LIST OF UPDATES FOR DRGD SECOND EDITION, SEPTEMBER 2016, REVISED SEPTEMBER 2017

<table>
<tr><th rowspan="2">NO.</th><th rowspan="2">REVISION</th><th colspan="2">UPDATES</th><th rowspan="2">REFERENCE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr>
<td>1.</td>
<td>September 2017</td>
<td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td>
<td><u>Addition</u> of the following <u>substance</u> and the <u>safety information/ statements</u> regarding the risk of hypersensitivity reaction;

<table>
<tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
<tr><td>38.</td><td>CHLORHEXIDINE

(Please refer Attachment 1)</td></tr>
</table>
</td>
<td>Directive No. 8 Year 2017. (Ref: BPFK/PPP/07/25 (13) Jld.1.)
Direktif Untuk Semua Produk Farmaseutikal Yang Mengandungi Chlorhexidine : Pengemaskinian Sisip Bungkusan, Label Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Reaksi Hipersensitiviti</td>
</tr>
<tr>
<td>2.</td>
<td>September 2017</td>
<td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td>
<td><u>Addition</u> of the following <u>substance</u> and the <u>additional information/ statements</u> on the increased risk of pneumonia;

<table>
<tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
<tr><td>48.</td><td>CORTICOSTEROID (INHALATION)

(Please refer Attachment 2)</td></tr>
</table>
</td>
<td>Directive No. 9 Year 2017. (Ref: BPFK/PPP/07/25 (14) Jld.1.)
Direktif Untuk Semua Produk Inhalasi Kortikosteroid Yang Digunakan Untuk Rawatan Chronic Obstructive Pulmonary Disease (COPD) : Pengemaskinian Sisip Bungkusan Dan Risalah</td>
</tr>
</table>

<table>
<tr><th rowspan="2">NO.</th><th rowspan="2">REVISION</th><th colspan="2">UPDATES</th><th rowspan="2">REFERENCE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Tambahan Berkenaan Peningkatan Risiko Pneumonia</td></tr>
<tr><td>3.</td><td>September 2017</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td><u>Addition</u> of the following <u>safety information/ statements</u> (as highlighted in yellow) regarding drug interaction between products containing Miconazole and Warfarin;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>108.</td><td>MICONAZOLE

(Please refer Attachment 3)</td></tr></table></td><td>Directive No. 10 Year 2017. (Ref: BPFK/PPP/07/25 (15) Jld.1.)
Direktif Untuk Semua Produk Yang Mengandungi Miconazole : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat</td></tr>
</table>

<table>
<tr><th rowspan="2">NO.</th><th rowspan="2">REVISION</th><th colspan="2">UPDATES</th><th rowspan="2">REFERENCE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>4.</td><td>September 2017</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td><u>Addition</u> of the following <u>substance</u> and the <u>additional information/ statements</u> regarding drug interaction between hepatic enzyme inducer and the effectiveness of contraception;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>96.</td><td>LEVONORGESTREL

(Please refer Attachment 4)</td></tr></table></td><td>Directive No. 11 Year 2017. (Ref: BPFK/PPP/07/25 (16) Jld.1.)
Direktif Untuk Semua Produk Kontraseptif Kecemasan Yang Mengandungi Levonorgestrel Dengan Maklumat Berkaitan Interaksi Antara Ubat-Ubatan Yang Dikelaskan Sebagai Hepatic Enzyme Inducer Dan Keberkesanan Kontrasepsi</td></tr>
<tr><td>5.</td><td>September 2017</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td><u>Addition</u> of the following <u>safety information/ statements</u> (as highlighted in yellow) regarding drug interaction between products containing Warfarin and Miconazole;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>181.</td><td>WARFARIN

(Please refer Attachment 5)</td></tr></table></td><td>Directive No. 12 Year 2017. (Ref: BPFK/PPP/07/25 (17) Jld.1.)
Direktif Untuk Semua Produk Yang Mengandungi Warfarin : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat</td></tr>
</table>

<table>
<tr><th rowspan="2">NO.</th><th rowspan="2">REVISION</th><th colspan="2">UPDATES</th><th rowspan="2">REFERENCE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>6.</td><td>September 2017</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td><u>Addition</u> of the following <u>substance</u> and the <u>additional information/ statements</u> on the changes of starting dose for the treatment of rheumatoid arthritis and ankylosing spondylitis;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>64.</td><td>ETORICOXIB

(Please refer Attachment 6)</td></tr></table></td><td>Directive No. 13 Year 2017. (Ref: BPFK/PPP/07/25 (18) Jld.1.)
Direktif Untuk Semua Produk Farmaseutikal Yang Mengandungi Etoricoxib : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Perubahan Dos Permulaan Bagi Rawatan Rheumatoid Arthritis Dan Ankylosing Spondylitis</td></tr>
<tr><td>7.</td><td>September 2017</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td><u>Addition</u> of the following <u>safety information/ statements</u> (as highlighted in yellow) for products containing Loperamide regarding the risk of serious adverse effect on the heart due to the use of higher than recommended dose and misuse;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>100.</td><td>LOPERAMIDE

(Please refer Attachment 7)</td></tr></table></td><td>Directive No. 14 Year 2017. (Ref: BPFK/PPP/07/25 (19) Jld.1.)
Direktif Untuk Semua Produk Farmaseutikal Yang Mengandungi Loperamide : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat</td></tr>
</table>

<table>
<tr><th rowspan="2">NO.</th><th rowspan="2">REVISION</th><th colspan="2">UPDATES</th><th rowspan="2">REFERENCE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td></td><td></td><td></td><td><table><tr><td></td><td></td></tr></table></td><td>Berkaitan Risiko Kesan Advers Pada Jantung Yang Serius Susulan Pengambilan Loperamide Melebihi Dos Yang Disyorkan Dan Isu Penyalahgunaan</td></tr>
<tr><td>8.</td><td>September 2017</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td><u>Addition</u> of the following <u>substance</u> and the <u>additional information/ statements</u> regarding the risk of adverse effect due to long term use and on the elevated circulating levels of Chromogranin A (CgA);

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>143.</td><td>PROTON PUMP INHIBITORS (PPI)

(Please refer Attachment 8)</td></tr></table></td><td>(i) Directive No. 15 Year 2017. (Ref: BPFK/PPP/07/25 (20) Jld.1.) Direktif Untuk Semua Produk Yang Mengandungi Proton Pump Inhibitors (PPI) : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Elevated Circulating Levels of Chromogranin A (CgA)

(ii) Directive No. 16 Year 2017. (Ref: BPFK/PPP/07/25 (</td></tr>
</table>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
				21) Jld.1.) Direktif Untuk Semua Produk Yang Mengandungi *Proton Pump Inhibitors (PPI)* : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Risiko Kesan Advers Akibat Penggunaan Jangka Panjang
9.	September 2017	**5.2.1 : VARIATION** **16.1 : VARIATION**	**5.2.1 VARIATION** **Addition of the following category for variation;** c) For biologic products, please refer to the Malaysian Variation Guidelines for Biologics (MVGB) and Section E: 16.1.3 "Variation Application for Biologic Products" **16.1 VARIATION** **Replacement of 16.1.3 OTHER INFORMATION with 16.1.3 VARIATION APPLICATION FOR BIOLOGIC PRODUCTS and addition of the following content;**	**Directive No. 2 Year 2017. (Ref: BPFK/PPP/07/25 (7) Jld.1.)** Direktif Untuk Melaksanakan *Malaysian Variation Guideline For Biologics (MVGB)*

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			Variation application for biologics shall follow the Malaysian Variation Guidelines for Biologics (MVGB) as stated in the directive issued by Director of Pharmaceutical Services under Regulation 29, CDCR 1984; **Directive No. 2 Year 2017. Ref: BPFK/PPP/07/25(7)Jld.1:** Direktif Untuk Melaksanakan *Malaysian Variation Guideline For Biologics (MVGB)* The MVGB will serve as a main document for all variation applications. The MVG will serve as a secondary document for all administrative changes. If there are variations that are not covered in both MVGB and MVG, the PRH should determine the classification of change based on a change-specific risk assessment using the principles and examples that have been set out in the MVGB. Please refer to section 3.0 (General Considerations) of the MVGB for further details. All applications submitted either via the QUEST3+ system or manually shall be accompanied by a cover letter, of which the content of the cover letter shall be in accordance to 4.1.2 and 4.1.3 of the MVGB.	
10.	September 2017	**1.2 : CATEGORIES OF PRODUCT** **(1.2.2 : BIOLOGICS)**	**1.2.2 BIOLOGICS** **Addition of statement on Cell and Gene Therapy Products (CGTPs)** (Please refer Attachment 9)	**Directive No. 6 Year 2017. (Ref: BPFK/PPP/07/25 (11) Jld.1.)** Direktif Untuk Menguatkuasakan Penggunaan *Guidance Document And Guideline For Registration Of Cell And Gene Therapy*

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	**DETAILS**	
		APPENDIX 3 : GUIDELINES ON REGISTRATION OF BIOLOGICS **(*IMPORTANT NOTES:)*** **(*3.1.1 DEFINITIONS*)**	**<u>APPENDIX 3 : GUIDELINES ON REGISTRATION OF BIOLOGICS</u>** **a) Addition of statement below on Cell and Gene Therapy Products (CGTPs) under *<u>IMPORTANT NOTES:</u>*** 8. Although a CGTP is regulated separately under different framework, the Guidance Document dan Guidelines For Registration of Cell and Gene Therapy Products (CGTPs), December 2015 should be read in conjunction with this document because a high risk CGTP which is categorized as class II, is regulated as a biologic product. A class II cell therapy is "highly processed", used for other than normal function, is combined with non-tissue components, or is used for metabolic purposes". For further details, please refer to **Directive No. 6 Year 2017. <u>Ref: BPFK/PPP/07/25 (11) Jld.1:</u>** Direktif Untuk Menguatkuasakan Penggunaan *Guidance Document And Guideline For Registration Of Cell And Gene Therapy Products (CGTPS), December 2015* Dan *Good Tissue Practice Guideline, 2ND Edition, December 2015).* **b) Addition of Cell and Gene Therapy Products (CGTPs) under *<u>3.1.1 DEFINITIONS:</u>*** Biologics include a wide range of products such as:	*Products (CGTPS), December 2015* Dan *Good Tissue Practice Guideline, 2ND Edition, December 2015*

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			1. Vaccines 2. Blood products 3. Monoclonal antibodies (therapeutics) 4. Recombinant proteins: - Insulins - Hormones - Erythropoetins and other hematopoietic factors - Cytokines: interferons, interleukins, colony-stimulating factors, tumour necrosis factors 5. Cell and Gene Therapy Products (CGTPs)	
11.	September 2017	**APPENDIX 3 : GUIDELINES ON REGISTRATION OF BIOLOGICS** **(*IMPORTANT NOTES:)***	**Amendment of the following statement;** 4. Every biologic is regulated as a new product and also considered 'high risk'**, ~~it must~~ both drug substance and drug product production** must comply to Good Manufacturing Practice strictly. Adoption of GMP as an essential tool of Quality Assurance System.	**Policy Meeting No. 01 Year 2017**
12.	September 2017	**SECTION D : INSPECTION & LICENSING**	**a) Amendments to Section 12.2 MANAGING CHANGES OF MANUFACTURERS FACILITY such as;** (i) Addition of tables on 'Immediate Notification', 'Periodical Notification' and documents required. (ii) Processing fee for layout application under 'Immediate Notification'.	**Policy Meeting No. 01 Year 2017**

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			b) Other amendments include information pertaining to recent guidelines, license applications, GMP certificate, etc. (Please refer Attachment 10)	
13.	September 2017	**3.3 : HOW TO APPLY** **APPENDIX 1: FEES (1.1 CHARGES FOR USB TOKEN OF QUEST MEMBERSHIP)**	**3.3 HOW TO APPLY** **Amendment of the following statement;** To conduct transactions via QUEST system, the applicant must first register a membership for QUEST system with NPRA and purchase a USB Token that contains a User Digital Certificate, from ~~Digicert Sdn. Bhd.~~ MSC Trustgate.com Sdn. Bhd., which shall be installed to the applicant's computer. For details, please refer to Frequently Asked Questions on QUEST System. **APPENDIX 1: FEES** **Amendment of fees under Appendix 1;** **1.1 CHARGES FOR USB TOKEN OF QUEST MEMBERSHIP** (Please refer Attachment 11)	**NPRA website:** http://npra.moh.gov.my/ FAQ (QUEST3+ system)

<table>
<tr><th rowspan="2">NO.</th><th rowspan="2">REVISION</th><th colspan="2">UPDATES</th><th rowspan="2">REFERENCE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>14.</td><td>September 2017</td><td>4.1 : FEES IMPOSED

APPENDIX 1: FEES
(1.4 Charges for Amendments to Particulars of a Registered Product;
1.5 Fee for Certificates;
1.6 Charges for Product Classification)</td><td>Amendment and addition of charges under Appendix 1;

Please refer to Appendix 1: Fees for fees imposed, which include:

a) Charges for USB Token of QUEST Membership;
b) Processing and Analysis Fee for Product Registration;
c) Charges for Application of Licence;
d) Charges for Amendments to Particulars of a Registered Product;
e) Fee for Certificates; and
f) Charges for Product Classification

(Please refer Attachment 12)</td><td>Circular Ref: (40)dlm.BPFK/PPP/01/03 Jld.3

Makluman Pelaksanaan Yuran Bagi Perkhidmatan Yang Dijalankan Oleh Biro Pengawalan Farmaseutikal Kebangsaan (BPFK) Kementerian Kesihatan Malaysia (KKM)</td></tr>
<tr><td>15.</td><td>September 2017</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td>a) Amendment of list for Berberine alkaloids (merging of substance no. 24 with no. 101) in Table 4: List Of Substances Which Requires Specific Labeling Requirements;

<table><tr><th>NO.</th><th>SUBSTANCES</th></tr><tr><td>~~24.~~</td><td>~~HERBAL CONTAINING NATURAL OCCURING BERBERINE (EXCEPT ALL SPP FROM GENUS BERBERIS WHICH IS BANNED)~~</td></tr></table></td><td>Memo from Complementary & Alternative Medicine Section, Ref: (82)dlm.BPFK/PPP/06/17 Jld.96</td></tr>
</table>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	

	BERBERINE ALKALOIDS – NATURAL OCCURING BERBERINE E.G. HYDRASTIS CANADENSIS (GOLDENSEAL), COPTIS CHINENSIS (COPTIS OR GOLDENTHREAD), FIBRAUREA CHLOROLEUCA ETC.
~~110.~~	~~NATURAL OCCURING BERBERINE ALKALOIDS IN PLANTS OTHER THAN GENUS BERBERIS (E.G. HYDRASTIS CANADENSIS (GOLDENSEAL), COPTIS CHINENSIS (COPTIS OR GOLDENTHREAD), FIBRAUREA CHLOROLEUCA ETC.)~~

b) Deletion of column in Table 5: Details of Specific Labelling Requirements (same labelling requirement is available in column no. 24);

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
~~110.~~	~~**NATURAL OCCURING BERBERINE ALKALOIDS IN PLANTS OTHER THAN GENUS BERBERIS (E.G. HYDRATIS CANADENSIS, COPTIS CHINENSIS, FIBRAUREA CHLOROLEUCA ETC)**~~ ~~The following warning shall be included in the label of~~

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			~~the product:~~ ~~**Warning:**~~ ~~**1. Not to be taken by babies, children under 12 years of age, pregnant women or lactating mothers.**~~ ~~**2. Consult your practitioner if you have conditions such as:**~~ ~~**- Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency**~~ ~~**- Haemolytic anemia**~~ ~~**- Glaucoma**~~ ~~**- Diabetes**~~ ~~**- High blood pressure**~~ ~~**- History of cardiovascular disease or**~~ ~~**- If you are using paclitaxel, cyclosporin or other chemotherapeutic agents.**~~ ~~***Reference :*** *Circular: Bil.(22)dlm.BPFK/PPP/06/12 Jld.26. Kawalan produk mengandungi bahan aktif yang mempunyai berberine secara semulajadi.*~~	

<table>
<tr><th rowspan="2">NO.</th><th rowspan="2">REVISION</th><th colspan="2">UPDATES</th><th rowspan="2">REFERENCE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>16.</td><td>September 2017</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td><u>Addition</u> of the following <u>substance</u> and the <u>warning statement</u>;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>155.</td><td>SALICYLIC ACID (NATURALLY OCCURING IN PLANTS E.G. WILLOW SALIX SPP)

Please state: “Individual allergic to aspirin/ other NSAID should avoid this product.”</td></tr></table></td><td>Drug Evaluation Committee Meeting No. 15/2017

(Memo from Complementary & Alternative Medicine Section, Ref: (82)dlm.BPFK/PPP/06/17 Jld.96)</td></tr>
<tr><td>17.</td><td>September 2017</td><td>APPENDIX 5 : GUIDELINE ON REGISTRATION OF NATURAL PRODUCT

(SECTION 2.7.4 : PROHIBITED VISUAL/ GRAPHIC/ STATEMENT ON PACKAGING MATERIAL (LABEL, BOX, PACKAGE</td><td><u>Deletion</u> of of the following statement in Table 12:

<table><tr><th>No.</th><th>Subject Matter</th><th>Example(s)</th><th>Notes</th></tr><tr><td>20.</td><td>Statement on sugars in traditional products</td><td>Example:
<s>- This product contains no sugar</s>
- This product contains no added sugar</td><td>Allowable on product label provided the product contains no fructose, glucose, sucrose or other kind of sugars with a potential to affect diabetics are not included in the formulation.</td></tr></table></td><td>Memo from Complementary & Alternative Medicine Section, Ref: (82)dlm.BPFK/PPP/06/17 Jld.96</td></tr>
</table>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
		INSERT OR CONSUMER MEDICATION INFORMATION LEAFLET))		
18.	September 2017	**5.2.1 : VARIATION**	**5.2.1 VARIATION** **Amendment of the following statement for variation;** b) For health supplement and natural product, ~~there are two (2) types of variation, which are Variation Type I and Variation Type II. For details, please refer to Section E: 16.1 Variation.~~ there are three (3) types of variation, which are Major Variation (MaV), Minor Variation Prior Approval (MiV-PA) and Minor Variation Notification (MiV-N). For details, please refer Malaysian Variation Guideline (MVG) For Natural (Traditional Medicine & Homeopathy) And Health Supplement Products (Abridged Evaluation) No change of any particulars of a registered product (except for Minor Variation Notification ~~for pharmaceutical products~~) shall be made without prior approval from NPRA. The registration of a product shall be reviewed for suspension or cancellation if changes are made without prior approval of the Authority.	**Directive No. 14 Year 2016. Ref: BPFK/PPP/07/25(45):** Direktif Untuk Melaksanakan *Malaysian Variation Guideline (MVG) For Natural (Traditional Medicine & Homeopathy) And Health Supplement Products (Abridged Evaluation*) **(**Memo from Complementary & Alternative Medicine Section, Ref: (82)dlm.BPFK/PPP/06/17 Jld.96)

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
		16.1.2 : VARIATION APPLICATION FOR HEALTH SUPPLEMENT AND NATURAL PRODUCTS	**16.1.2 VARIATION APPLICATION FOR HEALTH SUPPLEMENT AND NATURAL PRODUCTS** **Replacement of Variation Type I and Variation Type II with the following content;** Variation application for Health Supplement Products and Natural Products shall follow Malaysian Variation Guideline (MVG) For Natural (Traditional Medicine & Homeopathy) And Health Supplement Products (Abridged Evaluation) as stated in the directive issued by Director of Pharmaceutical Services under Regulation 29, CDCR 1984; **Directive No. 14 Year 2016. Ref: BPFK/PPP/07/25(45):** Direktif Untuk Melaksanakan *Malaysian Variation Guideline (MVG) For Natural (Traditional Medicine & Homeopathy) And Health Supplement Products (Abridged Evaluation*) 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 NPRA. The registration of a product shall be reviewed for suspension or cancellation if changes are implemented without prior approval of the Authority. All supporting documents in accordance to the specified conditions laid down for each type of variation should be submitted. For further information pertaining to conditions and supporting documents required for an application of variation, please refer toMalaysian Variation Guideline (MVG) For Natural (Traditional Medicine & Homeopathy) And Health Supplement Products (Abridged Evaluation).	

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			If deemed necessary, NPRA reserves the right to request for additional supporting documents and variation approval letters from other regulatory bodies for all categories of products. **MODE OF SUBMISSION** Applicant shall submit the variation application through the current online system. (Please refer Attachment 13)	
19.	September 2017	**16.2 : CHANGE OF MANUFACTURING SITE** **(16.2.4 : MODE OF SUBMISSION)**	**Replacement of manual submission for Change of Site (COS) with the following content;** **16.2.4 MODE OF SUBMISSION** ~~a) Complete application for COS with supporting documents shall be submitted manually to the respective Sections in Center for Product Registration, NPRA.~~ ~~b) For submission of COS Type II to Type V, applicant can download Form BPFK 415.3 from NPRA's website http://npra.moh.gov.my/ under Industry - Forms. Submission of completed application form with supporting documents shall be made together with processing fees, according to category of product, as stipulated in the form.~~	Memo from Complementary & Alternative Medicine Section, Ref: (82)dlm.BPFK/PPP/06/17 Jld.96

<table>
<tr><th rowspan="2">NO.</th><th rowspan="2">REVISION</th><th colspan="2">UPDATES</th><th rowspan="2">REFERENCE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td></td><td></td><td></td><td>Applicant shall submit the application through the current online system.</td><td></td></tr>
<tr><td>20.</td><td>September 2017</td><td>APPENDIX 5 : GUIDELINE ON REGISTRATION OF NATURAL PRODUCT

(SECTION 2.7.2 : SPECIFIC LABELING REQUIREMENT STATEMENTS/ WARNING & PRECAUTIONS)</td><td>Deletion of the following warning statements for product containing Red Yeast Rice;

<table><tr><th>~~No.~~</th><th>~~Substance~~</th><th>~~Specific cautionary statement~~</th></tr><tr><td>~~5.~~</td><td>~~For product containing Red Yeast Rice, please state:~~</td><td>~~“This product contains naturally occurring lovastatin. Please consult your doctor/ pharmacist before using this product.”~~

~~“Do not take this product if you are already on statin products (lovastatin, atorvastatin, fluvastatin, prasvastatin, simvastatin, rosuvastatin, etc).~~

~~“If you experience any allergic reactions or side effects such as lethargy, body and muscle aches, please stop using this product”~~

~~“Concurrent use of fibrates may cause severe myositis and myoglobinuria.”~~</td></tr></table>
All products containing Red Yeast Rice should refer to the warning statements as stated in Appendix 9, Section 9.2 Specific</td><td>Memo from Complementary & Alternative Medicine Section, Ref: (82)dlm.BPFK/PPP/06/17 Jld.96</td></tr>
</table>

<table>
<tr><th rowspan="2">NO.</th><th rowspan="2">REVISION</th><th colspan="2">UPDATES</th><th rowspan="2">REFERENCE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td></td><td></td><td></td><td>Labeling Requirement, Table 5: Details of specific labeling requirements.</td><td></td></tr>
<tr><td>21.</td><td>September 2017</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td><u>Addition</u> of the following <u>substance</u> and the <u>warning statement</u>;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>148.</td><td>RED YEAST RICE (Monascus purpureus)

“This product contains naturally occurring lovastatin. Please consult your doctor/ pharmacist before using this product.”

“Do not take this product if you are already on statin products (lovastatin, atorvastatin, fluvastatin, prasvastatin, simvastatin, rosuvastatin, etc).

“If you experience any allergic reactions or side effects such as lethargy, body and muscle aches, please stop using this product”

“Concurrent use of fibrates may cause severe myositis and myoglobinuria.”</td></tr></table></td><td>Memo from Complementary & Alternative Medicine Section, Ref: (82)dlm.BPFK/PPP/06/17 Jld.96</td></tr>
</table>

<table>
<tr><th rowspan="2">NO.</th><th rowspan="2">REVISION</th><th colspan="2">UPDATES</th><th rowspan="2">REFERENCE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>22.</td><td>September 2017</td><td>APPENDIX 5 : GUIDELINE ON REGISTRATION OF NATURAL PRODUCT

(SECTION 2.1.3 : PROHIBITED / BANNED INGREDIENT)</td><td>
a) <u>Deletion</u> of Cannabis sativa and Cannabis indica in Table 5: Ingredients (Botanicals and substance derived from animals) which are banned due to safety reasons;
<table>
<tr><th>Genus</th><th>Species</th><th>Part of Plant/ Animal Prohibited

(Whole plant/ animal unless otherwise specified)</th><th>Constituent of Concern Reason for Prohibition</th><th>Reasons for Prohibition</th></tr>
<tr><td rowspan="2">~~Cannabis~~</td><td>~~sativa~~</td><td rowspan="2"></td><td rowspan="2">~~Cannabinoids~~</td><td rowspan="2">~~- Potential abuse~~
~~- Psychoactive on CNS~~
~~- Prolonged heavy use may lead to tolerance and psychological dependence.~~</td></tr>
<tr><td>~~indica~~</td></tr>
</table>
b) <u>Addition</u> of Cannabis in Table 1: Botanicals (and botanical ingredients) containing scheduled poisons as listed under the Poison Act 1952;
</td><td>Drug Evaluation Committee Meeting No. 16/2017

(Memo from Complementary & Alternative Medicine Section, Ref: (82)dlm.BPFK/PPP/06/17 Jld.96)</td></tr>
</table>

<table>
<tr><th rowspan="2">NO.</th><th rowspan="2">REVISION</th><th colspan="2">UPDATES</th><th rowspan="2">REFERENCE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><th>Genus</th><th>Species</th><th>Common/ Local Name</th><th>Part of Plant/ Animal Prohibited

(Whole plant/ animal unless otherwise specified)</th><th>Constituent of Concern Reason for Prohibition</th></tr>
<tr><td>Cannabis

(controlled under Dangerous Drug Act 1952)</td><td>All species</td><td>Marijuana</td><td></td><td>Cannabinoids</td></tr>
</table>
</td><td></td></tr>
</table>

Attachment 1

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
38.	**CHLORHEXIDINE** The following statements shall be included in the package insert, label and RiMUP of pharmaceutical products containing Chlorhexidine: **Package Insert** **a) Warnings and Precautions:** [Product Name] contains chlorhexidine. Chlorhexidine is known to induce hypersensitivity, including generalised allergic reactions and anaphylactic shock. The prevalence of chlorhexidine hypersensitivity is unknown, but available literature suggests this is likely to be very rare. [Product Name] should not be administered to anyone with a possible history of an allergic reaction to chlorhexidine. If any signs or symptoms of a suspected hypersensitivity reaction such as itching, skin rash, redness, swelling, breathing difficulties, light headedness, and rapid heart rate develop, immediately stop using the product. Appropriate therapeutic countermeasures must be instituted as clinically indicated. **b) Undesirable Effects/Side Effects:** Immune system disorders Frequency not known: Hypersensitivity including anaphylactic shock **Label and Consumer Medication Information Leaflet (RiMUP)** [Product Name] contains chlorhexidine. Inform your healthcare provider if you have a known allergy to chlorhexidine. Stop using this product and seek immediate medical assistance if you experience rash, itching, swelling, breathing difficulties, light-headedness or rapid heartbeat. **Reference : Directive No. 8 Year 2017. Ref. BPFK/PPP/07/25 (13) Jld 1.** Direktif Untuk Semua Produk Farmaseutikal Yang Mengandungi Chlorhexidine : Pengemaskinian Sisip Bungkusan, Label Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Reaksi Hipersensitiviti

Attachment 2

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
48.	**CORTICOSTEROID (INHALATION)** The following statements shall be included in the package insert and RiMUP of inhaled corticosteriod used for treatment of Chronic Obstructive Pulmonary Disease (COPD) such as **budesonide** and **fluticasone** (product containing single active ingredient and in combination) and **beclomethasone** (only for combination product): **Package Insert** **a) Special Warnings and Precautions for Use:** Pneumonia in patients with COPD An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies. There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products. Physicians should remain vigilant for the possible development of pneumonia in patient with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD include current smoking status, older age, low body mass index (BMI) and severe COPD. **b) Undesirable Effects:** "Pneumonia (in COPD patients)" to be listed as "Common" adverse drug reaction in the "Infections and Infestations" SOC. **Consumer Medication Information Leaflet (RiMUP)** **a) Possible Side Effects** Pneumonia (infection of the lung) in COPD patients (common side effect) • Tell your doctor if you have any of the following while taking <product name> they could be symptoms of a lung infection: - Fever or chills;

	- Increased mucus production or change in mucus colour; - Increased cough or increased breathing difficulties. **Reference : Directive No. 9 Year 2017. Ref. BPFK/PPP/07/25 (14) Jld 1.** Direktif Untuk Semua Produk Inhalasi Kortikosteroid Yang Digunakan Untuk Rawatan *Chronic Obstructive Pulmonary Disease (COPD)* : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Tambahan Berkenaan Peningkatan Risiko *Pneumonia*

Attachment 3

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
108.	**MICONAZOLE** **1. Intravaginal preparations** The following boxed warning shall be included on the label and in the package insert of intravaginal preparations containing Miconazole: Sila dapatkan nasihat doktor atau ahli farmasi sebelum menggunakan keluaran ini jika anda mengambil ubat warfarin, iaitu sejenis ubat antipembekuan darah, kerana lebam/ pendarahan pada gusi/ hidung boleh berlaku secara spontan. (Please consult your physician/ pharmacist before using this product if you are on the anticoagulant medicine warfarin, because bleeding from nose/ gums or bruising may accur spontaneously). **Reference:** Circular (bil 45) dlm bpfkweb.bpkp.2.2001: Keputusan Mesyuarat Pihak berkuasa Kawalan Dadah (PBKD) ke 122 Berhubung Amaran Berkaitan Interaksi Ubat Bagi Semua Keluaran ANTIFUNGAL INTRAVAGINAL Yang Mengandungi Miconazole **2. Oral gel preparations** The following statements shall be included in the package insert and RiMUP of oral gel preparations containing Miconazole: **Package Insert** **a) Contraindications** Use of miconazole oral gel in combination with the following drug that is subjected to metabolism by CYP2C9 (see Interactions): • Warfarin **b) Interactions** Miconazole can inhibit the metabolism of drugs metabolized by the CYP2C9 enzyme system. This can result in an increase and/or prolongation of their effects, including adverse effects. Miconazole oral gel is contraindicated with the co-administration of the following drug that is subjected to metabolism by CYP2C9 (see Contraindications): • Warfarin

Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]

When you must not use it

Do not use [product name] if you are on warfarin therapy.

3. Preparations other than oral gel

The following statements shall be included in the package insert and RiMUP of preparations (other than oral gel) containing Miconazole:

Package Insert

a) Warnings and Special Precautions

In patients on warfarin, caution should be exercised and the anticoagulant effect should be monitored (see Interactions).

b) Interactions

Miconazole administered systemically is known to inhibit CYP2C9 enzyme system. Due to the limited systemic availability after topical application, clinically relevant interactions occur very rarely. In patients on warfarin which is subjected to metabolism by CYP2C9, caution should be exercised and the anticoagulant effect should be monitored (see Warnings and Special Precautions).

Consumer Medication Information Leaflet (RiMUP)

a) Before You Use [Product Name]

Before you start to use it

You must tell your doctor if you:

- are on warfarin therapy

Reference : Directive No. 10 Year 2017. Ref. BPFK/PPP/07/25 (15) Jld 1. Direktif Untuk Semua Produk Yang Mengandungi Miconazole : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat

Attachment 4

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
96.	**LEVONORGESTREL** The following statements shall be included in the package insert, label and RiMUP of emergency contraceptives containing Levonorgesteral: **Package Insert** **a) Recommended Dose:** Women who have used enzyme-inducing drugs during the last 4 weeks and need emergency contraception are recommended to use a non-hormonal emergency contraceptive, i.e. Cu-IUD or take a double dose of levonorgestrel (i.e. <number of> tablets taken together) for those women unable or unwilling to use Cu-IUD. **b) Interaction of Other Medicaments:** The metabolism of levonorgestrel is enhanced by concomitant use of liver enzyme inducers, mainly CYP3A4 enzyme inducers. Concomitant administration of efavirenz has been found to reduce plasma levels of levonorgestrel (AUC) by around 50%. Drugs suspected of having similar capacity to reduce plasma levels of levonorgestrel include barbiturates, phenytoin, carbamazepine, herbal medicines containing Hypericum perforatum (St. John's wort), rifampicin, ritonavir, and griseofulvin. For women who have used enzyme-inducing drugs in the past 4 weeks and need emergency contraception, the use of non-hormonal emergency contraception (i.e. a Cu-IUD) should be considered. Taking a double dose of levonorgestrel (i.e. 3 mg within 72 hours after the unprotected intercourse) is an option for women who are unable or unwilling to use a Cu-IUD, although this specific combination (a double dose of levonorgestrel during concomitant use of an enzyme inducer) has not been studied. **Label** *If you have used certain **other medicines in the last 4 weeks**, in particular treatment for epilepsy, tuberculosis, for HIV infection or herbal medicines containing St. John´s wort (see leaflet), <product name> may work less effectively. If you use these medicines take <number of>tablets of <product name>. If you are unsure or to ask for an alternative treatment speak to your doctor or pharmacist before using <product name>.*

Consumer Medication Information Leaflet (RiMUP)

a) Before you use <product name>

-Taking other medicines

If you have used any of the medicines below during the last 4 weeks, <product name> may work less effectively.Your doctor may prescribe another type of (non-hormonal) emergency contraceptive, i.e. a copper intrauterine device (Cu-IUD). If this is not an option for you or if you are unable to see your doctor promptly, you can take a double dose (i.e. <number of> tablets) of <product name>:

- medicines used to treat epilepsy (e.g. phenobarbitone, phenytoin, carbamazepine)
- medicines used to treat tuberculosis (e.g. rifampicin)
- medicines used to treat HIV (e.g. ritonavir, efavirenz)
- medicines used to treat fungal infections (e.g. griseofulvin)
- herbal remedies containing St. John's wort (Hypericum perforatum)

Speak to your doctor or pharmacist if you need further advice on the correct dose for you.

Consult your doctor as soon as possible after taking the tablets for further advice on a reliable form of regular contraception and to exclude a pregnancy.

Reference : Directive No. 11 Year 2017. Ref. BPFK/PPP/07/25 (16) Jld 1. Direktif Untuk Semua Produk Kontraseptif Kecemasan Yang Mengandungi Levonorgestrel Dengan Maklumat Berkaitan Interaksi Antara Ubat-Ubatan Yang Dikelaskan Sebagai *Hepatic Enzyme Inducer* Dan Keberkesanan Kontrasepsi

Attachment 5

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
181.	**WARFARIN** a) The following statements shall be included in the package insert of products containing Warfarin: **Caution** Topical preparations containing methyl salicylate should be used with care in patients on **Warfarin** and excessive usage is to be avoided as potentially dangerous drug interaction can occur. **Contraindications** Co-administration with miconazole oral gel (see Interactions). **Special Warnings and Precautions for Use**: • Calciphylaxis is a rare syndrome of vascular calcification with cutaneous necrosis, associated with high mortality. The condition is mainly observed in patients with end-stage renal disease on dialysis or in patients with known risk factors such as protein C or S deficiency, hyperphosphatemia, hypercalcaemia or hypoalbuminaemia. Rare cases of calciphylaxis have been reported in patients taking warfarin, also in the absence of renal disease. In case calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin. • Co-administration with topical miconazole (see Interactions). **Interactions** The following drugs have been reported to potentiate the warfarin effect (increase INR): • Miconazole **Adverse Drug Reactions**: Skin and subcutaneous tissue disorders Frequency 'not known': Calciphylaxis

b) The following statements shall be included in the RiMUP of products containing Warfarin:

Possible Side Effects:

Tell your doctor straight away if you have any of the following side effects :

[...]

A painful skin rash. On rare occasions warfarin can cause serious skin conditions, including one called calciphylaxis that can start with a painful skin rash but can lead to other serious complications. This adverse reaction occurs more frequently in patients with chronic kidney disease.

Before You Use [Product Name]

When you must not use it

Do not take [product name] together with miconazole oral gel

Before you start to use it

Some commonly used medicines and products that may interfere with [product name] include:

- *Miconazole*

Reference :

1. **Directive No. 15 Year 2016. Rujukan BPFK/PPP/07/25 (1) Jld 1.** DIREKTIF BAGI SEMUA PRODUK YANG MENGANDUNGI WARFARIN DENGAN RISIKO KESAN ADVERS CALCIPHYLAXIS
2. **Directive No. 12 Year 2017. Ref. BPFK/PPP/07/25 (17) Jld 1.** Direktif Untuk Semua Produk Yang Mengandungi Warfarin : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat

Attachment 6

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
64.	**ETORICOXIB** (Please also refer to COX-2 INHIBITORS) The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing Etoricoxib: **Package Insert** **Dosage and Administration:** Rheumatoid arthritis The recommended dose is 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60 mg once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered. Ankylosing spondylitis The recommended dose is 60 mg once daily. In some patients with insufficient relief from symptoms, an increased dose of 90 mg once daily may increase efficacy. Once the patient is clinically stabilised, down-titration to a 60 mg once daily dose may be appropriate. In the absence of an increase in therapeutic benefit, other therapeutic options should be considered. **Consumer Medication Information Leaflet (RiMUP)** **Recommended Dose/How Much to Use** Rheumatoid arthritis The recommended dose is 60 mg once a day, and may increase to 90 mg once a day if needed. Ankylosing spondylitis The recommended dose is 60 mg once a day, and may increase to 90 mg once a day if needed. **Reference : Directive No. 13 Year 2017. Ref. BPFK/PPP/07/25 (18) Jld 1.** Direktif Untuk Semua Produk Farmaseutikal Yang Mengandungi Etoricoxib : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Perubahan Dos Permulaan Bagi Rawatan Rheumatoid Arthritis Dan Ankylosing Spondylitis

Attachment 7

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
100.	**LOPERAMIDE** 1. The following boxed warning shall be included on the label of products containing Loperamide: **NOT RECOMMENDED FOR CHILDREN UNDER 6 YEARS OF AGE** 2. The following statement shall be included in the package insert of products containing Loperamide: **a) WARNING** Not recommended for children under 6 years of age. Its use has been associated with fatal episodes of paralytic ileus in infants and young children. Appropriate fluid and electrolyte therapy should be given to protect against dehydration in all cases of diarrhoea. Oral rehydration therapy which is the use of appropriate fluids including oral rehydration salts remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative. Drug-induced inhibition of peristalsis may result in fluid retention in the intestine, which may aggravate and mask dehydration and depletion of electrolytes. If severe dehydration or electrolyte imbalance is present Loperamide should be withheld until appropriate corrective therapy has been initiated. **c) Warnings and Precautions** The use of higher than the recommended doses for control of the diarrhea may cause abnormal heart rhythms and serious cardiac events leading to death. However, in adult patients receiving the recommended dosage of loperamide, cases of syncope and ventricular tachycardia have been reported. Some of these patients were taking other drugs or had other risk factors that may have increased their risk of cardiac adverse reactions. Abuse and misuse of loperamide, as an opioid substitute, have been described in individuals with opioid addiction (see Overdose). **d) Adverse Reactions** Post-marketing Experience

Cardiac Disorders: QT/QTc interval prolongation, Torsades de Pointes, other ventricular arrhythmias, cardiac arrest, syncope, and death (see Warnings and Precautions).

e) Overdose

In individuals who have intentionally ingested overdoses (reported in doses from 40 mg up to 792 mg per day) of loperamide HCl, prolongation of the QT/QTc interval, Torsades de Pointes, other ventricular arrhythmias and cardiac arrest, have been observed (see Warnings and Precautions). Fatal cases have also been reported.

3. The following statement shall be included in the RiMUP of products containing Loperamide:

a) If you use too much (overdose)

If you have taken more than the recommended dose of [product name], immediately contact your doctor or go to the Emergency Department of your nearest hospital for advice.

Symptoms may include :

- changes to your heartbeat such as increased heart rate and irregular heart rhythm (these symptoms can have potentially serious, life-threatening consequences)
- muscle stiffness
- uncoordinated movements
- drowsiness
- difficulty urinating
- weak breathing

Reference : Directive No. 14 Year 2017. Ref. BPFK/PPP/07/25 (19) Jld 1. Direktif Untuk Semua Produk Farmaseutikal Yang Mengandungi Loperamide : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Risiko Kesan Advers Pada Jantung Yang Serius Susulan Pengambilan Loperamide Melebihi Dos Yang Disyorkan Dan Isu Penyalahgunaan

Attachment 8

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
143.	**PROTON PUMP INHIBITORS (PPI)** **(Products containing Pantoprazole, Omeprazole, Lansoprazole, Esomeprazole, Rabeprazole, Dexlansoprazole)** The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing Proton Pump Inhitors (PPI): **Package Insert** **1. Warnings and Precautions:** Regular Surveillance Patients on proton pump inhibitor treatment (particularly those treated for long term) should be kept under regular surveillance. Subacute Cutaneous Lupus Erythematosus (SCLE) Proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus (SCLE). If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping {product name}. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors. Hypomagnesaemia Severe hypomagnesaemia has been reported in patients treated with PPI like {product name} for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPI with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment. Fracture Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%.

Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Clostridium Difficile Diarrhea
Published observational studies suggest that PPI therapy may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Vitamin B12 Deficiency
Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

2. Undesirable Effects/Side Effects:

Subacute Cutaneous Lupus Erythematosus (SCLE)
Skin and subcutaneous tissue disorders
Frequency 'not known': Subacute cutaneous lupus erythematosus

Interstitial Nephritis
Renal and urinary disorders: Interstitial nephritis

Hypomagnesaemia
Metabolism and nutritional disorders
Frequency “not known”: hypomagnesaemia.

Fracture
Musculoskeletal disorders
Frequency “uncommon”: Fracture of the hip, wrist or spine.

Clostridium Difficile Diarrhea
Infections & infestations: Clostridium difficile associated diarrhea.

Fundic Gland Polyps (Benign)
Gastrointestinal disorders
Frequency “common”: Fundic gland polyps (benign)

Vitamin B12 Deficiency
Metabolic/Nutritional: Vitamin B12 deficiency

3. Warnings & Precautions - Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. If the patient(s) are due to have a test on Chromogranin A level, [product name] treatment should be stopped for at least 5 days before CgA measurements to avoid this interference (see section Pharmacodynamic). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

4. Pharmacodynamic

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours.

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

Consumer Medication Information Leaflet (RiMUP)

i. Side Effects:

When you are taking this medicine, your doctor will want to monitor you (especially if you are taking it for long term). Hence, you should report any new and exceptional symptoms and circumstances whenever you see your doctor. Please tell your doctor promptly if you get any of the symptoms below:

- Rash (especially in areas exposed to the sun), possibly with pain in the joints.(Subacute Cutaneous Lupus Erythematosus, SCLE)
- Fever, extreme tiredness, pus/blood in urine.
- Involuntary muscle contractions, disorientation, convulsions, dizziness, increased heart rate
- Fracture in the hip, wrist or spine.
- Watery stool, stomach pain and fever that do not go away
- Anemic (pale skin, weakness, tiredness or lightheadedness), shortness of breath, a smooth tongue, nerver problems (numbness or tingling, muscle weakness and problems walking), vision loss and mental problems (depression, memory loss or behavioral changes).

a) Subacute Cutaneous Lupus Erythematosus (SCLE)

Frequency “not known”

b) Interstitial Nephritis
Kidney problems (interstitial nephritis)

c) Hypomagnesaemia
Frequency “not known”: Low levels of magnesium can also lead to a reduction in potassium or calcium levels in the blood.

d) Fracture
Frequency “uncommon”: Tell your doctor if you have osteoporosis or if you are taking corticosteroids (which can ncrease the risk of osteoporosis).

e) Clostridium Difficile Diarrhea
Severe diarrhoea which may be caused by an infection (Clostridium difficile) in your intestines.

f) Fundic Gland Polyps (Benign)
Frequency “Common”: Benign polyps in the stomach

g) Vitamin B12 Deficiency
Proton pump inhibitors may cause vitamin B12 deficiency.

ii. Before you start to use it

Tell your doctor before taking this medicine, if you are due to have a specific blood test (Chromogranin A).

Reference :

1. **Directive No. 16 Year 2017. Ref. BPFK/PPP/07/25 (21) Jld 1.** Direktif Untuk Semua Produk Yang Mengandungi *Proton Pump Inhibitors (PPI)* : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Risiko Kesan Advers Akibat Penggunaan Jangka Panjang
(no. 1, 2, i)
2. **Directive No. 15 Year 2017. Ref. BPFK/PPP/07/25 (20) Jld 1.** Direktif Untuk Semua Produk Yang Mengandungi *Proton Pump Inhibitors (PPI)* : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan *Elevated Circulating Levels of Chromogranin A (CgA)*
(no. 3, 4, ii)

Attachment 9

1.2 CATEGORIES OF PRODUCT

1.2.2 BIOLOGICS

1. Definition:

The term 'biopharmaceutical' was coined in the 80's to define proteins that were made by recombinant DNA technology [which includes hybridoma technology for monoclonal antibody (mAb) production].

1.1 Biologic/ Biological product refers to a product whose active substance is made by or derived from a living organism (plant, human, animal or microorganism) and may be produced by biotechnology methods and other cutting-edge technologies. This product imitates natural biological substances in our bodies such as hormones, enzymes or antibodies.

1.2 Biological substance is defined as a substance that is produced by or extracted from a biological source and that needs, for its characterization and the determination of its **quality**, a combination of physicochemical-biological testing together with the production process and its controls.

1.3 Biopharmaceuticals/ Biologics/ Biological products can also be defined as:

"a protein (including antibodies) or nucleic acid-based pharmaceuticals used for therapeutic, which is produced by means other than direct extraction from a native (non-engineered) biological source". This corresponds to the new biotechnology view (that is, by elimination, it is largely restricted to recombinant/ genetically engineered and mAb-based products).

1.4 The term 'Biotechnology product' and 'Biological product' are used to broadly refer to all biopharmaceuticals (by the broad biotechnology view).

Note:
Today, biologics have become inextricably intertwined with biopharmaceuticals, to the point where they are synonymous. The general consensus is that the term 'Biologic' and 'Biopharmaceutical' are interchangeable.

Biologics include a wide range of products such as: vaccines, blood products, monoclonal antibodies (therapeutics), recombinant proteins (including but not limited to insulins, hormones, erythropoetins and other hematopoietic factors), cytokines

(including but not limited to interferons, interleukins, colony-stimulating factors, tumour necrosis factors), cell and gene therapy products (CGTPs).

But does **not** include:

- Metabolites from microorganisms; e.g. antibiotics and some hormones;
- Macromolecules produced by chemical synthesis; e.g. peptides/ oligo-nucleotides produced by chemical synthesis;
- Whole blood or cellular blood components.

~~For details, please refer Appendix 3: Guideline on Registration of Biologics and Guideline on Registration for Biosimilars in Malaysia~~

2. For detail on registration of Biologics products, please refer Appendix 3: Guideline on Registration of Biologics.

Note: *This document is not intended to apply on the control of genetically modified live organisms designed to be used directly in humans, e.g. live vaccines*

3. Unlike small-molecule generic drugs, exact copies of biologics are impossible to produce because these are large and highly complex molecules produced in living cells. A 'biosimilar' medicinal product (a short designation for 'similar biological medicinal product') is considered as a new biological medicinal product developed to be similar in terms of quality, safety and efficacy to an already registered, well established, medicinal product. For details, please refer to Guideline on Registration for Biosimilars in Malaysia.

4. Cell and gene therapy products (CGTPs) is regulated as Biologic products. Unlike biotechnology products which are mostly purified proteins of cells, CGTPs contain living and functional cells. Therefore, CGTP is regulated under a separate framework. For details, please refer to: Guidance Document and Guidelines For Registration of Cell and Gene Therapy Products (CGTPs). This document provides information for manufacturers, applicants, healthcare professionals and the general public on legal arrangements in Malaysia for the registration of CGTPs. The implementation of the guideline will be compulsory on **1 January 2021** as stated in the **Directive No. 6 Year 2017. Ref: BPFK/PPP/07/25 (11) Jld.1:** Direktif Untuk Menguatkuasakan Penggunaan *Guidance Document And Guideline For Registration Of Cell And Gene Therapy Products (CGTPS), December 2015* Dan *Good Tissue Practice Guideline, 2ND Edition, December 2015).*

Attachment 10

SECTION D: INSPECTION & LICENSING

Inspection and licensing of manufacturing premises or facilities, importers and wholesalers of registered products or notified cosmetics on the basis of compliance with Good Manufacturing Practice (GMP) as well as Good Distribution Practice (GDP) are vital element of drug control. Compliance to GMP ~~is a~~ and GDP are prerequisite for the application of a manufacturing license as well as product registration or cosmetic notification whereas compliance to GDP is a prerequisite for the application of a wholesale license or import license.

12. INSPECTION

Inspection of GMP and GDP are conducted to ensure manufacturers', importers' and wholesalers' compliance towards the current GMP and GDP requirements besides ensuring the registered products and notified cosmetics that are put in the market are safe, efficacious and of quality.

The related GMP and GDP guidelines referred are as below in **Table XIII:**

Guidelines	Product Type/ Category
PIC/S Guide to Good Manufacturing Practice for Medicinal Products *	• Pharmaceuticals (Poison and Non-Poison) • Veterinary Medicinal Products • Investigational Medicinal Products • Active Pharmaceutical Ingredients
GMP Guideline for Traditional Medicines and Health Supplements, 1st Edition, 2008	• Traditional Products • Health Supplements
Guidelines on Good Manufacturing Practice (GMP) for Cosmetic (Annex 1, ~~Part 9~~ Part 10)	• Cosmetics
Guidelines on Good Manufacturing Practice (GMP) for Veterinary Premixes, 1st Edition, January 2015	• Veterinary ~~Premixes~~ Products
Guidelines on Good Distribution Practice (GDP); 2nd Edition, 2013	• For activities related to the storage and distribution by manufacturers, importers and wholesalers (where

Supplementary Notes For Management Of Cold Chain Products/ Materials Chapter 15 Guidelines On Good Distribution Practice (GDP)	applicable)

** Refer to Pharmaceutical Inspection Co-operation Scheme (PIC/S) website at www.picscheme.org*

Additional Information:

1. For manufacturing activity via campaign basis for carbapenem and monobactam product in area or manufacturing facility for cephalosporin product, please refer circular;
   - ~~Ref.~~ (1)dlm.BPFK/30/06/2 Bhgn 2, ~~Surat Pekeliling Berhubung Kebenaran Mengilangkan Keluaran-keluaran Carbapenem dan Monobactam dalam Fasiliti Pengilangan Keluaran-keluaran Cephalosporin (23 May 2013).~~

2. ~~For the requirement on Head of Production for pharmaceutical, radiopharmaceutical and veterinary manufacturer, please refer directives;~~
   - ~~Ref. (8)dlm.BPFK/PPP/07/25 Directive No. 2 Year 2014. Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 2 Tahun 2014 : Keperluan Ahli Farmasi Berdaftar Sepenuh Masa Untuk Mengetuai Bahagian Pengeluaran Premis Pengilang Produk Farmaseutikal, Radiofarmaseutikal, dan Veterinar Yang Berdaftar Dengan Pihak Berkuasa Kawalan Dadah (PBKD).~~
   - ~~Ref. (26)dlm.BPFK/PPP/07/25 Directive No. 2 Year 2015. Arahan Pengarah Kanan Perkhidmatan Farmasi Bil 2 Tahun 2015 : Keperluan Ahli Farmasi Berdaftar Sepenuh Masa Untuk Mengetuai Bahagian Pengeluaran Premis Pengilang Produk Farmaseutikal, Radiofarmaseutikal, dan Veterinar Yang Berdaftar Dengan Pihak Berkuasa Kawalan Dadah (PBKD) : Perlanjutan Tarikh Perlaksanaan.~~

   Please refer (8)dlm.BPFK/PPP/07/25 Directive No. 2 Year 2014 for the requirement on Head of Production for pharmaceutical, radiopharmaceutical and veterinary manufacturer.

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~~ be taken into consideration before the products are registered with the

Authority. NPRA as the secretariat to the DCA is responsible ~~to ensure~~ for ensuring 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 further details and forms, please refer to Guidance Document on Foreign GMP Inspection.

12.2 MANAGING CHANGES OF MANUFACTURERS, ~~IMPORTERS & WHOLESALERS~~ FACILITY

This section only focuses on changes of manufacturing and its storage / warehouse ~~facility changes~~ facilities. Changes on products particulars should be addressed under the Section E of Post Registration Process whereby it discusses on Amendments to Particular of a Registered Products.

Changes at ~~manufacturers, importers and wholesalers~~ manufacturers' facility can potentially have quality and safety impact. It is the responsibility of the site to assess information on the changes occurs through a formal change control system and risk management, where applicable. Manufacturers are recommended to have a system for categorizing types of changes. All changes to the manufacturing facility are required to ~~notify~~ be notified to the Centre for Compliance and Licensing (CCL) prior to implementation ~~of changes.~~

Notification of changes will be reviewed to assess the significance and it may be verified during scheduled GMP~~/GDP~~ inspection. The CCL will communicate further and arrange for an investigative/for-cause inspection focusing on these changes, if deemed necessary.

Additional Information:

1. **This section is applicable to local manufacturer only. Read further on change of importer or wholesaler particulars under Section E of Post Registration Process.**

2. **For further details, please refer to Table of Example Immediate and Periodical Notification.**

Types of notification are as follow:

12.2.1 Immediate Notification

This notification is applicable to ~~manufacturers, importers and wholesalers that~~ manufacturers who plan/undergo a major/significant/substantial change that could have an impact on the product quality and safety. The Immediate Notification shall be made ~~in writing~~ to or approved by the Centre for Compliance and Licensing (CCL) ~~for the purpose of approval and at least 6 months before the implementation of changes~~ prior to implementation. ~~The following information is needed:~~ The Immediate Notification can be submitted as follows:

~~a) Description of changes to the facility~~
~~b) Plan of changes (For example: Gantt Chart, Validation Master Plan, etc)~~
~~c) Details of the products affected, where applicable~~
~~d) Information on variation category, where applicable (e.g.: Major/Minor Variation)~~
~~e) Registration of Company Certificate (ROC), where applicable~~

~~Normally, proposed changes of local manufacturing facility may require a layout plan approval from CCL by completing 'Borang Permohonan Penilaian Pelan Susun Atur Premis Pengilang, BPFK-503. Example of changes that require immediate notification (these are non-exhaustive examples):~~

~~a) Change of manufacturing site of drug product / drug substance~~
~~b) Change of warehouse facility / alternative warehouse facility/ addition of warehouse facility (e.g. Cold room)~~
~~c) Major change of manufacturing process~~
~~d) Major renovation or introduction of new / addition to the facility (e.g: new processing line / new production block / addition of utility system)~~
~~e) Addition of repacking facility~~
~~f) Introduction of highly potent, sensitizing active substances or biological active substances to the site~~

a) Completing 'Borang Permohonan Penilaian Pelan Susun Atur Premis Pengilang, BPFK-503 for changes related to manufacturing layout and process flow

OR

b) Official writing which may include at least information such as;
- Description of changes to the facility
- Plan of changes (For example: Gantt Chart, Validation Master Plan, etc)
- Details of the products affected, where applicable

Types of changes are listed in Table A. **Example of Immediate Notification**

12.2.2 Periodical Notification

This notification is applicable to ~~manufacturer, importer and wholesaler that~~ manufacturer that plan/undergo a minor change that would not give any impact to the product quality and safety. ~~The notification shall also be made in writing to Centre for Compliance & Licensing with the information of changes. The notification details will be verified during GMP/GDP inspection or by documentation review, where necessary. Where applicable, proposed changes of local manufacturing facility may require a layout plan approval from CCL by completing 'Borang Permohonan Penilaian Pelan Susun Atur Premis Pengilang, BPFK-503.~~ The Periodical Notification can be submitted in the form of official writing which may include at least information such as;

- Description of changes
- Plan of changes (For example: Gantt Chart, Validation Master Plan, etc)

Example of changes that require Periodical Notification ~~(Below are non-exhaustive examples):~~ are as per **Table B. Example of Periodical Notification**

~~a) Change of manufacturing rooms (rename / relocate manufacturing rooms)~~
~~b) Addition of facility that does not give any impact to the existing site (e.g.: Addition of sampling room / QC / Office)~~
~~c) Change of key personnel (e.g.: QA/QC Manager, Production Pharmacist)~~
~~d) Minor change of manufacturing process~~
~~e) Addition of manufacturing equipments (e.g.: new capsulation / tableting machine)~~
~~f) Change of company name or address (e.g.: street name, postal code)~~

Table A. Example of Immediate Notification

Items	Example	Description	Requirement of BPFK-503	Type of Application under BPFK-503	Documentation Required	Remarks (If any)
1.	Change of manufacturing site (including drug substance if any)	Require submission of new layout plan	YES	New premise layout (Processing Fee= RM1000.00)	As per BPFK-503 requirement	
2.	Change of warehouse facility	Addition of new warehouse or alternative warehouse which affecting overall manufacturing / operation process e.g. addition of sampling room, cold room, new warehouse block	YES	New premise layout (Processing Fee= RM1000.00) OR Revision of existing premise layout or addition new warehouse in the same licensed premise	As per BPFK-503 requirement	

				Processing Fee= RM500.00)		
3.	**Change of equipment or manufacturing process**	**a. Applicable for changes of critical equipment**	**NO**	**NOT APPLICABLE**	**Notification to CCL, NPRA**	**Please refer further to Section E** **Verification of information by GMP inspection if necessary.**
		b. Change of critical step in manufacturing (including packaging) process	**NO**	**NOT APPLICABLE**	**Notification to CCL , NPRA**	
4.	**Major renovation or introduction of new line**	**a. Addition of new manufacturing and/or packaging line**	**YES**	**Revision of existing premise layout (Processing Fee=**	**As per BPFK-503 requirement**	

				RM500.00)		
		b. New production block	**YES**	**Revision of existing premise layout or addition new production block in the same licensed premise layout** **(Processing Fee= RM500.00)**	**As per BPFK-503 requirement**	**Verification of information by GMP inspection if necessary.**
		c. Change or addition of critical utility such as water system, pharmaceutical gases and HVAC	**NO**	**NOT APPLICABLE**	**Notification to CCL, NPRA**	
5.	**Change of manufacturing**	**Rename or relocate of manufacturing rooms without**	**YES**	**Revision of existing**	**As per BPFK-503**	

	rooms	**affecting process flow** **E.g. Tabletting Room to Compression Room**		**premise layout** **(Processing Fee= RM500.00)**	**requirement**	

Table B. Example of Periodical Notification

Items	**Example**	**Description**	**Requirement of BPFK-503**	**Type of Application under BPFK-503**	**Documentation Required**	**Remarks (If any)**
1.	**Change of or addition of QC facility**	**E.g. Retention sample, microbiological laboratory, stability chamber, etc.**	**NO**	**NOT APPLICABLE**	**Notification to CCL, NPRA**	**Verification of information by GMP inspection if necessary.**
2.	**Change of key personnel**	**Applicable to QA/QC Manager, Head of Production, Production Pharmacist**	**NO**	**NOT APPLICABLE**	**Notification to CCL**	**May involve information for manufacturing license holder**
3.	**Addition of manufacturing equipments without affecting existing**	**New capsulation or tabletting machine in the available room**	**NO**	**NOT APPLICABLE**	**Notification to CCL**	**Verification of information by GMP inspection if necessary.**

	manufacturing layout plan					
4.	**Change of company name or address**	**Change of building number, postal code, street name etc.**	**NO**	**NOT APPLICABLE**	**Notification to CCL**	**Please refer further to Section E** **May involve information for manufacturing license**

13. LICENSING

According to the Control of Drugs and Cosmetics Regulations 1984, any company that wants to manufacture, import or wholesale any registered products need to have a valid Manufacturer's License, Import License or Wholesaler's License.

13.1 TYPES OF LICENSES

Table XIV:

Type of Licenses	Activity
Manufacturer's License	~~Licensed Premises is allowed to: Manufacture registered products and to sell by wholesale or supply their products~~ Licensee is authorized to manufacture the registered products in the premises specified in the license and to sell by wholesale or supply the products
Import License	~~Licensed Premises is allowed to: Import and sell by wholesale or supply registered products~~ Licensee is authorized to import and sell by wholesale or supply the registered products from the address of the premises
Wholesaler's License	~~Licensed Premises is allowed to: Sell by wholesale or supply registered products~~ Licensee is authorized to sell by wholesale or supply the registered products from the address of the business premises specified in the license

13.2 LICENSE APPLICATION FORM

1. The license application for registered products (Manufacturer's License, Import License and Wholesaler's License) shall be submitted by filling Borang BPFK-413 Application for License for Registered Product.

2. The application form must be submitted with the following supporting documents.

~~a) Company's Organization Chart~~
~~b) Location Map of Premise~~
~~c) Layout Plan of Premise~~
~~d) List of Storage Equipments~~
~~e) Details of other products (Non-medicinal) stored at the same premise~~

a) A copy of Company/ Business Registration Certificate
~~f)~~ b) A copy of Business License (Local Authority) for business premise or store (if any)
~~g)~~ c) A copy of Applicant's/License Holder's Identity Card
~~h)~~ d) A copy of Annual Retention Certificate and/or Type A License (This document is necessary if products manufactured/ imported/ wholesale are Scheduled Poison A products or any other products that require a Pharmacist)
~~i)~~ e) A copy of previous license (For renewal application)

3. An application shall only be processed if it is complete and payment has been approved.

4. The processing fee shall not be refundable. The processing fee of an application for a Manufacturer's License is RM 1,000.00 and RM 500.00 for an Import License or a Wholesaler's License.

5. Each license is valid for **one (1) year.**

13.3 ADDITIONAL PRODUCT LIST OF LICENSE FOR REGISTERED PRODUCTS

1. Additional product list of License is issued based on the application submitted when the products are newly registered, change of manufacturer or importer or any registered ~~left out~~ products which are not listed from the products list of Manufacturer's License and Import License.

2. When submitting the application form for Additional Product List of License for Registered Products the documents that shall be attached together are a copy of Manufacturer's License/ Import License and a copy of approval letter from the Authority (The Authority's meeting result).

3. The application of additional list shall be submitted by filling Borang BPFK-413T Application for (Additional) Product List of License for Registered Product.

13.4 GMP CERTIFICATE

1. GMP Certificate is issued for the purpose of exporting locally manufactured registered products. It endorses that the local manufacturer complies with the current GMP requirements. These certificate are required by the overseas regulatory agencies for products registration in their countries. Thus, when filling in the GMP Certificate application form, the correct address of the overseas regulatory agencies given by the company is crucial.

2. The application of GMP Certificate shall be ~~submitted by filling~~ submitted online through QUEST3+ which is equivalent to the manual form Borang BPFK-420 *Permohonan Sijil Amalan Perkilangan Baik (APB)* *that is no longer in used.*

3. A fee of RM50.00 is payable on the issue of such certification.

Attachment 11

1.1 CHARGES FOR USB TOKEN OF QUEST MEMBERSHIP

~~Application category~~	~~Charges~~
~~First-time User~~	~~Package A~~ ~~(USB Token of 2-years validity + Guide Manual) : COST RM335~~ ~~Package B~~ ~~(USB Token of 1-year validity + Guide Manual) : COST RM320~~
~~Supplementary User~~	~~Package A~~ ~~(USB Token of 2-years validity + Guide Manual) : COST RM335~~ ~~Package B~~ ~~(USB Token of 1-year validity + Guide Manual) : COST RM320~~
~~Renewal of USB token~~	~~Package C1~~ ~~(New USB Token of 2-years validity) : COST RM280~~ ~~Package C2~~ ~~(Utilized old USB Token of 2-years validity) : COST RM100~~

	Validity Period	
	1 Year	2 Years
Main User – New, Replacement, Change Authorized Person (Certificate + USB Token)	RM 260.00	RM 290.00
Supplementary User – New, Replacement, Change Authorized Person (Certificate + USB Token)	RM 245.00	RM 275.00
Change Authorized Person (Certificate Only)	RM 58.00	RM 105.00
Postage (Semenanjung Malaysia)	RM 10.00	
Postage (Sabah/Sarawak)	RM 20.00	

Attachment 12

1.4 CHARGES FOR AMENDMENTS TO PARTICULARS OF A REGISTERED PRODUCT

Types of Amendment	Processing fee	
	Pharmaceutical	Natural Product
1. Change of Manufacturing Site (Type I)	RM 1,000.00	RM 100.00
2. Change of Manufacturing Site (Type II, III, IV, V)	RM 1,000.00	RM 500.00
3. Change of Product Registration Holder	RM 1,000.00	RM 500.00
4. Minor Variation Prior Approval (MiV-PA)	RM 150.00	RM 50.00
5. Major Variation (MaV)	RM 300.00	RM 100.00
6. Additional Indication	RM 1000.00	Not applicable

1.5 FEE FOR CERTIFICATES

Under the CDCR 1984, Regulation 16: *"The Director of Pharmaceutical Services may issue such certification on any matter relating to any product where such certification is required by any country importing such a product."*

Certificates	Fee	Validity
Issuance of one (1) Certificate of Pharmaceutical Product	RM 50.00	2 years

Issuance of one (1) Certificate of Good Manufacturing Practice (GMP)	RM 50.00	2 years
Issuance of one (1) Certificate of Declaration *(Sijil Deklarasi)*	RM 50.00	-
Issuance of one (1) Certificate of Indication *(Sijil Indikasi)*	RM 50.00	-

1.6 CHARGES FOR PRODUCT CLASSIFICATION

Category of Products	Processing fee	Timeline
• Food-Drug Interphase (FDI) • Medical Device-Drug-Cosmetic Interphase (MDDCI) • Pharmaceutical products • Health supplements and natural products	RM 300.00	7-14 working days upon receipt of complete application

Attachment 13

16.1.2 VARIATION APPLICATION FOR HEALTH SUPPLEMENT AND NATURAL 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 NPRA. The registration of a product shall be~~ **~~reviewed for suspension or cancellation~~** ~~if changes are implemented without prior approval of the Authority.~~

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

~~Table XVI:~~

~~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/ Consumer Medication Information Leaflet (RiMUP)/ 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~~
~~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~~

No.	Variation	
	Type I: Minor change	Type II: Major change
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)
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

No.	Variation	
	Type I: Minor change	Type II: Major change
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 variation 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, NPRA reserves the right to request for additional supporting documents and variation approval letters from other regulatory bodies for all categories of products.

The applicant shall provide to NPRA 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.

Variation application for Health Supplement Products and Natural Products shall follow Malaysian Variation Guideline (MVG) as stated in the directive issued by Director of Pharmaceutical Services under Regulation 29, CDCR 1984; **Directive No. 14 Year 2016. Ref: BPFK/PPP/07/25(45):** Direktif Untuk Melaksanakan *Malaysian Variation Guideline (MVG) For Natural (Traditional Medicine & Homeopathy) And Health Supplement Products (Abridged Evaluation*)

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 NPRA. The registration of a product shall be reviewed for suspension or cancellation if changes are implemented without prior approval of the Authority.

All supporting documents in accordance to the specified conditions laid down for each type of variation should be submitted. For further information pertaining to conditions and supporting documents required for an application of variation, please refer toMalaysian Variation Guideline (MVG) For Natural (Traditional Medicine & Homeopathy) And Health Supplement Products (Abridged Evaluation).

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

MODE OF SUBMISSION

~~**Table XVII:**~~

~~No~~	~~Variation~~	~~QUEST 2 & QUEST 3 Products~~
~~1.~~	~~Type I~~	~~Applicant shall submit application for Variation Type I and/ or Type II **manually** to the respective Sections in Center for Product Registration. For manual submission, applicant can download Form BPFK 416.4 from NPRA's website http://npra.moh.gov.my/ .~~ ~~Online submission for QUEST 2 products shall only proceed after all the documents are finalized through the correspondence email.~~ ~~All updates for QUEST 3 products will be done by the NPRA IT department.~~
~~2.~~	~~Type II~~	

Applicant shall submit the variation application through the current online system.