verification and validation documents: pre-clinical studies</td></tr>
<tr><td></td><td>analytical sensitivity</td><td colspan="3" rowspan="12">summary</td><td colspan="2" rowspan="12">detailed information</td></tr>
<tr><td></td><td>analytical specificity</td></tr>
<tr><td></td><td>precision</td></tr>
<tr><td></td><td>linearity</td></tr>
<tr><td></td><td>traceability</td></tr>
<tr><td></td><td>cut-off value</td></tr>
<tr><td></td><td>trueness</td></tr>
<tr><td></td><td>stability of reagent</td></tr>
<tr><td></td><td>stability of specimen type</td></tr>
<tr><td></td><td>devices containing instrument and articles</td></tr>
<tr><td></td><td>sterilisation validation</td></tr>
<tr><td></td><td>software validation and verification</td></tr>
<tr><td></td><td>devices containing biological material</td></tr>
<tr><td></td><td>clinical sensitivity</td><td colspan="3" rowspan="8">summary</td><td colspan="2" rowspan="8">detailed information</td></tr>
<tr><td></td><td>clinical specificity</td></tr>
<tr><td></td><td>comparison studies using clinical specimen</td></tr>
<tr><td></td><td>clinical studies/performance evaluation studies involving human specimen</td></tr>
<tr><td></td><td>reference interval</td></tr>
<tr><td></td><td>performance evaluation studies under simulated conditions of use</td></tr>
<tr><td></td><td>batch release</td></tr>
<tr><td></td><td>use of existing bibliography</td><td colspan="3">not required</td><td>may be required</td><td>required</td></tr>
<tr><td>4.4</td><td>device labelling</td><td colspan="3">required</td><td colspan="2">required</td></tr>
<tr><td>4.5</td><td>risk analysis</td><td colspan="3">may be required</td><td colspan="2">required</td></tr>
<tr><td>4.6</td><td>manufacturer information</td><td colspan="3">required</td><td colspan="2">required</td></tr>
</table>

A post-marketing surveillance system for medical devices was implemented in the first phase of implementation of the Health Product Act. Companies dealing with medical devices and manufacturers are required

- to keep records of complaints and product distribution,
- to report adverse events to the HSA within a stipulated time frame
- and to notify the HSA prior to the initiation of a product recall.

Any adverse event or potential adverse event that is associated with a medical device has to be reported to the HSA if

- it poses a serious threat to public health (to be reported within 48 hours),
- the death of a patient, user or other person occurred (to be reported within 10 days),
- a serious deterioration in the state of health of a patient, user or other person occurred (to be reported within 10 days)
- or no death or serious injury occurred but the event might lead to death or serious injury of a patient, user or other person if the event recurs (to be reported within 30 days).

All reports are collected and reviewed by the HSA and may lead to revision of the instructions for use or the inclusion of special warnings in the labelling. If the hazard is considered to be unacceptable, product registration will be withdrawn.

In summary, it can be said that Singapore is in the process of implementing the GHTF regulatory model in its centralized form with small additional requirements. The HSA itself is responsible for all parts of the pre- and post-market evaluation and monitoring, with the only exception being the certification to ISO 13485 and GDPMDS for the licensing of businesses.

With the licensing procedure a system to register all parties involved in the manufacture, the import or wholesale of medical devices in Singapore is already in place. The definition of the term medical device, the rule-based risk classification and the *Essential Requirements* were all adopted without changes.

Instead of the STED of the GHTF the HSA requires the submission of the CSDT which is based on the STED but contains additional requirements as detailed above. The reason for this is the anticipated implementation of the AMDD, where the use of the CSDT instead of the STED is a requirement. Another requirement over and above the GHTF model is the submission of the CSDT for class B devices.

Singapore will be the first country among the ASEAN members to implement medical device regulations according to the AMDD and based on this, is in line with most of the GHTF requirements.

3.2 Malaysia

3.2.1 General Information

Malaysia is located on the Southern half of the Malay Peninsula (Peninsular Malaysia) and the northern part of the island Borneo (East Malaysia). Economically, it is one of the fastest growing newly industrialized economies in Asia with an estimated GDP of $ 378.9 billion in 2009[2]. The estimated per capita GDP of $ 14,700 in 2009 is comparable to countries like Latvia and Lithuania.

The Malaysian healthcare system is generally considered to be efficient and widespread. It consists of a government-run universal healthcare system and a co-existing private healthcare system. The Malaysian market for medical equipment and supplies was estimated to be worth $ 826 million in 2009. In per capita terms, spending on medical equipment is similar to countries like Bulgaria and Serbia[49].

3.2.2 Regulation

Except for equipment that uses ionizing radiation, which is governed under the Atomic Energy Licensing Act (1984), there are no statutory requirements to register medical devices before marketing or to obtain a license to manufacture, import or distribute medical devices in Malaysia at present.

The Medical Devices Bureau (MDB) was founded as a division of the Ministry of Health Malaysia in 2005 to develop and implement a medical device regulatory program[50]. The MDB's responsibilities encompass the development of a Medical Device Bill and corresponding guidance documents. The Bill was finalised in 2008, but is still awaiting official adoption. A set of guidance documents[51] for the prospective legislation has been published on the website covering details on various aspects such as classification, essential principles of safety and performance, risk management, labelling and packaging, conformity assessment, etc.. Additionally, the MDB is responsible for the development of standards relating to medical devices and has adopted over 100 international medical device standards (ISO and IEC) as Malaysian Standards so far. A complete list can be found on the MDB's website[52].

As soon as the new Medical Device Bill is adopted and implemented the MDB will also be responsible for the licensing of companies dealing with medical devices, product registration and post-market surveillance.

In the meantime a Voluntary Registration Scheme for Establishments Dealing with Medical Devices (MeDVER) was launched in 2006 and will be ongoing until a full medical device legislation is in place. By the end of 2007, a total of 554 establishments had been registered and more than 4,000 medical devices had been listed. Please refer to chapter 3.2.4 for more details. A Voluntary Registration Scheme for Conformity Assessment Bodies (CAB) is also in the process of being developed to register all CABs operating or planning to operate in Malaysia.

3.2.3 Definition and Classification

As in Singapore the definition of the term medical device and the risk-based classification was adopted verbatim from the corresponding GHTF documents in Malaysia for the future legislation (see chapter 2.3.2).

3.2.4 Product Registration

As described above a voluntary on-line registration scheme for medical devices and companies dealing with medical devices is currently in place in Malaysia. This registration is considered to be the most basic level of regulatory control in the GHTF regulatory model facilitating a quick identification of devices and their distributors or manufacturers, respectively if regulatory intervention is required.

However, the participation in the voluntary registration scheme does not constitute approval of companies registering or the medical devices registered. Its purpose is solely to familiarize concerned parties with the registration process and to obtain a profile of companies dealing with medical devices and the medical devices currently marketed in Malaysia.

To create a MedVER account, the first step in the voluntary registration, the company needs to have a business registration with the Registrar of Companies Malaysia. The account will then be used to submit the Establishment Registration Form where details on the company and its responsible person are required in the first part. In the second part of the form details relating to the medical device, such as a description, the manufacturer, previous marketing approval in other countries and the respective classification in these countries, and the quality management system established by the company are requested. Applications are reviewed by the MDB and may be accepted or rejected.

The future medical device regulation in Malaysia will be based completely on the GHTF guidelines which are often referred to in the guidance documents published by the MDB. Definition, classification, *Essential Requirements* and the STED were all adopted from the corresponding GHTF documents. The system will be decentralized with CABs fulfilling part of the responsibilities as detailed in *chapter 2.3.3* of this thesis. At the moment only a voluntary registration of medical devices and all parties dealing with medical devices is in place. Although the Medical Device Bill was already passed by parliament in 2008, no further progress seems to have been achieved towards implementation since then. There is also no information if the implementation will be a step-wise process like in Singapore or if any adaptations to the legislation with regard to the AMDD, for example the adoption of the CSDT instead of the STED format will be made in the future.

3.3 Indonesia

3.3.1 General Information

The Republic of Indonesia is an island state located south of the Malay Peninsula and north of Australia comprising about 17,508 islands. With a population of around 230 million people, it is the world's fourth most populous country[2]. Indonesia has the largest economy in Southeast Asia and is a member of the G-20 major economies with an estimated GDP of $ 968.5 billion for 2009 which is larger than the GDP of countries like Australia or Taiwan. In contrast to this the estimated per capita GDP for 2009 is only $ 4,000 which is comparable to Paraguay or Honduras[2].

Despite its large economy Indonesia remains one of the poorest countries in Southeast Asia, lagging behind in many areas of healthcare provision. The Indonesian medical device market is relatively small in relation to Indonesia's population and was valued at $ 194 million in 2009, but it is expected to grow at a rate of 12.5% per annum reaching $ 348 million in 2014[53].

3.3.2 Regulation

Indonesia has had its own regulation of medical devices since 1976, which has been continually updated. Currently, *Ministerial Regulation No. 1184/Menkes/Per/X/2004 regarding Medical Devices and Household Safety*[54] is in force. The regulation often refers to the *Guidelines for Assessment of Medical Devices and Household Health Supplies* (Indonesian acronym: PKRT) for a detailed description of requirements regarding medical device registration.

The registration of medical devices is controlled by the *Directorate of Regulation for Production and Distribution of Medical Equipment* (Indonesian acronym: DirJen POM) within the national Ministry of Health. The DirJen POM is responsible for the licensing of manufacturers and distributors, registration of medical devices, pre-market evaluation, post-market surveillance activities and the evaluation of product advertisements and promotion.

As many of the Indonesian regulations concerning medical devices and all guidances and application forms are only available in Indonesian[55], only a very general overview can be given on the registration procedure and requirements.

3.3.3 Definition and Classification

The term medical device is defined in Article 2 of the *Ministerial Regulation No. 1184/Menkes/Per/X/2004*:

`Medical device' means any instrument, apparatus, machine, implant, in vitro reagent or diagnostic product or other similar or related article including components, parts and accessories:
used for diagnosis, prevention, treatment or alleviation of human disease, and/or;
diagnosis, monitoring, treatment, alleviation of or compensation for an injury, and/or;
for the purpose of influencing of the anatomy or of a physiological process, and/or;
for the purpose of supporting or sustaining life, and/or;
for the purpose of control of conception, and/or;

for the purpose of disinfection of medical devices, and/or;
for the purpose of diagnosis of a condition not disease as its primary intention;
providing information for medical purposes by means of in vitro examination of specimens derived from the human body;
and which does not achieve its target in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means
used and recognised as medical devices in accordance with progress in science and technology.

It is not a word for word adoption of the GHTF definition, but the discrepancies may be due to imprecise translation, as the Indonesian authorities claim to have adopted the GHTF definition completely[55].

For the classification of medical devices the United States system is used: Medical devices are classified into Class I, II, and III with increasing regulatory control from Class I to Class III (Art. 35 & 36 of the Regulation). Classifications for generic types of devices which are grouped into medical specialties are provided in Annex 15 and 15a of the Ministerial Regulation. Each of these generic types of devices is assigned to one of the three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device. The annexes are only available in Indonesian, therefore, more detailed information can not be given in this thesis.

3.3.4 Product Registration

Companies dealing with medical devices as manufacturers or importers/distributors have to obtain a manufacturing or a distributor license, respectively.

For manufacturers three different categories of manufacturing licenses are available depending on the risk class of the devices to be produced (Art. 23(2) of the regulation):

- category A:
  For the production of class III devices the PKRT has to be applied as a whole.
- category B:
  For the production of class I and II devices the PKRT has to be applied in terms of facilities, production process, documentation, sanitary hygiene and quality control.
- category C:
  For the production of certain class I and II devices application of the PKRT in terms of facilities, documentation, sanitary hygiene and quality control will be sufficient.

Medical device manufacturers must conform to the *Guidelines for Proper Manufacturing Methods of Medical Devices* and employ a *person in charge of technique* on a full time basis. The qualifications the person in charge of technique must meet are dependent on the classification of the manufacturing license, and thus, on the classification of the device to be manufactured.

During the licensing procedure an on-site inspection will be performed by the DirJen POM. The license will be valid for four years, after which it has to be renewed. A renewal is also necessary if there is

- a change of the name and/or address,
- a change of the *person in charge of technique,*
- or a change of classification.

In the case of these renewals, an on-site inspection only becomes necessary if there is a change in the manufacturing building. License holders are required to submit annual reports to the DirJen POM on production results. ISO 13485 standards are not implemented in Indonesia, but are accepted as demonstration that a foreign manufacturer of an imported device complies with the necessary requirements.

Distributors have to comply with the following requirements to obtain a distributor license (Art. 45 of the Regulation):

- possession of a business license and adequate facilities
- *person in charge of technique* employed full time
- provision of after-sale guarantee
- maintenance of records of procurement, storage and distribution
- in case of import of medical devices, an appointment letter from the foreign manufacturer

During the licensing procedure an on-site inspection will be performed by the DirJen POM. The validity of the license is unlimited, a renewal only necessary in the following cases:

- a change of the name and/or address
- a change of the *person in charge of technique*

License holders are required to submit annual reports to the DirJen POM on distribution results.

Before medical devices can be marketed in Indonesia, they have to be registered with the DirJen POM. Like in Singapore and Malaysia. The party registering needs to be a legal entity based in the country and a product registration can only be applied for by a licensed manufacturer or by a licensed distributor authorised by the manufacturer. The regulation lays down the following basic requirements to be fulfilled (Art. 32 of the regulation):

- safety and performance:

  A summary of the safety and performance studies conducted for the product has to be submitted, for class III products clinical tests and validation are required. Testing results from other countries are usually accepted, but testing of syringe sterility, condoms and HIV test kits have to be carried out in Indonesia. About 40 international standards have been adapted from ISO or other sources and can be used to demonstrate safety and performance. A risk analysis and assessment is only required for class III devices.

- quality:

  Information on raw materials and components, manufacturing process, specifications and

quality control, as well as a certificate of analysis must be provided.

- labelling:

  The label has to contain adequate, objective and complete information in Indonesian and English to prevent misunderstandings or misuse. Imported medical devices must be traceable to their origin and the responsible foreign manufacturer. The following particulars have to appear on the label:

  - product name
  - name and address of manufacturer and importer (if applicable)
  - main component
  - method of use
  - warnings and side effects
  - expiry date (if applicable)
  - batch and license number

Detailed information on the data to be submitted for product registration is given on the DirJen POM's web site exclusively in Indonesian.

Product registration usually takes three months and is valid for a period of three years. Upon registration a registration number is given to the medical device which must be part of the labelling.

The post-market surveillance system requires annual reports of manufacturers and distributors, but there is no mandatory adverse event reporting, collection of surveillance data or information sharing. If adverse events are reported, the DirJen POM is entitled to revoke the product registration.

The Indonesian medical device regulation already contains some elements of the GHTF model: The definition of a medical device was adopted and although classification is not rule-based as proposed in the GHTF guidelines, it is still a risk based approach. Registration of medical devices and of companies dealing with medical devices is already in place. The regulations represent a centralized approach excluding involvement of CABs.

Indonesia uses its own approach regarding quality management and the documentation to be submitted for pre-market approval, which are laid down in the PKRT and the *Guidelines for Proper Manufacturing Methods of Medical Devices*. Risk assessment is only needed for class III devices and post-market surveillance does not follow GHTF proposals at all. Unfortunately, more detailed information on requirements cannot be given in this thesis due to the limited availability of information in English.

3.4 Thailand

3.4.1 General Information

Thailand, located on the Southeast Asian mainland, has a population of 64 million people. With an estimated GDP of $ 538.6 billion in 2009 it is the second largest economy in the region after Indonesia. Its estimated 2009 per capita GDP of $ 8,100 though ranks it before Indonesia, but after Singapore, Brunei and Malaysia[2].

Despite continuing political unrest in the country the market for medical equipment and supplies has been undergoing a rapid growth during the last years and was estimated at $ 661 million in 2009, which is similar to Israel. In per capita terms ($ 10 in 2009) the market is similar to Argentina[56].

3.4.2 Regulation

Thailand has had its own medical device regulation since 1988 in the form of the Medical Device Act[57]. The agency regulating devices in Thailand is the Medical Device Control Division (MDCD)[58] of the Thai Food & Drug Administration (TFDA) under the Ministry of Public Health. The MDCD is responsible for licensing manufacturers, importers and distributors of medical devices as well as the registration and post-market surveillance of medical devices. All medical devices have to be registered with the MDCD before they can be placed on the Thai market.

Thailand is currently in the process of revising its medical device regulation in order to meet the requirements of the ASEAN MDD in the future, but at this time the old system is still in place.

3.4.3 Definition and Classification

Section 3 of the Thai Medical Device Act defines medical devices as follows:

(1) an instrument, product, or article that is used for medical practice, nursing, midwifery practice, general medical or veterinary practice, in pursuance of the governing laws;

(2) an instrument, product, or article that is used to affect health structure or any physiological function of human or animals;

(3) a constituent, component, part, accessory or part of instrument, product or article prescribed in (1) or (2);

(4) other instruments, products or articles notified in the Government Gazette by the Minister as medical devices.

It should be noted, that the definition encompasses medical devices for human use as well as for animal use.

Thailand has its own classification system, which, in contrast to the GHTF classification system, is not primarily risk based and which uses the following three classification groups:

- **Licensed Medical Devices:**

  This category includes devices that require a full assessment by the MDCD before they can

be manufactured, imported or marketed in Thailand. The following products are subject to this control:

- condoms
- examination gloves
- surgical gloves
- disposable hypodermic syringes
- HIV test kits for diagnostic use

- **Notified Medical Devices:**

  Devices in this category do not require a full assessment, but must be notified to the MDCD before they can be marketed:

  - physical-therapy devices
  - alcohol-detection devices
  - HIV test kits for research investigation
  - silicone breast implants

- **General Medical Devices:**

  This final category encompasses all other devices. These products also require registration with the MDCD, but the assessment will be solely based on a Certificate of Free Sale from the country of origin.

With the revision of the medical device regulation according to the ASEAN AMDD, the definition and the classification will be revised to conform to GHTF requirements.

3.4.4 Product Registration

The Medical Device Act requires that manufacturers, importers and distributors of *licensed medical devices* must have a license issued by the MDCD for their respective activities. The requirements are set out in section 14 of the Medical Device Act and Ministerial Regulations No. 1 -3[59]. The demands to be met are mainly concerned with maintenance of proper and hygienic facilities for production, packaging, storage of the raw material as well as the finished medical device and transportation, respectively.

Concerning the registration of medical devices the level of requirements depends on the classification of the corresponding device. The assessment will be performed by the MDCD, CABs are not foreseen in the current Thai legislation. Forms and guidelines relating to the registration procedures are only available in the national language.

A full registration is required for *licensed medical devices*. To obtain registration, manufacturers must demonstrate compliance with the Thai Industrial Standards Institute's standards, which are based on ISO standards. Compliance can further be ensured by testing or clinical evaluation depending on the type of medical device. Testing may be performed by the MDCD and affiliated laboratories.

For *notified medical devices* no full assessment, but a registration is needed, before they can be

placed on the Thai market. Along with a Certificate of Free Sale from the country of origin, detailed information has to be provided to the MDCD on the following particulars:

- a description of the medical device
- physical properties
- contents
- description of the production process
- copies of labelling with the indications for use
- instructions for use
- storage requirements
- shelf life (if applicable)
- name and address of manufacturer and importer/distributor

General medical devices constitute the class with the lowest level of regulatory control. A Certificate of Free Sale is sufficient to demonstrate that the device is freely manufactured and sold in the manufacturing country.

The registration process will usually take 3 months for *licensed* and *notified medical devices* or 10 days for *general medical devices*. The registration has to be held by a locally based legal entity and is valid for a period of 5 years.

As part of the post-market surveillance system, manufacturers, importers and distributors of *licensed and notified medical devices* are required to submit yearly reports on the numbers of devices produced and/or sold in Thailand. Adverse event reporting is another post-market obligation for manufacturers, importers and distributors of *licensed and notified medical devices*. Adverse events are defined as abnormal symptoms or health hazards including death or serious injury[60]. Written reports have to be submitted to the MDCD within 15 days, in the case of death or serious injury the MDCD must be informed within 24 hours. Adverse event reporting for general medical devices is voluntary.

The MDCD itself also conducts comprehensive post-market surveillance, including yearly site inspections for manufacturers of *licensed and notified products*, random sampling of products and testing at the government laboratory. A database system is used for the collection of surveillance data. The MDCD may order a recall of a product if it fails to meet the quality standards.

Labelling requirements are also regulated in the Medical Device Act. Labelling information on containers, packaging and accompanying documents in Thai is obligatory. Labels should include the following information:

- product name
- class and type
- name, address and country of origin of the manufacturer as well as the importer
- license number and lot number
- summarized usage instructions
- expiration date , if applicable

Single-use devices are to be explicitly labelled as such.

It can be summarized that the current system for medical device regulation in Thailand bears little similarity with the GHTF regulatory model and the AMDD. The definition of the term medical device is very general and does not state that the primary intended action of a medical device is not to be achieved by pharmacological, immunological or metabolic means. The distinction between medical devices and medicinal products is not clearly made. Veterinary uses are included in the definition which is not a part of the GHTF regulatory model or the AMDD. Classification is not risk-based, but rather a certain, small number of products is identified to require a higher level of regulatory control which is executed by the MDCD itself. The vast majority of medical devices is classified as general medical device. For this class of products the MDCD does not conduct a review of the conformity assessment, but rather relies on the evaluation of the device by benchmarked countries, such as the EU countries or the USA.

As a result of the classification process a registration or licensing of manufacturers, importers or distributors is not required for the vast majority of devices, although this is usually considered as the most basic form of regulatory control. Adverse event reporting remains voluntary for many products as well, because of the classification system.

3.5 Philippines

3.5.1 General Information

The Philippines are formed by a cluster of islands in the western Pacific Ocean. With a population of 92 million people they can be counted among the most populous countries in the world. Together with Indonesia, Malaysia and Thailand the Philippines are considered to be one of the newly industrialized countries in Southeast Asia and its GDP was estimated at $ 324.8 billion in 2009 which is in the range of Austria and Sweden. But as in the case of Indonesia the Philippines remain among the poorer countries in the area with a per capita GDP of $ 3,300 in 2009 which is comparable to Iraq or India[2].

Health care is mainly provided by private companies with medical device spending around $ 3 per capita in 2009 which is similar to health care spending in China or Vietnam. But despite recurrent political unrest the medical device market is expected to grow at about 10.8 % in the medium term[61].

3.5.2 Regulation

Medical devices have been regulated in the Philippines by the *Republic Act No. 3720 (Food, Drug and Cosmetics Act)* since 1963[62]. It was amended in 1987 by *Executive Order No. 175*[63] and since 1992 the *Memorandum Circular 007 s. 1992*[64] provides the listing of medical devices for mandatory registration. Presently, two authorities are jointly responsible for the regulation of medical devices: The *Bureau of Food and Drugs* (BFAD)[65] and its technical arm the *Bureau of Health Devices and Technology* (BHDT)[66] which is a part of the *Department of Health*. The BFAD is responsible for the

registration of companies dealing with medical devices, while the BHDT conducts product registration.

In 2009 the *Food, Drug and Cosmetics Act* was amended by *Republic Act No. 9711* (*Food and Drug Administration Act*)[67], which is planned to be implemented in the course of the next five years. Under the new law the BFAD will be restructured and renamed *Food and Drug Administration.* Following reorganization of this new agency, medical devices will be regulated by the newly appointed *Centre for Device Regulation, Radiation Health and Research*[68]. The *Food and Drug Administration Act* will base the regulation of medical devices largely on GHTF guidelines. However, at the time of writing this thesis in April 2010, no guidances relating to the new regulation of devices or the new regulating agency were available. There was also no information if there will be a step-wise implementation similar to Singapore or if a different approach will be followed. The old regulatory system for registration of medical devices is still in place at the moment and will be described in this chapter.

3.5.3 Definition and Classification

In the new legislation of 2009 the definition of the term medical device is a verbatim adoption of the GHTF definition. Until now, section 10(g) of the Republic Act No. 3720 provided the following definition:

"Devise" (sic.) means instrument, apparatus, or contrivances, including their components, parts, and accessories, intended

(1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or animals; or

(2) to affect the structure or any function of the body of man or animals.

It is worth noting, that the current definition includes medical devices for animals similar to the definition in Thailand, which will not be a part of the future legislation in the Philippines.

The new legislation will use the risk based classification system of the GHTF with risk classes I to IV, where class I represents the lowest risk and class IV the highest. The current system is not risk based but uses a list of 74 products included in *Memorandum Circular 007 s. 1992*[64], for which registration is mandatory. In addition to the listed products, registration for all sterile, invasive and implantable medical devices is obligatory as well[69].

3.5.4 Product Registration

The first step in the registration process is the *License to Operate* (LTO), which is a general requirement for all businesses dealing with medical devices in the Philippines and must be applied for at the BFAD. To obtain an LTO, the applicant has to be a locally based, registered business and employ a registered pharmacist who is responsible for supervision of all activities. Importers also have to present a contract with the foreign manufacturer whose devices they plan to import and the ISO- and GMP-certification of this manufacturer. The LTO will normally be granted within 90 days and is valid for two years. Businesses with an LTO are obliged to keep a batch distribution record as well as a product recall procedure and will be inspected on a regular basis by the BHDT.

Product registration is conducted by the BHDT. The following documentation has to be presented:

- Letter of Application
- valid LTO
- Free Sale Certificate from the country of origin
- valid ISO certification
- contract between manufacturer and local importer/distributor regarding the product
- specific use of the medical device and directions for use
- copy of latest *Certificate of Product Registration* (PRC, if applicable)
- composition of the device and technical specifications of all raw materials
- brief description of the manufacturing process
- technical specification and physical description of the device
- stability data (if applicable)
- complete labelling materials
- representative product sample (one of each size)
- biocompatibility studies, clinical data and a risk management (for implants and invasive medical devices)

The documentation is reviewed by the BHDT. For imported devices the assessment relies mainly on the certification of conformity to applicable standards. In contrast to this, domestically manufactured devices will be tested by accredited testing laboratories. A PRC will normally be issued within 90 days and be valid for one year for an initial application. After the first renewal the PRC is valid for five years.

There are no special labelling requirements at the moment, but requirements according to GHTF documents will be put in place with the implementation of the new law.

Post-market surveillance is virtually non-existent. The BHDT monitors different web-sites for product alerts, e.g. US FDA, Health Canada, TGA and MHRA, and takes relevant steps nationally if required. There is no mandatory adverse event reporting for businesses dealing with medical devices at the moment, but a post-market surveillance system according to GHTF guidelines is part of the new legislation, which is still awaiting implementation.

There is also no regulation concerning advertising except that approval by the BHDT cannot be used for advertising purposes.

In summary, it can be said that the Philippine regulatory bodies mainly rely on certification of products in the country of origin. Therefore, only the most basic controls according to the GHTF model are in place at the moment, namely registration of businesses dealing with medical devices. The registration of the devices themselves is restricted to certain products, so that only a small part of the products in the market is notified to the authorities. With the implementation of the new legislation this is about to be changed, but the transitional period may be long, as the necessary resources in the country with respect to trained personnel and finances are limited.

3.6 Vietnam

3.6.1 General Information

The Socialist Republic of Vietnam is the easternmost mainland country in Southeast Asia. Like the Philippines and Indonesia it is a populous country with over 88 million inhabitants. Since the introduction of economic reforms in 1986 Vietnam has developed from a planned economy into a "socialist-oriented market economy". Which allows privately owned enterprises. Vietnam has seen a steady economic growth over the last two decades, but is still considered as a developing country. Its GDP was estimated at $ 258.1 billion in 2009, which is similar to Romania and the Czech Republic. In terms of a per capita GDP of $ 2,900 in 2009 the country is relatively poor ranking beneath India and the Philippines[2].

In November 2008 a new law was passed which will make health insurance compulsory for all citizens by 2014 with the aim of improving the health care system of the country. The Vietnamese medical device market is estimated at $ 289 million with $ 3 per capita spending. Continued growth is expected at about 5.9 % per annum over the next years[70].

3.6.2 Regulation

The authority responsible for medical device regulation in Vietnam is the *Department of Medical Equipment and Health Works* (DMEHW) within the *Ministry of Health* (MoH). Additionally, the *Ministry of Science and Technology* (MOST) performs certain regulatory functions, which are relevant for medical devices.

In Vietnam, the regulatory process for imported medical devices is very different from the one for domestically manufactured devices. Technically, imported devices do not have to be registered as such, but an import license has to be applied for according to *Circular 08/2006/TT-BYT* of the MoH[71]. In contrast, medical devices which are manufactured in Vietnam require product registration prior to sale as laid down in *Circular 07/2002/TT-BYT* issued by the MoH[72].

3.6.3 Definition and Classification

There is no definition of the term medical device in Vietnamese regulation and no classification of devices. While all types of domestically produced medical devices have to be registered with the DMEHW, only certain types of imported medical devices require licenses. Those are:

- medical devices to be implanted into the human body, or which replace or supplement a physical function,
- 54 types of medical devices, which are specifically listed in *Appendix 7* to the *Circular 08/2006/TT-BYT* (e.g. CT scanners, magnetic resonance equipment, endoscopic diagnosis equipment, artificial bone, etc.),
- and devices that have a new function or new therapy, or devices that are being imported to Vietnam for the first time.

Appendix 7 is revised and updated annually by the MoH.

3.6.4 Product Registration

For the application for an import license and for registration of a domestically manufactured device, the applicant has to be a company incorporated and operating in Vietnam, but there is no special registration procedure for businesses dealing with medical devices in any form.

To apply for an import license the following conditions must be met:

- The technical personnel must be adequately trained by the manufacturer of the device in annual intervals.
- The chief technician must have a diploma in a field as defined in *section IV.1* of *Circular 08/2006/TT-BYT.*
- The company has to provide adequate headquarters, warehouses and technical equipment.

Application dossiers include the following documents:

- application form
- relevant documents demonstrating that the above requirements are met
- the original catalogue of each type of product
- instruction manuals and technical guide including specifications (originals and Vietnamese translation
- manufacturer's quality certificate (e.g. ISO 13485 certification or FDA approval)
- Certificate of Free Sale (FSC) from the country of origin

For devices that have a new function or new therapy or devices that are imported to Vietnam for the first time, clinical trials are also required. Foreign clinical trials are usually accepted, but if the DMEHW deems local trials in Vietnam necessary, these will be organised and conducted by the MoH. The results are evaluated by the DMEHW and the decision will usually be issued within 15 working days. The import license is valid for one year, at the end of which a completely new application has to be filed.

The first step in the registration of a domestically manufactured medical device is a quality announcement to MOST. For higher risk medical devices this is the Announcement of Standard Conformity (ASC). It consists of an announcement of compliance with ISO or IEC standards. For lower risk devices the simpler Announcement of Quality Standards (AQS) is made which contains a declaration of conformity with any sets of standards (Vietnamese, international or in-house). Both announcements will be reviewed by MOST, which takes 60 days in the case of an ASC or 15 days for an AQS.

After acceptance of the ASC or AQS, respectively, an application for product registration can be submitted to the DMEHW. The application contains the following documents:

- notarized copy of the manufacturer's business registration certificate
- the ASC or AQS
- technical documents
- user instructions
- results of chemical, physical, and safety tests are required for some devices

- results of clinical trials if applicable

The procedure for clinical trials for domestic medical devices is essentially the same as described earlier for imported medical devices.

According to *Circular No.34/1999/TT-BTM*[53] labelling of all kinds of goods marketed in Vietnam, which includes medical devices as well, has to be in Vietnamese and the following information is to be provided:

- the commodity's appellation
- name and address of the company responsible for the commodity (manufacturer, importer)
- quantity of commodity
- composition
- principal quantity criteria
- date of manufacture and expiry date
- instruction for use and preservation
- the commodity's origin

An approval decision is usually issued by the DMEHW within 15 days. The registration certificate is valid for three years.

The registration requirements and process in Vietnam do not bear any similarity to the GHTF model as described before. While all domestically produced medical devices are subject to review by the competent authority and to product registration, the majority of imported medical devices do not need any registration at all before they can be marketed in Vietnam. Post-market surveillance is not performed at all.

3.7 Laos, Brunei, Cambodia & Myanmar

3.7.1 General Information

Information on medical device regulation in Brunei, Laos, Cambodia and Myanmar on the internet is scarce, if available at all, but according to the MDPWG`s comparative study on the control of medical devices in ASEAN, all of them are currently in the process of developing specific guidelines regarding medical devices[55]. Due to the scant information , all four countries are combined in the following chapter.

Brunei is a small country situated on the north coast of the island of Borneo. Its small, but wealthy economy is based on oil and natural gas production accounting for nearly half of the GDP which was estimated at $ 19.43 billion in 2009. With $ 50,100, the per capita GDP is similar to Singapore, making Brunei one of the wealthiest countries not only in the region but in the world. Medical services are all provided by the government[2]. Market data for medical devices in Brunei was not available.

In contrast, the Lao People's Democratic Republic, one of the few remaining single-party socialist

republics in the world, is among the poorest countries in the region. Laos is a landlocked country, bordering Vietnam in the east and Thailand in the west. Since 1988 a gradual return to private enterprise and liberalisation of foreign investments could be observed and economic growth has been steady over the years. But Laos is still an underdeveloped country with a GDP of $ 15.07 billion and a per capita GDP of $ 2,100, which is comparable to North Korea[2].

The economic situation is similar in the Kingdom of Cambodia, which is situated south of Laos: Despite steady economic growth over the last decades, poverty is still widespread. The per capita GDP is similar to Laos with $ 1,900 in 2009[2].

Myanmar, formerly Burma, is the westernmost ASEAN country and under tight military control. With a per capita GDP of $ 1,200 in 2009, it is among the poorest nations in Southeast Asia with the lowest economic growth rate in the region. The United States, the European Union, Canada, and Australia have imposed financial and economic sanctions on Myanmar, prohibiting most financial transactions with Burmese entities, imposing travel bans on Burmese officials and others connected to the ruling regime, and banning imports of certain Burmese products[2].

In all three countries the health care infrastructure is generally underdeveloped. Market data for medical devices was not available.

3.7.2 Regulation

Brunei, Cambodia, Myanmar and Laos do not have regulations specifically aimed at medical devices. Legislation relating to medicinal products is usually used instead. The regulating agencies responsible for medical devices are

- the Ministry of Health in Brunei,
- the Department of Food and Drugs in the Ministry of Health of Cambodia,
- the Food and Drug Department for consumable medical devices and the Curative Medicine Department for medical equipment, both under the Ministry of Health in Laos,
- and the Food and Drug Administration of Myanmar.

3.7.3 Definition and Classification

Brunei uses the definition and classifications of the *Emergency Care Research Institute* (ECRI) for medical devices. Due to the lack of specific medical device legislation, Myanmar, Cambodia and Laos do not have a definition or classification.

3.7.4 Product Registration

Brunei and Laos do not have a licensing or registration system in place at all, while Myanmar relies on a voluntary registration system under its National Drug Law regulating the registration of condoms and domestically produced disposable syringes and blood bags. Cambodia relies on approval from countries with a well-established registration system and all imported consumables must undergo quality control in the country even though original certificates of analysis or sterility of the product are provided by the importer. Except for Myanmar, there is no requirement for post-

market surveillance in these countries. Myanmar has an Adverse Drug Reactions Reporting System, which is applied to both pharmaceuticals and medical devices. The regulatory authority provides guidelines for adverse event and vigilance reporting.

3.8 Hong Kong SAR

3.8.1 General Information

Hong Kong is located on China's south coast and with a land mass of 1,104 km^2 and a population of about 7 million people, it is one of the most densely populated areas in the world, similar to Singapore[2]. Until 1997 Hong Kong was a dependent territory under British rule, when sovereignty was passed to the People's Republic of China. Although it is now an official part of China, Hong Kong is governed as a special administrative region (SAR), retaining its laws and a high degree of autonomy, which was guaranteed by China to remain that way for at least fifty years after the transfer.

Hong Kong has a highly developed economy, serving as one of the world's leading financial centres. Its GDP was estimated at $ 301.6 billion for 2009. which is comparable to Switzerland and Austria. In comparison, the per capita GDP of $ 42,700 in 2009 places Hong Kong among the most affluent countries in the world, slightly lower than Singapore and Brunei, but in a range with the United States[2].

The market for medical equipment and supplies was estimated at $ 391 million in 2009, equalling $ 55 per capita, which is similar to Singapore. It is expected that the device market will expand at a rate of 6.4% per annum[74].

3.8.2 Regulation

Currently, there is no statutory control regarding medical devices in Hong Kong, but a voluntary administrative control system, the *Medical Device Administrative Control System* (MDACS), was developed in 2003, which, similar to the situation in Singapore, is intended to facilitate the transition to a long-term legal control. It is largely based in the GHTF documents as described in *chapter 2.3*. The voluntary control system is managed by the *Medical Device Control Office* (MDCO) in the Department of Health[75]. The MDCO was established in 2004 and consists of the *Medical Device Registration Section* and the *Post-Marketing Surveillance Section.*

Similar to Singapore the MDACS was phased in in a step-wise approach with the difference that regulations in Hong Kong are still voluntary, while they became legal requirements in Singapore.

Phase I started in November 2004 with the listing of high-risk medical devices (class IV, for device classification in Hong Kong please refer to *chapter 3.8.3*). In November 2005, the MDACS was extended to include medium-risk medical devices (class II and III). Phase III in October 2006 began the Conformity Assessment Body Recognition Scheme. In this phase the MDCO began to recognize Conformity Assessment Bodies (CAB) that can perform conformity assessment demonstrating that a device fulfils MDACS requirements. The listing of local manufacturers began in March 2007 with

phase IV, and the listing of importers in July 2007 with phase V. Currently, there is no procedure to list low-risk medical devices (class I), nor their manufacturers or importers. Voluntary listing of high-risk IVD medical devices (class IV) is expected to start in the near future.

3.8.3 Definition and Classification

The term medical device is defined in *Guidance Note GN-01: Overview of the Medical Device Administrative Control System*[76]. It is a verbatim adoption of the GHTF definition as detailed in *chapter 2.3.1*. Risk classes and classification rules for general medical devices[77] and IVD medical devices[78] were also adopted word for word, the only difference being that the risk classes are named class I to IV instead of A to D with increasing levels of inherent risk from I to IV.

3.8.4 Product Registration

Prerequisite of an application to include a device in the *List of Medical Devices*, is the appointment of a *Local Responsible Person* (LRP), who has to be a locally registered entity[76]. The LRP serves as the main contact point for the MDCO in Hong Kong and fulfils the following obligations:

- communication with users, importers, the public and the government
- management of pre-market and post-market procedures
- submission of the application for listing of devices
- maintenance of distribution records allowing for the tracing of devices sold in Kong Kong
- provision of a documented procedure for complaint handling
- provision of maintenance and service arrangements for the devices listed
- provision of tracking systems down to patient level and annual surveillance report for certain high-risk devices, such as implantable pace makers
- initiation of product recalls and managing of adverse incidents
- reporting of changes to MDCO

The application for listing as LRP can only be submitted together with the medical devices to be listed and appropriate documentation demonstrating that the LRP is able to perform these duties is part of the application.

The major component of the application is the conformity assessment, which covers a product's quality management system, the post-market surveillance system, the Summary Technical Documentation (STED)[79] and the Declaration of Conformity, all completely in line with GHTF proposals (please refer to table *table 2.2*). The *Essential Principles*[80] were adopted from the relevant GHTF document[18]. Conformity assessment is performed by the manufacturer and reviewed by independent CABs, which need to be certified by the MDCO under the Conformity Assessment Body Recognition Scheme. The MDCO is not involved in the review of the conformity assessment, but only responsible for the maintenance of the *List of Medical Devices*. The use of international standards to demonstrate to conformity is not an obligation, but manufacturers are strongly recommended to use them.

In addition to the conformity assessment, labelling samples have to be submitted together with the

application. The following elements are generally required as part of the labelling[81]:

- contact details of the manufacturer and the LRP
- Listing number of the device
- name of the device
- intended purpose (if not obvious)
- instructions for use
- batch code/lot number or serial number as applicable
- expiry date or date of manufacture where relevant and as appropriate
- any special storage or handling conditions
- any warnings, precautions, limitations or contraindications
- any undesirable effects

Contact details have to be provided in English and Chinese, the instructions for use should preferably be in both languages as well. If only one language is available a supplementary statement must be added to inform the user of this fact. All other information can be provided in either language, but should be in both, if possible.

Evaluation of the application by the MDCO usually requires 12 weeks and an approval to list the device will be valid for five years. Currently, no fees are charged for the inclusion of a device into the *List of Medical Devices,* but as CABs are required to review the conformity assessment, these will charge fees.

After approval the device will be included into the *List of Medical Devices* with the make and model of the device and the contact details of the manufacturer and the LRP. The list is accessible to the public online on the MDCO website[75].

Post-market surveillance activities, such as adverse incident reporting and product recalls fall into the responsibilities of the LRP. Therefore, efficient communication channels with the manufacturer are essential to be able to collect and deliver feedback, especially in the case of adverse events, to the manufacturer and vice versa. Requirements, procedures and definitions regarding adverse event reporting are covered in a Guidance Note by the MDCO[82], which follows the proposals of Study Group 2 of the GHTF. Incidents causing death, serious injury or pose a serious risk to public health have to be reported within 10 calendar days of becoming aware of the incident. For other reportable events the reporting period is 30 days. In case of alerts, modification notes or recalls the MDCO has to be informed within 10 calendar days of their issuance.

The listing of local manufacturers and importers is also part of the MEDACS. Manufacturers need to provide a valid business registration in Hong Kong and have a QMS in compliance with ISO 13485 or equivalent[83]. Compliance has to be demonstrated by means of certification by a recognized CAB. Listed manufacturers are required to submit a list of devices manufactured every year. All devices in the list are subject to adverse event reporting, even if they are not listed in the *List of Medical Devices*, including class I devices. The inclusion into the List of Local Manufacturers is valid for a period of five years.

Importers are obligated to keep complete distribution records and to have appropriate procedures

for product recall and adverse event assessment and reporting in place[84]. An approval of inclusion into the List of Importers of Medical Devices is valid for two years.

Both lists are publicly available on the MDCO web site[75].

In contrast to the other countries presented in this thesis, the administrative control system in Hong Kong fulfils all requirements of the GHTF regulatory model as described in *chapter 2.3*.

3.9 China

3.9.1 General Information

With over 1.3 billion people, the People's Republic of China, commonly known as China, is the most populous country in the world. Its land mass of 9.6 million km^2 make it the second largest country in terms of land area, second only to Russia[2].

China is one of the few remaining single-party states ruled by the Communist Party of China. Since the introduction of market-based economic reforms in 1978, China has become the world's fastest growing major economy, the world's largest exporter and second largest importer of goods behind the USA. Its GDP of $ 8.789 trillion (as estimated for 2009) is the second biggest in the world behind the USA. In contrast, the per capita GDP of $6,600 (as estimated for 2009) is comparably much lower, in a range with countries like Turkmenistan or Ukraine[2].

Current data on the size of the medical device market was not freely available on the internet.

3.9.2 Regulation

The *Regulations for the Supervision and Administration of Medical Devices* (RSAMD)[85] issued by the State Council in 2000 and revised in 2001 lay down the basic regulatory framework for medical devices in China. Additionally, several normative documents have been issued over the past years to regulate the market, for example *Provisions on the Classification of Medical Devices*[86], *Provisions on Medical Device Registration*[87] and *Administrative Regulation of Medical Device Specification, Label and Packaging Identification*[88].

The responsible regulatory authority is the *State Food and Drug Administration* (SFDA) and its municipal and provincial branches[89]. Within the SFDA the Department of Medical Device Supervision bears the following responsibilities:

- development of national medical device standards and supervision of their implementation
- publication of the classification list of medical devices
- registration of medical devices
- development and implementation of Good Manufacturing, Good Clinical and Good Distribution Practice for medical devices
- licensing of medical device manufacturers and distributors
- adverse event monitoring

Although the SFDA retains overall authority, the responsibility for supervision and administration of certain provisions of the Chinese medical device regulation are delegated to other levels of government within China: Responsibility for low risk and medium risk medical devices which are manufactured domestically is assigned to the municipal and provincial branches of the SFDA. High risk domestically produced and imported medical devices fall under the direct responsibility of the SFDA (for device classification please refer to *chapter 3.9.3*).

In addition, the General Administration of Quality, Supervision, Inspection and Quarantine (AQSIQ) maintains responsibility for certifying electrical safety for a wide variety of imported products, including certain categories of medical devices.

3.9.3 Definition and Classification

In Article 3 of the RSAMD the term medical device is defined as follows:

"Medical devices" as defined by these regulations refers to: any instrument, apparatus, appliance, material, or other article whether used alone or in combination, including the software necessary for its proper application. It does not achieve its principal action in or on the human body by means of pharmacology, immunology or metabolism, but which may be assisted in its function by such means; the use of which is to achieve the following intended objectives:

1. *Diagnosis, prevention, monitoring, treatment or alleviation of disease;*
2. *Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap conditions;*
3. *Investigation, replacement or modification for anatomy or a physiological process;*
4. *Control of conception.*

This definition is similar to the GHTF definition (chapter 2.3.1), but IVD medical devices are not included, having their own provisions in Chinese legislation, which were enforced from 2007. Generally speaking, the requirements for IVD medical devices are similar to the ones for general medical devices and will not be presented in this thesis.

Article 5 of the RSAMD specifies a risk-based system of three medical device classes with increasing risk from class I to III:

- **Class I:**
  low risk devices for which safety and effectiveness can be ensured through routine administration
- **Class II:**
  medium risk devices for which further control is required to ensure safety and effectiveness
- **Class III:**
  high risk devices, which are implanted into the human body, used for life support or sustenance or pose a potential risk to the human body, requiring strict control with respect to safety and effectiveness

The *Provisions on the Classification of Medical Devices*[86] give general guidance on the

determination of the risk class. Similar to the GHTF classification rules, classification depends on the intended purpose of the device: Main criteria are the period of use, the invasiveness and if the device operates by exchange of energy with the body (active device). On the web site of the SFDA a matrix of criteria is available by which a certain code can be assigned to a medical device[90]. Using this code, the appropriate risk classification can be identified in the classification catalogue provided by the SFDA, which is available only in Chinese[91].

3.9.4 Product Registration

Businesses dealing with medical devices in China are required to have a license issued by the provincial or municipal SFDA branch in whose jurisdiction they are located.

Manufacturers operating in China need a production license according to Article 19 of the RSAMD, where the following general requirements are laid down:

- qualified employees trained in the production of the device to be manufactured
- facilities appropriate to the production of the device
- appropriate equipment
- qualified personnel or institutions and equipment to carry out quality control of the manufactured devices

For class I manufacturers only a notification to the appropriate authority is required, while applications of class II and III manufacturers will be reviewed and approved by the relevant authority, before production of medical devices can be started.

Until recently, no clear regulation relating to GMP for medical devices were in place in China. However, a draft Chinese GMP for medical devices was published in December 2009, which will become effective from January 2011. It is based on the ISO 13485 standard and sets forth general GMP requirements including management responsibility, document control, design and development, production control, distribution and servicing, nonconforming product, complaints and adverse event monitoring, etc..

Manufacturers of class I devices will simply be required to set up GMP pursuant to the device GMP, while class II and III manufacturers will have to apply for GMP certification from the provincial branches of the SFDA (for class II and certain class III devices) or the central SFDA (for high risk class III devices). On-site auditing for GMP-certified manufacturers will be conducted by the provincial branches of the SFDA on an annual basis.

Other businesses, like importers and distributors, must have an operation license according to Article 23 of the RSAMD. The following requirements have to be fulfilled by the applicant:

- facilities appropriate for conducting business and handling medical devices
- qualified personnel to carry out inspections of medical devices
- ability to provide after-sales service, such as technical training and maintenance

Similar to the production license, only a notification is necessary for enterprises handling class I devices, while applications of businesses handling class II and III devices will be reviewed before approval will be given.

Both types of license, production and operation license, are valid for five years and have to be renewed on expiration. Chinese medical institutions are required by law (Article 26, RSAMD) to purchase medical devices only from businesses with a valid production or operation license.

According to the *Provisions on Medical Device Registration*[87] no medical device may be marketed in China without prior approval by the SFDA or its municipal or provincial branches, respectively. As the required documentation and the registration procedure for domestically manufactured and imported devices differ only slightly, only the process for imported devices will be detailed in this thesis:

Unlike many other Asian countries, China issues registration certificates and licenses in the name of the manufacturer, not a local agent or distributor. Therefore, a local agent conducting the registration process is not strictly necessary, but should be considered to improve communication with the SFDA.

Prior to filing the application the following two key steps in the process have to be performed for class II and III medical devices:

Firstly, the applicable product standards have to be transferred to Chinese national standards, which are usually based on the relevant international standards. If no Chinese national standard is available, an industry standard or a company-specified standard may be used instead. Together with samples of the device to be registered, the standards will be forwarded to one of the SFDA approved and appointed testing centres, where type testing will be performed. Each centre, having its own particular experience and expertise, will have different testing responsibilities. Testing reports from foreign laboratories may be recognized and accepted, if the foreign laboratory in question is credible and internationally well known. For a range of products with the same or a similar intended use, technical structure and specifications, only one typical device representing the safety and efficacy of the whole product range may be tested. The test report will be part of the application and reviewed by the SFDA during the registration process.

Secondly, for implantable devices entering the Chinese market for the first time and for medical devices which have no marketing authorisation in their country of origin, clinical trials have to be performed by at least two government-designated medical institutes in China. Clinical trial reports from the country of origin will be accepted for all other class II and III devices.

The actual application for registration of a medical device must be in Chinese and will be submitted to the municipal or provincial branch of the SFDA, where the local agent responsible for the registration process is situated. Following an initial review the application is forwarded to the central SFDA.

The documents required for an application for all classes of domestic and imported medical devices are detailed in the appendices of the *Provisions on Medical Device Registration*[87]. For imported medical devices the following list is applicable:

- SFDA application form
- business license of the manufacturer (including incorporation documents (extract from the Commercial Register), medical device manufacturing permit or other legal documents

which can prove the legitimate qualification of the manufacturer)

- business license of the agent conducting the registration and power of attorney from the manufacturer for the agent
- registration certificate from the country of origin
- applicable product standards and a description of the medical device
- instruction manual for the device
- type test reports issued by an SFDA-certified testing centre (required for class II and III devices only)
- clinical trial reports (required for class II and III devices only)
- Product Quality Guarantee issued by the manufacturer, certifying that the quality of the product to be registered in China is exactly the same as in the country of origin
- authorisation letter to a Chinese agent, who is responsible for reporting adverse events occurring in China (includes authorisation from the manufacturer, written commitment of the agent and business license of the authorised agency)
- after-sales authorisation letter to a Chinese agent responsible for after-sales services (includes authorisation from the manufacturer, written commitment of the agent and business license of the authorised agency)
- self declaration for authenticity of all submitted items

All documents must be submitted in Chinese or be accompanied by a Chinese translation. An on-site audit of the manufacturer's QMS by the SFDA is required for class III devices as part of the registration process.

The registration process usually takes four months and the registration certificate is valid for four years. A renewal has to be approved by the SFDA six months before the initial registration expires. The documents required for a renewal of the registration certificate include the previous registration certificate and in addition to the documents required for the initial registration, a follow-up report including a description of the monitoring of adverse events.

Medical devices imported into China must be labelled in Chinese according to the *Administrative Regulation of Medical Device Specification, Label and Packaging Identification*[92]. It focuses on the content of the technical manual, which should contain the following information:

- description of the technical performance of the device
- principles of operation of the device
- method of application
- indications for use
- description of clinical effectiveness
- date of expiry
- contraindications
- appropriate warnings and precautions describing serious adverse reactions, potential safety hazards, and any special care to be exercised
- instructions for maintenance and repair (if appropriate)

- storage and transport requirements
- packaging and accessories

The label should contain the following information:

- product name, model and specification
- contact details of manufacturer
- registration certificate number
- manufacturing date or batch number/serial number (as applicable)
- date of expiry (if applicable)

The regulation also has a number of prohibitions against absolute expressions on efficacy and comparison of safety and efficacy with products of other manufacturers.

3.9.5 Adverse Events

A system of adverse event reporting is still being developed in China. In December 2008, the SFDA released the *Provisions on Medical Device Adverse Event Monitoring and Re-evaluation* (SFDA document No. 766)[93]. The regulation specifies that, while the SFDA is responsible for nationwide monitoring of adverse events and re-evaluation activities, medical device manufacturers are required to establish an adverse event reporting procedure. Adverse events must be reported within the following time frames after becoming aware of the fact:

- Adverse events involving death must be reported within five business days.
- Adverse events involving serious injuries must be reported in 15 days.
- There is no mandated time frame for other adverse events.

Medical device manufacturers are also obligated to evaluate adverse events and conduct a re-evaluation of the safety information submitted for their product. The results of this re-evaluation must be reported to the central SFDA or its municipal or provincial branches for low risk devices. Manufacturers of class II and III medical devices must file an *Annual Report on Medical Device Adverse Events* with their local adverse event monitoring institution by the end of January each year.

3.9.6 China Compulsory Certification for Certain Devices

In addition to the registration by the SFDA, there is a compulsory product certification scheme by the AQSIQ, under which the following seven categories of medical devices are regulated:

- medical diagnosis X-ray equipment
- haemodialysis equipment
- hollow fibre dialysers
- extra-corporeal blood circuit for blood purification equipment
- electrocardiographs
- implantable cardiac pacemakers
- artificial heart-lung machines

This certification is referred to as *China Compulsory Certification* (CCC) and serves as evidence that these products can be imported, marketed and used in China. The CCC mark is administered by the *China National Certification and Accreditation Administration* (CNCA)[94], which designates the *China Quality Certification Centre* (CQC)[95] to process CCC mark applications. As a first step of certification an application is sent to the CQC including an introduction of the applicant, a product description and information about the manufacturing facilities. The documents will be reviewed by the CQC, which will then request test samples and additional technical documents if required. Testing of the device will be performed in an accredited laboratory in China and an on-site audit by Chinese officials will be conducted. After evaluation of the testing and auditing results the CQC will issue the certificate, which can then be attached to each product to be imported into China. To maintain the certification follow-up inspections by Chinese officials are required every 12 – 18 months.

The tests required under this certification scheme are very similar to the tests performed for the registration of medical devices by the SFDA. As a consequence, medical device manufacturers, who wanted to import any of these types of medical devices into China, had to comply with two very similar testing procedures, which were performed in parallel. To address this problem, the SFDA and the AQSIQ published a joint note declaring that both authorities were going to share a single testing process without duplication of tests or fees in late 2008[96].

3.9.7 Conclusion

China has developed its own medical device regulation independently of the GHTF. Although many approaches are similar, there are certain differences to be observed:

- The definition of the term medical device is almost identical, but IVD medical devices are excluded from the general definition in the RSAMD. A separate set of legislation is under development for IVD medical devices.
- The classification of medical devices is risk-based like the GHTF classification and uses similar criteria (active device, term of use, invasiveness), but as there are only three classes, devices may be categorized differently than in the GHTF system.
- The registration requirements are dependent on the risk class of the device, but in addition to an evaluation of the manufacturers quality management system and technical documentation, a compulsory type testing must be performed by accredited laboratories in China.

The registration of all classes of devices and all businesses dealing with medical devices, either as manufacturer or importer/distributor, which is considered by the GHTF to be the most basic form of regulatory control, is in place. The review of the registration documentation is always performed by the regulatory authority, parts of which are delegated to municipal or provincial authorities. CABs are not involved in the process. A system for post-market surveillance and QMS requirements for medical devices are still under development in China.

4 Discussion - Integration of Medical Device Regulation in Asia

To place a medical device on the market in Southeast Asia, which is considered belonging among the most promising future economies in the world, a wide variety of regulatory frameworks has to be managed at present:

Out of the 10 ASEAN member countries only 6 have laws or "administrative guidelines" specifically aimed at medical devices (see *table 4.1*). In the other four, pharmaceutical legislation is used as a substitute at the moment, but all are in the process of developing laws or guidelines as part of the healthcare integration project in the ASEAN countries.

Table 4.1: Status of medical device law in the observed Asian countries, n.a. = not applicable
[1]implementation in Singapore will be finalized in 2011

	medical device law	administrative guidelines (voluntary registration)	conformity to GHTF
Singapore	x[1]	n.a.	conformity to AMDD
Malaysia	n.a.	x	yes
Indonesia	x	n.a.	no
Thailand	x	n.a.	no
Philippines	x	n.a.	no
Vietnam	x	n.a.	no
Laos	--	--	n.a.
Brunei	--	--	n.a.
Cambodia	--	--	n.a.
Myanmar	--	--	n.a.
Hong Kong SAR	n.a.	x	yes
China	x	n.a.	no

Indonesia, Thailand, the Philippines and Vietnam all require that medical devices are registered according to their own national systems, which do not conform to the GHTF regulatory model. In Malaysia, the future system described in the administrative guidelines will conform completely to the GHTF guidelines, but currently registration of devices, distributors and manufacturers is only voluntary. In Singapore, the implementation of a medical device law, which will conform to the AMDD will be finalized in April 2011. The AMDD is based on the GHTF model, but not completely identical with it.

Like Malaysia, Hong Kong SAR does not currently require mandatory registration of medical devices, but the voluntary system used at the moment is an exact adoption of the GHTF model. China, in contrast, has developed an independent medical device legislation over the past years, which is not based on the GHTF recommendations.

Depending on the regulatory framework of each country, the definition and classification of medical devices may differ widely (see *table 4.2*). Thailand and the Philippines use their own definitions,

which are very general and do not distinguish clearly between medical devices and medicinal products. Notably, medical devices for veterinary use are included in the definition for both countries. Vietnam, although it has national provisions for the regulation of medical devices, does not have a definition of the term itself. In all three countries, medical devices are not classified based on a system of risk-based rules, but rather certain types of medical devices, that require registration, are listed in governmental documents.

Singapore, Malaysia, Indonesia and Hong Kong SAR have all adopted the GHTF definition for their national medical device law or administrative guidelines, respectively. The GHTF classification system with its four risk classes is also followed, except for Indonesia, where the US three class system was adopted instead.

Table 4.2: Overview definition and classification of medical devices in the observed Asian countries

	definition medical device	**classification**
Singapore	GHTF	GHTF (classes A - D)
Malaysia	GHTF	GHTF (classes I - IV)
Indonesia	GHTF	USA system (class I - III)
Thailand	own	own, list-based system (licensed, notified & general medical devices)
Philippines	own	mandatory registration of sterile, invasive, implantable and listed devices
Vietnam	--	import license for implantable & listed devices
Laos	--	--
Brunei	ECRI	ECRI
Cambodia	--	--
Myanmar	--	--
Hong Kong SAR	GHTF	GHTF (classes I - IV)
China	own	risk-based system (classes I - III)

China uses its own definition, which is very similar to the GHTF definition, but excludes IVD medical devices, which are to be treated separately. Its three class system is risk-based using criteria similar to the GHTF system, but as there are only three classes, a device may be placed in a different class from the GHTF model.

Laos, Cambodia and Myanmar do not have a definition or classification system due to the absence of relevant legislation. Brunei uses the ECRI definition and classification.

According to the GHTF recommendations, registration of medical device manufacturers, distributors and the medical devices to be placed on the market is to be considered as the most basic form of regulatory control to allow for a quick identification of devices and the responsible manufacturer or distributor, respectively. Another important parameter to ensure patient safety is the implementation of an efficient adverse event reporting system, which should be part of the overall legislative control of medical devices.

When comparing the current situation in the observed countries, it becomes obvious that this is not

always fulfilled (see *table 4.3*): Due to the absence of any specific legislation for medical devices in Laos, Brunei and Cambodia, there is also no registration or licensing system or any kind of adverse event reporting installed in these countries. Myanmar at least conducts registration of certain medical devices and adverse event reporting is mandatory as part of the Drug Adverse Event Reporting System, which covers not only pharmaceuticals but also medical devices, but there is no licensing system for manufacturers, importers and distributors.

Table 4.3: Overview registration of medical devices and manufacturers/distributors and adverse event reporting systems in the observed Asian countries
[1] no mandatory adverse event reporting

	registration of medical devices	**registration of manufacturers, distributors and importers**	**adverse event reporting system**
Singapore	yes	yes	yes
Malaysia	voluntary	voluntary	voluntary
Indonesia	yes	yes	(yes)[1]
Thailand	yes	for licensed medical devices only	for licensed and notified medical devices
Philippines	for listed medical devices only	yes	--
Vietnam	all domestically manufactured devices, for import listed medical devices only	yes	--
Laos	--	--	--
Brunei	--	--	--
Cambodia	--	--	--
Myanmar	registration of condoms and domestically manufactured disposable syringes and blood bags	--	within Drug Adverse Event Reporting System
Hong Kong SAR	voluntary	voluntary	voluntary
China	yes	yes	yes

While all medical devices have to be registered according to Thai national legislation, the registration of manufacturers, distributors and importers is limited to *licensed medical devices* only. These are considered to require the most stringent regulatory control, but this group of devices is limited to a very small number. Adverse event reporting exists, but is mandatory for licensed and notified medical devices only. This again, limits the amount of information to a very small and selected number of medical devices, while the majority of devices on the market is not subject to this kind of systematic control.

In contrast to this, the Philippines require the registration of all manufacturers, importers and distributors, but the registration of the devices themselves is limited to certain types, which are defined by law. In Vietnam, all domestically manufactured devices have to be registered, but only certain types of imported devices. An adverse event reporting system is completely absent in both countries.

In Singapore, Hong Kong SAR and Malaysia, all three types of this basic control are completely in line with the GHTF suggestions, although still voluntary in Hong Kong SAR and Malaysia at present. For China, these requirements are also fulfilled.

Based on these aspects alone, it can be deduced that regulatory requirements vary widely between many of the described countries and that there is room for improvement even at the most basic levels of control. Therefore, it is the explicit aim of the ASEAN member countries to further develop regulatory control of medical devices and as a result, patient safety.

One major focus of the AMDD is the standardization of medical device registration requirements and procedures, introducing the GHTF definition and classification system in all countries as well as the *Essential Principles of Requirements of Safety and Performance*. These provisions are exactly the same as the GHTF equivalent documents. The technical documentation, on the other hand, follows the CSDT of the AHWP, which is the Asian counterpart of the STED of the GHTF. It contains some smaller additions, which were already described in *chapter 3.1.4* of this thesis. Besides the CSDT, the AMDD also requires a Declaration of Conformity, which is in line with GHTF recommendations.

The AMDD contains guidelines not only for the review process of the documentation, but also the requirement to review and approve the applicant's internal systems for quality management and post-market surveillance. The extent of the review process depends on the risk class of the concerned medical device, which also conforms to the GHTF requirements.

Unlike the EU's medical device directives, the implementation of the AMDD requirements in all ASEAN member states will not mean that a single regulatory approval will enable marketing a product in every ASEAN member country, but that a single regulatory dossier can be submitted in every member country for an identical approval process. In effect, this will lead to an elevation of regulatory hurdles for market entrance in most of the ASEAN member states compared to the current situation.

Besides the registration process, the other major component of the AMDD is the postmarket alert system. The scope of medical device adverse events, which should be reported, is defined as well as the details, which should be included in adverse event reports. The purpose is to disseminate information on adverse events to regulators in all ASEAN member countries and to enable them to quickly identify defective or unsafe devices.

Presently, the AMDD is still at a draft stage with two major issues still needing resolution by the MDPWG:

One is disagreement about the language requirements of the labelling, the main question being if English labelling will be sufficient in all countries. However, even if English is the only requirement in the final draft of the AMDD, labelling in the local language may still be required for devices that are marketed to the public directly.

Additionally, no consensus has been reached yet on whether the final draft will allow for third-party assessment bodies. Some ASEAN members, like for example Malaysia, want to use independent CABs to carry out the review process, similar to the EU's Notified Bodies, while other members

favour a centralized review system completely in the hands of the regulatory authorities. In the current legislation or guidelines, only Malaysia of all the ASEAN member states has provisions, which include CABs in the review process.

The official deadline for all ASEAN member states to comply with the AMDD will be 2015. Singapore will be the first country to implement a version of the AMDD, where only English labelling is required and where review of conformity assessment is the sole responsibility of the regulatory authority, by 2011. Malaysia, which has been operating a voluntary system based on the GHTF recommendations for a few years, should also be ready to implement the AMDD fairly soon. However, some of the other the member states may not be able to meet the deadline in 2015, depending mainly on the resources available in each country. While the Philippines have already passed their Medical Device Bill in 2009, which incorporates most elements of the AMDD, there has not been made much progress towards implementation of the Bill due to the lack of resources. The same is true for all other member states, and especially for the poorer countries Laos, Cambodia and Myanmar.

Therefore, the complete implementation will certainly be a more long term approach, which should focus on the more basic points of regulatory control, like registration of all medical devices irrespective of their current classification in each country and all businesses dealing with medical devices. Especially the poorer countries should be allowed to rely on certification of medical devices in benchmarked countries, like the GHTF founding members, or the more advanced ASEAN members, like Singapore, instead of conducting reviews of the conformity assessment themselves. An efficient alert system for adverse events across all ASEAN member states would also make a huge contribution towards improved patient safety. The AHWP's Safety Alert Dissemination System (SADS) could certainly further this objective, including even more countries than the ASEAN member states, thereby building a larger database of adverse events by far.

The MDPWG does not consider the AMDD as the final step towards ASEAN medical device integration. Another proposal, which is still under discussion, is to allow mutual recognition of medical device product approvals across ASEAN countries. This would eliminate the need to submit separate applications in each ASEAN member country. However, only a limited form of mutual recognition is considered to be feasible at this point: ASEAN countries with more advanced regulatory systems would be designated to play the role of "reference member state". Before an official mutual recognition scheme exists, prior approval in Singapore will probably be already considered a significant aid to receive approval in other ASEAN countries.

Unlike the MDPWG for the ASEAN member countries, Hong Kong SAR bases its administrative guidelines for medical devices completely on the GHTF recommendations without any alterations. At present, the guidelines are still voluntary and there are no official statements available as to when a change towards legislative control could be expected. The administrative guidelines differ significantly from the medical device legislation in China, and a harmonisation does not seem probable at this point in time.

Unlike its pharmaceutical counterpart, the *International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH), the recommendations of

the GHTF for medical devices have not been transposed to binding national law even in all its founding members. Examples are, that the USA have not amended their classification system accordingly, or that the EU has not adopted the GHTF definition of the term medical device, for example. Global harmonisation is still an ongoing process among these member states and should be considered a long term approach similar to the ASEAN countries.

5 Summary

The rapidly growing economies of the Southeast Asian countries offer attractive opportunities for the marketing of medical devices: Increasing affluence across Southeast Asia is expected to lead to a growing demand in health care products, like for example medical devices.

This master thesis presents the current regulatory requirements for medical devices in the member countries of the Association of the Southeast Asian Nations (ASEAN) as well as Hong Kong SAR and China. ASEAN represents the following Southeast Asian countries: Singapore, Malaysia, Indonesia, Thailand, the Philippines, Vietnam, Laos, Brunei, Cambodia and Myanmar.

To place a medical device on the market in any of these countries, highly diverse regulatory requirements have to be met at the present time: Out of the 10 ASEAN member states only five have medical device laws (Singapore, Indonesia, Thailand, the Philippines, Vietnam), while one maintains a voluntary registration system using administrative guidelines (Malaysia). The remaining four countries do not have laws or guidelines specifically aimed at medical devices at all. Similar to Malaysia, Hong Kong SAR utilizes a voluntary registration system based on guidelines, while China has its own medical devices law.

Currently, there is no common definition of the term *medical device* in these countries, which leads to the fact that certain products may be subject to medical devices law in some countries, but not in others. Products for veterinary use, for example, have to fulfil national medical device requirements in Thailand and the Philippines at the moment, but not in any of the other countries.

Classification will also often follow specific national rules. The requirements for registration differ widely with mandatory registration for all classes of devices and licensing requirements for manufacturers, importers and distributors in some countries, while in other countries, there are no requirements at all due to the lack of relevant legislation or administrative guidelines. The standard of adverse event reporting also varies and does not always form a part of the existing regulations.

Therefore, it is the explicit aim of the ASEAN member countries to develop and harmonise regulatory control of medical devices in all its member countries with the introduction of the ASEAN medical device directive (AMDD). The AMDD will introduce a common set of rules in all member countries and is mainly based on the recommendations of the Global Harmonisation Task Force (GHTF), a voluntary international group of medical device regulatory authorities and medical device trade associations from the European Union, the United States of America, Canada, Japan and Australia. The ASEAN member countries will be required to pass national laws implementing the AMDD over the next years. Singapore is the first country to finalize this process in 2011, but the other countries will follow on their own time depending mainly on the resources available at the national level.

Hong Kong SAR also relies on the GHTF guidelines for its own national regulations: The GHTF recommendations were completely transposed into the administrative guidelines, building a voluntary registration system. However, there is currently no defined point in time, when the change from voluntary to mandatory registration will take place. In contrast to this, China has developed its

own medical device legislation independently from GHTF recommendations and is still in the process of further developing some aspects, like for example adverse event reporting, special requirements for IVD medical devices or GMP for medical devices.

A complete harmonisation of requirements for medical devices for the whole region is not to be expected in the near future, but major steps are already being taken in that direction. Until this goal is accomplished, companies intending to market products, which are considered to be medical devices in Europe, in these countries, have to verify for every single country, if and what specific requirements have to be met.

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Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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