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EVENTS

The International Conference on Harmonisation-Global Cooperation Group (ICH-GCG) ASEAN Training Workshop on ICH Guidelines Q8, Q9 & Q10

The ICH-GCG ASEAN Training Workshop on ICH Guidelines Q8, Q9 & Q10 was held from 26th-28th July 2010 at the Grand Dorsett Subang Hotel. This event was organised by the National Pharmaceutical Control Bureau (NPCB), and was officiated by the Director of Pharmacy Regulatory, Mr. Selvaraja Seerangam.

A total of 140 regulators and pharmaceutical industry representatives from Malaysia, other ASEAN countries (Cambodia, Indonesia, Laos, Philippines, Singapore) and Taiwan participated in this workshop.

The training course instructors were regulators and industry experts who were involved in the drafting of the ICH Q8, Q9 and Q10 guidelines and also involved in the ICH implementation working group (ICH IWG) dedicated to these documents.

Objectives of this training workshop were:

- To provide technical and practical knowledge on three ICH Guidelines: Q8 (Pharmaceutical Development), Q9 (Quality Risk Management) and Q10 (Pharmaceutical Quality System) as described in ICH guidelines.
- To learn about and understand an integrated implementation of these guidelines and how they impact the development and production of Active Pharmaceutical Ingredients (API) and medicinal products.
- To provide information on regulatory expectations in dossier assessment and Good Manufacturing Practice (GMP) inspection in the ICH regions.
- To discuss on the impact on and challenges for the European Pharmacopeia in implementing this new quality paradigm.
- To demonstrate suitability of sound pharmaceutical development based on quality risk management within an appropriate quality system for mid-sized and small companies.

IN THIS ISSUE

DCA EDITORIAL TEAM

SUMMARY OF PRESS RELEASE

1. *Animal Testing and Compliance to Good Laboratory Practice (GLP) of Organisation for Economic Co-operation and Development (OECD)*

The advancement in biomedical research over the years has dramatically improved the quality and prolonged duration of life in both human beings and animals. In means of searching for ways to heal both living organisms and other animals, protocols that require pre-clinical testing involving the use of animals have been incorporated in all internationally accepted drug discovery models.

Animals are necessary in the context of drug development process because animal studies are able to:

- Provide opportunity for certain amount of environment and genetic manipulation that is rarely feasible in humans
- Provide valuable information to a researcher due to the similarities between human and animals in terms of their anatomy and physiological functions
- Provide good understanding on various diseases as animals are also susceptible to the same diseases that affect human
- Identify unnecessary testing on humans if preliminary testing on animals shows that clinical use cannot be established
- Screen new treatments for toxicity to establish the safety profile of an investigational drug so that human subjects are not necessarily exposed to danger when investigation proceeds to clinical phase
- Provide unique insights into pathophysiology and aetiology of diseases and often reveal novel targets for directed treatment

The Ministry of Health (MOH) Malaysia wishes to clarify that it requires the innovator to undertake pre-clinical studies that involve the use of animals before these studies proceed to clinical phase involving human subjects as part of its regulatory requirement for innovator medicinal products. It is also emphasized that drug research institutions and laboratories which are involved in drug discovery studies and experiments are required to adhere to existing guidelines on Good Laboratory Practice (GLP) that stipulate strict conditions on the use of animals with utmost respect for their welfare. In addition to this, most of the animal studies conducted will have to undergo Ethical Review Process to ensure that the use

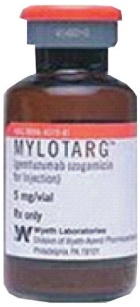
of animals at the designated establishment is justified as well as to provide independent advice on the experiments and standards of animal care, welfare and the ethical use of animals.

The Ministry of Health has embarked on the initiative to make Malaysia a member of the Organisation for Economic Co-operation and Development (OECD) and thus, is serious in ensuring that local institutions and laboratories involved in pre-clinical testing adhere to high GLP standards. Malaysia is a Provisional Member to this OECD Mutual Acceptance Data (MAD) system of GLP since October 2008. The National Pharmaceutical Control Bureau of the Pharmaceutical Services Division, Ministry of Health Malaysia is tasked with the establishment of a GLP Compliance Monitoring Programme and has been designated as the Compliance Monitoring Authority (CMA) for the pre-clinical safety testing of test items contained in pharmaceutical products, cosmetic products, veterinary drugs and food additives in the country.

Malaysia aims to attain full membership in the year 2012 if full compliance and adherence to GLP principles are demonstrated by CMA and research institutions in the country. This effort will enable local research institutions and laboratories to gain better access to markets and business opportunities by all 30 OECD countries which currently produce a combined 60% of the world's goods and services.

The MOH will also strive to ensure that all research facilities within its jurisdiction and surveillance conduct animal studies in a reasonable manner and in tandem with international standards and norms. Failure to comply may result in rejection of hard earned research findings and thus loss of investment.

2. *Banned Sale of Mylotarg® from Pfizer in the United States*



Mylotarg® is the trade name for Gemtuzumab ozogamicin that was approved under the U.S FDA's accelerated programme in May 2000. The accelerated approval programme is granted to allow the agency to approve a drug to treat serious diseases with unmet medical needs based on a surrogate endpoint i.e. how a patient feels, functions or survives. Mylotarg® was indicated to treat CD33 positive acute myeloid leukemia (AML) patients over the age of 60 with recurrent AML who were not considered candidates for other chemotherapy.

In 2004, Wyeth (now Pfizer) initiated a confirmatory post-approval clinical trial (SWOG Study S0106) that aimed to determine whether the addition of Mylotarg® to standard chemotherapy showed an improvement in clinical benefit (survival time) to AML patients. The trial was discontinued ahead of schedule when there were no observed improvements in clinical benefit, and a greater number of deaths

occurred in the group of patients receiving Mylotarg® compared to those receiving chemotherapy alone. At the initial stage of approval, Mylotarg® was also found to cause a serious liver condition known as veno-oclusive disease, which can be fatal.

Following the findings from the clinical trial, Pfizer voluntarily withdrew Mylotarg® from the U.S market. Mylotarg® will no longer be commercially available to new patients. However, as for current patients who are still receiving the drug, they may still complete their therapy following consultation with their health care professionals. Health care professionals should inform all patients regarding the drug's potential safety risks.

In response to the article published in Nanyang Siang Pau dated 23rd June 2010, a check on the National Pharmaceutical Control Bureau (NPCB) database showed that the product holder, Wyeth (Malaysia) Sdn. Bhd. had previously submitted the application to register this product. However, to date the documents for the process of registration have not been submitted. Therefore, evaluation for registration of this product has not been conducted. The NPCB will continue to monitor and ensure that products registered with the Drug Control Authority (DCA) are safe, efficacious and of quality.

3. *Report by Hong Kong Consumer Council on Toxic Chemicals Found in Nail Polishes*

On 16th August 2010, the Hong Kong Consumer Council reported via their official website regarding a nail polish test involving 42 models that was conducted by them. It was found that four models contained prohibited substances in cosmetic use such as Benzene, with concentration levels ranging from 9.7ppm to 260ppm while one model on the other hand, contained Dietylhexyl Phthalate (DEPH) with concentration level of 10ppm. Benzene and DEPH are prohibited substances in cosmetic product formulation in Malaysia as well as EU countries. Benzene can cause cancer upon long-term exposure and even at short-term exposure, it can cause headaches, vomiting, disorientation, shakiness, elevated heart rate as well as loss of consciousness. As for phthalates however, some animal studies have shown that high levels can cause birth defects while long-term exposure

in pregnant women may cause adverse effects on male genital development in newborns.

In addition to that, commonly used ingredients such as methanol, toluene and methyl methacrylate that are allowed to be part of cosmetics formulation within certain limits in both Malaysia and EU Countries were found to be in excess in certain models. One of the four models contained methanol nearly 20 times higher than the limit specified while toluene was at a concentration level of 27% which had exceeded the 25% allowable limit. Exposure to toluene may affect the central nervous system and cause irritation of the respiratory tract while methyl methacrylate may cause skin allergic reactions due to its moderate sensitising potential. No further information was provided as to the products involved or the company responsible for placing the products in the market.

A check on the Cosmetic Product Database of the National Pharmaceutical Control Bureau (NPCB), Ministry of Health of Malaysia confirmed that all cosmetic products notified in Malaysia do not contain these substances in their formulation.

Consumers are advised to read cosmetic product labels thoroughly before using them and to report to the NPCB if they experience any allergic reactions or adverse events from the use of these products. Information on product name, description of the side effects and product samples should be provided for further investigation.

Continuous post marketing surveillance programme is an on-going effort of the Ministry of Health to assess the safety, quality and claimed benefits of cosmetic products in Malaysia. Any new information relating to safety concerns of products under its purview will be evaluated and the appropriate regulatory action will be taken when necessary.

Did You Know?

The history of nail polish dates back to hundreds and thousands of years ago in both Ancient China and Egypt. Nail colour was a representation of their hierarchical status. People of the lower class usually applied a lighter and paler colour and those who used the same nail colours as the royalties will be punished to death.

4. *Safety Status of Antidiabetic Agents Containing Rosiglitazone (Avandia®, Avandamet® and Avandaryl®)*

On 23rd September 2010, the European Medicines Agency issued a statement regarding their recommendation to suspend the use of rosiglitazone (Avandia®) and rosiglitazone containing antidiabetic medicines, Avandamet® (combination of rosiglitazone/metformin) and Avaglim® (also known as Avandaryl in Malaysia, combination of rosiglitazone/glimepiride). This was following the review by the *Committee for Medicinal Products for Human Use* (CHMP) on data related to increased risk of cardiovascular events following the use of this medicine.

The United States Food and Drug Administration (USFDA) on the same date announced that it will significantly restrict the use of rosiglitazone to patients with Type II diabetes who cannot be controlled with other medications. USFDA also ordered GlaxoSmithKline (GSK) to convene an independent group of scientists to review key aspects of the company's clinical trial known as RECORD *(Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabtetes)*. USFDA may take additional actions once the independent re-analysis of RECORD is completed.

Facts

Rosiglitazone containing medicines are indicated as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes. It belongs to the thiazolidinedione class of drugs that works as an insulin sensitizer by binding to peroxisome proliferator-activated receptors (PPARs), enabling the body to make better use of insulin it produces and thus, resulting in better control of blood sugar levels.

In light of current regulatory actions taken by USFDA and EMA, the Drug Control Authority (DCA) recommends that prescribers restrict the use of rosiglitazone and not initiate this medicine on any new patients. Diabetic patients who are currently on rosiglitazone should seek advice from their doctors on whether they need to continue taking rosiglitazone or otherwise. The DCA will continue to monitor and review any new safety information regarding this product for further regulatory action if necessary.

NEW DIRECTIVES

Pharmaceuticals

Two directives for pharmaceutical products under the Control of Drugs and Cosmetics Regulations 1984 has been issued on 22nd July 2010 by the Senior Director of Pharmaceutical Services following the decision made by the DCA committee during the 228th DCA meeting on 27th May 2010. The directives are as follows:

1. **Directive 06/2010: Compulsory Warning Statement "Contraindicated in Children under 2 Years of Age" to be Included in Package Inserts of All Carbosysteine, Acetylcarbocysteine and Methylcarbocysteine (Mecysteine) Products**

   The directive stated that it is compulsory to include warning statement "Contraindicated in Children under 2 Years of Age" in package inserts of all Carbosysteine, Acetylcarbocysteine and Methylcarbocysteine (Mecysteine) products following the decision by the French Health Agency. The warning statement to be printed on package insert is as below:

   Contraindications

   - Contraindicated in children below 2 years of age

2. **Directive No. 07/2010: Compulsory Warning Statement in the form of *Boxed Warning* with "Severe Liver Injury" to be Included in Package Inserts of Propylthiouracil Products**

   The DCA committee has decided to make it compulsory for the boxed warning regarding the report on severe liver injury and acute liver failure (some of which have been fatal in adult and pediatric patient using propylthiouracil) to be printed on the package inserts. This was following the alert from the US Food and Drug Administration (FDA), in which the reports received via the Adverse Event Reporting System (AERS) have shown that the use of propylthiouracil impose a higher risk of hepatotoxicity as compared to carbimazole or methimazole.

Did You Know?

In US, the FDA has identified 34 cases of severe injury that involves 23 adult and 11 pediatric patients following the use of propylthiouracil. Among the adult patients, 13 were fatal and 5 required liver transplantation. As for pediatric patients however, 2 were fatal and 7 required liver transplantation.

The compulsory boxed warning to be printed on the package inserts of propylthiouracil is as below:

BOXED WARNING
Severe liver injury and acute liver failure, in some cases, have been reported in patients treated with propylthiouracil. These reports of hepatic reactions include cases requiring liver transplantation in adult and pediatric patients.

Propylthiouracil should be reserved for patients who cannot tolerate carbimazole/methimazole and in whom radioactive iodine therapy or surgery are not appropriate treatments for the management of hyperthyroidism.

Because of the risk of fetal abnormalities associated with carbimazole/methimazole, propylthiouracil may be the treatment of choice when an antithyroid drug is indicated during or just prior to the first trimester of pregnancy (see Warnings and Precautions).

Cosmetics

Two directives for cosmetics under the Control of Drugs and Cosmetics Regulations 1984 (Regulation No. 29) has been issued on 16th August 2010 by the Senior Director of Pharmaceutical Services, Ministry of Health Malaysia. This was following reports and complaints received via the Quality Monitoring Programme of notified cosmetics in the market, Cosmetic Section of Centre for Post-Registration of Products, National Pharmaceutical Control Bureau. The directives are as follows:

1. **Directive No. 01/2010: Cosmetic Products That Are Applied Externally Around the Eyes and Prohibited Packaging for Such Products**

   The directive has been issued following complaints regarding the sale of products such as eye toner that was initially notified as cosmetic products for external application around the eyes which have been misused as eye drops or sprayed into the eyes. The products have also been marketed and advertised with claims for treatment to improve eyesight, reduce short sightedness as well as refresh the nerves in the eyes and this has violated the Medicines (Advertisement and Sales) Act 1956, ASEAN Cosmetic Directives and Guidelines for Control of Cosmetic Products in Malaysia.

   The directive stated that:

   - Cosmetic products which are applied externally around the eyes are not allowed to be packaged in containers similar to eye drop or eye spray bottles. This is to avoid the products to be misused as eye drops or eye sprays.

   - Products intended to be used as drops or sprays are not classified as cosmetics and should

be regulated as pharmaceutical products that need to be manufactured in premises with Good Manufacturing Practice certification. These premises must be well equipped for the production of sterile products.

- Product holders who have notified such products as cosmetics are requested to recall the notified products immediately. Failure to do so will result in the cancellation of notification, as the products are no longer classified as cosmetic products since the use and safety of those products are uncertain and will thus require futher evaluation.

2. **Directive No. 02/2010: Products That Are Applied to the Male/Female Genital Area for Male/Female Sexual Enhancement Are Not Classified as Cosmetic Products**

The directive has been issued following complaints regarding the sale of products such as skin moisturizer that was initially notified as cosmetic products for application to the male/female genital area which have been misused for sexual treatments for male/female. The products have also been marketed and advertised with claims for male/female sexual enhancement and this has violated the Medicines (Advertisement and Sales) Act 1956, ASEAN Cosmetic Directives and Guidelines for Control of Cosmetic Products in Malaysia.

The directive stated that:

- Leave-on products applied to the male/female genital areas are not classified as cosmetic products since the safety of the use at the genital areas are unknown as well as to avoid exaggerated claims and advertisements which are out of cosmetics context.

- Product holders who have notified such products as cosmetics are requested to recall the notified products immediately. Failure to do so will result in the cancellation of notification, as the products are no longer classified as cosmetic products since the use and safety of those products are uncertain and will thus require futher evaluation.

OTHER NEWS

The Launching of the Quest3 System

QUEST 3
Quality Efficacy Safety 3

The National Pharmaceutical Control Bureau (NPCB) introduced an online product registration system in 2003 known as QUEST2, an acronym for Quality, Efficacy and Safety. Applications for the registration

of prescription, non-prescription, natural products as well as health supplements and notification of cosmetics can be submitted through this system. In addition to these, other processes such as licensing, approved variation, generation of registration number as well as correspondence can be done through this system. The QUEST2 system is also used in post-registration activities such as investigation of complaints of registered products, tests on suspected adulterated products, reports on adverse drug reactions and checking of product labels.

As one of its continuous improvement efforts, the NPCB has taken the initiative to upgrade the existing QUEST2 system to QUEST3. The QUEST3 system has been launched in stages starting from 1st June 2010. The system is scheduled to be fully operational by December 2010.

This current system uses web-based technology while maintaining the usage of smart card for user authentication purposes. Generally, QUEST3 involves the upgrading of existing modules in QUEST2 and the addition of new modules which were manually processed previously (e.g. New Chemical Entities and Biotechnology products). Apart from that, this system is also equipped with a smart system which screens each application in terms of prohibited ingredients that are not allowed to be registered by the Drug Control Authority (DCA) as well as several additional characteristics which enable the QUEST3 system to be more user-friendly.

The launching of modules will be as following:

Modules	Launched Date/ Expected Launching Date
Prescription and Non-Prescription Pharmaceutical Products (Full Evaluation Only)	1st June 2010
OTC Abridged, Traditional, Cosmetic Notification, Import Licenses, Manufacturing Licenses & Wholesaler Licenses	1st July 2010

Modules	Launched Date/ Expected Launching Date
New Chemical Entity (NCE) and Biotechnology Product	1st October 2010
Veterinary Products	1st November 2010

DCA NEWS

The Drug Control Authority (DCA) at its 231st meeting which was held on 26th August 2010, agreed to cancel the registration of the following products due to the adulteration with scheduled poisons.

No.	Product Name	Registration No.	Substances Detected
1.	Goji Plus Capsule	MAL08051654TC	Thiosildenafil
2.	VnG400	MAL20081810TE	Noracetildenafil
3.	Promax Capsule	MAL08082464TC	Thiodimethylsildenafil

CONTACTS & MAP

National Pharmaceutical Control Bureau + 603 - 7883 5400

CENTRES	EXTENSION NO.
Centre for Product Registration	5487
• New Drug Section	5522
• Generic Medicine Section	5490
• Biotechnology Section	8423
• Complementary Medicine Section	8415
• Active Pharmaceutical Ingredient Section	8424
• Veterinary Medicine Section	5500
• Regulatory Coordination Section	5502
Centre for Post-Registration of Products	5538
• Surveillance and Product Complaints Section	5552
• Pharmacovigilance Section	5543
• Variation Section	5588
• Cosmetic Section	5532
Centre for Organisational Development	5553
• Information Communication Technology Section	5555
• Quality System Section	5556
Centre for Compliance and Licensing	5564
• GMP Section	5566
• Quality, Certification, Licensing and GDP Section	5569
• Clinical Research and Compliance Section	5581
Centre for Quality Control	5429
• Bio-Pharmaceutical Testing Section	8457
• Research and Development Section	8448
• Pharmaceutical Chemistry Testing Section	5462, 5456, 5450
• Laboratory Services Unit	5431
• Natural Product Testing Section	5471
• Reference Standard Unit	5468
Centre for Administration	8458

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