LIST OF UPDATES ON DRGD FIRST EDITION, JUNE 2013

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
1.	June 2013	Section D: Inspection & Licensing	**Addition of the following information and link to the related circular at 12. Inspection:** Additional Information: For manufacturing activity via campaign basis for carbapenem and monobactam product in area or manufacturing facility for cephalosporin product, please refer circular (1)dlm.BPFK/30/06/2 Bhgn 2.	Pharmacy Regulatory Policy Meeting No. 1/2013, 20 March 2013 and Circular from Centre for Compliance and Licensing (1)dlm.BPFK/30/06/2 Bhgn 2, 23 May 2013: *Surat pekeliling berhubung kebenaran mengilangkan keluaran-keluaran carbapenem dan monobactam di dalam fasiliti pengilangan keluaran-keluaran Cephalosporin*
2.	June 2013	Section E: Post-Registration Process	**Amendment at 16.1 Variation as per Attachment 1 based on the directive on implementation of Malaysian Variation Guideline (MVG)**	Memo from Centre for Post-Registration of Product, (3)dlm.BPFK/17/VF/8 Jilid 9, 18 June 2013

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
3.	June 2013	Appendix 2: Requirements for Product Registration	**Addition of link to related circular at 2.1.3 Additional Information on Bioavailability/ Bioequivalence:** For modified-release products, dosage recommendations and regime must be supported by bioavailability studies.	Circular (3)dlm.BPFK/PPP/01/03 Jld. 3, 12 June 2013: *Keperluan Akreditasi Pusat Kajian Bioavailability/ Bioekuivalens Bagi Produk Dalam Bentuk Modified Released*
4.	June 2013	Appendix 8: List of Permitted, Prohibited and Restricted Substances	**Amendment of the following and addition of link to related circular at 8.2 List of Prohibited and Restricted Excipients:** Additional Information 1. Methylene Chloride/ Dichloromethane are not allowed as solvent in film-coating for locally manufactured products. ~~in order to protect workers during manufacturing process.~~ For detail on implementation, please refer circular (2)dlm.BPFK/30/06/2 Bhgn 2.	Pharmacy Regulatory Policy Meeting No. 1/2013 and Circular from Centre for Compliance and Licensing (2)dlm.BPFK/30/06/2 Bhgn 2, 23 May 2013: *Surat pekeliling berhubung larangan penggunaan methylene chloride atau dichloromethane (DCM) dalam proses pengilangan produk tempatan*

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	**DETAILS**	
5.	June 2013	Appendix 9: Labelling Requirements	**a) Addition of the following information at 9.1.3 Patient Information Leaflet after the last paragraph "**The draft copy of the PIL in both English and *Bahasa Malaysia* shall be submitted for evaluation": ***"Note:*** *PIL is not compulsory to be sold with the product but will be uploaded onto NPCB website as reference for patients or consumers.* *For OTC Products, if the product is intended to be sold without a PI or PIL, the information required to be included in the PI or PIL shall be printed on the unit outer-carton of the product."* **b) Addition of information on products containing Trimetazidine as per Attachment 2 below and link to related circular at 9.2 Specific Labelling Requirements.**	a) Memo from Section of Generic Medicine, Centre for Product Registration, Bil (10)dlm.BPFK/PPP/06/ 17 Jld. 34, 6 June 2013 b) Directive No. 5 Year 2013 (4)dlm.BPFK/PPP/07/25, 3 June 2013: *Direktif untuk menghadkan penggunaan produk mengandungi Trimetazidine dan mengukuhkan amaran berkaitan dengan risiko kesan advers simptom parkinson pada sisip bungkusan semua produk Trimetazidine*

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
6.	June 2013	Appendix 10: Guideline on Patient Dispensing Pack for Pharmaceutical Products in Malaysia	**Amendment as follows at Table 2: Dermatological Preparations Maximum Pack Size Recommendations For Pharmaceutical Products** **D07A Corticosteroids, plain** D07AC Corticosteroids, potent (group III): - Max 15g to 100g D07AD Corticosteroids, very potent (group IV): - Max 15g to 100g ****Note:** Pack size of 500g is ~~allowed~~ for hospitals and skin specialist clinics use.	Directive *Bil (4) dlm BPFK/PPP/01/03 Jld 1: Justifikasi Untuk Perubahan Pek Saiz Pesakit Untuk Penyakit Kulit Tertentu Bagi Produk-Produk Dematologi*

Note:

Highlight in yellow is the addition of words/ numbers/ phrases.

Attachment 1

16.1.1 VARIATION APPLICATION FOR FULL EVALUATION PRODUCTS

Variation application for full evaluation products shall follow Malaysian Variation Guideline (MVG) as stated in the directive issued by the Director of Pharmaceutical Services under Regulation 29, CDCR 1984 *Direktif untuk melaksanakan Malaysian Variation Guideline (MVG) (Reference: Circulars Bil (2) dlm BPFK/PPP/07/25.*)

If deemed necessary, NPCB reserves the right to request for additional supporting documents and variation approval letters from other regulatory bodies for all categories of product.

The registration of a product shall be **reviewed for suspension or cancellation** if changes that fall under Major Variation (MaV) and Minor Variation Prior Approval (MiV-PA) are implemented without prior approval of the Authority.

For the interim period before implementation of MaV and MiV-PA according to MVG, Appendix 12 is still applicable. Type I variations that are not listed under Minor Variation Notification (MiV-N) will be processed as a Type II variation.

MODE OF SUBMISSION

Table XIV:

No.	Variation	QUEST 2 Product	QUEST 3 Product
1.	Minor Variation Notification (MiV-N)	Applicant shall submit application for MiV-N via both manual and online QUEST 2 system. For manual submission, applicant can download Form BPFK 416.3 from NPCB's website www.bpfk.gov.my, and shall submit to the Variation Section, Centre of Post Registration, NPCB. For submission online, please scan the form and attach together with the revised draft of package insert and labelling as a single file.	Applicant shall submit application **manually** to the Variation Section, Centre of Post Registration, until further notice pertaining to online submission.

No.	Variation	QUEST 2 Product	QUEST 3 Product
2.	Minor Variation Prior Approval (MiV-PA) & Major Variation (MaV)	Applicant shall submit application via online QUEST 2 system.	Applicant shall submit application **manually** to the Variation Section, Centre of Post Registration, until further notice pertaining to online submission.

16.1.2 VARIATION APPLICATION FOR ABRIDGED EVALUATION PRODUCTS

Variation refers to change of particulars of a registered product. No change of any particulars of a registered product shall be made without prior approval from NPCB. The registration of a product shall be **reviewed for suspension or cancellation** if changes are ~~made~~ implemented without prior approval of the Authority.

There are two types of variation, which are Variation Type I and Variation Type II:

Table ~~XIV~~ XV:

No.	Variation	
	Type I: Minor change	Type II: Major change
1.	Change in name of manufacturer and/or other manufacturers without any change in address of site	Change of product name
2.	Replacement, addition or deletion of company logo on the packaging components (without any changes on graphic or label content)	Change in content of leaflet or prescribing information/ Patient Information Leaflet (PIL)/ Summary of Product Characteristics (SPC)
3.	Change in product owner	Change in content of label inclusive of change in graphics/ artwork
4.	Change in importer/ store address	Change in manufacturing process of the finished product

No.	Variation	
	Type I: Minor change	**Type II: Major change**
5.	Change or addition of imprints, bossing or other markings (except scoring/ break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marking	Change in overage of active ingredient or excipient
6.	Change in shape or dimensions of the container or closure without any other changes	Replacement of an excipient with a comparable excipient and/or change in content of excipient
7.	Change in pack size of the drug product (Finished product), without change in primary packaging material; **or** change in the number or units (e.g. tablets, ampoules) in a pack; **or** change in volume of non sterile preparations	Change in batch size
8.	Tightening of specification limits of drug product (finished product) and/or drug substance (active ingredient)	Change in hard capsule shell (color, size or source)
9.	Change in particular of manufacturer of drug substance (active ingredient) without any change in specification: - Change in manufacturer of drug substance - Addition of manufacturer of drug substance - Change in name and/or rephrasing of address of a manufacturer of drug substance	Change in finished product or active ingredient specification (includes addition of a new test parameter)

No.	Variation	
	Type I: Minor change	**Type II: Major change**
10.	Change in secondary packaging material (or change in any part of the primary packaging material that is not in contact with the finished product (e.g. color of flip off caps, color code rings on ampoules, change of needle shields i.e. different plastic used)	Change to in-process tests or limits applied during manufacture of the product
11.	Change in testing procedure of an excipient.	Change or addition in primary packaging material
12.		Change in shelf life of finished product: - As packaged for sale - After first opening - After dilution/ reconstitution
13.		Change in storage conditions
14.		Appointment, deletion or change of other manufacturers
15.		Addition or deletion of scoring/ break line on tablet
16.		Change in test procedure or analytical protocols of finished product
17.		Change or addition of fill volume and/or change of shape or dimension of container or closure for a sterile solid and liquid drug product

All supporting documents in accordance to the specified conditions laid down for each type of variations should be submitted. For further information pertaining to conditions and supporting documents required for an application of variation, please refer to Appendix 12: Conditions and Supporting Documents Required for Application of Variation Type I & Type II.

If deemed necessary, NPCB reserves the right to request for additional supporting documents and variation approval letters from other regulatory bodies for all categories of product.

The applicant shall provide to NPCB the reason for variation applied. For every variation being made, reason for variation/ remarks, should be clearly written and explained. Other supporting documents can be attached at F12 where such documents are necessary.

~~For variations which are not covered in this guidance document, please refer ASEAN Variation Guideline for Pharmaceutical Product 2012.~~

~~16.1.1~~ MODE OF SUBMISSION

Table ~~XV~~ XVI:

No.	Variation	QUEST 2 Product	QUEST 3 Product
1.	Type I	Applicant shall submit application for Variation Type I via both manual and online QUEST 2 system. For manual submission, applicant can download Form BPFK 416.2 from NPCB's website www.bpfk.gov.my, and shall submit to the Variation Section, Centre of Post Registration, NPCB.	Applicant shall submit application for Variation Type I and/or Type II **manually** to the Variation Section, Centre of Post Registration, until further notice pertaining to online submission.
2.	Type II	Applicant shall submit application for Variation Type II via online QUEST 2 system.	

~~16.1.2 RESPONSIBILITY OF APPLICANT~~

~~a) The applicant shall provide to NPCB the reason for variation applied. For every variation being made, reason for variation/ remarks, should be clearly written and explained. Other supporting documents can be attached at E12 (or F12) where such documents are necessary.~~

~~b) The applicant is responsible for ensuring that all the necessary validation has been conducted to demonstrate that the change does not reduce the quality, safety or efficacy of the product as per ASEAN Guideline on Submission of Manufacturing Process Validation Data for Drug Registration. Process validation report may be requested when deemed necessary.~~

16.1.3 OTHER INFORMATION

a) In the event that a variation application is complex, consultation with relevant officer is encouraged, prior to submission of the application into the online QUEST 2 system.

b) The online QUEST 2 variation module is an overwrite-system. For data already approved in the system which is intended to be retained, it shall be submitted together under “proposed change data”. For instance, whereby existing approved packaging is “HDPE bottle” while the proposed variation is to include “blister pack”, stability data for both packaging (combined into a single file) is required to be submitted during application for variation.

c) No correspondence with the applicant for Quest 2 variation module can be made. For any rejection made for a certain field, only the main field will be rejected (i.e. the supportive documents will be kept until the main field is resubmitted). However, if the main field is not resubmitted without any reason for a certain period of time, the supportive documents will be rejected and a new application shall be submitted.

Attachment 2

140. TRIMETAZIDINE

140.1 Indication of products containing Trimetazidine shall be amended as follows:

a) Indication of Trimetazidine for treatment of pectoris angina is limited to second-line add on therapy; and the indication in otology and ophthalmology field shall be removed.

b) Permitted indication is ***trimetazidine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies.***

140.2 The following warning statement shall be included in the package inserts of products containing Trimetazidine:

a) At part of ***Dosage and method of administration*****:**

For products containing Trimetazidine 20mg:

The dose is one tablet of 20mg of trimetazidine three times a day during meals.

The benefit of the treatment should be assessed after three months and trimetazidine should be discontinued if there is no treatment response.

Special populations

Patients with renal impairment:
In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 20mg twice daily, i.e., one in the morning and one in the evening during meals.

Elderly patients:
Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 20mg twice daily, i.e., one in the morning and one in the evening during meals. Dose titration in elderly patients should be exercised with caution.

For products containing Trimetazidine 35mg:

The dose is one tablet of 35mg of trimetazidine twice daily during meals.

The benefit of the treatment should be assessed after three months and trimetazidine should be discontinued if there is no treatment response.

<u>Special populations</u>

Patients with renal impairment:
In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 35mg in the morning during breakfast.

Elderly patients:
Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 35mg in the morning during breakfast. Dose titration in elderly patients should be exercised with caution.

b) At part of ***Contraindications*****:**

- ***Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders***
- ***Severe renal impairment (creatinine clearance < 30ml/min).***

c) At part of ***Special warnings and precautions for use*****:**

Trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia), which should be regularly investigated, especially in elderly patients. In doubtful cases, patients should be referred to a neurologist for appropriate investigations.

The occurrence of movement disorders such as parkinsonian symptoms, restless leg syndrome, tremors, gait instability should lead to definitive withdrawal of trimetazidine.

These cases have a low incidence and are usually reversible after treatment discontinuation. The majority of the patients recovered within 4 months after trimetazidine withdrawal. If parkinsonian symptoms persist more than 4 months after drug discontinuation, a neurologist opinion should be sought.

Falls may occur, related to gait instability or hypotension, in particular in patients taking antihypertensive treatment.

Caution should be exercised when prescribing trimetazidine to patients in whom an increased exposure is expected:
- ***moderate renal impairment,***
- ***elderly patients older than 75 years old***

d) At part of ***Side effects*:**

Nervous system disorders:
Frequency not known: ***Parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, restless leg syndrome, other related movement disorders, usually reversible after treatment discontinuation.***

Reference: Directive No. 5 Year 2013, [(4)dlm.BPFK/PPP/07/25](): Direktif untuk menghadkan penggunaan produk mengandungi Trimetazidine dan mengukuhkan amaran berkaitan dengan risiko kesan advers simptom parkinson pada sisip bungkusan semua produk Trimetazidine