BERITA UBAT-UBATAN

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EVENTS

TRAINING PROGRAMME: PHARMACEUTICAL REGULATORY SYSTEM

Early this year, Malaysia has proudly organized a training programme on Malaysia's Pharmaceutical Regulatory System for members of Regulatory Agency and Government officials from other countries at the Best Western Hotel, Petaling Jaya. Held on 14th to 18th March 2016, the programme was aimed to expose the sophistication of regulatory system applied in Malaysia to members of other regulatory agencies from different countries that are aligned with the pharmaceutical regulatory requirements at the international level.

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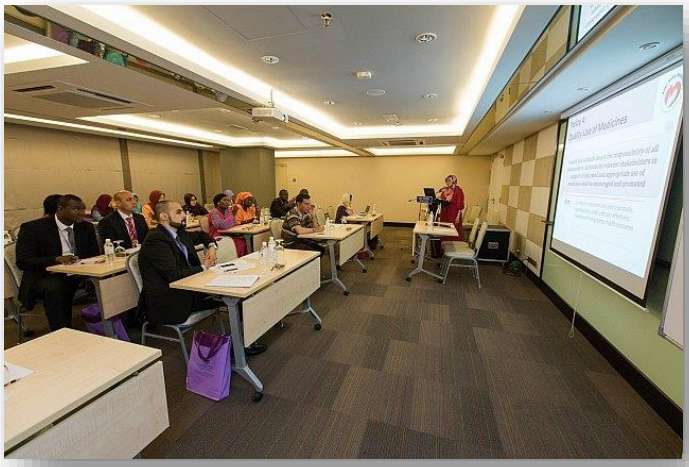
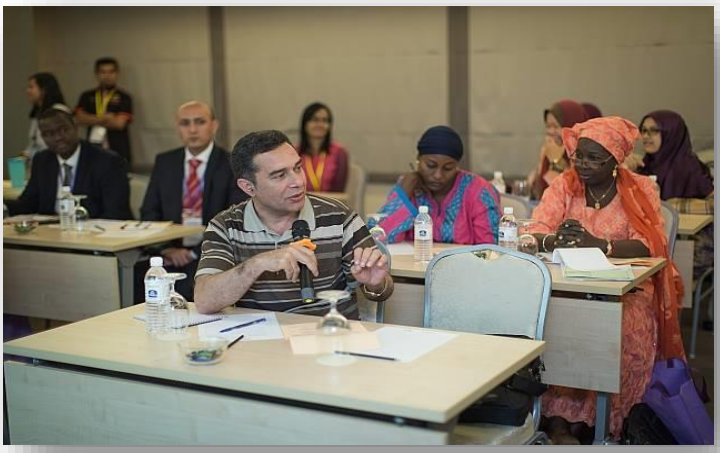
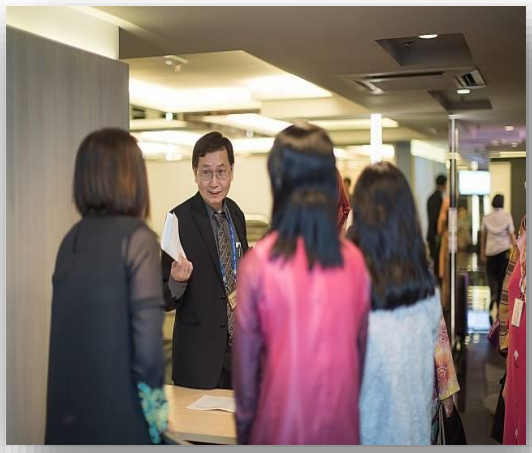
DCA EDITORIAL TEAM

The objective of this programme is to promote NPRA commitments in ensuring that therapeutic products marketed in Malaysia are of good quality, safe and effective as well as to aimed to deliver the latest regulatory information in Malaysia to the members of other regulatory agencies from different countries aligned with the pharmaceutical regulatory requirements at the international level.



"This successful event received overwhelming participation from 18 countries, comprising of participants including officials from their respective National Drug Regulatory Authority (NDRA) and observers from government agencies and the industry."





With speakers from both National Pharmaceutical Control Bureau and Pharmaceutical Services Division, Ministry of Health, the conference included a total of 11 plenary sessions on the 1st and 3rd day of the programme. This training programme serves as an important platform to increase awareness and understanding of the latest regulatory requirements for drugs in the country as well as to disseminate information related to the way forward of the Malaysian regulatory system. This in turn will contribute to the development of the pharmaceutical and health products industry in the country. In addition, the conference was also held to further strengthen cooperation between the participants of the conference which consisted of various relevant stakeholders.

NEW DIRECTIVES

The following directives have been issued under the Regulation 29 of the Control of Drugs and Cosmetics Regulations 1984 by the Senior Director of Pharmaceutical Services, YBhg. Dato' Eisah A. Rahman.

1. ***Directive No. 1 Year 2016 [Ref: (32) dlm. BPFK/PPP/07/25]: Requirements of Foreign Good Manufacturing Practice (GMP) Inspection for the Registration / Renewal of Registration of Pharmaceutical Product Registered with the Drug Control Authority.***

Following the decision made by the Drug Control Authority (DCA) in its 296th Meeting on 21st January 2016, this directive was issued to complement the Directive No. 1 Year 2012 pertaining to the requirements of GMP for the registration/ renewal of registration of imported pharmaceutical product.

The following instructions must be adhered to for all pharmaceutical product manufacturers from country of non-PIC/S members to acquire the GMP inspection by the DCA including those that have been audited by the competent authority of the PIC/S members which comes into force as follows:

New registration of pharmaceutical products starting from **1st July 2016**

Renewal of registration of registered pharmaceutical products starting from **1st January 2017**

With the issuance of this directive, the paragraph 3.1.1b with regards to manufacturers who have been inspected by the competent authority of the PIC/S or ICH members stated in the above said Directive No. 1 Year 2012 is therefore void.

Failure to ensure the validity of GMP certificates throughout the period of registration / renewal of registration of the pharmaceutical products could result in cancellation/ rejection of the product registration / renewal of registration.

2. ***Directive No. 3 Year 2016 [Ref: (34) dlm. BPFK/PPP/07/25]: Safety updates in product package insert pertaining to the adverse effects of QT prolongation and drug reaction with eosinophilia and systemic symptoms (DRESS) for All Products Containing Azithromycin (systemic formulation).***

Following the decision made by the Drug Control Authority (DCA) in its 295th Meeting on 7th January 2016, this directive was issued to enforce the said safety updates. The following safety updates shall be included in package insert of all products containing Azithromycin (systemic formulation):

Special Warnings and Precautions for Use:

Hypersensitivity

As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), dermatologic reactions including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (rarely fatal), and Drug Reaction with Eosinophilia And Systemic Symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Prolongation of QT interval

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including azithromycin. Prescribers should consider the risk of QT prolongation, which can be fatal, when weighing the risks and benefits of azithromycin for at-risk groups including:

- Patients with congenital or documented QT prolongation
- Patients currently receiving treatment with other active substances known to prolong QT interval, such as antiarrhythmic of Class IA and III, antipsychotic agents, antidepressants and fluoroquinolones
- Patients with electrolyte disturbance, particularly in cases of hypokalemia and hypomagnesemia
- Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency
- Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval

Adverse Drug Reactions:

Post-marketing experience:

Cardiac Disorders: Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongation and torsades de pointes (see **Special Warnings and Precautions for Use**).

Skin and Subcutaneous Tissue Disorders: Allergic reactions including pruritus, rash, photosensitivity, edema, urticaria, and angioedema. Rarely, serious cutaneous adverse reactions including erythema multiforme, SJS, TEN and DRESS have been reported.

Effective date of this safety updates in package insert of all products containing azithromycin (systemic formulation) are as follows:

New registration and products under evaluation: **1st March 2016**

Registered products: **1st September 2016**

The safety updates for registered products containing azithromycin (systemic formulation) shall be done via variation application.

This directive came into force starting from **1st March 2016.**

3. ***Directive No. 5 Year 2016 [Ref: (34) dlm. BPFK/PPP/07/25]: Evaluation on examination reports from bioequivalence study centres for product registration and notification of bioequivalence (BE) studies***

Following the decision made by the Drug Control Authority (DCA) in its 298th Meeting on 11th March 2016, this directive was issued to complement the Directive No. 13 Year 2011 pertaining to the submission of examination reports from bioequivalence (BE) study centres for evaluations.

Bioequivalence studies made for the purpose for product registration and notification in Malaysia should be carried out in the BE study centres listed under the compliance program of the National Pharmaceutical Control Bureau (NPCB).

However, examination reports from the BE study centres evaluated by other regulatory bodies recognized by NPCB listed below are accepted; -

1. United States of America, the Food and Drug Administration (USFDA)
2. European Medicines Agency (EMA)
3. Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom
4. French National Agency for Medicines and Health Products Safety (NSM)
5. Federal Institute for Drugs and Medical Devices (BfArM), Germany
6. Austrian Agency for Health and Food Safety (AGES)
7. Other European regulatory bodies depending on the scope of evaluation that had been conducted.

The conditions for examination reports received from the BE study centres to be submitted for evaluations are as follows:

1. A validity period of an examination report from BE study centre which is 3 years from the date of the final examination.
2. The information in the examination reports must not be censored unless vetting checks made by the regulatory body for the purpose of data protection.
3. For BE studies conducted before 1st January 2012, examination reports submitted within the valid study period and during the product registration application can be accepted for evaluation.
4. For BE studies conducted after 1st January 2012, only examination reports which has a valid period including the study period are accepted.

The examination report is still subjected to the scope of the evaluation carried out by the NPCB. If the evaluation scope is not fulfilled, the application will be rejected.

This directive came into force starting from **1st July 2016.**

4. *Directive No. 6 Year 2016 [Ruj Ref: (37) dlm. BPFK/PPP/07/25]: Safety updates in product package insert pertaining to the risk of teratogenic effect for all products containing mycophenolate (mycophenolate mofetil and mycophenolic acid).*

Following the decision made by the Drug Control Authority (DCA) in its 298th Meeting on 11th March 2016, this directive was issued to enforce the said safety updates.

The following safety updates shall be included in package insert of all products containing mycophenolate (mycophenolate mofetil and mycophenolic acid):

Contraindications: *(In package insert)*

- *[Product name] is contraindicated during pregnancy due to its mutagenic and teratogenic potential (see Use in Special Populations: Pregnancy).*
- *[Product name] is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see Use in Special Populations: Pregnancy).*
- *[Product name] is contraindicated in women who are breastfeeding (see Use in Special Populations Breastfeeding).*

Use in Special Populations: (In package insert)

Pregnancy

[Product name] is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraceptive methods. (see Contraindications).

Before the start of treatment, female and male patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention, and planning.

Prior to starting therapy with [product name], female patients of childbearing potential must have ***two negative serum or urine pregnancy tests*** *with a sensitivity of at least 25 mIU/mL; The second test should be performed 8-10 days after the first one and immediately before starting [product name]. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should they become pregnant.*

Due to the mutagenic and teratogenic potential of mycophenolate, ***women of child bearing potential*** *should use* ***two reliable forms of contraception*** *simultaneously, including at least one highly effective method, before beginning mycophenolate therapy, during therapy, and for six weeks following discontinuation of therapy, unless abstinence is the chosen method of contraception.*

Sexually active men *are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomised men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition,* ***female partners of male patients*** *are recommended to use highly effective contraception during treatment and for total of 90 days after the last dose of [product name].*

Congenital malformations, including multiple malformations have been reported post -marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy. The following malformations were most frequently reported:

- *Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;*
- *Abnormalities of the ear (e.g. abnormally formed or absent external/middle ear) and eye (e.g. coloboma, microphthalmos);*
- *Malformations of the fingers (e.g. polydactyly, syndactyly, brachydactyly):*
- *Cardiac abnormalities such as atrial and ventricular septal defects;*
- *Oesophageal malformations (e.g. oesophageal atresia);*
- *Nervous system malformations (such as spina bifida).*

In the medical literature, malformations in children from mycophenolate-exposed pregnancies have been reported in 23% to 27% of live births. For comparison, the risk of malformations is estimated at approximately 2% of live births in the overall population and at approximately 4% to 5 % in solid organ transplant patients treated with immunosuppressants other than mycophenolate.

Adverse Drug Reactions: (In package insert)

Post-marketing experience:

<u>Congenital Disorders:</u> Congenital malformations have been reported post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy (see Use in Pregnancy).

<u>Pregnancy, Puerperium and Perinatal Conditions:</u> Cases of spontaneous abortions mainly in the first trimester in patients exposed to mycophenolate have been reported (see Use in Pregnancy).

Cases of spontaneous abortions have also been reported in patients exposed to mycophenolate, mainly in the first trimester. In the medical literature, the risk has been reported at 45% to 49% following mycophenolate exposure, compared to a reported rate between 12 and 33% in solid organ transplant patients treated with other immunosuppressants.

Studies in animals have shown reproductive toxicity.

<u>Breastfeeding</u>

[Product name] is contraindicated during breastfeeding due to the potential for serious adverse reactions in nursing infants (see Contraindications). Studies in rats have shown mycophenolate to be excreted in milk. It is not known whether this medicine is excreted in human milk.

Effective date of this safety updates in package insert of all products containing azithromycin (systemic formulation) are as follows:

New registration and products under evaluation: **1st Jun 2016**

Registered products: **1st December 2016**

The safety updates for registered products containing azithromycin (systemic formulation) shall be done via variation application.

This directive came into force starting from **1st Jun 2016.**

SUMMARY OF PRESS RELEASE

PUBLIC ANNOUNCEMENT ON CAPSULE OF PAPAYA LEAVES, VIRGIN COCONUT OIL AND OTHER HERBAL PRODUCTS AS ANTI-DENGUE AND ANTI-ZIKA VIRUS FORMULATED BY UNIVERSITY TEKNOLOGI MALAYSIA (UTM)

The National Pharmaceutical Control Bureau (NPCB) would like to remind the public that the products of papaya leaves, virgin coconut oil and other herbal products in capsules formulated by UTM still must undergo several pre-clinical studies and further clinical studies to ensure the efficacy and safety of the herbal products claimed for the patients. UTM is also advisable to register with the DCA for such products before they are marketed or used for patients. This is because any product with high claims of medical or health benefits must be registered with the DCA first before the product can be manufactured, sold, distributed, imported, owned or provided to others.

Revisions made by the NPCB found that the product **'Anti D'ngue' is not registered with the DCA and also no approval was given for such products to be used on humans studies.**

To date, there is **no product with herbal-based formulation are registered by the DCA to treat Dengue fever or Zika virus.** Applicants who wish to register products with such health claims are advised to submit an application together with a complete report of pre-clinical and clinical studies to the NPCB which is an agency under MOH, responsible for regulating all therapeutic products in Malaysia. The application must be in accordance with such requirements described in the Product Registration Guidelines (Drug Registration Guidance Document) which can be found on the website www.bpfk.gov.my. Generally these products will be assessed and must comply to the criteria of quality, safety and efficacy before being registered.

All users are always advised to ensure products (including traditional products, herbs, health food and medicine) purchased is registered through product registration number that begins with the letter MAL which should be indicated on the label affixed to the product and hologram. Users are also advised to read the product label carefully before buying any product to understand the information content stated on the label such product's ingredient, indications, methods of administration and so forth.

TRADITIONAL PRODUCTS / HEALTH SUPPLEMENTS

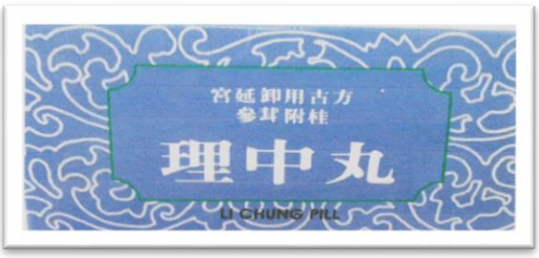
A) *Caution on Using Traditional Products Containing Scheduled Poisons*

The National Pharmaceutical Control Bureau (NPCB) would like to urge the public to refrain from buying and using a traditional product labeled as **"Li Chung Pill**" which had been found to contain scheduled poison, namely aconitine, mesaconitine and hypaconitine.

Product Name	**Registration Number**	**Adulterant Detected**	**Product Registration Holder and Manufacturer**
Li Chung Pill (Ubat Bebola)	MAL05061546T	Aconitine, Mesaconitine Hypaconitine	Herbal Land Manufacturer Sdn Bhd, Perak

These three alkaloids are potent toxins which can cause dangerous effects, especially to the nervous system and heart**. Aconite** can cause acute poisoning in a short period. Among the symptoms of poisoning are numbness in the oral cavity, tongue, face and body, muscle weakness, dizziness, nausea, vomiting, low blood pressure, breathing problems, heart failure and death. The usage in traditional medicines is prohibited. Members of the public who are using Li Chung Pill (Ubat Bebola) product are advised to IMMEDIATELY stop using it and they can seek further advice from the doctor, if they encounter any discomfort or adverse effects.

Registration of this product has been cancelled by the Drug Control Authority (DCA) at its 290th meeting on 3rd of August 2015. Any scheduled poison is not allowed to be formulated in a product which is classified as a traditional product under the Sale of Drug Act 1952 and Control of Drugs and Cosmetics Regulations 1984. All sellers are warned to stop sales and distribution of this product. Individuals who commit an offence under these laws will face penalty up to a period up to three (3) years for the first offence, and penalty up to RM50,000 and or imprisonment for a period up to five (5) years for a subsequent offence. A company found guilty can be fined up to RM50,000 for the first offence and a fine of up to RM100,000 for a subsequent offence.



COSMETICS

B) *Caution on Using Cosmetic Products Containing Scheduled Poisons*

The public is advised to avoid buying and using the following cosmetic product:

Product Name	Notification Number	Scheduled Poison Detected	Name of Product Notification Holder
Qu Puteh Whitening Pro 9	NOT151106644K	Mercury	Vida Beauty

The National Pharmaceutical Control Bureau (NPCB), Ministry of Health Malaysia had received a report of adverse effects of tinnitus (ringing in the ears) and hair loss from a consumer following the use of cosmetic products **Qu Puteh Whitening Pro 9** for about three months. The conditions resolved after stopping use. NPCB had sampled and tested the Qu **Puteh Whitening Pro 9** and the result was found to contain a **high level of mercury**.

Cosmetic products adulterated with mercury are usually marketed for skin lightening and anti ageing treatments such as for freckles, blemishes and wrinkles. However, exposure to mercury can damage the kidneys and the nervous system. It may also interfere with the development of the brain in unborn and very young children. Infants and children can accidently ingest mercury when they touch the cosmetic product containing mercury or any person using these products. The use of products containing mercury may cause skin rashes, irritation and other changes to the skin.

The notification of Qu Puteh Whitening Pro 9 has been cancelled and the company responsible for placing the product in the market has been instructed to immediately stop its sale and supply and to remove all physical stocks from the market within 72 hours.

Anyone who is in possession of this product is advised to immediately stop selling/distributing/using it. Sellers are reminded that **posession** of this product is an offence under the Control of Drugs and Cosmetics Regulations 1984. Any individual who commits an offence under these Regulations can be fined up to a maximum of RM25,000 or to imprisonment for a term not exceeding 3 years or both, and for a second or subsequent offence he shall be liable on conviction to a fine not exceeding RM50,000 or to imprisonment for a term not exceeding 5 years or to both. A company found guilty can be fined up to RM50,000 for the first offence and fined up to a maximum of RM100,000 for a subsequent offence.

CONTACTS & MAP

National Pharmaceutical Control Bureau (NPCB)	+ 603 - 7883 5400

CENTRES	EXTENSION NO.
Centre for Product Registration – Deputy Director	ONE-STOP CALL CENTRE 5511
• Active Pharmaceutical Ingredient Section	
• Biotechnology Section	
• Complementary Medicine Section	
• Generic Medicine Section	
• New Drug Section	
• Regulatory Coordination Section	
• Veterinary Medicine Section	
Centre for Post-Registration of Products – Deputy Director	5538
• Cosmetic Section	5532
• Pharmacovigilance Section	5543
• Surveillance and Product Complaints Section	5552
Centre for Investigational New Product – Deputy Director	5581
• BE Centre & Ethics Committee Compliance Section	8403
• GCP Compliance Section	8401
• GLP Compliance Section	8404
• Investigational Product Evaluation Section	8406
• Investigational Product Safety Monitoring Section	8405
Centre for Compliance and Licensing – Deputy Director	5564
• GDP Section	5568
• GMP 1 Section	5566
• GMP 2 Section	5567
• Licensing and Certification Section	5569
• Quality and Industry Development Section	8556
Centre for Organisational Development – Deputy Director	5553
• Helpdesk	5560, 5561, 5562
• Information and Communications Technology Section	5555
• Quality, Competency & Communication Coordination Section	8481
Centre for Quality Control – Deputy Director	5429
• Bio-Pharmaceutical Testing Section	8894
• Complementary Medicines Testing Section	8892
• Laboratory Services Section	5431
• Pharmaceutical Chemistry Testing Section	8490
• Reference Standard Section	5468
• Research Section	8446
Centre for Administration	8458

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