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

<table>
<tr><th rowspan="2">NO.</th><th rowspan="2">REVISION</th><th colspan="2">UPDATES</th><th rowspan="2">REFERENCE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>1.</td><td>March 2017</td><td>Section A: General Overview,</td><td>Amendments and addition under 1.4 Medical Device -Drug-Cosmetic Interphase Products, Table III: SUMMARY OF MEDICAL DEVICE-DRUG-COSMETIC INTERPHASE (MDDCI) PRODUCT CLASSIFICATION DECISION as per Attachment 1.</td><td>MDDCI Steering Committee Meeting No. 01/2016 and 02/2016</td></tr>
<tr><td>2.</td><td>March 2017</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td>Addition of the substance Melaleuca Leucadendra (Cajeput Oil) and warning statement for products containing the substance ;
<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>100.</td><td>MELALEUCA LEUCADENDRA (CAJEPUT OIL)

(Please refer Attachment 2)</td></tr></table></td><td>Directive No. 13 Year 2016, (Ref. (44)dlm.BPFK/PPP/07/25)
Direktif Bagi Semua Produk Yang Mengandungi Bahan Aktif Minyak Cajeput (Melaleuca Leucadendra) Dalam Bentuk Dos Topikal Dengan Menambah Kenyataan Amaran Berkaitan Risiko Masalah Pernafasan/ Kesukaran Bernafas</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>3.</td><td>March 2017</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td>Addition of the following statements (as highlighted in yellow) for products containing Warfarin;
<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>175.</td><td>WARFARIN

(Please refer Attachment 3)</td></tr></table></td><td>Directive No. 15 Year 2016 (Ref: BPFK/PPP/07/25 (1) Jld 1.)
Direktif Bagi Semua Produk Yang Mengandungi Warfarin Dengan Risiko Kesan Advers Calciphylaxis</td></tr>
<tr><td>4.</td><td>March 2017</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td>Addition of the following substance and the safety information/ statements;
<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>45.</td><td>CODEINE

(Please refer Attachment 4)</td></tr></table></td><td>Directive No. 16 Year 2016 (Ref: BPFK/PPP/07/25 (2) Jld 1.)
Direktif Bagi Semua Produk Yang Mengandungi Codeine Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers Respiratory Depression</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>5.</td><td>March 2017</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td>Addition of the following statements (as highlighted in yellow) for products containing Sodium Valproate;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>155.</td><td>SODIUM VALPROATE

(Please refer Attachment 5)</td></tr></table></td><td>Directive No. 17 Year 2016 (Ref: BPFK/PPP/07/25 (3) Jld 1.)

Direktif Bagi Semua Produk Yang Mengandungi Sodium Valproate Bagi Memperkukuhkan Amaran Berkaitan Risiko Abnormal Pregnancy Outcomes</td></tr>
<tr><td>6.</td><td>March 2017</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td>Addition of the following statements (as highlighted in yellow) for products containing Olanzapine ;

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>119.</td><td>OLANZAPINE
(Please also refer to ANTIPSYCHOTIC AGENT)

(Please refer Attachment 6)</td></tr></table></td><td>Directive No. 19 Year 2016. (Ref: BPFK/PPP/07/25 (5) Jld.1.)
Direktif Bagi Semua Produk Yang Mengandungi Olanzapine Dengan Maklumat Keselamatan Berkaitan Kesan Advers Drug Reaction With Eosinophilia And Systemic Symptoms (DRESS)</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>7.</td><td>March 2017</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

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

<table><tr><th>NO.</th><th>SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)</th></tr><tr><td>87.</td><td>INTERFERON ALPHA

(Please refer Attachment 7)</td></tr><tr><td>88.</td><td>INTERFERON BETA

(Please refer Attachment 8)</td></tr></table></td><td>Directive No. 1 Year 2017. (Ref: BPFK/PPP/07/25 (6) Jld.1.)
Direktif Bagi Semua Produk Yang Mengandungi Interferon Alfa Dan Interferon Beta : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers Pulmonary Arterial Hypertension (PAH)</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>March 2017</td><td>APPENDIX 8: LIST OF PERMITTED, PROHIBITED AND RESTRICTED SUBSTANCES</td><td>Addition of the following substance in Table 8.2.2 : LIST OF <u>RESTRICTED EXCIPIENTS</u>

8.2.2 LIST OF <u>RESTRICTED EXCIPIENTS</u>
<table><tr><th colspan="2">Excipients</th><th colspan="2">Restrictions</th></tr><tr><td colspan="4">4. Others</td></tr><tr><td>a) Phthalates</td><td>Variant</td><td colspan="2">Maximum Limit of Daily Exposures (mg/kg body weight/day)</td></tr><tr><td></td><td>Dibutyl Phthalate (DBP)</td><td colspan="2">0.01mg/ kg/ day</td></tr><tr><td></td><td>Diethyl Phthalate (DEP)</td><td colspan="2">4mg/ kg/ day</td></tr><tr><td></td><td>Polyvinyl Acetate Phthalate (PVAP)</td><td colspan="2">2mg/ kg/ day</td></tr></table></td><td>Circular Ref; (22)dlm.BPFK/PPP/01/03 Jld. 3

Pekeliling Bagi Menetapkan Had Maksima Pendedahan Harian Bahan Kimia Sintetik Phthalates Iaitu Dibutyl Phthalate (DBP), Diethyl Phthalate (DEP) Dan Polyvinyl Acetate Phthalate (PVAP) Bagi Formulasi Produk Berdaftar Dalam Bentuk Oral Dosage Form</td></tr>
</table>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
9.	March 2017	**APPENDIX 5 : GUIDELINE ON REGISTRATION OF NATURAL PRODUCTS**	**Amendment of the following statement ;** **3.2 HERBAL TEA** ~~(Under revision, kindly refer to Circular (19)dlm.BPFK/PPP/01/03 Jld.3)~~ Amended to; Please refer to Circular Ref: (19)dlm.BPFK/PPP/01/03 Jld.3. Pekeliling Kriteria Baru Pengkelasan Produk *Food-Drug Interphase* (FDI).	**Circular Ref: (19)dlm.BPFK/PPP/01/03 Jld.3.** Pekeliling Kriteria Baru Pengkelasan Produk *Food-Drug Interphase* (FDI).
10.	March 2017	**APPENDIX 4 : GUIDELINE ON REGISTRATION OF HEALTH SUPPLEMENTS**	**Addition of the following statements under Subappendix 4.5 : SPECIFIC DOSSIER REQUIREMENT FOR REGISTRATION OF HEALTH SUPPLEMENTS** **3. ACTIVE INGREDIENT** **Source of Active ingredient:** **USE OF PROTECTED/ ENDANGERED INGREDIENTS** **a) PROTECTED/ ENDANGERED WILDLIFE SPECIES** It is the responsibility of the applicant to ensure that the	Memo from Complementary & Alternative Medicine Section (46)dlm.BPFK/PPP/06/17 Jld.86

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			ingredient(s) derived from wildlife species its parts and derivatives used in the formulation **COMPLIES** with the Wildlife Conservation Act 2010 (Act 716) and International Trade in Endangered Species Act 2008 (Act 686). Both guidelines can be downloaded through this link http://www.wildlife.gov.my. The applicant shall contact the following department to obtain the necessary permit/ license. A copy of the permit/ license shall be attached together with the application form for product registration. Department of Wildlife and National Parks, Peninsular Malaysia Km. 10, Jalan Cheras, 56100 Kuala Lumpur, Tel: +603-90866800, Fax: +603-90753873 **b) ENDANGERED BOTANICAL SPECIES** It is the responsibility of the applicant to declare the source of the botanical ingredient if it is listed under the International Trade in Endangered Species Act 2008	

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			(Act 686). If the ingredient is from a local source, a special permit/ license shall be obtained from the: Division of Protection and Quarantine of Plants, Department of Agriculture, Tingkat 1-3, Wisma Tani, Jalan Sultan Salahuddin, 50632 Kuala Lumpur. Tel: +603 - 20301400, Fax: +603 - 26913550.	
11.	March 2017	**APPENDIX 4 : GUIDELINE ON REGISTRATION OF HEALTH SUPPLEMENTS**	**Amendment of the following statement at SECTION D : LABELLING REQUIREMENTS** "Please consult a ~~healthcare professional~~ doctor/pharmacist before taking this product".	Memo from Complementary & Alternative Medicine Section (46)dlm.BPFK/PPP/ 06/17 Jld.86

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
12.	March 2017	**APPENDIX 4 : GUIDELINE ON REGISTRATION OF HEALTH SUPPLEMENTS**	**Amendment of the following statement at SECTION E : PARTICULAR OF PRODUCT OWNER, MANUFACTURER, IMPORTER AND OTHER MANUFACTURER** • Other details such as ~~Section E1: Product Owner, Section E2: Manufacturer, Section E3: Repacker, Section E4: Other manufacturer involved in the manufacturing process, Section E5: Store address and Section E6 Importer~~ product owner, manufacturer, repacker, other manufacturer involved in the manufacturing process, store address and importer (If any) have to filled. It is mandatory for the ~~R~~repacker to acquire GMP certificate.	Memo from Complementary & Alternative Medicine Section (46)dlm.BPFK/PPP/ 06/17 Jld.86
13.	March 2017	**APPENDIX 4 : GUIDELINE ON REGISTRATION OF HEALTH SUPPLEMENTS**	**Addition of the following statement for each of the following section at SECTION A : PRODUCT PARTICULARS** • **Contraindication** • **Warnings and Precautions** • **Drug Interactions** • **Side Effects/ Adverse Reactions** • **Signs and Symptoms of Overdose and Treatment** Note : If there is no information available for this section, please state as 'Unknown'.	Memo from Complementary & Alternative Medicine Section (46)dlm.BPFK/PPP/ 06/17 Jld.86

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
14.	March 2017	**APPENDIX 6 : GUIDELINE ON REGULATORY CONTROL OF ACTIVE PHARMACEUTICAL INGREDIENTS (APIs)**	**Addition of the following statement under SECTION 4. PROCEDURE FOR SUBMISSION AND RELATED INFORMATION, 4. PROCEDURE FOR SUBMISSION AND RELATED INFORMATION** **(Please refer Attachment 9)**	Drug Evaluation Committee Meeting No. 05/2017
15.	March 2017	**APPENDIX 6 : GUIDELINE ON REGULATORY CONTROL OF ACTIVE PHARMACEUTICAL INGREDIENTS (APIs)**	**Addition of the following statement under SECTION 4. PROCEDURE FOR SUBMISSION AND RELATED INFORMATION, 5. OPTION 1 :DRUG MASTER FILE (DMF)** **(Please refer Attachment 10)**	Drug Evaluation Committee Meeting No. 05/2017

ATTACHMENT 1 :

NO	PRODUCT	INTENDED PURPOSE/ INDICATION AND MODE OF ACTION (MOA)	CATEGORY	CUSTODIAN AGENCY
2.	**Blood bag containing anticoagulant/ preservation agent**	To collect and preserve blood and its components (for use with cytapheresis device only) **NOTE :** It is not for direct intravenous infusion.	~~**Device-Drug combination product regulated as**~~ **MEDICAL DEVICE**	**MDA**
5.	**Dental Products** **i.Fluoride dental preparation** (eg. Toothpaste, tooth powder, mouthwash, dental varnish)	**[Addition of the following:]** d. As a desensitizing agent for the treatment of hypersensitive teeth, for sealing the dentinal tubules for cavity preparations or on sensitive root surfaces or to line cavity preparations under amalgam restorations.	**MEDICAL DEVICE**	**MDA**
29.	**Wart Products** (eg. pen applicator containing a caustic agent, cyryogenic kit with refrigerant)	a. Containing a caustic agent eg. trichloroacetic acid (TCA) that destroys warts by chemical coagulation of proteins.	**DRUG** ~~(If it contains a pharmacologically active substance)~~	

ATTACHMENT 2 :

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
100.	**MELALEUCA LEUCADENDRA (CAJEPUT OIL)** The following warning statement shall be included on the labels and in the package insert of products containing Melaleuca Leucadendra (cajeput oil) in topical dosage form: a) Malay language:- **AMARAN:** **Produk ini tidak boleh disapu pada muka, khususnya di kawasan hidung bayi dan kanak-kanak. Ia mungkin boleh menyebabkan masalah pernafasan / kesukaran bernafas.** b) English language:- **WARNING:** **This product should not be applied to the facial area, in particular around the nose of infants and small children. It might cause breathing problem / shortness of breath.**

ATTACHMENT 3 :

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
175.	**WARFARIN** a) The following statements shall be included in the package insert of products containing Warfarin: **CAUTION** Topical preparations containing methyl salicylate should be used with care in patients on Warfarin and excessive usage is to be avoided as potentially dangerous drug interaction can occur. ***Special Warnings and Precautions for Use***: *Calciphylaxis is a rare syndrome of vascular calcification with cutaneous necrosis,*

	associated with high mortality. The condition is mainly observed in patients with end-stage renal disease on dialysis or in patients with known risk factors such as protein C or S deficiency, hyperphosphatemia, hypercalcaemia or hypoalbuminaemia. Rare cases of calciphylaxis have been reported in patients taking warfarin, also in the absence of renal disease. In case calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin. ***Adverse Drug Reactions***: *Skin and subcutaneous tissue disorders* *Frequency 'not known': Calciphylaxis* b) The following statements shall be included in the RiMUP of products containing Warfarin: ***Possible Side Effects***: *Tell your doctor straight away if you have any of the following side effects :* [...] *A painful skin rash. On rare occasions warfarin can cause serious skin conditions, including one called calciphylaxis that can start with a painful skin rash but can lead to other serious complications. This adverse reaction occurs more frequently in patients with chronic kidney disease.*

Attachment 4 :

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
45.	**CODEINE** The following safety information/ statements shall be included in the package insert of products containing Codeine: **Therapeutic Indications** [Product name] is indicated for the relief of painful disorders such as headache, dysmenorrhea, conditions involving musculoskeletal pain, myalgias and neuralgias. It is also indicated as an analgesic and antipyretic in conditions accompanied by discomfort and fever, such as the common cold and viral infections. [Product name] is an effective analgesic after dental work and tooth extractions. Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone). Pada bahagian **Dosing and Administrations** Paediatric population: • Children aged less than 12 years: Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine. [Product name] is contraindicated in children below the age of 12 years for the symptomatic treatment of cold. • Children aged 12 years to 18 years: [Product name] is not recommended for use in children aged 12 years to 18 years with compromised respiratory function. **Contraindications** • In children below the age of 12 years for the symptomatic treatment of colds due to an increased risk of developing serious and life-

threatening adverse reactions.

- In all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to increased risk of developing serious and life-threatening adverse reactions.
- In women who are breastfeeding.
- In patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

Special Warnings and Precautions for use

CYP2D6 metabolism

Codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite. If a patient has a deficiency or is completely lacking this enzyme an adequate analgesic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal. Estimates of prevalence of ultra-rapid metabolisers in different populations are summarised below:

Population	**Prevalence %**
African/Ethiopian	29%
African American	3.4 to 6.5%
Asian	1.2 to 2.0%
Caucasian	3.6 to 6.5%
Greek	6.0%
Hungarian	1.9%
Northern European	1.0 to 2.0%

Post-operative use in children

There have been reports in the published literature that codeine given post-

	operatively in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, led to rare, but life-threatening adverse events including death. All children received doses of codeine that were within the appropriate dose range; however there was evidence that these children were either ultra-rapid or extensive metabolisers in their ability to metabolise codeine to morphine. Children with compromised respiratory function Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity. **Pregnancy and Lactation** Pregnancy Careful consideration should be given before prescribing the product for pregnant patients. Opioid analgesics may depress neonatal respiration and cause withdrawal effects in neonates of dependent mothers. As a precautionary measure, use of [Product name] should be avoided during the third trimester of pregnancy and during labor. Breastfeeding [Product name] is contraindicated in women during breastfeeding. At normal therapeutic doses codeine and its active metabolite may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant. However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.

Attachment 5 :

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
155.	**SODIUM VALPROATE** The following statements shall be included in the package insert of products containing Sodium Valproate: **Posology and Method of administration :** Female children, female adolescents, women of childbearing potential and pregnant women [Product Name] should be initiated and supervised by a specialist experienced in the management of epilepsy. Treatment should only be initiated if other treatments are ineffective or not tolerated and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably [Product Name] should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses. **Special warnings and precautions for use :** Female children/Female adolescents/ Women of childbearing potential/Pregnancy [Product Name] should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate. The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with [Product Name] plans a pregnancy or if she becomes pregnant. Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of [Product

Name] during pregnancy (see Fertility, Pregnancy and Lactation).

The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks.

In particular the prescriber must ensure the patient understands:

- The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.
- The need to use effective contraception.
- The need for regular review of treatment.
- The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.

In women planning to become pregnant, all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible:

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy.

Fertility, pregnancy and lactation:

[Product Name] should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated. Women of childbearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

Pregnancy Exposure Risk related to valproate

Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.

Congenital malformations

	Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established. Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems. Developmental disorders Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded. Studies in preschool children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems. Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ. There are limited data on the long term outcomes. Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study

	population. Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD). <u>Female children, female adolescents and woman of childbearing potential (see above and Special Warnings and Precautions for use)</u> If a Woman wants to plan a Pregnancy • During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child. • In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed • In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible. Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of epilepsy. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to: - Use the lowest effective dose and divide the daily dose valproate into several small doses to be taken throughout the day. - The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations. - Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure. - To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

Attachment 6

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
119.	**OLANZAPINE** (Please also refer to ANTIPSYCHOTIC AGENT) The following statements shall be included in the package insert and RiMUP of products containing Olanzapine: **Package Insert** **a) Special Warnings and Precautions for Use:** Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with olanzapine exposure. DRESS consists of a combination of three or more of the following: cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis. Discontinue olanzapine if DRESS is suspected. **b) Adverse Drug Reactions**: **Skin and subcutaneous tissue disorders** Very rare: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects**: Very rare: Serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia).

Attachment 7

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
87.	**INTERFERON ALPHA** The following statements shall be included in the package insert and RiMUP of products containing Interferon Alpha: **Package Insert** **a) Adverse Drug Reactions:** **Respiratory, thoracic and mediastinal disorders:** Frequency 'not known': Pulmonary arterial hypertension (class label for interferon products). Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alpha products, notably in patients with risk factors for PAH (such as portal hypertension, HIV infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alpha. **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects** Tell your doctor immediately if you experience: • Shortness of breath, persistent coughing, fatigue, chest pain, or swelling of the ankles, limbs and abdomen. These may indicate pulmonary arterial hypertension (high blood pressure in the arteries that supply the lungs). **Reference : Directive No. 1 Year 2017. Ref. BPFK/PPP/07/25 (6) Jld 1.** Direktif Bagi Semua Produk Yang Mengandungi Interferon Alfa Dan Interferon Beta : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers *Pulmonary Arterial Hypertension (PAH)*

Attachment 8

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
88.	**INTERFERON BETA** The following statements shall be included in the package insert and RiMUP of products containing Interferon Beta: **Package Insert** **a) Adverse Drug Reactions:** **Respiratory, thoracic and mediastinal disorders:** Frequency 'not known': Pulmonary arterial hypertension (class label for interferon products). Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products. Events were reported at various time points including up to several years after starting treatment with interferon beta. **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects** Tell your doctor immediately if you experience: • Shortness of breath, persistent coughing, fatigue, chest pain, or swelling of the ankles, limbs and abdomen. These may indicate pulmonary arterial hypertension (high blood pressure in the arteries that supply the lungs). **Reference : Directive No. 1 Year 2017. Ref. BPFK/PPP/07/25 (6) Jld 1.** Direktif Bagi Semua Produk Yang Mengandungi Interferon Alfa Dan Interferon Beta : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna Dengan Maklumat Keselamatan Berkaitan Risiko Kesan Advers *Pulmonary Arterial Hypertension (PAH)*

Attachment 9

4. PROCEDURE FOR SUBMISSION AND RELATED INFORMATION

4.2 REQUIRED INFORMATION

4.2.1 Documents required for each option of API Information submission are summarized as in table 1:

Table 1:

Summary of documents required for API Information Submission:

Option	Documents required
Option 1 (DMF)	• Part II-S ACTD via the online system (Open Part only) • DMF (*See Section 5 for details*) • Current GMP certificate or any other evidence of GMP compliance from a regulatory authority; and • Current Certificates of Analysis of API from API Manufacturer and finished product manufacturer (2 batches each).
Option 2 (CEP)	• Part II-S ACTD via the online system (as deemed appropriate) • CEP (*See Section 6 for details*); and, • Current Certificates of Analysis of API from API Manufacturer and finished product manufacturer (2 batches each).
Option 3 (Full ACTD)	• Full details of Part II-S ACTD via the online system.(See Section 7 for details) • Current GMP certificate or any other evidence of GMP compliance from a regulatory authority; and, • Current Certificates of Analysis of API from API Manufacturer and finished product manufacturer (2 batches each).

*GMP certificates for **ALL** manufacturers involved in manufacturing process of API.

Attachment 10

5. OPTION 1 : DRUG MASTER FILE (DMF)

5.7. Where the API and the finished product are manufactured by the same manufacturer, information on the production, quality control and stability of the API may be submitted as part of the dossier for the finished product (ACTD) rather than in a separate DMF. However, the company is not precluded from submitting a DMF for the API.

a. The DMF is divided into two parts, namely the Open (or PRH's) part and the Closed (or restricted) part.

b. The documents required for an application making a reference to a DMF are as follows:

- **From the PRH:**
  - Open part of the DMF, as part of the submitted product dossier (the open part contains most of the information in Part IIS (ACTD) - i.e. sections S1, S2.1 and S3 to S7);
    - S1 General Information
      - 1.1 Nomenclature
      - 1.2 Structure
      - 1.3 General Properties
    - S2 Manufacture
      - 2.1 Manufacture(s)/Site of Manufacture
        - **ALL** manufacturers involved in manufacturing process of API.
    - S3 Characterisation
      - 3.1 Elucidation of Structure and other Characteristics
      - 3.2 Impurities