SUMMARY OF POLICIES OF THE DRUG CONTROL AUTHORITY (DCA): 2009

DCA MEETING	POLICY
DCA 213 (19/02/2009)	**PUNITIVE ACTIONS AGAINST COMPANIES INVOLVED IN ADULTERATION OF PRODUCTS** The Drug Control Authority has decided to take strict punitive actions againts product registration holders, importers and manufacturers involved in adulterating products. This is due to the increasing incidents of product adulteration, in particular traditional products which can give harm to the safety of consumers.
DCA 214 (26/03/2009)	**1. THE IMPORTATION OF UNREGISTERED PRODUCTS FOR TREATMENT IN HOSPITAL** The permit to import of unregistered products through the special approval procedure by the DG of Health can only be granted on a "case to case" basis and this is upon the request by the Hospital's Physician on a "patient name basis". Any application for a direct importation of unregistered products from companies will not be considered. **2. ADDITIONAL INDICATION FOR PATENTED PRODUCTS** Approval for additional indication/s for patented products will not extend the patent period of such products.
DCA 215 (30/04/2009)	**1. CONTRAINDICATION AND WARNING STATEMENT FOR ORAL LIQUID PREPARATION FOR COUGH AND COLD TREATMENT** The DCA has decided that contraindication statement and safety warning must be included in the labels and package inserts of all oral liquid preparation products for cough ang cold treatment containing schedule poison anti-histamine, anti-tussive, expectorant and decongestant (in single/combination dose form). However, decision on warning statement for expectorant products containing Guaifenesin & Ipecac/Ipecahuanha pending for futher review. The "WARNING" section in labels and package inserts of products concerned must contain the following statements: **a."Not to be used in children less than 2 years of age" and** **b."To be used with caution and doctor's/pharmacist advice in children 2 to 6 years of age".** All products registration holders involved are given a grace period of 6 months

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	from the date of enforcement to update their labels and package inserts. **2. <u>BIOEQUIVALENCE (BE) STUDIES REQUIREMENT FOR PRODUCTS FOR-EXPORT-ONLY</u>** The DCA has agreed that "For Export Only Applications" of generic products will be exempted from BE studies requirement with a condition that a confirmation letter from the authority of importing country is submitted to the National Pharmaceutical Control Bureau (NPCB) stating that BE studies are not a requirement in the importing country OR alternatively, a confirmation letter from the product registration holder stating that BE studies are not required in the importing country.
DCA 218 (30/7/2009)	**1. <u>WARNING STATEMENT OF "POTENTIAL FOR AN INCREASE IN RISK OF HEPATOTOXICITY " TO BE PRINTED ON PACKAGE INSERTS OF PROPYLTHIOURACIL PRODUCTS</u>** The Drug Control Authority has decided that warning statement of "Potential for an increase in risk of hepatotoxicity" must be included in the package inserts of propylthiouracil products. The warning statement must be printed as below: ***"WARNINGS AND PRECAUTIONS"*** *Potential risk of serious hepatotoxicity or liver injury including liver failure and death. Patients who are initiated with propylthiouracil should be closely monitored for signs and symptoms of liver injury (e.g. fatigue, weakness, vague abdominal pain, loss of appetite, itching, easy bruising or yellowing of the eyes or skin) especially during the first six months. If liver injury is suspected, promptly discontinue propylthiouracil therapy.* *Propylthiouracil should not be used in pediatric patients unless the patient is allergic to or intolerant of the alternatives available.* **2. <u>WARNING STATEMENT OF "POSSIBLE INTERACTION BETWEEN CLOPIDOGREL AND PROTON PUMP INHIBITORS" TO BE PRINTED ON PACKAGE INSERTS OF CLOPIDOGREL PRODUCTS</u>** The DCA has decided that warning statement of "Possible interaction between clopidogrel and proton pump inhibitors" must be included in the package inserts of clopidogrel products. The warning statement must be printed as below: ***SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE*** *Pharmacogenetics: Based on literature data, patients with genetically reduced CYP2C19 function (intermediate or poor metabolisers) have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following*

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	myocardial infarction than do patients with normal CYP2C19 function. ***INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION*** *Since clopidogrel is metabolised to its active metabolite by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 (e.g., proton pump inhibitors) should be discouraged.* ***PHARMACOKINETIC PROPERTIES*** *The oxidative step is regulated primarily by Cytochrome P450 I soenzymes 2B6, 3A4, 1A1, 1A2 and 2C19.* ***3.*** **WARNING STATEMENT OF "POTENTIAL FOR AN INCREASE IN RISK OF SUICIDAL THOUGHTS OR BEHAVIOURS" TO BE PRINTED ON PACKAGE INSERTS OF ANTIEPILEPTIC PRODUCTS** The DCA has decided that warning statement of "Potential For an Increase in Risk of Suicidal Thoughts or Behaviours" must be printed on package inserts of antiepileptic products as follows: ***SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE*** **"Potential for an increase in risk of suicidal thoughts or behaviour"** The list of antiepileptic products registered with DCA that requires such warning statement are found below: Lamotrigine Sodium Valproate Phenytoin Gabapentin Topiramate Levetiracetam Carbamazepine Oxcarbazepine Vigabatrin Pregabalin Zonisamide **4.** **EXTENSION OF THE DATELINE FOR THE APPLICATION FOR THE REGISTRATION OF VETERINARY PRODUCTS CONTAINING POISONS** The dateline for the submission applications of registration for "existing veterinary products" has been extended from 30th June 2009 to 31st December 2009 (prescripition and non – prescription veterinary products).

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DCA 220 (01/10/09)	**1. <u>WARNING STATEMENT OF "INCREASED RISK FOR OPPORTUNISTIC INFECTIONS SUCH AS ACTIVATION OF LATENT VIRAL INFECTIONS INCLUDING BK VIRUS-ASSOCIATED NEPHROPATHY"</u>** The DCA has decided that warning statement of ***Increased Risk For Opportunistic Infections Such As Activation Of Latent Viral Infections Including BK Virus-Associated Nephropathy*** must be included in package inserts of immunosuppresant products following the research done by USFDA on Adverse Event Reporting System regarding the association between BK virus – associated nephropathy and usage of immunosuppressant. The warning statements must be printed as below: ***WARNINGS AND PRECAUTIONS*** *Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus associated nephropathy which has been observed in patients receiving immunosuppresants. These infections may lead to serious, including fatal, outcomes.* **2. <u>WARNING STATEMENT OF "SEVERE DRUG INTERACTION BETWEEN COLCHICINE AND P-GLYCOPROTEIN OR STRONG CYP3A4 INHIBITORS" ON PACKAGE INSERTS OF COLCHICINE PRODUCTS</u>** The DCA meeting has decided that the warning statement of "Severe Drug Interaction Between Colchicine and P-Glycoprotein or Strong CYP3A4 Inhibitors" must be included in package inserts of colchicines products following Adverse Drug Reactions Reports received by the FDA's Adverse Event Reporting System (AERS), pharmacokinetic studies and drug interaction studies by drug companies. The warning statement to be printed on package inserts of cholchicines products are: **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION** • *Potential risk of severe drug interactions, including death, in certain patients treated with* colchicine *and concomitant P-glycoprotein or strong CYP3A4 inhibitors such as clarithromycin, cyclosporin, erythromycin, calcium channel antagonists (e.g. verapamil and diltiazem)*, *telithromycin, ketoconazole, itraconazole, HIV protease inhibitors and nefazodone.* • *P-glycoprotein or strong CYP3A4 inhibitors are not to be used in patients with renal or hepatic impairment who are taking colchicine.* • *A dose reduction or interruption of* colchicine *treatment should be*

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<tr><th>DCA MEETING</th><th>POLICY</th></tr>
<tr><td></td><td>considered in patients with normal renal and hepatic function if treatment with a P-glycoprotein or a strong CYP3A4 inhibitor is required.
• Avoid consuming grapefruit and grapefruit juice while using colchicine.</td></tr>
<tr><td>DCA 221
(29/10/2009)</td><td>
1. <u>THE REVIEW OF GOOD MANUFACTURING PRACTICE (GMP) INSPECTION REQUIREMENTS FOR OVERSEAS MANUFACTURERS' PREMISES</u>

The DCA has agreed that:
a. The requirement for the GMP inspection on premises for products will be determined according to the degree of risk and the need of the product summarized based on the following matrix:

<table>
<tr><th></th><th>HIGH NEED</th><th>LOW NEED</th></tr>
<tr><td>HIGH RISK</td><td>CONDITIONAL REGISTRATION</td><td>INSPECTION REQUIRED</td></tr>
<tr><td>INTERMEDIATE RISK</td><td>CONDITIONAL REGISTRATION</td><td>INSPECTION REQUIRED</td></tr>
<tr><td>LOW RISK</td><td>INSPECTION NOT REQUIRED*</td><td>INSPECTION REQUIRED</td></tr>
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2. <u>GOOD CLINICAL PRACTICE (GCP) INSPECTIONS ON CLINICAL RESEARCH IN MALAYSIA</u>

The DCA has agreed for:

a. The Good Clinical Practice (GCP) inspections on clinical researches in Malaysia by the NPCB is to ensure that clinical researches are carried out in accordance to all the Good Clinical Practice (GCP) principles, standards etiquette and regulatory requirement that has been outlined.

b. An instruction or guideline will be issued under Regulation 29, Control of Drugs and Cosmetics Regulation 1984.

c. The GCP inspection will only start after the guideline is ready and approved by the DCA.

d. The implementation of this inspection will be implemented as a voluntary basis for 1 year to ensure all parties involved are fully prepared and to strengthen the competency of auditors.
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DCA 223 (24/12/2009)	**1. <u>ADDITIONAL STATEMENT OF "POTENTIAL RISK ASSOCIATED WITH CONCOMITANT USE OF CEFTRIAXONE WITH CALCIUM-CONTAINING INTRAVENOUS SOLUTIONS"ON THE PACKAGE INSERTS OF PRODUCTS CONTAINING CEFTRIAXONE</u>** The DCA has agreed that: a. Additional statement of "Potential risk associated with concomitant use of Ceftriaxone with calcium-containing intravenous solutions" must be included in the package inserts of products containing Ceftriaxone. Health Canada, U.S Food and Drug Adminitration (USFDA) and Medicines and Healthcare Products Regulatory Agency (MHRA) has announced to all members of the medical profession on the review of warning for the products containing Ceftriaxone according to the latest result from 2 in-vitro researches which studied the interaction between Ceftriaxone and Calcium by using adult and neonatal plasma (from umbilical cord blood). b. Amendment should be made on the package insert of all products containing Ceftriaxone are as follows: ***CONTRAINDICATION*** • *Ceftriaxone in contraindicated in neonates (≤28 days of age) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriaxone-calcium.* ***WARNINGS*** • *In patients other than neonates, Ceftriaxone and calcium-containing solutions may be administered sequentially to one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid.* • *Diluents containing calcium, such as Ringer's solution or Hartmann's solution, are not to be used to reconstitute Ceftriaxone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site, because precipitation of ceftriaxone-calcium can occur.*

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	2. <u>CANCELLATION OF THE REGISTRATION OF METERED DOSE INHALERS (MDIS) CONTAINING CHLOROFLUOROCARBON (CFC)</u> The DCA has agreed for: The cancellation of 'Metered Dose Inhalers' (MDI) containing Choloflourocarbon' (CFC) effective from 1st January 2010. **Reason for cancellation:** To achieve the 'complete phase-out' target in importation of products containing CFC effective from 1st January 2010 as agreed in the consensus meeting related to 'Strategy of Country in Handling Usage of CFC MDI' that was held on May 2004.