

**Development of the ASEAN Pharmaceutical Harmonisation  
Scheme  
- An Example of Regional Integration -**

Wissenschaftliche Prüfungsarbeit  
zur Erlangung des Titels

**'Master of Drug Regulatory Affairs'**

der Mathematisch-Naturwissenschaftlichen Fakultät  
der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

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Bonn, 2007



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## Acknowledgements

First of all I would like to thank my tutors Dr. Michael Gebauer, Dr. Anja Fiedler and Dr. Witold Krepski for their contribution. I would also like to acknowledge those colleagues, who enabled me to perform these postgraduate studies and writing of this thesis. My deepest thanks to my fiancé Jürgen Heil. Throughout the years of my studies he has been unfailingly supportive and patients that I did not have much time for him.

Though it was a very stressful time I have learnt a lot personally and professionally.

Thanks to all involved.

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## List of Abbreviations

ACCSQ	ASEAN Consultative Committee on Standards and Quality
ACTD	ASEAN Common Technical Dossier
ACTR	ASEAN Common Technical Requirements
AEC	ASEAN Economic Community
AEM	ASEAN Economic Ministers
AFTA	ASEAN Free Trade Area
APC	ASEAN Pharmaceutical Club
APRIA	ASEAN Pharmaceutical Research Industry Associations
ASA	Association of Southeast Asia
ASEAN	Association of Southeast Asian Nations
ASEAN-6	Brunei, Indonesia, Malaysia, Philippines, Singapore, Thailand
ASEC	ASEAN Secretariat
AMM	ASEAN Ministerial Meetings
ASC	ASEAN Standing Committee
BA/BE	Bioavailability/ Bioequivalence
Biotech	Biotechnology derived product
CDA	Center of Drug Administration
CTD	Common Technical Document
CLMV	Cambodia, Laos, Myanmar, Vietnam
CPP	Certificate of Pharmaceutical Product
EMG	Eminent Person Group
EU	European Union
GCG	Global Cooperation Group
GMP	Good Manufacturing Practice
GP	Generic Product
HLTF	High Level Task Force
HSA	Health Science Authority (Singapore)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH-CTD	ICH-Common Technical Document
ITG	Innovative Therapeutic Group
MALPHILINDO	Malaysia, Philippines, Indonesia
MaV	Major Variation
MiV	Minor Variation
MRA	Mutual Recognition Agreements
NCE	New Chemical Entity
NTA	Notice to Applicants

PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PMA	Post-Marketing Alert (System)
PPWG	Pharmaceutical Product Working Group
RH	Relative Humidity
SEATO	Southeast Asian Treaty Organisation
SEOM	Senior Economic Officials Meeting
SG	Singapore
SOM	Senior Officials Meeting
TOR	Table of Reference
UN	United Nations
WG	Working Group
WHO	World Health Organisation
WTO	World Trade Organisation



# **1 Introduction**

## **1.1 Preamble**

The Association of Southeast Asian Nations (ASEAN) comprising the member countries, Indonesia, Malaysia, Philippines, Singapore, Thailand, Brunei Darussalam, Vietnam, Laos, Myanmar and Cambodia was established in 1967 to promote regional peace and stability. Charting the new directions the ASEAN vision aims to forge closer economic integration towards building an ASEAN community by the year 2015.

The ASEAN's Pharmaceutical Product Working Group is contributing to this vision by establishing the pharmaceutical harmonisation scheme. The goal is to create common regulations for pharmaceuticals in the region, reduce barriers to trade and to ensure that pharmaceutical products penetrating the ASEAN markets show sufficient safety quality and efficacy.

In my thesis I would like to explain the legal background for the establishment of harmonised pharmaceutical legislation, first experiences with the implementation and a future outlook which is the mutual recognition of marketing authorisations between the ASEAN member countries.

Finally I want to point out in the case of Singapore, how its national registration routes can serve as an example for future pharmaceutical harmonisation activities in the ASEAN region.

## **1.2 Pre-ASEAN Southeast Asia**

Southeast Asia is a sub region of Asia, consisting of the countries that are geographically south of China, east of India and north of Australia. It lies in-between and has been influenced by the two ancient civilisations of China and India. The region is geographically, ethnically and culturally diverse (see map in Annex I).

Initially Southeast Asia was ruled by small kingdoms and principalities in which disputes over land and power led to constant clashes and shifting boundaries. The history of the countries within the region only started to develop independently from each other after the European colonialization was at full steam between the 17th and 20th century. Portugal, Spain, the Netherlands, England, France and the United States all had colonies in Southeast Asia and divided the region regardless of ethnic composition of the population within. Thailand was the only country in the region that maintained its independence throughout the period of colonial rule.

Europeans were profiting from the regions vast resources (e.g. rubber, tin, copper and oil) and establishing bridgeheads along the sea routes that were connecting Asia with the western world. The colonial empires imposed a variety of new languages and unfamiliar legal, economic and social systems to Southeast Asia.

At the same time European education sowed the seeds of the fledgling nationalist movements for independence in the colonial territories.

During the World War II Japan occupied large regions in Asia and was a catalyst to the demands of independence. After the World War II, between 1945 and 1960, there was a rapid withdrawal of European powers from South East Asia. It is notable that some of the exits from colonial rule were more benign than others; some had to be fought for, others were negotiated<sup>i</sup>. Most states of the region developed authoritarian governments dominated by the military or communist party.

The early years of independence were marked by the twin demands of nation building and post war reconstruction. Having achieved independence, the new governments of South East Asia were faced with challenges to their legitimacy by communist insurgencies, by border disputes and by great power intervention. The poverty rate was high and the inequality between the western educated elites and the mass of the population was marked.

By the middle of the 1960s leaders in Southeast Asia believed that regional cooperation was an answer to the areas external and internal threats. Unfortunately early attempts to create regional associations such as the South East Asian Treaty Organisation (SEATO), Association of Southeast Asia (ASA) and MALPHILINDO had not been promising; all were dissolved mostly due to territorial disputes:

- South-East Asian Treaty Organisation (SEATO)<sup>1</sup> existed from 1954-1977 and founded by Australia, France, New Zealand, Pakistan, Philippines, Thailand, Great Britain and the United States. This organisation was an American organised international military defence alliance created to oppose further communist gains in Southeast Asia. It was unable to intervene during the Vietnam conflicts as it proved to be ineffective in garnering substantial support from its members.
- Association of Southeast Asia (ASA) existed from 1961-65. It was formed on the initiative of the Malay prime minister and was the first step from the region to create a regional association. The member countries were Malaya Philippines and Thailand. With the aims to use regional cooperation on economic and cultural matters to strengthen Southeast Asian countries and thereby defend them from dangers of communist insurgencies and outside intervention. The aims were rather apolitical using friendly consultation and mutual assistance. Shortly after the organisation had been established there were territorial conflicts over Sabah between Malaya and Philippines that could not be resolved and led to the end of the association. The conflict was that both countries claimed

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<sup>i</sup> Federation of Malaya, indep. From Britain in 1957. Malaysia was formed in 1963. Singapore split off from Malaysia in 1965; Myanmar independency got recognized from Britain in 1948; Brunei indep. from Britain in 1984, Vietnam's independency got recognized from France in 1953; Cambodia indep from France in 1953; Laos indep. From France in 1949; Philippines got independent from US in 1946; Indonesia's independency was recognized by Dutch in 1949

territory rights over Sabah, an area located in the North-East of Borneo Island (today belonging to Malaysia). Philippines protested against the inclusion of Sabah in the newly created Malaysian State.

- MALPHILINDO: 1963-1966, compromising of Malaya, Philippines and Indonesia. It was looser in structure than ASA and was intended only as a form consultation on regional matters. The end of the association was triggered by territorial political conflicts between Indonesia and Malaya and Philippines.

The regional disputes that led to the end of the ASA and MALPHILINDO were quite complex and driven by the strong leaders of the newly independent states. These leaders were not willingly to collaborate nor compromise, led to break off diplomatic relations. The conflict was mainly arising out of the creation of Malaysia in 1963 which triggered a series of regional conflicts. Malaysia was created when the former British colonies Sabah and Sarawak on the northern coast of Borneo island and Singapore joined the Federation Malaya (Peninsula territories) which was already independent since 1957.

An armed rebellion in Brunei led the Sultanate to refrain from joining Malaysia. Philippines protested against the inclusion of Sabah in the new Malaysian State. The Philippines claimed it had a right to Sabah arguing that it had historic links with the territory.

Differences between the leaders in Singapore and Malaysia over how to manage ethnic relations in the new state led to the expulsion of Singapore from Malaysia in 1965.

President Sukarno who was governing Indonesia, the biggest country in Southeast Asia, challenged the whole premise of the Malaysian Federation plan and launched the Konfrontasi war 1961-66 to break it up. Sukarno believed that consolidation of Malaysia would increase British control over the region, threatening the newly independent Indonesia's state.

It can be seen as a combination of several environmental changes in the Southeast Asian region that have facilitated the creation of ASEAN in 1967<sup>2</sup>.

The political intraregional situation changed, Konfrontasi ended with the overthrow of president Sukarno in Indonesia. In Philippines leadership changed to the new president Marcos in 1965 who was easing off the tension in the Sabah conflict with Malaysia.

The founding members had until then gone through a period of conflicts among each other. These conflicts were pivotal events in Southeast Asian history because the intense diplomacy required to resolve them, created a new communications network among Southeast Asian leaders, who had previously been isolated from one another. The desire to institutionalize that communication network and

promulgate a regional code of conduct to prevent future conflicts was one of the key triggers that led to the creation of ASEAN.

ASEAN's formation was also propelled by concern about great power rivalry in the region, particularly amongst China, the Soviet Union and the United States of America (cold war). Regionalism was seen as a useful way to 'enhance the bargaining power of small and weak states in their dealings with the great powers.

### 1.3 Regional Cooperation in ASEAN

The Association of Southeast Asia was established on 08. August 1967, when the founding countries of Indonesia, Malaysia, Philippines, Singapore and Thailand signed the Bangkok Declaration<sup>3</sup> to pursue regional stability, ending interstate disputes and to protect the member states against communist expansion and insurgencies within their own borders. The declaration is a short idealistic statement of intentions. It emphasises the need to 'strengthen existing regional bonds', it talks in terms of 'solidarity and cooperation', of 'equality and partnership' in the search for 'peace, progress and prosperity'. Moreover it is emphasized that 'national identities' of their people should be maintained and 'external interference to subvert the national freedom of the states' should be avoided. This implies that the states should maintain their sovereignty and that ASEAN can be understood as intergovernmental organisation. At the end of the declaration it is made clear that the membership of the association is to be open to all of the nations in Southeast Asia.

Shortly after its independence Brunei acceded ASEAN on 08. January 1984. These six countries, namely Brunei, Indonesia, Malaysia, Philippines, Singapore and Thailand are often called the **ASEAN-6** as they were the initial drivers of ASEAN.

With the end of the cold war Vietnam has become ASEAN member country on 28. July 1995. Laos and Myanmar (syn. Burma) both acceded to the association on 23. July 1997. Cambodia joined its neighbour countries on 30. April 1999. These four new member countries that joined ASEAN almost 10 years later than the founding countries are often called the **CLMV-group**. They had to accept all agreements of the ASEAN at time of accession, but got prolonged timeframes to reach the set targets.

East Timor which is independent from Indonesia since 2002 has currently got observer status and requested ASEAN accession at the on 28. July 2006. Effective ASEAN membership is expected around 2011. Papua-Newguinea joins as observer since 1985.

ASEAN's founding members faced the characteristic problems of newly independent post-colonial states: ethnic secessionist demands threatening territorial integrity, communist insurgency and challenging regime security<sup>4</sup>

ASEAN initial focus was security and non-interferiority in times of the cold war. The end of the cold war had introduced new levels of complexity to the political and

strategic environment of Southwest Asia. ASEAN had to establish a new focus and decided to develop and foster initiatives towards closer economic cooperation in the region as well as with external stakeholders.

In the following years ASEANs member states were undergoing political reform, liberalisation and enjoying economic growth. ASEAN was cited as an exemplar of regional cooperation. At the same time the member states had, since ASEAN's inception in 1967, managed to prevent intra-regional disputes from escalating into armed conflict which was a great success.

The Asian economic crisis and inflation 1997-98 was a new challenge for the ASEAN states which struggled with financial decline and associated political and social instability. In addition, membership expansion by less developed semi-authoritarian states posed further challenges to the associations. This was the time for ASEAN to set new actions in order to boost economy and trade which means to increase ASEANs competitiveness within globalisation (Actual trade indicators are listed in Table 1).

In 1997, the year of the 30th anniversary the 'ASEAN vision 2020'<sup>5</sup> was born aiming to create the ASEAN community with a common market by the year 2020. Recently this due date was advanced to 2015<sup>6</sup>.

In order to implement the long-term vision, a series of action plans were drawn up to realize this vision.

With signing of the Bali Concorde II Declaration in 2003<sup>7</sup> ASEAN resolved that the ASEAN **Community** shall be established comprising three pillars for regional integration, namely:

- ASEANs **Security** Community, under the purview of ASEANs Foreign Affairs Ministers
- ASEANs **Economic** Community (AEC) under the purview of ASEANs *Economic* (Trade) ministers
- ASEANs **Socio-Cultural** Community (ASCC) under the purview of ASEANs Foreign Affairs Ministers

Worthwhile to mention is that through the Bali Concord II in 2003<sup>8</sup>, ASEAN has subscribed to the notion of democratic peace, which means all member countries believe democratic processes will promote regional peace and stability. Also the non-democratic members agreed that it was something all member states should aspire to.

**Table 1: Selected basic indicators for the ASEAN region in 2006 (ASEAN Secretariat)**

Basic Indicator	Size
Land Area	4 465 500 km <sup>2</sup>
Population	567 390 000 people
Annual popul. growth	1.6%
GDP total	1 064 351.3 million US \$
Total trade	1 442 656.9 million US \$
Foreign direct Investment	38 082.9 million US \$

## **2 ASEAN's Institutional Framework**

### **2.1 Decision Making Process**

ASEAN countries are a loose regional grouping, with no supranational institutions to provide common policy or stipulate any laws and regulation. Each member country still maintains its independent legal system and its laws and policies, except those mutually agreed within ASEANS co-operation programs. Every program implemented in ASEAN has been agreed among the member countries on a consensus basis.

The highest centrally decision making organ of ASEAN is the Summit a yearly meeting of the ASEAN heads of state and government. Further decisions for the region are taken by the different ministerial to which certain tasks have been dedicated. There are 17 ministerial levels which come together at formal or informal ministerial meetings, e.g. ASEAN Ministerial Meeting (AMM) of the Foreign Ministers, the ASEAN Economic Minister Meeting (AEM), Ministerial Meeting on Health, Social Welfare and Science and Technology<sup>9</sup>.

Under the ministerial bodies level there are 29 committees of senior officials and 122 technical working groups and task forces that support the ministerial bodies and ASEAN activities. They meet regularly throughout the year performing the pre-operative work for the respective higher-level meetings, where the proposals are endorsed and decisions are taken.

The annual **chairmanship country** of the major ASEAN meetings (e.g. like the Summit, AEM, AMM) rotates alphabetically between the ASEAN member countries. The calendar year sequence of ASEAN meetings and events, their chair country and venue is available on the ASEAN Secretariat's website<sup>10</sup>:

All ASEAN agreements can be divided into **flexible frame work agreements** similar to treaties and subsidiary agreements for implementation of the main framework agreements. These **subsidiary agreements** are usually made in form of 'Action Plans' or 'Protocols' annexed to the frame work agreements. These frame work agreements and their subsidiaries are usually agreed upon during the yearly summits.

All Agreements and actions plans are monitored and archived by the ASEAN-Secretariat and published on their website in order to make it accessible to public<sup>11</sup>.

### 2.1.1 ASEAN way

General, philosophy of the so called ASEAN way is to makes decisions based on consultation (*musjawarah*) and consensus finding (*mufakat*) by all member countries. This political process is derived from an ancient Javanese custom. The ASEAN way, means that all issues concerned would be discussed and debated until reaching final resolution with mutual recognition. There is no voting system to come to an agreement but only the open dialogue. For implementation of decisions the 'ASEAN-X' principle applies. This principle allows those who are ready to move forward with liberalization without being held back by the slower ones or absent ones.<sup>12</sup>

### 2.1.2 Crisis Management and Disputes

Originally the provision for resolution of disputes regarding enforcement of agreements was that of the 1976 Treaty of Amity and Cooperation which encouraged the ASEAN member states to find a solution through diplomatic negotiations (ASEAN way).

Recently ASEAN has shifted to the WTO style<sup>13</sup> by concluding to a Protocol on Enhanced **Dispute Settlements Mechanism**<sup>14</sup> which helps resolving issues, which are related to economic agreements. Member states which are party to a dispute may at any time agree to good offices, conciliation or mediation. In case member countries cannot agree on the subject matter on implementing ASEAN agreements, the dispute is referred to the Senior Economic Officials meeting (SEMO) for ruling. The parties to the dispute may appeal the ruling by SEMO to the ASEAN Economic Ministers (AEM) appeal body, which will make a final decision. Compensation and the suspension of the concession will apply to the party which failed to comply with the decision. The Protocol on Enhanced Dispute Settlement foresees dedicated timeframes for this procedure which enables effective enforcement of decisions

There are other crisis management mechanisms applying when regional political security is affected, but they remain merely used. They are the **High Council**<sup>15</sup> of the Treaty of Amity and Cooperation (2000/ASEANsec) and the **Troika**<sup>16</sup>. The aim of the High Council is to deal with long term dispute solving, whereas the Troika is an ad hoc body which should deal with urgent issues that need a fast respond. High Council and Troika are seldom used for interstate conflicts as often ASEAN members referred their bilateral disputes to international bodies, e.g. the international court of justice<sup>17</sup>.

## 2.2 Summit

Until now the highest decision making body of ASEAN is the meeting of ASEAN Heads of Government also known as the ASEAN Summit. These are annual meetings taking place usually in autumn. The first summit was in 1976 and the

following summits taking place infrequently. Since 2001 it was decided to meet yearly to address urgent issues affecting the region.

The sequence of the meetings is usually as follows:

Prior to the summit there are various meetings at the level of senior officials and the ASEAN Directors –General.

These are followed by **Joint Ministerial Meetings** of the Foreign and Economics Ministers of ASEAN and if needed with the respective counter parts from their so called dialogue partner countries.

During the formal **Summit ASEAN leaders** meet to take decisions for the region. These are followed by bilateral or plenary session meetings between ASEAN leaders with their dialogue partner countries. In total ASEAN has eleven dialogue partners, namely Australia, Canada, China, European Union, India, Japan, New Zealand, Republic of Korea, the Russian Federation, the United States and the United Nations. These are followed by joint dialogue meetings of the **ASEAN +3** meeting of ASEAN with China, Japan and South Korea. The biggest dialogue meeting is the **East Asian Summit** between ASEAN, China, Japan, South Korea, Australia and New Zealand and India, which is established since 2005.

During the summits and the preceding meetings intra- and inter-ASEAN agreements are signed. Further up-dates on progress of action plans and programs are presented and decisions are taken.

Throughout the year the different ASEAN bodies, committees and working groups work towards the targets set out in these agreements.

## 2.3 Secretariat of ASEAN

The ASEAN Secretariat was established 24.02.1976 by the ASEAN foreign ministers and has its legal basis in the Agreement on the Establishment of the ASEAN Secretariat, 1976 which has been constantly amended. The Secretariat is a standing body located in Jakarta, Indonesia and consists of a professional staff of around 100 members. The Secretariat is headed by Secretary-General of ASEAN, who is appointed on merit and accorded ministerial status. The Secretary-General of ASEAN has a five-year term and is mandated to initiate, advise, coordinate, helps effective decision making within the ASEAN bodies, monitors work plans and implements ASEAN activities. This includes participation to the heads of Government Meetings, ASEAN Ministerial Meetings, attend or dedicate a representative at all ASEAN committees. He acts as the channel for formal communications between, ASEAN permanent committees, ad hoc committees, experts groups, and other ASEAN bodies as well as international organizations and governments.

The around members of the ASEAN Secretariat professional staff are appointed on the principle of open recruitment and region-wide competition. The operational budget of the ASEAN Secretariat is prepared annually and funded through equal



contribution of all ASEAN member countries. The ASEAN Secretariat has no decision making role, as these decisions are taken and agreed at the Summits<sup>18</sup>.

Each ASEAN country has a National Secretariat in the Foreign Ministry which organises and implements ASEAN-related activities at the country level. At the head of each National Secretariat is a Director-General.

## **2.4 Committees in Third Countries**

ASEAN has established committees in its 'Dialogue Partner' countries to handle ASEANs external relations with these countries in international organisations. These committees comprise of ambassadors of all ASEAN Member Countries based in the capitals of the third countries. They conduct consultative meetings with their host government.

## **2.5 Standing Committee**

The ASEAN Standing Committee (ASC) is composed of the Directors-General of the ASEAN Departments of the respective Ministries of Foreign Affairs. The Directors-General meet as a body standing in for the ASEAN foreign ministers who meet in the ASEAN Ministerial Meetings (AMM). Chairman of the ASC is the foreign minister of the summit's host country.

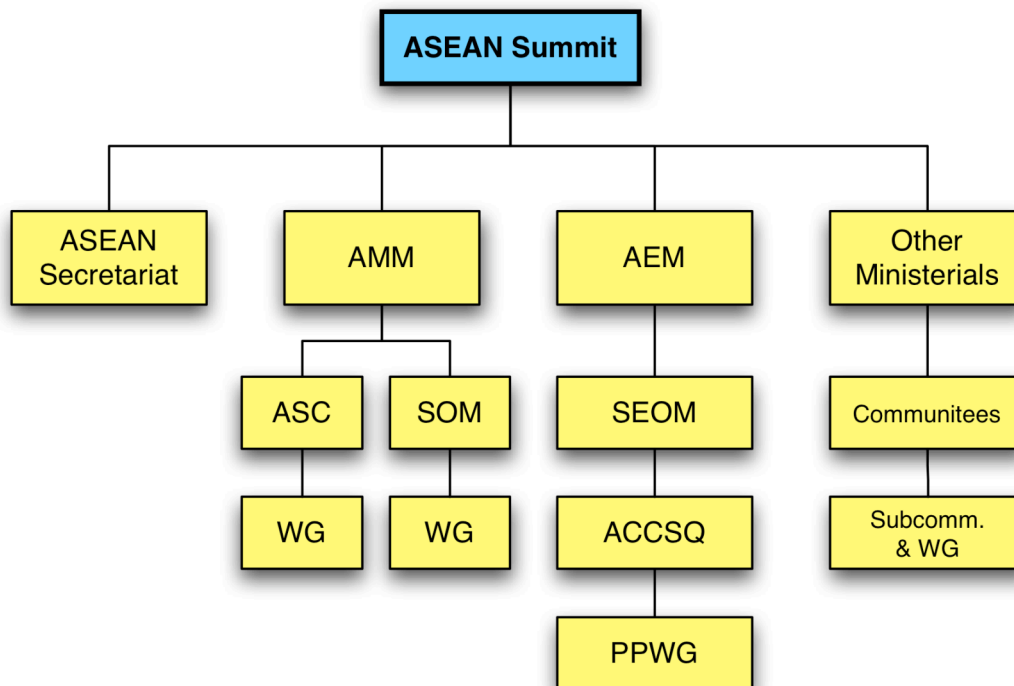
## **2.6 Ministerial Sectors**

There are various ministerial sectors and its meetings reporting jointly to the ASEAN leaders. Supporting these ministerial bodies are committees of senior officials, technical working groups and task forces. The 17 ministerial sectors come together at formal or informal ministerial meetings out of which the ASEAN Ministerial Meeting (AMM) and the ASEAN Economic Ministerial Meetings (AEMM) are the most important ones.

At the ASEAN Ministerial Meetings (AMM) level the ASEANs foreign ministers work together. The AMM is supported by the ASEAN Standing Committee and the ASEAN Senior Officials (SOM). The ministers of foreign affairs are in charge of two out of three pillars which shall form the ASEAN Community, they are Political-Security Cooperation and Socio-Cultural Cooperation. The AMM oversees ASEANs community-building efforts, external relations, strategic policy and development cooperation. The AMM is also responsible for institutional and organisational affairs. The AMM implements decisions of the ASEAN leaders (Summits) working with other sectorial bodies in ASEAN.

ASEAN Economic Ministers (AEM) are in charge for the pillar economic community. Under the purview of the AEM are its subordinated committees and working groups and its regular meetings such as the Senior Economic Officials Meeting (SEOM), Asean Consultive Committee on Standards and Quality Meetings and Product Working Groups-Meetings (ACCSQ).

The described organisational structure is shown in **Figure 1**



AEM	ASEAN Economic Ministers
AMM	ASEAN Ministerial Meeting
SEOM	Senior Economic Officials Meeting
ASC	ASEAN Standing Committee
SOM	Senior Officials Meeting
ACCSQ	ASEAN Consultative Committee on Standards and Quality
WG	Working Group

**Figure 1: Organisational Structure of ASEAN**

## 2.7 The ASEAN Charter as Future Institution

ASEAN's founding document was a two-page 'Declaration', but not a treaty registered at the United Nations. The Declaration just adhered to some general principles of international behaviour. When ASEAN was formed in 1967 the newly independent post-colonial states wanted to maintain their national sovereignty. This background has led to the ASEAN governments to prefer informal processes, weak regional institutions and the 'ASEAN way' in making decisions by consensus. Over the years of confidence building among the ASEAN members states certain inter-states norms and behaviours have evolved and more binding agreements were signed. The ASEAN objectives and principle norms are currently scattered in several documents adopted over the years. ASEAN has operated 40 years without a formal charter.

Globalisation and a political changing environment were the reason for ASEAN governments and stakeholder's decision to establish the ASEAN charter<sup>19</sup>.

The charter should state the objectives of the region and would serve as an institutional framework of codifying ASEAN norms and rules as well as confer legal personality to the grouping and determine the relations between ASEAN bodies.

A High Level Task Force (HLTF) under the Foreign Ministers is currently preparing the first draft of the ASEAN charter that shall be available by end of 2007. When drafting the charter the HLTF takes into account the recommendations from the Eminent Person Group (EPG). The EPG comprising senior statesmen, are in contact with various stakeholders<sup>20</sup> from civil society, private business and academics. The 'Report of the EPG on the ASEAN charter'<sup>21</sup> was presented at the 12. Summit in January 2007.

The EPG recommends in their report that the ASEAN charter shall be registered with the United Nations secretariat and thereby should confess itself being an intergovernmental ruled organisation.

Registering the ASEAN charter under the Art 102 of the UN Charter would give ASEAN legal personality as an international organisation, so that it could act more confidently on behalf of the region as a whole. It would enable ASEAN to enter treaties with other countries effectively. At the moment ASEANS ten separate members act as separate parties<sup>22</sup>.

The EPG recommends including in the charter that ASEANS objective should be a custom union. This would go beyond the current goal of a common market. The custom union would be a further developed stage of economic integration. The EPG further recommends to strengthening democratic values and respect of human rights. A defined process is proposed to engage interaction with representatives from civil society, interparliamental organisations and private sector. There are several other recommendations from the EPG to streamline the decision making process, e.g. reduce number of ministerial, introduce a majority voting instead of the current lengthy 'ASEAN way' of consensus finding is lengthy. The ASEAN secretariat general should be empowered to sign on behalf of all ASEAN leaders for certain agreements. The ASEAN Summit should be renamed to ASEAN council as the supreme policy making organ. In order to redress non-compliance by member states EPG proposes sanctions that could possibly lead to the temporary suspension of ASEAN membership. The new charter proposals could theoretically put Myanmar's membership in jeopardy if the junta continued to put up roadblocks to democracy.

The next summit end of 2007 will show to which extend the relatively drastic reform proposals of the EPG will be integrated into the draft ASEAN charter.

### **3 Economic Integration on the Healthcare Sector**

Under the purview of the ASEANS Economic Ministers (AEM) is the pillar Economic Cooperation with the aim to establish one ASEAN Economic Community (AEC)<sup>23</sup>.

Economic integration activities are to strengthen the implementation of its existing economic initiatives including the ASEAN Free Trade Area (AFTA), ASEAN Framework Agreement on Services, ASEAN Investment Area, Dispute Settlement and the initiative for ASEAN integration of the CLMV accession countries.

Worth while to mention is that ASEAN initially contained a loose form of preferential trade agreements (PTA). After the end of the cold war ASEAN intensified its economic integration with reducing tariff and non-tariff barriers by accepting common standards.

A further development of the preferential trade agreements was the launch of the ASEAN Free Trade Area (AFTA) in 1992. AFTA determined that among ASEAN member countries all tariff lines in the defined inclusion lists have been brought down to 0-5 %, which was realised for ASEAN-6 in 2003. There is now a commitment to remove all tariffs in intra-ASEAN trade by the year 2010 for the ASEAN-6 and for CLMV by 2015.<sup>24</sup>

The end goal of AEC is the single common market which goes beyond a free trade area, allowing labour, service and capital crosses borders within the regions market..

In order to reach this goal ASEAN conducted a economic competitiveness study<sup>25</sup>. This study highlighted ASEAN's fragmented markets, high transaction costs, and unpredictable policy environment as obstacles to further growth.

The main recommendation of the study was the need to start with the liberalisation and integration of a few priority sectors in which ASEAN had clear comparative advantage. These recommendations were taken into account at the 9<sup>th</sup> ASEAN Summit by signing the Bali Concorde II in October 2003 (see section 1.3). Eleven priority sectors were agreed upon in order to accelerate market integration. They were: wood-based products, automotives, rubber-based products, textiles and apparel, agro-based products, fisheries, electronics, e-ASEAN, healthcare (pharmaceuticals), air travel, tourism. For each of these priority sectors protocols and roadmaps were initiated to identify measures that shall be implemented within clear set timelines. The ASEAN Economic Ministers were tasked to implement and monitor these activities in collaboration with its committees and working groups.

### **3.1 Elimination of Technical Barriers Trade**

One of the Committees under ASEAN Economic Ministers is the Asean Consultive Committee on Standards and Quality (ACCSQ) that was formed in 1992 to support and complement the ASEAN Free Trade Area (AFTA).

ACCSQ meetings are twice a year around March and August. The primary objective of ACCSQ is to facilitate trade and to eliminate technical barriers to trade. It is often the duplicative testing procedures arising from different systems of conformity assessment in various countries that have become serious barriers to trade. The Committee and its working groups try to harmonize national standards with

international standards and implement mutual recognition arrangements on conformity assessment.

ACCSQ either implements or monitors the implementation by its Working Groups and Product Working Groups. There are various working groups under the ACCSQ, e.g. 'Pharmaceutical Product Working Party'(PPWG), the ' Medical Device Working Party' as well as the 'Group of Standards and Mutual Recognition' and the 'Working Group on Accreditation and Conformity Assessment'. The ACCSQ has a joint work program including set targets and timelines for each of the working parties, which is regularly up-dated and published in the web<sup>26</sup>. Each of the working parties has to provide annual reports to the ACCSQ. Topics that need agreement from ASEANs leaders are channelled to the yearly summits via the ASEAN Ministers.

ACCSQ and mainly its PPWG are in charge of accelerating the economic integration of the priority sector healthcare, which covers pharmaceuticals.<sup>ii</sup>

## **4 ASEAN's Regulations on Pharmaceuticals**

Harmonisations of Pharmaceuticals Standards all began in 1997, when the 13<sup>th</sup>. ACCSQ meeting in March 1997 saw the need to establish a Pharmaceutical Product Working Group. A proposal was set up by Malaysia, which was endorsed by the relevant bodies. Accordingly PPWG had its first meeting in Sept 1999 with Malaysia as Chair and Thailand as Co-Chair.

The main objective of the PPWG is to develop a harmonisation scheme of pharmaceutical regulation. The ultimate goal is to eliminate technical barriers to trade, however ensuring those pharmaceutical products penetrating the ASEAN market are safe, efficacious and of quality.<sup>27</sup>

All PPWG meetings are convened by the chair of the PPWG, or in his absence by his co-chair. There are usually one or two PPWG meetings per year. At the end of each PPWG meeting it is determined the date and country in charge for organising the next venue of the next meeting.

The participants are a representative from the ASEAN Secretariat, representatives from national health authorities and any ACCSQ member wishing to participate. The first PPWGs were not open to foreigners, or industry. Initially the meetings were for drug regulators from the region only. As of 2001 also members from international organisations (e.g. WHO, ICH) are invited to hold presentations and to participate in working sessions.<sup>28</sup> Whereas nowadays most of the PPWG plenary sessions are open to invited guest and observers from local industry associations. There are

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<sup>ii</sup> Legal Basis for the latest work program of ACCSQ and PPWG are the documents signed by ASEAN Leaders at the 10. Summit in November 2004. They are the "Vientiane Action Program 2004-2010" and the "ASEAN Framework Agreement for the Integration of Priority Sectors".& Appendix "Roadmap for Integration of the Healthcare Sector", which includes measures (= action items), responsible subcommittee or working group and due dates for implementation. Measure no. 43: MRA, no 44: ACTD Implementation, no. 45: Harmonising the Labeling of Pharmaceutical Products, no. 46 Harmonised Placement System, 47. Twinning System for Mutual Regulatory Capacity and Resources Development 49 Post-Marketing Alert System

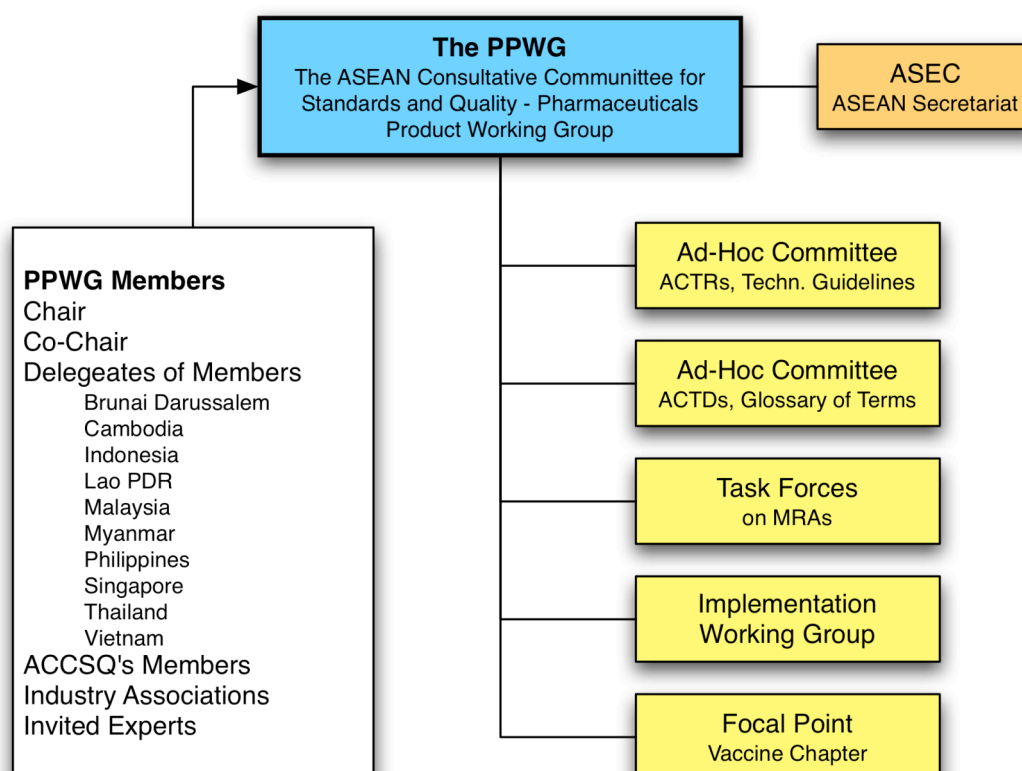
around 300 participants joining each PPWG meeting. Often the PPWG meetings are preceded by meetings of different ad hoc working groups..

During the PPWG meetings industry usually raises their voice through representatives from local trade associations that are in dialogue with Health Authority delegates. Lately dialogue between health authority and industry is channelled via two 'regional' trade associations to the PPWG. These are the ASEAN Pharmaceutical Club (APC), composed of members from local generic trade associations and the ASEAN Pharmaceutical Research Industry Associations (APRIA), mainly with representatives of multinational companies situated in ASEAN. It has been decided that these regional industry associations shall submit position papers 3 months prior the PPWG meetings to the PPWG Chair<sup>29</sup>.

In previous times several trade associations were working in each country. Consensus finding among trade associations was very time consuming.

Observers from industry wishing to participate to the PPWG have to request for participation to these meetings via their local trade association. The host country of the PPWG defines how many participants can join the PPWG and allows each local trade association to nominate a number of participants.

Figure 2 shows the organisational structure of the PPWG meetings. Each PPWG meeting is joined by the ASEAN Secretariat and the different working groups present their achievements.



**Figure 2: PPWG Meetings Organisational Structure**

## Consultation Procedure

The PPWG determined that the topics selected for harmonisation would be divided into Safety, Quality and Efficacy to reflect the three criteria which are the basis for approving medicinal products. It was also agreed that ad hoc expert working groups and committees shall be set up to discuss scientific and technical aspects of each harmonisation topic. The working groups should judiciously take into account requirements of national regulatory agencies and existing good international regulatory principles, without over-regulation or simply adopting systems of reference agencies.

In order to develop a harmonisation of pharmaceutical regulations it was necessary to establish an operational proceeding that leads to an efficient work program.

Following Consultation procedure was developed by the PPWG for identifying topics for harmonisation and to establish a work program<sup>30</sup>.

The first step is to exchange and review information on the existing pharmaceutical requirements and regulations among ASEAN member countries.

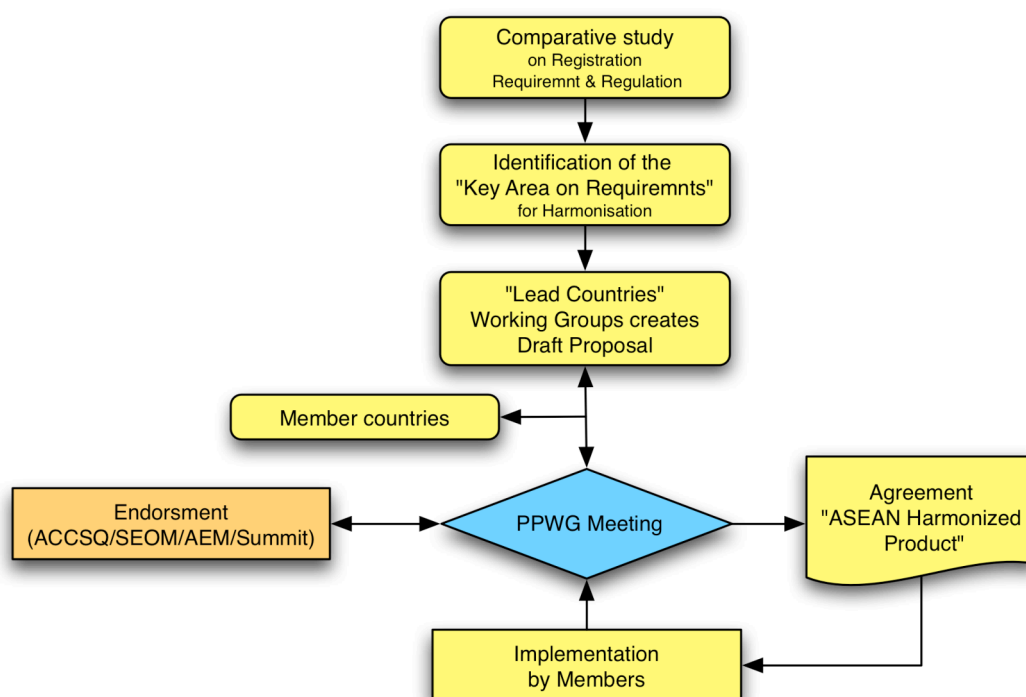
The next step is to conduct comparative studies, between ASEAN regulations and other international accepted standards, e.g. ICH, WHO guidelines.

Following surveys and comparative studies the ASEANs 'Key areas' for harmonisation are identified.

1. The PPWG assigns a 'Lead Country' and 'ad hoc' or 'permanent' working groups that should set up to discuss scientific and technical aspects of each harmonisation topic. These working groups shall prepare a draft proposal of how to harmonise the identified key area. As there are various international guidance documents, ASEAN has to determine which of these are applicable for the ASEAN region. If there is no existing international guidance or in case the international guidance is not applicable for ASEAN, the region will develop their own. The working groups are in open dialogue with industry representatives and experts from international organisations.
2. The lead country of the working groups presents the draft proposals for harmonisation of a specific key area at the PPWG meeting for discussion and agreement. If there are objections the draft and successive revisions are circulated for comments to the individual ASEAN health authorities who send it to their respective national industry association. The lead country is tasked to revise the draft proposals, taking into account comments received from health authorities and industries. Once consensus is reached the final draft is agreed by regulators of ASEAN at the PPWG meetings. Agreements are made upon common consensus of all member states. Often Myanmar delegates could not attend the PPWG meetings, in this case they send their position by post-mail.
3. Ratification: Once PPWG agreed on the final draft, it is channelled to the appropriate higher bodies for endorsement or decision.

4. These harmonisations decisions are implemented within clear set timelines. Implementation follows according to the respective national procedures and the implementation is monitored by the respective lead country of the working group. PPWG reports their achievements back to the ACCSQ. At all PPWQ meetings a delegate from the ASEAN secretariat is present to channel and make connection to other ASEAN bodies. New regulatory ASEAN guidelines should be published on the ASEAN-Secretariat's homepage and on each individual health authority's homepage.
5. Implementation goes along with Training, Support and Assessment. PPWG organises various trainings for regulators and industry with support from international organisations. On the other hand there are intra-ASEAN trainings, where more developed ASEAN countries train others, e.g. twinning system between CVML and ASEAN-6 countries. PPWG networks with various international organisations and regulators from other regions, (e.g. WHO, ICH-GCG, APEC) in order to working towards adopting a harmonised best practice approach for ASEAN. They seek funding and training from cooperation projects with its international dialogue partners.

The above described procedure is illustrated in Figure 3.



**Figure 3: PPWG's consultation procedure**



This 'PPWG Consultation Procedure' shows similarity to the 'Formal ICH Procedure' (=category1)<sup>31</sup>. In both procedures topics are determined, both have dedicated expert working groups that are led by the chair person (ASEAN) or rapporteur (ICH). There exists a similar sequence on drafting, consultation and adoption of guidelines for both procedures.

Though there is a significant difference, which has their nature in the institutional structure of ASEAN and ICH. The ICH has a Steering Committee (SC). This is the body that governs the ICH, determines the policies and procedures for ICH. It selects topics for harmonisation and monitors the progress of harmonisation initiatives (ICH Glossary). For example, the SC officially has to agree before a topic can reach the next step of the ICH procedure. The number of SC member is determined. Agreement by the SC means that at least one of the SC members for each of the six ICH parties has to give their assent.

For the SC there is no exact equivalent in ASEAN. The SC can only partially be compared to the PPWG meetings. The PPWG meetings are the occasions where the expert working groups present their draft proposals to the panel of PPWG members to seek their adoption by consensus, and not by a partial vote like the SC. Another difference is that the PPWG does not have the legal right to take a decision. The PPWG can only 'adopt for proposal to a higher body'. The higher bodies endorse the PPWGs proposals or take a final legally binding decision.

Therefore the ASEAN decision making process can be very lengthy compared to the ICH process.

The PPWG has working groups who monitoring the progress on the different topics on pharmaceutical harmonisation, whereas the PPWG itself is monitored by the ACCSQ.

Like the ICH 'category two procedure' the PPWG has established Questions and Answers Documents (Q&A) to assist in the implementation of existing guidelines. The Q&A documents will be version controlled. Currently Indonesia has been appointed as lead country in drafting amore detailed mechanism for the decision making process and up-dating the Q&A <sup>32</sup>documents.

Currently ASEAN has no revision and maintenance procedure in place to review existing guidelines like the ICH (categories three and four procedure). The PPWG Focus Discussion Group<sup>33</sup> already identified that the PPWG should set up a mechanism to assess new ICH guidelines or other existing international guidelines that are new to ASEAN. This is another action item on which the PPWG will follow up in future.

The ACCSQ-Working Group on Standards and MRA is currently creating a guideline on 'Good Regulatory Practice' which should assist regulatory authorities in developing technical regulations in such a way that it can protect the legitimate

objective of its member countries without creating unnecessary technical barriers to trade. Once this draft is adopted it will be applicable for health authorities.<sup>34</sup>

## 4.1 ASEAN Pharmaceutical Product

At the first PPWG meeting the Terms of Reference were agreed and it was decided that the topics selected for harmonisation would be divided into Safety, Quality and Efficacy to reflect the three criteria which are the basis for approving medicinal products. One of the PPWGs key topic is the idea of an 'ASEAN pharmaceutical product'. This means that same regulatory requirements apply for the registration of a medicinal product among the ASEAN member countries. The PPWG developed the ASEAN Glossary of terms, the ASEAN Common Technical Dossier (ACTD), the ASEAN common technical requirements (ACTR)<sup>35</sup> and its guidelines. An overview of available guidance documents is found in Annex IV.

The **ACTD** gives information on the format and structure of the dossier that shall be commonly used for applications in the ASEAN region. The ACTD should serve as a locator for documentation that has been compiled for a marketing authorisation application. It does not give any recommendations on the actual content of the dossier. The ACTD is similar to the European Notice to Applicants Volume 2B Presentation and Format of the dossier (EU-CTD).

The **ACTR** is a set of written material intended to guide applicants to prepare an application in a way that is consistent with the expectations of all ASEAN Drug Regulatory Authorities. It is guidance for the preparation of the ACTD. It can be compared to the EU NTA Volume 2 C.<sup>iii36</sup>

There are four ASEAN specific ACTR-quality guidelines and several other international guidelines that have been adopted as reference guideline to be followed when planning a submission.

The **ACTD check-lists** give recommendations to which extend documentation has to be provided for the different product classifications. The different ASEAN product classifications are namely a New Chemical Entity, Biotechnology derived products, Major/ Minor Variations or Generic Products. Until now these classifications are not clearly defined. The applicant therefore has to apply the regulations of each national regulatory authority and consult them for advice, e.g. pre-submission meetings.

A **Questions and Answers (Q&A)** documents for the ACTD quality has already been established and shall be up-dated on a regular basis by the relevant expert working group. Further Q&A documents are in planning also for the other parts of the dossier (e.g. for the ACTRs Quality guidelines on Stability, Process validation, Analytical validation guidelines).

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<sup>iii</sup> Notice to Applicants (NTA) Vol. 2, Eudralex published by the EU Commission, Enterprise Directorate- General,

The **ACTD Glossary** of terms is valid for ACTD and ACTR and helps to have a common understanding when working in different expert working groups. The PPWG agreed that the ASEAN - glossary is based on regional definitions and international guidelines. The different ASEAN member countries realised that different terms were used by different organisations, e.g. WHO, ICH.<sup>37</sup> PPWG therefore created the ASEAN glossary, which was adopted in 2002.

#### **4.1.1 Updates on the Common Dossier**

The advantage of the ACTD is that one dossier can be used for the whole region rather than generating different registration dossiers. ACTD should therefore significantly reduce time and resources needed to compile applications. The harmonised format should also facilitate the regulatory review. Thailand was the lead country to develop the overall ACTD organisation with input from the different working groups<sup>iv</sup>. for the administrative part, quality, non-clinical and clinical part The ACTD organisation and its structure have been adopted at the 7<sup>th</sup> PPWG Meeting in 2003. After a trial period that started in 2003 it was agreed that ACTD shall be implemented by all ASEAN member countries originally by 31 Dec 2006. The due date for implementation was postponed to 31 Dec 2008 in order to allow member countries to transpose ACTD requirements into their local regulations. Currently further guidelines to point out details of the ACTD and questions and answers documents are developed in parallel to the stepwise ACTD implementation. During the transition period 2003-2008 the following dossier formats are optional to use, either national dossier format or ICH-CTD format or ACTD format. Currently it is under discussion whether flexibility on the dossier format, will be allowed for specific product categories after the implementation due date of 31.12.2008. The term 'product categories' still needs to be defined. It is feasible that a product category will be assigned for products with a high interest of public health. They need a fast access to the ASEAN market and in such specific case it might be allowed that the respective innovative products and Biologics can be submitted in ICH-CTD format even beyond 2008.

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<sup>iv</sup> Lead countries for the working groups that establish the ACTD were for Part I: Administrative part, chair: Malaysia, Part II: quality, chair: Indonesia, Part III Non-Clinical, chair: Philippines, Part IV: Clinical chair: Thailand.

**Table 2: Transition and implementation dates of ACTD & ACTR  
(status 2. PPWG, Oct 2006)**

Countries	Start of transition period	National due dates for implementation
Singapore	April 2004 (8.PPWG)	Dec 2005
Malaysia	July 2003 (8.PPWG)	Dec 2005
Thailand	June 2004	Dec 2007
Indonesia	2005	Dec 2007
Vietnam	not determined	Dec 2007
Philippines	Jan 2005	Dec 2008
Brunei Darussalam	April 2006 (for Part I&II)	Dec 2008
Cambodia	not determined	Dec 2008
Lao PDR:	not determined	Dec 2008
Myanmar	not determined	Dec 2008

#### 4.1.2 Differences between ACTD and ICH-CTD

Guidance on the structure and format of ACTD is given in the document called 'ACTD organisation'. This document is similar to the ICH Guideline M4 (R3) 'Organisation of CTD', but there are differences in numbering, granularity and naming of sections. The different structure between the ACTD and the ICH CTD can be seen in annex III.

The ACTD consists of Parts I to IV which have subsections A to F. In comparison the ICH-CTD has five Modules with subsections that are numbered. The administrative data of Part I is part of ACTD, whereas Module 1 of the ICH-CTD is purely country specific. Any additional data not contained in the main sections of the ACTD should be included as addenda to the relevant section.

The summaries of the quality (Part II), non-clinical (Part III) and clinical (Part IV) are located at the beginning of each part of the ACTD. The ICH-CTD dedicates these summaries a separate Module 2. As the ACTD does not have such summary part it consists only of four Parts and not five.

The rationale for ASEAN member countries not to adapt ICH-CTD but to develop their own ACTD was that the majority of pharmaceuticals registered in ASEAN are Generics and health authorities mainly review the quality part.

Consolidating the quality data under a single part facilitates review<sup>38</sup>, rather than having this information separated over two Modules like in the ICH-CTD (M2 contains Quality Overall Summary and M3 Body of data).

The ACTD organisation describes details of the ACTD format, e.g. paper size, and fonts, use of acronyms and abbreviations. This is identical to the ICH.

The **ACTD pagination** is more flexible than the ICH-CTD. The preamble of the ACTD organisations just mentions the ACTD index and that the dossier should be

numbered with the first page of each part designated as page 1. No further granularity, segregation or pagination is defined. Compared to the ASEAN the requirements of the ICH-dossier are more complex as pointed out in the M4R3 'Granularity Document'<sup>39</sup>.

Issues occur, when reformatting the ICH CTD to the ACTD format, due to the different numbering of sections, pagination and cross-references. Defining the extent of granularity of the ACTD is up to the applicant to decide.

**Electronic submission** is foreseen according to the preamble of the ACTD organisation but until now it is not further specified for ASEAN. It is not specified if this will be similar to the e-CTD or whether this will be a on-line submission like it is already common practice in Malaysia and Singapore.

On-line submission here means, that parts of the ACTD are typed or up-loaded to a on-line database from health authorities. In Malaysia Part I and II can be submitted via the on-line system (Quest 1&2) but part III and IV may be provided as hard copy, e.g. CD. In Singapore just the ACTD part I documents have to be submitted online via the PRISM portal, the rest can optionally be submitted on-line or as CD <sup>40</sup>. Initially in Malaysia the system was slow, unstable and not user friendly as trade associations reported. Today these issues have been resolved.

#### **Administrative Data:**

As in ASEAN the Part I belongs to the ACTD the format and sections have been harmonised. The ACTD Part I requirements 'Administrative Data and Product Information' was developed by Malaysia as lead country and adopted by the PPWG in 2002<sup>41</sup>. It includes a common template for the application form and distinguishes between the different types of product information for Generic, NCE and 'over the counter products'. Like in most non-ICH countries national approval in ASEAN countries is based on clinical and efficacy evaluation by reference countries. Therefore certain documents are required as evidence for an approval in reference countries. These are an authorisation letter of the product owner, a Certificate of Pharmaceutical Product (CPP)<sup>42</sup>, GMP certificate, site master file from the manufacturing plant etc. An authorisation letter confirms that the local affiliate is entitled to register products in an ASEAN country on behalf of the product owner.<sup>43</sup>

So far the labelling and packaging requirements have been tried to harmonise similarity to blue box in Europe<sup>44</sup>. Anyhow there remain a lot of country specific needs. This makes it difficult to create an ASEAN pack which could be used in all ASEAN member countries, leaving a space on the pack where country specific requirements would fit in. The country specific requirements in labelling should now be published on the ASEAN Secretariat's webpage and on the drug regulatory authority's homepage for reference<sup>45</sup>. An example for different labelling requirements is that in Philippines the generic name has to appear above the brand name, whereas in Indonesia it should appear under the brand name. In Indonesia the minimal size of the generic name is 80% of the brand name, which hardly leaves any room left for a blue box statement. Another challenge is the different local

language and the different scripts in each individual ASEAN country (e.g. Thailand, Vietnam, Indonesia, and Malaysia).

If an ASEAN harmonised pack similar to the EU blue box could be created, this would encourage greater supply by multinational industries to the ASEAN region. Multinational companies often have a minimum order quantity that has to be reached by local affiliates. This means if a local affiliate orders less medicinal products than the minimum order quantity the multinational company would not be interested in distributing the medicinal product to the local affiliate. The reason is that the cost in supply (shipment, import licence, GDP) would be more expensive than the actual benefit from the marketing of the product in the respective country. If ASEAN packaging could be harmonised further this would enable multinational companies to supply stocks to the ASEAN as a region instead of country specific packs. This would facilitate trade and increase availability of pharmaceuticals on the ASEAN market. Current practice is that multinational companies produce country specific packs, which is very costly or produce international packs, that are locally redesigned by posting stickers with the national requirements on these packs.

## **4.2 Increasing Technical Requirements**

The ASEAN Common Technical requirements are a set of written material intended to guide applicants to prepare application dossiers in a way that is consistent with the expectations of all ASEAN Drug Regulatory Authorities<sup>46</sup>. The ACTR is guidance for preparation of the ACTD and has been divided into three areas concerning quality, efficacy and safety. Each guidance provides useful information on the content expected in the dossier and a check-list which cross-references from the ACTD sections to the relevant accepted ICH-guidelines or national Pharmacopoeia. These accepted references shall be taken into consideration when planning the preparing Part II-IV of the ACTD dossier. Some ICH guidelines which are beyond the scope of ASEAN were not adopted.

### **4.2.1 ASEAN Quality Guidelines**

The majority of pharmaceutical products reviewed by ASEAN Drug Regulatory Authorities are generics. For generic applications especially the quality (Part II ACTD) is of importance as non-clinical (Part III) and clinical (Part IV) do not need to be submitted. Therefore PPWG has reviewed available international guidelines and determined which ones were applicable for ASEAN. Four 'ASEAN ACTR-Quality Guidelines' were developed to set standards and provide guidance especially for local generic manufacturers. Hereby existing international guidelines are more or less transposed into simplified ASEAN guidelines with the exception of the ASEAN stability guideline.

The ACTD and ACTR hereby clearly indicates that for NCE and Biotechnological Products the ICH reference guidelines should be followed. For Generics and Variations the respective ASEAN Guidelines can apply.

The ASEAN Stability Guideline which sets adequate quality standards for hot and humid conditions (zone IV/IVb) of the region goes beyond ICH requirements. This guideline must be followed for all product classifications NCE, Biotech and Generics and Variations.

ASEAN adopted all WHO Guidelines for quality, the existing Pharmacopoeias of UK and USA (BP, USP) and 11 ICH-Quality Guidelines namely Q1A, Q1B, Q2A, Q2B, Q3A, Q3C; Q5A, Q5B, Q5C, Q5D; Q6A, Q6B.

In the following I will briefly explain the four ASEAN specific quality guidelines.

### **Analytical Validation**

'The ASEAN Guideline for Validation of Analytical Procedures', which was developed with Thailand as lead country and adopted in 2003<sup>47</sup>. This one ASEAN guideline mainly incorporated the two ICH Guidelines Q2A 'Validation of Analytical Methods Definition and Terms' and ICH Q2B 'Validation of Analytical Procedure Methodology' which are today known as Q2(R1). The objective of this guideline is to guide industry to demonstrate that an analytical procedure is suitable for its intended purpose.

### **Process Validation Guideline**

'The ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration' was developed with Singapore as lead country and adopted in 2003<sup>48</sup>. In 2003 there was no harmonised ICH guideline available that was dealing with process validation and the details of the pharmaceutical development as required in ACTD Part II (section P.2.4 and P.3.5) or ICH-CTD (section 3.2.P.2 and 3.2.P.3.5). The Guideline ICH -Q8 'Pharmaceutical Development' at that time was still in the process of being established and was adopted in Tripartite Region only in November 2005.

Therefore ASEAN countries saw the need to establish a Process Validation Guideline which mainly applies to the generic manufacturing of the drug product. The ASEAN Guideline is very similar to the CPVP-Note for Guidance on Process validation of 2001. According to the ASEAN Guideline on Process validation typically 3 consecutive production batches should be validated prior to marketing of the product. At time of submission such a validation report might not be available. Therefore the applicant should provide at submission at least a validation scheme and a commitment to provide the outstanding data before launching of the pharmaceutical product. The applicant is obliged to notify the health authority if any batch under the validation study is unsuccessful.

### **BA/BE Studies guideline**

The ASEAN Guideline for the conduct of Bioavailability and Bioequivalence studies was developed with Malaysia as lead country and adopted in 2004<sup>49</sup>. It incorporates the EU 'Note for Guidance on the investigation of BA and BE', CPMP/EWP/QWP/1401/98 of July 2001 with some adaptations for ASEAN use. These adaptations include references to other ASEAN quality guidelines and WHO

guidelines. The ASEAN guideline took the definition of essential similar products from the former EU NTA 1998. Thereafter a medicinal product is essential similar to an originator product if it contains the quantity and quality of active substance and the same pharmaceutical form. For immediate release products the concept of essential similar applies also to different oral forms e.g. tablets and capsules with the same drug substance. An important difference to the EU Guidance was, that ASEAN did not adapt the definition that essential similar medicinal products should have the same quantitative and qualitative composition in terms of excipients. This definition was also argued in EU by the generic industry and with implementation of the New Medicines legislation in 2005 discarded.

EU and ASEAN define that for an innovator product the full clinical dossier including clinical and non-clinical has to be submitted. A reference product used in BE studies must be an innovator product.

In order to broaden this restriction ASEAN added that 'if the innovator product is not available in the country, an alternative comparator product approved by drug regulatory authorities of the respective country can be used. (Section 2.5 last paragraph). Accordingly also section 3.5 of the ASEAN BA/BE Guideline was amended that the choice of the reference product should be agreed by the respective national regulatory authority. In the EU guidance the applicant only has to justify the use of the comparator but does not necessarily require the confirmation from health authority.

A common ASEAN Reference List for an ASEAN comparator for BA/BE studies is considered at a later stage. In the interim, current national list prevails. (see section 4.2.1).

### **Stability Study Guideline**

This guideline was developed with Indonesia as lead country and adopted in July 2004<sup>50</sup>. The current version is the one from February 2005, where minor changes have been incorporated<sup>51</sup>. The ASEAN countries developed their own guideline with more stressful stability testing than ICH and WHO recommended at that time. The reason for this decision was that the ASEAN regulators saw the need to address stability test conditions that reflect the natural meteorological conditions prevailing in the region. ASEAN humidity conditions are higher than in some regions that were previously defined as climatic zone IV.

The ASEAN guideline describes specifications for stability studies that have to be fulfilled in order to show that a product is stable over the entire period of its shelf-life. The guideline includes examples of a protocol of stability study, a report format, reduced design and extrapolation of data examples of packaging material parameters. These parameters include packaging material, thickness of packaging and permeability coefficient

The stability of finished product relates to factors such as chemical physical properties that can be influenced by the manufacturing process or packaging



material. On the other hand the stability is also determined by environmental factors such as temperature and humidity.

Latest conditions measured by ASEAN nations showed that the average mean kinetic temperature is 27.76 °C and the average relative humidity is up to 78.79 Relative Humidity (RH)%<sup>52</sup>. Therefore the ASEAN stability guideline requires real time storage conditions for solid dosage forms with permeable primary packaging at 30°C ±2°C/75%RH±5% RH (see table Table 3Table 1). At time of submission it is required to provide 12 months real time data and a commitment to provide follow-up stability data for the rest of the shelf-life. Further at least 6 months accelerated stability data at 40°C ±2°C/75%RH±5% RH have to be provided with the marketing authorisation application. The selection of batches used for stability studies are 3 primary batches for NCEs and can be 2 pilot scale batches for generics and variations in conventional dosage forms. For products with impermeable primary packaging the storage conditions are 30°C ±2°C and can be any relative humidity.

The provision of stability data according to the ASEAN guideline will be mandatory with the implementation of the ACTD and ACTRs in January 2009. Currently discussions are on-going regarding the transition period. Until end of 2008 various storage conditions are accepted for filing. However companies are expected to have on-going stability data at 30°C/75RH beyond January 2009. Any filing after January 2009 must have stability data based on 30/75 conditions. Where products deteriorate at 30°C/75RH it should be justified to label 'store below 25°C' or it should be ensured that moisture impermeable primary packaging is used.

During dialogue sessions between industry and regulators at the 12. PPWG in October 2006 the concern was raised that there are different classifications of variations amongst the countries, leading to different stability data requirements in the various countries. The proposal from the industry association is to have one standard to follow either EMEA or US FDA guidelines and not to newly create an ASEAN variation guideline. Therefore it was decided at the 12. PPWG meeting that an ASEAN expert group will look into the differences between the US and EU variation guidelines and make recommendations on the requirements subsequently<sup>53</sup>. Worthwhile to mention here is that the WHO currently also establishing variation guidelines and that the EU is in process to change the concept of its variation guidelines. It will be interesting to see which guideline ASEAN will follow or if they will create one for their region.

**Table 3: ASEAN Storage Conditions**

Storage Condition	Storage Condition
Products in containers permeable to water vapours	30°C ±2°C/75%RH±5% RH
Products in containers impermeable to water vapours	30°C ±2°C/RH not specified
Accelerated studies	40°C ±2°C/75%RH±5% RH
Stress studies for analytical process validation	40°C ±2°C/75%RH±5% RH

From section 4.6 ACTR Stability Guideline

### 4.2.2 Conflicting Global Stability Requirements

The first harmonisation initiatives on stability test requirements for new drug applications that was the finalisation of the ICH Q1A guideline in 1993, valid for the tripartite region US, EU and Japan require long term stability test at 25°C/60% RH. In the following years a series of ICH, WHO, regional and national guidelines were developed, defining storage conditions for long term or real time data stability testing (see Table 5). WHO's initially proposed for zone III and IV countries long term stability testing at 30°C/ 75 RH<sup>54</sup>.

In 2000 ICH proposed to the WHO to change its long term stability test to 30°C/60 RH an intermediate testing condition for climatic zone I and II in the ICH-Q1A guideline and discussions on global harmonisation began. The scope was to create stability test requirements that could be employed world wide. Meanwhile in 2001 ASEAN's PPWG adopted in the WHO long term testing conditions as one of its key elements for incorporation into the ASEAN stability guideline<sup>55</sup>

WHO conducted a survey amongst their member states to find consensus if 30°C/65% RH can be regarded as the long-term storage conditions for hot and humid regions. As no significant objections were raised in this survey WHO revised its stability guideline from 30°C/ 70 RH to 30°C/ 65 RH in 2001. ICH changed the intermediate storage conditions of 30°C/60 RH to 30°C/65 RH, which was now optional to use as long term storage condition for zone I&II in the revised Q1A R2 guideline as of 2003. At the same time ICH published a new ICH Q1 F guideline for climatic zones III and IV requiring long term stability studies at 30°C/65 RH. This was the first time ICH adopted a guideline which did not apply for their tripartite region, but for non-ICH countries.

Until today there is no legal basis for classification of climatic zones nor a legal definition of what are the criteria for grouping the world's countries into zones. In order to find a common consensus on the definitions of climatic zones WHO and ICH guidelines cross-refer to the literature from W. Grimm<sup>56</sup>, who distinguishes the zones by their characteristics prevalent annual climatic conditions and their storage conditions as described in Table 4.

**Table 4: Grimm's Climatic Zones Definition**

Climatic Zone	Definition	Long Term Storage Condition
I	Temperate Climate	21°C/ 45% RH
II	Subtropical and Mediterranean Climate	25°C/ 60% RH
III	Hot, dry climate	30°C/ 35% RH
IV	Hot, humid climate	30°C/ 70% RH

The change of the WHO stability requirements to less stressful storage condition led to scientific re-evaluation of the needs for zone IV countries. However, based on new calculations<sup>57</sup> and discussions, some countries in climatic zone IV expressed

their wish to include a larger safety margin for medicinal products to be marketed in their region than in the new ICH Q1F and the revised WHO Guideline. As a consequence, several countries and regions have changed their own stability testing guidelines, up to storage conditions of 30°C/75 % RH concluding that it was more appropriate for their countries.

In the case of ASEAN, Grimm included in his initial calculation only 4 ASEAN cities, even though ASEAN region is one of the most hottest and most humid region of the world. The new calculations specifically examining all 10 countries of the ASEAN region showed that the southern part of the ASEAN region faced a higher level of humidity than the mean value calculated for climatic zone IV.

Due to this escalating divergence in global stability testing requirements, the ICH has decided to withdraw ICH Q1F in June 2006 <sup>58</sup>.and to leave the definition of storage conditions in climatic zones III and IV to the respective regions and WHO.

The WHO started its consultation procedure, but no consensus could be reached among the parties what stability condition should be applied for climatic zone IV. The 40<sup>th</sup> WHO Expert Committee Meeting on Specifications for Pharmaceutical preparations in October 2005, finally decided that the WHO stability guideline will be changed to reflect the conditions for zone IV as follows:

- zone IV a (tropical dry) - stability testing at condition at 30°C/65 RH and
- zone IV b (tropical humid) - stability testing at conditions at 30°C/ 75 RH

It was agreed that each individual member state within the former zone IV would need to indicate which of the above conditions would be applied in its territory. Once WHO has received the feedback of all climatic zone IV countries the WHO stability guideline will be revised, with the intention to include a comprehensive listing of member states and their stability testing conditions.

The WHO Eastern Mediterranean Region (EMR) established a draft 'Stability Guideline of Active Substance and Pharmaceutical Products' <sup>59</sup> which includes already in ANNEX I A an assignment list of climatic zones and recommended long term storage conditions for EMR countries. It gives guidance for semi-permeable packaging and how to calculate water loss. This guideline also provides recommended labelling statements for different testing conditions. Currently the EMR stability guideline is used to develop a global guideline that will replace the current amended WHO Stability Guideline. This decision was a result of several discussions at international WHO meetings<sup>60</sup> throughout the year 2006.

The future will show, if after all these back and forth one global WHO stability guideline can be created that serves the needs of more than 190 non-ICH countries.

The stability requirements discussion shows how important it is to have cross-regional collaboration. Perhaps these discussions trigger ICH-Global Coordination Group (GCG) to shift its focus to having regular meetings with WHO and members

of regional harmonisation initiatives in non-ICH countries in order to share information on harmonisation (see section 6). Regional countries had expressed their concern that initially there was a lack of information on the change of ICH/WHO stability guidelines to regional and national countries. On the other hand perhaps initially some regional countries were not aware of the impact of the situation, and therefore did not provide feedback. It shows that within globalisation it gets even more important to openly communicate and to clarify responsibilities.

**Table 5: Developments of International Stability Guidelines**

Year	Stability Guideline	Climatic Zone	Long term Storage conditions	Intermediate Storage conditions
1993	ICH Q1A	I&II	25°C/60% RH	30°C/60%RH
1996	WHO GL	III&IV	30°C/70% RH	----
2001	WHO GL Rev 1	III&IV	30°C/65% RH	----
2003	ICH Q1AR2	I&II	25°C/60% RH	30°C/65% RH
2003	ICH Q1F	III&IV	30°C/65% RH	---
2004	ASEAN GL	IV	30°C/75% RH	---
2005	Brazil FR	IV	30°C/75% RH	---
2005	WHO GL Rev 2	IV a& IV b	30°C/65% RH& 30°C/75% RH	30°C/75% RH
2006	ICH Q1F withdrawal	III&IV	---	---
2006	EMR GL draft	I-IVa	country wise required long term –storage conditions are listed in Annex I; testing at higher humidity is also acceptable	

GL Guideline

Rev Revision

WHO GL WHO Technical report Series, No. 863, 1996 Annex 5 ' Guidelines for Stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms' (=original stability guideline)

WHO GL Rev 1 37<sup>th</sup> Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations 22-26. October 2001 adopted revision of the original WHO stability guideline to change the real time/long-term storage conditions for climatic zone to 30°C/65 RH

WHO GL Rev 2 at 40<sup>th</sup> WHO Expert Committee Meeting on Specifications for Pharmaceutical preparations 24-28 October 2005: Decision two split zone IV in IVa: hot and dry and IVb hot and humid

Brazil FR Federal Resolution –RE no 1 of 29.07.2005, published in the Brazilian Federal Register 01.08.2005 with attached Guide for stability studies (replacing previous resolution RE no 398, 12. 11.2004 requiring 30°C/65% long term data which replaced already resolution 560 of 02. 04.2002 requiring 30°C/70% RH)

EMR GL Regional Guide for the WHO Eastern Mediterranean Region 'Stability testing of Active Substance and Pharmaceutical Products' draft version 1 of 28.02.2007 and revised version 2, of 13.04.2007

### **4.2.3 New Reference Guidelines for Safety and Efficacy**

In ASEAN documentation for safety and efficacy are not required for Generic Products registrations, Minor Variations and some Major Variations. Usually only non-clinical and clinical overviews and summaries need to be submitted for NCE, Biotechnological products and Major variations if the originator products are already registered and approved for marketing authorisation in a reference country. The full study reports may only be needed upon special request from HA. Regarding the details where to locate these non-clinical reports in the dossier, the applicant should refer to the ACTD Part III Non-Clinical and for the clinical reports to ACTD Part IV.

#### **ACTR Safety:**

Following ICH Guidelines have been adopted by the PPWG, and thereby been defined as applicable ACTR Safety Guidelines for the ASEAN region. These 15 ICH Safety Guidelines are S1A, S1B; S1C & S1C(R), S2A, S2B, S3A, S3B, S4, S4A, S5A, S5B(M), S6, S7A, M3.

#### **ACTR Efficacy:**

After long debates, the PPWG <sup>61</sup> came to following decision regarding the ACTR Efficacy Guidelines, some ICH were 'adopted', others declared as a 'reference' only and two were 'not adopted'.

'Adopted' as ACTR-Efficacy Guidelines were following 11 ICH Guidelines, namely E1, E2A, E2C, E3, E4, E6, E7, E8, E9, E10, E11.

Accepted as 'Reference' Guideline are E2C(A), E2D, E2E, E12A. This means that each ASEAN member country may refer to these guidelines as reference, but there is no obligation to implement them into national guidelines.

There were two ICH Efficacy Guidelines E5(R1) and E2B(R3), not being adopted. This means that there is no obligation to implement these guidelines in the national member states.

The ICH- E5(R1) 'Ethnic Factors in the Acceptability of Foreign Clinical Data' describes intrinsic characteristics of the drug recipient and extrinsic characteristics associated with environment and culture that could affect the results of clinical studies carried out in regions. It describes the concept of the 'bridging study' that a new region may request to determine whether data from another region are applicable to its population. It is known that some pharmaceutical products are metabolised differently by Asians than in Caucasians. Therefore many Asian countries like China, Korea and Taiwan ask for local studies or bridging studies, as evidence that there is no ethnic sensitivity. The PPWG came to the decision not to adopt the E5 (R1), due to lack of experience and resources in ASEAN to implement bridging studies. It was proposed to encourage that ASEAN countries participate in 'Global Drug Development Programs' instead.

The ICH-E2B(R3) 'Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports' could not be adopted by the PPWG as the ASEAN member states do not have the capacity nor budget for maintaining

the 'Medical Dictionary for Regulatory Activities' Terminology or the 'Electronic Standards for the Transfer of Regulatory Information (ESTRI) technology. ESTRI is a standardised system for the electronic transmission of safety cases.

Most ASEAN countries currently join the WHO program for international drug monitoring shared with Uppsala monitoring centre (Sweden). ASEAN has already implemented a safety monitoring program called the Post Marketing Alert (PMA) on regional level (see section 4.3)

### 4.3 Mutual Recognition Agreements

A new initiative is the implementation of Mutual Recognition Agreements (MRA) as stated in the Healthcare Roadmap Measure 43<sup>62</sup>. The PPWG identified that Mutual recognition marketing authorisations is only possible once the ACTR and ACTD have been fully implemented in all member states, by end of 2008.

Member countries are encouraged to use the ASEAN-X principle (see section 2.1.1), meaning MRA implementation can proceed when 2 or more countries are ready. The identified areas for MRA are:

1. **MRA on the Post-Marketing Alert System (PMA)** has been set up. Its objective is to establish an efficient and effective system of alert on post-marketing issues affecting the safety and quality of pharmaceutical products. Further it should enhance the pharmacovigilance capabilities among member countries through mutual exchange of drug safety data. One common reporting form with country specific glossaries has been agreed. After a trial phase between Singapore and Malaysia since December 2005, the PMA shall be accepted as a formal system. This makes the PMA compulsory for all ASEAN member countries. This system should also support the recently established WHO International Medicinal Anti-Counterfeiting Taskforce Program (IMPACT)<sup>63</sup>.
2. **MRA on Good Manufacturing Practice (GMP) inspections:** A task force was created with the co-chairs Singapore and Malaysia. A GMP inspections report form has been set up and a code of GMP practice is established. These countries shall accept each others GMP inspection report. Member countries, which are not ready, are encouraged to consider the acceptance of the GMP inspections report of those, who have implemented the MRA. Primary criteria for MRA are that countries should get PIC/S<sup>v</sup> <sup>64</sup> membership first. Current PIC/S member countries are Singapore, Malaysia; and soon Thailand, who applied for membership. It is expected that the sectorial MRA on GMP inspections will be signed by all members by the end of 2007<sup>65</sup>.
3. **MRA on Bioavailability and Bioequivalence.** Indonesia and Malaysia are Co-chairs for this task force that was established as follow-up of the implementation of the BA/BE Guideline. In most of the ASEAN countries the innovator products

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<sup>v</sup> PIC/S Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

are normally used as comparator. However, there exist different variants of innovator products in the region. The task force therefore saw the need to establish one common list of comparators valid for the whole region. In the interim national drug lists prevail. Further it was agreed to encourage member countries to accept BE studies conducted by recognised BE centres in the region, in order to reduce unnecessary repetition of BE studies and transaction cost for industry. The PPWG supports accreditation of BE centres by national regulatory authorities or other accreditation bodies (e.g. WHO collaborating centres)<sup>66</sup>. In order to facilitate the procedure the task force has created a common study report form. This group is also in charge of creating a ASEAN list of comparators, that can commonly used for Generic BA/BE studies. WHO has already establishes a list of comparators<sup>67</sup> for essential medicines. Perhaps this list could be of help when defining the ASEAN comparator list.

#### 4.4 Recent Initiatives to Enhance Harmonisation

ASEAN member countries join the **WHO Vaccines chapter program**. Thailand has been appointed as the focal point to coordinate the work with WHO and the member countries. Currently the PPWG action focuses on capacity building. In this respect a survey has been conducted in which also the status of clinical trial regulations in the member countries will be examined.<sup>68</sup>

Another future plan was the creation of an ASEAN Pharmaceutical Advisory Group of experts (10 PPWG 5.4)

An ASEAN **Guidance on Reference Drug Information (AGREDI)**<sup>69</sup> is planned to be established in collaboration with the WHO. A guidance document would be necessary for ASEANs health authorities to improve the availability and constancy and accuracy of drug information approved and published by ASEAN health authorities. The idea is to create an ASEAN set of harmonised drug information among ASEAN countries. This action item was moved to one of the future plans of harmonisation activities of ASEAN. It will probably be taken up again when ACTD and ACTR are fully implemented. Once this goal is reached the PPWG will focus on MRA acceptance of product registration. This will also require harmonising the drug information.

**Harmonised Placement System** as outlined in the Healthcare roadmap<sup>70</sup> can only be possible, once ACTD and ACTR have been fully implemented in all member states, which is as of 2009 onwards only. Full recognition of approval process for pharmaceutical products can only be realized after the full implementation of ACTD by all member countries. While awaiting the full implementation by members, Mutual Recognition Arrangement could still be worked out in some specific areas such as laboratory testing and Good Manufacturing Practice.

#### 4.5 ACTD and ACTR Challenges

The newly development common ASEAN registration requirements with the emphasis on quality data required by the ACTD and ACTR are generally more

extensive in details than most of the previous national requirements. Usually submission of a CPP that included a GMP statement was sufficient. With the new common ASEAN requirements it is required to mention the manufacturer for the final batch release in the application form. This information was previously not part of a submission and is also not indicated on CPPs. New requirements are the need to provide drug substance information, analytical validation, process validation data for the manufacture of the drug product and the new stability requirements. In the past most of the national regulatory authorities even accepted stability data for zone I and II conditions. With the establishment of the new ASEAN Stability Guideline the region regards themselves belonging to zone IVb (see section 4.2.2). Further MRA for GMP requirements, an ASEAN Post Marketing Alert System have been introduced. Accreditation of BA/BE centres will be harmonised soon.

On long term the region will benefit from these harmonisation efforts. Though on short term, these new requirements are a high challenge to regulators and industries. Close collaboration between both parties is essential in order to maintain a common understanding.

With the introduction of the new requirements more details are included in a new marketing application file, which will have to be maintained throughout the life cycle of the pharmaceutical product. This will result in more consequential changes (variations). It will also require more capacity building at national regulatory authorities' level.

Until now in a lot of ASEAN member states variations are free of charge, e.g. Thailand. There is a certain risk that fees for the different categories of applications will increase in order to compensate the additional work load. ASEAN currently seeks funding and training from international organisations, dialog partner countries as well as from industries. Therefore hopefully the pharmaceutical products will maintain affordable for the public.

Current immediate implementation issues seen by ASEANs regional trade associations (APC&APRIA, see section 4) are the need for a harmonized ACTD content, a mechanism for consistent interpretation of the guidelines and establishment of regional variation guidelines. Future harmonisations and implementation plans should focus on further harmonisation of packaging and labelling requirements, (definition of OTC) and recognition of PAN-ASEAN product registrations among the region.

Industry organisations and health care professionals are concerned that a mandatory use of ACTD implementations might delay the access of innovative medicinal products to ASEAN countries.

It was therefore decided that in the interest of public health the use of ICH-CTD can be accepted for specific product categories (e.g. innovative products) even beyond 2008<sup>71</sup>.



One of the trade associations proposal to the regulators was to accept the mapping approach. This means that ICH-CTD is submitted accompanied with an ACTD index that is cross referring to the ICH-CTD sections and pages. The mapping approach is already commonly used during the transition period of the dossier formats.

At this point ASEAN harmonised only the dossier format and not the contents of the ACTD. ASEANs regulators intend to look into harmonisation of content at a much later stage, after implementation of the format.

At the moment registration procedures and the required documentation for a marketing application vary in between the national member countries. This leaves room for interpretation and for health authorities to request for additional information if they see a need to. The risk is high that single countries could overachieve the commonly meant ASEAN requirements. This would be again a barrier to trade and would not be within the interest of the AEC.

## **5 Singapore**

In ASEAN as in many non-ICH countries registration procedures rely on the approval and assessment of reference countries. This is the reason why many developing countries ask for a Certificate of Pharmaceutical Product issued by the health authority of the reference country.

It enables countries with limited drug regulatory capacity to obtain partial assurance from exporting countries that the pharmaceutical products, which they plan to import, are safe, effective and of good quality. In countries where a CPP is mandatory for approval, usually just a relatively small dossier is required restricted to administrative parts and summaries.

There are different common practice about the amount and the timing of the CPP. In some developing up to three CPP are required for submission. This can be a trade barrier or lead to delayed access of pharmaceuticals to public.

In the case of Singapore the Health Authorities, have the knowledge and capacity to evaluate clinical data and therefore there exist registration procedures where a product can be submitted without a CPP. It can be seen as a kind of risk based approach. The more CPPs are provided the faster is the evaluation by Singapore's health authority as they can rely on reference or bench mark approvals.

If ASEAN would harmonise their registration systems, Singapore could be serve as a good model.

### **5.1 Singapore's Evaluation Routes**

Within ASEAN Singapore can be regarded as one of the countries with the most developed and transparent pharmaceutical system in the region. Pharmaceutical product registration procedures were implemented for the first time in 1987<sup>72</sup>, and since then have been developed steadily. Singapore has transposed all ASEAN guidelines into national law. The Health Science Authority (HSA) is one of the big

drivers for the pharmaceutical harmonisation initiatives within the region. Singapore is lead country of the implementation working group (IWG) which is supporting the ACTD and ACTR implementation in ASEAN. In several cases Singapore was the first country participating in trial implementations of new initiative within ASEAN, e.g. ACTD, PMA, MRA of GMP inspections following the ASEAN-X principle (see section 2.1.1).

In the following I would like to explain how Singapore has incorporated the ASEAN guidelines into national law. Singapore might even serve as an example how outstanding pharmaceutical harmonisation areas could be implemented in ASEAN in future. The PPWG goals are to achieve mutual recognition of the approval process and marketing authorisations in the region. This can only be achieved if the registration procedures for obtaining marketing authorisations are harmonised. Singapore has three clear defined registration routes, which reach from simple routes that rely on bench mark countries approvals, to more complex registration routes with independent evaluation of the full set of pre-clinical and clinical data.

There are essentially 3 evaluation routes for medicinal products in Singapore. The routes that will be used depend on whether the submission can meet criteria and data requirements set out for each route<sup>73</sup>. In the following I will describe the routes which also appear in Figure 4.

### **Pre-submission Meeting**

The applicant may request in for a pre-submission meeting at least 2 months before the planned submission. The request for the meeting should be in written and the relevant points for discussion should be listed. The applicant usually request for a meeting in order to seek guidance from the relevant HAS divisions which registration route to take. In the case the applicant intends to use the full evaluation route the meeting is with the Innovative Therapeutic group (ITG) in all other cases with the Centre for Drug Evaluation. The regulators will provide advice, which is not binding or a guarantee for later approval.

### **Submission**

Once the registration route is determined the applicant will make file an on-line application form via PRISM. For details to the on-line submission please refer to section 4.1.1. Product licences are specific to the name, strength active ingredients, the product name and the dosage form. Therefore product that differs in any of these will require a different product licence applications. The dossier has to be compiled according to the ACTD structure and ACTR Guidance documents. The fees have to be paid up-front, the fee for a full evaluation route are much higher than for the other routes. The HAS will validate the submitted data within 14 days and provide the applicant a confirmation on the reference number and completed validation. Checklists for the relevant registration indicate which documents are needed. They should help the applicant when compiling the dossier.

### **Full evaluation**

The full dossier evaluation route applies to innovative pharmaceutical products that

have not been approved by any competent drug regulatory authority, at the time of submission to HAS.

The full evaluation requires the full set of ACTD data, including pre-clinical and clinical study reports. There is a checklist which specifies which documents have to be submitted for using this registration route. Responsible HAS division is the ITG. The HAS evaluation time is 270 working days (without clock-stop). It provides first in world evaluation and approval of new and innovative products. It enables faster access to new pharmaceutical products with no need to wait for approval by another agency. This registration was developed by the HAS to be regional life science hub.

### **The Abridged Evaluation route**

This registration route applies to imported pharmaceutical products that have been evaluated and approved by at least one competent drug regulatory agency. As proofs for an approval by another regulatory agency an approval letter certifying the registration status is sufficient. As of January 2007 a CPP as proof is no longer required, as the ordering of such documents was lengthy and delayed the access to market. The HAS evaluation time is 180 working days (without clock-stop). This was the original registration route in Singapore and is up-to now also the most commonly used one.

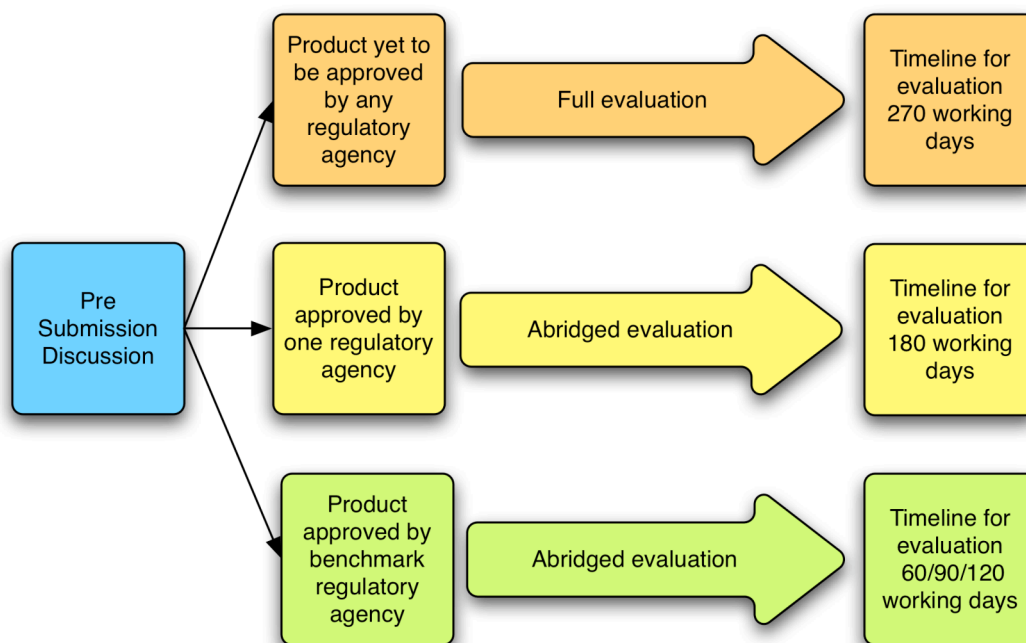
### **The Verification route**

This registration route applies to medicinal products that have been approved by at least two bench mark agencies. These bench mark or reference countries are Australia, Canada, EU (EMA-Centralised Procedure Approval), UK and US. In the case that Australian is chosen as reference country the HAS accepts a verification route submissions based on just *one* approval. It is worth while to mention that a verification dossier should be submitted within 3 years from the date of approval of the chosen primary reference country. The product submitted in Singapore must be the same as that approved for registration by bench mark agencies in terms of composition, manufacturing site and label. This route has quite specific criteria that have to be fulfilled. On the other hand, the evaluation by the agencies is the fastest, as they rely on the approval of up to two bench mark. Approval is granted either after 60, 90, or 120 working days depending on the complexity of clinical or quality (CMC<sup>vi</sup>) documentation submitted.

The advantages of the this three route procedure for new drug applications is that different risk based evaluation routes take account of the products international registration status and provided flexibility for companies in planning their submission.

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<sup>vi</sup> CMC= Chemistry Manufacturing Controls



CDA: Centre for Drug Evaluations is under the (HAS) and responsible for formulating drug regulatory policies, for evaluation of applications and regulatory decision on product licence approvals.

Pre-Submission: Discussion for Full-evaluation are with the Innovative Therapeutic group (ITG) for all others the CDA is responsible

**Figure 4: Evaluation routes for new drug applications in Singapore**

## 5.2 Developments in Singapore

The Singapore health authority focus is to becoming a centre of excellence in ASEAN for biologics and biotechnological products. In this respect they continue to strengthen the regulatory framework to create an environment to support the development of biomedical science in Singapore. Further internal capabilities for the evaluation of these products is envisaged, by closer collaboration with bench mark agencies. HAS Singapore has already signed 'memorandum of interest' with its Australian counter part laying out its intentions to jointly collaborate and cooperate in their regulatory frame work for pharmaceuticals. This includes the exchange of information, development of professional competencies and since Jun 2003 mutually recognition of the others new drug approval process. A 'Memorandum of Interest' for exchange of medicinal products including Traditional Chinese Medicines has been signed with China <sup>74</sup>. Currently Singapore has 15 WHO collaborating centres. These centres work with WHO to carry out field studies and serve as reference and training centres for the region. They could also become ASEAN BA/BE centres. If in ASEAN Mutual recognition of evaluation process is achieved, Singapore become a centre of excellence for Biotechnological medicinal products and a reference country for those regulatory agencies that do not have the capacity to evaluate and test Biotech products or vaccines.

## 6 Regional and Global Harmonisation Initiatives

Harmonization of various elements of drug regulatory activities has taken place in the last decade and has involved regional and global organisations. The driving force behind the harmonization effort is the need to improve availability of pharmaceutical products and respond to the forces of international trade with adequate standardized technical regulations on safety, quality and efficacy. By reducing unnecessary duplication of regulatory requirements, it is proposed that therapeutic advances will be made more rapidly and at a lower developmental cost. A prerequisite of any harmonized approach to international drug regulation is the existence of a functional drug registration process, pharmaceutical inspection services and certified compliance with good manufacturing practice.

The challenge of **ASEAN** was to define regional accepted standards for pharmaceutical harmonisation which facilitates intra and inter-ASEAN trade of pharmaceuticals. It is a great challenge to develop standards for the region that are appreciated by trade partners and that encourage foreign direct investment. Especially as some of the CVLM countries are still regarded as developing countries.

The ASEAN countries had to define their regional standards by taking into account available international guidelines. The aim of the existing international standards hereby varies.

**ICH**<sup>75</sup> was established in 1990 with the aim is to created harmonised guidelines for the drug development of innovator products for research based industries in the tripartite region (US, EU, Japan). These are all high income countries. Therefore the ICH omissioned the generic industry as they were not within the scope of ICH. The ICH guidelines do not address specific requirements for category of products and therefore they are valid for all pharmaceutical products (NCE, Biotech, Generics essential drugs for neglected disease etc.).

Anyhow ICH advocacy seminars have been held in different regions of the world and participating countries look at ICH guidelines as the international norm or gold standard even if they are not affordable or reachable by some of the low developing countries. Further to mention in the context is that ICH Guidelines cannot be automatically applied to all countries in the world is that ICH countries.(e.g. stability discussion section 4.2.1)

With a mandate of 191 member states (=85% of the world population) **WHO**<sup>76</sup> aims are to set global standards for non-ICH countries for promotion and protection of public health. These standards should assure that pharmaceutical products show the appropriate safety efficacy and quality. The WHO tries to avoid unjustified high standards that would make pharmaceutical products unaffordable for the local public health. In many countries, essential drugs required for the prevention and treatment of locally endemic conditions that are not supplied by multinational industries but by local or generic manufacturers. If they are unable to meet what may be

unsubstantiated quality standards, the adverse impact of the withdrawals of these drugs on the health of the population would be far more drastic than that of any hypothetical risk by failing to achieve ICH standards. A concern commonly voiced in this complex debate is that setting of different standards for the process of drug regulatory harmonisation by ICH and WHO will effectively produce a dual standard- a higher one for the more affluent countries and a lower one for poorer countries.

Following the completion of the majority of harmonised ICH activities in 1997 it was agreed that further phase of harmonisation activities should be continued. The terms of ICH were amended to include provisions of up-dating existing guidelines and global harmonisation. In this context the ICH-Global Coordination Group (GCG) was created in 2003, taking into account WHO and recommendations of Regional Harmonisation Initiatives (non-ICH countries) for existing ICH guidelines. The aim of GCC is to disseminate finalised ICH guidelines with an anticipated goal of acceptance by non-ICH countries.

This can be seen as a further step of harmonisation beyond the regions in direction globalisation harmonisation to avoid redundancy or contradictory guidelines.<sup>vii</sup>

ICH is opening its restricted memberships and focus from the ICH region to regional initiatives to share views within globalisation.

Any international mechanism or organization which develops guidance relevant for countries outside their own regions should ensure that those countries are made aware of these developments and are directly approached to take part in the consultation process. For the ICH, the Global Cooperation Group should be stressed as a way to work with regional harmonization initiatives.<sup>77</sup>

Maybe the debate around the stability studies for zone III and IV were the trigger for ICH to seek collaboration with non-ICH regions and WHO.

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<sup>vii</sup> ICH-GCG was established in 1999 as subcommittee of the CH Steering committee: The initial focus was the sharing of information on ICH guidelines for interested non-ICH parties. In 2001 the ICH shifted its focus to further develop activities in collaboration with other regional harmonisation initiatives (non-ICH countries). As part of the ICH 6 Meeting in Osaka 2003 GCG met identified partners APEC, PPWG, GCC, PANDRAH and SADC and TOR and WHO as observer. The scope is to meet 2-3 times per year with these permanent representatives. First GCG meeting in November 2004.

## **7 Summary**

ASEAN is a model of a regional integration initiative undergoing dynamic development and changes. It has become one of the most successful regional groupings of developing nations, to promote cooperation, and trade in the face of wider international competition and economic upheavals. Since its inception four decades ago, ASEAN is now at a crucial stage in transforming itself from a regional Association into a dynamic, integrated economic Community.

ASEAN's drug regulatory authorities and industry have worked very close regionally but also increasingly with global organisations to develop a number of harmonised documents. These are the common submission dossier known as the ASEAN Common Technical Dossier and the ASEAN Common Technical Requirements, which are steadily evolving.

Largely they have been realised already, the next step will be to focus on mutual recognition of pharmaceutical registrations and implementing a harmonised placement system. There is still much work to be carried out in the implementation.

The future will show if this can be achieved by the versioned end goal of economic community in 2015.

Already now ASEAN can be regarded as an example of having developed a successful pharmaceutical harmonisation scheme.

ASEAN is increasingly playing a major role in pharmaceutical industry.

## 8 Bibliography

- <sup>1</sup> South-East Asian Treaty Organisation (1954) collective defense treaty informally known as the Manila Pakt; between Australia, France, New Zealand, Pakistan, Philippines, Thailand, Great Britain and the United States , United Nations Treaty Series 209, 28
- <sup>2</sup> a) Shaune, N s. below. b) Murphy, A (2002). “From conflict to cooperation in Southeast Asia, 1961-1967: The disputes arising out of the creation of Malaysia and the establishment of the Association of Southeast Asian Nations “, Colombia Universities, AAT 3048198, c) Leifert, M (1989)., ASEAN and the Security of South-East Asia, London Routledge, d) Dorsch, J.; Wagner C. (1999) “ASEAN und SAARC: Entwicklung und Perspektiven regionaler Zusammenarbeit in Asien”, Abera Academic Press,
- <sup>3</sup> ASEAN’s Foreign Ministers (1967) The ASEAN Declaration (Bangkok Declaration); ASEAN Sec <http://www.aseansec.org/1212.htm>
- <sup>4</sup> Collins A.(2003) “Security and Southeast Asia: Domestic, Regional, and Global Issues”, Singapore: Institute of Southeast Asian Studies, 128
- <sup>5</sup> ASEAN Leaders (1997) “ASEAN Vision 2020”; signed at 2nd Informal ASEAN Summit, published at the ASEAN Sec under <http://www.aseansec.org/5228.htm>
- <sup>6</sup> ASEAN Leaders (2005) 11. Summit 2005, ASEAN Sec
- <sup>7</sup> ASEAN Leaders (2003) “Declaration of the ASEAN Concorde II”, 9th. ASEAN Summit, published by the AEAN Sec <http://www.aseansec.org/15159.htm>
- <sup>8</sup> ASEAN Leaders (2003) “Declaration of ASEAN Concorde II” <http://www.aseansec.org/15159.htm>
- <sup>9</sup> ASEAN Sec (2007) “Organizational Chart and Description” published by the ASEAN Secretariat <http://www.aseansec.org/13103.htm>
- <sup>10</sup> ASEAN Sec (2007) “Chairs of the Summits, ASC and AMM” published y the ASEAN Sec <http://www.aseansec.org/chairmanship.htm>;
- <sup>11</sup> All ASEAN Summits Documents such as Agreements and Tretaties and Reports published by the ASEAN Sec : <http://www.aseansec.org/4933.htm>
- <sup>12</sup> a) Narine S. (1997) “ASEAN and the ARF: The limits of the ASEAN way”. Asian Survey 37(10):961-978;b) Benny Teh Cheng Guan (2004) “ASEAN’s regional Integration Challenge: The ASEAN Process”; The Copenhagen Journal of Asian Studies 20; 70-93, d) Amitav, A( 2001) Constructing a Security Community in Southeast Asia: ASEAN and the Problem of Regional Order, New York Routledge 47-68
- <sup>13</sup> WTO (1994) “Understanding on Rules and Procedures Governing the Settlement of Dispute” published [http://www.wto.org/english/thewto\\_e/whatis\\_e/tif\\_e/displ\\_e.htm](http://www.wto.org/english/thewto_e/whatis_e/tif_e/displ_e.htm)
- <sup>14</sup> ASEAN Leades (2004) “ASEAN Protocol on Enhanced Dispute Settlement Mechanism,” signed at 10. Summit, published by ASEAN Sec <http://www.aseansec.org/16754.htm>
- <sup>15</sup> ASEAN Leaders (2001) “Rules and Proceedure of the High Council of the Treaty of Amity and Cooperation in Southest Asia” , ASEAN Sec <http://www.aseansec.org/3639.htm>
- <sup>16</sup> ASEAN Leaders (2000) “The ASEAN Troika”, signed at the 33<sup>rd</sup> AMM; ASEAN Sec <http://www.aseansec.org/3637.htm>



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- <sup>17</sup> Amitav Acharya, (2006), „How can ASEAN tackle crises“, Straits Times, 19. July 2006  
<http://www.futureworldaffairs.blogspot.com/2006/07/how-asean-can-tackle-crises.html>
- <sup>18</sup> The ASEAN Secretariat Roles and Responsibilities, published by the ASEAN Sec  
<http://www.aseansec.org/68.htm>
- <sup>19</sup> ASEAN Leaders (2007) “Cebu Declaration on the Blueprint of the ASEAN Charter” signed at the 12. Summit, published by the ASEAN Sec <http://www.aseansec.org/19257.htm> and the Kuala Lumpur Declaration signed by ASEAN leaders at the 11. ASEAN Summit 2005
- <sup>20</sup> Rodolfo C. Serino,(2005) “Framing the ASEAN charter ISEAS perspective” Institute of Southeast Asian Studies, printed by Utopia press Pte Ltd, ISBN 9812303693
- <sup>21</sup> Eminent Persons Group (2006) “Report of the Eminent Persons Group” presented at the 12. Summit; Jan 2007; published by the ASEAN sec <http://www.aseansec.org/19247.pdf>
- <sup>22</sup> Thanadisillapakul L.(2005) Director of the Institute of International Business and Economic Law Studies, Thailand „Open Regionalism and Deeper Integration: The Implementation of ASEAN Investment Area (AIA) and ASEAN Free Trade Area (AFTA)" published by the University of Dundee UK <http://www.dundee.ac.uk/cepmlp/journal/html/vol6/article6-16.html>
- <sup>23</sup> ASEAN Leaders ( 2003) “Declaration of the ASEAN Concorde II” signed at the 9. ASEAN, published by the ASEAN sec <http://www.aseansec.org/15159.htm>
- <sup>24</sup> AFTA details published by the ASEAN Sec: <http://www.aseansec.org/12021.htm>
- <sup>25</sup> High Level Task Force (2003) “Recommendations of the High Level Task force on ASEAN Economic Integration” Report presented at the 9. Summit, published by the ASEAN sec <http://www.aseansec.org/hltf.htm>
- <sup>26</sup> Current ACCSQ work program published by the ASEAN Sec  
<http://www.aseansec.org/WorkProgramme.doc>
- <sup>27</sup> PPWG Terms of Reference Article 1 ff
- <sup>28</sup> Zahn (2001) ” Developments from ASEAN’s ACCSQ Pharmaceutical Product Working Group”, Regulatory Affairs Journal, 12-2001, 985-988
- <sup>29</sup> 12. PPWG Meeting (2006), report item 9, and Annex 12
- <sup>30</sup> PPWGs Organizational Structure and Workflow were discussed at the 12. PPWG Meeting (Oct 2006), Annex 21 and at the GCG(Oct 2006); Yuppadee presentation published on the GCG homepage <http://www.ich.org/cache/comp/276-254-1.html/12 PPWG>
- <sup>31</sup> Formal ICH Procedure (Version dated 21.10.2002) published on the ICH homepage  
<http://www.ich.org/cache/comp/276-254-1.html>
- <sup>32</sup> 12. PPWG Meeting (2006) point 19 of the report and Annex 10 contains information a mechanism for the decision making process and up-dating the Q&A is in preparation
- <sup>33</sup> 9. PPWG Meeting (2005)
- <sup>34</sup> Good Regulatory Practice Draft Guideline, 12. PPWG meeting (2006) report item 3, annex 6
- <sup>35</sup> ACTD&ACTR formats and guidelines published at the ASEAN Sec :  
<http://www.aseansec.org/18215.htm>

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- <sup>36</sup> EU Commission (2007) Notice to Applicants Vol. 2, EUDRALEX published by the EU Commission, Enterprise Directorate- General, <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm>
- <sup>37</sup> Zahn M (2001) " Developments from ASEAN's ACCSQ Pharmaceutical Product Working Group", Regulatory Affairs Journal, 12-2001, 985-988
- <sup>38</sup> Lim. J (2003), from HSA Singapore presented at the Symposium of APEC Network of Pharm. Reg sciences 17. Nov 2003
- <sup>39</sup> ICH M4R3 Granularity <http://www.ich.org/cache/compo/276-254-1.html>
- <sup>40</sup> Health Authorities of Singapore and Malaysia publish details on on-line submission on their homepage a) Singapore's On-line System Prism: <http://www.hsa.gov.sg/html/business/prism.html> and b) Malaysia's On-line system "Quest 2" under <http://www.bpfk.gov.my>
- <sup>41</sup> ACTD Part I, adopted at the 6. PPWG Meeting (2002) annex 10.
- <sup>42</sup> CPP requirements according to the WHO certification scheme: [http://www.who.int/medicines/areas/quality\\_safety/regulation\\_legislation/certification/guidelines/en/index6.html](http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/guidelines/en/index6.html)
- <sup>43</sup> product owner: see definition in the ASEAN Glossary
- <sup>44</sup> EU blue box requirements in EU: NTA Vol 2, chapter 7 for MRP and 2C for CP products
- <sup>45</sup> The country specific requirements in labeling should now be published on the ASEAN Secretariat's webpage as mentioned in point 35 of the 12. PPWG meeting (2006) report, a compilation of country specific labelling requirements in Annex 16 of 12. PPWG meeting
- <sup>46</sup> Decision to have ACTR was adopted at the 5. ACCSQ PPWG Meeting (2002), def. in the ASEAN Glossary
- <sup>47</sup> ASEAN Analytical Validation Guideline adopted at the 7. PPWG Meeting (2003), annex 9
- <sup>48</sup> ASEAN Process Validation Guideline adopted at 7. PPWG Meeting (2003), annex 10(3)
- <sup>49</sup> ASEAN BA/BE Guideline adopted at the 8. PPWG Meeting (2004), annex 13
- <sup>50</sup> ASEAN Stability guideline, see section 7.1 of the 8. PPWG Meeting (2004) report and annex 11
- <sup>51</sup> see section 5.3 of the 9. PPWG report (2005) and annex 11
- <sup>52</sup> Real Time Stability Conditions in ASEAN: For ASEAN there are various calculations that all come to the result that the relative humidity (rel. RH) in ASEAN is higher than initially though. Several calculations concluded that the rel. RH can be even up to 80%. Further details a) presentation by Susanne Walters WHO at Jakarta meeting 13-14 Jan 2004; b) measured data from the US National Oceanic&Atmospheric Administration 1996, c); Article: Zahn, Manuel, Feb 2004, „ASEAN: New Proposed storage Conditions for Stability Testing, Regulatory affairs Journal, page 100-102; d) Turner, Nick, Zahn, Manuel „The new Stability testing
- <sup>53</sup> SAPI (2006) Notes on the 12. PPWG Meeting
- <sup>54</sup> WHO(2006) Initial Stability Guideline WHO-Technical Report No.865, annex 5, 1996
- <sup>55</sup> Singh, S.(2006) „Recent Developments on Long term stability test conditions“, The Pharma Review, 12/2006, web:

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[http://www.aapspharmaceutica.com/inside/Focus\\_Groups/Stability/imagespdfs/PharmaReviewDec2006.pdf](http://www.aapspharmaceutica.com/inside/Focus_Groups/Stability/imagespdfs/PharmaReviewDec2006.pdf)

<sup>56</sup> *Drugs Made in Germany*“, 28:196-202, 1985 and 29:39-47 (1986)

„Drug Stability Testing-Classification of countries according to climatic zone“ R. Diets, K. Feilner, F. Gerst, W. Grimm, *Drugs made in Germany* 36, page 99 ff (1993)

<sup>57</sup> See real time stability ref. above

<sup>58</sup> Kopp, S. (2006) „Stability Testing of Pharmaceutial products in a Global Environment“, *Regulatory Affairs Journal*, page 291-294, May 2006

<sup>59</sup> Regional Guide for the WHO Eastern Mediterranean Region „Stability testing of Active Substance and Pharmaceutical Products“ draft version 2, of 13.04.2007 availabl at [http://www.who.int/medicines/services/expertcommittees/pharmprep/QAS06\\_179\\_StabilityGuidelineSept06.pdf](http://www.who.int/medicines/services/expertcommittees/pharmprep/QAS06_179_StabilityGuidelineSept06.pdf)

<sup>60</sup> Justina A.Molzon/USFDA (2006) presented at the Annual meeting of the American Association of Pharmaceutical Science October 2006 up-dates on stability from ICDRA in April 2006 and the 41. WHO Expert Commitee Meeting on Specifications for Pharmaceutical preparations 16-20 October 2006 ;presentations available at: <http://www.aapspharmaceutica.com/meetings/files/101/MolzonJustinaHarmonizationEffortsAPQSymposium.pdf>

<sup>61</sup>9. PPWG Meeting (Aug. 2005) report item 5, and annex 6, the meeting made a decision on acceptance of ICH-Efficacy Guidelines

<sup>62</sup> ASEAN Leaders (2004) “Vientiane Action Program 2004-2010” and the “ASEAN Framework Agreement for the Integration of Priority Sectors” signed at the 10.Summit 2004. One Appendix of this agreement is the Roadmap for Integration of the Healthcare Sector, which includes measures (= action items), responsible subcommittee or working group and due dates for implementation. Measure no. 43 is MRA, no 44 is ACTD Implementation, no. 45 Harmonizing the Labeling of Pharmaceutical Products, no. 46 Harmonized Placement System, no. 47. Twinning System for Mutual Regulatory Capacity and Resources Development 49 Post-Marketing Alert System.

<sup>63</sup> MRA on the Post-Marketing Alert System (PMA), details see 11. PPWG Meeting (2006) report item 5.2 and annex 13., 12. PPWG Meeting (2006) report item 7.2

<sup>64</sup> PIC/S details see <http://www.picscheme.org/index.php>

<sup>65</sup> 12.. PPWG Meeting (2006) item 6.2, Annex 17&18; 11. PPWG meeting (2006) report item 5, Annex 12; 10.PPWG Meeting (2005) report, item 6.2, 9. PPWG Meeting report, item 6.1

<sup>66</sup> MRA on BA/BE: 12. PPWG item 5, Annex 8&11. PPWG item 4Annex 7&8, 10. PPWG item 5

<sup>67</sup> WHO (2006) Technical report series 937, item 12 and annex 7&8 [http://whqlibdoc.who.int/trs/WHO\\_TRS\\_937\\_eng.pdf](http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf)

<sup>68</sup> Vaccine Chapter: Developing Countries' Vaccines Regulators (DCVR) Network: ASEAN Cooperation with WHO: 12. PPWG Meeting (Nov 2006) report item 6.2, Annex 19; 11. PPWG Meeting (Mar 2006) item 6.2/Annex 15; 10. PPWG Meeting Report 7.2, Annex 12(Aug 2005).

<sup>69</sup> ASEAN Reference Drug Information, a colloaboration with WHO, 10. PPWG Meeting (2005) report item 7 and annex 11

<sup>70</sup> Harmonized Placement System: is measure no. 54 of the Healthcare Roadmap

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<sup>71</sup> Use of ICH-CTD beyond 20008 for certain product categories is accepted for certain product categories: see 12. PPWG Meeting Item 55.5., no.29 and annex 14.

<sup>72</sup> HAS (2007) CDA history [http://www.hsa.gov.sg/html/cda/about\\_cda.html](http://www.hsa.gov.sg/html/cda/about_cda.html)

<sup>73</sup> Details on the Singapore Registration Routes are in the “Guidance on Medicinal product Registrations in Singapore”, effective February 2007, which are published on the HAS homepage web <http://www.hsa.gov.sg/docs/DrugRegistrationGuideline.pdf>

<sup>74</sup> Memorandum of Understanding between SG and China:  
[http://www.hsa.gov.sg/docs/PRelease\\_HSA\\_SFDAMOU\\_Sep03.pdf](http://www.hsa.gov.sg/docs/PRelease_HSA_SFDAMOU_Sep03.pdf)

<sup>75</sup> ICH History <http://www.ich.org/cache/compo/276-254-1.html>

<sup>76</sup> WHO History: <http://www.who.int/en/>

<sup>77</sup> ICDRA (2006)  
[http://www.who.int/medicines/areas/quality\\_safety/regulation\\_legislation/icdra/en/index.html](http://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra/en/index.html)

All Pharmaceutical product Working Groups Meeting reports and presentations can be retrieved upon request from the ASEAN sekretariat in Jakarta, Indonesia

## Annex I: Map of South East Asia



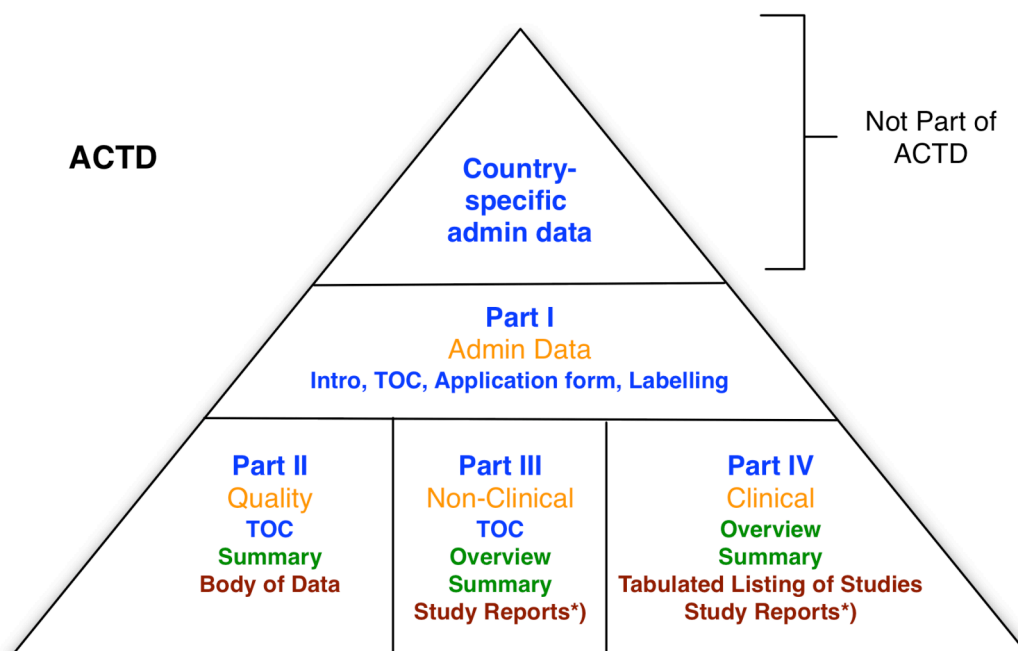
802914AI (R02106) 6-02

## Annex II: ASEAN Chronology

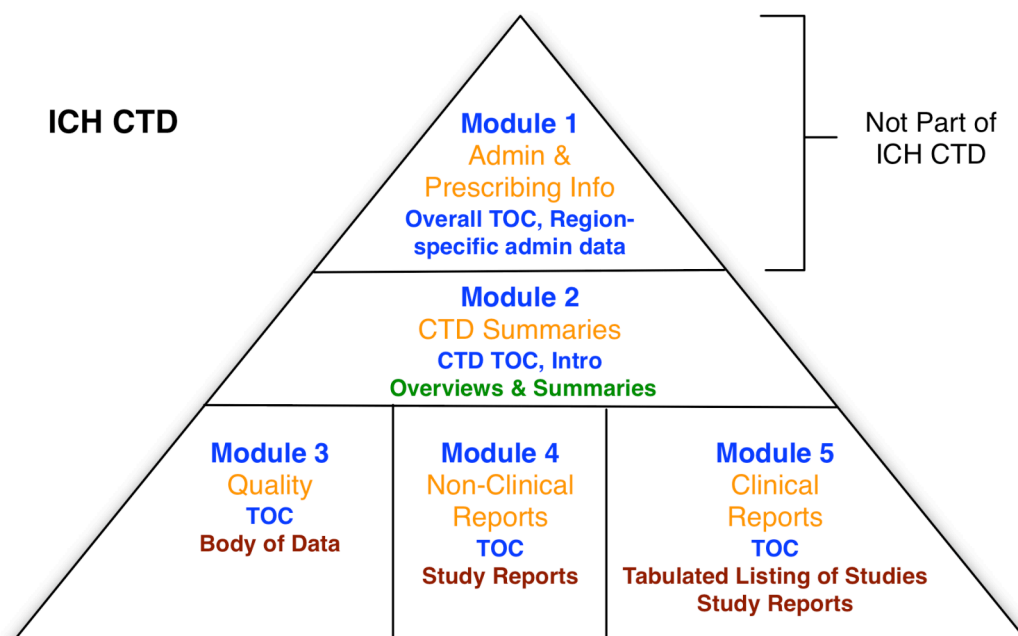
**Table 6: ASEAN - sequence of events since its establishment**

1967	Bangkok Declaration/ Formation of ASEAN
1976	23-24. February. 1. ASEAN Summit in Bali/ID:
1977	23-24. February. 2. ASEAN Summit in Kuala Lumpur/MY
1984	7. January. Admission of Brunei Darussalam
1987	3. ASEAN Summit in Metro Manila/PH
1992	4. ASEAN Summit in Singapore
	ACCSQ formed by Asean Economic Ministers
1995	Admission of Vietnam
	5. ASEAN Summit in Bangkok/TH
1996	1. Informal ASEAN Summit in Jakarta/ID
1997	Admission of Laos and Myanmar
	2. Informal ASEAN Summit in Kuala Lumpur/MY
	ACCSQ proposed to have a pharmaceutical harmonisation
1998	ASEAN Summit in Hanoi/Vietnam
1999	Admission Kingdom of Cambodia admitted as 10. ASEAN member country
	1. PPWG Meeting in Kuala Lumpur/Malaysia/Establishment of PPWG
	3. Informal ASEAN Summit in Metro Manila/PH
2000	2. PPWG Meeting in Bangkok/TH
	4. Informal ASEAN Summit in Singapore
2001	3. ACCSQ-PPWG Meeting in Ho Chi Min/VN
	4. ACCSQ-PPWG meeting in Bali/ID
	7. ASEAN Summit in Bandar Seri Begwan/Brunei
2002	5. ACCSQ-PPWG Meeting in Yangon/Myanmar
	6. ACCSQ-PPWG Meeting in Siem Rep/Cambodia
	8. ASEAN Summit Phnom Penh, Cambodia
2003	7. ACCSQ-PPWG Meeting in Penang/MY
	9. ASEAN Summit in Bali/ID
2004	21-23. August, 8. ACCSQ-PPWG Meeting Bangkok Thailand
	10 ASEAN Summit in Vietienne/Laos Framework Agreement on 11 priority sectors (inc. Healthcare) Healthcare Roadmap attached to ASEANs Sectorial Integration Protocols
2005	9. ACCSQ-PPWG Meeting in Manila/PH
	10. ACCSQ-PPWG Meeting in Singapore
	11. ASEAN Summit in Kuala Lumpur/MY
2006	11. ACCSQ-PPWG Meeting in Hanoi/Vietnam
	12. ACCSQ-PPWG Meeting
2007	12. ASEAN Summit in Singapore
	13. ACCSQ PPWG Malaysia

## Annex III: Dossier Triangle



\*) upon request



## Annex IV: Table where to find ASEANs dossier & guidelines

ACTD	ACTR
ASEAN Glossary	
Organisation	<ul style="list-style-type: none"> <li>N.A.</li> </ul>
<ul style="list-style-type: none"> <li>Part I: Administrative data and product information</li> </ul>	<ul style="list-style-type: none"> <li>N.A.</li> </ul>
<ul style="list-style-type: none"> <li>Part II: Quality data (ID)</li> <li>p.3-9 ACTD Check-list on product classifications</li> </ul>	<ul style="list-style-type: none"> <li>ACTR-Quality (table which is cross-referring the ACTD section to the relevant applicable ASEAN or ICH-GL)</li> <li>Adopted ICH-Guidelines are Q1A, Q1B, Q2A, Q2B, Q3A, Q3C; Q5A, Q5B, Q5C, Q5D; Q6A, Q6B. WHO Quality Guidelines and for Generics and Variations US, UK and National Member States Pharmacopoeia are accepted</li> <li>GL Analytical Validation and Q&amp;A Document to be adopted at 13.PPWG</li> <li>GL Process Validation (SG) Q&amp;A Document to be adopted at 13.PPWG</li> <li>GL Stability (ID) and Q&amp;A Documents adopted 12. PPWG</li> <li>GL BA/BE (MY)</li> </ul>
<ul style="list-style-type: none"> <li>Part III: Non-Clinical Document (PH)</li> <li>p. 67 ACTD Check-list for product classification (ACTD on Non-Clinical data for product registration)</li> </ul>	<ul style="list-style-type: none"> <li>ACTR Safety/Non-Clinical (table which is cross-referring from the ACTD sections to the relevant applicable ICH-GL)</li> <li>Adopted ICH Guidelines are S1A, S1B; S1C &amp; S1C(R), S2A, S2B, S3A, S3B, S4, S4A, S5A, S5B(M), S6, S7A, M3</li> </ul>
<ul style="list-style-type: none"> <li>Part IV: Clinical Document (TH)</li> <li>ACTD Check-list for Product Classification (TH)</li> </ul>	<ul style="list-style-type: none"> <li>ACTR Clinical adopted to follow the ICH-Efficacy Guidelines: E1, E2A, E2C, E3, E4, E6, E7, E8, E9, E10, E11</li> <li>Accepted Reference Guidelines the ICH Efficacy Guidelines: E2 C(A), E2D, E2E, E12A</li> <li>Not adopted: E2B(M), E5</li> </ul>

ACTD&ACTR: published on the ASEAN sec homepage:<http://www.aseansec.org/18215.htm> or available at the ASEAN Secretaria



## Erklärung

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

Huningue, den 04. April 2007

Ruth Lätzel