



Screening TAT Pilot Project

NDA, GDA, MAV-1 & 2

Current

❖ Screening timelines:

Application Type	Dossier Type	Time to 1 st Communication*
NDA, GDA, MAV-1, MAV-2	Full and abridged	25 working days
NDA, GDA, MAV-1	All verification, excluding CECA	25 working days
GDA	Verification CECA	14 working days

* 1st communication in the form of an Input Request or acceptance/non-acceptance notification

Current

- ❖ Timeline(s) for review of response(s) after 1st and subsequent round(s) of queries are not committed i.e. overall screening turnaround time (TAT) for each application is unpredictable.
 - ❑ Limitations: unpredictable screening TAT → affects overall application/product planning (e.g. product launch) for the industry

- ❖ No cap on the number of rounds of screening queries → as many as required to obtain a complete dossier for evaluation.
 - ❑ Limitations: strain on resources for both industry and HSA

Concept

- ❖ Concept of screening TAT pilot project to:
 - ✓ Improve on the observed limitations of the current system
 - ✓ Address feedback provided by industry over the years on the need for published screening timelines beyond time to 1st communication for better transparency and to facilitate planning

Screening TAT Pilot Project

❖ Objectives:

- ✓ To formulate the actual screening TAT based on data collected
- ✓ To derive a potential cap on the number of rounds of screening queries

❖ Duration: 1 year

❖ Applications involved: All NDAs, GDAs and MAV-1 & 2 applications regardless of dossier type (full, abridged, verification, or verification CECA) will be included in this pilot project

Screening TAT Pilot Project

❖ Impact on industry:

- ✓ Screening process proceeds as usual (i.e. status quo)
- ✓ Focus of current project is data collection
- ✓ During the pilot phase, there is no cap on the number of rounds of screening queries
- ✓ Please note that in future, a maximum number of rounds of screening queries may be imposed (e.g. 3 rounds), and applicants may be asked to withdraw the application if the dossier is still deficient after the stipulated number of rounds has been exceeded

MIV Applications

Screening TAT Pilot Project

❖ Objectives:

- ✓ To formulate the actual screening TAT based on data collected
- ✓ Same concept as screening TAT pilot project for NDA, GDA and MAV
- ✓ No cap on the number of rounds of screening queries

❖ Duration: 6 months

❖ Applications involved: MIV-1

Implementation

Screening TAT Pilot Project

❖ Follow-up:

- ✓ Industry email blast
- ✓ Implementation: 01 Oct 2014 (NDA/GDA/MAV); 01 Nov 2014 (MIV-1)

❖ Completion:

- ✓ The overall screening TAT and cap on number of rounds of screening queries will be announced to the industry

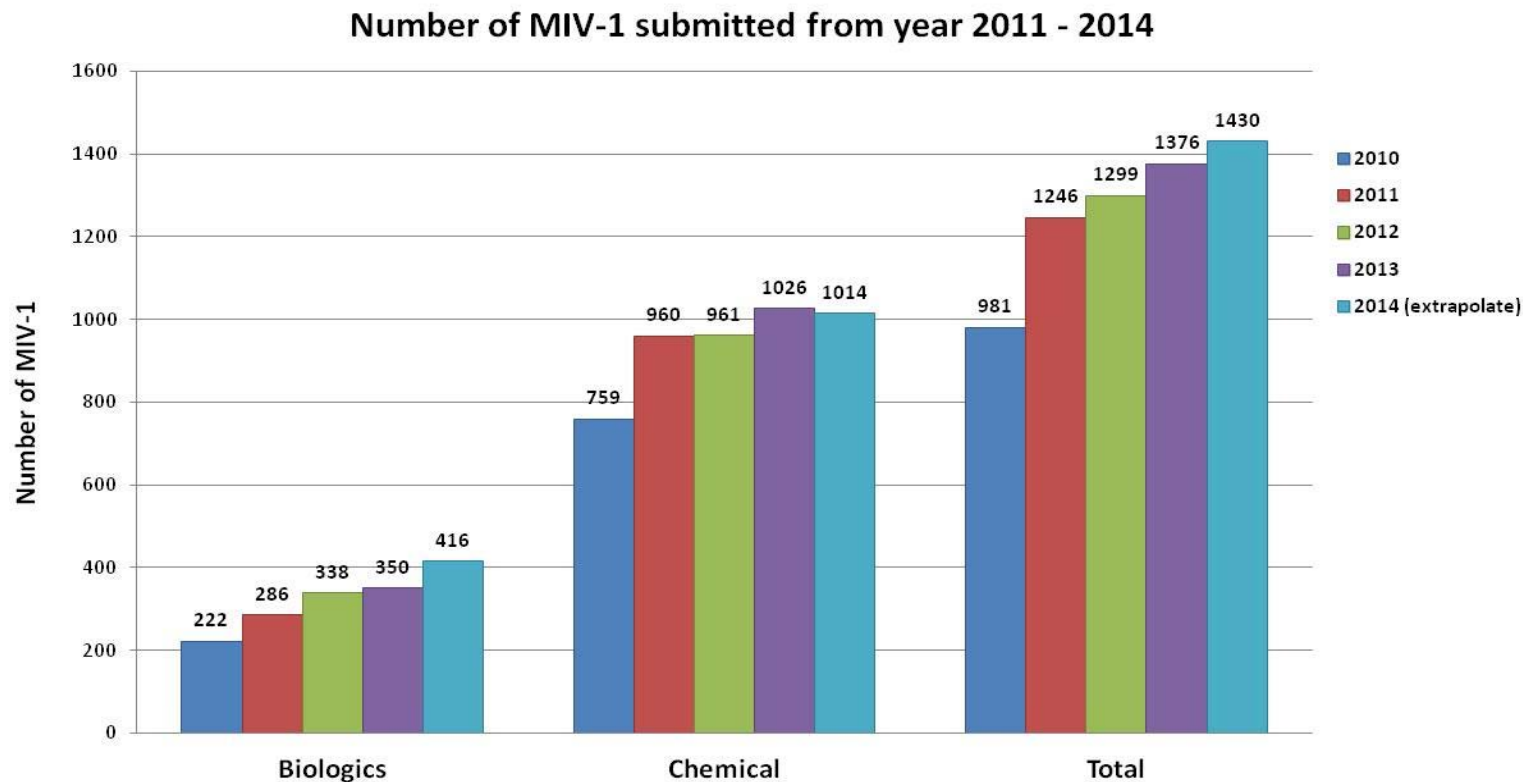
❖ Reminder:

- ✓ Industry is strongly encouraged to submit complete dossiers and to provide complete responses to queries in a timely manner so as to generate representative screening data that will accurately and fairly reflect the time required for screening of most applications

Minor Variation Applications (MIVs) Update

Background

- ❖ Increasing numbers of MIV-1 submissions from 2010 to 2014 (data extrapolated based on 6 months' data)
- ❖ Average of 120 MIV-1 submissions per month (2014)
- ❖ Same approval timeline of 120 working days



Background

❖ Process improvement

- ❑ To facilitate better planning for the industry – screening timeline transparency
- ❑ Minimize requests for expedited review
- ❑ Minimize possible mix-ups/errors during the regulatory process
- ❑ To facilitate our work for better screening and evaluation timeline

PRISM Application Form

0.4 Amendment Details

Current situation

- ❖ Current free-text format resulting in lengthy and inaccurate information entered
 - Unable to categorise type of MIV-1 changes
 - Difficulty in tracking non-consequential changes

Proposed Changes

- ❖ To use a drop-down listing with checklist titles in Appendix 15 and 16 may be selected
 - Clear and accurate variation changes at one glance
 - Useful for data analysis

PRISM Application Form

0.4 Amendment Details

Current situation - examples

0. Licence/Permit/Certificate/Listing Summary

0.1 Licence/Permit/Certificate/Listing No.:

0.2 Start Date:

0.3 Expiry Date:

0.4 Amendment Details:

We would like to apply for the following section changes pertaining to

- 1. Drug Substance Changes S4.2 Analytical Procedures • Analytical Procedures of Working Cell Bank, Intermediates and Drug Substance o Changes were made to improve control, increase comprehension, reduces the sources of error, and conform to current instrumental requirements. S2.3 Control of Materials S4.1 DS Specification • Testing Specifications of the Working Cell Bank and Drug Substance o The testing specification was updated to harmonize names and numbers of analytical procedures with those given in the respective documents. • Testing Specification for raw material o The testing specifications for raw material were updated to reflect current EP requirements S7 Stability Data • Stability Data of Drug Substance o The expiry date for –1b Drug Substance is extended from 18 to 36 months. • The extension is supported by real time data. 2. Drug Product Changes • P5.2 Analytical Procedures o Minor changes in different methods for testing of the drug product. • Changes were made to improve control, increase comprehension, reduces the sources of error, and conform to current instrumental requirements. • P5.1 Finished Product Specification o The testing specification was updated to harmonize names and numbers of analytical procedures with those given in the respective documents. Please find the DRB Amendments summary for details.

0. Licence/Permit/Certificate/Listing Summary

0.1 Licence/Permit/Certificate/Listing No.:

0.2 Start Date:

0.3 Expiry Date:

0.4 Amendment Details:

1. Change in product licence holder nam

. The address will remain at
 . Commerce supporting doc-uments are enclosed in the application. 2.
 as the batch releaser is the registered
 manufacturer for is also responsible for the
 manufacturing, bulk, fil-ing, labelling, packaging, testing and final release to the
 market. 3. Change of Batch Size and Addition /Deletion of In-process limits of
 The above changes have been applied, approved in the EU
 and implemented but has by mistake never been filed for in Singapore. The updated
 batch size has been adequately justified by process validation, batch analyses and
 stability data. This change is also to harmonise the description of the manu-facturing
 process between the countries in which the drug product is regis-tered. • Minor
 change in the manufacturing process • Change in batch size of the finished product to
 . The change has already been implemented
 but has by mistake never been applied for. The updated batch size has been
 adequately justified by process validation, batch analyses and stability data. • Change
 of in-process test: Addition of new test and deletion of non-significant in-process test.
 • Widening of the approved IPC limits 4. Update and PI harmonization between

PRISM Application Form

0.4 Amendment Details

Proposed Changes

❖ Drop-down listing for PRISM 0.4 Amendment Details

- Only **ONE** MIV-1 Checklist Title as Primary Change per submission, unless for ***consequential changes****
- For variations not covered under Appendices 15 and 16, e.g., those provided as a result of MIV Inquiries, please choose “Others” and enter the summary of the variation change (free-text)
- Details of the variation changes to be provided in the “Table of Summary of Change”
- Mock-up design



0. Licence/Permit/Certificate/Listing Summary

0.1 Licence/Permit/Certificate/Listing No.:

0.2 Start Date:

0.3 Expiry Date:

0.4 MIV Checklist Number (Main Change): CHEM_MIV3

0.5 MIV Checklist Number (Consequential Change(s)): CHEM_MIV1
CHEM_MIV2
OTHERS

(Note: Actual PRISM screenshots will be shared with the industry before implementation)

Consequential changes

Current situation

- ❖ Non-consequential MIV-1 changes to be submitted separately and not bundled in one submission
- ❖ Implemented on 1st July 2011
- ❖ Received feedback that multiple submissions of variation changes are limited by the number MIV-1 submissions allowed in PRISM, i.e., 3

Proposed change

- ❖ Increase in number of MIV-1 submissions in PRISM from 3 to 5
 - ❑ For easy planning of multiple MIV-1 submissions
 - ❑ Allow submission of non-consequential changes as separate MIV-1 applications

Consequential changes

Proposed Changes

- ❖ For consequential changes, the main change should be reflected as the primary change in PRISM Section 0.4

0. Licence/Permit/Certificate/Listing Summary	
0.1 Licence/Permit/Certificate/Listing No.:	
0.2 Start Date:	
0.3 Expiry Date:	
0.4 Amendment Details:	• Additional manufacturer for the intermediate by Pharmaceuticals and Chemicals Ltd., using a different synthetic pathway • Update in the intermediate specification details, including the addition of a specification and associated test method for formaldehyde in the intermediate

Primary change – B1 Addition of manufacturing site of DS

Secondary change – B8 Change of specification of DS [where European Pharmacopoeial certificate of suitability (CEP) is available]

Consequential changes

Proposed Changes

- ❖ For a CMC MIV-1 application, MIV-1 changes to the product labelling is **not** considered as a consequential change and should not be submitted in one MIV-1 application

E.g.: **Primary** B17 Change of Shelf Life of drug product
Non-consequential change ~~B22 Change of Content of Product Labelling~~

- ❖ MIV-2 changes are **allowed** to ride on MIV-1 application

E.g.: **Primary** B22 Change of Content of Product Labelling
Secondary C1 Change of Drug Product Name

Changes after acceptance

Current situation

- ❖ Increasing number of requests to replace original proposed labelling materials with newer versions at various time points of evaluation
- ❖ Ad-hoc requests to add additional MIV-1 changes not originally submitted for
- ❖ Additional review time needed for undeclared discrepancies between updated PI submitted midway through evaluation versus that initially submitted

Changes after acceptance

Proposed initiatives

❖ For timely processing of MIV-1 applications

- ❑ Requests to replace proposed labelling materials (PI/outer carton/inner label) with a newer version after acceptance will **not** be accepted

Exception: HSA-initiated PI changes related to safety/efficacy concerns

- ❑ Requests for additional changes to ride on existing MIV-1 application will not be accepted
 - A CMC-related MIV-1 requesting for additional safety updates to the PI after acceptance will not be accepted.
 - A clinical-related MIV-1 requesting for additional safety updates to the PI after acceptance will not be accepted
- Submit new changes in separate MIV1/2 application

Annotations for labelling materials

Current situation

- ❖ Additional screening and evaluation time spent on deciphering actual proposed changes to labelling materials
- ❖ Embedded changes not annotated
- ❖ Resulting in delay in approval

Annotations for labelling materials

Inappropriate annotation

- Current approved text not intended to be deleted was annotated:

Pregnancy

~~The safe use of ABCXYZ™ in pregnant females has not been established. Safety in animals have shown reproductive toxicity have been associated with findings in some animal reproductive studies. Hence, administration of ABCXYZ™ in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to foetus~~

Pregnancy

The safe use of ABCXYZ™ in pregnant females has not been established. Safety in 20 rodents have shown reproductive toxicity have been associated with findings in some animal reproductive studies. Hence, administration of ABCXYZ™ in pregnancy should be considered only if the physician deems the benefit to the mother outweighs the possible risk to foetus

Amended text in red not annotated although entire section is highlighted



Inappropriate annotation

- Applicants inserting own comments within the PI itself

Pregnancy

*Inclusion of description within the PI
of how text is relocated*

[The following text is moved to 'Warnings and precautions', page/line XX]

~~The safe use of ABCXYZ™ in pregnant females has not been established. Safety in animals has been associated with findings in some animal reproductive studies. Hence, administration of ABCXYZ™ in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to foetus.~~

Warnings and precautions

*Inclusion of description within PI but
actual text not reproduced.*

[Text from Pregnancy section, page/line XX moved here]



Annotations for labelling materials

Proposed change

- ❖ Annotations should be made based on the actual text to be added, and on current approved labelling materials.
- ❖ Current approved text proposed for deletion should be ***struck through***, whereas addition of new proposed text should be **underlined or highlighted**
- ❖ IR will be sent for the applicant to amend proposed PI if annotations are not properly made

Annotations for labelling materials

Proper annotation

- Strikethrough for deletion, highlight (or underline) for addition

Pregnancy

Strikethrough for deletion

~~The safe use of ABCXYZ™ in pregnant females has not been established. Safety in animals have shown reproductive toxicity have been associated with findings in some animal reproductive studies.~~
Hence, administration of ABCXYZ™ in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to foetus.

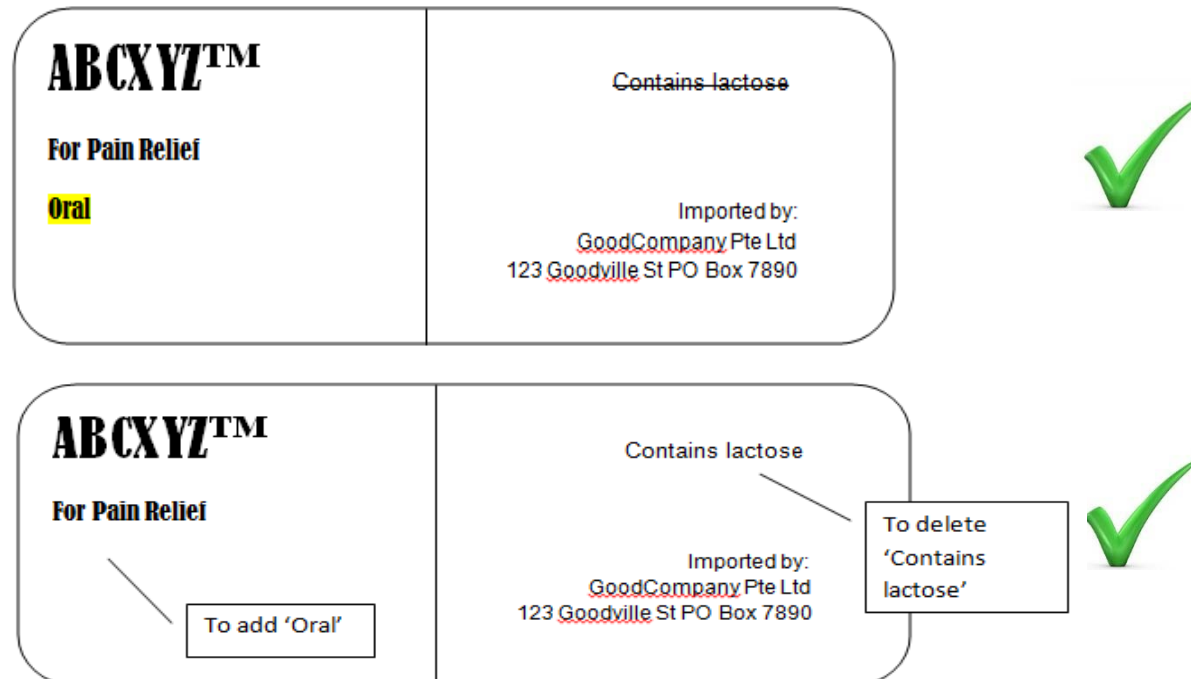
Highlighting of new text



Annotations for labelling materials

Proper annotation

- Annotation on labelling artwork with comment box



Annotations for labelling materials

Proposed change

- ❖ Current approved text that are not intended to be deleted should not be annotated.

Pregnancy

~~The safe use of ABCXYZ™ in pregnant females has not been established. Safety in animals have shown reproductive toxicity have been associated with findings in some animal reproductive studies. Hence, administration of ABCXYZ™ in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to foetus~~

Pregnancy

The safe use of ABCXYZ™ in pregnant females has not been established. Safety in 20 rodents have shown reproductive toxicity have been associated with findings in some animal reproductive studies. Hence, administration of ABCXYZ™ in pregnancy should be considered only if the physician deems the benefit to the mother outweighs the possible risk to foetus

Amended text in red not annotated although entire section is highlighted



Pregnancy

The safe use of ABCXYZ™ in pregnant females has not been established. Safety in animals-20 rodents have shown reproductive toxicity have been associated with findings in some animal reproductive studies. Hence, administration of ABCXYZ™ in pregnancy should be considered only if the physician deems the benefit to the mother outweighs the possible risk to foetus



Annotations for labelling materials

Proposed change

- ❖ Deletion of entire paragraphs of text to be replaced by new ones (clearly annotated) are generally acceptable for
 - Major content overhaul e.g for 'grandfather' products
 - Change of PI to PIL for P, GSL products, or vice versa for POM

Annotations for labelling materials

Proposed change

- ❖ Translocation of current approved text from one section to another can be allowed.

Example of moving entire text to another section

Pregnancy *Strikethrough entire section*

~~The safe use of ABCXYZ™ in pregnant females has not been established. Safety in animals has been associated with findings in some animal reproductive studies. Hence, administration of ABCXYZ™ in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to foetus.~~

Warnings and precautions

The safe use of ABCXYZ™ in pregnant females has not been established. Safety in animals has been associated with findings in some animal reproductive studies. Hence, administration of ABCXYZ™ in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to foetus.

Highlight text in new location with comment on type of change

Comment [MW(1)]: Moved from Pregnancy section



Annotations for labelling materials

Proposed change

- ❖ HSA-initiated PI safety update of pending MIV-1/MIV-2 applications
 - ❑ Only changes related to safety update and editorial changes allowed and these should be clearly communicated to the evaluator in charge.
 - ❑ Provide updated, clearly annotated PI based on initial proposed PI for the MIV-1/MIV-2.

Use in Pregnancy

The safe use of ABCXYZ™ in pregnant females has not been established. Safety in ~~animals~~ **20 rodents** have shown reproductive toxicity have been associated with findings in some animal reproductive studies. Hence, administration of ABCXYZ™ in pregnancy should be considered only if the **physician deems the** benefit to the mother outweighs the possible risk to foetus

Serious skin reactions

Serious skin reactions (e.g. Stevens Johnson syndrome) have been reported in patients receiving ABCXYZ. It is recommended that patients be informed about the signs of serious skin reactions, and that use of ABCXYZ be discontinued at the first appearance of skin rash.

*Retain annotations of amendments
from initial proposed PI*



Comment [MW(2): Safety update as per DHCPL as communicated through email on 1/7/14

MIV updates - Timelines

Tentative implementation timeline:

1st Nov 2014

For further clarifications, email:

HSA_MedProd_Registration@hsa.gov.sg

Pointers

- ❖ Applicants are strongly encouraged to indicate in the introductory letter:
 - If the proposed change(s) affects multiple products,
 - If there are pending (MAV/MIV) applications for the same product
 - PRISM enhancement in the works for applicant to indicate related applications to HSA
- ❖ Submit applications for multiple strengths of the same product at the same time for ease of resource planning

Do it RIGHT at the first time!