WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 8, Issue 3, 1165-1179 Research Article ISSN 2278 – 4357

REGULATORY OVERVIEW OF POST APPROVAL CHANGES OF THERAPEUTIC PRODUCT IN SINGAPORE

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Article Received on
13 Jan. 2019,

Revised on 03 Feb. 2019,
Accepted on 24 Feb. 2019,

DOI: 10.20959/wjpps20193-13321

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ABSTRACT

Post approval changes can be addressed as specific changes implemented during the product lifecycle in a stepwise approach to get better, faster and accurate results by the company as per the norms set by the regulatory agency which is based on the proposed plan and test to verify that there is no change in product quality. Singapore which is regulated by Health Sciences Authority (HSA) addresses post approval change as a variation which can be major variation or minor variation. Health Sciences Authority (HSA) has clearly defined the regulatory framework for post approval changes with appropriate guidelines and checklists. This article depicts the overview of post approval changes in Singapore which includes the classification, submission procedure with target timelines and fees, data requirements, steps in selecting the suitable variations by the applicant.

KEYWORDS: Post approval changes, major variation, minor variation, HSA, MAV, MIV

INTRODUCTION

In the life cycle management of pharmaceutical product, post approval changes are considered as a fundamental part.[1] Post approval changes can be addressed as specific changes implemented during the product lifecycle in a stepwise approach to get better, faster and accurate results by the company as per the norms set by the regulatory agency which is based on the proposed plan and test to verify that there is no change in product quality.[2] All the changes done for approved product should be monitored carefully and follow proper regulatory pathway.

Table I: Terminology to describe post approval changes in following countries.

Countries	Terminology
India	Post Approval Changes
US	Scale Up & Post Approval Changes
EU	Variations
Singapore	Variations
Health Canada	Post-Notice of Compliance (NOC) Changes
Australia	Variations

Health Sciences Authority (HSA) is the regulating agency in Singapore for manufacture, import and sale of therapeutic products, medical devices, complementary health products, cosmetics, tobacco products and blood products.[3] HSA has implemented guidance on therapeutic product registration where a specific section describes about post approval process of therapeutic products.[4]

Therapeutic product is defined as any substance that is intended for use in humans for a therapeutic, preventive and diagnostic purpose. It can be any chemical or botanical element obtained naturally or chemically or it can be micro-organism metabolite or any substance derived from a biological system. Therapeutic product is not a medical device, blood components, Chinese proprietary medicine, quasi medicine, mediated oil or balm and any traditional medicine.[4]

Classification of Post Approval Changes[4]

The submission of application for post approval changes (variations) are classified into two types as follows:

- Major Variation Application (MAV)
- Minor Variation Application (MIV)

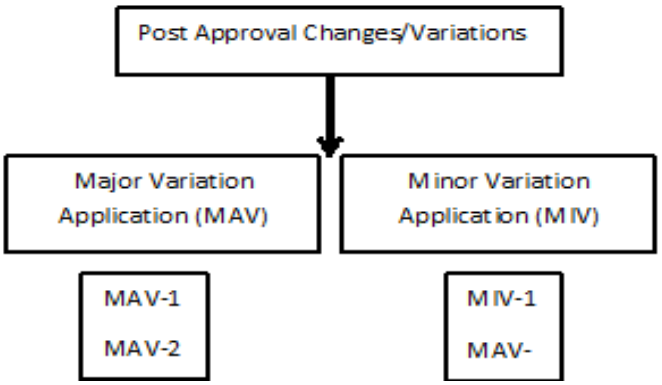

Fig. 1: Classification of type of application submission for post approval changes (variations).

Major Variation Application (MAV) stands for major variation application for an approved product. MAV are categorized into two. It may be either MAV-1 or MAV-2. Prior approval from HSA is required before implementation of MAV applications.

- MAV-1 stands for variation with respect to dosing regimen, approved indication, patient groups, and inclusion of clinical information regarding the product use. For examples like additional strains of bacteria with in vivo data to expand the indications in case of antimicrobial products, additional viral genotypes to expand the indications in case of antiviral products.
- MAV-2 stands for reclassification i.e. change to be done in current forensic classification of approved product.

Minor Variation Application (MIV) for an approved product: MIV are two types. It may be either MIV-1 or MIV-2 (Notification).

- MIV-1 is a minor variation which requires prior approval from HSA before implementation. All the minor variations for chemicals and biologics are described in the dossier requirements checklist for MIV-1 under appendix 13 and 14 respectively in the HSA website.[5,6]
- MIV-2 is of two types. One is MIV-2 as notification and another as MIV-2 (Do and Tell). Both are minor variations which are specified in the Part B and Part C Checklist of dossier requirements for MIV-2 for chemicals and biologics under appendix 13 and 14 respectively in the HSA website.[5,6]

➢ MIV-2 as notification can be incorporated within 40 days if no query is raised by HSA upon submission.

➢ HSA prior approval for MIV-2 (Do & Tell) is not required. The application can be submitted with 6 months to HSA with the incorporation of specified changes.

➢ HSA can Re-categorize application i.e. MIV to MAV-1, MIV-2 to MIV-1. As per the correct category, notification will be sent to the applicant whether they are required to resubmit or withdraw application.

Steps for selection of variation category and suitable application type for post approval variations[7]

Step 1: Checking whether the change proposed belongs to MAV-1, MIV-1 or 2 with the help of self-guided tool addressed by HSA.

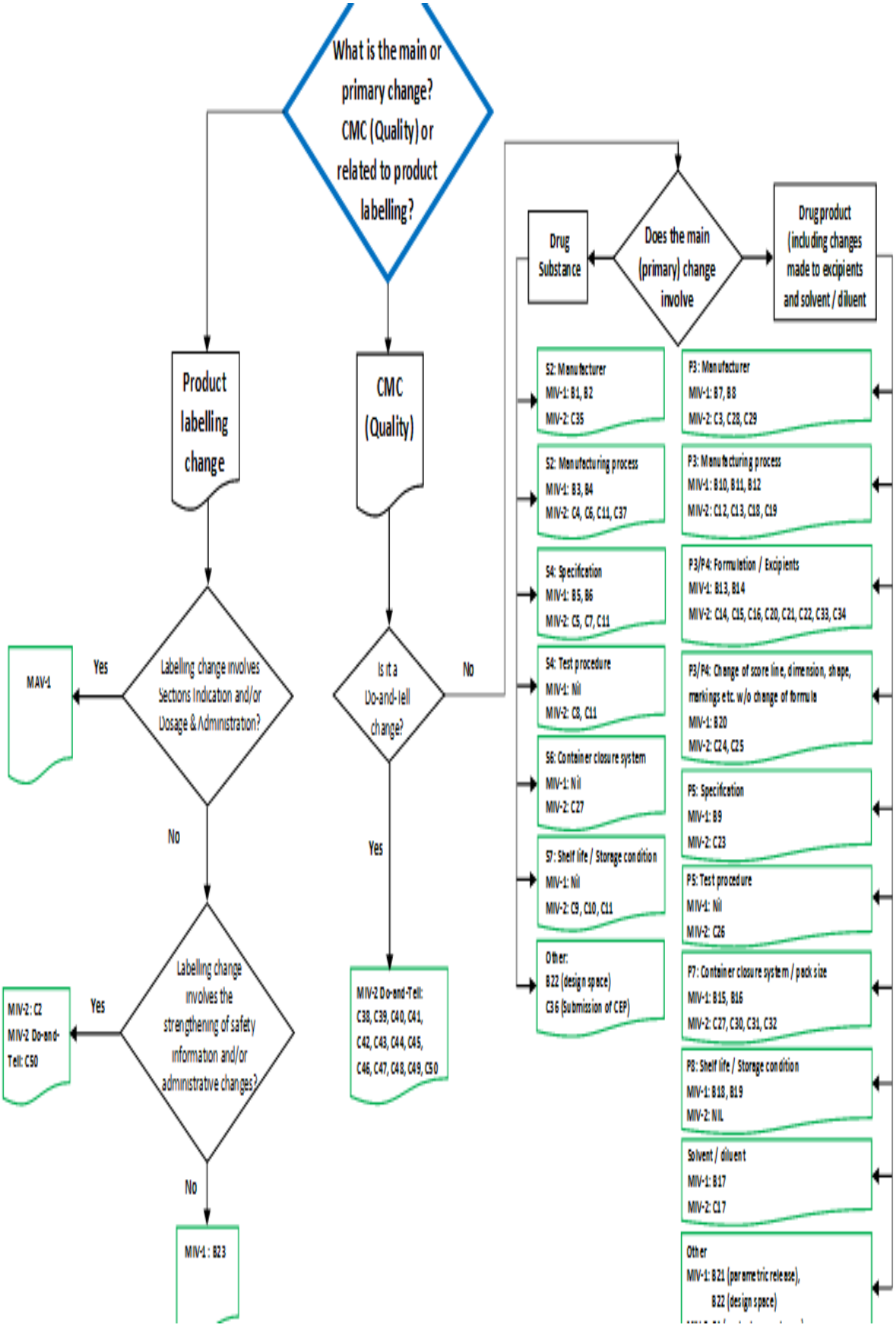

Fig. 2: Self-guided tool addressed by HSA to check whether the proposed change belongs to MAV-1, MIV-1 or MIV-2 for Chemical Products.[8]

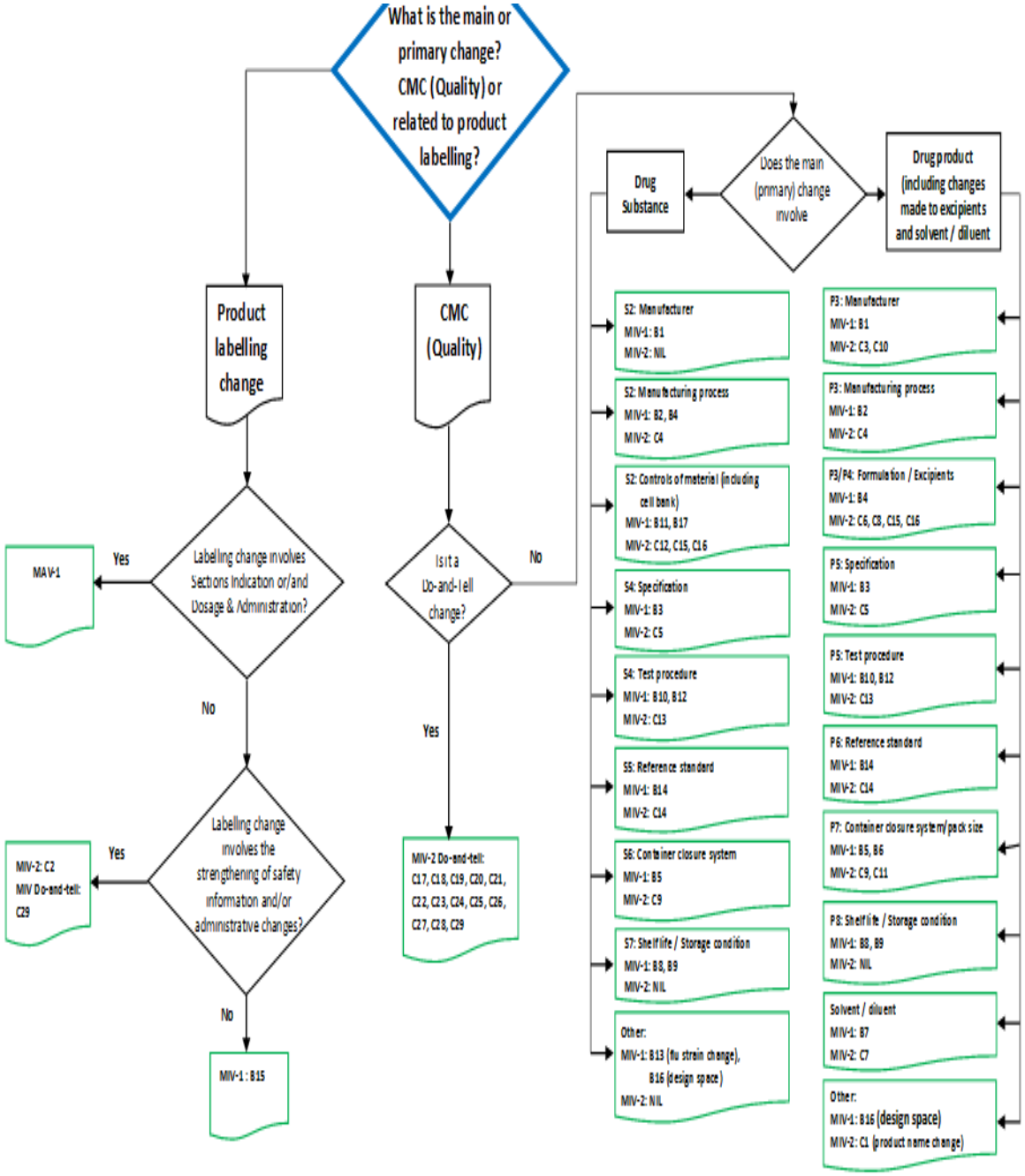

Fig. 3: Self-guided tool addressed by HSA to check whether the proposed change belongs to MAV-1, MIV-1 or MIV-2 for Biological Products.[8]

Step 2: For application MIV-1 and MIV-2 applicant should meet the documentary requirements as per Appendix 13 which addresses for chemical and Appendix 14 for biologicals respectively

- Self-guided tool helps in determining the variation for product in particular.
- Applicant must procced to step 3 using an enquiry form after step 1 and 2 only if one is not able to determine the type of application for variation.

Step 3: Enquiry form for Post approval variation

Applicant needs to provide information regarding changes proposed in the enquiry form and should show that the determined variation is not found in the self-guided tool and guidelines. The completed enquiry form must in Microsoft word format and mailed to HSA_TP_Enquiry@hsa.gov.sg.

General Submission Procedure for Variation Application[4]

There are 5 steps to be followed which are as follows:

1. Pre-submission preparation
2. Application submission
3. Application screening
4. Application evaluation
5. Regulatory Decision

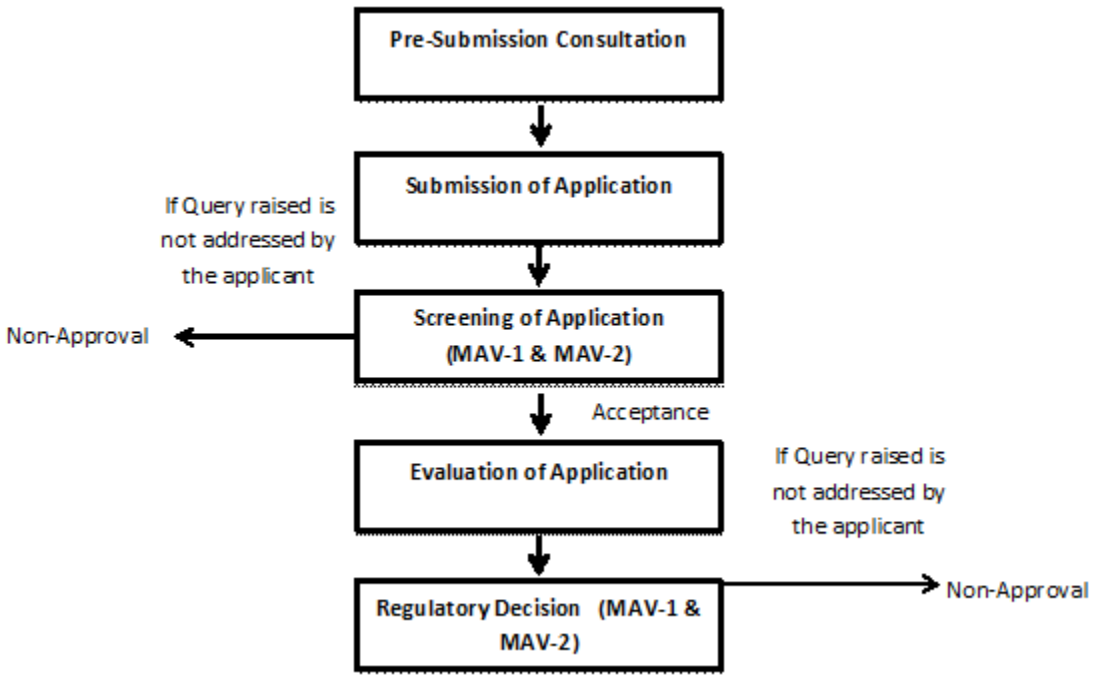

Fig. 4: Variation Application Submission Process.

1. Pre-submission preparation: There are two methods by which applicant can seek information from HSA before submission which includes pre-submission enquiry and pre-submission notification.

- Pre-submission enquiry can be done by the applicant via the online feedback form available on the HSA website. For MIV submission, a complete MIV filing enquiry form via the online feedback form available on the HSA website must be submitted by the applicant.
- Pre-submission notification or meeting request should be initiated by the applicant in writing with the proper agenda, date of proposal, purpose and time of meeting through online feedback form available on the HSA website. At least 3 weeks before the meeting date, the pre-submission request should be initiated by the applicant. It is not mandatory to have pre-submission meeting for an application filed through the full evaluation route.

2. Submission of Application: Mainly two steps, first online submission of application via PRISM followed by variation technical dossier submission.

- Variation Application Dossier: Within two working days of the submission of PRISM application technical dossier should be submitted. The date on which actual dossier accompanying technical application is considered as date of submission where the time starts for processing.
- The format of dossier submission is in CTD or ACTD format same as that of original new drug application. A duly completed checklist must be accompanied for each MAV application by the applicant and thereby attached in PRISM.
- The complete data requirements of application must follow Parts I to IV of ACTD format or module 1 to 5 of ICH CTD format.
- Part I or Module 1 documents should be submitted in softcopy in PRISM. Applicants can choose to submit in full in PRISM section or softcopies in the CD or DVD in PDF format for Part II to IV or Modules 2 to 5.
- When submitting in CD or DVD format, the dossier should be organized in folders and subfolders and include in all documents bookmarks to facilitate document retrieval. Labelling for the CD/DVD should be done properly which should specify PRISM application number and date, Name of the product, Type of application and CD or DVD contents i.e. Modules 2 to 5.
- All documents supporting the application must be in English language. In case if the documents are not in English, a translation certificate or verified translation is required.

3. Screening of Application

- Screening of application will start once the receipt of the technical dossier will be considered as submission date. Screening of application aims to ensure application correctness and dossier completeness. If there is any identification of re-routing of evaluation during screening of application by the agency, the applicant is notified of this change in the form of input request.
- The MAV application submitted without clinical data or without reports of assessment in case of verification route will not be subjected for screening. The applicant will receive input request for withdrawing such application.
- A screening query is raised to the applicant through input request via PRISM, if the dossier submitted is found to be incomplete. The total number of input request sent for MAV application is two. The responding time given for each applicant is 20 working days from the date of input request issued. As stated in input request if all the deficiencies by the applicant are addressed then only further the application is considered for evaluation.
- In case of MIV-1 applications, within 3 working days of submission via PRISM, acceptance notification is received by the applicant.

4. Evaluation of Application

- Once the screening is completed, application will proceed to evaluation phase. Evaluation query is raised to the applicant through input request if additional information or clarification is required. If the applicant fails to respond to query within the timeframe raised by HSA, the application is considered for withdrawal. There will be no additional submission of data once the application is accepted by the HSA.
- Applicant can check the evaluation stages progress for the full and abridged evaluation route of MAV-1 applications through Track@PRISM

Table II: Stages of Evaluation Routes.

Notification sent to applicant	**Evaluation Stages**			
	Stage I	**Stage II**	**Stage III**	**Stage IV**
Application type & Evaluation route	Acceptance for evaluation	Evaluation in progress	Evaluation in midway	Completed Evaluation
MAV-1- Full or Abridged	Application is accepted, Start of evaluation timeline	Application evaluation is in progress	Application evaluation is in midway, First set of queries from HSA can be raised	Evaluation of application is completed. Further, application undergoes for regulatory decision, queries can be expected at this stage also.

There are four stages involved in evaluation of MAV-1 application.

- Stage I stands for acceptance which means evaluation of application has started.
- Stage II shows evaluation of application is in progress.
- Stage III shows evaluation is in progress. First set of queries can be raised from HAS.
- Stage IV stands for completed evaluation of application. Application further undergoes for decision from Regulatory body. Queries can be expected at this stage also.

MAV -1 Evaluation Routes

For MAV-1 application full, abridged and verification evaluation routes are applicable. For each route of evaluation, eligibility criteria and requirements of document are different.

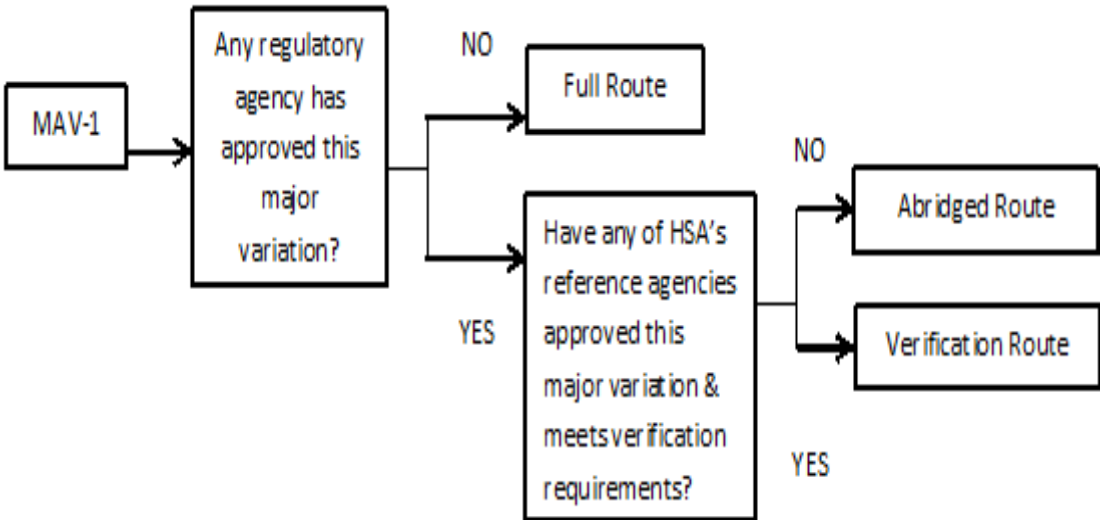

Fig. 5: Schematic flow of evaluation route for MAV-1.

- Full evaluation route is applicable for major variation which has not received approval from any regulatory agency during the submission time.
- Abridged evaluation route is applicable for major variation which has been evaluated and received approval by at least one regulating agency.
- Verification evaluation route: At least two of the reference agency of HSA must be evaluated and approved for major variation. One of the reference regulating agencies should be considered as primary reference agency for qualifying supporting documents for variation.

Another criteria to be followed under verification route is to submit application within three years from the approval date of chosen reference agency. The variation application of product should not be withdrawn, rejected by any of the regulating agency in order to evaluate under

verification route. Primary reference agencies of HSA are Health Canada (HC), United States Food and Drug Administration (USFDA), United Kingdom Medicine and Healthcare Regulatory Agency (UK MHRA), European Medicines Agency (EMA) and Therapeutics Goods Administration (TGA).

- If the primary reference agency is Health Canada then complete set of clinical evaluation reports including all annexes, documents of question and answer between Agency and sponsor must be considered.
- If the primary reference agency is USFDA then complete set of clinical evaluation reports including all annexes, documents of question and answer between Agency and sponsor, FDA sponsor authorization must be considered. The application should be filed only after HSA receives reports of assessment from FDA.
- If the primary reference agency is UK MHRA then complete set of clinical evaluation reports as per Day 70, Day 120, Day 200 as per national, decentralized and mutual recognition procedure including all annexes, documents of question and answer between Agency and sponsor, FDA sponsor authorization must be considered.
- If the primary reference agency is EMA then complete set of clinical evaluation reports as per centralized procedure including all annexes, documents of question and answer between Agency and sponsor, FDA sponsor authorization must be considered.
- If the primary reference agency is TGA then complete set of clinical evaluation reports including all annexes, documents of question and answer between Agency and sponsor must be considered along with delegate's overview, pre-ACPM response and ACPM minutes.

MAV-2 Evaluation Routes

- For MAV-2 applications only the abridged route of evaluation is applicable.

MIV-1 Evaluation Routes

- For MIV-1 applications, abridged or verification route is applicable.

MIV-2 applications can be filed per registered product at any one time.

Applicants are informed about the variation application approval through the generated email and registration information of product will be updated as per changes approved in PRISM. To view the latest information on registration and post approval commitments of their respective products applicant can seek to Enquire@PRISM.

Target Processing Timelines[9]

- For MAV-1, MAV-2 the target processing timeline for screening is considered to be 50 working days from the date of acceptance of application.
- Evaluation timeline for MAV-1 application is 270 days under full evaluation route, 180 days under abridged evaluation route, 60 days under verification route.
- For MAV-2 application, evaluation timeline is 180 days under abridged route.
- For MIV-1 application, target processing timeline is 120 working days through abridged route and through verification route it is 90 working days.
- The relevant checklists must be referred by the applicant to ensure the submission is complete in order to avoid delay in application processing.
- Notification timeline for MIV-2 applications: The proposed changes by the applicant can be incorporated within 40 working days from the submission date of complete application if HSA doesn't raise any objection.

Variation Application Fees[10]

- From time to time fees may subject to revision so the applicants are requested to see HSA website for current information.
- With the help of GIRO or other electronic mode of payments such as eNets or eCredit card payment can be done.
- Screening fee is only applicable for MAV-1 which has to be paid at the time of online submission via PRISM. For other type of variation applications screening fee is not applicable. Once the application is submitted through PRISM screening fee is non-refundable.

Evaluation fee are of two types for MAV-1 applications.

- For a single strength of product or the first product in a product series of different strengths.
- For each subsequent product in a product series of different strengths.

Payment for MAV-1 application should be done upon acceptance of technical dossier for evaluation which is non-refundable.

Payment for MIV-1 application should be done upon application submission via PRISM which is non-refundable.

Payments done through GIRO, upon application acceptance the evaluation fee will be debited. Payments made through electronic mode like eNets, eCredit card, evaluation fee is collected along screening fee. The fees collected will be refunded in case if the application is not accepted for evaluation.

Applicant can opt for progressive payment scheme. This scheme is applicable for applicant who done payment via GIRO.

Table III: Variation applications applicable for progressive payment scheme.

Application type & Evaluation route	Evaluation Stages			
	Acceptance for evaluation	Evaluation in progress	Evaluation in midway	Completed Evaluation
MAV-1- Full or Abridged	30%	40%	20%	10%

The payment scheme selected cannot be changed once the application is submitted. Under the progressive payment scheme if at evaluation stage there is withdrawal of application then fees which has been charged but not debited from the GIRO account would remain payable. The paid fee is non-refundable.

Applicable fees for chemical drugs and biologics under MAV-1

- Screening under abridged and verification dossier is $500 and for full dossier it is $2,500.
- Evaluation under abridged route for first strength is $5,500.
- Evaluation under abridged route for subsequent strength is $2,750.
- Evaluation under verification route for first strength is $8,250.
- Evaluation under verification route for subsequent strength is $2,750.
- Evaluation under full dossier is $550

Applicable fees for chemical drugs and biologics under MIV-1

- Evaluation fees is $550

Re-routing of evaluation during screening

- If there is any re-routing of variation application an input request is sent to the applicant. In case of the change of application between different types of application i.e. change in between MAV-1, MAV-2, MIV-1 or MIV-2 then the applicant should withdraw and resubmit the applicant if the applicant wish to continue.

- If there is change in evaluation routes i.e. full to abridged, verification to abridged or abridged to verification then the applicant should withdraw and resubmit the applicant if the applicant wish to continue.

Dossier Requirements for MAV-1[4]

- Administrative and product information i.e. Module I of ICH CTD or Part I of ACTD has to be provided for MAV-1 application evaluated under full, abridged and verification route.
- Common technical documents overview and summaries i.e. Module 2 of ICH CTD or incorporated in Part II, Part III and Part IV have to be provided for MAV-1 application evaluated under full, abridged and verification route.
- Quality documents i.e. Module 3 of ICH CTD or Part II of ACTD is not required to submit for MAV-1 applications.
- Non-clinical documents i.e. Module 4 of ICH CTD or Part III of ACTD is not required to submit for MAV-1 applications. Only if the MAV-1 proposed is regarding non-clinical data then non-clinical summary and overview along with the applicable report are required under full evaluation route. For abridged and verification route non-clinical overview can be given for cases as applicable.
- Clinical documents i.e. Module 5 of ICH CTD or Part IV of ACTD has to be submitted for MAV-1 application under full evaluation route. Under abridged and verification route, pivotal study reports and synopses of all studies applicable to requested dosing, indication, patient group to be submitted.

Dossier Requirements for MAV-2[4]

- Table of contents
- Introduction with reclassification justification
- PRISM application form
- Product labels, approved summary of product characteristics, package insert and package information labelling.
- Proof of approval for the reclassified product in US, Canada, UK or Australia
- Status of registration in other countries

Module 2 or Part IV – Clinical safety summary should include following:

- Product forensic classification in US, Canada, UK or Australia and duration of sale to that classification.
- Experience of patient exposure of the product
- Worldwide Summary of safety profile of product and local adverse drug reactions, data obtained from post marketing surveillance, and literature published.
- Analysis of hazards with respect to drug abuse, whether deliberate or accidental.

CONCLUSION

The applicant can propose changes once the therapeutic product is in the market, provided the proposed changes are approved by HSA under the suitable categories. In present scenario of Singapore post approval variation application are categorized as MAV-1, 2 and MIV-1, 2. The submission process with the target processing timelines and fees are described.

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