LIST OF UPDATES FOR
DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD) THIRD EDITION,
SECOND REVISION JANUARY 2022
(September 2021 Updates)

There are five (5) amendments for the September 2021 DRGD Updates as below:

Main Body of DRGD Third Edition, First Revision July 2021

Section E: Post-Registration Process

1. Amendment of 21.1 Pharmacovigilance, Page 60
2. Amendment of 21. Post-Marketing Activities, Page 62

Appendices of DRGD Third Edition, First Revision July 2021

Appendix 4: Guideline on Registration of Biologics

3. Amendment of H. Post Marketing Surveillance for Vaccines, Page 10

Appendix 13: Designation and Registration of Orphan Medicines

4. Amendment of 4.2 Registration Requirements and Conditions, page 11
5. Amendment of 5.2 Pharmacovigilance, Page 13 and 14

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1. Section E: Post-Registration Process, Page 60 is amended by -

(a) substituting the reference “Malaysian Pharmacovigilance Guidelines” with the reference “Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021” in *21.1 Pharmacovigilance*.

2. Section E: Post-Registration Process, Page 62 is amended by -

(a) inserting a new statement in *21. Post-Marketing Activities*:

“21. 4. Notification of Product Quality Issue

NPRA may notify other regulatory authority or stakeholder relating to the recall and/or other regulatory action of a defective medicinal product in order to protect public health.”

3. Appendix 4: Guideline on Registration of Biologics, Page 10 is amended by -

(a) substituting the reference “Malaysian Pharmacovigilance Guidelines” with the reference “Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021” in *H. Post Marketing Surveillance for Vaccines*.

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4. Appendix 13: Designation and Registration of Orphan Medicines, Page 11 is amended by -

(a) substituting the reference “Malaysian Pharmacovigilance Guidelines” with the reference “Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021” in *4.2 Registration Requirements and Conditions*.

5. Appendix 13: Designation and Registration of Orphan Medicines, Page 13 and 14 is amended by -

(a) substituting the reference “Malaysian Pharmacovigilance Guidelines” with the reference “Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders, First Edition, August 2021” in *5.2 Pharmacovigilance*.

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There are four (4) amendments for the October 2021 DRGD Updates as below:

Appendices of DRGD Third Edition, First Revision July 2021

Appendix 20: Specific Labelling Requirements

1. Addition of new ingredient and safety information, No. 14, Anastrozole, Page 20
2. Addition of new ingredient and safety information, No. 31, Bortezomib, Page 33
3. Amendment of existing safety information, No. 93, Insulin, Page 91
4. Amendment of existing safety information, No. 126, Mycophenolate (Mycophenolate Mofetil and Mycophenolic Acid), Page 121

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Amendment of Appendix 20: Specific Labelling Requirements

1. **Addition of new ingredient 14. Anastrozole and safety information on page 20** as follows in accordance with Directive No. 21, 2021: *Direktif Untuk Semua Produk Yang Mengandungi Anastrozole: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Depression* as decided in DCA Meeting No. 365, which takes effect on 1 November 2021 –

"14. ANASTROZOLE

The following statements shall be <u>included in the package insert and Consumer Medication Information Leaflet (RiMUP)</u> for products containing anastrozole;

<u>Package Insert</u>

a) Adverse Effects/ Undesirable Effects:

<u>Psychiatric disorders</u>

Frequency 'very common': Depression

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

a) Side effects:

Frequency 'very common': Depression"

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2. **Addition of new ingredient 31. Bortezomib and safety information on page 33** as follows in accordance with Directive No. 20, 2021: *Direktif Untuk Semua Produk Yang Mengandungi Bortezomib: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Guillain-Barré Syndrome dan Demyelinating Polyneuropathy* as decided in DCA Meeting No. 365, which takes effect on 1 November 2021 –

"31. BORTEZOMIB

The following statements shall be included in the package insert for products containing bortezomib;

Package Insert

a) Adverse Effects/ Undesirable Effects:

Nervous system disorders

Frequency 'rare': Guillain-Barré syndrome, Demyelinating polyneuropathy"

3. **The specific labelling requirements for existing ingredient, No. 93 Insulin on page 91 is amended** in accordance with Directive No. 18, 2021: *Direktif Untuk Semua Produk Yang Mengandungi Insulin (Termasuk Produk Kombinasi): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Cutaneous Amyloidosis* as decided in DCA Meeting No. 365, which takes effect on 1 November 2021 by–

(a) inserting "(including combination products)" to the substance name.

(b) inserting the following statement:

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"93. INSULIN (INCLUDING COMBINATION PRODUCTS)

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing insulin (including combination products);

Package Insert

a) Posology and Method of Administration:

Injection sites should always be rotated within the same region in order to reduce the risk of lipodystrophy and cutaneous amyloidosis.

b) Warnings and Precautions:

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and cutaneous amyloidosis. There is a potential risk of delayed insulin absorption and worsened glycaemic control following insulin injections at sites with these reactions. A sudden change in the injection site to an unaffected area has been reported to result in hypoglycaemia. Blood glucose monitoring is recommended after the change in the injection site, and dose adjustment of antidiabetic medications may be considered.

c) Adverse Effects/ Undesirable Effects:

Skin and subcutaneous tissue disorders

Frequency "not known": Cutaneous amyloidosis

Description of selected adverse reactions

Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions.

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Consumer Medication Information Leaflet (RiMUP)

a) Before you use [product name]:

Before you start to use it

Skin changes at the injection site:

The injection site should be rotated to prevent skin changes such as lumps under the skin. The insulin may not work very well if you inject into a lumpy area. Contact your doctor if you are currently injecting into a lumpy area before you start injecting in a different area. Your doctor may tell you to check your blood sugar more closely, and to adjust your insulin or your other antidiabetic medications dose.

b) Side effects:

Frequency 'not known': Changes at the injection site (Cutaneous amyloidosis)"

4. **The specific labelling requirements for existing ingredient, No. 126 Mycophenolate (Mycophenolate Mofetil and Mycophenolic Acid on page 121 is amended** in accordance with Directive No. 19, 2021: *Direktif Untuk Semua Produk Yang Mengandungi Mycophenolate (Mycophenolate Mofetil dan Mycophenolic Acid): Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko De Novo Purine Synthesis Inhibitors-Associated Acute Inflammatory Syndrome* as decided in DCA Meeting No. 365, which takes effect on 1 November 2021 by–

(b) inserting the following statement:

"126. MYCOPHENOLATE (MYCOPHENOLATE MOFETIL AND MYCOPHENOLIC ACID)

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The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing mycophenolate (mycophenolate mofetil and mycophenolic acid);

Package Insert

a) Adverse Effects/ Undesirable Effects:

General disorders and administration site conditions: (uncommon) de novo purine synthesis inhibitors-associated acute inflammatory syndrome

General disorders and administration site conditions

De novo purine synthesis inhibitors-associated acute inflammatory syndrome has been described from post-marketing experience as a paradoxical proinflammatory reaction associated with mycophenolate mofetil and mycophenolic acid, characterised by fever, arthralgia, arthritis, muscle pain and elevated inflammatory markers. Literature case reports showed rapid improvement following discontinuation of the medicinal product.

Consumer Medication Information Leaflet (RiMUP)

a) Side effects:

Tell your doctor or pharmacist if you notice any of the following: fever, joint pain and muscle pain."

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There are five (5) amendments for the November 2021 DRGD Updates as below:

Appendices of DRGD Third Edition, First Revision July 2021

Appendix 2: Medical Device - Drug - Cosmetic Interphase (MDDCI) and Combination Products

1. Amendment of Table I: MEDICAL DEVICE-DRUG-COSMETIC INTERPHASE (MDDCI) AND COMBINATION PRODUCTS CLASSIFICATION DECISION, Page 15

Appendix 6: Guideline on Registration of Health Supplements

2. Amendment of 4. Tests for Microbial Contamination, Page 40

Appendix 7: Guideline on Registration of Natural Products

3. Amendment of 2.3 Excipients, page 31
4. Amendment of 2.7.5 Test for Microbial Contamination, Page 57

Appendix 18: List of Permitted, Prohibited and Restricted Substances

5. Amendment of 2.2. List of Restricted Excipients, Page 9

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1. Appendix 2: Medical Device - Drug - Cosmetic Interphase (MDDCI) and Combination Products, Page 15 is amended by -

(a) substituting the custodian division "NPRA" with "MDA" for product no. 26 (i) (b) in *Table I: MEDICAL DEVICE-DRUG-COSMETIC INTERPHASE (MDDCI) AND COMBINATION PRODUCTS CLASSIFICATION DECISION*.

2. Appendix 6: Guideline on Registration of Health Supplements, *Table 8* Notes section in *4. Tests for Microbial Contamination,* Page 40 is amended by –

(a) substituting "(May be omitted for product containing probiotics)" with "[Not applicable to products containing viable microorganisms as active ingredient (Example: product containing probiotics from bacteria)]" after TAMC : Total Aerobic Microbial Count.

(b) substituting "Molds" with "Moulds" in TYMC : Total Yeasts & Molds Count.

(c) adding "[(Not applicable to products containing viable microorganisms as active ingredient (Example: product containing probiotics from yeasts)]" after TYMC : Total Yeasts & Molds Count.

(d) substituting the reference "British Pharmacopoeia 2012" with the reference "latest version of British Pharmacopoeia".

3. Appendix 7: Guideline on Registration of Natural Products, Page 31 is amended by -

(a) substituting "0.4" with "0 to 4" in the Menthol information under *c) List of Restricted Excipients* in *2.3 Excipients*.

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4. Appendix 7: Guideline on Registration of Natural Products, *E. Herbal Medicine for External Use* Notes section in *2.7.5 Test for Microbial Contamination*, Page 57 is amended by -

(a) substituting "Molds" with "Moulds" in TYMC : Total Yeasts & Molds Count.

(b) substituting the reference "British Pharmacopoeia 2012" with the reference "latest version of British Pharmacopoeia".

5. Appendix 18: List of Permitted, Prohibited and Restricted Substances, Page 9 is amended by -

(a) substituting "0.4" with "0 to 4" in the Menthol information under *2. Sweeteners / Flavouring Agent* in *2.2. List of Restricted Excipients*.

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There are three (3) amendments for the December 2021 DRGD Updates as below:

Appendices of DRGD Third Edition, First Revision July 2021

Appendix 14: Evaluation Routes

1. Addition of information in 2. Full Evaluation (Conditional Registration), Page 1

Appendix 20: Specific Labelling Requirements

2. Amendment of existing safety information, No. 14, Antidepressants, Page 20
3. Addition of new ingredient and safety information, No. 59, Decitabine, Page 56

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Amendment of Appendix 14: Evaluation Routes

1. **Addition of information in 2. Full Evaluation (Conditional Registration) on page 1** as follows after "The validity of conditional registration is one year. Thereafter, the conditional registration may be renewed two (2) times (with the possibility of two (2) extensions of one (1) year each)."–

"All registration applications for pharmaceutical products during disaster that fulfil the eligibility conditions shall be automatically given **priority review** status and shall be processed within **70 working days*** from the date the complete application is received. If the product has been conditionally approved or given emergency use authorization or listing by any DCA reference countries or WHO (hereby referred as Recognition Pathway), the time taken for reviewing process would be significantly shortened.

*Note: The timeline has been revised from 120 working days to **70 working days**."

Amendment of Appendix 20: Specific Labelling Requirements

2. **The specific labelling requirements for existing ingredient, No. 14 Antidepressants on page 20 is amended** in accordance with Directive No.23, 2021: *Direktif Untuk Semua Produk Yang Mengandungi Citalopram, Desvenlafaxine, Duloxetine, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Venlafaxine dan Vortioxetine: Pengemaskinian Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Dengan Maklumat Keselamatan Berkaitan Risiko Postpartum Haemorrhage (PPH)* as decided in DCA Meeting No. 367, which takes effect on 1 January 2022 by –

(a) inserting the following substance names and statements:

"CITALOPRAM, DESVENLAFAXINE, DULOXETINE, ESCITALOPRAM, FLUOXETINE, FLUVOXAMINE, PAROXETINE, SERTRALINE, VENLAFAXINE AND VORTIOXETINE

The following statements shall be included in the package insert and Consumer Medication Information Leaflet (RiMUP) for products containing citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine and vortioxetine;

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Package Insert

a) Pregnancy and lactation:

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth.

*An additional statement should also be included in the package insert of vortioxetine: Although no studies have investigated an association between vortioxetine treatment and postpartum haemorrhage, there is a potential risk, taking into account the related mechanism of action.

Consumer Medication Information Leaflet (RiMUP)

a) Before you use <product name>:

Before you start to use it: If you take <product name> near the end of your pregnancy there may be an increased risk of heavy vaginal bleeding shortly after birth, especially if you have a history of bleeding disorders. Your doctor should be aware that you are taking <product name> so they can advise you."

3. **Addition of new ingredient 59. Decitabine and safety information on page 56** as follows in accordance with Directive No.24, 2021: *Direktif Untuk Semua Produk Yang Mengandungi Decitabine: Pengemaskinian Sisip Bungkusan Dengan Maklumat Keselamatan Berkaitan Risiko Differentiation Syndrome* as decided in DCA Meeting No. 367, which takes effect on 1 January 2022 –

"59. DECITABINE

The following statements shall be included in the package insert for products containing decitabine;

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Package Insert

a) Warnings and Precautions:

Differentiation syndrome

Cases of differentiation syndrome (also known as retinoic acid syndrome) have been reported in patients receiving decitabine. Differentiation syndrome may be fatal. Treatment with high dose IV corticosteroids and hemodynamic monitoring should be considered at first onset of symptoms or signs suggestive of differentiation syndrome. Temporary discontinuation should be considered until resolution of symptoms and if resumed, caution is advised.

b) Adverse Effects/ Undesirable Effects:

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Frequency 'Very rare': Differentiation syndrome"

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There are two (2) amendments for the January 2022 DRGD Updates as below:

Main Body of DRGD Third Edition, First Revision July 2021

Section E: Post-Registration Process

1. Amendment of information in 18. Maintenance of Registration (Re-registration), Page 50
2. Addition of information in 19. Withdrawal of Product Registration, Page 54

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Amendment of Section E: Post-Registration Process

1. Amendment of 18. Maintenance of Registration (Re-registration) on page 50 by –

(a) deleting the word, "(Re-registration)" from the title, *18. Maintenance of Registration (Re-registration)*.

(b) adding the following information after item h):

"i) Products manufactured and sold or supplied by the PRH before the product registration expiry date or cancellation date, do not require to be recalled from the market and may be sold until end of product shelf life. However, products with quality, safety and/or efficacy issues shall be recalled immediately from the market upon the product registration expiry date or cancellation date or at any other time stipulated by NPRA.

j) The PRH shall submit a written request to the DCA Secretary to deplete any existing unsold stocks after the product registration expiry date or cancellation date. If approval is granted, the PRH shall be held responsible for the batches and quantity requested in the event of any pharmacovigilance issues or quality defects associated with those product batches sold after the product registration expiry date or cancellation date."

2. Amendment of 19. Withdrawal of Product Registration on page 54 by –

(a) adding the following information after item b):

"c) Products manufactured and sold or supplied by the PRH before the registration termination date, do not require to be recalled from the market and may be sold until end of product shelf life. However, products with quality, safety and/or efficacy issues shall be recalled immediately from the market upon the product registration termination date or at any other time stipulated by NPRA.

d) The PRH shall submit a written request to the DCA Secretary to deplete any existing unsold stocks after the registration termination date. If approval is granted, the PRH shall be held responsible for the batches and quantity requested in the event of any pharmacovigilance issues or quality defects associated with those product batches sold after the registration termination date."