Briefing Session: Updates to Registration Requirements

3 and 7 March 2014

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Outline

- Stability data requirements
- Drug Master File procedures
- Variations procedures

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- Stability data requirements
- Drug Master File procedures
- Variations procedures

Stability data requirements

- Site specific stability data
  - Amount of DP stability data has been reduced *at time of submission* of new product application
    - Chapter C, section 14.3.2, subsection *Drug Product Stability*, p. 40-41
    - Chapter D, section 17.3.2, subsection *Drug Product Stability*, p. 57-58
  - *Not* applicable to biological products

Stability data requirements

- Site specific stability data
  - Multiple DS manufacturers
    - DP stability dataset has been reduced
    - Must fulfill following conditions:
      1. Full CTD S section or CEP for each DS from each proposed DS manufacturer
      2. Same DS specification used by proposed DP manufacturer for control of DS

Stability data requirements

- Site specific stability data
  - Multiple DS manufacturers
    - Dataset to submit:
      3. Minimum one set of DP stability data using DS that represents all proposed DS manufacturers for that DS
      4. If (3) above not met, then commitment letter to conduct DP stability (one production batch) using DS for each DS manufacturer not represented at time of submission

Stability data requirements

- Site specific stability data
  - Multiple DS manufacturers

Example 1. DS site A and B, DP site Z

	Dataset submitted:	With commitment letter for:
Chemical DS *(non-sterile and sterile)*	One set of DP data using A+Z	1 production batch using B+Z
	One set of DP data using B+Z	1 production batch using A+Z
	One set of DP data using A+Z & B+Z	No commitment needed

Note: one set of DP data = # batches required at time of submission

Stability data requirements

- Site specific stability data
  - Multiple DS manufacturers

Example 2. DS #1 site A and B, DS #2 site A and D, DP site Z

Dataset submitted:	With commitment letter for:
One set of DP data using DS1 A + DS2 A	1 production batch using DS1 B + DS2 D
One set of DP data using DS1 B + DS2 A	1 production batch using DS1 A + DS2 D
One set of DP data using DS1 A + DS2 D	1 production batch using DS1 B + DS2 A
One set of DP data using DS1 B + DS2 D	1 production batch using DS1 A + DS2 A
One set of DP data using DS1 A + DS1 B + DS2 A + DS2 D *(any combination)*	No commitment needed *(all proposed DS manufacturers represented)*

Note: one set of DP data = # batches required at time of submission

Stability data requirements

- Site specific stability data
  - Multiple DS manufacturers

*1. Full **CTD S section** or CEP for each DS from each proposed DS manufacturer*

- Rationale:
  - Allows comparison of manufacture & quality of DS from each of the proposed manufacturers
    - » Impurity profile, residual solvents
    - » Particle size, polymorphism, stereoisomerism
    - » Specification

Stability data requirements

- Site specific stability data
  - Multiple DS manufacturers

*1. Full CTD S section or **CEP** for each DS from each proposed DS manufacturer*

- Rationale:
  - DS manufacturers supported by CEP considered equivalent (Ph. Eur.)
    - » Additional tests as stated on CEPs will be evaluated accordingly

Stability data requirements

- Site specific stability data
  - Multiple DS manufacturers

2. Same DS specification used by proposed DP manufacturer for control of DS

- DS specification captures all test parameters and limits from multiple DS manufacturers
- If same test parameter amongst different DS manufacturers, then limit should be aligned
- If not, then limit remains the same in DS specification by DP manufacturer

Stability data requirements

- Site specific stability data
  - Multiple DS manufacturers

2. Same DS specification used by proposed DP manufacturer for control of DS

Example 3. DS site A and B, DP site Z

DS site A DS spec	DS site B DS spec	DP site Z DS spec
Assay 98.0-102.0%	Assay 98.5-101.5%	Assay 98.0-102.0%
Impurity A NMT 0.2%	Impurity A NMT 0.2%	Impurity A NMT 0.2%
Methanol NMT 3000ppm	–	Methanol[1] NMT 3000ppm
–	Ethanol NMT 5000ppm	Ethanol[2] NMT 5000ppm

[1] tested for DS site A [2] tested for DS site B

Stability data requirements

- Site specific stability data
  - Multiple DS manufacturers

2. Same DS specification used by proposed DP manufacturer for control of DS

- Rationale:
  - DP manufacturer responsible for quality of DS that goes into the final DP for market
  - Only one DS specification is registered upon approval of application
    - » Product life-cycle → variation to change DS specification refers to one from DP manufacturer

Stability data requirements

- Site specific stability data
  - Multiple DS manufacturers

3. Minimum one set of DP stability data using DS that represents all proposed DS manufacturers for that DS

- Rationale:
  - Conditions #1 & 2 allow us to evaluate equivalency of DS quality from proposed DS manufacturers (e.g. CTD S7 data) → predict behaviour when in DP stability study

Stability data requirements

- Site specific stability data
  - Multiple DS manufacturers

4. If condition (3) is not met, then commitment letter to conduct DP stability (one production batch) using DS from each DS manufacturer not represented at time of submission

- Rationale:
  - Satisfy site-specific stability data requirement but also aligning to MIV approach
  - *May* require post-approval licensing condition depending on outcome of evaluation

Stability data requirements

- Site specific stability data
  - Multiple DP manufacturers
    - For multiple bulk product manufacturers
    - Following dataset required at time of submission:
      1. DP stability batches from each proposed DP manufacturer should be represented
      2. Number of batches from each proposed DP manufacturer must meet submission requirement

Stability data requirements

- Site specific stability data
  - Multiple DP manufacturers

Example 4. DS site A, DP site Y and Z

	Dataset submitted:
NDA and GDA *(unstable DS or critical dosage form)*	3 batches of DP data using A+Y, and, 3 batches of DP data using A+Z
GDA *(stable DS and non-critical dosage form)*	2 batches of DP data using A+Y, and, 2 batches of DP data using A+Z

Stability data requirements

- Site specific stability data
  - Multiple DP manufacturers
    - Rationale:
      - Need sufficient number of DP stability batches from each proposed bulk product manufacturer to evaluate trends in stability
      - Different bulk product manufacturers may not need same equipment to manufacturer bulk product of comparable quality
        - » Process validation (CTD P3.5) must be performed for each manufacturer

Stability data requirements

- Site specific stability data
  - Multiple DS *and* DP manufacturers
    - Increasingly complex but not unexpected
    - Dataset required at time of submission will be combination of requirements for multiple DS manufacturers *and* multiple DP manufacturers

Stability data requirements

- Site specific stability data
  - Multiple DS *and* DP manufacturers

Example 5. DS site A and B, DP site Y and Z

Site	DP site Y	DP site Z
DS site A	2	3
DS site B	1	0

Site	DP site Y	DP site Z
DS site A	3	0
DS site B	0	3

Site	DP site Y	DP site Z
DS site A	3	1
DS site B	0	2

Site	DP site Y	DP site Z
DS site A	3	3
DS site B	0*	0*

**** Not all DS sites are represented ∴ require commitment to conduct stability on one production DP batch (from either site Y or Z) using DS site B***

Stability data requirements

- Site specific stability data
  - Multiple primary (1°) packaging sites
    - Same container closure system
    - Dataset to submit:
      1. Minimum one set of DP stability data from one proposed 1° packaging site
      2. Transport validation of bulk DP to other proposed 1° packaging site(s), unless justification submitted
      3. Minimum 6 months of DP stability data from other 1° packaging site(s) with commitment to provide upon completion

Stability data requirements

- Site specific stability data
  - Multiple primary (1°) packaging sites

1. Minimum one set of DP stability data from one proposed 1° packaging site.

- Rationale:
  - Standard submission requirement → must have at least one set of DP stability data from at least one proposed site

Stability data requirements

- Site specific stability data
  - Multiple primary (1°) packaging sites

2. Transport validation of bulk DP to other 1° packaging site(s), unless justification submitted

- Rationale:
  - Enable us to determine if bulk DP will be affected by transport to another location for 1° packaging
    - » Different CCS for transporting bulk DP than for marketing purposes
    - » Other factors: climatic zones, microbial contamination (e.g. bulk liquids)

Stability data requirements

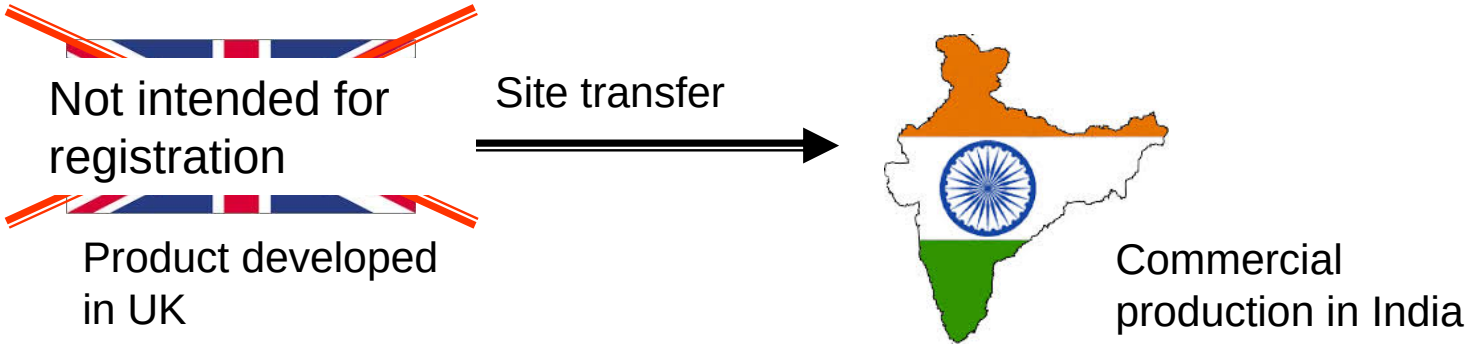
- Site specific stability data
  - Multiple primary (1°) packaging sites

3. Minimum 6 months of DP stability data from other 1° packaging site(s) with commitment to provide data upon completion

- Rationale:
  - Alignment to variation guideline requirement for adding or replacing 1° packaging site

Stability data requirements

- Site specific stability data
  - DP manufacturer of development/pilot batches
    - This DP manufacturer NOT intended for registration



Stability data requirements

- Site specific stability data
  - DP manufacturer of development/pilot batches
    - Intent: Development/pilot batches to support proposed shelf-life and storage condition
      - Batches have been manufactured by process *similar* to commercial process
      - Stability studies have already been performed → knowledge gained on DP quality during storage in CCS; *unlikely* that production scale-up will impact on stability

Should be same formulation and CCS as commercial

Stability data requirements

- Site specific stability data
  - DP manufacturer of development/pilot batches
    - Dataset to submit:
      1. Complete CTD P3 section from development/pilot DP manufacturer
      2. Batch analyses or CoAs (CTD P5.4) of stability batches from development/pilot DP manufacturer
      3. One set of minimum of 12 months of stability data from development/pilot DP manufacturer, as per ASEAN guideline

Stability data requirements

- Site specific stability data
  - DP manufacturer of development/pilot batches
    - Dataset to submit:
      4. One set of minimum of 6 months of stability data from proposed DP manufacturer
      5. A commitment to provide the completed stability studies (up to proposed shelf-life) from proposed DP manufacturer

Stability data requirements

- Site specific stability data
  - DP manufacturer of development/pilot batches

1. Complete CTD P3 section from development/pilot DP manufacturer.

- Rationale:
  - Enable us to compare batches made at development/pilot DP manufacturer against proposed commercial DP manufacturer

Stability data requirements

- Site specific stability data
  - DP manufacturer of development/pilot batches

1. Complete CTD P3 section from development/pilot DP manufacturer.

- Rationale:
  - » Determine if there any differences between sites (e.g. equipment, process)
  - » Determine if differences *may* have impact on DP quality (e.g. process validation)

Stability data requirements

- Site specific stability data
  - DP manufacturer of development/pilot batches

2. Batch analyses or CoAs (CTD P5.4) of stability batches from development/pilot DP manufacturer.

- Rationale:
  - Enable us to compare development/pilot batches to batches made at proposed DP manufacturer
    - » Batches at release of comparable quality

Stability data requirements

- Site specific stability data
  - DP manufacturer of development/pilot batches

3. One set of minimum of 12 months of stability data from development/pilot DP manufacturer, as per ASEAN guideline.

- Rationale:
  - Standard submission requirement → using development/pilot batches to support *proposed* shelf-life and storage condition

Stability data requirements

- Site specific stability data
  - DP manufacturer of development/pilot batches

4. One set of minimum of 6 months of stability data from proposed DP manufacturer.

- Rationale:
  - Alignment to variation guideline requirement for adding DP manufacturing site

Stability data requirements

- Site specific stability data
  - DP manufacturer of development/pilot batches

5. A commitment to provide the completed stability studies (up to proposed shelf-life) from proposed DP manufacturer.

- Rationale:
  - Stability guideline requirement when full stability dataset not provided at time of approval

Stability data requirements

- ASEAN stability guideline
  - 5th draft or version 6
  - Scope: NCEs, generics, variations (chem)
  - Implementation date: **1 April 2014**
    - Alignment with implementation of ASEAN Variation Guideline
    - Additional 6 months grace period → full implementation will be 1 October 2014

Stability data requirements

- ASEAN stability guideline
  - Things to note:

Section 4.7.7, 4.7.8 and 4.7.9 of ASEAN stability GL

    - Number of batches required:

	Current	Adopted ASEAN GL
NDA, chemical	3 batches	3 batches (NCEs)
GDA	2 batches (conventional dosage form & stable DS); 3 batches (critical dosage form or unstable DS)	2 batches (conventional dosage form & stable DS); 3 batches (critical dosage form or unstable DS)
Variations , chemical	MIV-1: 2 batches	Variations, major & minor (MaV, MiV) (AVG): 2 batches (conventional dosage form & stable DS); **3 batches** (critical dosage form or unstable DS)

Stability data requirements

- ASEAN stability guideline
  - Things to note:

Section 4.7.7, 4.7.8 and 4.7.9 of ASEAN stability GL

    - Amount of 30°C/75% DP data required:

	Current	Adopted ASEAN GL
NDA, chemical	12 months ASEAN, OR, 6 months ASEAN + 12 months ICH	12 months (NCEs)
GDA	12 months ASEAN, OR, 6 months ASEAN + 12 months ICH	6 months (conventional dosage form & stable DS), 12 months (critical dosage form or unstable DS)
Variations , chemical	MIV-1: 6 months	Variations, major (MaV): 6 months Variations, minor (MiV) : **3 months**

Outline

- Stability data requirements
- Drug Master File procedures
- Variations procedures

Drug Master File procedures

- Minor changes to Drug Master File (DMF) filing procedures
  - Chapter C, section 14.3.1, p. 36-37
  - Chapter D, section 17.3.1, p. 54-55
  - Implementation date: **1 April 2014**

Drug Master File procedures

- Submission of new DMF

	Applicant		*DMF Holder*	
	Current	**1 April 2014**	Current	**1 April 2014**
DMF	Applicant part (AP)	Applicant part **in PDF**	Applicant part (AP) and Restrict part (RP)	Applicant and Restrict parts **in PDF**
Letter of Access	Copy	Copy	Original	Original
DMF submission form	–	–	–	**Must submit**

Drug Master File procedures

- Submission of DMF update

	Applicant		*DMF Holder*	
	Current	**1 April 2014**	Current	**1 April 2014**
DMF	Updated AP	Updated AP **in PDF**	Updated AP and/or RP	Updated AP and/or RP **in PDF**
Summary table of changes	–	**+ (AP only)**	– /+	**+ (AP and/or RP)**
Letter of Access	–	–	–	–
DMF submission form	–	–	–	**Must submit**

Drug Master File procedures

- DMF Submission Form
  - New Appendix 18
  - Rationale:
    - Facilitate work-sharing amongst agencies within Consortium
      - Information requested quickly identifies if DMF submitted to other agencies → request for assessment report or work-share evaluation

Outline

- Stability data requirements
- Drug Master File procedures
- Variations procedures

Variation procedures

- Minor changes to Variation filing procedures
  - Appendix 15 (chemical) & 16 (biologic)
  - Implementation date: **1 April 2014**

Variation procedures

- Variation filing procedure
  - Documents in Table A must be submitted

Table A. MIV Application Hard Copy and Electronic Copy Requirements

	Soft Copy	Hard Copy
PRISM application form	PRISM	N/A
Table of Contents	PRISM	N/A
Declaration of product licence holder for MIV-1 or MIV-2	PRISM	1 set
Checklist for MIV(s)	PRISM	N/A
Table of Amendment Details	PRISM	N/A
MIV-specific Supporting documents - Administrative (Module 1/Part 1) - Other supporting documents	 PRISM PRISM/CD#	 1 set+ N/A
Current and proposed product labelling (annotated *and* pristine copies), where applicable	PRISM	N/A

+ *Only documents which require proof of authenticity are required to be submitted in hardcopy for Module 1 (e.g. CPPs, approval letters not available online, authorisation letters, GMP certificate, declaration letters, etc)*

 # All supporting documents may be submitted via PRISM or CD-ROM – do not combine PRISM attachments with a CD submission

Variation procedures

- Variation filing procedure
  - Documents in Table A must be submitted

Table A. MIV Application Hard Copy and Electronic Copy Requirements

	Soft Copy	Hard Copy
PRISM application form	PRISM	N/A
Table of Contents	PRISM	N/A
Declaration of product licence holder for MIV-1 or MIV-2	PRISM	1 set
Checklist for MIV(s)	PRISM	N/A
Table of Amendment Details	PRISM	N/A
MIV specific Supporting documents - Administrative (Module 1/Part 1) - Other supporting documents	 PRISM PRISM/CD#	 1 set+ N/A

Declaration can be incorporated into Introduction Letter
→ wording, name & signature, date

etc)
 # All supporting documents may be submitted via PRISM or CD-ROM – do not combine PRISM attachments with a CD submission

Variation procedures

Declaration of the product licence holder for MIV-1

I hereby submit an application for the concerned product to be varied in accordance with the proposals given above. I declare that (please tick the appropriate declarations)

- ☐ There are no other changes than those identified in *Section 0.4 Amendment Summary*;
- ☐ All Conditions for the change(s) concerned are fulfilled; and,
- ☐ The required documents as specified for the change(s) have been submitted.

Name	Signature	Date

Variation procedures

- Variation filing procedure
  - MIV checklists
    - "C" = conditions that must be fulfilled for the MIV to apply
    - "D" = documents that **must** be submitted
    - Still need to provide copy of checklist but no more checkboxes
    - State justification for *not* submitting required document for that MIV
      - If state "N.A.", must state why

Variation procedures

- Variation filing procedures

Example 6.

B8	Change of Specification of Drug Substance [where European Pharmacopoeial Certificate of Suitability (CEP) is available]
	a) Specification limits are widened b) Deletion of test parameter and limits

– Change from in-house specification to CEP but removed test parameter

e.g. tests for ethanol & isopropanol in in-house specification now tested under loss on drying as per CEP

Variation procedures

Example 6.

B8 Change of Specification of Drug Substance [where European Pharmacopoeial Certificate of Suitability (CEP) is available] a) Specification limits are widened b) Deletion of test parameter and limits	
D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by EDQM. 2. A declaration from the applicant that the relevant stability studies of the drug product in accordance with the *ASEAN Guideline on Stability Study of Drug Product* have been started and that the relevant stability studies will be finalised; data should be provided only if outside of the specification (with proposed action). 3. Specification of the drug substance. 4. Results of batch analysis from the drug substance manufacturer* demonstrating compliance with the Ph. Eur monograph and including additional test/limits listed on the CEP. 5. Additional data to address any relevant parameter(s) not addressed in the CEP, such as stability data (S7) if a re-test period is not stated on the CEP and physicochemical characteristics (e.g. particle size, polymorphism etc), if applicable. ** If the drug substance manufacturer is CEP certified and the drug product manufacturer claims otherwise (USP, JP, In-house etc), data covering S4.1 to S4.5 from the drug product manufacturer should be submitted.*

Variation procedures

Example 6.

B8	**Change of Specification of Drug Substance [where European Pharmacopoeial Certificate of Suitability (CEP) is available]** a) Specification limits are widened b) Deletion of test parameter and limits
D	1. A valid European Pharmacopoeial Certificate of Suitability (CEP) for the drug substance, latest version, with all annexes issued by EDQM. 2. A declaration from the applicant that the relevant stability studies of the drug product in accordance with the *ASEAN Guideline on Stability Study of Drug Product* have been started and that the relevant stability studies will be finalised; data should be provided only if outside of the specification (with proposed action). 3. Specification of the drug substance. 4. Results of batch analysis from the drug substance manufacturer* demonstrating compliance with the Ph. Eur monograph and including additional test/limits listed on the CEP 5. Additional data to address any relevant parameter(s) not addressed in the CEP, such as stability data (S7) if a re-test period is not stated on the CEP and physicochemical characteristics (e.g. particle size, polymorphism etc), if applicable. *Justification: attached CEP states re-test period and there is no additional testing required on drug substance.* ** If the drug substance manufacturer is CEP certified and the drug product manufacturer claims otherwise (USP, JP, In-house etc), data covering S4.1 to S4.5 from the drug product manufacturer should be submitted.*

Justification for not submitting document

Variation procedures

Example 6.

B8 Change of Specification of Drug Substance [where European Pharmacopoeial Certificate of Suitability (CEP) is available]

a) Specification limits are widened

When document NOT submitted in MIV dataset:

- Justification should be inserted into MIV checklist under relevant document no.
- State reason(s) OR location of document(s) if need more space and/or have supporting data
- Can state "N.A." but **must still** provide reason(s) ± supporting data

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compliance with the Ph. Eur monograph and including additional test/limits listed on the CEP

5. Additional data to address any relevant parameter(s) not addressed in the CEP, such as stability data (S7) if a re-test period is not stated on the CEP and physicochemical characteristics (e.g. particle size, polymorphism etc), if applicable.
   N.A. Please refer to Attachment 1.

** If the drug substance manufacturer is CEP certified and the drug product manufacturer claims otherwise (USP, JP, In-house etc), data covering S4.1 to S4.5 from the drug product manufacturer should be submitted.*

Variation procedures

- Implementation of ASEAN Variation Guideline (AVG)
  - Phase 1
    - Incorporated AVG technical requirements & terminology into checklists
    - New checklists added based on frequently-asked MIV Inquiry forms

Questions & Answers

Thank You