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MALAYSIAN TRANSITION STRATEGY FOR THE PHASE-OUT OF CHLOROFLUOROCARBON IN METERED DOSE INHALERS

METERED DOSE INHALERS AND THE OZONE LAYER

Metered Dose Inhalers (MDIs) are the most widely used inhalation device for the treatment of asthma and Chronic Obstructive Pulmonary Disease (COPD). MDIs use a propellant to aerosolize the drug formulation into a cloud of respirable particles and, until 1995, all MDIs use chlorofluorocarbons (CFCs).

Ozone, an allotrope of oxygen, is a poisonous pale blue gas with a pungent smell. Ozone is present in the earth's atmosphere at altitudes from the surface to a height of at least 1,000 kilometers.

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However, more than 90% of the ozone is found in the stratosphere, an area commonly known as the ozone layer.

The ozone layer protects humans from the harmful effects of the solar ultraviolet (UV) radiation. The ozone layer also protects animal life and plants by shielding them from UV-B radiation which in high doses can be damaging to natural life.

When released, CFCs disperse unchanged in the lower atmosphere and rise gradually to the upper atmosphere where they remain for many years. Eventually, they are broken down by the sun's radiation and release active chlorine which can destroy ozone molecules.

INTERNATIONAL AGGREEMENTS

Malaysia ratified the Vienna Convention for the Protection of the Ozone Layer and the Montreal Protocol on Substances that Deplete the Ozone layer (ODS) in 1989.

The country is committed to phase-out the consumption of ODS by 2010 according to the Control Measures under The Montreal Protocol.

MALAYSIA'S TRANSITION STRATEGY

Objective and Target

In tandem with the proposed transition of CFC phase-out in developed countries, Malaysia has taken proactive steps to reduce usage of CFC in MDIs and completely phase it out by year 2010.

Strategy Principles

Based on consensus among stakeholders and the Drug Control Authority (DCA), the Malaysian Transition Strategy is based on the following principles:

- The health of patients and their access to supplies of medicine will be safeguarded.
- All those involved must work towards a smooth and efficient transition towards CFC-free treatment of asthma and COPD.
- The transition strategy will be developed and implemented in consultation with stakeholders, in a transparent and consistent manner.
- Healthcare professional, patient education and voluntary acceptance of CFC-free treatments will form the basis of the strategy.

Action Plan For Phase-Out

- Set up a database on matters pertaining to availability, usage of CFC MDIs and alternatives available.
- Develop education and awareness programmes for healthcare professionals, patients, caregivers and general public on the need for changes to CFC-Free inhalers.
- Ensure dissemination of information through professional associations, pharmaceutical industry and support groups.
- Develop mechanisms for delivery of messages.
- Propose monitoring mechanism during the transitional period and possible remedial actions to be implemented if the initial target reductions in CFC volumes are not met.

IMPLEMENTATION

In line with the government's commitment to reduce the consumption and complete the phase-out of ozone depleting substances, the Drug Control Authority has made the following decisions:

- New application for registration of MDIs containing CFC will not be accepted and no such products will be registered after **31 December 1998.**
- Registration of other products containing CFC not intended for the treatment of asthma and COPD will be revoked effective **1 January, 1999.**
- Registration of MDIs containing CFC for asthma and COPD to continue until a date is set by the Meeting of the Parties of the Montreal Protocol (exemption given for "essential-use" until the year 2005)

  In May 2004 at the consensus meeting on the Malaysian Transition Strategy for the Phase-out of CFC MDIs, it was agreed that existing Marketing Authorisations of CFC MDIs will be permitted until the year 2010.

CONCLUSION

The Malaysian Transition Strategy on the Phase-Out of CFC MDIs is evidence of Malaysia's commitment to develop a National Strategy for the phase-out of CFC MDIs in Malaysia.

This National Transition Strategy is the result of consultation with many stakeholders representing health professionals, patient groups, pharmaceutical associations, government agencies and related organizations.

With the major tasks being laid down, Malaysia is committed to ensure the complete phase-out of CFC in MDIs by the year 2010 in line with the country's obligation to the Montreal Protocol.

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21st Meeting of ASEAN Working Group On Technical Cooperation in Pharmaceuticals (AWGTCP)

The 21st AWGTCP was held from 22 – 24 September 2004 in Vientiane, Lao PDR. This working group meeting was attended by delegates from Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Singapore and Thailand.

The Asean Secretariat and representatives from the World Health Organisation (WHO) were also in attendance. In addition an expert from Japan in the area of counterfeit drugs was invited to lead the discussion on the subject.

The meeting of the AWGTCP, an important event of the ASEAN in Pharmaceutical Sector, is held annually on alphabetical rotation among ASEAN member countries. The objectives of the AWGTCP are to strengthen the pharmaceutical sectors in all ASEAN countries to ensure the sufficient and regular supplies of effective and safe essential drugs of acceptable quality, to achieve self-reliance in development of human resources within the region in certain fields, and to facilitate the development of a viable pharmaceutical industry in the ASEAN region, taking into consideration the strength and diversity

among ASEAN member countries. It is also part of the mission of AWGTCP to intensify human resources development and capacity building in identified priority areas and strengthening national, regional and international collaboration.

The first meeting of the AWGTCP convened in November 1979, in Indonesia about 25 years ago. During the past 25 years, the AWGTCP achieved some fruitful cooperation and substantial gains not only in strengthened technical cooperation in pharmaceuticals but also in partnership promotion among member countries.

The workplan for year 2004 to 2008 was reviewed at this meeting taking into consideration the financial and technical constraints. It was also hoped that WHO would continue working together with AWGTCP in addressing all the new challenges. A representative from the Ministry of Health and Welfare, India briefed the meeting on India's scope of cooperation and TOR under the proposed ASEAN-India Working Group on Health and Pharmaceuticals.

The next 22nd AWGTCP meeting will be held in Kuala Lumpur, Malaysia tentatively in November 2005.

Cosmetic Sub-Programme, Post Marketing Surveillance Product Safety Evaluation PMS/PSE(1)

In 2004 the EC-ASEAN Economic Cooperation Programme on Standards, Quality and Conformity Assessment, under the Cosmetic Sub-Programme had conducted various activities for the implementation of its second component, Post Marketing Surveillance / Product Safety Evaluation (PMS/PSE). Starting from early August 2004, the Centre for Quality Control (CQC), National Pharmaceutical Control Bureau (NPCB) had actively participated in various activities related to the capacity building of laboratory expertise. They were assessment / inventory of the existing capacity, regional training on basic knowledge in chemical and biological testing, on the job training in chemical and biological testing and regional training on accreditation of laboratory scheme.

Malaysia also coordinated a workshop in September 2004, where eight test methods for cosmetic products were identified for harmonization among ASEAN countries. They are:

1. Identification of Tretinion in Cosmetics Products

2. Identification of Prohibited Colorants in Cosmetics Products

3. Identification and determination of Hydroquinone in Cosmetic Products

4. Identification and determination of 2-phenoxy-ethanol, 1-phenoxypropan-2-ol, methyl, ethyl, propyl, butyl and benzyl 4-hydroxybenzoate in cosmetic products

5. Identification of Hydrocortisone Acetate, Dexamethasone, Betamethasone and Triamcinolone Acetate

6. Preservative Efficacy Testing

7. Determination of Heavy Metals (Mercury, Lead, Arsenic & Cadmium) in Cosmetic Products

8. Microbial Limit Test for Cosmetic Products

Indonesia, Malaysia, Thailand and Singapore were each assigned to conduct and coordinate two test methods for harmonisation. Malaysia's was given the responsibility to coordinate the test methods on the identification of steroids (Betamethasone, Dexamethasone, Hydrocortisone Acetate and Triamcinolone Acetate) and preservative efficacy test (PET). On the job training was successfully conducted for these two test methods at CQC, NPCB in December 2004. The regional laboratory training on the harmonised test methods were attended by participants from the ASEAN countries.

Future plan for this component is to conduct "Proficiency Test Scheme" which will be participated by all the ASEAN countries. By the time the ASEAN Cosmetic Directive is enforced, all the ASEAN regulatory laboratories should be competent and capable to carry out all the harmonised test methods for cosmetic products.

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HEALTH SUPPLEMENT UNIT
Centre for Product Registration

Health Supplement Unit (HSU), a new unit formed under the Centre for Product Registration was officiated on 1st June 2004. It caters for the registration of health supplement products; which are "products intended to supplement the diet taken by mouth in forms such as pills, capsules, tablets, liquids or powders and not represented as conventional food / sole item of a meal or diet". These products may contain ingredients of:

- Vitamins, minerals, amino acids,
- Natural substances of plant and/or animal origin,
- Enzymes, substances with nutritional and/or physiological function.

Registration of these products was previously handled by the Non-Poisons Unit and Traditional Medicines Unit. With the formation of HSU, applications for health supplements registration are now being streamlined to expedite the process.

The National Pharmaceutical Control Bureau (NPCB) through HSU collaborates closely with the Food Quality Control Division (FQCD), Ministry of Health Malaysia since there are various products available which are not clear in their market as "food" or "drugs". Being categorized as "Food-Drug Interface" products, they include a variety of the so called health products. A Committee for the Classification of Food-Drug Interface (FDI) products has been formed since year 2000. The main objective of the committee is to assist NPCB and FQCD in classifying an application from the industry which is not clear of a food or drug (FDI product) in a consistent manner. This committee also helps NPCB and FQCD in providing scientific and technical inputs as well as strengthening and updating the relevant regulations on these products.

In Malaysia, new manufacturers and traders dealing with health supplements have increased in recent years. The great demand for health supplements has resulted in the influx of application for their registration. In view of the current demand and market competition, the timely availability and accessibility of these products to consumers is given due attention. To facilitate and promote trade, registration procedures need to be regularly reviewed to keep abreast with current trends, without compromising product quality and safety. As health supplements are not regulated in many countries worldwide, the evaluation of these products is indeed a great challenge particularly with regards to safety issues.

Currently, the unit has only three (3) evaluators to handle the registration applications. Efforts are taken to recruit more officers to enable the unit to handle the mounting work load.

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CLINICAL TRIAL REGULATORY UNIT
Centre for Product Registration

The Clinical Trial Regulatory Unit (CTRU) was set up in July 2004, as part of the Centre for Product Registration at National Pharmaceutical Control Bureau. The core function of this unit is to evaluate the documents for the application of Clinical Trial Import Licenses (CTILs) and Clinical Trial Exemptions (CTXs) for unregistered product for the purpose of conducting trials in Malaysia.

In ensuring strict adherence to the Good Clinical Practice (GCP) guidelines and other regulatory requirements being followed, inspection may be carried out by this unit at the site of a trial, at the sponsor and /or contract organization's facilities, or at other establishments deemed appropriate.

CTRU works closely with Clinical Research Centre (CRC), Ministry of Health (MOH), and Malaysia in providing GCP training to investigators. CTRU is also a secretariat for the National Committee for Clinical Research (NCCR) and Bioavailability/ Bioequivalence (BA/BE) sub-committee established under NCCR. NCCR is a committee dedicated to the promotion and enhancement on the standard of clinical trial activities in Malaysia. Whereas, BA/BE committee is dedicated to promoting and enhancing the standard of the BA/BE centres in Malaysia.

As the number of clinical trials increase tremendously (up to 5-folds) since 1996, a mechanism needs to be set up to ensure clinical trials are conducted with the highest level of ethical and scientific standards. Therefore, the CTRU has been set up with a foresight on the conduct of regulatory inspections to ensure strict adherence to the Malaysian GCP Guidelines, which is an adaptation of the ICH E6 Guidelines.

At present, the CTRU is equipped with two officers, one being the head of the unit. With the steady increase in the number of applications for CTIL/CTX every month, efforts have been taken to staff more evaluators to this unit so that the inspection arm can operate at the desired level.

We foresee more innovative trials, such as biosimilar studies, herbal medicines with therapeutics claims and trials involving cosmetics products, being conducted in Malaysia. With that, we face greater challenge ahead in ensuring proper implementation of GCP and GLP in ensuring a condusive environment for the conduct of clinical trials in Malaysia, and in accordance to international scientific standards.

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DCA NEWS

1. ADDITIONAL WARNINGS ON ALL ANTIDEPRESSANT DRUGS

The Drug Control Authority (DCA) at its 165th meeting held on 23rd December 2004 decided that warning regarding **'Suicidality in Children and Adolescents Treated with Antidepressants'** should be included in the package inserts of all antidepressant products.

The warnings are:

Suicidality in Children and Adolescents

- ❑ Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.
- ❑ Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.
- ❑ Patients started on the therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- ❑ Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.
- ❑ A statement regarding whether the particular drug is approved for any pediatric indication(s) and, if so, which one(s).

The registration holder needs to study the suitability of the medication guides (MedGuides) as practiced by the United States. The purpose of MedGuides is to provide information to the patient and caregivers on the suicidality adverse effects and this information should be given during treatment. MedGuides must be amended to suit its uses in Malaysia and should be revised by the DCA before being distributed.

2. POSTPONEMENT OF REGISTRATION APPLICATION OF CRESTOR 20MG, 40MG BASED ON SAFETY ISSUES.

At its 165th meeting DCA had agreed on the postponement of registration approval for the above mentioned product based on safety issues.

It has been decided in the meeting that the product (CRESTOR) with strengths of 5mg and 10mg will be registered. The applicant was asked to withdraw the registration application for

strengths of 20mg & 40mg that were still being evaluated by National Pharmaceutical Control Bureau.

3. HEXYLRESORCINOL AS ALLOWED ACTIVE INGREDIENT TO BE REGISTERED WITH THE DRUG CONTROL AUTHORITY (DCA).

The DCA at its 165th meeting decided that **hexylresorcinol** will be taken out from the List of Active Ingredients Not Allowed to be registered with the Drug Control Authority as stated in the Drug Registration Guidance Document. It was been decided that the use of hexylresorcinol is permitted in all pharmaceutical preparations based on the following reasons:

i) The documented reference (Martindale) no longer states that the substance causes irritation on the skin or oral mucosa EXCEPT at high concentrations.

ii) Hexylresorcinol Lozenges is a preparation that is included in the official monograph of the latest edition of the United States Pharmacopoeia (USP).

iii) Preparations containing hexylresorcinol had been registered and marketed in a number of countries such as Australia, Canada, United Kingdom and United States of America.

iv) Lozenges containing active substances from the same chemical group (PHENOLIC ANTISEPTICS) such as Amylmetacresol have already been registered in Malaysia.

4. NEW INFORMATION REGARDING CARDIOVASCULAR SAFETY ON CELEBREX (CELECOXIB), BEXTRA (VALDECOXIB) AND NAPROXEN

At the same 165th meeting, the DCA decided on the following information for the above mentioned products.

- **CELEBREX**

  Based on emerging information, including preliminary reports from one of several long term National Institutes of Health (NIH) prevention studies, the risk of cardiovascular events (composite endpoint including MI, CVA and death) may be increased in patients receiving Celebrex. Subsequently, the DCA will be analyzing all available information from these studies to determine whether additional regulatory action is needed.

◆ **NAPROXEN**

Patients who are currently taking naproxen products should be advised to carefully follow the instructions on the label and not to exceed the recommended doses for naproxen (220 milligrams twice daily). Naproxen should not be taken for longer than ten days unless a physician directs otherwise.

◆ **BEXTRA**

Based on action taken by US FDA, The DCA has instructed Pfizer (M) Sdn. Bhd to include a 'boxed warning' in the package insert about the risk of life-threatening skin reactions 'Steven-Johnson Syndrome and Toxic Epidermal Necrolysis' & Cardiovascular Risks.

5. IRESSA - NEW FINDING FROM ISEL STUDY

The registration application of IRRESA was approved in the 150th DCA meeting but the findings of the ISEL Clinical Study showed that the efficacy could be doubted.

Based on that study, it has been decided in the 165th DCA Meeting held on 23rd December 2004, these actions must be taken:

a) To obtain the complete results of the clinical studies regarding the product.

b) To obtain the relevant information and additional data due to the absence of the data regarding Caucasian or Oriental Patients.

c) The company will be instructed to stop all product promotion activities in accordance with the actions taken by the USFDA.

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