UPDATES ON MALAYSIAN VARIATION GUIDELINE FOR PHARMACEUTICAL PRODUCTS 2013

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NATIONAL PHARMACEUTICAL CONTROL BUREAU
MINISTRY OF HEALTH MALAYSIA
Mission: To be a world renowned regulatory authority for medicinal products and cosmetics.
Vision: To safeguard the nation's health through scientific excellence in the regulatory control of medicinal products and cosmetics.

Overview of the presentation

1. Drafting of the ASEAN Variation Guideline (AVG) for Pharmaceutical Products
2. Adoption and adaptation of AVG in Malaysian Variation Guideline (MVG) for Pharmaceutical Products
3. Contents of MVG
   - Introduction,
   - Definition,
   - Scope,
   - Procedures, timeline and processing fees,
   - Changes leading to new product registration,
   - Major variation (MaV),
   - Minor variation-prior approval (MiV-PA),
   - Minor variation-notification (MiV-N)
4. Implementation of MVG

Drafting of the ASEAN Variation Guideline (AVG) for Pharmaceutical Products

16th ACCSQ PPWG (Manila, Philippines) – 2009 Endorsed the formation of TWG chaired by Malaysia and co-chaired by Singapore.

With EMA Variation Guideline, WHO Variation Guideline and some of the variation guidelines of ASEAN Member States as reference, **1st draft of AVG** was drafted and circulated.

The comments from Member States and the industry were incorporated to become the **2nd draft AVG** in the year 2009.

ASEAN Variation Guideline Workshop was held in NPCB, Ministry of Health, Malaysia from 8-10 Feb, 2010

Following the AVG Workshop, **3rd draft of AVG** was circulated for further review.

Comments were received and **ASEAN Variation Guideline (4th draft)** was circulated for further comments in year 2010.

Drafting of the ASEAN Variation Guideline (AVG) for Pharmaceutical Products

Comments were received and **ASEAN Variation Guideline (5th draft)** was circulated for further comments by end of 2010.

ASEAN Variation Guideline 6th draft were presented in the 18th ACCSQ-PPWG Meeting in Singapore in the year 2011. The 6th draft was improvised and circulated.

Comments from Member States and the industry were studied and incorporated in the **ASEAN Variation Guideline 7th draft** in the year 2012.

The ASEAN Variation Guideline 7th draft was presented in the **19th ACCSQ-PPWG Meeting** in Bangkok. Adopted in principle with proposed implementation latest within one year of adoption ie. by 31 July 2013.

Following the adoption of 7th draft of AVG, minor amendments were made and circulated as 7.1th draft. It was further commented and finalized as 7.2th draft.

Malaysia to adopt the AVG and drafts the **Malaysian Variation Guideline for Pharmaceutical Products** in 2013.

Drafting of the ASEAN Variation Guideline (AVG) for Pharmaceutical Products

- Major variation (MaV) – 16 variations
- Minor variation prior approval (MiV-PA) – 35 variations
- Minor variation notification (MiV-N) – 10 variations

- Both MaV and MiV-PA require prior approval from the authority.

- MiV- N is based on 'Do and Tell' which means marketing authorization holder can implement the change first and notify the authority later.

- MiV-N are mostly administrative changes only.

- Variations are arranged according to administrative part, drug substance and drug product; as per EMA variation guideline.

- Supporting documents are also arranged according to ACTD format.

Adoption and adaptation of AVG in Malaysian Variation Guideline (MVG)

- Adoption of ASEAN Variation Guideline (AVG) for Pharmaceutical Products 2012 by the 19th ACCSQ PPWG Meeting, implementation by 31 July 2013.

- Malaysia as the Lead Country for AVG has drafted Malaysian Variation Guideline (MVG) for Pharmaceutical Products 2013 with the AVG as the backbone and incorporated with country specific requirements.

- MVG is used for pharmaceutical products only and not including biologics. MVG for TM/HS (not drafted yet) will follow the same format but with modifications appropriate to the abridged evaluation.

- Will replace current variation guideline ie. Appendix 12 of Drug Registration Guidance Document (DRGD).

- Processing fees to be imposed for both MaV and MiV-PA. MiV-N is FOC.

Adoption and adaptation of AVG in Malaysian Variation Guideline (MVG)

- No change in the categorization of variation but minor adjustment to supporting documents.

- Due to current regulatory policy of NPCB, only one site is allowed for every manufacturing step except quality testing site.

- Timeline for each type of variation is stated clearly.

- Incorporated with different types of change of manufacturing site (COS) applications customized with set of supporting documents for each type of COS application.

- Added with major change in manufacturing process of drug substance, change of patient information leaflet (PIL) and change of importer.

- Increased number of variations in MVG:
  - 17 MaV
  - 36 MiV-PA
  - 11 MiV-N

Contents of Malaysian Variation Guideline (MVG)

1. Introduction:

Throughout the life of a pharmaceutical product, the product registration holder is responsible for the product that is placed in the market and is also required to take into account technical and scientific progress, and to make any amendments that may be required to enable the pharmaceutical products to be manufactured and checked by means of generally accepted scientific methods. Such amendments have to be approved by National Pharmaceutical Control Bureau (NPCB).

2. Scope

It concerns the variation applications submitted by the product registration holder for pharmaceutical products for human use only and not including biologics.

Contents of Malaysian Variation Guideline (MVG)

3. Definition:

Major variation (MaV)

Variation to a registered pharmaceutical finished product that may affect significantly and/or directly the aspects of quality, safety and efficacy and it does not fall within the definition of minor variation and new registration.

Minor Variation (MiV-N & MiV-PA)

Variation to a registered pharmaceutical finished product in terms of administrative data and/or changes with minimal/no significant impact on the aspects of efficacy, quality, and safety.

Contents of Malaysian Variation Guideline (MVG)

4. PROCEDURE, TIMELINE AND PROCESSING FEES

Minor Variation - Notification

Type of variation	Minor variation (Notification) MiV-N
Procedure	Notification "Do & Tell" If the notification fulfils the requirements (conditions and supporting documents) as per described under MiV-N, product registration holder must notify NPCB. NPCB shall acknowledge receipt of a notification.
Timeline for NPCB to acknowledge the variation notification	Within 20 working days following receipt of a notification.

Contents of Malaysian Variation Guideline (MVG)

4. PROCEDURE, TIMELINE AND PROCESSING FEES

Minor Variation – Notification

4.1.1 A MiV-N application may be rejected in specific circumstances with the consequence that the product registration holder must cease to apply the already implemented variation.

Contents of Malaysian Variation Guideline (MVG)

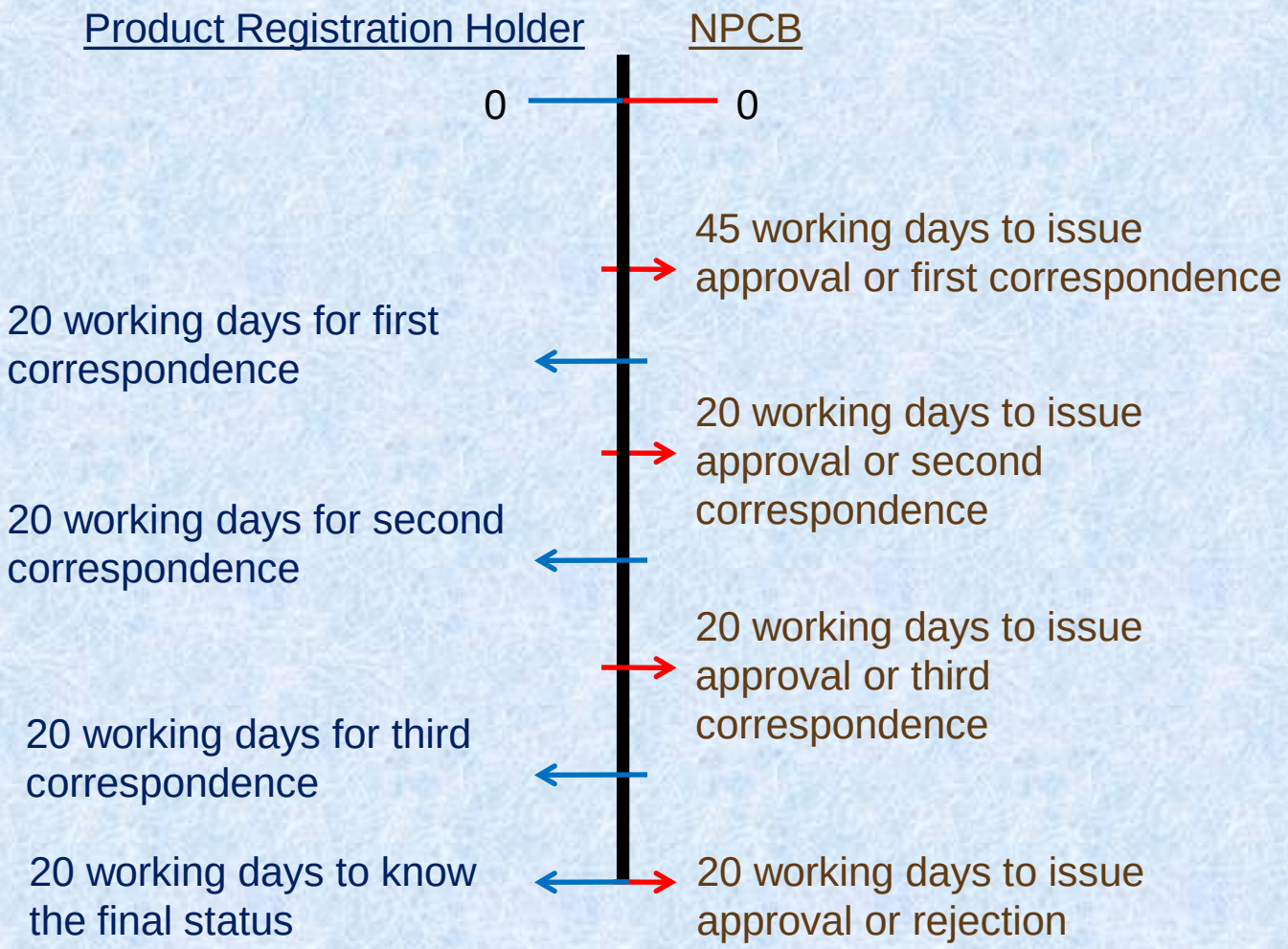
4. PROCEDURE, TIMELINE AND PROCESSING FEES
Major variation and minor variation – prior approval

Type of variation	**Minor variation (Prior approval) MiV-PA**	**Major variation MaV**
Timeline for NPCB to evaluate the variation application	Within **45 working days** following receipt of an application.	Within **60 working days** following receipt of an application.
Approval or correspondence	Approval or first correspondence shall be issued to product registration holder within **45 working days**, provided all conditions and supporting documents are fulfilled. Subsequent correspondences which fulfill the requirements will be granted approval within **20 working days.** After third correspondence, application may be rejected if still does not fulfill requirements.	Approval or first correspondence shall be issued to product registration holder within **60 working days,** provided all conditions and supporting documents are fulfilled. Subsequent correspondences which fulfill the requirements will be granted approval within **30 working days.** After third correspondence, application may be rejected if still does not fulfill requirements.
Timeline for product registration holder to reply	Within **20 working days** failing which application will be rejected. Auto-reminder will be sent 10 working days before the deadline.	Within **30 working days** failing which application will be rejected. Auto-reminder will be sent 15 working days before the deadline.
Implementation of the variation	Within **6 months** after the product registration holder has been informed of the approved variations.	

Contents of Malaysian Variation Guideline (MVG)

4. PROCEDURE, TIMELINE AND PROCESSING FEES

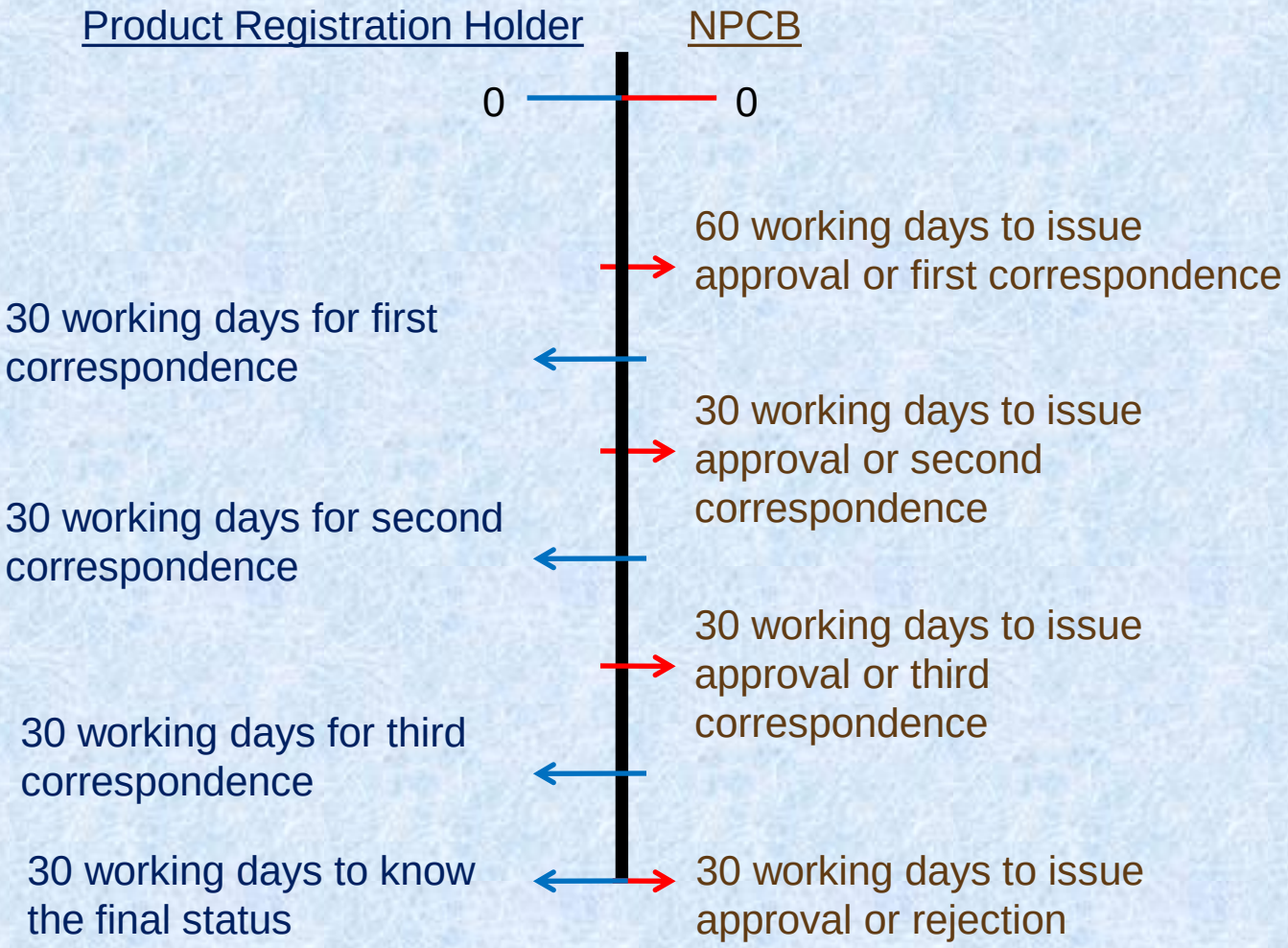
Minor variation – prior approval



Contents of Malaysian Variation Guideline (MVG)

4. PROCEDURE, TIMELINE AND PROCESSING FEES

Major variation



Contents of Malaysian Variation Guideline (MVG)

4. PROCEDURE, TIMELINE AND PROCESSING FEES

4.3.1 NPCB reserves the right to re-categorize the application type, where deemed appropriate. Re-categorization may require the product registration holder to withdraw the original application and resubmit a new application according to the correct category.

4.3.2 Variation application is submitted along with a declaration letter which is undersigned by the product registration holder that declares

- There is no other change except for the proposed variation;
- The change will not adversely affect the quality, efficacy and safety of the product;
- All conditions for the variation concerned are fulfilled; and
- The required supporting documents as specified for the variation have been submitted.
- The proposed change has been checked in reference with the currently approved data in the system.

Contents of Malaysian Variation Guideline (MVG)

4. PROCEDURE, TIMELINE AND PROCESSING FEES

4.4 Processing fees for variation and change of manufacturing site applications

Type of Application	Processing Fee (RM)
MiV-N	No fee
MiV-PA	150
MaV	300
Additional Indication	1000
Type of Application (MaV5)	For pharmaceuticals in RM
COS Type I	500
COS Type II, III, IV, V	1000

Contents of Malaysian Variation Guideline (MVG)

5. CHANGES LEADING TO A NEW PRODUCT REGISTRATION

5.1 Changes to the Active Pharmaceutical Ingredient (API).

- *Change of the API to a different API including change in the salt or isomer form of the API.*
- *Inclusion of an additional API to a multicomponent product.*
- *Removal of one API from a multicomponent product.*
- *Change in the strength of one or more APIs.*
- *Increase in overage.*

5.2 Changes to the pharmaceutical form/dosage form.

5.3 Changes in the route of administration (exception for parenteral route).

5.4 Changes in the manufacturing site of drug product.

- *Addition of a new manufacturing site to the currently approved site for the same manufacturing process.*
- *Change from a currently approved contract manufacturer or own plant to another contract manufacturer not under crisis situation.*

Contents of Malaysian Variation Guideline (MVG)

	Major Variation
MaV-1	Change and/or additional indication/dosing regimen/patient population/inclusion of clinical information extending the usage of the product
MaV-2	Change of content of product labeling
MaV-3	Change and/or addition of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
MaV-4	Major change of manufacturing process of the drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
MaV-5	Change of the manufacturing site of the drug product
MaV-6	Replacement of the alternative site for the primary packaging (direct contact with drug product)
MaV-7	Change of the specification drug substance and/or drug product [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
MaV-8	Change of batch size of sterile drug product
MaV-9	Change of batch size of non-sterile drug product

Contents of Malaysian Variation Guideline (MVG)

	Major Variation
MaV-10	Major change in the manufacturing process for the drug product
MaV-11	Qualitative or quantitative change of excipient
MaV-12	Quantitative change in the coating weight of tablets or weight and/or size of capsule shell for modified release oral dosage form
MaV-13	Change in primary packaging material for sterile product a) Qualitative and quantitative composition and/or b) Type of container and/or c) Inclusion of primary packaging material
MaV-14	Change or addition of pack size/fill volume and/or change of shape or dimension of container or closure for sterile solid and liquid drug product
MaV-15	Inclusion or replacement of the solvent/diluent for the drug product
MaV-16	Extension of shelf-life of the drug product
MaV-17	Change of storage conditions of the drug product (Lowering from the current approved storage condition)

Contents of Malaysian Variation Guideline (MVG)

	Minor Variation – Prior Approval
MiV-PA1	Change of drug product name
MiV-PA2	Change of product labeling (in accordance to country specific labeling requirement)
MiV-PA3	Change of patient information leaflet
MiV-PA4	Replacement of the company or party responsible for batch release
MiV-PA5	Change and/or addition of alternative manufacturer/site of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is available]
MiV-PA6	Change of batch size of drug substance [where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
MiV-PA7	Change of in-process controls applied during the manufacture of the drug substance [including tightening and addition of new in-process test and where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
MiV-PA8	Minor change of manufacturing process of the drug substance[where European Pharmacopoeial Certificate of Suitability (CEP) is not available]
MiV-PA9	Change of the specification of drug substance
MiV-PA10	Change of the test procedure of non-compendial drug substance

Contents of Malaysian Variation Guideline (MVG)

	Minor Variation – Prior Approval
MiV-PA11	Change of shelf-life or retest period for drug substance
MiV-PA12	Change of storage condition for drug substance
MiV-PA13	Revision of European Pharmacopoeial Certificate of Suitability (CEP) of drug substance
MiV-PA14	Change of batch size of non-sterile drug product
MiV-PA15	Reduction or removal of overage
MiV-PA16	Qualitative or quantitative change of excipient
MiV-PA17	Quantitative change in coating weight of tablets or weight and/or size of capsule shell for immediate release oral dosage form
MiV-PA18	Change of the colouring/flavouring agent of the product [addition, deletion or replacement of colourant(s)/flavour(s)]
MiV-PA19	Deletion of the solvent/diluent for the drug product
MiV-PA20	Change of in-process controls applied during the manufacture of the drug product (including tightening and addition of new in-process test)
MiV-PA21	Minor change of the manufacturing process for non-sterile product.
MiV-PA22	Change of specifications of an excipient
MiV-PA23	Change of a test procedure for an excipient, including replacement of an approved test procedure by a new test procedure

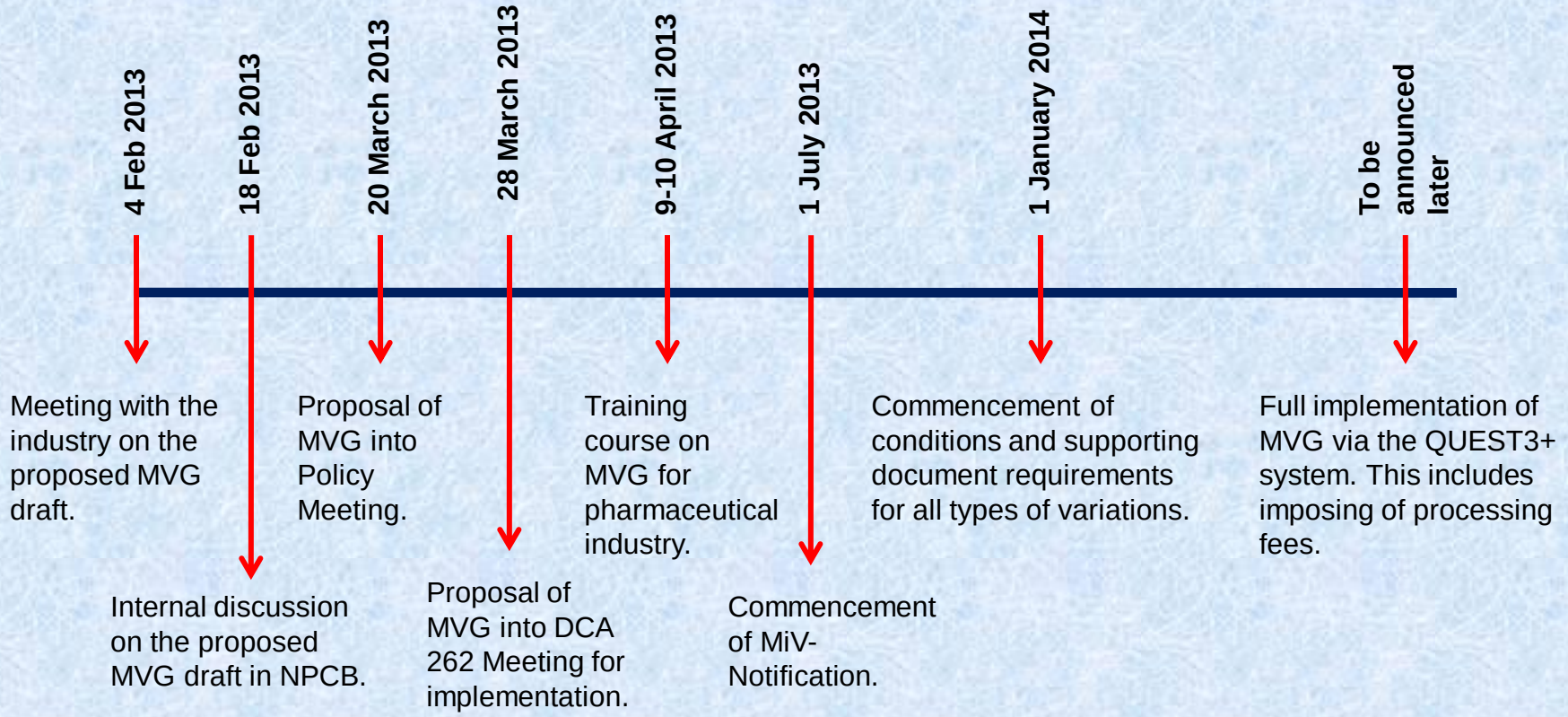
Contents of Malaysian Variation Guideline (MVG)

	Minor Variation – Prior Approval
MiV-PA24	Change of release and shelf-life specifications of the drug product
MiV-PA25	Change of imprints, bossing or other markings on the tablets or printing on capsules including addition or change of inks used for product marking
MiV-PA26	Change of dimensions and/or shape of tablets, capsules, suppositories or pessaries without change in qualitative and quantitative composition and mean mass
MiV-PA27	Change in the test procedure of the drug product (including replacement or addition of a test procedure)
MiV-PA28	Change in primary packaging material for non-sterile product a) Qualitative and quantitative composition and/or b) Type of container and/or c) Inclusion of primary packaging material
MiV-PA29	Replacement of a manufacturer for secondary packaging
MiV-PA30	Change of pack size/fill volume and/or change of shape or dimension of container or closure for non-sterile product
MiV-PA31	Change of outer carton pack sizes for a drug product
MiV-PA32	Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)
MiV-PA33	Addition or replacement of measuring device for oral liquid dosage forms and other dosage form
MiV-PA34	Reduction of shelf-life of the drug product
MiV-PA35	Change of storage conditions of the drug product (Increasing from the current approved storage condition)
MiV-PA36	Change of release and shelf-life specifications of the drug product

Contents of Malaysian Variation Guideline (MVG)

	Minor Variation – Notification
MiV-N1	Change in name and/or address of the product registration holder
MiV-N2	Change of importer and/or store address
MiV-N3	Change of product owner
MiV-N4	Change in ownership of manufacturer
MiV-N5	Change of the name or address (for example: postal code, street name) of the manufacturer of drug product
MiV-N6	Change of the name or address (for example: postal code, street name) of the company or manufacturer responsible for batch release
MiV-N7	Change of the name and/or address (for example: postal code, street name) of a manufacturer of the drug substance
MiV-N8	Withdrawal/deletion of the alternative manufacturer(s) for drug substance
MiV-N9	Renewal of European Pharmacopoeial Certificate of Suitability (CEP)
MiV-N10	Change of specifications of the drug product and/or drug substance and/or excipient, following the updates in the compendium
MiV-N11	Deletion of pack size for a product

Implementation of Malaysian Variation Guideline (MVG)



THANK YOU

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