LIST OF UPDATES FOR DRGD SECOND EDITION, SEPTEMBER 2016, REVISED JANUARY 2018

<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>January 2018</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 serious adverse effects on heart and cardiovascular patients;

<table>
<tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
<tr><td>90.</td><td>HYOSCINE (FOR INJECTION ONLY)

(Please refer Attachment 1)</td></tr>
</table>
</td>
<td>Directive No. 17 Year 2017. (Ref: BPFK/PPP/07/25 (22) Jld.1.)
Direktif Untuk Semua Produk Yang Mengandungi Hyoscine (Bentuk Dos Injeksi Sahaja) : Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers Serius Pada Pesakit Jantung Dan Kardiovaskular</td>
</tr>
<tr>
<td>2.</td>
<td>January 2018</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 information/ statements</u> on the increased risk of hepatotoxicity in patients with Cockayne Syndrome;

<table>
<tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
<tr><td>113.</td><td>METRONIDAZOLE (ALL PRODUCTS EXCEPT FOR EXTERNAL USE)

(Please refer Attachment 2)</td></tr>
</table>
</td>
<td>Directive No. 18 Year 2017. (Ref: BPFK/PPP/07/25 (23) Jld.1.)
Direktif Untuk Semua Produk Yang Mengandungi Metronidazole (Kecuali Produk Untuk Kegunaan Luar) : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna</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>(RiMUP) Dengan Amaran Berkaitan Risiko Hepatotoxicity Dalam Kalangan Pesakit Cockyne Syndrome</td></tr>
<tr><td>3.</td><td>January 2018</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> on the adverse effects due to misuse and dependency;
<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>177.</td><td>TESTOSTERONE

(Please refer Attachment 3)</td></tr></table></td><td>Directive No. 19 Year 2017. (Ref: BPFK/PPP/07/25 (24) Jld.1.)
Direktif Untuk Semua Produk Yang Mengandungi Testosteron : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Kesan Advers Susulan Penyalahgunaan Dan Kebergantungan 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>January 2018</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td><u>Addition</u> of the following <u>substance</u> and <u>information/ statements</u> on the limitation of use in children and <u>warning information/ statements</u> for use in pregnancy and lactation;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>183.</td><td>TRAMADOL

(Please refer Attachment 4)</td></tr></table></td><td>Directive No. 20 Year 2017. (Ref: BPFK/PPP/07/25 (25) Jld.1.)
Direktif Untuk Semua Produk Yang Mengandungi Tramadol Dengan Maklumat Bagi Mengehadkan Penggunaan Tramadol Dalam Kalangan Kanak-Kanak Dan Amaran Berkaitan Penggunaan Dalam Kalangan Ibu Mengandung Dan Ibu Menyusu</td></tr>
<tr><td>5.</td><td>January 2018</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) on the adverse effects on pathological gambling and impulse-control problems;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>16.</td><td>ARIPIPRAZOLE

(Please refer Attachment 5)</td></tr></table></td><td>Directive No. 22 Year 2017. (Ref: BPFK/PPP/07/25 (77) Jld.1.)
Direktif Untuk Semua Produk Yang Mengandungi Aripripazole : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Kesan Advers Pathological Gambling</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>Dan Impulse-Control Problems</td></tr>
<tr><td>6.</td><td>January 2018</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 drug interactions with products containing opioid;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>22.</td><td>BENZODIAZEPINE

(Please refer Attachment 6)</td></tr></table></td><td>Directive No. 23 Year 2017. (Ref: BPFK/PPP/07/25 (28) Jld.1.)
Direktif Untuk Semua Produk Yang Mengandungi Opioid Dan Benzodiazepin : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat</td></tr>
<tr><td>7.</td><td>January 2018</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;

(i) drug interactions with products containing benzodiazepine,
(ii) adverse event Serotonin Syndrome due to interaction with Serotonergic Drugs and adverse events Adrenal Insufficiency and Androgen Insufficiency due to long term use of opioids.</td><td>Directive No. 23 Year 2017. (Ref: BPFK/PPP/07/25 (28) Jld.1.)
Direktif Untuk Semua Produk Yang Mengandungi Opioid Dan Benzodiazepin : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan</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>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
<tr><td>130.</td><td>OPIOID

(Please refer Attachment 7)</td></tr>
</table></td><td>Interaksi Ubat

Directive No.27 Year 2017. (Ref: BPFK/PPP/07/25 (32) Jld.1.)
Direktif Untuk Semua Produk Yang Mengandungi Opioid : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers Serotonin Syndrome Kesan Daripada Interaksi Dengan Serotonergic Drugs Dan Risiko Kesan Advers Adrenal Insufficiency Dan Androgen Deficiency Akibat Penggunaan Jangka Panjang</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>8.</td>
<td>January 2018</td>
<td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td>
<td><u>Addition</u> of the following <u>information/ statements</u> (as highlighted in yellow);
<table>
<tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
<tr><td>47.</td><td>CODEINE
Please also refer to OPIOID.</td></tr>
<tr><td>183.</td><td>TRAMADOL
Please also refer to OPIOID.</td></tr>
<tr><td>9.</td><td>ALPRAZOLAM
Please refer to SEDATIVE – HYPNOTIC PRODUCTS and BENZODIAZEPINE.</td></tr>
<tr><td>28.</td><td>BROMAZEPAM
Please refer to SEDATIVE – HYPNOTIC PRODUCTS and BENZODIAZEPINE.</td></tr>
<tr><td>44.</td><td>CLOBAZAM
Please refer to SEDATIVE – HYPNOTIC PRODUCTS and BENZODIAZEPINE.</td></tr>
<tr><td>56.</td><td>DIAZEPAM
Please refer to SEDATIVE – HYPNOTIC PRODUCTS and BENZODIAZEPINE.</td></tr>
</table></td>
<td>Directive No. 23 Year 2017. (Ref: BPFK/PPP/07/25 (28) Jld.1.)
Direktif Untuk Semua Produk Yang Mengandungi Opioid Dan Benzodiazepin : 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></td><td></td><td></td><td><table>
<tr><td>105.</td><td>LORAZEPAM
Please refer to SEDATIVE – HYPNOTIC PRODUCTS and BENZODIAZEPINE.</td></tr>
<tr><td>115.</td><td>MIDAZOLAM
Please also refer to BENZODIAZEPINE.</td></tr>
<tr><td>123.</td><td>NITRAZEPAM
Please refer to SEDATIVE – HYPNOTIC PRODUCTS and BENZODIAZEPINE.</td></tr>
<tr><td>185.</td><td>TRIAZOLAM
Please refer to SEDATIVE – HYPNOTIC PRODUCTS and BENZODIAZEPINE.</td></tr>
</table></td><td></td></tr>
<tr><td>9.</td><td>January 2018</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> on the risk of spontaneous abortion, on multiple congenital abnormalities and use in lactation;

<table>
<tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
<tr><td>71.</td><td>FLUCONAZOLE

(Please refer Attachment 8)</td></tr>
</table></td><td>Directive No. 24 Year 2017. (Ref: BPFK/PPP/07/25 (29) Jld.1.)
Direktif Untuk Semua Produk Yang Mengandungi Fluconazole : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Baharu Berkaitan Risiko</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>Spontaneous Abortion Serta Memperkukuhkan Maklumat Keselamatan Berkaitan Multiple Congenital Abnormalities Dan Penggunaan Dalam Kalangan Ibu Menyusu</td></tr>
<tr><td>10.</td><td>January 2018</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td><u>Addition</u> of the following <u>substance</u> and <u>information/ statements</u> regarding the use in patients with moderately reduced kidney function and <u>warning information/ statements on lactic acidosis</u>;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>109.</td><td>METFORMIN

(Please refer Attachment 9)</td></tr></table></td><td>Directive No. 25 Year 2017. (Ref: BPFK/PPP/07/25 (30) Jld.1.) Direktif Untuk Semua Produk Yang Mengandungi Metformin : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Penggunaan Dalam Kalangan Pesakit Yang Mempunyai Moderately Reduced Kidney Function Dan Pengukuhan Amaran Lactic Acidosis</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>11.</td><td>January 2018</td><td>APPENDIX 8 : LIST OF PERMITTED, PROHIBITED AND RESTRICTED SUBSTANCES

8.2 : LIST OF PROHIBITED AND RESTRICTED EXCIPIENTS</td><td><u>Amendment</u> of the following <u>restriction</u> for <u>menthol</u>;

<table>
<tr><th colspan="2">8.2.2 LIST OF <u>RESTRICTED EXCIPIENTS</u></th></tr>
<tr><th>Excipients</th><th>Restrictions</th></tr>
<tr><td colspan="2">2. Sweeteners/ Flavouring Agent</td></tr>
<tr><td>a) Menthol</td><td><s>Limited to not more than 10mg/day</s>

0.4mg/kg body weight/day (dosage and use in children should be clearly stated).</td></tr>
<tr><td>b) Saccharin and Salts</td><td>Limited to not more than 5mg/kg/day</td></tr>
<tr><td>c) Cyclamates</td><td>Limited to not more than 1.5mg/kg body weight/day</td></tr>
</table>
</td><td>Directive No. 26 Year 2017. (Ref: BPFK/PPP/07/25 (31) Jld.1.)
Direktif Pindaan Had Harian Pengambilan Menthol Dalam Persediaan Oral</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>12.</td>
<td>January 2018</td>
<td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td>
<td><u>Addition</u> of the following <u>warning information/ statements</u> (as highlighted in yellow) regarding risk of Infantile Hypertrophic Pyloric Stenosis (IHPS);

<table>
<tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
<tr><td>20.</td><td>AZITHROMYCIN

(Please refer Attachment 10)</td></tr>
</table>
</td>
<td>Directive No. 28 Year 2017. (Ref: BPFK/PPP/07/25 (33) Jld.1.)
Direktif Untuk Semua Produk Yang Mengandungi Bahan Aktif Azithromycin Dan Erythromycin Kecuali Persediaan Topikal/Eksternal Dan Ubat Untuk Kegunaan Mata : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan Risiko Infantile Hypertrophic Pyloric Stenosis (IHPS)</td>
</tr>
<tr>
<td>13.</td>
<td>January 2018</td>
<td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td>
<td><u>Addition</u> of the following substance and <u>warning information/ statements</u> regarding risk of Infantile Hypertrophic Pyloric Stenosis (IHPS);

<table>
<tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
</table>
</td>
<td>Directive No. 28 Year 2017. (Ref: BPFK/PPP/07/25 (33) Jld.1.)
Direktif Untuk Semua Produk Yang Mengandungi Bahan Aktif Azithromycin Dan Erythromycin Kecuali Persediaan Topikal/Eksternal Dan Ubat Untuk Kegunaan</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>64.</td><td>ERYTHROMYCIN

(Please refer Attachment 11)</td></tr></table></td><td>Mata : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan Risiko Infantile Hypertrophic Pyloric Stenosis (IHPS)</td></tr>
<tr><td>14.</td><td>January 2018</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td><u>Addition</u> of the following <u>information/ statements</u> (as highlighted in yellow) on Immune-mediated Necrotizing Myopathy (IMNM);<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>170.</td><td>STATINS

(Please refer Attachment 12)</td></tr></table></td><td>Directive No. 29 Year 2017. (Ref: BPFK/PPP/07/25 (34) Jld.1.)
Direktif Untuk Semua Produk Yang Mengandungi Statin : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Immune-Mediated Necrotizing Myopathy (IMNM)</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>15.</td><td>January 2018</td><td>APPENDIX 1: FEES

1.1 CHARGES FOR USB TOKEN OF QUEST MEMBERSHIP</td><td><u>APPENDIX 1: FEES</u>

Amendment of fees under Appendix 1;

1.1 CHARGES FOR USB TOKEN OF QUEST MEMBERSHIP

(Please refer Attachment 13)</td><td>NPRA website:
http://npra.moh.gov.my/

FAQ (QUEST3+ system)</td></tr>
<tr><td>16.</td><td>January 2018</td><td>APPENDIX 1: FEES

1.6 CHARGES FOR PRODUCT CLASSIFICATION</td><td>Amendment as below;

<table><tr><th>~~Category of Products~~</th><th>Processing fee</th><th>Timeline</th></tr><tr><td>• ~~Food-Drug Interphase (FDI)~~

• ~~Medical Device-Drug-Cosmetic Interphase (MDDCI)~~

• ~~Pharmaceutical products~~

• ~~Health supplements and natural products~~</td><td>RM 300 per product for each application</td><td>7-14 working days upon receipt of complete and satisfactory application</td></tr></table></td><td></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>17.</td><td>January 2018</td><td>1.3 FOOD - DRUG INTERPHASE PRODUCTS</td><td>Amendment as in Attachment 14 (as highlighted in yellow).</td><td>FDI COMMITTEE MEETING BIL 02/17</td></tr>
<tr><td>18.</td><td>January 2018</td><td><s>1.3.6</s> 1.3.31 NEGATIVE LIST FOR <s>FOOD</s> FDI</td><td><u>Addition</u> of the following 15 ingredients:
<table>
<tr><th>No.</th><th>Ingredient</th><th>Common/Other name</th></tr>
<tr><td>1</td><td>Antiaris toxicaria (Pers.) Lesch.</td><td>Bark cloth tree, antiaris, false iroko, false mvule, upas tree</td></tr>
<tr><td>2</td><td>Aspidosperma Quebracho-Blanco Schltdl.</td><td>Kebrako, White Quebracho</td></tr>
<tr><td>3</td><td>Atropa Spp. (all species)</td><td>Antropa belladonna (deadly nightshade)</td></tr>
<tr><td>4</td><td>Calotropis Spp. (all species)</td><td>Apple of Sodom, Crown flower</td></tr>
<tr><td>5</td><td>Cannabis Spp. (all</td><td>Marijuana, Hemp</td></tr>
</table></td><td>FDI COMMITTEE MEETING BIL 02/17</td></tr>
</table>

NO.	REVISION	UPDATES			REFERENCE
		SECTION/ APPENDIX	DETAILS		
				species)	
			6	***Catharanthus Spp. (all species)***	Periwinkle
			7	***Chondodendron Spp. (all species)***	
			8	***Claviceps Spp. (all species)***	Ergot
			9	***Colchicum Spp. (all species)***	Autumn crocus, Meadow saffron, Naked lady
			10	***Dioscorea Hispida***	
			11	***Dryopteris Spp. (all species)***	Mountain woodfern, Spinulose woodfern, Spreading woodfern, Fancy fern
			12	***Euphorbia Spp. (all species)***	Spurge
			13	***Garcinia morella Desr.***	Gamboge
			14	***Hyoscyamus Spp. (all***	

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			species)	
			15 ***Rauvolfia Spp. (all species)***	
19.	January 2018	**1.3.3.2 GENERAL CLASSIFICATION FLOWCHART OF FOOD-DRUG INTERPHASE (FDI) UNDER FOOD OR DRUG**	**Addition of a new flowchart.** Please refer to Attachment 15.	FDI COMMITTEE MEETING BIL 02/17
20.	January 2018	**1.3.5 PICTORIAL GUIDE TO CLASSIFICATION OF FOOD OR DRUG ~~FOOD-DRUG INTERPHASE~~ PRODUCTS**	**Amendment to pictorial guide.** Please refer to Attachment 16.	FDI COMMITTEE MEETING BIL 02/17

<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>21.</td><td>January 2018</td><td>APPENDIX 4:
Guideline On Registration Of Health Supplements

SECTION 4.5:
Specific Dossier Requirement For Registration Of Health Supplements

TABLE 5:
List of Non-Permissible Product Name for Health Supplement Products</td><td><u>Addition</u> of word “Defence” and “Immunity”;

Existing:
Table 5 : List of Non-Permissible Product Name for Health Supplement Products
<table><tr><th>No.</th><th>Issue</th><th>Example</th></tr><tr><td>14.</td><td>Other prohibited product names</td><td>Minda, IQ, Smart, Unique, Ultra Mega, Detox</td></tr></table>
New:
<table><tr><th>No.</th><th>Issue</th><th>Example</th></tr><tr><td>14.</td><td>Other prohibited product names</td><td>Minda, IQ, Smart, Unique, Ultra Mega, Detox, Defence, Immunity</td></tr></table></td><td>Drug Evaluation Committee Meeting No. 21/2017

(Memo from Complementary & Alternative Medicine Section, Ref: (19)dlm.BPFK/PPP/06 /17 Jld.101)</td></tr>
</table>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
22.	January 2018	**APPENDIX 4:** Guideline on Registration of Health Supplements **SECTION F:** Supplementary Documents **Finished Product Quality Control (FPQC)**	**<u>Amendment</u> on the requirements of heavy metal tests (as highlighted in yellow);** **Finished Product Quality Control (FPQC)** ➢ The certificate must be complete with the product specification and result. The list of tests and specifications must be same with finished product specification document. ➢ Quality Control Test For Health Supplement Product are as follows: **1. Limit Test for Heavy Metals** a) Lead : NMT 10.0 mg/kg or 10.0 mg/litre (10.0ppm) b) Arsenic : NMT 5.0 mg/kg or 5.0 mg/litre (5.0ppm) c) Mercury : NMT 0.5 mg/kg or 0.5 mg/litre (0.5ppm) d) Cadmium : NMT 0.3 mg/kg or 0.3 mg/litre (0.3ppm) ** Required for products with ingredients from natural sources. The test shall be conducted ~~either~~ on the ~~raw material or~~ finished product.*	Memo from Complementary & Alternative Medicine Section, Ref: (19)dlm.BPFK/PPP/06/17 Jld.101

<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>23.</td>
<td>January 2018</td>
<td>APPENDIX 5:
Guideline on Registration of Natural Product

SECTION 2.7.2:
Specific labeling requirement statements/ warning & precautions</td>
<td>
<u>Removal</u> of the warning statements item (4) i.e. For product containing St John’s Wort (Hypericum perforatum).

Existing:

<table>
<tr><th>No.</th><th>Substance</th><th>Specific cautionary statement</th></tr>
<tr><td>4.</td><td>For product containing St John’s Wort (Hypericum perforatum), please state:</td><td>The product may interact with other medicines. Please consult a doctor/ pharmacist before using it.</td></tr>
</table>

New:

All products containing St John’s Wort (Hypericum perforatum) should refer to the warning statements as stated in Appendix 9, Section 9.2 Specific Labeling Requirement, Table 5: Details of specific labeling requirements.
</td>
<td>Memo from Complementary & Alternative Medicine Section, Ref: (19)dlm.BPFK/PPP/06 /17 Jld.101</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>24.</td><td>January 2018</td><td>APPENDIX 5: Guideline on Registration of Natural Product

SECTION 2.5: Quality Control</td><td>Revision of information in sub-section 2.5.1 Sample for Testing;

2.5.1 SAMPLE FOR TESTING

Sample for testing shall be submitted to the ~~Drug Analysis Division, NPRA~~ Center of Quality Control, NPRA within 14 working days ~~of payment confirmation by the NPRA.~~ from the screening approval date. Import permit will be issued after screening approval for imported products.

Applicant need to proceed for payment within 30 days once the sample is submitted.

Delay in sample submission / payment will result in rejection of the new product registration application.</td><td>Memo from Complementary & Alternative Medicine Section, Ref: (19)dlm.BPFK/PPP/06 /17 Jld.101</td></tr>
<tr><td>25.</td><td>January 2018</td><td>APPENDIX 5: Guideline on Registration of Natural Product

SECTION 2.7: Labelling Requirement</td><td><u>Insertion</u> of a tick (√) in the column of package insert under ‘Indication’.

New:

<table>
<tr><th>No.</th><th>Items</th><th>Immediate Label</th><th>Outer Label</th><th>Package Insert</th><th>Blister Pack</th></tr>
<tr><td>5.</td><td>Indication</td><td>√</td><td>√</td><td>√</td><td></td></tr>
</table>
</td><td>Memo from Complementary & Alternative Medicine Section, Ref: (19)dlm.BPFK/PPP/06 /17 Jld.101</td></tr>
</table>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
26.	January 2018	**6. GENERAL CONDITIONS FOR REGISTRATION OF DRUG PRODUCTS UNDER THE CONTROL OF DRUGS AND COSMETICS REGULATIONS 1984**	**<u>Addition</u> of a new <u>condition</u> under product registration;** **6.11 CONDITIONS PERTAINING TO PATENT** For the purpose of registration of generic products, PRH shall provide patent declarations as below: i) PRH shall comply with all legal provisions in Malaysia; ii) The government/ authority is not liable for any offence committed by the PRH as a result of any breach of any law; and iii) PRH shall indemnify the government if any claim is made against the government as a result of any breach of any law by the applicant whether intentionally or otherwise. PRH shall conform to Patent Act 1983 (Act 291) and shall not market, sell, offer for sale, or store any registered product containing any patented active ingredient(s) of which the patent duration is yet to expire.	**Drug Control Authority Meeting (DCA) No. 319** **Drug Evaluation Committee Meeting No. 01/2018**

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
27.	January 2018	**SECTION 8: FLOW OF REGISTRATION PROCESS** **8.7 REJECTED APPLICATION**	**<u>Amendment</u> on the <u>timeline</u> for appeal process (as highlighted in yellow);** **8.7 REJECTED APPLICATION** As stipulated in Regulation 18, CDCR 1984: a) Any person aggrieved by the decision of the Authority or the Director of Pharmaceutical Services, a written appeal may be made to the Minister of Health Malaysia; b) **<u>All notice of appeals</u>** shall be made **<u>within fourteen (14) days</u>** from the date of notification from the Authority; - ~~A~~ A period of ~~180~~ 60 days from the date of ~~notice of appeal~~ appeal confirmation is given for submission of any additional information/ supplementary data/ documents for ~~New Drug Products and Biologics.~~ all categories of product. ~~- A period of 90 days is allowed for other categories of product.~~ - The <u>appeal shall not be considered</u> if all the required information is not submitted within the specified timeframe given. **Any request for extension of this period shall not be considered too.** c) Any decision of the Minister made on an appeal shall be final.	**Policy Meeting No. 03 Year 2017**

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			Re-submission for product registration of a rejected application due to reason of safety and efficacy shall not be accepted within **two (2)** years after the rejection. However, if the product is registered in the reference countries, submission of application can be made earlier. **Deletion of sub-section 8.7.1 PROCESS OF APPEAL FOR QUEST 2 PRODUCT and Figure 5.** **Amendment of 8.7.2 PROCESS OF APPEAL FOR QUEST 3 PRODUCT and Figure 6** (Please refer to Attachment 17) **Amendment of 8.7.3 TEMPLATE FOR AN APPEAL LETTER** (Please refer to Attachment 17)	
28.	January 2018	**APPENDIX 5:** Guideline On Registration Of Natural Product **Appendix 5 Outline**	**Addition of sub-section 2.5.7: Certificate of Analysis (Active Ingredient) and 2.5.8: Certificate of Analysis (Finish Product) (as highlighted in yellow);** **Outline:** **2. General Requirements for Registration of Natural Products** 2.5 Quality Control	**Directive No. 3 Year 2017. (Ref: BPFK/PPP/07/25 (8) Jld.1.)** Direktif Untuk Menguatkuasakan Keperluan Sijil Analisa Produk Siap *(Certificate of Analysis (COA) For Finished Product)* Semasa Permohonan Pendaftaran Baru

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			2.5.1 Sample for Testing 2.5.2 Quality Testing for Specific Ingredient 2.5.3 Limit Test for Heavy Metals 2.5.4 Disintegration Test 2.5.5 Test for Uniformity of Weight (For Tablets and Capsules Only) 2.5.6 Tests for Microbial Contamination 2.5.7 Certificate of Analysis (Active Ingredient) 2.5.8 Certificate of Analysis (Finished Product)	Produk Semulajadi Dan Produk Suplemen Kesihatan Dengan *General Claims*
29.	January 2018	**APPENDIX 5:** Guideline On Registration Of Natural Product **SECTION 2.5:** Quality Control	**Addition of wording 'Active Ingredient' under sub-section 2.5.7: Certificate of Analysis and new description for sub-section 2.5.8: Certificate of Analysis (Finish Product) (as highlighted in yellow) together with the example of Certificate of Analysis (COA) for Finished Product;** **2.5 QUALITY CONTROL** **2.5.7 CERTIFICATE OF ANALYSIS (Active Ingredient)** Applicants will have to submit a certificate of analysis for each active ingredient used, which may be purchased from the supplier. This requirement is not applicable for raw materials that are processed in-house.	**Directive No. 3 Year 2017. (Ref: BPFK/PPP/07/25 (8) Jld.1.)** Direktif Untuk Menguatkuasakan Keperluan Sijil Analisa Produk Siap *(Certificate of Analysis (COA) For Finished Product)* Semasa Permohonan Pendaftaran Baru Produk Semulajadi Dan Produk Suplemen Kesihatan Dengan *General Claims*

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			2.5.8 CERTIFICATE OF ANALYSIS (Finished Product) Starting from 1st January 2018, **2 batches of Certificate of Analysis (COA) for Finished Product** must be submitted upon submission of new product registration for Natural Product / Health Supplement with the general claim. (Reference: Directive No.3 Year 2017, BPFK/PPP/07/25(8)Jld 1 : Direktif Untuk Menguatkuasakan Keperluan Sijil Analisa Produk Siap (Certificate of Analysis (COA) For Finished Product) Semasa Permohonan Pendaftaran Baru Produk Semulajadi dan Produk Suplemen Kesihatan Dengan General Claim) Example of Certificate of Analysis (COA) for Finished Product. (Please refer to Attachment 18)	
30.	January 2018	**APPENDIX 4:** Guideline On Registration Of Health Supplements **SECTION B: PRODUCT FORMULA**	**Addition of 'Certificate of Analysis of Finished Product' and 'Example of Certificate of Analysis (COA) for Finished Product' (as highlighted in yellow);** **SECTION B: PRODUCT FORMULA** • **Batch Manufacturing Formula** • **Manufacturing Process** • **In Process Quality Control (IPQC)**	**Directive No. 3 Year 2017. (Ref: BPFK/PPP/07/25 (8) Jld.1.)** Direktif Untuk Menguatkuasakan Keperluan Sijil Analisa Produk Siap *(Certificate of Analysis (COA) For Finished Product)* Semasa Permohonan

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			• **Finished Product Quality Specification** • **Provide details of quality control specifications including a list of tests for both release and shelf life specifications (if they are different) and state the limits of acceptance.** • **Certificate of Analysis of Finished Product** Starting from 1st January 2018, **2 batches of Certificate of Analysis (COA) for Finished Product** must be submitted upon submission of new product registration for Natural Product / Health Supplement with the general claim. (Reference: Directive No.3 Year 2017, BPFK/PPP/07/25(8)Jld 1 : Direktif Untuk Menguatkuasakan Keperluan Sijil Analisa Produk Siap (Certificate of Analysis (COA) For Finished Product) Semasa Permohonan Pendaftaran Baru Produk Semulajadi dan Produk Suplemen Kesihatan Dengan General Claim) **Example of Certificate of Analysis (COA) for Finished Product** (Please refer to Attachment 19) • **Stability Data**	Pendaftaran Baru Produk Semulajadi Dan Produk Suplemen Kesihatan Dengan *General Claims*

<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>31.</td>
<td>January 2018</td>
<td>APPENDIX 4: Guideline On Registration Of Health Supplements

ATTACHMENT 1: CHECKLIST OF DOSSIER REQUIREMENT FOR HEALTH SUPPLEMENTS</td>
<td><u>Deletion</u> of statement '* LOC to submit during post registration' at;

Table 15: Checklist for General/ Nutritional and Medium Claim
<table>
<tr><th>No.</th><th>Field</th><th>General or Nutritional Claims</th><th>Functional Claims</th></tr>
<tr><td>F10</td><td>Attachment of Certificate of finished product (COA of finished product)</td><td>√
<s>* LOC to submit during post registration</s></td><td>√</td></tr>
</table>
</td>
<td>Directive No. 3 Year 2017. (Ref: BPFK/PPP/07/25 (8) Jld.1.)
Direktif Untuk Menguatkuasakan Keperluan Sijil Analisa Produk Siap (Certificate of Analysis (COA) For Finished Product) Semasa Permohonan Pendaftaran Baru Produk Semulajadi Dan Produk Suplemen Kesihatan Dengan General Claims</td>
</tr>
<tr>
<td>32.</td>
<td>January 2018</td>
<td>(i) SECTION C: QUALITY CONTROL

(ii) APPENDIX 4: Guideline On Registration Of Health Supplements</td>
<td>Amendments as highlighted in yellow;

(i) SECTION C: QUALITY CONTROL
Please refer to Attachment 20.

(ii) SECTION B: PRODUCT FORMULA
Example of Finished Product Quality Specification
Please refer to Attachment 21.</td>
<td>Memo from Centre of Quality Control, Ref: NPRA.600-2/1/18 Bil.(1)</td>
</tr>
</table>

Attachment 1

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
90.	**HYOSCINE (FOR INJECTION ONLY)** The following statements shall be included in the package insert for products containing Hyoscine: **Package Insert** **a) Contraindications:** <Product name> should not be administered to patients with tachycardia. **b) Warnings and Precautions:** <Product name> can cause tachycardia, hypotension and anaphylaxis, therefore use with caution in patients with cardiac conditions such as cardiac failure, coronary heart disease or cardiac arrhythmia and patients with cardiovascular disease (e.g. acute myocardial infarction, hypertension and conditions associated with tachycardia or hypertension, and in cardiac surgery). Monitoring of these patients is advised. Emergency equipment and personnel trained in its use must be readily available. **c) Adverse Effects/Undesirable Effects:** Immune system disorders Not known: anaphylactic shock including cases with fatal outcome, anaphylactic reactions. Cardiac disorders Common: tachycardia **Reference : Directive No. 17 Year 2017. Ref. BPFK/PPP/07/25 (22) Jld 1.** Direktif Untuk Semua Produk Yang Mengandungi Hyoscine (Bentuk Dos Injeksi Sahaja) : Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers Serius Pada Pesakit Jantung Dan Kardiovaskular

Attachment 2

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
113.	**METRONIDAZOLE (ALL PRODUCTS EXCEPT FOR EXTERNAL USE)** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products (except for external use) containing Metronidazole; **Package Insert** **a) Warnings and Precautions:** Cases of severe hepatotoxicity/ acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued. Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole. **Consumer Medication Information Leaflet (RiMUP)** **a) Before you use <product name>:** Inform your doctor if you are affected by Cockayne syndrome. Cases of severe liver toxicity/ acute liver failure in patients with Cockayne syndrome have been reported with products containing metronidazole. Stop taking <product name> and tell your doctor immediately if you develop: stomach pain, decreased appetite, nausea, vomiting, fever, unusual tiredness, yellowing of the skin and the whites of the eyes, dark-coloured urine, light or clay-coloured stools or itching. **Reference : Directive No. 18 Year 2017. Ref. BPFK/PPP/07/25 (23) Jld 1.** Direktif Untuk Semua Produk Yang Mengandungi Metronidazole (Kecuali Produk Untuk Kegunaan Luar) :

	Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan Risiko *Hepatotoxicity* Dalam Kalangan Pesakit *Cockyne Syndrome*

Attachment 3

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
177.	**TESTOSTERONE** The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing Testosterone; **Package Insert** **a) Warnings and Precautions:** Drug Abuse and Dependence Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids (AAS). Abuse of testosterone and other AAS are seen in adults and adolescents, including athletes and body builders. Testosterone and AAS abuse can lead to serious adverse outcomes particularly cardiovascular and psychiatric adverse events (See Section Adverse Effects/Undesirable Effects). If testosterone abuse is suspected, check serum testosterone concentrations to ensure they are within therapeutic range. However, testosterone levels may be in the normal or subnormal range in men abusing synthetic testosterone derivatives. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and AAS. Conversely, consider the possibility of testosterone and AAS abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events. Continued abuse of testosterone and other AAS may result in dependence and withdrawal symptoms. Individuals taking supratherapeutic doses of testosterone may experience withdrawal symptoms lasting for weeks or months which include depressed mood, major depression, fatigue, craving, restlessness, irritability, anorexia, insomnia, decreased libido and hypogonadotropic hypogonadism. Drug dependence in individuals using approved doses of testosterone for approved indications has not been documented. **b) Overdose:** Chronic Overdose Caused by Abuse Chronic overdose caused by abuse of testosterone and other anabolic

androgenic steroids (AAS) can lead to serious adverse outcomes particularly cardiovascular and psychiatric adverse events (See Sections Warnings and Precautions and Adverse Effects/ Undesirable Effects).

c) Adverse Effects/Undesirable Effects:

Abuse-Related Adverse Reactions
Serious adverse reactions have been reported in individuals who abuse testosterone and anabolic androgenic steroids (AAS) and include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, cerebrovascular accident, hepatotoxicity, and serious psychiatric manifestations, including major depression, mania, paranoia, psychosis, delusions, hallucinations, hostility and aggression.

The following adverse reactions have also been reported in men: transient ischemic attacks, convulsions, hypomania, irritability, dyslipidaemias, testicular atrophy, subfertility, and infertility.

The following additional adverse reactions have been reported in women: hirsutism, virilisation, deepening of voice, clitoral enlargement, breast atrophy, male-pattern baldness, and menstrual irregularities.

The following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth, and precocious puberty.

Because these reactions are reported voluntarily from a population of uncertain size and may include abuse of other agents, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Consumer Medication Information Leaflet (RiMUP)

a) How to use <product name>:

If you use too much (overdose):
If you have taken more than the recommended dose of <product name>, contact your doctor immediately or go to the Emergency Department of your nearest hospital. Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention.

Taking more than the recommended dose of <product name> for a long period of time can cause serious health problems including effects on the heart, liver, and reproductive functions, as well as serious psychiatric problems.

	b) While you are using it: Things you must not do: Do not take more than the recommended dose of <product name>. Individuals who have taken more than the recommended dose for a long period of time may experience withdrawal symptoms lasting for weeks or months after abrupt discontinuation or a significant dose reduction of <product name>. These include: changes in mood and appetite, fatigue, insomnia, decreased sex drive as well as loss of function of the testes and ovaries. **Reference : Directive No. 19 Year 2017. Ref. BPFK/PPP/07/25 (24) Jld 1.** Direktif Untuk Semua Produk Yang Mengandungi Testosteron : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Kesan Advers Susulan Penyalahgunaan Dan Kebergantungan Ubat

Attachment 4

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
183.	**TRAMADOL** The following statements shall be included in the package insert and RiMUP of products containing Tramadol: **Package Insert** **a) Recommended Dosage:** Adults and adolescents (12 years and older) <Product name> is not approved for use in patients below 12 years old. Paediatric population The safety and efficacy of <product name> has not been studied in the paediatric population. Therefore, use of <product name> is not recommended in patients under 12 years of age. **b) Contraindications:** - Children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids. - Adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems. **c) Warnings and Precautions:** Paediatric population The safety and efficacy of <product name> has not been studied in the paediatric population. Therefore, use of <product name> is not recommended in patients under 12 years of age. Respiratory depression Administer <product name> cautiously in patients at risk for respiratory depression, including patients with substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression, as in these patients, even therapeutic doses of <product name> may decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered. When large doses of tramadol are

administered with anaesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures.

Cytochromes P450 (CYP) 2D6 Ultra-Rapid Metabolism

Some individuals may be CYP2D6 ultra-rapid metabolisers. These individuals convert tramadol more rapidly than other people into its more potent opioid metabolites O-desmethyltramadol (M1). This rapid conversion could result in higher than expected opioid-like side effects including life-threatening respiratory depression. The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16-28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

d) Pregnancy and Lactation:

Pregnancy

Tramadol has been shown to cross the placenta. There are no adequate and well-controlled studies in pregnant women. Safe use in pregnancy has not been established. <Product name> is not recommended for pregnant women.

Lactation

Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.

e) Adverse Effects/Undesirable Effects:

Respiratory depression (rare)

Consumer Medication Information Leaflet (RiMUP)

a) Before you use <product name>

When you must not use it:

- you are less than 12 years old.
- you have slow or shallow breathing, or other breathing problems.

	- you are pregnant. - you are breastfeeding. **b) While you are using it:** Things to be careful of: - Tramadol is not to be used during breast-feeding. Small amounts of tramadol is excreted into breast milk. On a single dose it is usually not necessary to interrupt breast-feeding. If you have taken <product name> when you are breastfeeding, seek immediate medical attention if you notice your baby has any changes in their breathing (such as weak, difficult or fast breathing). **Reference : Directive No. 20 Year 2017. Ref. BPFK/PPP/07/25 (25) Jld 1.** Direktif Untuk Semua Produk Yang Mengandungi Tramadol Dengan Maklumat Bagi Mengehadkan Penggunaan Tramadol Dalam Kalangan Kanak-Kanak Dan Amaran Berkaitan Penggunaan Dalam Kalangan Ibu Mengandung Dan Ibu Menyusu

Attachment 5

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
16.	**ARIPIPRAZOLE** (Please also refer to ANTIPSYCHOTIC AGENTS) The following statements shall be included in the package insert and RiMUP of products containing Aripiprazole: **Package Insert** **a) Warnings and Precautions:** Pathological gambling and impulse-control problems Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported include: increased sexual urges, compulsive shopping, binge or compulsive eating, and other impulsive and compulsive behaviours. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, or other urges, while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases urges were reported to have stopped when the dose was reduced or the medication was discontinued. Patients who are at higher risk for impulse-control problems (e.g. personal or family history of obsessive-compulsive disorder, impulse-control disorder, bipolar disorder, impulsive personality, alcoholism, drug abuse or other addictive behaviours) would require closer monitoring for new or worsening of uncontrollable urges. Impulse-control problems may result in harm to the patient and others if not recognised. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole. **b) Adverse Effects/Undesirable Effects:** Psychiatric disorders Pathological gambling, hypersexuality, impulse-control problems (See Section Warnings and Precautions). **Consumer Medication Information Leaflet (RiMUP)**

	a) Before you use <product name> Before you start to use it Talk to your doctor or pharmacist if you have: • a history of excessive gambling or other unusual urges (e.g. increased sexual urges, binge or compulsive eating, and compulsive shopping). **b) Side effects:** Side effects may include: • Excessive gambling or other unusual urges, such as increased sexual urges, binge or compulsive eating, and compulsive shopping. If you or your family members notice that you are having unusual urges or behaviours, talk to your doctor or pharmacist. **Reference : Directive No. 22 Year 2017. Ref. BPFK/PPP/07/25 (27) Jld 1.** Direktif Untuk Semua Produk Yang Mengandungi Aripripazole : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Kesan Advers *Pathological Gambling* Dan *Impulse-Control Problems*

Attachment 6

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
22.	**BENZODIAZEPINE** The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing benzodiazepine such as alprazolam, bromazepam, chlordiazepoxide, clobazam, clonazepam, clorazepate potassium, diazepam, lorazepam, midazolam, nitrazepam and triazolam; **Package Insert** **a) Warnings and Precautions:** Risks from Concomitant Use with Opioids Profound sedation, respiratory depression, coma, and death may result from the concomitant use of <product name> with opioids. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use. If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response. If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when <product name> is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined. Screen patients for risk of substance use disorders,

including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of opioids (See Drug Interactions).

b) Drug Interactions:

Opioids

Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.

The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions).

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Consumer Medication Information Leaflet (RiMUP)

a) Taking other medicines:

Taking <product name> with an opioid medicine (medicine to relieve pain) can depress your central nervous system. Inform your doctor if you are currently taking any opioid medicine.

Seek medical attention immediately if you or the person taking this medication experience(s) symptoms of unusual dizziness or lightheadedness, extreme sleepiness, slowed or difficult breathing, or unresponsiveness.

Reference : Directive No. 23 Year 2017. Ref. BPFK/PPP/07/25 (28) Jld 1. Direktif Untuk Semua Produk Yang Mengandungi Opioid Dan Benzodiazepin : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat

Attachment 7

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
130.	**OPIOID** The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing opioid such as alfenanil, buprenorphine, codeine, dihydrocodeine, fentanyl, methadone, morphine, nalbuphine, oxycodone, pentazocine, pethidine, remifentanil, tapentadol and tramadol; **Package Insert** **a) Warnings and Precautions:** 1. Risks from Concomitant Use with Benzodiazepines Profound sedation, respiratory depression, coma, and death may result from the concomitant use of <product name> with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use. If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response. If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when <product name> is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of

substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (See Drug Interactions).

2. Serotonin Syndrome with Concomitant Use of Serotonergic Drugs
Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of <product name> with serotonergic drugs (See Interactions with Other Medicaments). This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal (See Interactions with Other Medicaments). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue <product name> if serotonin syndrome is suspected.

3. Adrenal Insufficiency
Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

4. Sexual Function/Reproduction
Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (See Postmarketing Experience)

b) Adverse Effects/ Undesirable Effects:

Postmarketing Experience:

Serotonin syndrome (See Warnings and Precautions)

Adrenal insufficiency (See Warnings and Precautions)

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Infertility: Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

c) Drug Interactions:

1. Benzodiazepines

Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.

The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions).

Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

2. Serotonergic Drugs

The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. If concomitant use is warranted, carefully observe the

patient, particularly during treatment initiation and dose adjustment. Discontinue <product name> if serotonin syndrome is suspected. Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (See Warnings and Precautions).

Consumer Medication Information Leaflet (RiMUP)

a) While you are using it <product name>:

Things to be careful of:

- Serotonin syndrome: <Product name> may cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. If you have some or all of these symptoms: feeling confused, feeling restless, sweating, shaking, shivering, hallucinations, sudden jerks in your muscles or a fast heartbeat, seek medical attention immediately.
- Adrenal insufficiency: Long-term use of <product name> may cause adrenal insufficiency, a potentially life-threatening condition that may present with non-specific symptoms and signs such as nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. Seek medical attention if you experience a constellation of these symptoms.
- Infertility: Long-term use of <product name> may cause reduced fertility. It is not known whether these effects on fertility are reversible.

b) Taking other medicines:

Taking <product name> with a benzodiazepine (medicine used as sedatives or to treat anxiety) can depress your central nervous system. Inform your doctor if you are currently taking any benzodiazepine.

Seek medical attention immediately if you or the person taking this medication experience(s) symptoms of unusual dizziness or lightheadedness, extreme sleepiness, slowed or difficult breathing, or unresponsiveness.

Reference :

	1. **Directive No. 23 Year 2017. Ref. BPFK/PPP/07/25 (28) Jld 1.** Direktif Untuk Semua Produk Yang Mengandungi Opioid Dan Benzodiazepin : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Interaksi Ubat 2. **Directive No. 27 Year 2017. Ref. BPFK/PPP/07/25 (32) Jld 1.** Direktif Untuk Semua Produk Yang Mengandungi Opioid : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers *Serotonin Syndrome* Kesan Daripada Interaksi Dengan *Serotonergic Drugs* Dan Risiko Kesan Advers *Adrenal Insufficiency* Dan *Androgen Deficiency* Akibat Penggunaan Jangka Panjang

Attachment 8

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
70.	**FLUCONAZOLE** The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing Fluconazole: **Package Insert** **a) Pregnancy and Lactation:** Use During Pregnancy There have been reports of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150mg of fluconazole as a single or repeated dose in the first trimester. Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom <product name> may be used if the anticipated benefit outweighs the possible risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential hazard to the fetus. Effective contraceptive measures should be considered in women of child-bearing potential and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose. There have been reports of multiple congenital abnormalities in infants whose mothers were treated with high-dose (400mg/day to 800mg/day) fluconazole therapy for coccidioidomycosis (an unapproved indication). The relationship between fluconazole use and these events is unclear. Adverse fetal effects have been seen in animals only at high-dose levels associated with maternal toxicity. There were no fetal effects at 5 mg/kg or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 mg/kg and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60 times the recommended human dose) to 320 mg/kg, embryolethality in rats were increased and fetal abnormalities included wavy ribs, cleft palate and abnormal craniofacial ossification.

Case reports describe a distinctive and a rare pattern of birth defects among infants whose mothers received high dose (400-800mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease.

Use During Lactation

Fluconazole is found in human breast milk at concentrations similar to plasma. Breast-feeding may be maintained after a single dose of 150mg fluconazole. Breast-feeding is not recommended after repeated use or after high-dose fluconazole.

Consumer Medication Information Leaflet (RiMUP)

a) Before you use <product name>

Inform your doctor if you have such conditions:

- Pregnant or planning to become pregnant
  <Product name> may cause harm to your unborn baby. You should not take <product name> while you are pregnant unless your doctor has told you to. Inform your doctor if you are pregnant or planning to become pregnant.
  If you are a woman of child-bearing potential, avoid becoming pregnant during treatment. Use effective contraception during treatment and for 1 week after treatment.

- Breast-feeding
  <Product name> is excreted in human breast milk, hence its use in nursing mothers is not recommended.However, breast-feeding may be maintained if you took a single dose of <product name> 150mg. Breast-feeding is not recommended after a high dose (more than 150 mg) or repeated use of <product name>.

Reference : Directive No. 24 Year 2017. Ref. BPFK/PPP/07/25 (29) Jld 1. Direktif Untuk Semua Produk Yang Mengandungi Fluconazole : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Baharu Berkaitan Risiko *Spontaneous Abortion* Serta Memperkukuhkan Maklumat Keselamatan Berkaitan *Multiple Congenital Abnormalities* Dan Penggunaan Dalam Kalangan Ibu Menyusu

Attachment 9

<table>
<tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr>
<tr><td>109.</td><td>

METFORMIN

The following statements shall be included in the package insert and RiMUP of pharmaceutical products containing Metformin:

Package Insert

1. Recommended Dosage:

a) Products containing Metformin as a single active ingredient:

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

<table>
<tr><th>GFR mL/min</th><th>Total maximum daily dose (to be divided into 2-3 daily doses)*</th><th>Additional considerations</th></tr>
<tr><td>60-89</td><td>3000 mg</td><td>Dose reduction may be considered in relation to declining renal function.</td></tr>
<tr><td>45-59</td><td>2000 mg</td><td rowspan="2">Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose.</td></tr>
<tr><td>30-44</td><td>1000 mg</td></tr>
<tr><td><30</td><td>-</td><td>Metformin is contraindicated.</td></tr>
</table>

* The text “to be divided into 2-3 daily doses” should be omitted for extended release products containing metformin as single agent.

</td></tr>
</table>

b) Combination products containing Metformin:

Renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis should be reviewed before considering initiation of metformin in patients with GFR <60 ml/min.

If no adequate strength of <Product name> is available, individual monocomponents should be used instead of the fixed dose combination.

GFR mL/min	Metformin	[other monocomponent]
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	
<30	Metformin is contraindicated.	

2. Contraindications:

- Severely reduced kidney function (GFR <30 mL/min)
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)

3. Warnings and Precautions:

Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis.

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Renal function

GFR should be assessed before treatment initiation and regularly there after [See Section Recommended Dosage]. Metformin is contraindicated in patients with GFR <30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function [See Section Contraindications].

<u>Consumer Medication Information Leaflet (RiMUP)</u>

a) Before you use <product name>:

Do not take <product name>:

- If you have severely reduced kidney function.
- If you have lactic acidosis [too much lactic acid in the blood (see “Risk of lactic acidosis” below)] or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate

in the blood and which can lead to diabetic pre-coma. Symptoms of acidosis may include stomach pain, abnormal breathing and drowsiness (if severe).

b) Before you start to use it:

Risk of lactic acidosis

<Product name> may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration, liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease). If any of the above apply to you, talk to your doctor for further instructions.

Stop taking <product name> for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.

Stop taking <product name> and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.

Symptoms of lactic acidosis include:

- vomiting
- stomach ache (abdominal pain)
- muscle cramps
- a general feeling of not being well with severe tiredness
- difficulty in breathing

Lactic acidosis is a medical emergency and must be treated in a hospital.

During treatment with <product name>, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

Reference : Directive No. 25 Year 2017. Ref. BPFK/PPP/07/25 (30) Jld 1. Direktif Untuk Semua Produk Yang Mengandungi Metformin : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan Penggunaan Dalam Kalangan Pesakit Yang Mempunyai *Moderately Reduced Kidney Function* Dan Pengukuhan Amaran *Lactic Acidosis*

Attachment 10

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
20.	**AZITHROMYCIN** 1. The following statement shall be included in the package insert of product that contains Azithromycin: **Special Warnings and Precautions for Use** **Hypersensitivity** As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), dermatologic reactions including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (rarely fatal), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued. **Prolongation of the QT interval** Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including azithromycin (see section 4.8). Prescribers should consider the risk of QT prolongation, which can be fatal, when weighing the risks and benefits of azithromycin for at-risk groups including: • Patients with congenital or documented QT prolongation • Patients currently receiving treatment with other active substances known to prolong QT interval, such as antiarrhythmics of Classes IA and III, antipsychotic agents, antidepressants, and fluoroquinolones • Patients with electrolyte disturbance, particularly in cases of hypokalemia and hypomagnesemia • Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency • Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval **Adverse Drug Reactions**

Post-marketing experience:

Cardiac Disorders: Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongation and torsades de pointes (see **Special Warnings and Precautions for Use)**.
Skin and Subcutaneous Tissue Disorders: Allergic reactions including pruritus, rash, photosensitivity, edema, urticaria, and angioedema. Rarely, serious cutaneous adverse reactions including erythema multiforme, SJS, TEN and DRESS have been reported.

Reference: Circular Bil (34) dlm BPFK/PPP/07/25. Directive Bil 3 Year 2016.
Direktif Untuk Semua Produk Yang Mengandungi Azithromycin (Formulasi Sistemik): Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Kesan Advers *QT Prolongation* Dan *Drug Reaction With Eosinophilia And Systemic Symptoms (DRESS)*

2. The following statement shall be included in the package insert and RiMUP of products containing azithromycin (except topical/ external and ophthalmic preparations);

Package Insert

a) Warnings and Precautions:

Infantile hypertrophic pyloric stenosis (IHPS) has been reported following the use of azithromycin in infants (treatment up to 42 days of life). Parents and caregivers should be informed to contact their physician if vomiting and/ or irritability with feeding occurs.

b) Adverse Effects/Undesirable Effects:

Postmarketing Experience:

Gastrointestinal Disorders: infantile hypertrophic pyloric stenosis.

Consumer Medication Information Leaflet (RiMUP)

Side Effects

If you notice that the child vomits and/or irritability with feeding occurs, contact doctor immediately as it may be due to the Infantile Hypertrophic Pyloric Stenosis (IHPS).

	Reference : Directive No. 28 Year 2017. Ref. BPFK/PPP/07/25 (33) Jld 1. Direktif Untuk Semua Produk Yang Mengandungi Bahan Aktif Azithromycin Dan Erythromycin Kecuali Persediaan Topikal/ Eksternal Dan Ubat Untuk Kegunaan Mata : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan *Risiko Infantile Hypertrophic Pyloric Stenosis (IHPS)*

Attachment 11

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
64.	**ERYTHROMYCIN** The following statement shall be included in the package insert and RiMUP of products containing erythromycin (except topical/ external and ophtalmic preparations); **Package Insert** **a) Warnings and Precautions:** There have been reports of infantile hypertrophic pyloric stenosis (IHPS) occurring in infants following erythromycin therapy. In one cohort of 157 newborns who were given erythromycin for pertussis prophylaxis, seven neonates (5%) developed symptoms of non-bilious vomiting or irritability with feeding and were subsequently diagnosed as having IHPS requiring surgical pyloromyotomy. Since erythromycin may be used in the treatment of conditions in infants which are associated with significant mortality or morbidity (such as pertussis or chlamydia), the benefit of erythromycin therapy needs to be weighed against the potential risk of developing IHPS. Parents and caregivers should be informed to contact their physician if vomiting and/ or irritability with feeding occurs. **b) Adverse Effects/Undesirable Effects:** Postmarketing Experience: Gastrointestinal Disorders: infantile hypertrophic pyloric stenosis. **Consumer Medication Information Leaflet (RiMUP)** **Side Effects** If you notice that the child vomits and/or irritability with feeding occurs, contact doctor immediately as it may be due to the Infantile Hypertrophic Pyloric Stenosis (IHPS). **Reference : Directive No. 28 Year 2017. Ref. BPFK/PPP/07/25 (33) Jld 1.** Direktif Untuk Semua Produk Yang Mengandungi Bahan Aktif Azithromycin Dan Erythromycin Kecuali Persediaan Topikal/ Eksternal Dan Ubat Untuk Kegunaan Mata : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Berkaitan *Risiko Infantile Hypertrophic Pyloric Stenosis (IHPS)*

Attachment 12

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
170.	**STATINS** The following statement shall be included in the package inserts and RiMUP of ALL products containing statins (single active or in combination): a. Atorvastatin b. Fluvastatin c. Lovastatin d. Pravastatin e. Rosuvastatin f. Simvastatin g. etc. **Package Insert** **a) DRUG INTERACTION**: Concurrent use of fibrates may cause severe myositis and myoglobinuria. **b) UNDESIRABLE EFFECTS**: There have been rare post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median 3 weeks). Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins. **c) Warnings and Precautions:** There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by: • persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment;

- muscle biopsy showing necrotizing myopathy without significant inflammation;
- improvement with immunosuppressive agents.

d) Adverse Effects/Undesirable Effects:

Musculoskeletal disorders:
Frequency not known: Immune-mediated necrotizing myopathy

Consumer Medication Information Leaflet (RiMUP)

Side Effects

If you have muscle problems that do not go away even after your doctor has told you to stop taking {product name}, please refer to your doctor. Your doctor may do further tests to diagnose the cause of your muscle problems.

References:

1. **Circular (14) dlm.BPFK/PPP/07/25. Directive No. 7 Year 2014.** Direktif Untuk Semua Produk Statin: Memperkukuhkan Amaran Berkaitan Risiko Kesan Advers Kognitif Dan Peningkatan HBA1C Serta *Fasting Blood Glucose (FBG)*
2. **Directive No. 29 Year 2017. Ref. BPFK/PPP/07/25 (34) Jld 1.** Direktif Untuk Semua Produk Yang Mengandungi Statin : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Berkaitan *Immune-Mediated Necrotizing Myopathy (IMNM)*

Attachment 13

1.1 CHARGES FOR USB TOKEN OF QUEST MEMBERSHIP

	~~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~~	

No.	Type	Validity Period		
		1 year (RM)	2 years (RM)	3 years (RM)
1.	Main User – New, Replacement, Change of Authorized Person (USB Token + Digital Certificate)	275.60 (260)	307.40 (290)	355.10 (335)
2.	Supplementary User – New, Replacement, Change of Authorized Person (USB Token + Digital Certificate)	259.70 (245)	291.50 (275)	339.20 (320)
3.	Renewal (Digital Certificate only – using existing MSC TG USB Token)	50.90 (48)	100.70 (95)	148.40 (140)
4.	Change Authorized Person (Digital Certificate only – using existing MSC TG USB Token)	50.90 (48)	100.70 (95)	148.4 (140)

** price in bracket ( ) is without GST 6%*

Attachment 14

1.3.2 DEFINITION OF FDI PRODUCTS

Generally FDI products are products with combination of food ingredients and active ingredients for oral consumption. ~~for oral consumption containing a combination of food ingredients with active substances for oral consumption~~. Examples of food ingredients are fruit, vegetables, meat, poultry, milk, cocoa and cereal. Examples of active ingredients ~~substances~~ are vitamins, minerals, herbs, enzymes, probiotics, prebiotics, amino acids, peptides, coral calcium, ~~and~~ fatty acids, collagen, chia seed, astaxanthin, lutein and other ingredients that are not traditionally consumed as food. FDI products may be presented in the form of powder, liquid, semisolid forms such as gel/jelly, chewable tablet, drops, granule etc.

Such products as below are not categorized as FDI products due to its presentation and function:

A. FOOD ~~based~~ PRODUCTS THAT ARE NOT CATEGORIZED AS FDI PRODUCTS AND REGULATED BY FSQD INCLUDE :

1. 100% food ingredients.

~~1.~~2. Food ~~based~~ products **with or without** active ingredients (eg; herbs, vitamins, minerals, etc) as below:
   i) Instant drink products containing sugar and/or creamer (e.g. premix coffee, tea, chocolate, soy, cereal).
   ii) Meat essence products (liquid) (e.g. chicken essence, ostrich essence, duck essence, fish essence etc.)
   iii) Ready to drink products (beverages) without dosing instruction in cheered pack/ canned / packet drinks.
   iv) Cordial products with recommended dilution ratio (e.g. dates cordial, grape cordial)~~.~~
   v) Vinegar products (liquid) (e.g. apple vinegar, dates vinegar etc.)
   vi) Honey products (liquid).

~~2.~~3. Energy drink products, ~~i~~isotonic drink products, sport nutrition products and special purpose food products.

~~3.~~4. Products in conventional food form e.g. biscuit, cake, confectionery, candy/sweet, gummy, noodle.

4.5. Products used for cooking and food preparation (e.g. cooking oil (olive oil, coconut oil, sunflower oil), herbs and spices) turmeric powder.

5.6. Herbs and spices in crude form without medicinal/health claim.

B. PRODUCTS THAT ARE NOT CATEGORIZED AS FDI PRODUCTS AND REGULATED BY NPRA INCLUDE :

1. Products containing active ingredient(s) with or without excipient.; or

2. Products containing specific active ingredients which possess high pharmacological or therapeutic potencies. Examples of the ingredients are paracetamol, glucosamine, tranexamic acid, aspirin, substances listed in Poisons Act 1952 . ; or

3. Products containing specific active ingredients which possess dose-related therapeutic potencies such as:
    - Plant sterols/ stanols and esters that are consumed ≥ 3.5g/day
    - Psyllium husk that are consumed ≥ 3.5g/day
    - Products containing senna ≥ 0.5g ; or

4. Products in pharmaceutical dosage form such as soft gel, capsule or tablet (that is to be directly swallowed), sublingual, buccal, spray into the mouth, etc.

1.3.3 CLASSIFICATION FOR FDI PRODUCTS

It is important to determine the category of a product that falls within the food-drug interphase (FDI) whether the products are regulated as drug (under the NPRA's purview) or, as food (under the FSQ's purview) because different regulatory requirements apply.

The classification of FDI products are based on criteria, as outlined below:

a) Main criteria

i) Negative List For Food as listed *in Table 1: Negative List For FDI ~~Food~~*:

- FDI products containing ingredient(s) from Negative List for FDI~~Food~~ shall be regulated by NPRA ; or ~~.~~

ii) Medicinal/ health claim refer to the term "medicinal purpose" as stipulated in the Sales of Drug Act 1952, Section 2:

- FDI products not containing ingredient(s) from Negative List For FDI ~~Food~~ and with medicinal/ health claim shall be regulated by NPRA ; or

- FDI products not containing ingredient(s) from Negative List For FDI ~~Food~~ and without medicinal/ health claim shall be regulated by FSQD.

iii) **Products intended to be used or capable, or purported or claimed to be capable for a medicinal purpose (e.g. products used for the health benefit of eyes, body weight control, gastrointestine, brain, etc.)** shall be regulated by NPRA.

~~*(Reference: Circular Bil (19)dlm.BPFK/PPP/01/03 Jld.3)*~~

b) Other criteria

- When there is greater uncertainty regarding the safety of a FDI product, such shall be regulated by NPRA. This is to enable closer monitoring of such products, so as to safeguard the health of the consumer.

  Reference : Pekeliling Kriteria Baru Pengkelasan Produk (07 August 2014)
  Circular No. (19)dlm.BPFK/PPP/01/03 Jld.3)

Table 1: Summary table of Classification of Food Drug Interphase Product

NO.	DRUG	NON-DRUG
i.	Contain Active ingredient and with medicinal/ health claim	Not containing Active ingredient from **Negative List For Food** and **NO** medicinal/ health claim
i.	Contain Active ingredient listed in **Table 2: Negative List for Food with** medicinal/ health claim	
i.	Contain Active ingredient listed in **Table 2: Negative List for Food without** medicinal/ health claim	
v.	Formulated in pharmaceutical dosage form (eg. tablet, capsule, liquid,softgel, sublingual, etc)	
v.	When there is greater uncertainty regarding the safety of an FDI product, such shall be regulated by NPRA. This is to enable closer monitoring of such products, so as to safeguard the interest of the consumer.	

1.3.3.1 NEGATIVE LIST FOR FDI

Table 1: Negative List For FDI

No.	Ingredient	Common/Other name
1	***Actaea racemosa***	Black Cohosh, Cimicifuga racemosa
2	***Antiaris toxicaria (Pers.) Lesch.***	Bark cloth tree, antiaris, false iroko, false mvule, upas tree
3	***Artemisia Spp. (all species)***	Wormwood, Mugwort
4	***Aspidosperma Quebracho-Blanco Schltdl***	Kebrako, White Quebracho
5	***Atropa Spp. (all species)***	Antropa belladonna (deadly nightshade)
6	***Azadirachta indica***	Nimba, Neem
7	**Bile**	
8	***Brucea javanica, Brucea amarissima***	Sumatrana amarissimus, Java brucea
9	***Bufo gargarizans Cantor, Bufo melanostictus Schneider, Bufo vulgaris Lour***	Toad, Samsu, kodok, kerok
10	***Calotropis Spp. (all species)***	Apple of Sodom, Crown flower
11	***Cannabis Spp. (all species)***	Marijuana, Hemp
12	***Catharanthus Spp. (all species)***	Periwinkle
13	***Chelidonium majus***	Celandine, Great Celandine, Nipplewort
14	***Chondodendron Spp. (all species)***	

15	***Claviceps Spp. (all species)***	Ergot
16	***Colchicum Spp. (all species)***	Autumn crocus, Meadow saffron, Naked lady
17	***Conium maculatum***	Hemlock
18	***Coptis chinensis, Coptis teeta***	Chinese Goldthread
19	***Croton tiglium L.***	Croton
20	***Datura spp. (all species)***	Jimson weed, Devil's apple, Green Dragon, Zombie's Cucumber, Moon Weed, Trumpet Lily, Stinkweed
21	***Digitalis spp.(all species)***	
22	***Dioscorea Hispida***	
23	***Dryobalanops lanceolata Burck***	Borneo camphor, Kapur, Malay Camphor, Sumatra camphor
24	***Dryopteris Spp. (all species)***	Mountain woodfern, Spinulose woodfern, Spreading woodfern, Fancy fern
25	***Euphorbia Spp. (all species)***	Spurge
26	***Fritillaria spp.***	Fritillary Bulb
27	**Gamma-amino Butyric Acid (GABA)**	
28	***Garcinia Morella Desr.***	Gamboge
29	***Gelsemium semperi virens***	Palaung Thay
30	**Glucosamine**	
31	**Glutathione**	
32	***Gypsum Fibrosum***	
33	**Hyaluronic acid**	
34	***Hyoscyamus Spp. (all species)***	

35	***Hypericum perforatum***	St. John's Wort
36	***Juniperus sabina***	Savin, Savine
37	***Mahonia aquifolium, Mahonia repens, Mahonia nervosa***	Mahonia Aquifolium: Oregon Grape, Mountain Grape, Barberry. Mahonia Repens: Creeping Barberry, Creeping Mahonia, Creeping Oregon-Grape
38	***Melanorrhoea usitata Wall.***	Vanish tree
39	***Monascus purpureus***	Red yeast rice
40	***Mucuna pruriens***	Cowhage, Cowage
41	***Mylabris phalerata, Mylabris cichorii***	Blister beatle, Mylabris
42	**Natto extract**	Fermented soy bean extract
43	***Nerium indicum***	Indian oleander, Exile Tree.
44	***Nerium oleander***	Indian oleander, Exile Tree.
45	**Pearl**	
46	***Phellodendron amurense, Phellodendron chinense***	Amur Cork tree
47	**Placenta**	
48	***Plumbago indica***	Rose-coloured leadwort
49	***Plumbago zeylanica***	White leadwort
50	***Psilocybe cubensis***	Boomers, Gold caps
51	***Rauvolfia Spp. (all species)***	
52	**Resveratrol**	
53	***Sanguinaria canadensis***	Bloodroot, Indian Paint
54	***Scilla sinensis***	

55	***Simmondsia Chinesis***	Jojoba
56	***Sophora tomentosa***	Sea coast Laburnum, Silver Bush
57	***Spigelia marilandica***	Worm grass, Pinkroot
58	***Stichopus spp.***	Gamat
59	***Strophanthus spp.(all species)***	Kombe
60	***Strychnos ignatii, Strychnos lucida, Strychnos roberans***	Nux-vomica
61	***Symphytum peregrinum***	Comfrey

Notes:

This list :

- is a compilation by the FDI committee.
- is not meant to be exhaustive and will be reviewed from time to time.
- shall be read in conjunction with the current laws and regulations together with other relevant legislations, where applicable, governing pharmaceutical and natural products for human use in Malaysia

Notes:

Applicant may verify on FDI product classification with NPRA in order to determine whether the product shall be registered by the Authority or otherwise by seeking classification service from NPRA (http://npra.moh.gov.my/index.php/application-forms).

Reference Circular:Bil.(97)dlm.BPFK/PPP/01/03 Jld. 2

1.3.4 ADDITIONAL NOTES

1. Substances listed in the prohibited/ banned ingredient list of the Drug Registration Guidance Document (DRGD) and Schedule Poison shall not be permitted for use in any FDI products.

2. Products categorized as a natural product are not allowed to contain creamer.

3. Food products are not allowed to be packed in blister pack/ any other form of packaging which resembles the packing of drug product.

4. Any foods or combination of foods that are regulated by FSQD shall not be in pharmaceutical dosage form, such products are advised to reformulate into a non-pharmaceutical dosage form.

~~5. Food products shall not have name/ brand name with the word of 'stem cell'.~~

~~6.~~5. Products containing only ingredient(s) such as roselle, jasmine, rose, chamomile, chrysanthemum flower, ginger (rhizome), vanilla(stem), mint leaf, lemon peel and cinnamon bark (with/without C*amelia sinensis*) will be regulated by FSQD.

~~7.~~6. Fruit ingredients that are not commonly consumed as food in Malaysia will be considered as active ingredient.

Attachment 15

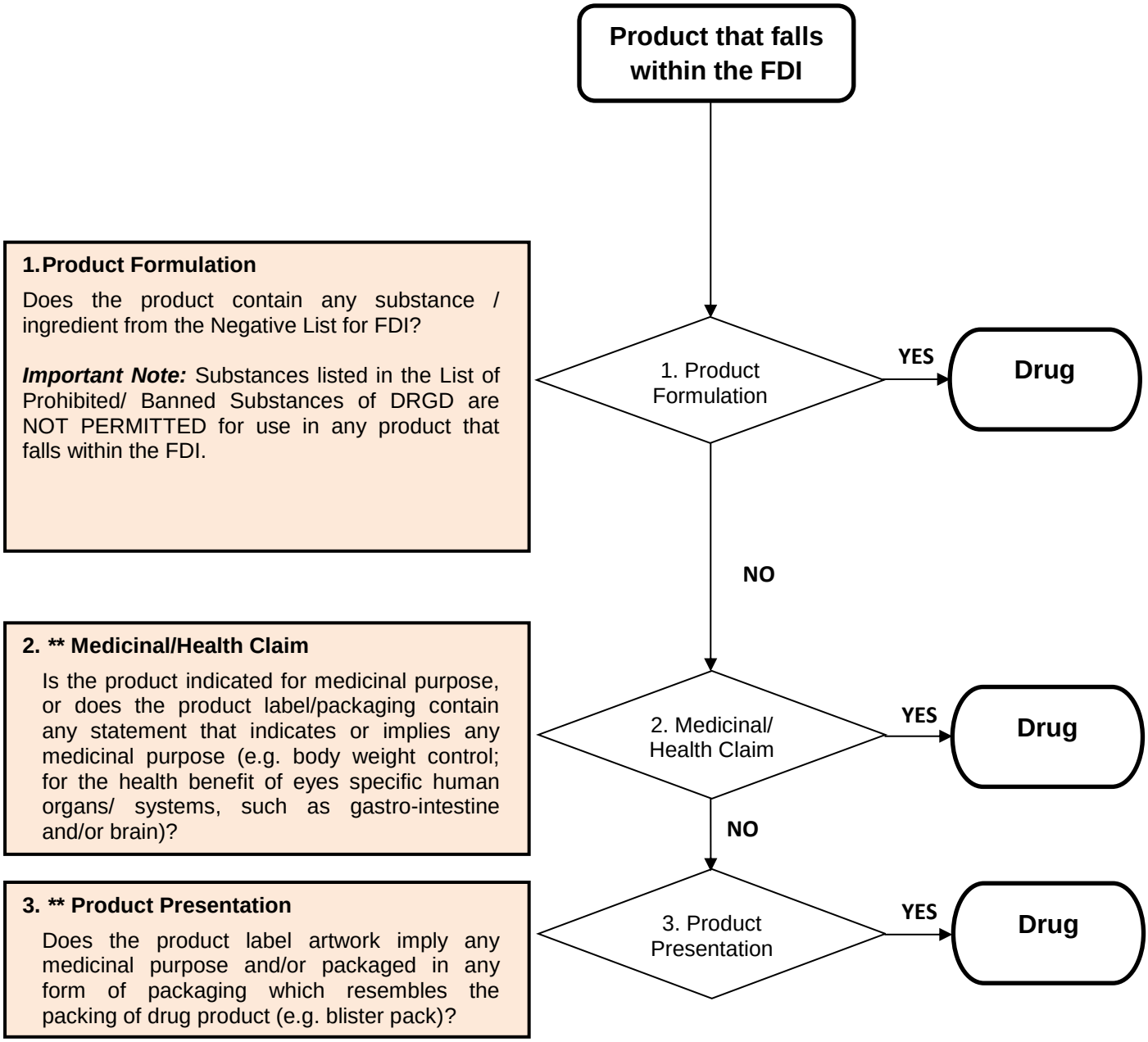
1.3.3.2 GENERAL CLASSIFICATION FLOWCHART OF FOOD-DRUG INTERPHASE (FDI) UNDER FOOD OR DRUG

- It is important to determine the category of a product that falls within the food-drug interphase (FDI) whether the products are regulated as drug (health supplement or natural product under the NPRA's purview) or, as food (under the FSQ's purview) because different regulatory requirements apply. Therefore, the following flowchart serves only as guide to help you determine the category of the product that falls within the FDI.

- Should you have any doubt or uncertainty pertaining to the category of your product, you may contact the relevant regulatory agencies for clarification, or seek classification service from the NPRA by submitting a classification application.

- Please take note that you are encouraged to familiarize yourself with the governing legislations and other regulatory requirements and guidelines that apply to your product before using this guide.

Note: ** NPRA reserves the right to use its discretion to make decision if issue of subjectivity arises.


Product that falls within the FDI
1. Product Formulation
Does the product contain any substance / ingredient from the Negative List for FDI?
Important Note: Substances listed in the List of Prohibited/ Banned Substances of DRGD are NOT PERMITTED for use in any product that falls within the FDI.
1. Product Formulation
YES
Drug
NO
2. ** Medicinal/Health Claim
Is the product indicated for medicinal purpose, or does the product label/packaging contain any statement that indicates or implies any medicinal purpose (e.g. body weight control; for the health benefit of eyes specific human organs/ systems, such as gastro-intestine and/or brain)?
2. Medicinal/ Health Claim
YES
Drug
NO
3. ** Product Presentation
Does the product label artwork imply any medicinal purpose and/or packaged in any form of packaging which resembles the packing of drug product (e.g. blister pack)?
3. Product Presentation
YES
Drug

Attachment 16

1.3.5 PICTORIAL GUIDE TO CLASSIFICATION OF FOOD OR DRUG PRODUCTS

Legend :

	Regulated by FSQD
	Regulated by NPRA
	Classification of FDI under food or drug

PRODUCT

DRUG

1. **Products as defined in the Regulation 2, CDCR 1984.**

2. **Products containing 100% active ingredient(s) with or without excipient.**

3. **Products containing specific active ingredients which possess high pharmacological or therapeutic potencies.** (e.g. paracetamol, glucosamine, tranexamic acid, aspirin, substances listed in Poisons Act 1952.

3. **Products containing specific active ingredients which possess dose – related therapeutic potencies** such as: - Plant sterols/ stanols and esters that are consumed ≥ 3.5g/day
- Psyllium husk that are consumed ≥ 3.5g/day
- Products containing senna ≥ 0.5g

4. **Products in pharmaceutical dosage form** such as soft gel, capsule or tablet (that is to be directly swallowed), sublingual, buccal, spray into the mouth, etc.

1. Products containing ingredient(s) from Negative List For FDI

2. Products not containing ingredient(s) from Negative List For FDI and with medicinal/ health claim

3. Products intended to be used or capable, or purported or claimed to be capable for a medicinal purpose. (e.g. products used for the health benefit of eyes, body weight control, gastrointestine,

FOOD

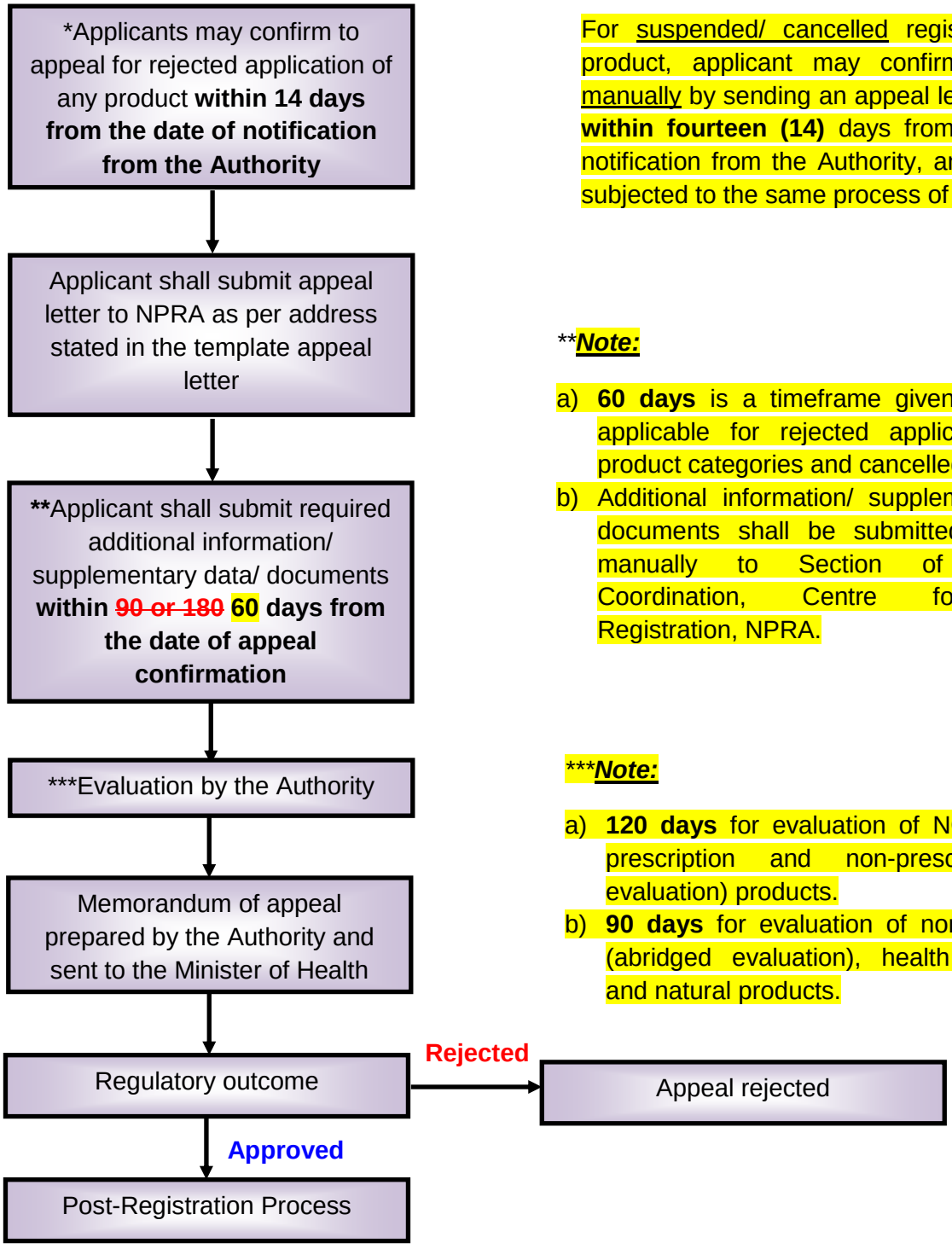
1. **100% food ingredients**
2. **Food products with or without active ingredients as below;**
   - i) Instant drink products containing sugar and/or creamer (e.g. premix coffee, tea, chocolate, soy, cereal)
   - ii) Meat essence products (liquid) (e.g. chicken essence, ostrich essence, duck essence, fish essence and etc.)
   - iii) Ready to drink products (beverages) without dose instruction in cheered pack/ canned /packet drinks
   - iv) Cordial products with recommended dilution ratio (e.g. dates cordial, grape cordial)
   - v) Vinegar products (liquid) (e.g. apple vinegar, dates vinegar and etc.)
   - vi) Honey products (liquid)
3. **Isotonic drink products, sport nutrition products and special purpose food products**
4. **Products in conventional food form e.g. biscuit, cake, confectionery, candy/sweet, gummy, noodle**
5. **Products used for cooking and food preparation (e.g. cooking oil (olive oil, coconut oil, sunflower oil), herbs and spices)**
6. **Herbs and spices in crude form without medicinal/health claim**

Products not containing ingredient(s) from Negative List for FDI and without medicinal/ health claim.

Attachment 17

~~8.7.2 PROCESS OF APPEAL FOR QUEST 3 PRODUCT~~

Figure ~~6~~ 5:



* ***Note:***

For suspended/ cancelled registration of a product, applicant may confirm to appeal manually by sending an appeal letter to NPRA **within fourteen (14)** days from the date of notification from the Authority, and it shall be subjected to the same process of appeal.

*****Note:***

a) **60 days** is a timeframe given to applicant applicable for rejected application for all product categories and cancelled registration.
b) Additional information/ supplementary data/ documents shall be submitted via online/ manually to Section of Regulatory Coordination, Centre for Product Registration, NPRA.

******Note:***

a) **120 days** for evaluation of NCE, Biologic, prescription and non-prescription (full evaluation) products.
b) **90 days** for evaluation of non-prescription (abridged evaluation), health supplement and natural products.

8.7.~~3~~2 TEMPLATE FOR AN APPEAL LETTER

***LETTERHEAD* SYARIKAT PEMEGANG PENDAFTARAN PRODUK**
Nama dan alamat pemegang

Tarikh:

Y. B. Menteri Kesihatan Malaysia
d/a Bahagian Regulatori Farmasi Negara
Kementerian Kesihatan Malaysia
Lot 36, Jalan Universiti,
46200 Petaling Jaya
(u.p. Setiausaha PBKD)

Y. B.,

PERATURAN 18 – RAYUAN TERHADAP PENOLAKAN PERMOHONAN PENDAFTARAN

NAMA PRODUK : Sila nyatakan nama produk (*Please state the product name*)
NO. RUJUKAN : Sila nyatakan nombor pendaftaran produk (*Please state reference number of the product*)

Dengan segala hormatnya, pihak kami ingin membuat rayuan terhadap penolakan permohonan produk seperti di atas.

2. Alasan – alasan rayuan serta data tambahan/ maklumat akan dihantar kepada pihak Y.B. dalam tempoh ~~*90 hari/ 180 hari~~ 60 hari dari tarikh ~~surat ini dikeluarkan.~~ pengesahan penerimaan rayuan oleh pihak Y.B.

Sekian, terima kasih.

Yang benar,

Tandatangan Wakil Pemegang

(NAMA WAKIL PEMEGANG)
Jawatan Wakil Pemegang

Attachment 18

Example of Certificate of Analysis for Finished Product (Natural Product)

Certificate of Analysis

Company name/ Address :

Product Name :

Batch no. :

Dosage form :

Packaging :

Date of manufacture :

Date of expiry :

Test Parameter	Specifications	Results	Method
Appearance/ Organoleptic: Odour Colour	To describe the characteristic		
Disintegration	DRGD		
Uniformity of weight			
Assay: (All standardize compounds claimed on label)	To specify		
Microbial Contamination Test TAMC, TYMC, specified microorganism	DRGD		
Heavy Metal Contamination			
Lead (Pb)	NMT 10 ppm		
Cadmium (Cd)	NMT 0.3 ppm		
Mercury (Hg)	NMT 0.5 ppm		
Arsenic (As)	NMT 5 ppm		

NMT = Not More Than

Signature :
Name :
Designation : (At least by Quality Control Manager or equivalent)
Date of signature :

Note: The above parameter are only as an example, other tests may be required for specific product.

Attachment 19

Example of Certificate of Analysis for Finished Product (Health Supplement)

Certificate of Analysis

Company name/ Address :

Product Name :

Batch no. :

Dosage form :

Packaging :

Date of manufacture :

Date of expiry :

Test Parameter	Specifications	Results	Method
Appearance/ Organoleptic: Odour Colour	To describe the characteristic		
Disintegration	DRGD		
Uniformity of weight			
Assay: (All active ingredients/ compounds claim on label)	To specify		
Microbial Contamination Test TAMC, TYMC, specified microorganism	DRGD		
Heavy Metal Contamination			
Lead (Pb)	NMT 10 ppm		
Cadmium (Cd)	NMT 0.3 ppm		
Mercury (Hg)	NMT 0.5 ppm		
Arsenic (As)	NMT 5 ppm		

NMT = Not More Than

Signature :
Name :
Designation : (At least by Quality Control Manager or equivalent)
Date of signature :

Note: The above parameter are only as an example, other tests may be required for specific product.

Attachment 20

SECTION C: QUALITY CONTROL

The requirement for the submission of the protocol of analysis (POA), analytical method validation (AMV) and product samples for laboratory testing are presented in this section.

The submission of POA and AMV to the Centre for Quality Control shall be done via the online system (Quest system). Documents to be submitted are listed below:

Documents to be submitted via online Quest system for finished product:

1. E12 : Complete protocol of analysis for finished product including preservatives and diluents (if any).
2. E13 :
   1. Complete testing methods and results for the AMV with all relevant validation parameters, including acceptance criteria and supporting raw data (e.g. chromatograms, spectrums etc.)
   2. Summary of AMV which includes all the relevant validation characteristics, its acceptance criteria and results.

*** For Biologics, all documents above mentioned except raw data.**

Documents to be submitted as hardcopy for finished product [applicable for Biologics]:

1. Certificate of analysis for active drug substance (2 batches) and recent batches of finished product (local manufacturer 1 batch, overseas manufacturer 2 batches)
2. Complete protocol of analysis for finished product (including preservatives and diluents, if any)
3. Complete testing method for the AMV.
4. Complete results for the AMV with all relevant validation parameters, including acceptance criteria and supporting raw data (e.g. chromatograms, spectrums etc.)

Note:

1. A cover letter consisting of the following information should be enclosed with every hard copy document submission:
   i) Name of product;
   ii) Reference Number/ Protocol Number;

iii) Contact person (name/ email address/ telephone no.);
iv) Name and address of company.

2. Documents submitted should be well organized and indexed.

Documents to be submitted via online Quest system for for Active Pharmaceutical Ingredient, API:

1. S 4.2 : Complete protocol of analysis for drug substance(s)

2. S 4.3 : Complete testing methods and results for the AMV for drug substance(s) with all relevant validation parameters, including acceptance criteria and supporting raw data (e.g. chromatograms, spectrums etc.)

Documents to be submitted as CD [applicable for Active Pharmaceutical Ingredient, API]:

1. Certificate of analysis for active drug substance(s) (2 batches).
2. Complete protocol of analysis for drug substance(s).
3. Complete testing method for the AMV for drug substance(s).
4. Complete results for the AMV for drug substance(s) with all relevant validation parameters, including acceptance criteria and supporting raw data (e.g. chromatograms, spectrums etc.)

9. GUIDELINE FOR THE SUBMISSION OF PROTOCOL OF ANALYSIS (POA)

This guideline consists of general and specific requirements for the POA submission. The general requirements are referred to POA content whilst details of the test methods are illustrated in the specific requirements

9.1 GENERAL REQUIREMENTS

a) The POA shall be written in *Bahasa Malaysia* or English only.

b) The POA shall contain the following information:

i) Name of product;
ii) Name and address of manufacturer;
iii) Name, signature and designation of authorized person;
iv) Effective date and Review date.

c) The POA shall comply with the following requirements:

i) To provide updated testing methods, shelf-life specifications and certificate of analysis for the intended product to be registered.
ii) References used must be clearly stated.
iii) The latest version of British Pharmacopoeia (BP) and United State Pharmacopeia (USP) shall be used as the main references.
iv) All tests and its specification listed in BP and/or USP in General Monographs and Specific Monographs shall be the minimum requirement. However, a specific testing method for quantitative analysis shall be accepted.
v) All test specifications set by the manufacturer shall be in line or more stringent than official pharmacopoeias (BP and USP).

d) Details of test methods shall include the following items:
i) List of equipment and apparatus;
ii) List of chemical, reagents and media;
iii) Preparation of solutions such as sample, standard, mobile phase, medium etc.;
iv) Setting up of analytical instrumentation;

v) System suitability tests (resolution, percentage of Relative Standard Deviation (%RSD), tailing factor and theoretical plate for High Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC) methods);
vi) Complete formula for calculation and interpretation of results;
vii) Specification or acceptance criteria.

e) Photocopies or methods directly copied from pharmacopoeias shall not be accepted. In cases where test methods are adopted from official pharmacopeia, details of specifics requirements should be submitted.

f) All relevant data collected during chemical and microbiological testing such as chromatograms HPLC/ GC, test reports and formulae used for calculating should also be submitted.

g) All documents should be arranged and labelled accordingly.

9.2 SPECIFIC REQUIREMENTS

The specific requirements for test methods are based on type of tests and dosage forms of product as stated in **Table IX** below:

Categories	Type of Tests	Specific Requirements
Physical & Performance	Physical test (friability, uniformity of weight, pH, etc)	Specific method for the intended analysis
	Disintegration test	Specific method for related dosage forms

Categories	Type of Tests	Specific Requirements
Tests	Dissolution test	a. Dissolution parameters should include: i) type of apparatus ii) type and volume of dissolution medium iii) rotation rate iv) temperature of solution v) sampling time b. Complete formula for calculation especially for extended and delayed release products. c. Method of analysis for example HPLC, UV, etc.
Quality Test	Identification test such as color test, Fourier Transform Infrared (FTIR), Thin Layer Chromatography (TLC) etc.	Specific method for the intended analysis
	Impurities/ degradation/ purity test	a. Analysis method should include:- i) Placebo solution (if any) ii) Relative retention times of impurities or degradation product b. Complete formula for calculation c. Method of analysis for example HPLC, TLC, etc.
	Assay and uniformity of content	Specific method for the intended analysis

Categories	Type of Tests	Specific Requirements
	Biological Assay of Antibiotics	a. Procedure for preparation of following solutions/ substances:- i) Culture medium ii) Buffer solutions iii) Diluents iv) Microorganisms used in assay b. Detailed test method (diffusion or turbidimetric method), which includes: i) Preparation of standard solutions (including steps to counteract the antimicrobial properties of any preservatives, etc present in the sample) ii) Preparation of test solutions (including any steps to neutralize the antimicrobial properties of any preservatives, etc present in the sample) iii) Test for Media Sterility and Growth Promotion Test iv) Dilution schemes for test and standard solutions. • Application of test & standard solutions (volume, use of latin squares, etc.) • Incubation temperature & time • Interpretation of result • Detailed calculation for the test including ANOVA table and other data showing validity of test results.

Categories	Type of Tests	Specific Requirements
Safety tests	Pyrogen Test	a. List of depyrogenated or pyrogen-free apparatus, glassware and reagents b. Temperature recording system c. Retaining conditions of the animals d. Selection of animals for test e. Preliminary test/ Sham test procedure f. Detailed test procedure g. Volume and dose of injection h. Interpretation of test results
	Bacterial Endotoxins Test (BET) or Limulus Amebocyte Lysate (LAL) Test	a. Certificate of analysis for endotoxin and LAL (limulus amebocyte lysate) reagent b. List of depyrogenated or pyrogen-free apparatus, glassware and reagent c. Preparation of standard solutions, LAL reagent/ substrate, sample d. Detailed calculation for determination of maximum valid dilution (MVD) e. The product's endotoxin limit concentration (ELC) and source of information f. Detailed calculation for determination of endotoxin limit concentration if the ELC is not in BP, USP, JP or EP g. Detailed test procedure h. Calculation and interpretation of test result

Categories	Type of Tests	Specific Requirements
	Sterility Test	a. List of media and reagent i) Culture media ii) List of rinsing solution, buffer solution and diluent iii) Neutralizing agent (if any) b. Preparation of media & Composition of Rinsing Buffer c. Test for Media Sterility and Growth Promotion Test d. Preparation of test sample (including steps to eliminate antimicrobial activity due to antibiotic samples or samples which contain preservatives). e. Detailed test procedure for sterility test i) Quantity of sample / Volume of sample ii) Membrane filtration / Direct inoculation iii) Open System or Closed System (if uses Membrane filtration method) iv) Volume of rinsing fluid
	Microbial Contamination Test	Required for ALL non-sterile products a. Preparation of media b. Test for Growth Promoting, Inhibitory and Indicative Properties of Media c. Preparation of test sample (including neutralizing of preservatives for samples that contain preservatives) d. Total Viable Aerobic Count • Detailed test procedure for Total Aerobic Microbial Count TAMC) and Total Yeasts and Moulds Count (TYMC) by Plate Count, Membrane Filtration or Most-Probable Number

Categories	Type of Tests	Specific Requirements
		(MPN) method. e. Test for Specified Microorganisms • Detailed test procedure for each specific microorganism tested (including identification and confirmation test) • Specification and acceptance criteria For details, please refer circular; Bil (4) dlm. BPFK/PKK/12/05. Maklumat Lanjutan Tentang Spesifikasi Baru Untuk Ujian Kontaminasi Mikrobial (30 Mac 2010).
	Quality Testing for Specific Ingredient	For a product containing specific ingredient such as Aphanizomenonflosaquae, Red Yeast Rice (Monascus purpureus), ingredient(s) derived from seafood and placenta, please refer to Appendix 4 and Appendix 5 for the testing requirement(s).

Note:

1. Finished product testing shall be conducted on every batch produced as per approved finished product specifications.
2. Manufacturer shall ensure that products manufactured locally or overseas are free from any contamination of *Burkholderia cepacia*. Please refer to these circulars for details:
   Ref. (90)dlm.BPFK/PPP/01/03/ Jld. 2
   Ujian Kontaminasi *Burkholderia cepacia* (19 December 2012).
3. Products are not allowed to send for gamma radiation treatment for the control of microbial contamination. Please refer to this circular for details:
   Ref. (54)dlm.BPFK/02/5/1.3.
   Aktiviti Pendedahan Produk Berdaftar kepada Sinar Gamma (18 April 2006)

10. GUIDELINE FOR THE SUBMISSION OF ANALYTICAL METHOD VALIDATION (AMV) DOCUMENTS

10.1 TYPES OF ANALYTICAL PROCEDURES TO BE VALIDATED

a) Identification tests

b) Quantitative tests for impurities' content

c) Limit tests for control of impurities

d) Quantitative tests of the active ingredient in the sample (assay and dissolution)

e) Pyrogen or Bacterial endotoxin test

f) Sterility test

g) Microbial Contamination Test

h) Biological Assay of Antibiotics

10.2 TYPICAL VALIDATION PARAMETERS FOR CHEMICAL TESTS

10.2.1 FULL VALIDATION FOR IN-HOUSE METHODS

Please refer to Table IX on next page.

TABLE IX:

Characteristics	Type of Analytical Method			
	Identification	Testing for Impurities		**Assay:** - dissolution (measurement only) - content/ potency
		Quantitation	Limit	
Accuracy		√		√
Precision **Repeatability** **Interm. Precision**		√ √ (1)		√ √ (1)
Specificity (2)	√	√	√	√
Detection Limit		(3)	√	
Quantitation Limit		√		
Linearity		√		√
Range		√		√

10.2.2 PARTIAL VALIDATION FOR COMPENDIAL/PHARMACOPOEIAL METHODS

TABLE X:

Characteristics	Type of Analytical Method			
	Identification	Testing for Impurities		**Assay:** - **dissolution (measurement only)** - **content/ potency**
		Quantitation	Limit	
Precision **Interm. Precision**				√ (1)
Specificity (2)	√	√	√	√
Detection Limit		(3)	√	
Quantitation Limit		√		

Note:

√ signifies that this characteristic is normally evaluated.

(1) In cases where reproducibility has been performed, intermediate precision is not needed.

(2) Lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s).

(3) May be needed in some cases.

10.3 TYPICAL VALIDATION CHARACTERISTICS FOR MICROBIOLOGICAL TESTS:

Table XI:

Microbiological tests	Validation characteristics
Bacterial Endotoxin Test	a. Test for Confirmation of Labelled Lysate Sensitivity(Verification of criteria for standard curve) b. Test for Interfering Factors (Inhibition/ Enhancement tests)
Sterility Test	Validation (Bacteriostasis or Fungistasis) Test • Quantity of Sample/ Volume of Sample • Membrane filtration/ Direct inoculation • Open System or Closed System (if uses Membrane filtration method) • Volume of rinsing fluid
Microbial Contamination Test	a. Validation of total viable aerobic count (suitability of the counting method in the presence of product) 1 batch b. Validation of test for specified microorganism (suitability of the test method) 1 batch
Microbiological Assay of Antibiotics	Linearity of the dose response relationship

Note:

1. All the analytical validation done by the industry should be in accordance to ASEAN Guidelines for Analytical Procedures, ICH Technical Requirements for Registration of Pharmaceuticals for Human Use under Validation of Analytical Procedures: Text and Methodology Q2 (R1), British Pharmacopoeia (BP), United States Pharmacopoeia (USP), or Japanese Pharmacopoeia (JP).
2. The applicants should ensure all documents available in the online Quest system are of the latest versions. All correspondence on the protocol of analysis and analytical method validation should comply with any relevant circulars regarding the registration process. Failure to do so may cause cancellation or rejection of product registration.

11. GUIDELINE FOR THE SUBMISSION OF PRODUCT SAMPLES FOR LABORATORY TESTING

The submission of sample for laboratory testing is as part of the registration process. This guideline consists of the general and specific requirements for the submission of samples to the Centre for Quality Control for laboratory testing. The general requirements define the condition of the samples to be submitted whereas the specific requirements illustrate the additional details needed according to the category of product.

The applicant is given a period of **14 working days** from the date of screening approval to send samples for laboratory testing. If the samples are not submitted within the specified time frame, the application will be rejected

The applicants shall comply with these requirements and failure to meet any of these requirements may cause rejection of the samples.

11.1 GENERAL REQUIREMENTS

a) After the screening has been approved, applicants must make appointment with the Laboratory Services Unit for the submission of registration samples for laboratory testing.

b) Requirements for samples:

i) A cover letter consisting of the following information should enclosed with every sample submission :

- Name and reference no of product;
- Name and address of holder;
- Name, email address and contact number of authorized person;

ii) Samples submitted must be in their original packaging & labelling.

iii) Samples submitted must be from the same manufacturing premise as stated in the application for registration.

iv) Samples submitted must have an expiry date of least one (1) year from the date of submission and must be from the same batch number

c) For imported products, applicants are required to submit the original import permit together with the samples for laboratory testing. The import permit will be issued by the Centre for Registration for natural product and Centre for Quality Control for pharmaceutical products. The applicant should ensure that the import permit is endorsed by the enforcement officer at the entry point.

11.2 SPECIFIC REQUIREMENTS

11.2.1 NATURAL PRODUCTS

a) Quantity of samples submitted must be:

   i. a minimum of 6 separate containers of all dosage forms with total contents of not less than 200 g or 200 mL; OR

   ii. a minimum of 60 pieces of plasters or patches with total of not less than 200g.

b) Centre for Quality Control will conduct testing for Heavy Metals, Microbial Contamination Test, Disintegration Test, Uniformity Of Weight and screening for adulteration for the samples submitted.

c) The result of the tested sample is final and there is no provision for appeal.

11.2.2 PHARMACEUTICAL PRODUCTS

(Upon request from NPRA)

a) An official certificate of analysis and the recent shelf-life specification from the manufacturer for the same batch of sample must be submitted with the sample.

b) Quantity of samples submitted must be in accordance with the quantity requested.

c) Other materials such as HPLC columns, reagents, etc must be submitted when requested.

d) Reference standards are required to be submitted along with the pharmaceutical products. Requirements for these reference standards are as follows:

i) The type & quantity of reference standards submitted must be in accordance with the type & quantity requested;

ii) Reference standards submitted must have an expiry date of least one (1) year from the date of submission. In special situations, an expiry date of not less than six (6) months can be accepted;

iii) All reference standards must be accompanied by an official certificate of analysis for the same batch with the stated purity (as is, dried, anhydrous etc.) and all other relevant information (water content, loss on drying etc.);

iv) All reference standards must be properly labeled with name, batch number, purity and expiry date;

v) All reference standards must be submitted in small sealed air-tight amber glass containers.

Attachment 21

Example of Finished Product Quality Specification

Finished Product Quality Control (FPQC) - Finished product Specification/ Specification Sheet

Company name/Address:
Product Name:
Batch no.
Dosage form:
Packaging:
Date of manufacture:
Date of expiry:

No.	Test	Method	Specification	Reference
1.	Appearance/ Organoleptic: Odour Colour	Ex: Macroscopic/ Microscopic	To describe the characteristic	In-house/ pharmacopoeia (e.g. BP/USP etc)
2.	Assay: (All active ingredients/ compounds claim on label)	HPLC/ GC/ MS/ UV	To specify	To specify
3.	Disintegration/Dissolution	To specify	DRGD	DRGD
4.	Uniformity of weight	To specify		
5.	Water content	To specify		
6.	Microbial contamination TAMC, TYMC, specified microorganism	To specify	DRGD	DRGD
7.	Heavy Metal Contamination: Lead, Arsenic, Cadmium, Mercury	To specify	DRGD	DRGD
8.	Etc:			

Signature:
Name:
Designation: (At least by Quality Assurance Manager or equivalent)
Date of signature:

*** The above parameters are only as an example; other test may be required for specific product.**