EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Webinar on Regulatory and Procedural Aspects of Type I variations

15 November 2016, 13:30 – 16:00 (GMT)

Presented by Procedure Managers in Human Medicines Evaluation Division

1. Welcome / Introduction

Alberto Ganan Jimenez

This webinar aims at supporting applicants in the preparation of their submissions of Type IA and Type IB variations….

We intend to:

- give an overview of the aspects checked during validation,
- provide examples of the most common validation issues identified during validation or processing of these procedures,
- increase awareness of the guidance documents and tools that could be used in the preparation of the submissions

…..with the ultimate target of reducing the number of issues raised during validation.

High rate of validation issues*
48% IAs#, 44% IBs, 48% IIs

- Improving the quality of submissions
- Reduce the number of VSI "*Right first time*"
- Reduce the administrative burden
- Timely implementation of changes

*2015 data.

#In the case of IAs, issues that required clarification or further documentation

The Agency aims at:

continuously monitoring and improving our procedures, guidance and interaction with stakeholders

INFORM

e.g. news items, Q&As, platform meeting, Workshops, Info-Days

CONSULT

e.g. surveys, guidelines development, public consultations on deliverables

COOPERATE

e.g. focus groups, technical expert groups

- An EMA/Industry platform on centralised procedures was established in 2014 (2 meetings/year)
- An EMA survey on post authorisation procedures took place in 2015
- As a follow up action, an initiative to improve the quality of submissions was launched during 2016

Initiative to improve the quality of submissions and reduce the number of validation issues during 2016

Analysis of VSI in Type IB C.I.2 scopes
Q1 2016

- Analysis of VSI
- Interaction with MAH to discuss challenges in preparation of submissions

Extend analysis to other types of variations.
Q2-4 2016

- Identification of aspects for trainings, update of guidance

Webinar to MAH
Q4 2016

- Presentation to MAH:
- Aspects checked at validation
- How to complete the eAF
- EMA guidance
- Practical examples of common mistakes

Development of guidance on classification
Q1 2017

- Completion of EMA procedural and regulatory guidance

Agenda - Session 1

Item	Agenda	Time
1.	**Welcome / Introduction** Alberto Ganan Jimenez	13:30 – 13:40
2.	**General overview of validation issues for type IA and IB variations** Simona Villa-Colciago and Michalina Najda	13:40 – 14:05
3.	**Electronic Application Form. Aspects to consider when preparing your submission.** Simona Villa-Colciago	14:05 – 14:20
4.	**Documentation requirements. Aspects to consider when preparing your submission.** Blanka Zakutna, Birgitte Jorgensen	14:20 – 14:35
5.	**Update of safety Product Information for Generics** Birgitte Jorgensen	14:35 – 14:50

Agenda - Session 2

Item	Agenda	Time
	Coffee Break	14:50 – 15:05
6.	**GMP and Inspection related documentation** Laetitia Deguil	15:05 – 15:30
7.	**Applications affecting an Active Substance Master File (ASMF) and CEP** Carlos Aicardo	15:30 – 15:50
8.	**Concluding remarks** Alberto Ganan Jimenez	15:50 – 16:00

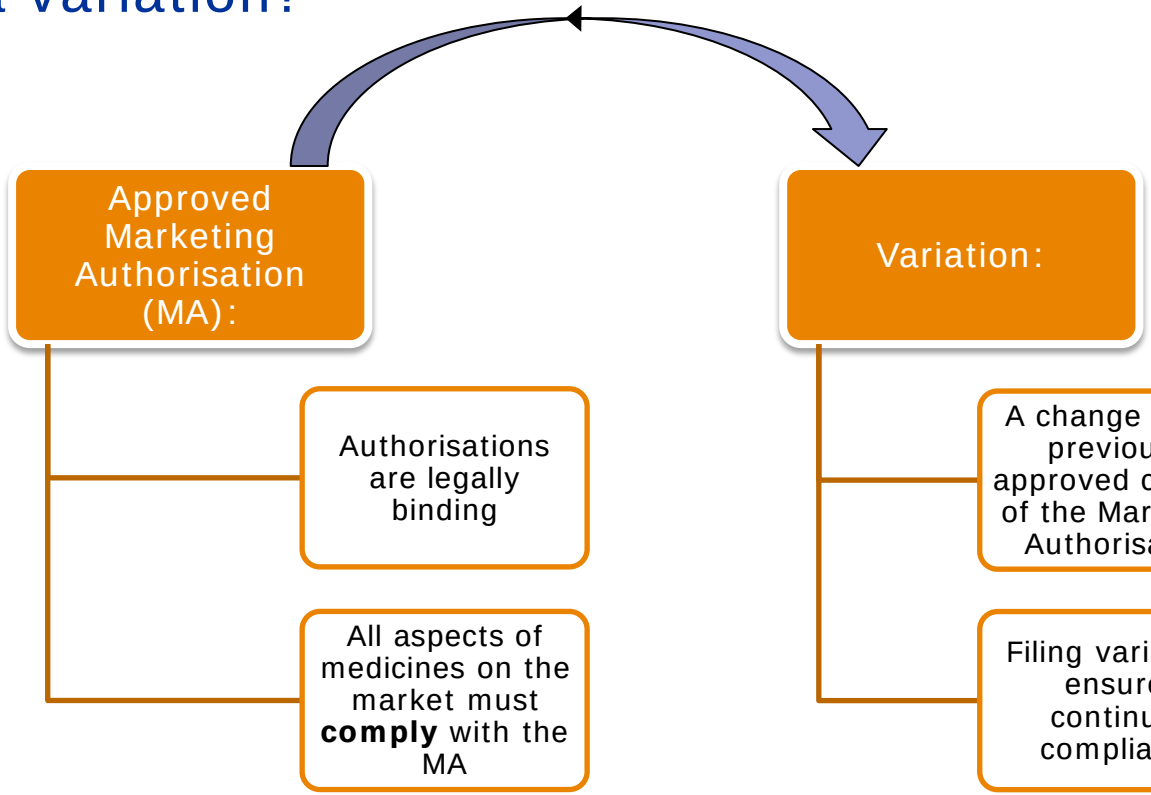
2. General overview of validation issues for type IA and IB variations

Simona Villa-Colciago and Michalina Najda

Contents

1. Introduction – what is a variation
2. Types of variations and Centralised Procedure overview
3. Type IA/IA$_{IN}$ variations – Definition
   - Review Process
   - Negative outcome
   - Most common validation issues
   - Implementation date
   - Commission Decision
   - Fees
4. Type IB Variations
   - Definition
   - Process
   - Most common validation issues
   - Fees

What is a variation?



- Administrative
- Quality
- Safety
- Efficacy

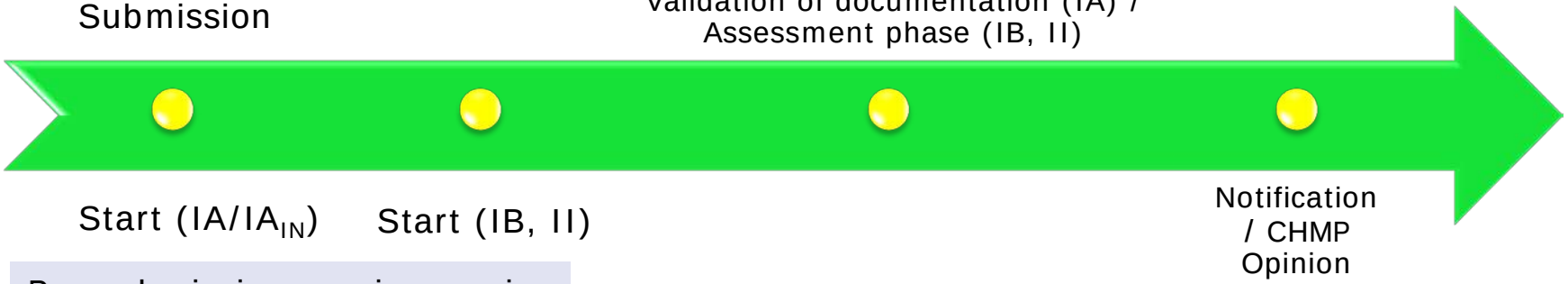
Types of variations

Variations Regulation (1234/2008) as amended by (712/2012)

Variations Guidelines (2013/C 223/01)

- Type IA – “Do and tell” for changes implemented in previous 12 months
- Type IA_{IN} - “Do and tell” and requires immediate notification after implementation
- Type IB – “Tell, wait and do” and requires notification before implementation (wait 30 days after submission of procedure)
- Type II – More detailed changes (“Tell and do”) and requires approval before implementation (usually 60 day review; range 30-90 days)
- Extension applications – e.g. additional strengths, pharmaceutical form and route of administration (up to 210 day review)

Handling of variations in the centralised procedure



Pre-submission queries service (PQS):
For IA/IBs
IAquery@ema.europa.eu

IBquery@ema.europa.eu

For Type IIs /other:

Procedure designated PM

Procedure Manager (PM) - oversees all aspects of the management of procedure;
→ first point of contact with MAHs and Rapporteurs

Procedure assistant (PA) – supports PM and MAH (Annexes, EPAR updates)

For IAs and IBs, a procedure specific PM is assigned upon receipt of submission. For IBs, MAH is informed of the assigned PM at start of procedure or during validation phase (if VSI during validation)

Type IA/IA$_{IN}$ variations - Definition

According to Commission Regulation (EC) No 1234/2008, Type IA/IA$_{IN}$ procedures are **minor variations** which have only a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned.

These are clearly classified in the Guidelines on the details of the various categories of variations and in the CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) 1234/2008 .

Type IA variations do not require assessment. These are simple, administrative procedures.

Review process

The Agency will review the Type IA/IA$_{IN}$ variation(s) within 30 calendar days following receipt. By day 30 the Agency will inform the MAH by Eudralink about the outcome of the review (favourable or unfavourable).

During the review the Agency will verify the documentation against the validation checklist and in particular:

- whether the application form has been properly filled in;
- the presence and correctness of the required documentation and
- compliance with the required conditions, in accordance with the Classification Guideline.

In exceptional cases, during the review process the Agency may issue a request for supplementary information (VSI) in case deficiencies have been identified in the submission, responses to which are due within **4 working days** as part of a new eCTD sequence.

Negative outcome

Common causes for negative outcome of the review:

- incorrect scope applied for;
- incorrect scope classification (e.g. a ‘z’ indent submitted as a Type IA/IA_{IN} in the absence of a CMDh Art. 5 Recommendation to classify it as such);
- insufficient/inadequate documentation provided;
- no responses provided to the VSI issued.

Most common validation issues

Application Form

- All approved presentations are listed but the change(s) applied for affect(s) only specific ones
- Implementation date missing
- A.7 scope for deletion of >1 site is repeated more than once

Ensure that only **affected** presentations are listed under section 2 of the application form (see also footnote 8)

The **date of implementation** for each Type IA/IA_{IN} variation should be indicated (as per with Annex IV, point 2(a) of Commission Regulation (EC) No 1234/2008)

A single A.7 scope can be applied for to delete >1 site

Relevant Guideline page

- The copy of the relevant page from the guideline has not been attached or applicable conditions/ documentation have not been ticked

The copy of the guideline page should always be submitted and relevant conditions/documentation ticked. Not compulsory for .z scopes

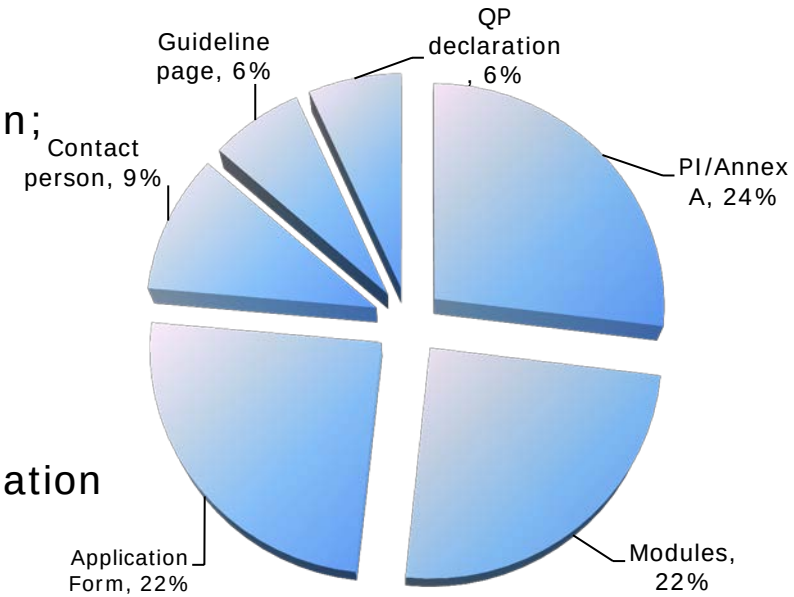
Most common validation issues

Product Information and Annex A	• The change(s) applied for modify(ies) the Product Information but only the EN version is provided or no languages at all. • The change(s) applied for modifies Annex A but is has not been provided	One file per language should be submitted and saved in eCTD under Module 1.3.1 (PDF version) and under the 'Working documents' folder outside the eCTD structure (Word version in tracking mode) One file per language should be submitted and saved in eCTD under Module 1.2 (PDF version) or under the 'Working documents' folder outside the eCTD structure (Word version in tracking mode).
eCTD	• Documents in eCTD are incorrectly updated/removed	Module(s) affected by the change(s) should be properly updated to ensure the correct dossier's life cycle.

Most common validation issues

Analysis of Type IA/IA$_{IN}$ applications submitted between 01 Sept 2015 and 01 Sept 2016:

- 48% of submissions triggered either a request for clarifications or additional information;
- most common validation issues:
  - Incorrect update/missing Annex A/PI: 24%
  - Incorrect update/missing Module(s): 22%
  - Application Form incorrectly filled in: 22%
  - Discrepancy in details of contact person: 9%
  - Guideline page missing, conditions/documentation not ticked: 6%
  - Incorrect or missing QP declaration: 6%
  - Other issues: 11%



Implementation date

The implementation date is dependent on the type of change(s) applied for and should be intended as follows:

Quality changes: when the company makes the change in its own quality system (to allow to manufacture conformance batches and generate any needed stability studies to support a Type IA_{IN} variation before making an immediate notification).

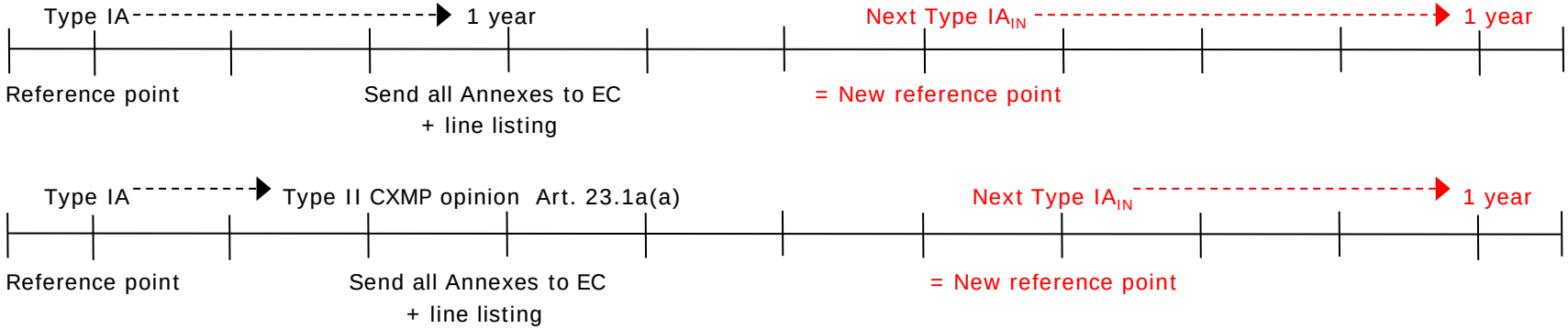
Product Information (PI): when the company internally approves the revised PI, which will then be used in the next packaging run.

Change in name of the MAH: the date when the new name is reflected by the Chamber of Commerce.

Change in the address of the MAH: the date of the physical move.

Commission decision

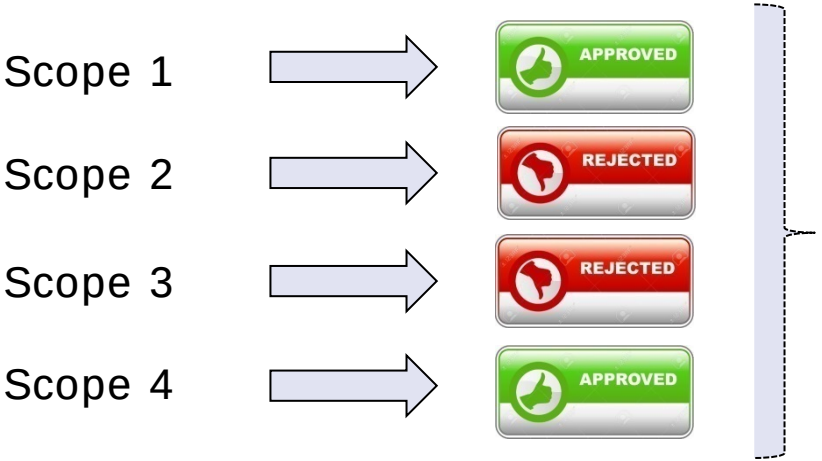
For Type IA/IA$_{IN/}$/IB variations affecting the PI, the Commission decision (CD) will be updated within 1 year unless an opinion triggering an immediate CD is finalized in the meantime. In this case, the Type I changes will be included in the annexes to that opinion and consequently reflected in the resulting CD.



Note: in case of an upcoming submission of a variation, extension or other regulatory procedure affecting the PI, the MAH should also include as a grouping application any Type IA/IA$_{IN}$ changes affecting the PI that have not been previously notified to keep the PI up-to-date and to facilitate document management.

Fees Type IA

The Agency will charge 1 Type IA/IA_{IN} fee x scope x product, as declared in the application form, at the start of the procedure, irrespective of the outcome (positive, negative, partial/full withdrawal).



4 fees invoiced

Fees for new presentation/pack size(s)

New presentations/pack sizes: the application form should list under the section 'Variations included in this application' the applicable scope as many times as the new presentations/pack sizes (each additional presentation/pack size attracts a separate fee);

e.g.: addition of **1 new presentation** within the approved range for **2 strengths** and **1 new presentation** outside the approved range for **1 strength**

Variation	Selected
B.II.e.5 a) 1.	2
B.II.e.5 a) 2.	1

B.II.e.5	Change in pack size of the finished product	Procedure type		Top
a)	Change in the number of units (e.g. tablets, ampoules, etc.) in a pack			
☒ 1.	Change within the range of the currently approved pack sizes	☒ IA_{IN}	☐ IB^{n}	Implement. Date: 2016-10-19 + −
☒ 1.	Change within the range of the currently approved pack sizes	☒ IA_{IN}	☐ IB^{9}	Implement. Date: 2016-10-19 + −
☒ 2.	Change outside the range of the currently approved pack sizes	IB		+ −

Fees for IG submissions

IG submissions: the total fee will be calculated as 1 fee x scope x product (e.g. 1 scope, 2 products = 2 fees; 2 scopes, 3 products = 6 fees).

The change(s) applied for should not be repeated as many times as the products included in the IG. It is understood that the same change(s) apply/ies to all products included in the application:

e.g.: addition of **1 new manufacturer** responsible for primary packaging and **2 new manufacturers** responsible for secondary packaging.

# of products included in the IG submission: 5

Variation	Selected
B.II.b.1 b)	1
B.II.b.1 a)	2

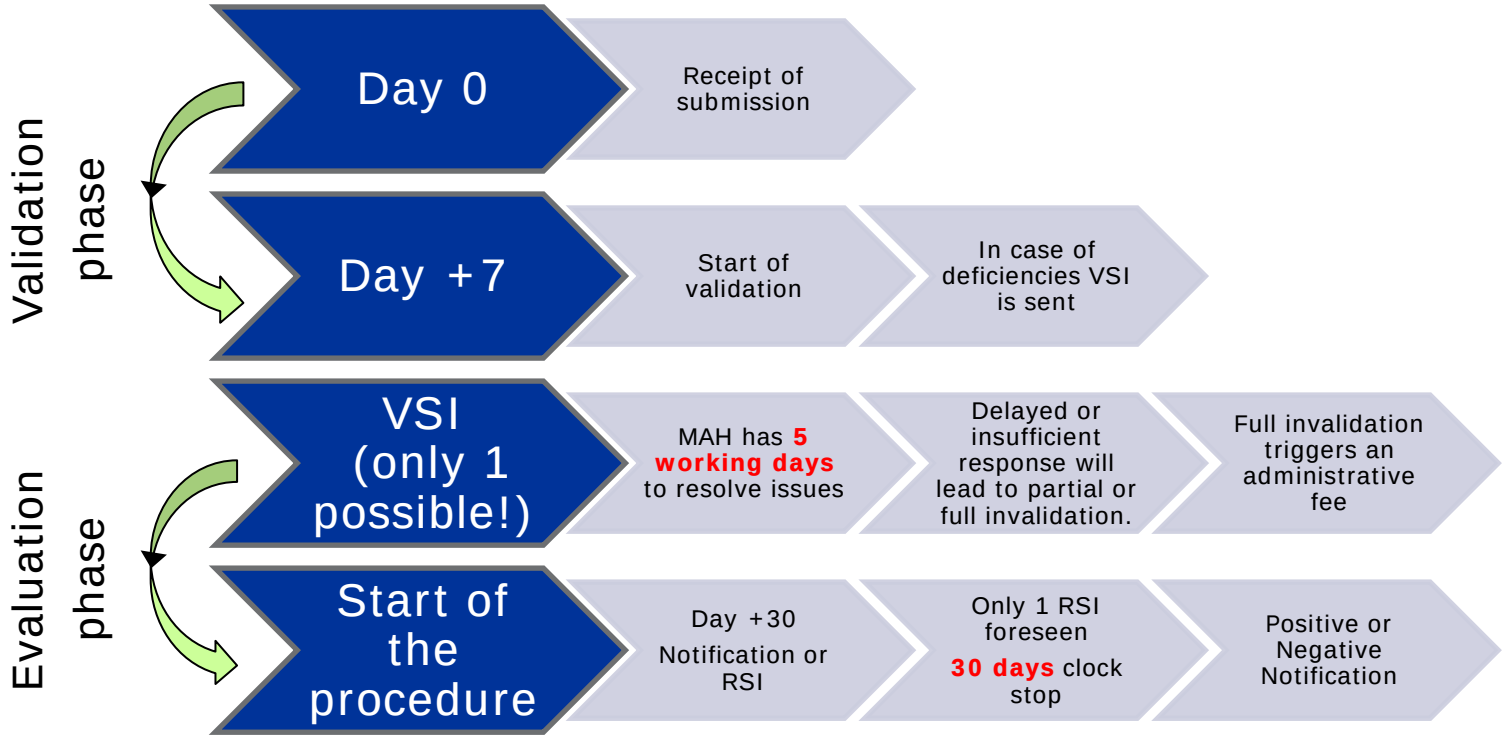
B.II.b.1	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	Procedure type		Top
☒ a)	Secondary packaging site	☒ IA_{IN}	☐ IB^{8}	Implement. Date: 2016-10-19
☒ a)	Secondary packaging site	☒ IA_{IN}	☐ IB^{9}	Implement. Date: 2016-10-19
☒ b)	Primary packaging site	☒ IA_{IN}	☐ IB^{8}	Implement. Date:

Type IB variation definition

Commission Regulation (EC) No 1234/2008 ('the Variations Regulation') defines a minor variation of Type IB as a variation which is neither a Type IA variation nor a Type II variation nor an Extension.

- "**Tell, Wait and Do**" – upon acknowledgment of receipt of a valid notification MAH must wait 30 days to ensure notification is deemed acceptable by Agency.
- Variation Guidelines contains examples of changes which are considered Type IB.
- When one or more conditions for Type IA/IA_{IN} variations are not met, such change should be classified as IB unless explicitly listed as type II.
- Unforeseen variations (change is not specifically classified in Variation Regulation or as CMDh Art 5 recommendation) should be submitted as Type IB or Type II, depending on the impact of the change(s) on the quality, safety and efficacy of the finished product.
- The Rapporteur is involved in assessment of changes.

Type IB procedure



Validation issues – checklist

- **Transparency** – checklist is publicly available (http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196337.pdf)
- Upon receipt of the application the Procedure Manager validates documentation against validation checklist.
- Different types of issues:
  - Blocking issues – presented in **Bold** font. Must be satisfactorily resolved by MAH prior to start of the procedure.
  - Issues related to information needed for documentation check – presented in *Italics*. Not blocking issues
  - Issues presented in Normal font. In case, no other issues identified they are highlighted in variation report for future improvement

Validation issues – checklist

Covers different sections of the submission:

Supporting documentation

Product information

Application Form

RMP

Cover letter

ASMF

Type IB submission checklist[1]	Yes	n/a
TECHNICAL SUBMISSION REQUIREMENTS		
• Dossier is submitted in eCTD format[2] and is technically valid (i.e. has passed eCTD technical validation criteria)		
COVER LETTER[3]		
• Present, dated and signed. • Refers to the same medicinal product(s), EU numbers and procedure as listed in the application form. • Where applicable, previous regulatory and/or procedural advice requested to the Agency is attached.		
APPLICATION FORM[4]		
• **Present, correct version, dated and signed by the contact person authorised for communication as specified in section 2.4.3 of the initial Application Form or a letter of authorisation is attached.** • **States the name and address of the MAH and of the contact person as previously notified to the Agency.**		
'Type of application' • Correctly identified by ticking the box(es) Type IA, Type IA_{IN} (in case of grouped variations) and Type IB. It should also be specified whether the procedure is foreseen or unforeseen in the classification guidance. • Indicates whether it is a single or a grouped submission.		
'Products concerned by this application' • EU marketing authorisation number(s) of (all) affected presentation(s) is/are listed.[5] • Is/are the same as that/those indicated in the Present/Proposed table, Precise Scope and cover letter.		
'Types of change(s)' • **All changes applied for are correctly classified according to the Guideline on the details of the various categories of variations (2013/C 223/01).** • **When two or more changes fall under the same indent, the scope number is indicated as many times as there are changes (e.g. scope B.II.e.5.a.2 is repeated 'x' times for 'x' additional new pack sizes).** • **In case of grouped variations including changes categorised as type IA,** **- the date of implementation for Type IA changes is provided,**		

Most common validation issues

44% of submissions require rework *

Application Form deficiencies:	• No precise scope provided • Annexes impacted are incorrectly selected • Present/proposed table is not provided • Editorial changes are not listed	Ensure Application Form is filled in according to guideline and is consistent with the submission content
Classification deficiencies:	• Incorrect scope applied for • Incorrect number of scopes applied for • Not all changes applied for	In case of doubts contact IBquery@ema.europa.eu for advice
Missing documentation:	• Justification for changes • GMP documentation • Discrepancies between provided documentation	Check against the Classification guideline and make sure all affected documents are updated and submitted

* Based on data from January 2015 – August 2015

Fees

- The fee will be charged upon validation of the procedure and should be paid within 30 days of the date of the invoice (“Due Date”).
- For an application that has been found not to be valid, an administrative fee for the validation of the application shall be charged.
- A scope can be withdrawn from the application during the entire procedure:
  - withdrawal during validation (i.e. before start of the procedure): no fee is charged;
  - withdrawal during evaluation phase: the full fee will be charged.

3. Electronic Application Form. Aspects to consider when preparing your submission

Simona Villa-Colciago

Contents

Introduction

The **eAF** was developed to:

- Bring Industry and NCAs towards a single application process
- Have higher data quality due to more structured data entry and usage of controlled terms
- Add built in business validation rules to guide the applicants in filling the form in correctly
- Have validation rules for the form in place and publicly available
- Remove manual data extraction processes
- Re-use data
- Import data into databases

Where to find the eAF

The application form can be found at:
http://esubmission.ema.europa.eu/eaf/index.html

Forms

Currently accepted version of forms :

- Initial MAA Human and Vet, Variations and Renewal: 1.20,1.20.0.1 and 1.20.02 and 1.20.0.3
  We strongly recommend using the latest version of the forms where possible.

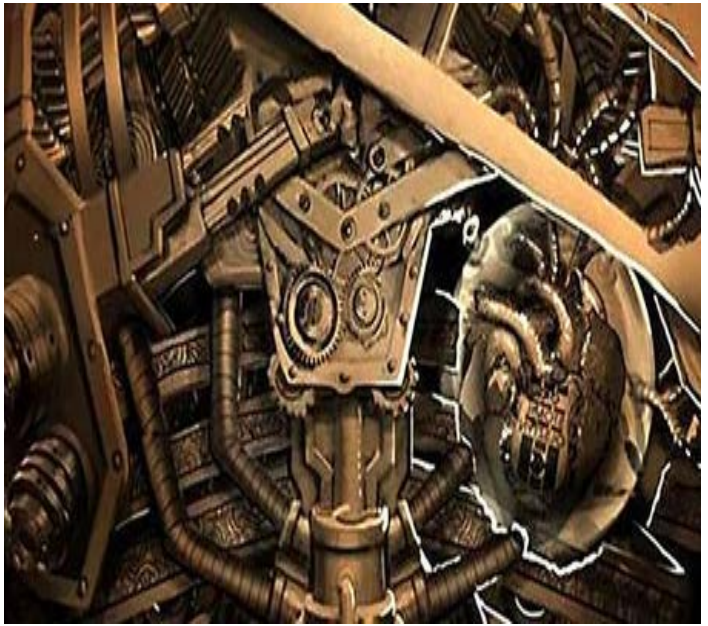
Please Note: eAFs should be signed and locked using Adobe Reader versions 10 and 11
For reviewing locked and signed forms we recommend using Adobe Reader or Adobe Acrobat versions 10 and 11

Form	Notice to Applicant Revision	Electronic Forms version 1.20	Release Notes version 1.20
MAA-Human	Revision 12	MAA-Human Form 18.10.2016 **New**	MAA-H Release Notes 18.10.2016 **New**
Variation	Revision June 2015	Variation Form 18.10.2016 **New**	Variation Release Notes 18.10.2016 **New**
Renewal	Revision June 2012	Renewal Form 18.10.2016 **New**	Renewal Release Notes 18.10.2016 **New**
MAA-Vet	Revision 7.4	MAA-Vet Form 18.10.2016 **New**	MAA-Vet Release Notes18.10.2016 **New**

eAF - Breakdown

The application form set-up is the following:

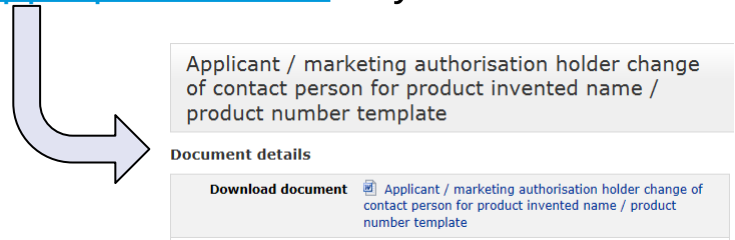
- MAH and contact information
- Products concerned
- Reflection of scopes
- Information regarding the change
- Validation of form

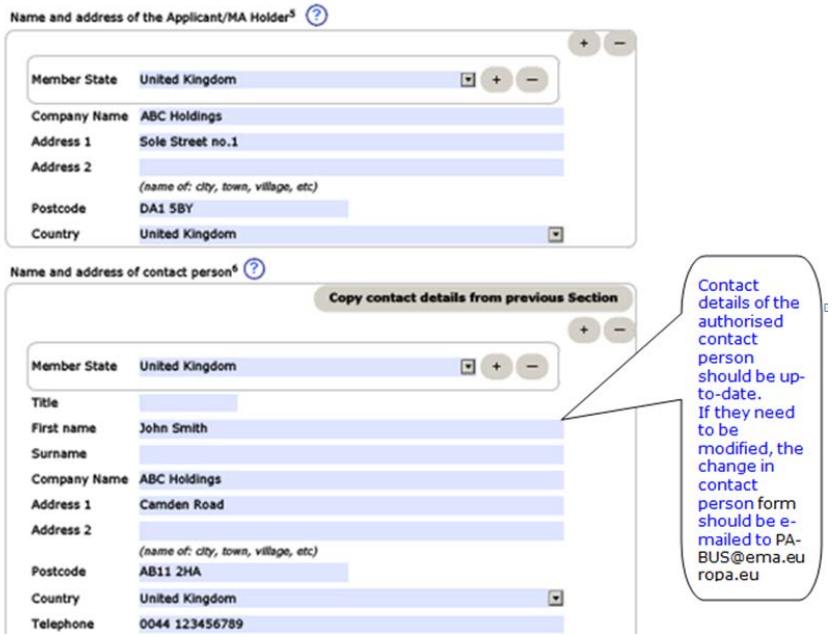


MAH and contact information

The information in this section should always correspond to the details of the product registered with the EMA.

If there is a deviation of contact person, the variation submission should contain an updated letter of authorisation or the appropriate form duly filled in.





Products concerned

This section should only contain the product(s) and presentation(s) affected by the change(s) applied for in the current submission (see also footnote 8).

2. PRODUCTS CONCERNED BY THIS APPLICATION[7]

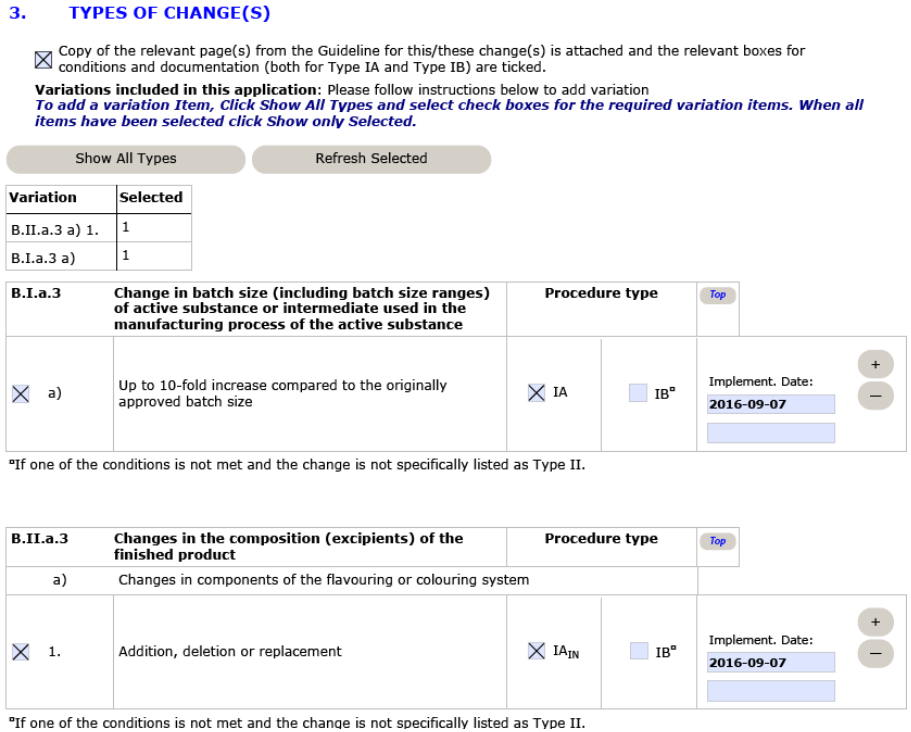
Form and Strength information is provided in footnote

Active Substance
ACETYLSALICYLIC ACID

MA Number(s)	Invented Name	MA Holder Name	Pharmaceutical Form	Strength	Unit	
EU/1/08/123/001	WonderPil	ABC Holdings	Film-coated tablet	500	mg	Clone
EU/1/08/123/002	WonderPil	ABC Holdings	Film-coated tablet	500	mg	Clone
EU/1/08/123/003	WonderPil	ABC Holdings	Film-coated tablet	500	mg	Clone

Reflection of scopes

- It is of paramount importance that this information mirrors the changes applied for.
- For variations concerning a **single product**, identical scopes (changes) should be repeated as many times as needed
- For **IG applications**, the same scope (change) must be applied to all products concerned by the application. The scope(s) applied for **should not** be repeated for each product as this will incur into unnecessary fees being invoiced.
- The number products in Section 2 and the number of scopes Section 3 dictate the total fee invoiced.



3. TYPES OF CHANGE(S)

☒ Copy of the relevant page(s) from the Guideline for this/these change(s) is attached and the relevant boxes for conditions and documentation (both for Type IA and Type IB) are ticked.

Variations included in this application: Please follow instructions below to add variation

To add a variation Item, Click Show All Types and select check boxes for the required variation items. When all items have been selected click Show only Selected.

Show All Types | Refresh Selected

Variation	Selected
B.II.a.3 a) 1.	1
B.I.a.3 a)	1

B.I.a.3	Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance	Procedure type		Top
☒ a)	Up to 10-fold increase compared to the originally approved batch size	☒ IA	☐ IB°	Implement. Date: 2016-09-07

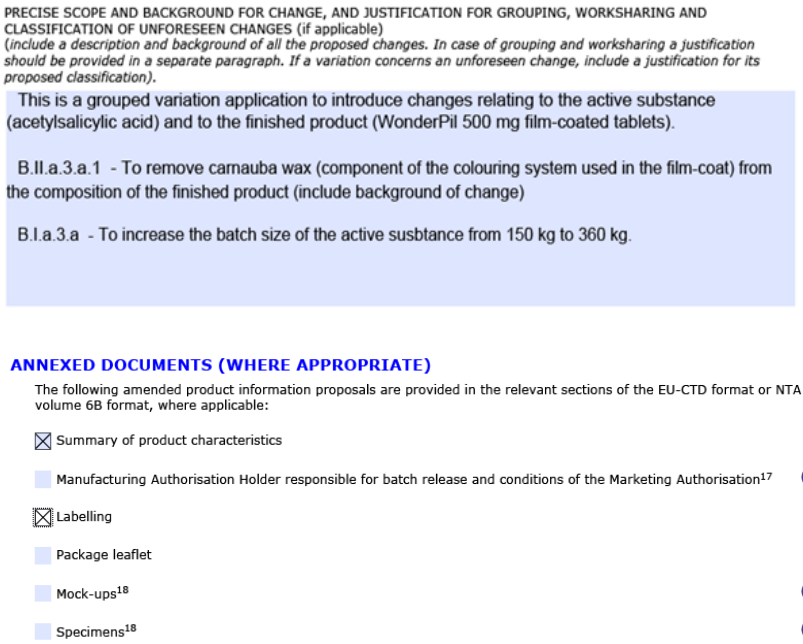
°If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.a.3	Changes in the composition (excipients) of the finished product	Procedure type		Top
a)	Changes in components of the flavouring or colouring system			
☒ 1.	Addition, deletion or replacement	☒ IA_{IN}	☐ IB°	Implement. Date: 2016-09-07

°If one of the conditions is not met and the change is not specifically listed as Type II.

Information regarding the change(s) applied for

- Precise scope and background for change
  - Should be clear and concise
  - For grouped applications, each scope applied for should be identified by catalogue (e.g. B.I.a.1.a, B.I.a.1.f)
  - A brief background for the change should be included in this section.
- Annexes affected
  - When the Product Information is modified the correct Annex(es) should be ticked in this section.



PRECISE SCOPE AND BACKGROUND FOR CHANGE, AND JUSTIFICATION FOR GROUPING, WORKSHARING AND CLASSIFICATION OF UNFORESEEN CHANGES (if applicable)

(include a description and background of all the proposed changes. In case of grouping and worksharing a justification should be provided in a separate paragraph. If a variation concerns an unforeseen change, include a justification for its proposed classification).

This is a grouped variation application to introduce changes relating to the active substance (acetylsalicylic acid) and to the finished product (WonderPil 500 mg film-coated tablets).

B.II.a.3.a.1 - To remove carnauba wax (component of the colouring system used in the film-coat) from the composition of the finished product (include background of change)

B.I.a.3.a - To increase the batch size of the active susbtance from 150 kg to 360 kg.

ANNEXED DOCUMENTS (WHERE APPROPRIATE)

The following amended product information proposals are provided in the relevant sections of the EU-CTD format or NTA volume 6B format, where applicable:

- ☒ Summary of product characteristics
- ☐ Manufacturing Authorisation Holder responsible for batch release and conditions of the Marketing Authorisation[17]
- ☒ Labelling
- ☐ Package leaflet
- ☐ Mock-ups[18]
- ☐ Specimens[18]

Information regarding the change(s) applied for

- Present and proposed table
  - Can be presented as part of the eAF or as an Annex and should reflect **all** the changes applied for.
  - If changes are made to the Product Information these should also be reflected here
  - Editorial changes should also be described in detail in this section.

Validation of form

- Declaration of the applicant
  - For Type IA procedures, boxes 2 and 3 should always be ticked.

☒ Where applicable, all conditions as set for the variation(s) concerned are fulfilled;

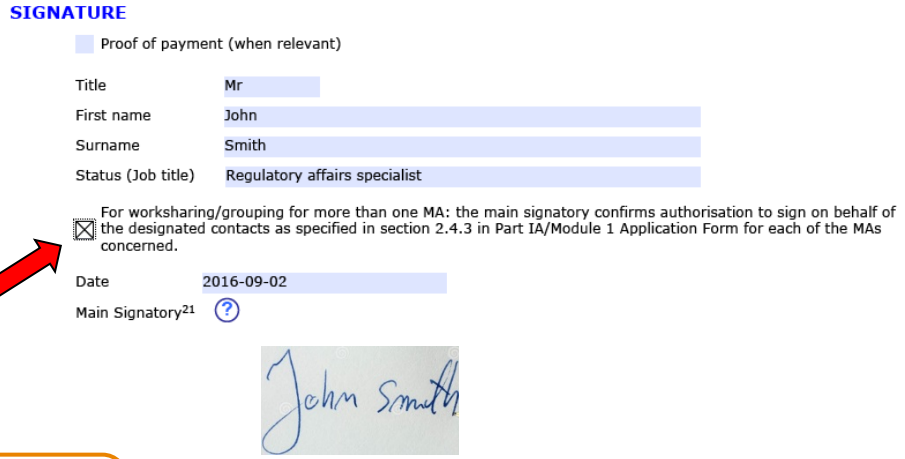
☒ For type IA notifications: the required documents as specified for the changes concerned have been submitted;

  - The last box should always be ticked in case of IGs or WS (worksharing) procedures

☒ For worksharing or grouped variations affecting more than one MA: the MAs concerned belong to the same MAH.

Validation of form

- Signature
  - The person signing the application form should always be the person authorised by the MAH to do so.
  - The last box should always be ticked for IGs or WS (worksharing) procedures

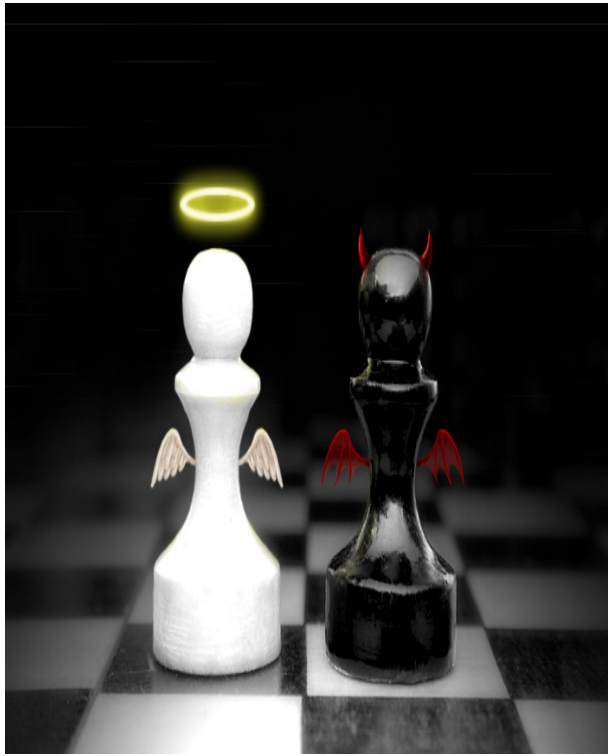


Tip: before signing the application form ensure that a copy is saved separately in case further changes are needed. Once signed, the form is locked.

IA vs IB

IA

- Implementation date/ justification should always be present.
- The extract from the classification guideline should have relevant conditions and documentation ticked (except for .z scopes classified as Type IA/IA_{IN} following Art. 5).



IB

- No guideline page is needed for .z scopes.
- The extract from the classification guideline should have the relevant documents ticked (justification for missing documents speeds up the process).

Most common validation issues

MAH and contact information

- Person authorised to communicate on behalf of the applicant is different than the official registered contact

Ensure the person signing the form is the person authorised to communicate on behalf of the MAH.

Products concerned

- All authorised presentations are reflected instead of only those affected by the change.

e.g. if the change only affects the 200mg film-coated tablets, these are the only presentations to be listed here.

Most common validation issues

Information regarding change

- IG scopes multiplied by number of products, resulting in over charging
- Not all changes (including editorial) are presented in the present and proposed table
- Not all changes are applied for as scopes in section “Types of changes”
- Implementation date missing for IA variations

MAHs and ASMF holders can contact IAquery@ema.europa.eu, IBquery@ema.europa.eu or the relevant PM for the product in case of doubts on classification or have other queries.

Date of implementation should always be mentioned for IA scopes.
All changes in the dossier should be described in the application form.
All changes to the authorisation which fit into an indent of the variation guideline should be classified accordingly.

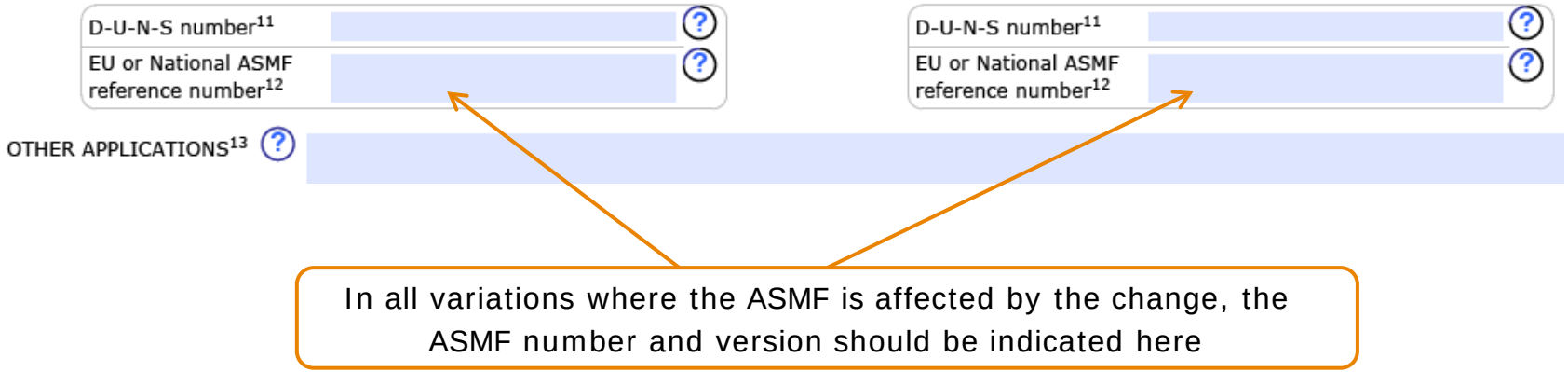
Annexes to the eAF

- When the PI is affected, only annexes in EN are submitted (when linguistic review is not required)
- Editorial changes in the PI not reflected in the eAF
- Annex IV of a previous Renewal/ PSUR still included in the PI
- Changes beyond the scope of the variation are made to the PI

Procedure-specific requirements should be followed (e.g. linguistic review)
All changes in the PI should be detailed in the present and proposed section/Annex.

Most common validation issues – cont.

ASMF number and version number not mentioned on the Application form in the present and proposed section.



Mock application form

A sample of a pre-filled application form is published on our website in order to provide practical guidance.

The mock application form can be found at:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500179305.pdf

4. Documentation requirements – aspects to consider when preparing your submission

Blanka Zakutna, Birgitte Jorgensen

Supporting documentation

- Classification Guideline
- Documentation
- PI
- RMP
- GMP
- ASMF, CEP

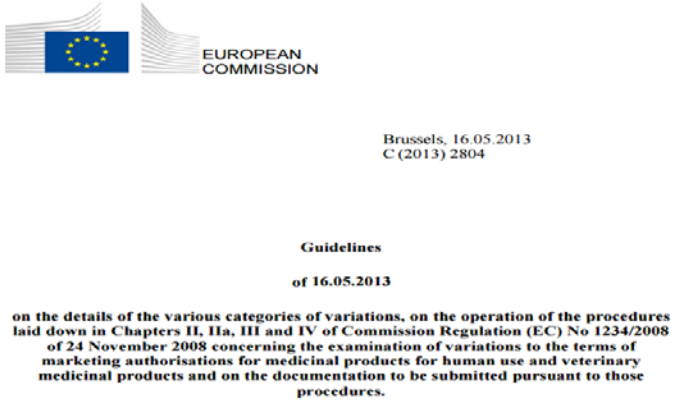
- The MAH is responsible for the quality of the submitted documentation
- The MAH should ensure that the Type I variations fully comply with the data and documentation requirements as specified in the Variations Guideline
- In grouping of variations, the MAH should clearly identify each change as well as the related supportive documentation for the change

Classification guideline

- Copy of the relevant page(s) from the Classification Guideline should be attached for each change applied for
  - Not applicable to unforeseen changes (.z scopes in the Classification guideline)

- The relevant conditions and documentation should be ticked, as specified in the Classification Guideline

Classification Guideline



EUROPEAN COMMISSION

Brussels, 16.05.2013
C (2013) 2804

Guidelines

of 16.05.2013

on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures.

Documentation / Amended sections of the dossier

The documentation to be provided is listed in Annex IV of the Variations Regulation and in the Commission Classification guideline

- The submitted documentation should be presented in accordance with the appropriate EU-CTD (EU common technical document) format headings and numberings
- The amendments in the relevant sections of the dossier should correctly reflect the changes applied for and listed in the Present and Proposed table of the Application form.

Copy of the relevant pages from the Classification Guideline

B.II.d.2 Change in test procedure for the finished product		Conditions to be fulfilled	Documentation to be supplied	Procedure type
☒	a) Minor changes to an approved test procedure	1, 2, 3, 4,	1,2	IA
	b) Deletion of a test procedure if an alternative method is already authorised	4	1	IA
	c) Substantial change to, or replacement of, a biological/ immunological/ immunochemical test method or a method using a biological reagent or replacement of a biological reference preparation not covered by an approved protocol			II
	d) Other changes to a test procedure (including replacement or addition)		1, 2	IB
	e) Update of the test procedure to comply with the updated general monograph in the Ph. Eur.	2, 3, 4, 5	1	IA
	f) To reflect compliance with the Ph.Eur. and remove reference to the outdated internal test method and test method number*	2, 3, 4, 5	1	IA

Conditions

n/a	1.	Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure. This condition is not applicable as the method is performed according to Ph. Eur. 2.2.3
☒	2.	There have been no changes of the total impurity limits; no new unqualified impurities are detected
☒	3.	The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method);
☒	4.	The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).
	5.	The registered test procedure already refers to the general monograph of the Ph. Eur. and any changes are minor in nature and require update of the technical dossier.

B.II.b.3 Change in the manufacturing process of the finished product		Conditions to be fulfilled	Documentation to be supplied	Procedure type
✓	a) Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions.	1, 2, 3, 4, 5, 6, 7	1, 3, 4, 6, 7, 8	IA
	b) Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product			II
	c) The product is a biological/immunological medicinal product and the change requires an assessment of comparability.			II
	d) Introduction of a non-standard terminal sterilisation method			II
	e) Introduction or increase in the overage that is used for the active substance			II
	f) Minor change in the manufacturing process of an aqueous oral suspension.		1, 2, 4, 6, 7, 8	IB

Conditions

✓	1.	No change in qualitative and quantitative impurity profile or in physico-chemical properties.
✗	2.	The product concerned is not a biological /immunological or herbal medicinal product.
✓	3.	The manufacturing principle including the single manufacturing steps remain the same, e.g. processing intermediates and there are no changes to any manufacturing solvent used in the process.
✓	4	The currently registered process has to be controlled by relevant in-process controls and no changes (widening or deletion of limits) are required to these controls.
✓	5.	The specifications of the finished product or intermediates are unchanged.
✓	6.	The new process must lead to an identical product regarding all aspects of quality, safety and

Not fulfilled, as biological product

Copy of the relevant pages from the Classification Guideline

B.I.e.5 Implementation of changes foreseen in an approved change management protocol		Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	The implementation of the change requires no further supportive data	1	1, 2, 4	IAIN
b)	The implementation of the change requires further supportive data		1, 2, 3, 4	IB
c)	Implementation of a change for a biological/immunological medicinal product		1, 2, 3, 4, 5	IB

Conditions

X	1.	The proposed change has been performed fully in line with the approved change management protocol. In agreement with the Agency, some minor change have been made and are described in [illegible]

Documentation

X	1.	Reference to the approved change management protocol. Included in the Cover Letter
X	2.	Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products. Included in the Cover Letter
X	3.	Results of the studies performed in accordance with the approved change management protocol.
X	4.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate). The following sections are amended: 2.3.S Drug substance 2.3.A Appendices 3.2.S.1 General information 3.2.S.2.2 Description of manufacturing process and process 3.2.S.2.3 Control of materials 3.2.S.2.4 Control of critical steps

Documentation

√	1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including identification method [illegible] relevant, and including revised product information as appropriate. **Module 3.2.P.1**
√	2.	A declaration that the required stability studies have been started under ICH/VIC[illegible] indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
	3.	The results of stability studies that have been carried out under ICH/VICH conditions, on the relevant stability parameters, on at least two pilot* or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
N A	4.	Sample of the new product, where applicable (see Notice to Applicants Requirements for samples in the Member States).
√	5.	Either a Ph. Eur. Certificate of Suitability for any new component of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by the competent authority and shown to comply with the scope of the current Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).
√	6.	Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate. **Module 3.2.P.5.3**
	7	Justification for the change/choice of excipients etc. must be given by appropriate development pharmaceutics (including stability aspects and antimicrobial preservation where appropriate).
	8.	For solid dosage forms, comparative dissolution profiledata[16] of at least two pilot scale* batches of the finished product in the new and old composition. For herbal medicinal products, comparative disintegration data may be acceptable.

The applicant is advised to add clarifications as these can speed up the validation of the procedure.

PI – Product information

A revised product information must be submitted if the Type I changes affect any of the annexes (i.e. annex A, SPC, annex II, labelling and/or package leaflet).

- PI should only include the changes declared in the Present/Proposed table in the AF
- PI should correctly reflect the scope of the variation and should be **based on the latest approved version** (i.e. previously concluded IA/IB or CHMP Opinion)

Two different submission requirements for:

- ➢ Type IA and IB procedures without linguistic review of Product information
- ➢ Type IB procedures with linguistic review of Product information

PI – Product information

When preparing the Product information Annexes for Type I submissions, MAHs should refer to the following guidance documents:

- the checklist for the submission of Annexes, which provides guidance on formatting, naming convention and administrative details,
- the QRD convention for preparation of Word versions,
- the guidance on how to correctly prepare the PDF versions.

PI requirements at the time of submission

		Type IA and IB without linguistic review of PI	Type IB with linguistic review of PI
Annex I-IIIB • SmPC • Annex II • Labelling • PL	eCTD	a complete set of annexes of the product information in all EEA languages in PDF (clean) – *correctly formatted* 	complete set of Annexes of the product information in EN (only) in PDF (clean)- *correctly formatted* 
	Electronically (outside eCTD)	complete set of annexes of the product information in all EEA languages in word (highlighted) 	complete set of Annexes of the product information in all EEA languages in word (highlighted) 
Annex A	eCTD	All EEA languages in PDF (clean) 	
	Electronically (outside eCTD)	all EEA language versions in word (highlighted) 	

Amendments to the dossier – Editorial changes

- MAH may include Editorial changes to the dossier in a variation concerning that part of the dossier (up to “fourth level” of eCTD structure)
  - If the variations affects ‘3.2.S.2.1’ editorial changes can be submitted in sections ‘3.2.S.2.1-3.2.S.2.7.’
- Changes that can be classified as a variation as per Variations Guideline should be submitted under the appropriate variation category and cannot be considered as editorial.
- Changes to the scientific content (e.g. removal of obsolete specifications, update of dossier to bring it in line with current manufacturing process) cannot be accepted as an editorial change.

Classification of changes: questions and answers
4. Editorial changes

- The MAH should clearly identify the proposed editorial changes in the application form.
  - A brief description of the editorial changes should be also provided in the **precise scope** of the application form
  - The editorial changes should be detailed in the **present / proposed table** or provided as a separate Annex to the Application form

- A statement from the MAH confirming that the proposed editorial change(s) do(es) not change the content of the concerned part of the dossier beyond the scope of the variation submitted should be included.

Example of submission of editorial changes

PRECISE SCOPE AND BACKGROUND FOR CHANGE, AND JUSTIFICATION FOR GROUPING, WORKSHARING AND CLASSIFICATION OF UNFORESEEN CHANGES (if applicable)
(include a description and background of all the proposed changes. In case of grouping and worksharing a justification should be provided in a separate paragraph. If a variation concerns an unforeseen change, include a justification for its proposed classification).
.
.
.
Editorial changes
In addition, the MAH wishes to take the opportunity of this submission to present an editorial change in the section S.6 Container Cosure System related the 'Manufacturer 1'.
This editorial change is further detailed in the 1.2 Rationale, section 7.

Additionally, the ASMF holder has also brought several editorial changes to improve the readability of the updated sections and to remove some inadequate level of details regarding Analytical Procedures (S.4.2), Analytical Validation (S.4.3) the Container Closure System (S.6).

Sections affected by the scopes of the variation - 3.2.S.4.4, 3.2.S.6 and 3.2.S.7.3

Sections where editorial changes are allowed- 3.2.S.4.1-5, 3.2.S.6 and 3.2.S.7.1-3

Example of declaration from the MAH

The changes proposed as editorial do not change the information of the concerned parts of the dossier beyond the scope of the variation submitted within which the editorial changes are being submitted.

Examples of Present and proposed table

Table 2
Changes to the Dossier - 3.2.S.2 –

Present				Proposed				Justification
Sterility	USP <71>, EP requirements §2.6.1 MAH AG (SOP # OR-12-00005)	Sterile	Reject	Sterility	USP <71>, EP ~~requirements~~ §2.6.1 ~~MAH AG~~ **FACILITY 1** (SOP # OR-12-00005)	Sterile	Reject	For consistency the facility is named and not the company name.
Viruses	In Vitro Assay MAH AG (SOP # VN-13-35017)	Free of detectable viral contamination	Reject	Viruses	**In-vitro assay methods** ~~MAH AG~~ **FACILITY 2** (SOP # VN-13-35017)	Free of detectable viral contamination	Reject	For consistency the facility is named and not the company name.

Present	Proposed Changes
Annex I	Annex I
3. PHARMACEUTICAL FORM Prolonged-release tablet. Blue, biconvex, round tablet of 11.9 mm diameter debossed with "NB-890" on one side.	**3. PHARMACEUTICAL FORM** Prolonged-release tablet. Blue, biconvex, round tablet of 12.0-12.2 mm diameter debossed with "NB-890" on one side.

Parameter corrected to be in line with the diameter stated in Module 3.2.P.5.1.

SmPC for the TIP: **3. PHARMACEUTICAL FORM** ... The 10 mg film-coated tablets are pale yellow to yellow, oval shaped film-coated tablet with breaking line and engravings '1 0' on one side and 'M M' on the other side. The tablet can be divided into equal doses.	**SmPC for the TIP:** **3. PHARMACEUTICAL FORM** ... The 10 mg film-coated tablets are pale yellow to yellow, oval shaped film-coated tablet with breaking line and ~~imprint~~engravings '1 0' on one side and 'M M' on the other side. The tablet can be divided into equal doses.

Term modified as per QRD guideline

Present		Proposed		Justification
Editorial changes				
Appearance of the **container (10021.01)**	100 ml colourless plastic vials, grey rubber-stopper, aluminium cap with deep purple flip-off component	Appearance of the **vial (10011.01)**	100 mL colorless plastic vial, grey rubber-stopper, aluminum cap with deep purple flip-off component	Editorial change of test title. No changes in test procedure or acceptance criteria are proposed. The test code was updated from 10021.01 to 10011.01.
Bacterial endotoxins test (BET)	Procedure Assay of **3** units for bacterial endotoxins with the turbidimetric technique in accordance with Ph. Eur. 2.6.14, "Bacterial Endotoxins" and USP <85>, "Bacterial Endotoxins Test".	Bacterial endotoxins test (BET)	Procedure Assay of **three** units for bacterial endotoxins with the turbidimetric technique in accordance with Ph. Eur. 2.6.14, "Bacterial Endotoxins", **and JP <4.01> or** USP <85>, "Bacterial Endotoxins Test".	Editorial change to include reference to JP <4.01> in the test procedure
Sterility	Principle Membrane filtration in accordance with Ph. Eur./USP Procedure Determine the sterility of 20 units in accordance with Ph. Eur. 2.6.1, "Sterility" and USP <71>, "Sterility Tests" – considered as harmonized by the ICH – by the membrane filtration method. Incubate for at least 14 days.	Sterility	Principle Membrane filtration in accordance with Ph. Eur./USP/**JP** Procedure Determine the sterility of 20 units in accordance with Ph. Eur. 2.6.1, "Sterility" and USP <71>, "Sterility Tests" – **and JP 4.06, "Sterility Tests"** considered as harmonized by the ICH – by the membrane filtration method. Incubate for at least 14 days.	Editorial change to include reference to JP <4.06> in the test procedure

Documentation requirements for Risk Management Plan (RMP)

- The pre-notification checklist on Type IA/IA$_{IN}$ and pre-notification checklist on Type IB published as part of the Post-Authorisation guidance (PAG) contain a dedicated section on RMP.

- The pre-notification checklist for type IBs details the main blocking issues.

- Confirm that especially the blocking issues have been correctly implemented in the eApplication Form and that other submission requirements are met.

Type IB submission checklist[1]	Yes	n/a
CHANGES TO THE RMP		
• **The Version number correctly reflected.**		
• The changes to the RMP should be included in the Application Form in the 'Present and Proposed' table or provided as a separate Annex (except in case of update to the latest RMP template). • **RMP, based on the latest approved version, only including the changes covered by the scope of the variation with tracked changes, or** • **RMP including a summary of changes from the previous RMP version (mandatory in case update to the latest RMP template).**		

RMP submission requirements for MAH

How should I submit a procedure with an update to the RMP?

- The submission of a new RMP version is required for any procedure that affects the RMP
- RMP clean version is required in eCTD sequence

  In addition, applicants should submit
- An RMP track change version (preferably submitted as a word working document)

  or
- A summary of changes -> this is mandatory if the RMP is being updated to a new template.

For large updates of an RMP, a summary of the changes should be submitted in addition to the RMP track change version.

Procedure for provision of RMP by MAH

Applicable to all RMP submissions

- Changes to the RMP can be submitted as part of other variations or as a stand alone variation (under C.I.11) (i.e. for changes in RMP linked to changes implemented in the PI, no additional scope is required for the update (e.g. update of safety information of PI and consequential reclassification of a risk in RMP)).
- Multiple minor RMP changes can be included under one single C.I.11 scope

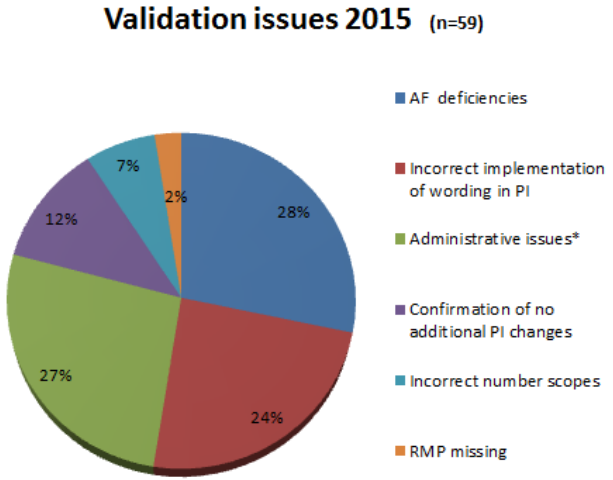
Applicable to generic products

- An updated RMP should be submitted when the changes in the PI of the originators products warrants an update of the RMP (e.g. new important identified risk, risk minimisation measures).
- The Agency will not provide the updated RMP of the reference product.

5. Update of safety Product information for Generics

Birgitte Jorgensen

Changes in the PI following assessment of the same change in the reference product



*(EMA letter and/or Originator PI missing; incorrect wording of scope)

The correct implementation of the wording in alignment with the reference product in all EEA languages is key for the safe and effective use of the medicinal product

The precise scope of the application should provide confirmation that no additional changes, except from those necessary to bring the annexes in line with the reference product, have been made.

Any issue should be agreed with EMA prior to submission (IBquery@ema.europa.eu)

The EMA process of communication of changes in the reference product – safety procedure

For updates following reference product
- Type II (safety variations)
- Renewal
- IB (safety variation)
- PSUR

EMA will inform the MAH to submit a IB within 60 days of communication. (Translations provided).
Number of C.I.2 scopes should be in accordance with scopes for the reference product

Any clarifications questions prior to submission should be addressed to IBquery
(e.g. the reference contains additional changes) before submission

The EMA process of communication of changes in the reference product - Signals

Signals: addressed to all INN concerned
(published online: EPITT <number>)
Classified as C.I.z type IA_{IN} (as per CMDh Art. 5 Recommendation)

The MAHs must submit according to the advice published by PRAC. All translations are available on the website.
The MAHs will not receive a request to submit a variation.

Any clarifications questions prior to submission should be addressed to IAquery.

Procedure for provision of translation by MAH

If the translation have been provided in all languages (generics, class labelling, etc.)

- The changes should be implemented as copy-paste – the text provided has undergone linguistic review at Member State level
  - If sections don't apply this should be justified
  - If there are issues with the translation, please contact IBquery
  - The full set of annexes must be provided at submission (clean PDF and highlighted working documents)

- For procedures requiring linguistic review
  - The full set of highlighted working documents is required at submission
  - The assessment runs in parallel, therefore changes are possible after the conclusion of this process

EMA Procedure for check of translation

- Upon receipt the EN annexes are checked to ensure that:
  - the correct baseline of PI is used. It should be based on PI adopted in previously concluded procedures and do not include any change of ongoing procedures.
  - no additional changes other than those included in the scope are incorporated
  - the changes have been implemented as applied for

- A random review is carried out on few languages other than EN to ensure that:
  - the changes from the EN have been implemented in the same sections
  - all changes, as implemented by the reference product, have been implemented correctly
- A random review is carried out to ensure that the Product information PDF complies with the QRD convention

Procedure for provision of translation by MAH – special cases

If issues have been identified with the translation of the originator of any languages

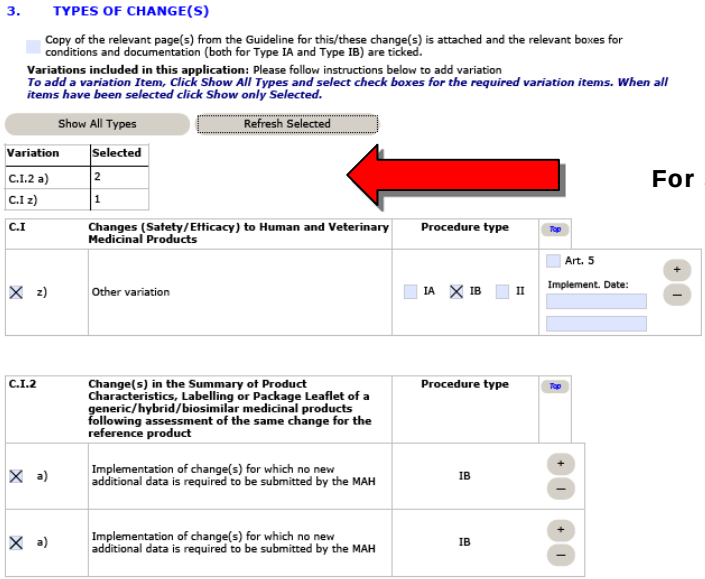
- Prior to the submission, please provide IBquery with a present-proposed table with an explanation of the mistake to agree on the acceptability of the change.
  - Example of MAH of a generic highlighting issue on Originator's PI

FR (France) Package Leaflet	Current originator's FR PI	Proposed amendment	Current originator's EN PI	Description of change in EN
Section Title & Paragraph	**[redacted] text FR**	**Proposed**	**[redacted] text EN**	**Comment**
3. How to take [redacted]	[…]Prenez les comprimés dans les 30 minutes suivant la fin d'un repas (petit déjeuner ou dîner).	[…]Prenez les comprimés dans les 30 minutes suivant la fin d'un repas (petit déjeuner ou dîner) et avalez-les entiers avec de l'eau.	[…] Take the tablets within 30 minutes after the end of a meal (breakfast and dinner) **and swallow whole with water**.	Addition of missing sentence. Change to comply with originator EN text.

Repeated scopes

- The number of scopes should be consistent throughout the submission (e.g. extracts from classification guidance, cover letter and application form)

- <u>One scope per PI change of the originator applies.</u> This information is included in the EMA communication requesting the submission (*e.g. PSUSA + type II for originator = two C.I.2.a scopes for generic).*



3. TYPES OF CHANGE(S)

Copy of the relevant page(s) from the Guideline for this/these change(s) is attached and the relevant boxes for conditions and documentation (both for Type IA and Type IB) are ticked.

Variations included in this application: Please follow instructions below to add variation

To add a variation Item, Click Show All Types and select check boxes for the required variation items. When all items have been selected click Show only Selected.

Show All Types | Refresh Selected

Variation	Selected
C.I.2 a)	2
C.I z)	1

C.I	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products	Procedure type	Top
☒ z)	Other variation	☐ IA ☒ IB ☐ II	☐ Art. 5 Implement. Date:

C.I.2	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product	Procedure type	Top
☒ a)	Implementation of change(s) for which no new additional data is required to be submitted by the MAH	IB	
☒ a)	Implementation of change(s) for which no new additional data is required to be submitted by the MAH	IB	

For submissions with several changes with the same classification

Coffee break

6. GMP and Inspection related documentation

Laetitia Deguil

Contents

- What is **G**ood **M**anufacturing **P**ractice (GMP)
  - Legal Basis
  - GMP assurance system in the EEA vs third countries
  - Annexes to the electronic Application Form (eAF)
    - Manufacturing and Importation Authorisation or equivalent (MIA – annex 5.6)
    - Good Manufacturing Practice certificate (GMP certificate – annex 5.9)
    - Qualified Person declaration (QP declaration – annex 5.22)
    - Flowchart (optional for variations - annex 5.8)
  - Module 3.2.P.3.1 – overview of manufacturers of the finished product (FP)
  - Module 3.2.S.2.1 – overview of manufacturers of the active substance (API)
- Most common validation issues
- GMP related guidance (on slide 117)

What is GMP?

Legal Basis

- **Directive 2003/94/EC** - medicinal products for **human** use.
- **Directive 91/412/EEC** - medicinal products for **veterinary** use.
- System ensuring that active substances and products are consistently manufactured and controlled according to high quality standards.

➢ Purpose - to minimize the risks involved with the quality of medicines.

EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines

- **Part I**: GMP principles for the manufacture of **medicinal products**.
- **Part II**: GMP for **active substances** used as starting materials.
- **Part III**: GMP related **documents**, which clarify regulatory expectations.

GMP assurance system in the EEA vs third countries - MIA annex 5.6

A system of **manufacturing authorisations** ensures that all products authorised on the European market are manufactured/imported only by authorised manufacturers, whose activities are regularly inspected by the competent authorities, using Quality Risk Management principles.

All applications introducing a new manufacturing site and/or activity shall be supported*:

- by a valid MIA (EEA sites) or equivalent (MRA/3rd country), or
- a EudraGMDP reference (EEA sites only)

*in accordance with Article 8.3(k) of Directive 2001/83/EC (not applicable to API manufacturers).

Sites in the EEA and MRA/3rd country - What is a MIA?

Manufacturing authorisations are required by all pharmaceutical manufacturers in the EU whether the products are sold within or outside of the Union.

- All manufacturers/importers of medicines located in the *EEA* must hold a **manufacturing and importation authorisation (MIA)** issued by an EEA National Competent Authority (NCA).
- All ***valid*** MIAs are uploaded to EudraGMDP by the relevant NCA and will be cross-checked for validity during validation of Initial MAAs and Variations.

Manufacturing authorisations equivalents e.g. drug licences, establishment licences etc. shall be provided for manufacturers outside the EU located in 3rd countries, including countries where Mutual Recognition Agreements (MRA) apply, showing that the manufacturer is authorised in his own country to produce medicinal products.

GMP assurance system in the EEA vs third countries – GMP certificate annex 5.9

- Each EEA NCA is responsible in supervising the MIA holders (MIAH) within their territory by performing routine GMP **inspections** to ensure adherence to the GMP principles.
- For products manufactured **outside the EU**, manufacturers are verified by routine GMP **inspections** to confirm that they operate according to EU GMP standards.
- The **responsibility** to inspect a 3rd country site falls on the **NCA** known as the **Supervisory Authority** (not the Rapp/CoRapp) of the country where the product is imported (Batch Release site).
- Following an inspection, NCAs will issue a **GMPc *or*** a **GMP Non-Compliance Statement**.

Sites in the EEA and MRA/3rd country – What is a GMP Certificate?

- A valid **GMP certificate** ensures that the current site located in the EEA or outside* has been inspected and complies with the GMP principles.
- A **GMPc** is usually valid for 3 years, however, this could be reduced or extended using regulatory risk management principles.
- GMPc / EudraGMDP references should be submitted as supporting documentation to a MIA or MIA equivalent to verify GMP compliance but not instead of a MIA.

*__Exception__: Mutual Recognition Agreements (MRA) with different scopes for certain countries whereby the GMP status is recognized by the EEA thus not requiring an EEA inspection (Australia, Canada, Japan, New Zealand, Switzerland, Israel-ACCA). *There is no operational agreement with the USA at the present time (FDA Inspection reports are used as supporting information but are not accepted instead of an EEA GMP certificate).*

QP declaration annex 5.22 – what is it and its content

- A (revised) **QP Declaration/written confirmation** is required for all Initial MAAs and Variations on changes to API & Finished Product manufacturers or Batch Release sites, and special scopes to update the QP Declaration.
- MIA Holders are obliged to use only APIs that have been manufactured in accordance with GMP.
- For **each active substance**, applicant should attach a declaration(s):
  - **from** the **Qualified Person** of the MIAH(s) listed as the Batch Release (Certification) site **and** from the **Qualified Person** of the MIAH(s) located in the EEA listed as manufacturing the finished product where the API is used as a starting material
  - **that** the API is manufactured in compliance with the GMP principles for starting materials.
  - The QP declaration should refer to an **audit** and show the **date** of the audit.
  - A single QP declaration may be submitted on behalf of all QPs involved (provided all relevant sites are clearly indicated in the single declaration).

QP declaration annex 5.22 – what is it and its content

Applies to **APIs** only (chemical & biological but not blood or blood components and excludes quality control and packaging only sites).

Sections of the **QP Declaration** to pay particular attention to if using the suggested template:

- The correct API is listed on the first page;
- Part A: **all API** Manufacturers (including intermediate sites) and their responsibilities/activities;
- Part B: only **EEA** MIA Holders using the API as a starting material and/or performing Batch Release of the finished product;
- Part C: under (i) confirm that an audit has been performed; and under (ii) list the details of the audits for all the API manufacturers from Part A (MIAH, auditing body – MIAH or contracted 3rd party*, API site, date of audit and justification if the audit exceeds 3 years)

  *Cannot be based on GMP Certificate issued by an EEA authority!
- Part E: Signatory must be by the QP, dated recently and issued by a site listed in Part B.

QP declaration annex 5.22 – tips for successful completion

Reference Number e.g. EMEA/H/C/00xxxx/0000 (procedure number for IMAA or variation)

PART A: Concerned active substance manufacturing sites

Name of Active Substance: only one API listed as per dossier (one QP declaration per API)

Name and Address of Active Substance Manufacturing Site[1,2]	**Manufacturing Operation / Activity[3]**
Site A listed in 3.2.S.2.1/2.5.3 (eAF)/5.8/ASMF **Full name** as per supporting documentation **Full address** aligned with dossier as per supporting documentation JKL Incorporated Grand Avenue 10 00000 City Arkansas USA	Full or partial manufacture of the active substance, micronisation including intermediates Manufacturer of active substance
Site B Same as above	Same as above

PART B: Manufacturing / Importer Authorisation Holder(s) (MIAHs) to which this QP declaration applies

This QP declaration is applicable to the following registered MIAH(s), that use the active substance as a starting material and/or is responsible for QP certification of the finished batch of a human or veterinary medicinal product, where the active substance is registered as a starting material and is manufactured at the sites listed in Part A:

MIAH Site (EEA sites ONLY)	**MIAH Number**	**Manufacturing Activity**
Site 1 - performing Batch Release (Certification) listed in 3.2.P.3.1/2.5.2 (eAF)/5.8 **Full name** as per supporting documentation **Full address** aligned with dossier as per documentation XYZ Limited Calle etc, 2 00000 Madrid Spain	MIA number from authorisation	Batch Release and all other relevant activities for the site Batch Release Batch Control testing
Site 2 - performing Manufacture of the Finished Product in EEA (if applicable to application) listed in 3.2.P.3.1/2.5.2 (eAF)/5.8 using the API as starting material **Full name** as per supporting documentation **Full address** aligned with dossier as per documentation MNP GmbH Strasse 4 00000 Berlin Germany	Same as above	Relevant activities e.g. M-FP Processing of non-sterile medicinal product Quality Control – Chemical/Physical

QP declaration annex 5.22 – tips cont'd

PART C: Basis of QP Declaration of GMP Compliance

Please tick section (i), complete the table in section (ii) and, if applicable, add the supplementary supporting information to section (iii).

(i) X On-site audit of the active substance manufacturer(s)

(ii) Audit(s) of the active substance manufactured at the site(s) listed in PART A has/have been completed either by the MIAH(s) listed below or by a third party auditing body(ies) i.e. contract acceptor(s) on behalf of the MIAHs i.e. contract giver(s) as listed:

MIAH Site (or contract giver)	Auditing body (contract acceptor)	Site audited	Date of audit[4]
Site 1 or 2 from Part B MNP GmbH Strasse 4 00000 Berlin Germany	Leave blank if site 1 or 2. If 3rd party then list name/address. NB: NCA not acceptable here **If MNP – leave blank** **If contractor :** BDE Auditors Ltd Address, city, country	Site A Full name and address as per Part A JKL Incorporated Grand Avenue 10 00000 City Arkansas USA	Should be in last 3 years, if over then justify below 01/03/2015 If over 3 years 05/05/2010[4]
Site 1 or 2 from Part B	Leave blank if site 1 or 2. If 3rd party then list name/address NB: do not list NCA here	Site B Full name and address as per Part A	Should be in last 3 years

4 Justification should be provided if the date of last audit exceeds 3 years:

Provide justification for audits exceeding 3 years here (if applicable) – the last audit took place on 05/05/2010 [provide reasons and explain]…

(iii) Supplementary supportive information (optional):

Summary of supporting information provided

If relevant and informative, list results of inspections or GMP certificates issued by EEA, MRA or other recognised authority together with other supporting information (optional).

Responsibilities in the case of multiple MIAH(s):

- This declaration is made on behalf of all the involved QPs named on the relevant MIAH(s) specified in Part B; ***→ one declaration is acceptable if all relevant sites are listed in Part B, otherwise please submit as many declarations as applicable for each relevant MIAH***
- A documented procedure defining GMP responsibilities is in place and that technical agreements exist between the named companies concerning management of GMP responsibilities.

Part E: Name and Signature of QP responsible for this Declaration

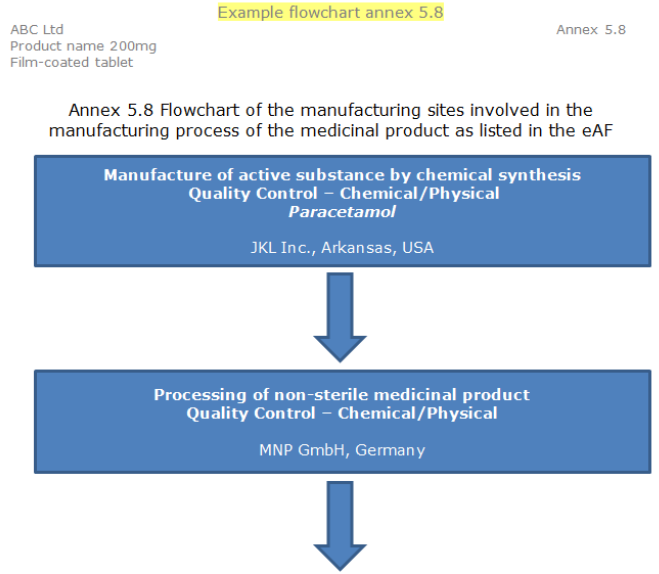
This declaration is submitted by:

Signatory **Signed by QP** **Print name** **Name of QP signing e.g. First & Last Name** **Date** **Recent date** **Status (job title)** **e.g. Qualified Person**	**MIAH Site** **Site from Part B** **Full name** **Full address as per Part B** MNP GmbH Strasse 4 00000 Berlin Germany **MIAH number** **As per Part B and supporting documentation**

Flowchart annex 5.8 (optional for variations)

All manufacturing site details including their names, addresses and activities should be aligned and consistent throughout the dossier e.g. eAF / 5.8 / 5.22 / 3.2.P.3.1 / 3.2.S.2.1 / PI for Initial MAAs and in the background scope / present & proposed table and where relevant in Variations and be consistent with the supporting documentation.

The flowchart annex 5.8 (mandatory in Initial MAAs, optional in Variations) should list all manufacturing sites for the FP and API including their names, location and activities in a clear way with the same terminology used in the eAF and relevant modules.



Relevant sections of the dossier: Module 3.2.P.3.1

Module 3.2.P.3.1 relates to manufacturers of the Finished Product (FP).

All FP sites should be listed by their full name, full address and all relevant activities as mentioned in the eAF of Initial MAAs and Variations.

An updated module 3.2.P.3.1 should always be submitted when making changes to manufacturers of the FP.

Example 3.2.P.3.1

ABC Ltd
Product name 200mg
Film-coated tablet

Module 3 Quality
3.2.P.3.1

Module 3.2.P.3.1 – Manufacturers of the finished product [Product name]

All sites details and activities should be consistent with the supporting documentation and aligned throughout the dossier.

Site details	**Activities**
Full name of site as per supporting documentation **Full street address** **Postcode** **City** **Country**	Same terminology as per eAF, annex 5.8, annex 5.22
MNP GmbH Strasse 4 00000 Berlin Germany	Processing of non-sterile medicinal product Quality Control – Chemical/Physical
QRS S.A 1 Rue de Paris 00000 Paris France	Primary Packaging Secondary Packaging
XYZ Limited Calle etc, 2 00000 Madrid Spain	Batch Release Batch Control testing

Relevant sections of the dossier: Module 3.2.S.2.1

Module 3.2.S.2.1 relates to manufacturers of the active substance (API).

All API sites should be listed by their full name, full address and all relevant activities as listed in the eAF of Initial MAAs and Variations.

An updated module 3.2.S.2.1 should always be submitted when making changes to manufacturers of the API.

Example 3.2.S.2.1

ABC Ltd
Product name 200mg
Film-coated tablet

Module 3 Quality
3.2.S.2.1

Module 3.2.S.2.1 – Manufacturers of the active substance - *Paracetamol*

All sites details and activities should be consistent with the supporting documentation and aligned throughout the dossier.

Site details	**Activities**
Full name of site as per supporting documentation **Full street address** **Postcode** **City** **Country**	Same terminology as per eAF, annex 5.8, annex 5.22
JKL Incorporated Grand Avenue 10 00000 Arkansas USA	Manufacturer of active substance Quality Control – Chemical/Physical

Most common validation issues

eAF	• Incorrect scope applied for and not in line with the actual scope of change; • Change of address is physical rather than administrative and wrong scope has been used; • Discrepancies in activity terminology performed by the manufacturer (i.e. term used “packaging” implies primary and secondary packaging, whereas the manufacturer is authorised to perform secondary packaging only and thus cannot be registered for primary packaging).	Ensure correct scope is chosen Ensure the correct scope is used e.g. A.x scopes for administrative address changes and B.I/B.II scopes for physical location address changes Ensure the terminology used in clear, detailed and consistent with the eAF
Conditions in guideline not met	• The product is sterile and one of the conditions is that it cannot be sterile; • The implementation date and/or the conditions of transport and bulk storage should be specified and validated but are missing.	Ensure that conditions are met Ensure the implementation date and/or conditions of transport and bulk storage are specified

Most common validation issues

Official documentation

- Company letter submitted instead of official documentation. A company statement in a letter is not acceptable instead of an official document.
- No official documentation provided.

An updated MIA/GMPc is valid as official documentation provided it shows the new name and/or new address of the site

Official document = Chamber of Commerce document or proof of establishment or MIA/GMPc

Present and proposed table

- P&P missing
- Completed incorrectly and does not reflect the changes applied for.

Ensure the P&P is submitted within the eAF

Ensure P&P is clear and correctly completed with the present manufacturers and the proposed changes to the relevant manufacturers

Most common validation issues

Discrepancies

- Name of manufacturers and/or site details inconsistent throughout the dossier and/or against the supporting documentation e.g. name differs, address is not aligned, postcodes are different, etc.

Ensure all documentation is consistent

eAF vs present & proposed table vs MIA/GMP vs 3.2.P.3.1/3.2.S.2.1 vs 5.22

Certificate of Suitability (CEP)

- CEP issued by EDQM for an API manufacturer submitted instead of GMP certificate. A CEP does not replace a GMPc nor confirms GMP compliance and can only be submitted as supportive documentation to a GMPc.

Ensure GMPc is submitted

Most common validation issues

MIA/GMP certificates	• Missing (paper and/or EudraGMDP reference); • Invalid MIAs and/or GMP certificates and/or wrong scope of medicinal product covered e.g. vet medicinal product MIA/GMPc for human products or document covers investigational medicinal products only; • Activity not authorised or restrictions apply to relevant activity or pharmaceutical form	Ensure MIA and GMPc is submitted or correct EudraGMDP reference is provided Ensure MIA/GMPc is valid and covers the correct scope of medicinal product Ensure activity is authorised / not restricted
Module 3	• Required information of the variation scope not reflected in module 3 (3.2.P.3.1 and/or 3.2.S.2.1) or not updated correctly; • Missing or additional sites in module 3.2.P.3.1/3.2.S.2.1.	Ensure modules 3.2.P.3.1 and/or 3.2.S.2.1 are submitted and updated correctly Ensure no other site changes are made except those for the relevant sites in the variation scope

Most common validation issues

QP declaration

- Annex 5.22 missing or lack of justification for omission;
- Missing API sites in Parts A & C, non-EEA sites listed in Part B, NCA inspections listed as audits in Part C instead of internal audits performed by the MIAHs (or contracted 3rd party), the audit date of a site on the QP declaration exceeds 3 years and no justification for exceeding this period has been provided or no audit date provided;
- Parts of the declaration have been deleted and/or amended and therefore no longer compliant.

Ensure QP declaration is provided

Ensure all API site(s) are listed in Part A

Ensure only **EEA** MIAH(s) site(s) are listed in Part B

Ensure all API internal site audits are provided in Part C (no NCA audits)

Ensure the contents of the QP declaration complies with the guidance

7. Applications affecting an Active Substance Master file (ASMF) and CEP

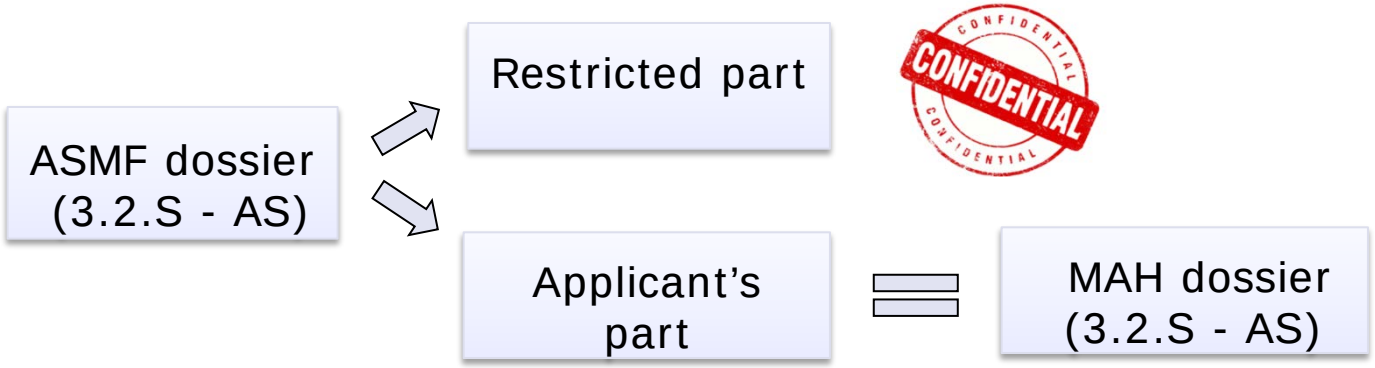
Carlos Aicardo

Contents

1. Concept of ASMF
2. Submission requirements for ASMF
3. ASMF specific submission documents
4. Most common validation issues regarding ASMF
5. Concept and most common validation issues regarding CEP

ASMF – Active Substance Master File

Separate dossier that contains information on the manufacture of the AS. The MAH contracts the ASMF holder to manufacture the active substance.



AP should contain sufficient information to enable the MA holder to take full responsibility for an evaluation of the suitability of the specifications for the active substance to control the quality of this active substance

CHMP Active Substance Master File guideline

ASMF – Submission requirements

Different documentation / requirements needed depending on the type of changes

ASMF holder:

- ASMF dossier (if new ASMF being registered)
- Letter of Access: (Annex 2 of the ASMF Guideline);
- Submission Letter and Administrative Details (Annex 3 of the ASMF Guideline)
- A commitment to inform the applicant and the EMA of any change in the ASMF

Question 27 of the pre-authorisation guidance

MAH

- AF including ASMF number
- Copy of the revised sections of the Applicant's part of the ASMF, if applicable, which should be identical to the ones submitted by the ASMF holder.

In cases where a new ASMF is being introduced as part of a Type II variation, in addition:

- Letter of Access (Annex 2 of the ASMF Guideline),
- Copy of the complete current version of the Applicant's part of the ASMF in Module 3

Example 1 –Introduction of changes to an existing ASMF

e.g. To introduce minor changes to the solvents volumes used in step 3 of the manufacturing process of the active substance reflected in the restricted part of ASMF

ASMF holder:

- Updated ASMF dossier (RP and AP as applicable)
- Submission Letter and Administrative Details (Annex 3 of the ASMF Guideline)

Marketing authorisation holder

- Application form including ASMF number
- Affected sections of Module 3.2.S with a copy of the revised sections of the Applicant's part of the ASMF, if applicable, which should be identical to the ones submitted by the ASMF holder.

Example 2 – Introduction of a new manufacturer supported by an ASMF

e.g. To add a new manufacturer for the active substance clopidogrel besylate supported by an ASMF. The new manufacturer is *Example 1 344 Street 1 Capital E28 589, Country*

ASMF holder:

- ASMF dossier (or updated ASMF dossier with new administrative information if the ASMF is used for other medicinal products)
- Letter of Access: (Annex 2 of the ASMF Guideline);
- Submission Letter and Administrative Details (Annex 3 of the ASMF Guideline)
- A commitment to inform the applicant and the EMA of any change in the ASMF

MAH

- Application form including ASMF number
- Letter of Access (Annex 2 of the ASMF Guideline),
- Copy of the complete current version of the Applicant's part of the ASMF in Module 3

ASMF specific documents

Relevant documents located as annexes in CHMP Active Substance Master File guideline

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2013
Committee of Human Medicinal Products CHMP/QWP/227/02 Rev 3/Corr *
Committee of Veterinary Medicinal Products EMEA/CVMP/134/02 Rev 3/Corr *

Guideline on Active Substance Master File Procedure
Final

Additional guidance on how to complete ASMF documents

Additional guidance on documents relating to an active substance master file

Additional guidance on completing the Annex 2-letter of access, Annex 3-submission letter and administrative details for documents relating to an active substance master file and Annex 4-withdrawal of access letter of the active substance master file procedure guidance (CHMP/QWP/227/02 Rev 3, EMEA/CVMP/134/02 Rev 03)

Letter of access (Annex 2)

To be provided by ASMF holder and MAH when a new manufacturer supported by an ASMF is introduced

ANNEX 2

(< FROM ACTIVE SUBSTANCE MASTER FILE HOLDER ON HEADED PAPER>)

TEMPLATE LETTER OF ACCESS

[Address of Competent Authority/EMA]

[Date]

Number of Active Substance Master File:

<EU/ASMF/XXXXX[4] or National ASMF reference number[5]>

Name of Active Substance:
Internal API Code (if applicable):
Active Substance Master File holder: [name and address]

The aforementioned Active Substance Master File holder hereby authorises the <name of National Competent Authority> <EMA including all CHMP and CVMP Members and their experts> to refer to and review the above mentioned Active Substance Master File in support of the following Marketing Authorisation Application(s) or Marketing Authorisation Variation(s)[6] submitted by [Name of Marketing Authorisation Holder/Applicant] on [planned date of submission]:

ASMF specific documents – Annex 3

ANNEX 3

(< FROM ACTIVE SUBSTANCE MASTER FILE HOLDER ON HEADED PAPER>)

Template Submission Letter and Administrative Details for documents relating to an Active Substance Master File (ASMF)[8]

From: <ASMF Holder name>
<ASMF Holder address>
<ASMF Holder address>
<ASMF Holder <Post code> Town>
<ASMF Holder Country>

To: <Name and Address of Competent Authority>

<Date>
<Reference>

Subject: Submission of documents relating to an ASMF

for <Name of Active Substance> - <EU/ASMF/XXXXX[9] or national ASMF reference number> [10]

Dear Sir or Madam:

This Active Substance Master File is submitted in relation to the following product:

Medicinal product	<Name of the medicinal product>[11]
Allocated procedure number (as applicable)	<EMEA/H/C/product reference number/procedure reference> <RMS/H/product reference number/procedure reference> <National Marketing Application/Authorisation Reference>
(Intended) Submission date of the marketing authorisation application or variation (if known)	<DD/MM/YYYY>

Must contain complete present and proposed table of changes in case of an update to a currently authorised ASMF

Table of Changes between different versions of the ASMF

This section should only be completed for updates to an already submitted ASMF.

The Table of Changes should be included as a separate document to the main Submission Cover Letter. The ASMF holder should use the following example templates for the table. If the changes have been previously authorised in a National or European procedure, the ASMF holder should annotate the table with the procedure number.

Table of Changes example template

TABLE OF CHANGES		
	PRESENT	**PROPOSED**
	ASMF holder's RP and/or AP Version Number [version number]/date (dd-mm-yyyy)	ASMF holder's RP and/or AP Version Number [version number]/date (dd-mm-yyyy)
Section (CTD or NtA, as appropriate)	Current situation	Description of change

Most common validation issues (ASMF holder)

Annex 3	• Present/proposed table not provided by ASMF holder • Version number of the ASMF not reflected	Ensure Annex 3 is appropriately completed
Submission	• ASMF number not applied for in advance (if applicable) • ASMF dossier not submitted at time of validation	Ensure that ASMF number has been applied for prior to submission Ensure ASMF dossier is updated/provided in advance or simultaneous submission from MAH
Classification	• Incorrect scope applied for by the MAH • Incorrect number of scopes applied for by the MAH • Not all changes applied for by the MAH	The ASMF holder should communicate all changes to the MAH to allow adequate classification and number of scopes to be applied for by the MAH while protecting the ASMF confidential information in the restricted part

Effective communication between the MAH and ASMF holder is key to avoid delays in the approval of changes

Most common validation issues (MAH)

Application form	• ASMF number not indicated • No precise scope description provided • No indication if the restricted part of the ASMF is affected	Ensure that a similar approach to other type I variations is applied when filling in the application form
Classification	• Incorrect scope is applied for • Incorrect number of scopes is applied for • Not all changes are applied for	All changes need to be correctly classified - MAHs and ASMF holders may contact IBquery@ema.europa.eu or IAquery@ema.europa.eu in case of doubts on classification
Submission	• ASMF dossier not submitted at the time of validation • If changes to the Applicant part, Module 3.2.S not updated accordingly	• Liaise with ASMF holder to ensure that ASMF dossier is submitted in advance or simultaneously with submission from MAH • Changes to the ASMF AP should also be reflected in the MAH dossier

Effective communication between the MAH and ASMF holder is key to avoid delays in the approval of changes

Avoiding validation issues

Q27 – Pre-submission guidance

27. How shall I submit an Active Substance Master File (ASMF)? ***Rev. Aug 16***

Includes information on

- **Concept of ASMF**
- **Documentation requirements**
- **Links to relevant guidelines**
- **eCTD submission requirements**

IB – Pre-notification checklist

Specific section covering application affecting an ASMF

Type IB submission checklist[1]	Yes	n/a
CHANGES TO AN ASMF		
MAH should submit: • **Application form listing the ASMF number in the 'Present and Proposed' table (last row).** In order to avoid validation comments, the EMA strongly recommends submission of the variation application once the ASMF holder has requested and obtained an EMEA ASMF reference number[9] and has successfully carried out the submission of relevant sections of the ASMF in the appropriate eCTD format. • **Revised sections of the dossier (open part) corresponding to ASMF open part.**		
MAH should liaise with ASMF holder to ensure that the following documentation is submitted: • Submission letter and administrative details (Annex 3 of the ASMF Guideline)[10,11]. • Detailed table of changes, clearly showing the present and proposed situation. Dossier section number(s) is/are indicated at the lowest possible level. • **Revised sections of the ASMF dossier (open/restricted part) reflecting changes to the previously accepted version, as applicable.**		

The MAH is accountable to ensure that ASMF holder has provided the required documentation

What is a CEP?

European Directorate for the Quality of Medicines & HealthCare

CEP – Certificate of suitability: certifies that a substance complies with the quality standards specified in the specific monograph and applicable general monographs of the Ph. Eur. for this substance.

TSE certificate – granted by EDQM, guarantees compliance with the general monograph on products with TSE risk – applies to substances of animal origin.

Directive 2003/63/EC

*Where the active substance and/or raw and starting material or excipient(s) are the subject of a monograph of the EP, the applicant can apply for a certificate of suitability that, where granted by the EDQM, shall be presented in the relevant section of the Module. Those certificates of suitability …**are deemed to replace the relevant data of the corresponding sections described in the Module***

Registration

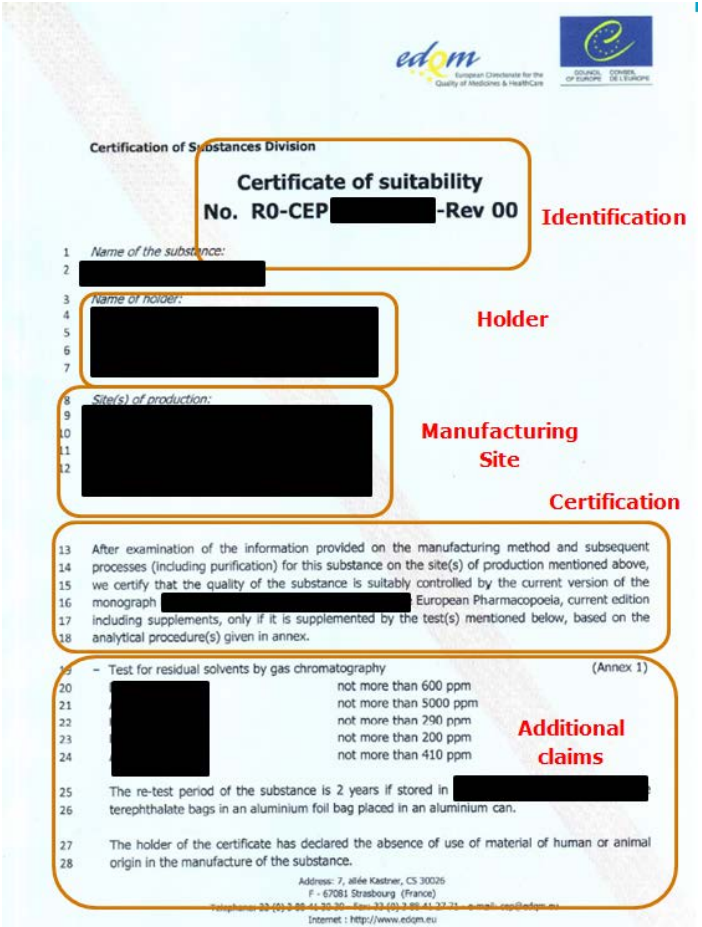
(1) Accepted at the time of MAA

(2) Variation procedure

Content of certificate

1. Certificate identification
2. Name of holder & Manufacturing site
3. Certification
4. Annex: additional claims
    a) Specifications
    b) Re-test period
    c) Endotoxin free

Present in Module 3.2.R – Regional Information



Most common validation issues

Classification	• **Incorrect number of scopes applied for when the update of the CEP covers more than one renewal or revision *e.g. from R0-CEP-xxxx-xx-rev.01 to R0-CEP-xxxx-xx-rev.04***	**Different scenarios apply– Refer to Section 7.2.2 of the EMA post-authorisation guidance**
Submission	• Update of dossier with additional claims not included in CEP certificate (e.g. re-test period, new residual solvent specifications)	For every claim not present in the Ph. Eur. Monograph or CEP certificate a separate variation is applicable (e.g. introduction of a re-test period B.I.d.1.a.1)
Documentation	• QP declaration(s) not provided for CEP certificates when new manufacturing sites of the active substance and intermediates are included	A QP declaration listing the manufacturing sites (both active substance/intermediates) needs to be provided

A similar approach is used for updates of TSE certificates

Avoiding validation issues

EMA Post-Authorisation Guidance

7.2.2. How should I submit an updated Certificate of Suitability (CEP)? (Classification category B.III.1) *NEW Oct 2016*

In line with the Marketing Authorisation Holder's (MAH) obligation to keep the dossier up to date, a new or updated Certificate of Suitability (CEP) for an active substance (AS), excipient or starting material/reagent/intermediate used in the manufacturing process of the AS should be submitted as a variation. It is however understood that only the versions of the CEP (i.e. updated certificates) which were used in the manufacturing process of a batch of finished product (FP)/ AS need to be included in the dossier.

Includes information on

- **Rules on classification on submission of new or updated CEP certificates**

If with the submission one or more revisions of the CEP are omitted, the MAH should confirm in the variation application form (section 'Precise scope and background for change') that substance/material from the omitted CEP version(s) **was not used in the manufacture of the FP and/or AS during the validity of this certificate(s).** Additionally, it should be confirmed that any changes introduced by the omitted CEP update(s) do not affect the quality of the AS and/or FP.

Take home message

- ASMF - Different submission requirements are applicable depending on the type of changes applied for
- Effective communication between the MAH and ASMF holder is key to avoid delays in the approval of changes
- The use of the pre-authorisation guidance and pre-notification checklist is advised when preparing the submission for ASMF
- Section 7.2.2 of the EMA post-authorisation guidance contains additional information on classification for changes affecting CEP

8. Concluding remarks

Alberto Ganan Jimenez

Concluding remarks

- >40% of IA/IB submissions require a request for supplementary information to amend issues raised during validation.

- A high number of issues are linked to administrative deficiencies related to application form, Annexes, documentation and classification.

- A number of documents and guidance available on the EMA website can be used to support applicants in the preparation of submissions. These include procedural and regulatory guidance, checklists and how to fill the eAF in.

Concluding remarks

- The Agency has established a pre-submission query service through dedicated mailboxes for Type IAs and Type IBs to support applicants in classification queries and queries on pre-submission aspects.

- The Agency aims at continuously monitor and improve our procedures, guidance and interaction with stakeholders.

- Follow up sessions will be organised in 2017 on aspects identified for further guidance is needed and on other post authorisation procedures (e.g. Type IIs)

Your feedback matters……

Please provide your feedback on today's session by completing the following survey by Monday 21st November:

Feedback survey of the webinar

https://ec.europa.eu/eusurvey/runner/WebinarRegProceduralaspectsTypeIvariations

Your feedback will be very valuable for improving our communications with stakeholders and to identify areas where further training is needed.

Thank you for your attention

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Useful links – Procedural guidance

Applicant / marketing authorisation holder change of contact person for product invented name / product number template

CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) 1234/2008

CMDh Questions & Answers

Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

Commission Regulation (EU) No 712/2012 of 3 August 2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

Useful links – Procedural guidance

- Electronic Application Form
- Eudralex – EU Legislation
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008
- Post-authorisation procedural advice for users of the centralised procedure
- PRAC recommendations on safety signals
- Procedural guidance on the handling of variations

Useful links – Type IA and Type IB variations

CLASSIFICATION OF CHANGES: QUESTIONS AND ANSWERS

- Type IA and Type IB variations

Fees payable to the European Medicines Agency

Mock application form

Post-authorisation guidance on IB variations: Question and answer for RMP – updated in June 2016

PRE-NOTIFICATION CHECKLIST

- Type IA variations
- Type IB variations

Useful links – Type IA and Type IB variations

PRE-SUBMISSION QUERIES SERVICE: QUESTIONS AND ANSWERS

- Type IA and Type IB variations

PRODUCT INFORMATION

- Templates
- Formatting checklist **(Type IA and Type IB without linguistic review)**
- QRD convention
- Guidance on how to PDF files

QUESTIONS AND ANSWERS

- Type IA variations
- Type IB variations

Submission time table for Type IB variation requiring linguistic review

Useful links – GMP guidance

Compilation of Community Procedures on Inspections and Exchange of Information

- Includes the Union Format for **Manufacturer's Authorisation** / Union Format for a **GMP** Certificate, terminology, etc.

EudraGMDP

EU public database that contains:
- Manufacturing and importation authorisations for EEA Sites
- Good Manufacturing Practice (GMP) certificates for EEA + 3rd country sites
- Statements of non-compliance with GMP for EEA + 3rd country sites
- GMP inspection planning in 3rd countries

MRA information

Q&A – GMP

QP declaration recommended template and guidance

Useful links – ASMFs and CEPs

Additional guidance on how to complete ASMF documents

CHMP ASMF guideline

EDQM – Database CEP certification search

EMA Post-authorisation guidance – Section 7 - Classification of changes

Q27 – Pre-authorisation guidance