LIST OF UPDATES ON DRGD FIRST EDITION, MARCH 2013

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
1.	March 2013	Appendix 5, Guideline on Registration of Natural Products	- **Replacement of information** at 2.1.3 (c) ASEAN Harmonisation Negative List of Ingredients with information as in **Attachment 1**: - Renumbering of tables in the appendix.	Memo from Sub-Section of Complementary Medicine (11)dlm.BPFK/PPP/06/17 Jilid 30, 20 February 2013
2.	March 2013	Appendix 8: List of Permitted, Prohibited and Restricted Substances	At 8.1.2 List of Restricted Active Ingredients and Combinations: **Amendment** on substance **No. 16 Dextromethorphan** from "Single Active Ingredient Tablet Formulation" to "Single Active Ingredient in Tablet Form, including lozenges"	Drug Evaluation Committee No. 5/2013, 6 March 2013
3.	March 2013	Appendix 9: Labelling Requirements	**Amendment from:** **Patient Information Leaflet (PIL)** or in *Bahasa Malaysia* known as *Risalah Maklumat Ubat Pesakit (RiMUP),* is compulsory for products containing scheduled poison which are self-administered by patients. For details, please refer to *Direktif Penguatkuasaan Keperluan Mengemukakan Risalah Maklumat Ubat Pengguna (RiMUP) Bil. 5 Tahun 2011* Bil (15) dlm BPFK/PPP/01/03 Jld 1 and Garispanduan Pelaksanaan Risalah Maklumat Ubat untuk	Memo from Center for Post-Registration of Products (16)dlm.BPFK/17/FV/14, 14 March 2013

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			Pengguna (RiMUP) PIL may also be submitted for OTC products in place of a package insert (PI). However, if the product is intended to be sold without a PI or PIL, the information required to being included in the PI or PIL shall be included in the unit outer carton of the product. The draft copy of the PIL in both version of English and *Bahasa Malaysia* shall be submitted for evaluation. **Amendment to:** **Patient Information Leaflet (PIL)** or in *Bahasa Malaysia* known as *Risalah Maklumat Ubat Pesakit (RiMUP),* is compulsory for products which are self-administered by patients, including: a) Scheduled poisons (Category A); b) Over-the-Counter, OTC products (Category X); c) Health supplements with high claims (disease risk reduction). For details, please refer to: i) *Direktif Penguatkuasaan Keperluan Mengemukakan Risalah Maklumat Ubat untuk Pengguna (RiMUP) Bil. 5 Tahun 2011* Bil (15) dlm BPFK/PPP/01/03 Jld 1 ii) *Garispanduan Pelaksanaan Risalah Maklumat Ubat untuk Pengguna (RiMUP)* The draft copy of the PIL in both English and *Bahasa Malaysia* shall be submitted for evaluation.	

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4.	March 2013	Section D: Inspection & Licensing	**Addition of the paragraph and link:** **12.1 FOREIGN GMP INSPECTION** PRH must provide acceptable evidence to show that the manufacturer of the product follows an internationally accepted standard of Good Manufacturing Practice (GMP) and recognized by the Authority in Malaysia. The Control of Drugs and Cosmetics Regulations 1984 (CDCR) requires that the standard of manufacture and quality control of medicinal products manufactured outside Malaysia is taken into consideration before the products are registered with the Authority. NPCB as the secretariat to the DCA is responsible to ensure all manufacturers of registered products in Malaysia are able to provide acceptable evidence that the manufacturing premises conform to current GMP requirements. Hence, foreign manufacturers are also subjected to GMP conformity assessments through acceptable GMP evidence or GMP inspection. For details and forms, please refer Guidance Document on Foreign GMP Inspection.	Premises Inspection Evaluation Committee No. 3/2013, 14 March 2013

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5.	March 2013	Section E: Post Registration Process	**Deletion of 'EMEA' and addition of 'Switzerland' in the following paragraph, as highlighted in yellow:** **16.4.2 VERIFICATION PROCESS** For new indication which has been registered in European Countries~~/ EMEA~~ (United Kingdom, Sweden and/or France) and one of the other Authority's reference countries (United States of America, Australia, Canada, ~~and~~ Japan and Switzerland).	Memo from Section of New Medicine (2)dlm.BPFK/PPP/06/17 Jilid 31, 13 March 2013
6.	March 2013	Appendix 2: Requirements for Product Registration	**Addition of the following paragraph:** Effective 1st March 2013, biowaiver may be granted to generic immediate release oral solid dosage form products containing BCS Class I active ingredients listed in the Guidance On Biopharmaceuticals Classification System (BCS) – Based Biowaiver document. BCS Based biowaivers takes the three major factors that govern the rate and extent of drug absorption from immediate-release solid dosage forms into accounts i.e. solubility and permeability of the drug substance/ API, and dissolution characteristics of the dosage form. This BCS approach provides an opportunity to waive *in vivo* pharmacokinetic bioequivalence testing for certain categories of immediate-release drug products. (Directive *Arahan di Bawah Peraturan 29, Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984 Bil. 1 Tahun 2013*, 14 October 2011, 28 February 2013, Bil (101)dlm.BPFK/PPP/01/03 Jld 2).	Memo from Sub-Section of Generic Medicine (7)dlm.BPFK/PPP/06/17 Jilid 31, 21 March 2013

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7.	March 2013	Appendix 5, Guideline on Registration of Natural Products *For Ginseng: Appendix 4, Appendix 5 and Appendix 9	**2.4 Product Name** **Item No. 11:** Issue: **Addition of 'or referring to the profession'.** Example: **Addition of 'Herbalist, Doctor'.** **Addition of new item which is numbered as No. 13:** Issue: **Prohibited use of product names referring to any religious content** Example: **Maksum, Mahmudah, Arifbillah** **2.7 Labelling Requirement** **d) Example of label approved by the Authority** Replacement with a new example. **2.7.2 Specific Labelling Statements/ Warning & Precautions** a) Amendment from: • For products containing **GINSENG** (including all Panax genus), please state: - "Safe use of ginseng in pregnant women and children has not been established." - "Do not exceed the stated dose." "Safety on long term use has not been established." To:	Memo from Sub-Section of Complementary Medicine (24)dlm.BPFK/PPP/06/17 Jilid 31, 29 March 2013

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		SECTION/ APPENDIX	DETAILS	
			• For products containing **GINSENG** (including all PANAX genus), please state: - "Contraindicated in pregnant women." - "Safe use in lactating women and children has not been established." - "Do not exceed the stated dose." - "Safety on long term use has not been established." b) Addition of the following: • For product containing **naturally occurring SALICYLIC ACID** (e.g. Willow *Salix* spp.), please state: "People allergic to aspirin/ other NSAID should avoid this product." • For products containing **GAMAT/ STICHOPUS spp.** for **ORAL USE ONLY**, please state**:** "Please consult your pharmacist, doctor, or other healthcare providers about any other supplements/ medications you are taking and other health care problems. There may be a potential for interactions or side effects." **2.7.4 Prohibited Visual/ Graphics/ Statement On Label Of Natural Products** a) Amendment of the title 2.7.4 to the following: "Prohibited Visual/ Graphics/ Statement on Packaging Material (Label, Box, Package Insert or Patient Information	

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			Leaflet)” b) Addition of the following paragraph under this title 2.7.4: "General requirement: The graphics printed on outer and inner label has to be standardized to avoid confusion to the customers."	

Attachment 1

c) Ingredients (Botanicals and Substance Derived from Animals) which are banned due to safety reasons:

Table 5:

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
Abrus	*precatorius*	Seed	Abrin, Agrus, Agglutinin	- Potent inhibitor of protein and DNA synthesis - Severe diarrhea - Severe stomach cramp - Severe gastroenteritis
Adonis	*vernalis*		Adonitoxin	Uncontrolled dose can damage heart and cause death
Animal parts containing hormones (All species)				
Antiaris	*toxicaria*	Latex, sap	Cardiac glycoside (antiarin), Cardenolides & alkaloids with cardiac arresting potential	- Latex is highly poisonous - Paralyze heart muscle and cause death
Aristolochia	*All species*		Aristolochic acid	Reported to cause kidney toxicity, interstitial nephropathy
Calotropis	*gigantean*	Latex	Cardiac glycosides, calotropin	Severe mucous membrane irritation characterized by vomiting, diarrhea, bradycardia, convulsion and death
	procera			

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
Cannabis	*sativa*		Cannabinoids	- Potential abuse - Psychoactive on CNS - Prolonged heavy use may lead to tolerance and psychological dependence
	indica			
Catharanthus	*roseus*		Vinca alkaloids	Bone marrow depression, central and peripheral (including autonomic) neurotoxicity
Cerbera	*manghas*	Seed	Digitoxynglycoside, Cerberine, Cerberoside, thevetin	- Drastic purgative and emetic - Burning in the stomach sensation, vertigo, nausea, violent purgation and colic - Heart failure
	odollam	Seed	Cerberine, Cerberoside, odollin, odolotoxin, thevetin and cerapain	- Gastro intestinal symptoms - cardiac toxicity - Nausea, severe retching, vomiting, abdominal pain, blurring of vision - Arterial block and nodal rhtym, hyperkalaemia - Irregular respiration, collapse and death from heart failure
Cinchona	*All species*		Quinine and derivatives	- Resistance of malarial vector - Use of bark is contraindicated in pregnancy and ulcers, intestinal or gastric, and if taken concommitantly with anticoagulants can increased their effects

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
				- Can elicit thrombocytopenia with purpura - Cinchona alkaloids are toxic. Can cause symptoms such as blindness, deafness, convulsions and paralysis
Citrullus	*Colocynthis*	Seed, fructus	Curcubitacin	- Carcinogenic effects, induce infertility in both sexes - Enterohepatonephro-toxicity
Dryopteris	*filix-mas*	Rhizome	Filicin, aspidinol	Hepatotoxic and blindness
Euphorbia	*antiquorum*	Latex	Apha euphorbol, Beta amyrin cycloartenol Euphol	Inflammation of the gastrointestinal mucous membrane, irritate skin, difficult respiration, eyes pupil dilated
	trigona			
Excoecaria	*agallocha*	Latex	Excoecaria phorbol	- Highly irritant to skin - Cause blindness if it enters the eye - Biocidal
Garcinia	*acuminate*	Gum resin	Cambogic acid, β-guttiferin, α-1 guttiferin	Vomiting, hypercarthasis, sympathetic irritation of sympathetic nervous system, caused death by gastro-enteritis
	hanburyi			
	morella			
Gelsemium	*elegans*	Root, leaf, rhizome	Gelsemine & gelseminine (Gelsemium indole alkaloid)	Paralysis, shortness of breath, muscle stiffeningcoma, hypocyclosis

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
Hyoscyamus	*muticus*		Hyoscyamine, atropine, hyoscine	Difficulty in swallowing and talking, transient bradycardia followed by tachycardia with palpitation and arrhythmias, CNS depression, coma
Jatropha	*multifida*	Fruit, seed	Phytotoxin (toxalbumin - Curcin	Nausea, vomiting, serious purgative action
Lantana	*camara*		Lantadene, Lancamaron	Cause toxicity in buffalo, cattle, sheep and goat. Symptoms include photosensitive dermatitis, jaundice and yellowing of mucous membrane and loss of appetite with a decrease in ruminal motility
Lobelia	*chinensis*		Lobeline	- Stimulant and has peripheral and central effects - Excessive use can cause nausea, vomiting and dizziness
	tupa			- Stimulant and has peripheral and central effects - Caused arrhythmias
Lytta	*vesicatoria*	Whole body, tincture	Cantharidin	- Excessive salivation, abdominal pain, swelling of kidney and urogenital system, headache, vomiting and diarrhea accompanied by bleeding - Burning of the mouth, dysphagia, nausea, hematemesis, gross

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
				hematuria and dysuria - Renal dysfunction and related to acute tubular necrosis and glomerular destruction
Melaleuca	*alternifolia*		Tea tree oil	Skin irritation, respiratory distress, vomiting, diarrhea and cytotoxic for oral administration. *** Banned in oral preparation**
Papaver	*All species*		Morphine and derivatives, codeine	- Potential abuse - Dependence, palpitation, hallucination, euphoric activities, CNS depression - Nervous system toxicity - Possible death from circulatory and respiratory failure
Pilocarpus	*pinnatifolius*	Bark	Pilocarpine	Bronchospasm, ocular problem, miosis, blurred vision
	jaborandi			
Podophyllum	*emodii*	Root, leaf	Podophyllin resin	- Serious systemic toxicity with excessive amounts (persistent nausea and vomiting, tachypnea, fever, stupor, coma, tachycardia, neuropathy and death) - Renal failure and hepatotoxicity
	peltatum			
Solanum	*dulcamara*	Leaf, flowering tops	Solanaceous alkaloids	Typical antimuscarinic effect e.g. dry mouth, mydriasis

Genus	Species	Part of Plant/ Animal Prohibited *(whole plant/ animal unless otherwise specified)*	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
Strophantus	*All species*		Strophantus alkaloids	Cardiac effect similar to digoxin
Symphytum	*pregrinum*		Pyrrolizidine alkaloid	Reported to cause liver toxicity