LIST OF UPDATES FOR DRGD SECOND EDITION, SEPTEMBER 2016, REVISION JULY 2018

(April 2018 Updates)

* Please note that this monthly list of updates will only be updated in the full version of DRGD in July 2018 revision. However, the effective dates are as stated below in the respective column.

NO.	UPDATES		EFFECTIVE DATE	REFERENCE
	SECTION/ APPENDIX	DETAILS		
1.	**5. TYPES OF APPLICATION** **5.1.4 REGISTRATION OF PRODUCT FOR EXPORT ONLY (FEO)**	**<u>Addition</u> of the following information;** **a) Registration of FEO product only applies to locally manufactured product,** **b) Imported product for pack/repack locally and for re-export falls under *Regulation 7(2)(b); Control of Drugs and Cosmetic Regulations 1984*,** **c) Documents required for FEO registration of pharmaceutical product includes:** **(i) COA of finished product for at least 1 pilot batch.** **(ii) Stability data (real time and accelerated stability study) for at least 1 pilot batch.** (Please refer Attachment 1) (changes as highlighted in yellow)	**15 March 2018**	**Directive No. 11 Year 2018. (Ref: BPFK/PPP/07/25 (11) Jld.2)** Direktif Kaji Semula Pendaftaran Produk Untuk Tujuan Eksport Sahaja (FEO)

NO.	UPDATES		EFFECTIVE DATE	REFERENCE
	SECTION/ APPENDIX	DETAILS		
2.	**5. TYPES OF APPLICATION** **5.1.4 REGISTRATION OF PRODUCT FOR EXPORT ONLY (FEO)**	**<u>Addition</u> of the following information;** **Conditions for the registration of FEO products:** **(i) Countries which do not impose specific regulatory requirements as Malaysia (e.g. formulation with banned/ prohibited ingredients, zone IVB stability study, bioavailability/ bioequivalence study, API evaluation etc.); OR** **(ii) Countries which have different requirements such as different formulation (e.g. colour or strength of ingredients), shape or manufacturing process, etc. as compared to a registered product; OR** **(iii) Difference in classification category of the products (e.g. as food in the importing country) for health supplements and traditional products.** (Please refer Attachment 1) (changes as highlighted in yellow)	**1 May 2018**	**Policy Meeting No. 01 Year 2018**

<table>
<tr><th rowspan="2">NO.</th><th colspan="2">UPDATES</th><th rowspan="2">EFFECTIVE DATE</th><th rowspan="2">REFERENCE</th></tr>
<tr><th>SECTION/ APPENDIX</th><th>DETAILS</th></tr>
<tr><td>3.</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> on the adverse effect of photosensitivity;

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

(Please refer Attachment 2)</td></tr></table></td><td>1 May 2018</td><td>Directive No. 12 Year 2018. (Ref: BPFK/PPP/07/25 (12) Jld.2)
Direktif Untuk Semua Produk Yang Mengandungi Mesalazine : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Kesan Advers Photosensitivity</td></tr>
<tr><td>4.</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 the risk of increased ALT level due to drug interaction between ethinylestradiol with the combination product containing ombitasvir / paritaprevir / ritonavir and dasabuvir;

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

(Please refer Attachment 3)</td></tr></table></td><td>1 May 2018</td><td>Directive No. 13 Year 2018. (Ref: BPFK/PPP/07/25 (13) Jld.2)
Direktif Untuk Semua Produk Yang Mengandungi Ethinylestradiol : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Risiko Peningkatan Para Alanine Transaminase (ALT)</td></tr>
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<tr><td></td><td></td><td></td><td></td><td>Akibat Interaksi Dengan Produk Kombinasi Ombitasvir / Paritaprevir / Ritonavir Dan Dasabuvir</td></tr>
<tr><td>5.</td><td>APPENDIX 9 : LABELLING REQUIREMENTS

(9.2 : SPECIFIC LABELLING REQUIREMENTS)</td><td><u>Addition</u> of the following substance and <u>safety information/ statements</u> regarding Anaphylactic/ Anaphylactoid Reaction and Severe Cutaneous Adverse Reactions (SCAR);

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(Please refer Attachment 4)</td></tr></table></td><td>1 May 2018</td><td>Directive No. 14 Year 2018. (Ref: BPFK/PPP/07/25 (14) Jld.2)
Direktif Untuk Semua Produk Yang Mengandungi Carbocisteine Dan Acetylcysteine : Pengemaskinian Label, Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Anaphylactic/ Anaphylactoid Reaction Dan Severe Cutaneous Adverse Reactions (SCAR)</td></tr>
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Direktif Untuk Semua Produk Yang Mengandungi Carbocisteine Dan Acetylcysteine : Pengemaskinian Label, Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Anaphylactic/ Anaphylactoid Reaction Dan Severe Cutaneous Adverse Reactions (SCAR)</td>
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Attachment 1

5.1.4 REGISTRATION OF PRODUCT FOR EXPORT ONLY (FEO)

a) Refers to locally manufactured products for ~~export only which are not marketed locally with a different formulation (e.g. colour or strength of ingredients) or shape compared to a registered product;~~ exporting purpose only and not marketed locally. This does not apply to imported products meant to be packed/repacked locally and to be re-export (the application falls under Regulation 7(2)(b), Control of Drugs and Cosmetic Regulations 1984. A separate application form may be obtained from the NPRA website).

b) ~~For products containing ingredients/ formulations which are not allowed by the Authority for local use, applicant shall submit a confirmation in writing from the competent authority of the importing country that there is no objection to the importation and sale of the said ingredients/ formulations. Evidence of registration of the said formulation with the competent authority in importing country may be submitted as supporting data;~~

Applications for registration of FEO products are only accepted in the following condition(s) and to be supported with evidence issued by the competent Authority of the importing countries (self-declaration is not accepted):

(i) Countries which do not impose specific regulatory requirements as Malaysia (e.g. formulation with banned/ prohibited ingredients, zone IVB stability study, bioavailability/ bioequivalence study, API evaluation etc.); OR

(ii) Countries which have different requirements such as different formulation (e.g. colour or strength of ingredients), shape or manufacturing process, etc. as compared to a registered product; OR

(iii) Difference in classification category of the products (e.g. as food in the importing country) for health supplements and traditional products.

c) ~~Upon application,~~ Applicant may apply for a Certificate of Pharmaceutical Product (CPP) ~~will be issued to the applicant~~ for the registered FEO products.

d) For a registered product intended for exportation as well as to be sold in Malaysia:

- New application for registration for export only will NOT be required if there is no change in the formulation and appearance of the registered product.
- Applicant may apply a CPP ~~will be issued to the applicant~~ for the registered product and together with an explanation/ declaration letter of any difference(s) to the importing country (e.g. a product exported with a different product name), ~~upon application.~~

e) For a registered product, now intended to be for export only and no longer for sale in Malaysia:

- Application for registration as a FEO product is required.

- The existing registration number (i.e. MAL number) will remain the same but with the addition of the administrative code E (For Export Only)

f) Applications for registration of FEO products are processed based on abridged evaluation. However, the additional following requirements must be fulfilled for pharmaceutical products (not applicable to health supplements and traditional products):
   (i) Certificate of Analysis (COA) of finished product for at least 1 pilot batch; AND
   (ii) Minimum 6 months stability data (real time and accelerated stability study) for at least 1 pilot batch.

g) ~~Applications shall be submitted by using an application form BPFK 438.1 (for Generic Medicines/ Health Supplements) and BPFK 438.1 (T) (for Traditional Products).~~
   ~~***Note:*** *The applicant must first register membership for QUEST system with NPRA and subsequently purchase a USB Token that contains a User Digital Certificate, from MSC Trustgate.com Sdn. Bhd. This is to enable the applicant to access the system for product updating once the application for registration is approved. For further detail, please refer Section A General Overview under 3.3 How To Apply.*~~
   Application is via online submission in QUEST system.

Reference: Bil (11)dlm.BPFK/07/25 Jld.2 Direktif Kaji Semula Pendaftaran Produk Untuk Tujuan Eksport Sahaja (FEO)

Attachment 2

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	MESALAZINE The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing mesalazine; **Package Insert** **a) Warnings and Precautions:** Photosensitivity More severe reactions are reported in patients with pre-existing skin conditions such as atopic dermatitis and atopic eczema. **b) Adverse Effects/ Undesirable Effects:** Skin and Subcutaneous Tissue Disorders Frequency "rare": Photosensitivity **Consumer Medication Information Leaflet (RiMUP)** **a) Side Effects:** Photosensitivity: Itchy eruption and exaggerated sunburn on patches of sun-exposed skin **Reference: Directive No. 12 Year 2018. Ref. BPFK/PPP/07/25 (12) Jld 2.** Direktif Untuk Semua Produk Yang Mengandungi Mesalazine : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Amaran Kesan Advers *Photosensitivity*

Attachment 3

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	ETHINYLESTRADIOL Please refer to CYPROTERONE ACETATE WITH ETHINYLESTRADIOL IN COMBINATION for products containing cyproterone acetate 2mg with ethinylestradiol 0.035mg in combination. The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing ethinylestradiol; **Package Insert** **a) Contraindications:** [Product name] is contraindicated for concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir (See Section Warnings and Precautions and Section Interactions with Other Medicaments). **b) Warnings and Precautions:** ALT elevations During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir with/without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Patients who are taking ethinylestradiol-containing medicinal products must switch to an alternative method of contraception (e.g. progestin only contraception or non-hormonal methods) prior to initiating ombitasvir / paritaprevir / ritonavir and dasabuvir therapy (See Section Contraindications and Section Interactions with Other Medicaments).

c) Interactions with Other Medicaments:

Concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (See Section Contraindications and Section Warnings and Precautions). Therefore, users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. [Product name] can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Consumer Medication Information Leaflet (RiMUP)

a) Before You Use <product name>:

When you must not use it:
Do not use <product name> if you have Hepatitis C and are taking the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir.

Taking other medicines:
Do not use <product name> if you have Hepatitis C and are taking the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir. Your doctor will prescribe another type of contraceptive before starting the treatment with these medicinal products.

Reference: Directive No. 13 Year 2018. Ref. BPFK/PPP/07/25 (13) Jld 2. Direktif Untuk Semua Produk Yang Mengandungi Ethinylestradiol : Pengemaskinian Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Risiko Peningkatan Paras Alanine Transaminase (ALT) Akibat Interaksi Dengan Produk Kombinasi Ombitasvir / Paritaprevir / Ritonavir Dan Dasabuvir

Attachment 4

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	CARBOCISTEINE The following statements shall be included in the label, package insert and Consumer Medication Information Leaflet (RiMUP) for products containing carbocisteine; **Label** <Product name> may cause severe allergy and serious skin reactions. Stop using <Product name> and seek medical assistance immediately if you experience any of the following symptoms: • Severe allergy: breathing difficulties, light headedness, skin swellings or rash. • Severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation. **Package Insert** **a) Adverse Effects / Undesirable Effects:** Immune System Disorders: Anaphylactic / anaphylactoid reaction Skin and Subcutaneous Tissue Disorders: Severe cutaneous adverse reactions (SCAR) e.g. erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In most of these cases reported at least one other drug was administered at the same time, which may have possibly enhanced the described mucocutaneous effects. **Consumer Medication Information Leaflet (RiMUP)**

	a) Side Effects: <Product name> may cause severe allergy and serious skin reactions. Stop using <Product name> and seek medical assistance immediately if you experience any of the following symptoms: • Severe allergy: breathing difficulties, light headedness, skin swellings or rash. • Severe skin reaction: skin reddening, blisters, rash, fever, sore throat or eye irritation. **Reference: Directive No. 14 Year 2018. Ref. BPFK/PPP/07/25 (14) Jld 2.** Direktif Untuk Semua Produk Yang Mengandungi Carbocisteine Dan Acetylcysteine : Pengemaskinian Label, Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan *Anaphylactic/ Anaphylactoid Reaction* Dan *Severe Cutaneous Adverse Reactions* (SCAR)

Attachment 5

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	ACETYLCYSTEINE The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing acetylcysteine; **1. Injectable products with the indication as antidote for paracetamol overdose** **Package Insert** **a) Warnings and Precautions:** Hypersensitivity Reactions Serious acute hypersensitivity reactions during acetylcysteine administration including rash, hypotension, wheezing, and/or shortness of breath, have been observed in patients receiving intravenous acetylcysteine for paracetamol overdose and occurred soon after initiation of the infusion (see Adverse Effects/Undesirable Effects). If a severe hypersensitivity reaction occurs, immediately stop the infusion of acetylcysteine and initiate appropriate treatment. Acute flushing and erythema of the skin may occur in patients receiving acetylcysteine intravenously. These reactions usually occur 15 to 60 minutes after initiating the infusion and often resolve spontaneously despite continued infusion of acetylcysteine. If a reaction to acetylcysteine involves more than simply flushing and erythema of the skin, it should be treated as a hypersensitivity reaction. Management of less severe hypersensitivity reactions should be based upon the severity of the reaction and include temporary interruption of the infusion and/or administration of antihistaminic drugs. The acetylcysteine infusion may be carefully restarted after treatment of the hypersensitivity symptoms has been initiated; however, if the

	hypersensitivity reaction returns upon re-initiation of treatment or increases in severity, acetylcysteine should be discontinued and alternative patient management should be considered. **b) Adverse Effects / Undesirable Effects:** <u>Immune System Disorders:</u> Anaphylactic/anaphylactoid reaction <u>Skin and Subcutaneous Tissue Disorders:</u> Severe cutaneous adverse reactions (SCAR) e.g. erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In most of these cases reported at least one other drug was administered at the same time, which may have possibly enhanced the described mucocutaneous effects. **2. All other products (not indicated for treatment of paracetamol overdose)** **<u>Package Insert</u>** **a) Contraindications:** [Product name] is contraindicated for concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir (See Section Warnings and Precautions and Section Interactions with Other Medicaments). **b) Warnings and Precautions:** ALT elevations During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir with/without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Patients who are taking ethinylestradiol-containing medicinal products

must switch to an alternative method of contraception (e.g. progestin only contraception or non-hormonal methods) prior to initiating ombitasvir / paritaprevir / ritonavir and dasabuvir therapy (See Section Contraindications and Section Interactions with Other Medicaments).

c) Interactions with Other Medicaments:

Concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (See Section Contraindications and Section Warnings and Precautions). Therefore, users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. [Product name] can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Consumer Medication Information Leaflet (RiMUP)

a) Before You Use <product name>:

When you must not use it:
Do not use <product name> if you have Hepatitis C and are taking the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir.

Taking other medicines:
Do not use <product name> if you have Hepatitis C and are taking the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir. Your doctor will prescribe another type of contraceptive before starting the treatment with these medicinal products.

Reference: Directive No. 14 Year 2018. Ref. BPFK/PPP/07/25 (14) Jld 2. Direktif Untuk Semua Produk Yang Mengandungi Carbocisteine Dan Acetylcysteine : Pengemaskinian Label, Sisip Bungkusan Dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan *Anaphylactic/ Anaphylactoid Reaction* Dan *Severe Cutaneous Adverse Reactions* (SCAR)