Challenges and opportunities in the **ASEAN emerging regulatory landscape**

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Keywords
Association of South East Asian Nations (ASEAN); Asia Pacific (APAC); Emerging markets; ASEAN common technical dossier (ACTD); ASEAN common technical requirements (ACTR); Pharmaceutical Product Working Group (PPWG); Product registration; Lifecycle management; Post-approval variation.

Abstract
The ASEAN region is becoming an increasingly attractive prospect for pharmaceutical companies. ASEAN is experiencing impressive growth across a number of industries, including the healthcare sector, and the region's regulatory framework is developing. Broad differences in infrastructure, economic stability, language, population size and existing legislation across ASEAN's ten member states make cohesion within ASEAN challenging. However, efforts have been made and the ASEAN common technical dossier (ACTD) has now been implemented to varying degrees across all of the member states. The official timeframes for product registration, variations and renewals also vary between member states and the guidelines governing the regulatory requirements are more defined in some states than others. If pharmaceutical companies are prepared to meet the region's challenges, the potential rewards may be great. Planned initiatives like the ASEAN Economic Community (AEC) aim to create a single marketplace for the region to further improve their economic strength through increased harmonisation.

Introduction

The Asia Pacific (APAC) region is currently undergoing a period of rapid growth. Its current population of four billion already constitutes 60% of the world's population, and this figure is on course to reach five billion by 2050.[1] From the perspective of the pharmaceutical industry, the APAC region represents a large and rapidly expanding market. Between 2001 and 2010, the industry's sales more than doubled from US$97 billion to US$214.2 billion.[2] To put these sales into context, the world's largest pharmaceutical market – the US – saw a pharmaceutical sales value of US$325.8 billion in 2012.[3] These APAC figures are not surprising considering the region includes the world's second and third largest pharmaceutical markets, Japan and China.[4] Global investors are beginning to look in depth at other areas in the region demonstrating potential for new and exciting growth. One such area demonstrating this growth is the Association of South East Asian Nations (ASEAN).

ASEAN was established in 1967 with the aim of promoting regional growth, peace and harmonisation among member states by assisting each other in economic, social, cultural, technical, scientific and administrative matters. Five countries initially signed the ASEAN declaration, founding the association: Thailand, Malaysia, Indonesia, Philippines and Singapore. Over the years, the organisation expanded to include Brunei, Vietnam, Laos, Myanmar (also known as Burma) and Cambodia. As of 2014, the region encompassed a population of over 620 million people[5] and it is expected to grow to approximately 650 million people by 2020.[6]

The ASEAN collaboration is achieved through mutual assistance initiatives in the form of training, education and maintaining close relationships with other similar organisations with a focus on harmonisation.[7] One of the first initiatives by the group was the establishment of the ASEAN Free Trade Area (AFTA), which was designed to promote economic development and improve competitiveness through the elimination of trade barriers.[8] The agreement was established in 1992, by the six-member ASEAN member states at that time, and has subsequently been a joining requirement. Figures suggest that the increased harmonisation is beneficial; if the ASEAN region were to be viewed as a single economy, it would be the seventh largest in the world with a combined GDP of US$2.4 trillion in 2013.[9] In 2013, the five largest ASEAN economies combined – Thailand, the Philippines, Singapore, Malaysia and Indonesia – received greater foreign investment, at US$128.4 billion, than China, which received US$117.6 billion.[10]

This article aims to give an overview of the ASEAN region's current regulatory framework and efforts to harmonise regulatory objectives. Consideration will also be given to the numerous challenges and potential for future opportunities within the region.

ASEAN current regulatory affairs landscape

In 1999 ASEAN established the Pharmaceutical Product Working Group (PPWG) in an effort to develop a more sophisticated regulatory framework, which is at varying stages of implementation across the region. PPWG is comprised of representatives from each of the ten member states' respective regulatory bodies (or government factions responsible for the regulation of pharmaceuticals), with attendance of each country being voluntary. The role of the PPWG has been to incorporate elements of the International Council for Harmonisation (ICH), relevant to ASEAN, into regional guidance. The PPWG is tasked with creating committees to assess the opportunities for regional regulatory harmonisation and to develop common guidelines; the findings of these committees are then reported back through the ASEAN Consultative Committee for Standards and Quality (ACCSQ).[11]

Dossier preparation and submission process

A key area of focus for the PPWG is the inclusion of the ASEAN common technical dossier (ACTD) and the ASEAN common technical

Table 1: Comparison of the ASEAN ACTD and ICH CTD component structure.

Components	ASEAN ACTD	ICH CTD
Comprehensive table of contents and regionally specific administrative documents	Part I	Module 1
Quality, nonclinical and clinical overall summaries	Included in Parts II, III & IV	Module 2
Quality documents	Part II	Module 3
Nonclinical study reports	Part III	Module 4
Clinical study reports	Part IV	Module 5

requirements (ACTR) into the necessary requirements for product registration in the region. The ACTR provides guidelines for the compilation of a submission, in accordance with the ACTD structure, and is comparable to the notice to applicants (NtA) Volume 2C in Europe. The ACTD incorporates ICH guidelines and is comparable with the common technical document (CTD), as described in Table 1. Currently the ACTD is utilised in all of the member states to varying degrees, for example the health authority in Singapore, Health Sciences Authority (HSA), will accept submissions in either the CTD or ACTD format. Many of the ASEAN national health authorities require new registration submissions to be made using their own specified regional documents alongside elements of the ACTD. For example, a new registration submission in Laos requires the safety and efficacy documents outlined in parts I–IV of the ACTD and the health authority specific 'LP2' form.[12]

There are multiple registration categories for new products throughout ASEAN, and the applicable categorisation will vary based on the member state in which the product is to be registered. For example, Thailand currently has just two major distinctions for new drug applications, "modern" or "traditional". Modern products are then divided further into four sub-categories: household remedies whose sales require no licence; ready-packed drugs that can be sold in drugstores by nurses or other medical professionals; dangerous drugs; and specially controlled drugs.[13] There are plans to replace the existing Thai sub-categories, with prescription-only, pharmacy-dispensing and home remedies, through the "New Drug Act of B.E.2546 (2003)". The anticipated reclassification of the drug categories in Thailand would align them more closely with the categories used in Singapore: Prescription Only Medicines (POM), Pharmacy Only (P) and General Sales List (GSL).[14] However, these categories are based on the assumption that patients will receive their medicines via a pharmacy and this is not the case in all of the member states. In Malaysia, drugs are often dispensed to patients directly by their physician, eliminating the need for the intermediary step of visiting the pharmacy.[15]

Approval timelines, following the submission of a product registration application, vary between the individual member states. The timelines can also vary within each state based on the type of product being registered. In Indonesia for example, orphan drugs have an approval period of 100 days; products which have been already been approved in countries with respected regulatory evaluation systems have an approval period of 150 days, and new products not covered by the previous two options have an approval period of 300 days.[16] The respective product approval times for each of the ASEAN member states have been summarised in Table 2.

Traditional medicines are still widely used throughout ASEAN, predominantly in the rural populations where, as previously discussed, access to modern healthcare services can be limited. Traditional medicines are considered to be an important part of the culture in Asia and the Product Working Group for Traditional Medicines and Health Supplements (TMHSPWG) was established in 2004 as part of economic initiatives designed to make the ASEAN region more competitive. Among other things, the TMHSPWG has been tasked with: harmonising technical requirements for traditional therapy registration; creating guidelines regarding good manufacturing processes (GMP); substantiation of therapeutic claims; and labelling requirements.[17]

National online submission portals are beginning to be used for submissions in some member states, for instance, registration applications in Singapore can be made via its online submissions platform, PRISM.[18] In Malaysia, Part I and II of the ACTD must be submitted to its regulatory authority via its online platform, QUEST3, but Part III and IV can be submitted locally in a hard copy.[19] Currently there is no centralised submission portal to facilitate a simultaneous dossier submission across multiple ASEAN member states.

Post-approval variations

ASEAN have produced a central guidance document, "ASEAN Variation Guideline for Pharmaceutical Products"[20] which sets out the post-registration variation categories and their parameters. Variation applications can be categorised as a "major variation" (MaV) or a "minor variation" (MiV). MaVs cover any changes to a registered product that may significantly impact its quality, safety or efficacy, and MiVs relating to administrative changes, or changes that will have little effect of the quality, safety or efficacy of the product. MaVs require prior approval from the national regulatory bodies and the variation applications require extensive documentation to substantiate the proposed change. According to ASEAN guidelines MaVs will be approved "within a duration subject to country-specific proposal". For example, in Singapore MaVs are

Table 2: Official product approval timelines in ASEAN member states.[16,21,22]

Member state	Regulatory agency/responsible government department	Time taken for product approval
Brunei Darussalam	Ministry of Health	• New drug approval timeframe will be subject to Ministry of Health evaluation queue • Priority may be given to orphan drugs
Cambodia	Ministry of Health	• Innovative drug: Approximately three months • Generic drug: Approximately six months
Indonesia	National Agency of Drug and Food Control (NADFC)	• Export-only drug: 40 days • Orphan drug: 100 days • New drug approved in respected reference market: 150 days • New drug: 300 days
Laos	Ministry of Health – Department of Food and Drug Registration (FDD)	• New drug: Approximately six months
Malaysia	Drug Control Authority (DCA)	• New drug: 210–245 working days
Myanmar	Ministry of Health	• Common/established drug: Approximately six months • Less common drugs/non-new chemical entities: Approximately six months • New chemical entities: Approximately 12 months
Philippines	Food and Drug Administration (FDA)	• Product registration: 8–12 months based on the volume of work associated with the submission • New drug: Possibly 12+ months
Singapore	Health Sciences Authority (HSA)	• New drug (full dossier application): 270 working days • New drug (abridged dossier application): 180 working days • Generic drug (abridged dossier application): 240 days
Thailand	Thailand Food and Drugs Administration	• Innovative drug: 1.5–2 years
Vietnam	Ministry of Health	• New drug: Legislation is six months. In practice, 8–12 months according to ministry of health workload.

further subdivided into MAV-1 and MAV-2 categories and they have approval times of approximately 270 and 180 days respectively.[18,21] Indonesia has a similar approval time of between 150–300 days depending on the complexity of the variation. The remaining member states have not issued clear guidance on the expected time taken for MaV approval.

Minor variations are further sub-divided into "minor variation – notification" (MiV-N), and "minor variation – prior approval" (MiV-PA). MiV-Ns are so called "Do and Tell" variations – where the market authorisation holder (MAH) may implement the necessary change and notify the relevant health authority thereafter – which are appropriate for small changes such as change of address for the MAH. The MiV-N variations are comparable to EU Type IA variations. MiV-PA variations require prior approval from the relevant health authority before the change can be implemented; similarly to MaVs the period of time associated with the approval of MiV-PA variations will vary depending on the approval timelines associated with member states. Examples of MiV-PA variations include labelling changes, an additional site of product manufacture, or changes to the excipients of a registered product. The MiV-PA variations are comparable to Type IB variations in the EU.

Renewal applications in ASEAN are required to be submitted every five years in almost all of the member states. The renewals process is particularly sophisticated for products registered in Singapore; renewal applications can be submitted via an online platform, "Renew@PRISM", and more than one product renewal can be included per application. A key benefit of Singapore's online submission platform, PRISM, is that it will generate an automatic notification to the MAH two months before and again one month before the expiry of a product licence. Each successful renewal in Singapore extends the licence of the product for a year, at which point a new renewal application is required.[23]

Additional post-approval activities

The harmonisation of adverse event reporting and pharmacovigilance (PV) in ASEAN presents a real challenge due to the previously discussed differences between the member states. As PV activities are also a relatively new concept in the region there is a shortage

of qualified persons with the necessary expertise to support the function.[24] One example of a harmonised initiative which has seen successful implementation in ASEAN is the post-marketing alert (PMA) system. The PMA system is designed to facilitate knowledge sharing between the ten member states' regulatory authorities regarding any post-marketing safety concerns that have led to the suspension or withdrawal of a particular product. The PMA system can also be used circulate notifications on new restrictions and product safety. However, the PMA system is not widely utilised by all ASEAN members, perhaps in part due to a lack of regional awareness on the importance PV plays in continually improving drug safety.[25]

ASEAN member states have similar restrictions in their legislation covering the advertising of medicinal products. No member state permits pharmaceutical advertising aimed directly at consumers; however, they allow advertising aimed at healthcare professionals. In some member states, pharmaceutical companies can publicly advertise the sale of products which are available as over-the-counter drugs, or their equivalent. For instance, in Thailand it is possible to promote products registered in the "Household Remedies" category, once they have received approval from the Thai regulatory body.[26]

Challenges facing ASEAN

One of the largest challenges facing ASEAN is the harmonisation of a diverse group of countries. The ten member states have large contrasts in a number of key fields, for example, different languages and vast ranges in population.

The ASEAN region has a population of more than 600 million,[27] however, distribution is uneven across the individual nations. For example, with a population of 252 million, Indonesia represents a potential market 610 times the size of Brunei Darussalam, which has a population of just 413,000 people.[27] There is also broad economic diversity; in 2014 the most urban member state, Singapore, had an average GDP per capita of US$82,800, one of the highest in the world,[28] whereas Laos had an average GDP per capita of just US$5,000.[28]

The economic inequalities between the countries extend to differences in healthcare spending at both the individual and national level. In 2013, the total healthcare expenditure in Indonesia was US$26.6 billion, equating to approximately US$106 per capita, whereas Myanmar had a total healthcare expenditure of US$1.1 billion, which equated to approximately US$20 per capita.[29]

Consideration should also be given to the fact that the level of health insurance coverage is not uniform across the region. In most member states, a large proportion of the healthcare bill is paid for by the individual, rather than the state.[30] More than 50% of healthcare spending in Cambodia, the Philippines and Singapore is paid for out-of-pocket, giving a clear sense of how the varying GDPs of the member states can have an impact on the overall size of the region's pharmaceutical industry.

Desirable healthcare products and services vary by country and are also impacted by the region's uneven distribution of wealth. For example, branded pharmaceuticals with a higher price tag may be more popular in the wealthier states of Singapore or Brunei than in the lower income member states, where generic products would be preferable. However, factors other than financial implications contribute to the type of pharmaceuticals sought after in different member states. For instance, Cambodia's higher birth rate would suggest an increased demand for paediatric products and vaccines. Singapore's ageing population would indicate a bias towards products used in the treatment of chronic diseases more associated with elderly patients, such as diabetes or certain cancers.[31]

Variations in infrastructure cause uneven distribution networks, impacting the standard of healthcare available throughout ASEAN member states. Access to healthcare professionals and services tends to be concentrated in urban areas and it can be difficult for those residing in remote and rural areas to get access to quality pharmaceuticals and treatment.[32]

In addition to financial and social constraints, the ASEAN regulatory industry faces challenges due to a gap between the regulatory legislation issued by national governments, and the actual enforcement of these laws at a local level. The majority of pharmaceutical products in the region are imported, either as the final product, or as base materials which are then manufactured into the finished product locally. There are serious problems with high volumes of counterfeit products making their way onto the market. Counterfeit products have been found to be more prevalent in the poorer economic states, such as Cambodia, where they often lack the funding to effectively enforce the regulations.[33]

Intellectual property (IP) rights are another challenge within the ASEAN region. There is a high degree of variation in the legislation regarding IP and a general lack of expertise on the subject. This has created hurdles for the regulation of the pharmaceutical industry in terms of their ability to ensure the production of safe and efficacious products. In Indonesia, for example, patents are only extended to products that have been manufactured within the country; therefore, any foreign products that have been registered in Indonesia are at risk of local companies manufacturing the same product and marketing it at a reduced price as a generic under a new name.[30] The lack of clear pathways to IP protection in the region has led to a negative impact on the relationships between ASEAN regulatory groups and the international pharmaceutical markets.

Future regulatory opportunities for ASEAN

Despite the numerous challenges, ASEAN initiatives are already beginning to demonstrate a positive impact on the state of regulatory affairs. For example, at a meeting of the World Health Organisation (WHO) in 2004, the representatives of ASEAN raised concerns about the stability zone assigned to their region. The ASEAN delegates highlighted that the existing zone IV stability designation (30°C/65% RH) did not adequately meet the climatic conditions in their region. The WHO responded to the claims by sub-dividing zone IV into zone IVa (30°C/65% RH) and zone IVb (30°C/75% RH).[34] All ASEAN member states were then assigned to stability zone IVb.

The impressive market growth statistics demonstrated across the ASEAN region, and the trend towards increased healthcare spending in many of the member states, would suggest that ASEAN's regulatory affairs will continue to develop through increased industry awareness and investment.

In 2007, ASEAN member states committed to the creation of an integrated economic region known as the ASEAN Economic Community (AEC). The ASEAN pharmaceutical sector falls under the jurisdiction of the new AEC, through the AFTA, and the aim is that a single market would further increase the region's ability to compete globally, through improving its economic development. However, it has become evident that the original implementation date of 2015 was unrealistic and the move towards economic harmonisation will need to be more of a gradual transition.[35]

Conclusion

ASEAN must now focus on increased harmonisation of the regulatory framework, implemented equally across all member states, to ensure every individual has access to genuine, safe and efficacious medicine, irrespective of their location or demographic. The challenge facing ASEAN is how they can achieve their aims, while accommodating the varying stages of development of each member state, without becoming entrenched in bureaucratic systems which would lead to delays in product registration, and ultimately in patient care.

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