National Pharmaceutical Control Bureau (NPCB)
Ministry of Health
MALAYSIA

Berita Ubat-ubatan
NEWSLETTER OF THE DRUG CONTROL AUTHORITY MALAYSIA

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MALAYSIA BECOMES A MEMBER OF THE PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME (PIC/S)

Background

The Pharmaceutical Inspection Convention (PIC) was founded in October 1970 by the European Free Trade Association (EFTA) under the title of "The Convention for the Mutual Recognition of Inspections In Respect of the Manufacture of Pharmaceutical Products". However, due to some incompatibility between the Convention and the European law, it was not possible for new countries to be admitted as members of PIC. Consequently, a new arrangement called "Pharmaceutical Inspection Co-operation Scheme" or PIC Scheme was established.

The PIC Scheme, which was enforced in November 1995, is an informal and flexible co-operative arrangement between pharmaceutical inspection authorities. The PIC and PIC Scheme, jointly referred as PIC/S, operate concurrently by one joint Committee and Secretariat, currently based in Geneva, Switzerland. Together, they provide an active and constructive co-operation in the field of Good Manufacturing Practice (GMP).

With due regard to public health, the objectives of PIC/S are:

- To facilitate the networking and confidence building between participating authorities
- To provide the framework for the exchange of information and experience in GMP
- To promote quality assurance of inspections and quality systems of inspectorates
- To co-ordinate the mutual training of inspectors and other related experts
- To enhance common efforts towards global harmonization of GMP

As of January 2002, there are 26 Participating Authorities in the PIC/S. They include Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Liechtenstein, **Malaysia**, Netherlands, Norway, Portugal, Romania, Singapore, Slovak Republic, Spain, Sweden, Switzerland and the United Kingdom.

Relevant information and publication pertaining to PIC/S may be acquired via its web-site at http://www.picsheme.org/.

Need for International Recognition

Imposition of regulatory barriers to international pharmaceutical trade particularly with respect to GMP compliance by certain countries prompted Malaysia's desire to seek international recognition. Malaysia realizes the crucial need of gaining mutual confidence among inspection authorities to acquire marketing authorisation. Many countries including the

Gulf States and Indonesia require exporting countries to be members of PIC/S or being inspected and certified by recognised regulatory bodies prior to marketing authorisation. Hence, it is for this reason that the Malaysian Organisation of Pharmaceutical Industries (MOPI) has strongly proposed that Malaysia applies to become member of PIC/S to facilitate export of pharmaceuticals to capture potential markets.

With globalisation and trade liberalisation, Malaysia needs to adapt to current global environment. Competitive edge could only be achieved by continuously improving the standard of GMP, promoting quality assurance of inspections and implementing higher or equivalent standards of quality system for our local GMP inspectorate. Nevertheless, concerted and strategic efforts between the Ministry of Health and the pharmaceutical industry are important.

Road to Accession

Consequently between 1997 to 2000, the National Pharmaceutical Control Bureau (NPCB), supported by the local pharmaceutical industry led by MOPI jointly undertook efforts to strengthen the implementation of GMP, with the ultimate goal of Malaysia becoming a member of PIC/S. Some of these initiatives include conducting basic and specialised training courses on GMP for GMP auditors and local industry personnel, technical collaboration with relevant agencies, GMP Pharmaceutical Technical Working Group and awareness seminars on PIC/S.

Before a regulatory authority can become a member of the PIC/S, a detailed assessment is undertaken to determine whether the authority has the arrangements and competence necessary to apply an inspection system comparable to that of current PIC/S members. The assessment involves an examination of the authority's inspection and licensing system, quality system, legislative requirements, inspector training, etc, and followed by a visit by PIC/S delegation to observe inspectors carrying out actual GMP inspections on selected manufacturing facilities producing sterile, non-sterile and traditional medicines.

A formal application was submitted to the PIC/S Secretariat in February 2000. Upon preliminary review, the Committee of Officials at its meeting held in October 2000 decided to send a PIC/S Delegation to Malaysia in March 2001. The purpose of the five-day visit is to assess the local GMP inspection and licensing system. A six-member delegation comprising of representatives from Australia, United Kingdom, Singapore, Slovak Republic and Switzerland conducted the assessment, which included observations of inspections on four different manufacturing facilities.

Following the evaluation of Malaysia's GMP system and the visit in March 2001, the Quality System operated by our Inspectorate was reported as excellent and a model for other inspectorates. Malaysia's system of legislation for the audit and licensing of manufacturers of medicines was reported as close to being comparable to that referred in Article 8 of the PIC/S 1/95 required for membership. The Committee of Officials at its meeting in May 2001 had decided to accept Malaysia as a new Member of PIC/S effective from 1st January 2002. PIC/S was impressed by Malaysia's efforts to accede rapidly and successfully into the Scheme.

However, to ensure that necessary remedial actions had been taken, a short follow-up visit was conducted end of October 2001. The three-day visit included observations of inspections on two manufacturing premises, one sterile and one non-sterile, and verification of the previous plan of corrective actions. The outcome of the second visit was fruitful, hence confirming Malaysia's accession into PIC/S as from 1st January 2002.

At the last PIC/S Committee of Officials Meeting held on 24 - 26th November 2001 in Geneva, the decision of Malaysia and Greece becoming newly accepted members as of 1st January 2002 was officially announced. Welcoming us on board PIC/S, the Committee commended Malaysia for the excellent efforts taken.

Asian Participation

Singapore's National Pharmaceutical Administration (now known as Health Sciences Authority) became the 23rd Member and the first Asian Agency to join PIC/S. Singapore applied back in 1997 and was admitted on 1st January 2000. Malaysia is the second Asian country to gain accession. As for the other Asian countries, Indonesia, Macau and Thailand have

recently expressed their interest and intent to join the Scheme.

Meanwhile, the application for membership by the National Laboratories for Foods and Drugs of Chinese Taipei is currently still pending. Chinese Taipei submitted application much earlier than Singapore and Malaysia.

Future Outlook

Inspired by the milestone achievement, relentless efforts are currently being formulated and undertaken to introduce and implement new regulatory requirements in other relevant areas. Inspection of manufacturing premises and facilities for Blood Banks, active pharmaceutical ingredients, medicinal gases, products for Clinical Trials and hospital manufacturing are now in the pipeline under 8th Malaysia Plan.

Driven by determination of "MALAYSIA BOLEH" and premised on sound technical infrastructure and synergistic partnership between NPCB and local industry, our quest for global excellence has indeed become a reality. Malaysia's speedy and successful accession into PIC/S has indeed earned recognition and reputation in the international arena with regards to implementation of GMP and licensing. With this new benchmark, Malaysia can now participate in joint PIC/S inspections.

Looking positively ahead, it is important that international harmonisation efforts towards fostering mutual recognition agreements (MRA) with relevant agencies and economies be implemented. While providing opportunities for strengthening global co-operation in GMP, Malaysia's entry into PIC/S has indeed brought winds of change, setting new horizons for the domestic pharmaceutical sector.

19th Meeting of the ASEAN Working Group on Technical Co-operation in Pharmaceuticals, Brunei Darussalam

At the above meeting held on 26th-28th March 2002 in Brunei Darussalam, Malaysia was represented by Mr. Lai Lim Swee, Deputy Director of Pharmaceutical Services, Ministry of Health and Mdm. Hasiah bt. Abdullah, Deputy Director of the National Pharmaceutical Control Bureau, Ministry of Health.

Malaysia is the coordinator for the Training Centre for Strengthening of Quality Assurance and Non-Pharmacopoeial Analytical Methods.

A progress report on the activities implemented by Malaysia during the period October 2000 - February 2002 was presented and the meeting noted that:-

i. Malaysia has developed a method for the determination of fluoride in toothpaste using ion chromatography. This method has been validated in accordance to the ICH guidelines by the National Pharmaceutical Control Bureau and a protocol has been developed for inter laboratory testing among ASEAN countries. This protocol has been sent to Philippines, Singapore, & Thailand for comments and testing. Malaysia has yet to receive any response from these countries.

ii. Malaysia felt that this aspect of method development should be discontinued, as it is the responsibility of the manufacturers and not the regulatory agencies to develop and validate methods for their products. Instead, it has proposed that a training program be set up for training of evaluator of regulatory agencies on the evaluation of analytical method validation data submitted by manufacturers in their registration dossiers. Malaysia also wish to propose a training course for laboratory auditor on auditing quality control laboratories for Good Laboratory Practices (GLP).

iii. In 2001 Malaysia received a total of 9 WHO Fellows from various countries namely Bangladesh, Mongolia, Nepal and Vietnam under the Training Programme in Quality Control of Pharmaceuticals. Two laboratories technicians

sponsored by the Government of Brunei Darussalam were also trained under this program. The courses provided under this programme were designed specifically to cater to the needs of the individual fellows. The course contents include training in pharmaceutical analysis (areas covered include dosage performance testing, pharmaceutical microbiology, pharmacology and toxicology), testing of traditional medicine and preparation and handling of reference standards.

iv. On August 2001 Malaysia conducted a 5-day workshop on The Evaluation of Analytical Method Validation Data at the National Pharmaceutical Control Bureau (NPCB), Ministry of Health, Malaysia. The objective of the workshop was to familiarize the participants with analytical method data submitted by manufacturers and to train them in the technique of evaluating those data. The workshop was funded by the Malaysian Government and invitation to participate was extended to all ASEAN Member Countries. A total of 27 participants comprising mainly officers from the NPCB together with 2 participants from Indonesia and one from Cambodia attended the workshop.

v. Malaysia participated in the production and utilization of ASEAN Reference Standards (ARS) as follows:

a. At the meeting held in Bangkok on 2nd - 4th August 2000, Atenolol, Albendazole, Gemfibrozil, Indomethacin, Methyldopa and Hyoscine hydrobromide (subject to water re-testing) which were proposed by Malaysia have been adopted as ARS.

b. In 2001, Malaysia packed a total of 1528 vials of the 6 ARS and distributed 995 vials to 8 ASEAN Member Countries, ie. Cambodia, Indonesia, Lao PDR, Myanmar, Philippines, Singapore, Thailand, Vietnam.
Malaysia also received a total of 408 vials of 17 ARS from Indonesia, Philippines, Singapore, Thailand and Vietnam.

c. On a goodwill basis, Malaysia sent 18 ARS with a total of 189 vials to Cambodia, to enable her to have a ready stock of the substances adopted prior to year 2000.

d. Malaysia had earlier proposed 7 items for the next ARS Production & Utilization meeting. In July 2001, Malaysia received the following raw materials from the Japan Pharmaceutical Manufacturers Association (JPMA):-

Methylparaben (1 x 150 gm),
Propylparaben (2 x 75 gm),
Riboflavin (1 x 150 gm).

e. In February 2002, Malaysia received 3 proposed substances, namely Dextromethorphan hydrobromide 8g, Phenylpropanolamine hydrochloride 10g, Dequalinium chloride 8g (and their respective USP primary reference standards) from Singapore for collaborative studies under the ARS Production & Utilization Programme.

f. On 25th February 2002, three JPMA delegates namely, Mr. Kazuyoshi Hirai, Director, Project Coordination Department, Mr. Takayoshi Matsumura, JPMA GMP committee member and Mr. Hiroyuki Arai, JPMA International committee member visited the NPCB and had discussions with officers from the Reference Standard Unit (RSU) on methods pertaining to production of reference and working standards and the test protocol used. The SOP in reference to the control of inventory of reference and working standards, expiry date/validity and storage conditions were also discussed at length.

Herbal Products containing Kava Kava

Dietary supplements containing Kava Kava (Piper methysticum) have been promoted for a variety of uses, to relieve anxiety, stress and insomnia. The products are marketed to all segments of the population, including children, women, men and the elderly.

In December 2001, products containing herbal extracts of this plant were implicated in cases of liver toxicity in Germany and Switzerland. Based on their assessment of the adverse events reported to them, the regulatory authority in these 2 countries have prohibited the sale of such products.

It is believed that the active properties of this plant, the kavalactones, have an effect on the liver enzymes which causes serious hepatic adverse effects like hepatitis, cirrhosis and liver failure.

Based on the seriousness of the side effects, the DCA, at its 131th meeting held on 28 December 2001, agreed to suspend the registration of all products containing kava kava until further information on the safety of this ingredient is established.

As at December 2001, there were 13 registered products containing kava kava in Malaysia.

Registration holders of these products were given until February 28 2002 to furnish information regarding the procedure for extracting the active ingredients. They were also required to recall their products from the market with immediate effect if the kava lactones were extracted with the solvent acetone since only this type of extract is associated with the serious adverse effect.

To date, the DCA secretariat has cancelled the registration of 9 products containing Kava Kava.

Products Containing Aristolochic Acid

Further to the report on the cancellation of registration for all products containing Aristolochic Acid (see Berita Ubat-ubatan December 2001 issue), the DCA has decided that appeals against product cancellation will be considered if the registration holder can show proof that his product does not contain Aristolochic Acid.

Tests for Aristolochic Acid can be carried out by the Doping Centre, Universiti Sains Malaysia, Penang or the Laboratory Division of NPCB.

If it is confirmed that a particular product does not contain Aristolochic Acid, the product will be re-registered. All costs for the tests will be borne by the registration holder.

2 traditional products which have been tested by the Doping Centre USM and found not to contain Aristolochic Acid are **Pil Chi Kit Teck Aun** (MAL19950914T) and **Pil Hong Sah Cap Labu** (MAL19950916T). They are currently registered with the DCA.
