ASEAN Harmonization on GMP Inspection and Training of Inspectors

by Sia Chong Hock, Robert Tribe, and Dr. Chan Lai Wah

This article provides a progress report on the harmonization of GMP inspection and training of inspectors being led by the Association of Southeast Asian Nations (ASEAN).

Background

The Association of Southeast Asian Nations (ASEAN) was founded in 1967, and it comprises 10 Southeast Asian Member States. In alphabetical order, they are Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar (Burma), Singapore, Philippines, Thailand, and Viet Nam. A map of Southeast Asia is shown in Figure 1.

The 10 ASEAN Member States have very diverse racial, religious, socio-cultural, political, economic, and geographical backgrounds. Hence, the task of integrating ASEAN is a highly challenging one. However, ASEAN has the political will and resolve to create an ASEAN Economic Community (AEC), as it is aware of the economic competition that it faces from its larger Asian neighbors as well as other economic powers from the rest of the world. They include (with their population in brackets), Taiwan (23 million), South Korea (49 million), Japan (127 million), India (1.2 billion), China (1.3 billion), Australia (22 million), Canada (34 million), United States (314 million), and the European Union (about 500 million).

Collectively, ASEAN as a 10-member group, is not small. A key strength of ASEAN is its combined population (and potential market) of about 600 million people. This can be turned into a big economic advantage if rules and regulations are harmonized, and made transparent. If not, ASEAN will face strong competition globally and it will not be an attractive destination for potential investors.

Need for ASEAN Economic Integration

On 2 September 2003, ASEAN leaders agreed at the 35th ASEAN Economic Ministers Meeting in Phnom Penh, Cambodia, to establish an ASEAN Economic Community (AEC) by 2020. The AEC is expected to develop ASEAN into a highly competitive region of equitable economic development, with a single market and production base, which is fully integrated into the global economy.2

On 29 November 2004, the ASEAN Secretariat issued a media release entitled “ASEAN Accelerates Integration of...
Priority Sectors” following the 10th ASEAN Summit in Vientiane, Laos. This ASEAN Framework Agreement on Integration of Priority Sectors represented a major step toward the realization of AEC. Eleven priority sectors, including health care, of which pharmaceutical products are a component, were identified. An ASEAN Sectoral Mutual Recognition Arrangement (MRA) on GMP Inspection for Manufacturers of Medicinal Products, was one of the priority initiatives. On 13 January 2007, the Cebu Declaration on the Acceleration of the Establishment of an AEC by 2015, was signed at the 12th ASEAN Summit, held in Cebu, Philippines. The Cebu Declaration accelerated the establishment of AEC from 2020 to 2015.

ASEAN MRA Taskforce on GMP Inspection

With the AEC 2015 as the backdrop, and an ASEAN Sectoral MRA on GMP Inspection as one of the priority initiatives, an ASEAN MRA Taskforce on GMP Inspection was formed in 2005. This taskforce was charged with the responsibility to deliver the ASEAN Sectoral MRA on GMP Inspection for Manufacturers of Medicinal Products, as its main outcome. Singapore and Malaysia were appointed as the Chair and Co-Chair of this taskforce respectively, as both Singapore and Malaysia were the only two ASEAN Member States that were members of the Pharmaceutical Inspection Co-operation Scheme (PICS) based in Geneva. The PICS inspection framework had been used as the basis for working out the ASEAN Sectoral MRA on GMP Inspection, i.e., ASEAN Member States had agreed to adopt the PICS inspection framework as its benchmark.

Altogether, the ASEAN MRA Taskforce on GMP Inspection held seven round table meetings in six different ASEAN cities between 2005 and 2008. The first meeting was held in August 2005 in Singapore, where the terms of reference, benchmark, and framework of the MRA were agreed upon. The second meeting was held in March 2006 in Hanoi, where a GMP gap analysis was conducted among the 10 ASEAN Member States, presented, and discussed. By the third meeting in October 2006 in Jakarta, a technical working draft of the MRA was put up for discussion. A special (adhoc) technical meeting was held in April 2007 in Hanoi, where the legal aspects and implications of the MRA on all 10 ASEAN Member States were scrutinized. At the fourth meeting in July 2007 in Kuala Lumpur and the fifth meeting in February 2008 in Vientiane, Laos, the contents of the MRA were further deliberated to “ensure that no stones were left unturned.” By the sixth meeting in July 2008 in Brunei Darulssalam, there was consensus on the contents of the ASEAN Sectoral MRA on GMP Inspection, from both technical and legal perspectives, and the MRA was ready to be signed in 2009 as targeted.

The ASEAN Sectoral MRA on GMP Inspection for Manufacturers of Medicinal Products was signed by the Economic Ministers of all 10 ASEAN Member States on 10 April 2009 in Pattaya, Thailand. This MRA comprises 19 Articles as shown in Table A.

Under Article 4, the scope of the MRA covers medicinal products in finished dosage forms, and they include both Over-The-Counter (OTC) and prescription medicines. However, the scope of the MRA excludes Active Pharmaceutical Ingredients (APIs), biologicals, and traditional and herbal medicinal products. Under Article 8 of the MRA, ASEAN

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Table A. Nineteen Articles of ASEAN Sectoral MRA on GMP Inspection for Manufacturers of Medicinal Products.
Member States are obliged to operate a PICS-equivalent GMP inspection framework. They are also obliged to accept the GMP certificates or inspection reports issued by the listed Inspection Services, i.e., the inspectorates of ASEAN Member States whose GMP inspection systems meet the PIC/S framework.6

Since the signing of the ASEAN MRA in Pattaya on 10 April 2009, three more MRA taskforce meetings had been held. These (post-MRA) meetings were held in Manila (May 2009), Yogyakarta (July 2010), and Singapore (June 2011) respectively. Although the ASEAN MRA was signed in 2009, ASEAN Member States agreed to give themselves a two-year grace period before its implementation in 2011. The mood at these post-MRA taskforce meetings was generally more relaxed than the pre-MRA taskforce meetings for the simple reason that the MRA had been signed, sealed, and delivered. The delivery of this first MRA in ASEAN for the pharmaceutical sector was regarded as a landmark achievement.

The final ASEAN MRA taskforce meeting was held in Singapore on 7 June 2011. After the meeting in Singapore, the taskforce was dissolved and a Joint Sectoral Committee (JSC) established, to oversee the implementation of the MRA, which had come into force in 2011.

With the establishment of JSC, following the dissolution of the ASEAN MRA Taskforce in 2011, ASEAN inspectorates (Inspection Services) can now apply for listing. The proce-
ASEAN Harmonization

The implementation of the ASEAN Sectoral MRA on GMP Inspection is expected to bring about many benefits to ASEAN Member States. These benefits include:

- The avoidance of duplication of GMP inspections within the 10 Member States of ASEAN
- Saving of time, resources, and costs for both the ASEAN regulators and the industry
- Facilitation of import, export, and overall trade in medicinal products across the ASEAN region
- Quicker access of medicinal products by ASEAN patients
- Increased competitiveness of ASEAN as a group, viz-a-viz, India, China, Japan, and other bigger industrialized countries of the world

In order to achieve maximum benefits from the MRA, ASEAN would need to level up the inspection system of all its National Drug Regulatory Authorities to meet the PICS framework. This leveling up process also would need to incorporate a program for training and continual training of ASEAN GMP inspectors.

Training of ASEAN GMP Inspectors

Why is the training of an inspector so important? The popular sport, soccer (football), will be used as an analogy. In the game of football, the manufacturers are like the players while the inspectors (such as those from the United States FDA, Australia TGA, European Union EMA and ASEAN) play the role of the referee. The referee has the unenviable tasks of confronting any errant player, blowing the whistle when rules are not obeyed, and issuing the yellow and red cards when rules and regulations are flouted repeatedly. The referee also has to prevent football from becoming football brawl, where the game becomes unruly and players fight with one another or with the referee, and the field and stadium may be set on fire. The key role of the referee is to maintain a level and orderly field where the football players abide by the rules of the game. In a similar manner, the inspectors have to maintain a level playing field for the pharmaceutical manufacturers using the PICS GMP standard or other equivalent GMP codes and the legal requirements, as the yardstick.

Thus, the training of the referee or the inspector is very critical, and there is a need to level up the competency of ASEAN GMP inspectors. Competency encompasses the educational qualification, experience, training, and skills sets (both hard and soft skills) of the GMP inspector. In Singapore, many of the GMP inspectors have a pharmacy or pharmaceutical science educational background from the National University of Singapore, and most have relevant industry experience before they join the Singapore Health Sciences Authority as GMP inspectors. Both hard and soft skills sets are crucial to the performance of a GMP inspector in the field. The hard skills sets expected of a GMP inspector include knowledge of:

- Pharmacology (covering drug actions, indications, contra-indications, etc.)
- Pharmaceutical Chemistry (including drug syntheses and analyses)
- Pharmaceutical Microbiology (including sterilization and disinfection processes)
- Pharmaceutical Technology (including manufacturing processes and their controls)
- Pharmaceutical Laws (i.e., Medicines Act and Health Products Act)
- GMP and Quality Standards (including validation and stability studies)

Most of the hard skills are covered in the existing Pharmacy undergraduate program of the National University of Singapore. However, in addition to this, a GMP inspector also would need to possess inter-personal and soft skills set, such as confidence, assertiveness, professional integrity, fairness, perseverance, tact, and diplomacy. He also should have good oral and written communication skills, including the ability to put up a clear unambiguous inspection report in a narrative format using standard English.
As the professional knowledge and skills of a GMP inspector have to remain current and relevant, a continual training program for all ASEAN GMP inspectors has to be put in place. As a first step toward developing this continual GMP training program, a Training Needs Analysis (TNA) was conducted in 2010. This TNA was a collaborative effort between the ASEAN MRA Taskforce on GMP Inspection and ISPE. The key objectives of this TNA survey was to find out the preferred topics for GMP training of ASEAN inspectors, their preferred training delivery methods; and to explore ways and means to make GMP training more effective and appropriate for ASEAN inspectors. The TNA was conducted via an online survey from May to June 2010. A questionnaire was sent to all ASEAN GMP inspectors. The survey was carried out on an “anonymous” basis, i.e., no personal details were requested from the inspectors. Altogether, 71 ASEAN GMP inspectors responded, and this figure represented about 30% of the total number of inspectors within the ASEAN region. The responders included trainees, qualified inspectors, as well as managers and heads of ASEAN inspectorates.

The key findings of the TNA survey are as follows:

- 17% indicated training needs in cross contamination control
- 26% indicated training needs in pharmaceutical water systems
- 30% indicated training needs in facility design and layout
- 13% indicated that they have no formal training in PICS GMP standard
- 12% indicated that they have no formal training in the PICS Quality System Requirements for Pharmaceutical Inspectorates

The TNA survey also highlighted variation in training methodology and training frequency among ASEAN Member States, and a strong preference by ASEAN inspectors for training methods which offered mock inspections, hands-on experience, practical training with case studies, and not just theoretical classroom lectures. These findings were presented at the ninth meeting of the ASEAN MRA Taskforce on GMP Inspection, held in Singapore in June 2011. ISPE was invited to this meeting. ISPE was represented by Robert Tribe and Linda Ambrose. It was a highly fruitful ISPE-ASEAN meeting.

At the ninth ASEAN MRA Taskforce Meeting, ISPE suggested a three-tiered GMP inspector training curriculum comprising:

- Level 1: Induction training for recruits
- Level 2: PICS GMP training for trainee inspectors
- Level 3: Specific subject training for qualified inspectors

Training delivery methods that were explored included coached (mock) inspections, classroom training sessions, online training courses (conducted via “live” or recorded webinars), and the publication of guidance documents for use as educational and reference materials. However, there are several challenges and issues that need to be sorted out. Going forward, the new ASEAN Joint Sectoral Committee (which has taken over from the ASEAN MRA Taskforce) would have to decide on the appropriate training methods for each module, identify trainers with industry and regulatory experience, identify trainees with the potential to become trainers (for continuity of the program), seek out companies which can provide venues for coached (mock) inspections, and most importantly, to determine the overall costs and identify funding sources for the training program.

**Conclusion**

ASEAN needs to harmonize its pharmaceutical regulations in response to the establishment of an ASEAN Economic Community (AEC) by 2015. The establishment of AEC is critically needed to turn ASEAN into a highly competitive region of equitable economic development with a single market and production base, which is fully integrated into the global economy.

The good thing is that an ASEAN Sectoral MRA on GMP Inspection has been agreed upon by all ASEAN Member States and signed in 2009 by all its 10 Economic Ministers, using the PICS GMP inspection framework as the benchmark. A Joint Sectoral Committee (JSC) has been established to oversee the implementation of this ASEAN Sectoral MRA on GMP Inspection for Manufacturers of Medicinal Products. As part of the implementation of this MRA, ASEAN is actively collaborating with PICS, ISPE, and other stakeholders to level up its inspectorates, as well as the competency of its GMP inspectors. The ASEAN inspectorates are aware that no regulatory authority can work in isolation in a globalized world with its associated sets of challenges. The way forward is collaboration, collaboration, and more collaboration.

Figure 5. Ninth Meeting of the ASEAN MRA Taskforce on GMP Inspection, Singapore, June 2011, with participation from ISPE.
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