APPENDIX 14 *GUIDELINE ON MINOR VARIATION APPLICATIONS FOR BIOLOGICAL THERAPEUTIC PRODUCTS*

1. INTRODUCTION

This document describes the requirements of a Minor Variation Application (MIV) submitted for an existing registered biologic drug product in Singapore. Product registrants should be familiar with the contents of this document, Chapters F and H of the Guidance on Therapeutic Product Registration in Singapore and the governing legislation prior to submitting an MIV to HSA. The appropriate variation may be selected with the aid of the MIV self-guided tool. Changes that do not require notification to HSA are listed in Section 4 of this document.

In exceptional situations, the evaluation timeline for MIV-1 applications may be extended beyond that published, for example, for extensive grouping of changes. In such cases, the extended timeline will be communicated to the applicant.

2. APPLICATION PROCESS

An MIV is submitted via the "*Amendment Application for Therapeutic Products Registration*" form in PRISM.

Product registrants should disclose **all** proposed changes in *Section 0 Registration Summary* under *Section 0.3 MIV Checklist Number (Primary Change)* and *Section 0.4 MIV Checklist Number (Secondary Change(s));* and in the *Table of Amendment Details*, which can be downloaded via the link indicated in *Section 0.6 Table of Summary of Changes*. Any undisclosed variation(s) embedded in the submitted data, or any follow-on changes not specifically requested by HSA, will **not** be considered for evaluation. Please refer to Section 2 of Appendix 17 for more information on submitting a minor variation application.

3. DOCUMENTARY REQUIREMENTS

The following documents listed in Table A must be submitted with each MIV submission:

Table A MIV Application Submission Requirements

	Softcopy
PRISM Application Form	PRISM
Table of Contents	PRISM / eCTD
Cover Letter	PRISM / eCTD
Checklist for MIV(s)	PRISM / eCTD
Table of Summary of Changes	PRISM / eCTD
MIV-specific Supporting Documents - Administrative (Module 1/Part 1) - Other supporting documents	 PRISM / eCTD PRISM / CD/DVD / eCTD / cloud-based file exchange software (EasiShare)#
Approved and Proposed Product Labelling (annotated and pristine copies), where applicable	PRISM / eCTD

*All supporting documents may be submitted via PRISM or CD/DVD or eCTD or cloud-based file exchange software (EasiShare)– do not combine PRISM attachments with a different mode of submission*

The checklists for MIV-1 and MIV-2 (Notification and Do-and-Tell) for biologic drug products are located in Appendix 14A, 14B and 14C. These checklists serve as guides on the required documents relevant to each proposed MIV. When submitting the Checklist, the following should be included:

- A copy of the relevant checklist(s) to each proposed MIV(s) – justifications should be provided below the respective document description if there is any omission of documentation; and
- A *Table of Summary of Changes* which concisely describes the proposed MIV(s). The following information must be stated in the Table:
  - Section(s) of the original dossier affected by the change(s);
  - Approved and proposed change(s);
  - Reason(s) for the change(s); and
  - Registration status and date of the proposed change(s) in other countries/agencies that had approved the variation(s), especially the country of origin and HSA's reference agencies.

For an MIV application with multiple related or unrelated variations, <u>all</u> of the supporting documents for <u>each</u> individual variation should be submitted. If the required documents have not been submitted, justifications must be provided.

This document reflects the current thinking of HSA on the minimum data necessary for assessment. Product registrants are responsible for ensuring that all necessary validations were conducted to demonstrate that the change does not adversely affect the quality, safety or efficacy of the drug product concerned. HSA reserves the right to request for additional information if deemed appropriate.

4. CHANGES THAT DO NOT REQUIRE NOTIFICATION TO HSA

<u>Note:</u> Change = addition/replacement/deletion, unless otherwise specified

4.1. Product Labels

a) The following changes to an outer or inner/blister label where the label content and colour scheme remain unchanged and the revised label meets the current Appendix 7 requirements:
   i) Change in text font type or size (e.g., Calibri 11 to Arial 10)
   ii) Change in placement of text, batch number, manufacturing date and expiry date on label (e.g., shift from front panel to side flap)
   iii) Change in format of expiry or manufacturing date (e.g., from MMYY to DDMMYY)

b) The following content changes to an outer or inner/blister label:
   i) Deletion of information that is no longer a requirement in accordance with Appendix 7 (e.g., manufacturing date, name and address of either manufacturer or product owner or registrant)
   ii) Change of registration number, licence number or distributor information which are relevant only to a foreign country

iii) Change of non-English text as long as the information is consistent with the approved English text

iv) Change of machine-readable codes (e.g., barcode, QR code) for logistic purposes or e-labelling

v) Change of anti-counterfeit features

vi) Addition/Deletion of poison label

c) Change in the dimensions of the outer carton with no change in the label artwork

4.2. Raw Materials

a) Change in the supplier of a raw material which is not of mammalian or avian origin if the specification of the raw material remains unchanged.

4.3. Excipients

a) Change in the supplier of an excipient which is not of mammalian or avian origin if the specification of the excipient remains unchanged.

4.4. Packaging Materials of a Drug Substance

a) Change in the supplier of primary packaging material of a drug substance if the packaging material type and specification remain unchanged.

b) Change in the secondary packaging material of a drug substance if the retest period or shelf-life of the drug substance remains unchanged.

c) Change in the secondary packaging material of a bulk drug substance or process intermediate if the hold time of the bulk drug substance or process intermediate remains unchanged.

4.5. Packaging Materials of a Drug Product

a) Change in the supplier of primary packaging material of a drug product if the packaging material type and specification remain unchanged.

b) Change in the secondary packaging material of a bulk drug product or process intermediate if the hold time of the bulk drug product or process intermediate remains unchanged.

4.6. Reference Standards

a) Introduction of a new reference standard which is qualified in accordance with the approved qualification protocol and when the current reference standard is available for direct comparison.

b) Extension of the shelf-life or retest period of a reference standard which is qualified in accordance with the approved qualification protocol.

4.7. Post-Approval Stability Protocol for a Drug Substance

a) The following changes in the post-approval stability protocol where the approved retest period/shelf-life of drug substance remains unchanged.

i) Change of sampling frequency in accordance with ICH Q5C Guidelines, e.g., adjust sampling frequency to annual time-points after completion of the stability study of primary batches.

ii) Change of time-points beyond the approved retest period/shelf-life.

4.8. Post-Approval Stability Protocol for a Drug Product

a) The following changes in the post-approval stability protocol where the approved shelf-life drug of product remains unchanged.

i) Change of sampling frequency in accordance with ICH Q5C Guidelines, e.g., adjust sampling frequency to annual time-points after completion of the stability study of primary batches.

ii) Change of time-points beyond the approved shelf-life.

4.9. Change of Production Activities Within the Same Manufacturing Site

a) Decommissioning of a duplicate manufacturing line.

b) Change of location for QC testing within the same manufacturing site (e.g., different building), with successful test method verification performed at the new location.

4.10. Medical Device Supplied with Therapeutic Products

a) The non-reportable changes provided under GN-21 Section 2.3 will be applicable.
