AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

Variation regulation and classification guideline

Marco Franceschin

Study Visit Serbia Kazakhstan 9-13/07/2018

Public Declaration of transparency/interests*

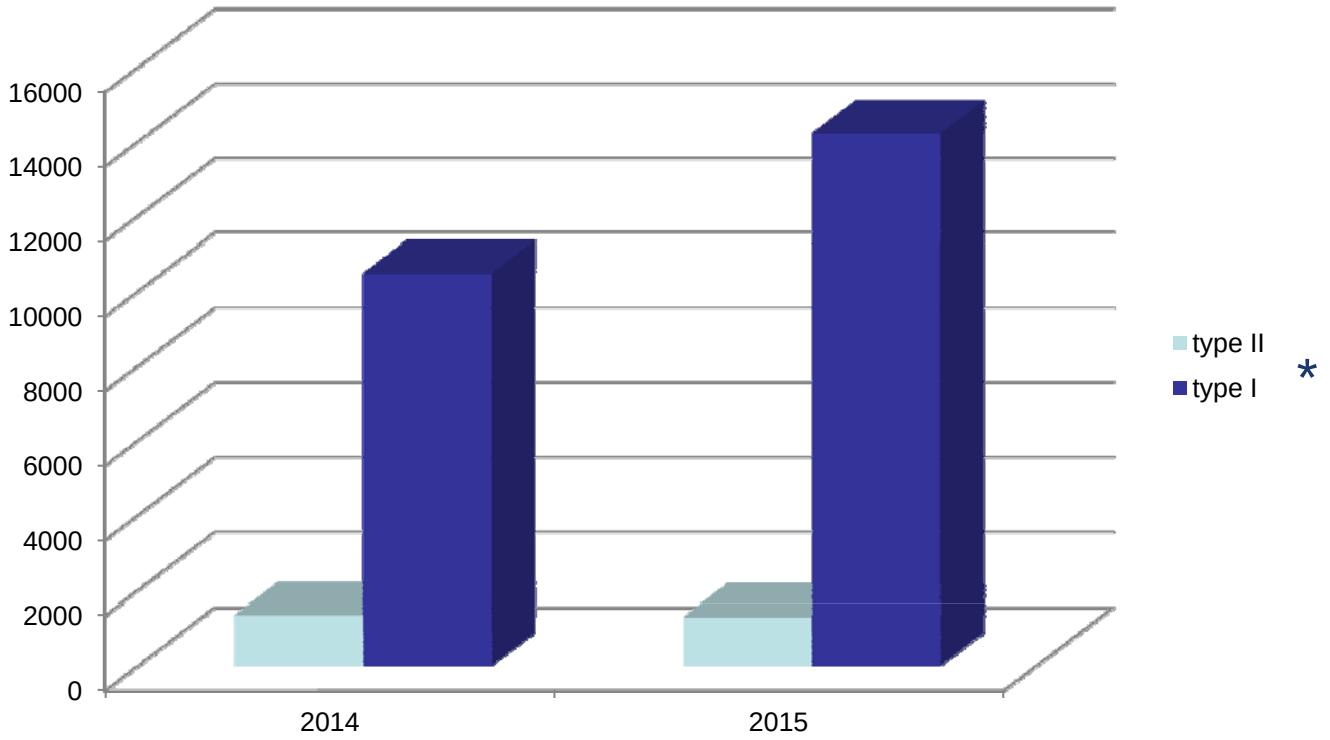
The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

*Marco Franceschin, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (25.03.2015) and published on the Official Journal of 15.05.2015 according to EMA policy /626261/2014 on the handling of the conflicts of interest for scientific committee members and experts.

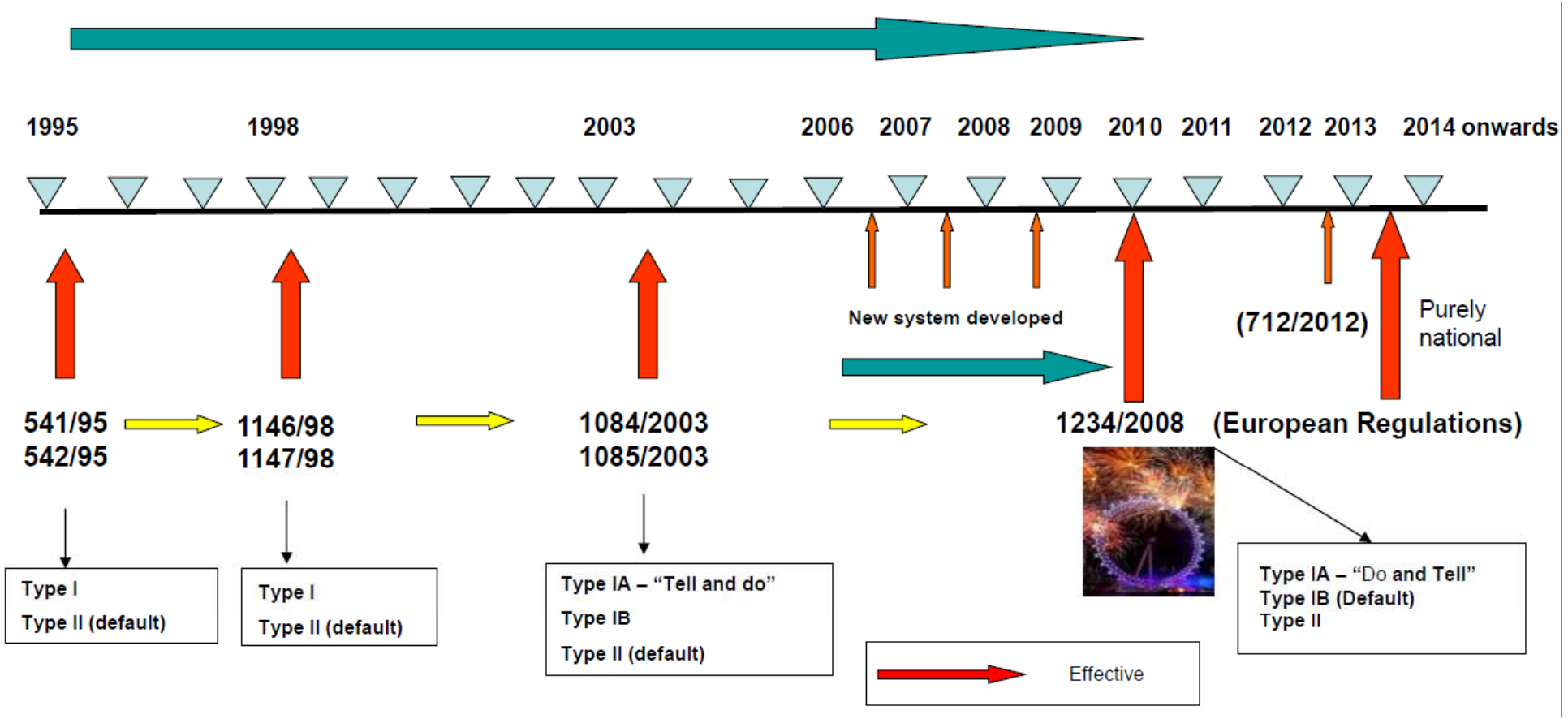
N.B. I am not receiving any compensation

Type I and type II variations submitted: an overview in Italy



*the reported values (aggregate for national and MR/DC procedures) include also grouping and WS procedures

European Variations System - Evolution



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New Variation Regulation

Regulation EC No 1234/2008

now updated by EC/712/2012 (3 August 2012)

Implementation of specific changes:-

Within 90 days (2 November 2012)

Within 12 months (4 August 2013) – Purely National

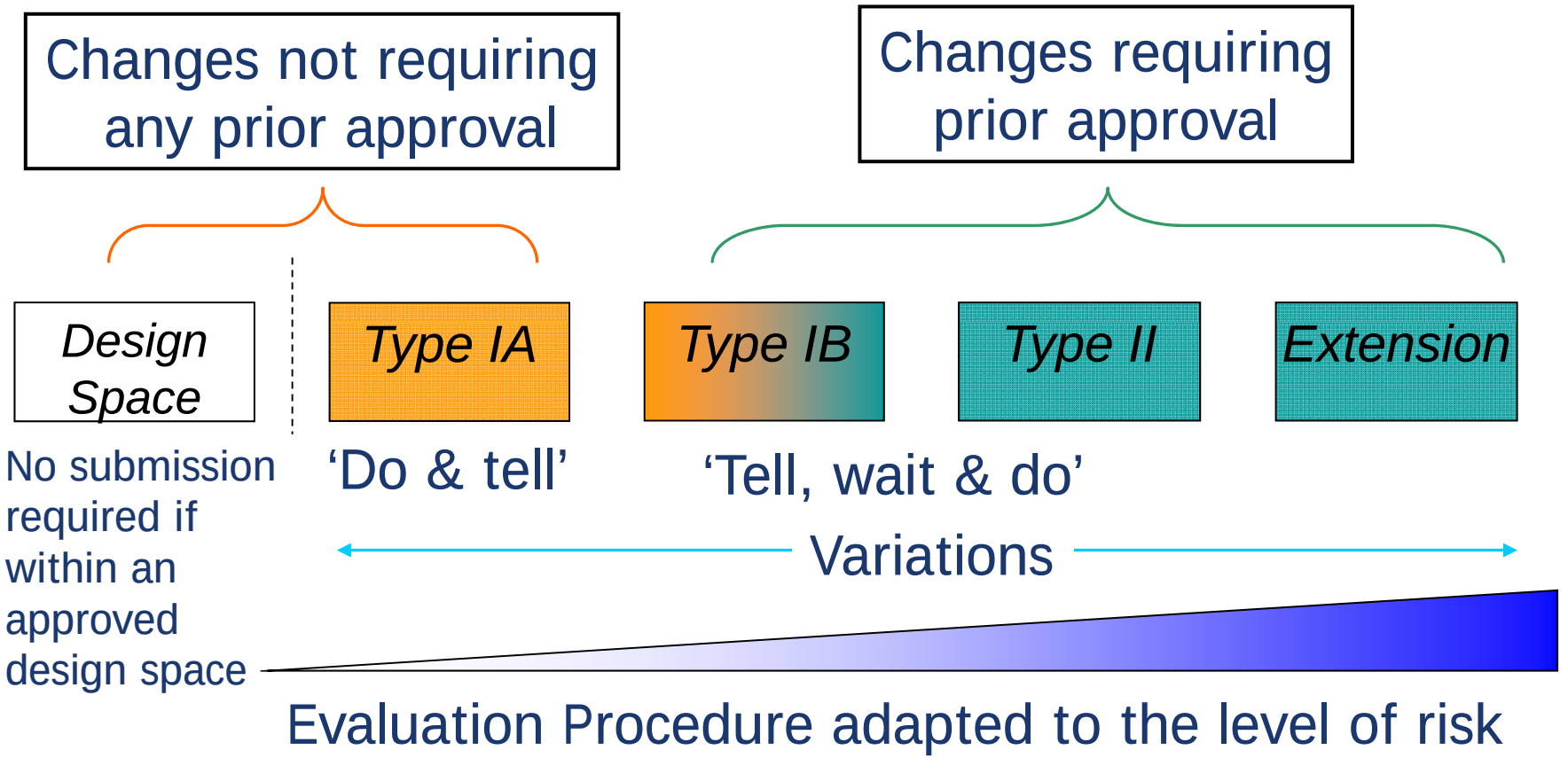
Regulation applied from 1 January 2010 - CP and MRP/DC products only (optionally NAP: also in Italy)

Updated Regulation has applied from 4 August 2013 – purely National (mandatory for all MS)

Regulation - Classification Rules

- Type IA and Type II pre-defined (high-level) in Annex II
- Extensions pre-defined in Annex I
- Unlisted variations = Type IB by default, with option for
  - MAH to submit as Type II
  - Competent Authority to require Type II at validation (safeguard-clause)
- Because of the Type IB default, guideline needs to cover all types of changes, including admin, quality, clinical, pharmacovigilance etc.

Summary - Types of Variations



Classification Guideline (key document)

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.

Classification Guideline (key document)

Current version – Official Journal C223/1 – 02/08/2013 (separate from Regulation)

- Procedural aspects
- Classification
- Type IA – conditions and documentation requirements fully defined (30 days)
- Type IA - IA/IA_{IN} – appropriately identified

Classification Guideline (key document)

- Type II – changes defined (*no documentation requirements) (30, 60, 90 days)

- Type IB – EXAMPLES defined with documentation requirements (no conditions) (30 days, except worksharing) (facilitate submission & validation, ensure consistency, Avoid Art. 5)

(* exception relates to Design Space categories)

Classification Guideline – Structure

Example – finished product manufacturer

B.II.b) Manufacture

B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product		Conditions to be fulfilled	Documentation to be supplied	Procedure type
a)	Secondary packaging site	1, 2	1,3, 8	IA_{IN}
b)	Primary packaging site	1, 2, 3, 4, 5	1, 2, 3, 4, 8, 9	IA_{IN}
c)	Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/ immunological medicinal products.			II
d)	Site which requires an initial or product specific inspection			II
e)	Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products.		1, 2, 3, 4, 5, 6, 7, 8, 9	IB
f)	Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products manufactured using an aseptic method excluding biological/ immunological medicinal products.		1, 2, 3, 4, 5, 7, 8	IB

Conditions

1. Satisfactory inspection in the last three years by an inspection service of one of the Member States of the EEA or of a country where an operational Good Manufacturing Practice (GMP) mutual recognition agreement (MRA) exists between the country concerned and the EU.
2. Site appropriately authorised (to manufacture the pharmaceutical form or product concerned).
3. Product concerned is not a sterile product.
4. Where relevant, for instance for suspensions and emulsions, validation scheme is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches.
5. Product concerned is not a biological/immunological medicinal product.

Type II biological/immunological

Examples (IB)

Article 5

Recommendation on unforeseen variations

1. Prior to the submission of a variation whose classification is not provided for in this Regulation, a holder may request a recommendation on the classification of the variation as follows:

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

RECOMMENDATION OF THE COORDINATION GROUP FOR MUTUAL RECOGNITION AND DECENTRALISED PROCEDURES - HUMAN (CMDh) ON THE CLASSIFICATION OF AN UNFORESEEN VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION

CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008

Section of the Classification Guideline	Date issued	Summary of the proposed change	Proposed classification	Proposed conditions, where relevant
A. ADMINSTRATIVE CHANGES				
A.z	04/04/2016	Change in the nomenclature of the container material for immediate packaging of the finished product.	IA	The material of the container closure system must remain the same.
B. QUALITY CHANGES				
B.I. ACTIVE SUBSTANCE				
B.I.a) Manufacture				
B.I.a.z	26/05/2015	Re-arrangement and amendment of equipment in the plasma pooling line of the active substance which has already been included in the approved dossier.	IA	1) No changes to the manufacturing process are applied 2) New equipment is identical in construction and already listed in 3.2.A.1 3) Re-arranged pooling operations take place in an area already approved for this step (no new manufacturing site) 4) Demonstration of GMP approval of the

Type IA notifications - Key Points

"Do and Tell" – implemented before notification
(MAH – flexibility & responsibility)

- Type IA_{IN} – immediate notification
  (generally within 2 weeks of implementation)
- Type IA – notification within 12 months of implementation

30 day procedure: scientific check (NO assessment)
- The NCA will not request clarification, additional information or documentation from the MAH.

Company should cease to apply a change if not acceptable.

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CHAPTER 3

CMDh BEST PRACTICE GUIDE FOR THE PROCESSING OF TYPE IA MINOR VARIATIONS (NOTIFICATIONS) IN THE MUTUAL RECOGNITION PROCEDURE

Doc. Ref.: CMDh/293/2013/Rev.21
July 2014

According to the Regulation minor variations of Type IA do not require prior approval but can be implemented prior to notification to the relevant authorities ("Do and tell"). Type IA notifications are listed in the Commission guideline on the classification of variations and these notifications should be submitted within twelve months following implementation, so called "*annual reports*", taking into account the guidance on possible grouping of variations. However, the notification should be submitted immediately after the implementation of the variation in the case of specific minor variations requiring immediate notification. These notifications are specifically identified as IA_{IN} in the guideline.

It is possible for a MAH to include a Type IA variation in the submission of a Type IA_{IN} variation, or with another upcoming variation, rather than waiting to include it in an annual report. Further information about the grouping of Type IA variations is available in Chapter 6 of this Best Practice Guide; however, the timetable and principles for grouped variations, consisting of Type IA changes only, is the same as the procedure outlined in this Chapter of the Best Practice Guide.

Type-IA variations: questions and answers

This page lists questions that marketing-authorisation holders (MAHs) may have on type-IA variations. It provides an overview of the European Medicines Agency's position on issues that are typically addressed in discussions or meetings with MAHs in the post-authorisation phase. Revised topics are marked 'New' or 'Rev.' upon publication.

A PDF version of the entire post-authorisation guidance is available:

European Medicines Agency post-authorisation procedural advice for users of the centralised procedure

These questions and answers have been produced for guidance only and should be read in conjunction with the rules governing medicinal products in the European Union, volume 2, notice to applicants.

MAHs must in all cases comply with the requirements of Community legislation. Provisions that extend to Iceland, Liechtenstein and Norway by virtue of the European Economic Area agreement are outlined in the relevant sections of the text.

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1. When should I submit my type-IA or -IAIN variation? Rev. July 2013

Commission Regulation (EC) No 1234/2008 ('the Variations Regulation') and the Commission 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 and on the documentation to be submitted pursuant to those procedures ('the Variations Guidelines') set out a list of changes to be considered as type-IA variations. Such minor variations have only a minimal impact or no impact at all, on the quality, safety or efficacy of the medicinal product, and do not require prior approval before implementation ('do-and-tell' procedure). The Classification Guideline clarifies the conditions that must be met in order for a change to be considered a type-IA variation.

Such minor variations are classified in two subcategories, which impact on their submission:

- **Type-IA variations requiring immediate notification ('IAIN')**
  The Classification Guideline specifies the type-IA variations that must be notified (submitted) immediately to the national competent authorities or European Medicines Agency following implementation, in order to ensure the continuous supervision of the medicinal product.
- **Type-IA variations not requiring immediate notification ('IA')**
  Variations that do not require immediate notification may be submitted by the MAH within 12 months after implementation, or may be submitted earlier should this facilitate dossier lifecycle maintenance or when necessary, to ensure that the latest product information is reflected in certificates of pharmaceutical products, for example.

The 12-month deadline to notify minor variations of type IA allows for an annual reporting for these variations, where a MAH submits several minor variations of type IA that have been implemented during the previous 12 months.

Most of these type-IA variations do not have an impact on the product information. However, in case of an upcoming submission of a variation, extension or other regulatory procedure that will affect the product information, the MAH should also include any type-IA changes affecting the product information, in order to keep the product information up-to-date and to facilitate document management.

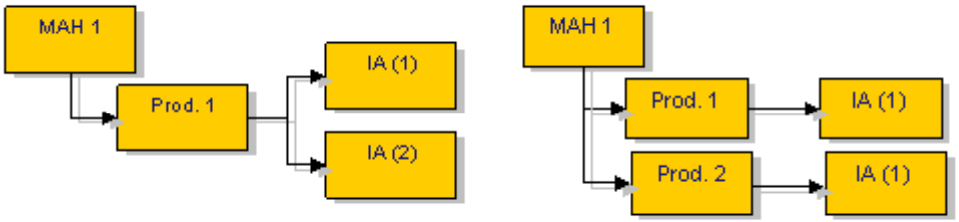
There are no recommended submission dates for type-IA variations.. However, MAHs are encouraged to avoid submitting type-IA notifications shortly before or during the Agency holiday periods (e.g. the end of July and Christmas).

2. Can I group the submission of type-IA and -IAIN variations? Can they be grouped with other types of variation? Rev. September 2014

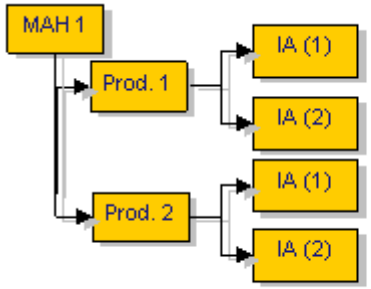
Article 7(2)(a) of the Variations Regulation sets out the possibility for a MAH to group several type-IA or -IAIN variations under a single notification to the same relevant authority, or to group them with other types of variation.

Possible grouping of type-IA and -IAIN changes only

- Several type IA or IAIN affecting one medicinal product:
  This means, for instance, that a type-IA variation, which is normally not subject to immediate notification, can be included in the submission of a type-IAIN variation;
- One type IA or IAIN affecting several medicinal products from the same MAH:



- Several type IA and / or IAIN affecting several medicinal products from the same MAH, provided that those variations are the same for all medicinal products and are submitted to the same relevant authority:



Possible grouping of type IA and IAIN with other types of variation

- Type IA/IAIN can also be grouped with other variations (e.g. Type IB, Type II, Extension), as listed in Annex III of Commission Regulation 1234/2008. Groupings not included in the aforesaid Annex should be discussed and agreed with the Agency prior to submission.
- Such grouped submissions will follow the review procedure of the highest variation in the group. Please also refer to "What type of variations can be grouped?".

It must be noted, however, that when submitting type-IA or -IAIN variations as part of a group, the legal deadlines for submission of each variation should be respected, i.e. a type IAIN should always be submitted immediately, whether or not it is grouped with other variations, and any type-IA variations should always be submitted within 12 months following their implementation.

Submission of IA variations and the “12 months period” by the implementation date

Type IA variations - not requiring immediate notification - should be submitted to all relevant authorities within 12 months following the implementation of the variation.

However sometimes the situation occurs where such implemented IA change is replaced again within the course of those 12 months, before it has been notified to the relevant authorities.

Submission of IA variations and the “12 months period” by the implementation date

Examples:

- A new site where batch control/testing takes place (IA n° B.II.b.2.a) is implemented on 01/01/2015 and this site is deleted again (IA n° A.7) on 01/10/2015: we expect the company to submit both variations given the fact that the site performed batch control/testing during this 9-month period.
- Another example is the subsequent implementation of several updated versions of a CEP in the 12 month period following the implementation of the first CEP version. We expect a IA variation (IA n° B.III.1.a.2, grouped if possible) for every CEP version that was implemented at a certain point in time.

Submission of IA variations and the “12 months period” by the implementation date

Type IA variations submitted after the 12 months following implementation:

Not all MS deal this issue in the same way: some (majority, including IT) of the MS requests the submission of a type IB variation in case of submission after 12 months, due to the lack of the “general condition” for a type IA variation; other MSs accept type IA variations:

please check with your NCA!

Sources of useful information

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

Q/A-LIST FOR THE SUBMISSION OF VARIATIONS ACCORDING TO COMMISSION REGULATION (EC) 1234/2008

Doc. Ref: CMDh/132/2009/Rev.43
September 2016

Question 5.2

What is meant by "implementation" for Type IA variations?

Answer:

For quality changes, implementation is when the Company makes the change in its own Quality System.

This interpretation allows companies to manufacture conformance batches and generate any needed stability studies to support a Type IAIN variation before making an immediate notification[1] because the change will not be made in their own Quality System until these data are available.

For changes to the pharmacovigilance system, 'implementation' is when the Company makes the change in its pharmacovigilance system (i.e. when it internally approves the DDPS or summary of pharmacovigilance system incorporating the changes).

For product information, it is when the Company internally approves the revised product information. The revised product information will then be used in the next packaging run.

Question 5.3

If a Type IA variation is part of a group containing Type II, do I have to wait for the implementation of the IA variation until the group assessment is completed?

Answer:

The principle of Type IA notification applies also when the Type IA variation is part of a grouped application. The Type IA change may be implemented before submission of the grouping. In case a Type IA change is dependent on the outcome of other changes in a grouped application this change may be submitted with an implementation date in the future and the change will be implemented as soon as the complete grouped application is approved.

Question 4.11

Must all changes in a grouped application according to article 7 of the Regulation (EC) 1234/2008 apply to all strengths and pharmaceutical forms that have been included in this group?

Answer:

Yes, all the changes in one variation application must apply to all the products that are listed in the application form. It is not allowed that single changes of this grouped application do only concern parts of the list of products.

Question 3.2

How to apply for the deletion of more than one manufacturing site?

Answer:

In case more than one manufacturer in one MA has to be deleted a single variation of type IA under classification category A.7 to delete all manufacturing sites may be submitted. However,

it has to be assured that there is still one approved manufacturing site left in the documentation performing the same function as the one(s) concerned by the deletion.

Question 3.10

How should a deletion of a pharmaceutical form or strength be submitted?

Answer: In case of MRP/DCP or purely national licences the submission of a variation is not necessary, if they have been authorised as an independent marketing authorisation. In such cases, a withdrawal notification letter should be sent to the member state(s) concerned and the RMS has to be informed via email. Since in some MS a given pharmaceutical form or strength might have not received a marketing authorisation which is separate to the marketing authorisation for other pharmaceutical forms or strengths, in such cases the deletion of a pharmaceutical form or strength should be submitted as a variation C.I.7, only in those MS(s) according to a national procedure. It is the responsibility of the applicant to identify before submission which MS requires a variation and which MS requires a withdrawal application. In case of doubt applicants may contact the MSs in advance of the submission.

In what concerns the need for update of combined product information further to withdrawal/deletion of a strength/pharmaceutical form, if common combined product information must be updated to delete information concerning strength/pharmaceutical form deleted for all MS, a type IB variation under category C.I.z should be submitted to allow complete review across all section of the combined product information.

If only national versions of combined product information are affected, applicants should confirm with national competent authorities which is the most appropriate procedure for updating the product information.

Question 3.17

We wish to register a new site of active ingredient manufacturer by Type IA change code B.III.1 notification, as the manufacturer holds a Ph Eur Certificate of Suitability (CEP). The CEP does not state a re-test period but we have stability data to support this. Can we tick condition 4 and include the stability with the Type IA change code B.III.1 notification?

Answer:

The Type IA notification procedure is intended to be a simple and rapid process for minor changes and does not include the assessment of data. In this case, the stability data will need to be assessed. This can be done by either submitting a Type IB change code B.I.d.1 variation to change the re-test period of the active substance in parallel with the Type IA change code B.III.1, or as a group with the Type IA change (the resultant group would default to a Type IB procedure time table).

As change code B.I.d.1 is a Type IB notification, condition 4 of the Type IA notification will have to be ticked, as omission of re-testing before manufacture will not be acceptable until the new re-test period has been approved.

Question 2.8

In case the MAH in one member state is changed, is a variation in all member states necessary to introduce the new summary of the pharmacovigilance system or DDPS (veterinary) of the new MAH or is a purely national variation in the member state concerned sufficient?

Answer:

In case of the transfer of a MAH in one member state the new summary of the pharmacovigilance system or DDPS (veterinary) of the new MAH has to be submitted to all member states concerned via MRP variation (as type IA_{IN} notification, C.I.8.a, or under category C.II.7 as applicable). This is also applicable when using the Art. 57 database as the classification guideline (C.I.8) also requires a "proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance and a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC". Therefore, a variation for the introduction of a new summary PSMF after a change of the MAH still has to be submitted, later changes of the contact details of the QPPV or location of the PSMF do not require variations anymore when they are introduced via the Art. 57 database.

However, the transfer of the MA to a new MAH is to be handled as an independent purely national application according to Art. 1(2) of the Regulation (EC) 1234/2008 as there is a change of the legal entity. The fees are set by each CMS and the management of the procedure is dealt with by each CMS. The current registered MAH should send a notification to the RMS to specify which CMSs and MAHs are concerned with this national procedure.

Remark: The change in the name and/or address of the MAH (i.e. the MAH remains the same legal entity) for a product registered through MRP or DCP, is processed at MRP level via a type IA_{IN} No. A.1 variation.

Article 57

- As of 1 February 2016 MA holders are no longer required to submit Type IA variations in relation to administrative changes to the QP responsible for PV and PV system Master File.

C.I.8 Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use (*)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location		1, 2	IA_{IN}

Documentation

1. Summary of the pharmacovigilance system, or update of the relevant elements (as applicable):
   - — Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance and a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC.
   - — Contact details of the QPPV, Member States in which the QPPV resides and carries out his/her tasks
   - — PSMF location
2. PSMF number (if available)

Note: This variation covers the introduction of a PSMF irrespective of whether or not the technical dossier of the MA contained a DDPS.

Once the Article 57 database is functional, changes in QPPV, including contact details (telephone and fax numbers, postal address and e-mail address) and changes to the location of the PSMF (street, city, postcode, country) may be updated through the Article 57 database only (without the need for a variation).

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Chiarimenti sulla presentazione di variazioni all'AIC (10/06/2014)

Avviso alle Aziende Farmaceutiche

10/06/2014

L'Agenzia Italiana del Farmaco porta all'attenzione di tutte le aziende farmaceutiche alcuni chiarimenti in merito alla presentazione delle variazioni dei termini di una Autorizzazione all'Immissione in Commercio di medicinali presentate secondo procedura nazionale, di mutuo riconoscimento/decentrata (MR/DC) ai sensi del Regolamento CE n° 712/2012 e in linea con la nuova "*classification guideline*" della Commissione Europea datata 16/05/2013, al fine di favorire la corretta presentazione da parte delle Aziende delle domande concernenti variazioni all'AIC.

Si allega inoltre l'aggiornamento della nota esplicativa per l'applicazione della determina AIFA del 25 agosto 2011 relativa alla procedura del "silenzio/assenso" (S/A) per il rilascio del relativo provvedimento amministrativo adottata da AIFA ai sensi del comma 1bis dell'art.35 del Decreto Legislativo 24 aprile 2006, n.219 e s.m., aggiornata in linea con il Regolamento CE n° 712/2012 e la nuova "*classification guideline*" della Commissione Europea", nonché l'aggiornamenti dei modelli per la pubblicazione in Gazzetta Ufficiale della Repubblica italiana per variazioni rientranti nell'applicazione del silenzio/assenso e che impattano sugli stampati, aggiornati a seguito dell'entrata in vigore della Determinazione del Direttore Generale dell'AIFA n. 371 del 14/04/2014 concernente " Criteri per l'applicazione delle disposizioni relative allo smaltimento delle scorte dei medicinali" (Determina scorte).

In allegato:

- *Chiarimenti sulla presentazione di Variazioni all'AIC ai sensi del Regolamento (CE) n° 1234/2008 come modificato dal Regolamento (EC) n° 712/2012*
- *Aggiornamento della nota esplicativa per l'applicazione della determina AIFA del 25 agosto 2011*
- *Modello Gazzetta Ufficiale per articolo 1 comma 2 della Determina AIFA n. 371 del 14/04/2014*
  - *Formato .odt*
  - *Formato .pdf*
- *Modello Gazzetta Ufficiale per articolo 1 comma 5 della Determina AIFA n. 371 del 14/04/2014*
  - *Formato .odt*
  - *Formato .pdf*

Allegati

Chiarimenti sulla presentazione di Variazioni all'AIC ai sensi del Regolamento (CE) n° 1234/2008 come modificato dal Regolamento (EC) n° 712/2012
Aggiornamento nota esplicativa per l'applicazione della Determina AIFA del 25/08/2011
Modello Gazzetta Ufficiale per articolo 1 comma 2 - Formato .odt
Modello Gazzetta Ufficiale per articolo 1 comma 2 - Formato .pdf
Modello Gazzetta Ufficiale per articolo 1 comma 5 - Formato .odt
Modello Gazzetta Ufficiale per articolo 1 comma 5 - Formato .pdf

Link correlati

- Variazioni Tipo I - Determina AIFA del 25 agosto 2011
- Determina n. 371 del 14 aprile 2014 (G.U. n. 101 del 03/05/2014)
- Chiarimenti AIFA sulla Determinazione del Direttore Generale n° 371 del 14 Aprile 2014

Argomenti correlati

- Procedure Reference Member State (RMS) e Variazioni all'AIC

B.II.d) Control of finished product

B.II.d.1 Change in the specification parameters and/or limits of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of specification limits	1, 2, 3, 4	1, 2	IA
b) Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release	1, 2, 3, 4	1, 2	IA_{IN}
c) Addition of a new specification parameter to the specification with its corresponding test method	1, 2, 5, 6, 7	1, 2, 3, 4, 5, 7	IA

7. The change does not concern any impurities (including genotoxic) or dissolution.

The previous version was:

7. The change does not concern a genotoxic impurity.

Other sources of useful information

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

CMDv
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Veterinary

EXAMPLES FOR ACCEPTABLE AND NOT ACCEPTABLE GROUPINGS FOR MRP/DCP PRODUCTS

Doc. Ref: CMDh/173/2010/Rev.15
June 2016

1. ACCEPTABLE GROUPINGS

- Changes in primary packaging or to include a new primary packaging of the finished product is proposed (under category B.II.e.1 (a.1/2/3/4 or b.1/2) and related changes, etc to set different shelf-life and/or storage conditions for the new presentation of the medicinal product with respect to the currently authorized one (under category B.II.f.1)
- Changes in primary packaging or to include a new primary packaging of the finished product (under category B.II.e.1 (a.1/2/3/4 or b.1/2) and related changes, e.g. different specification parameters and/or limits and/or test procedures for the immediate packaging of the finished product are applied, and/or a new supplier of packaging components B.II.e.2/3 and/or B.II.e.7.

3. ACCEPTABLE AS SINGLE CHANGE INSTEAD OF GROUPING

- For a change in the shape/dimensions of a tablet/capsule (B.II.a.2 – a or b) or a change/addition of imprints/markings (B.II.a.1 – a or b) a consequential change is e.g. in the finished product specification "appearance" and the corresponding IPC are modified. The submission of these changes in total are acceptable as a single variation under the a.-m. category.
- When adding/changing a colouring agent (B.II.a.3.a) consequential changes as e.g. the finished product specification in respect of appearance/odour/taste and if relevant, deletion of an identification test are regarded as part of this variation and may be submitted as a single variation procedure.

New!

- Addition of a new finished product (FP) bulk manufacturing site: changes to the manufacturing process, batch size and in-process controls to adapt to the new manufacturing site settings may be submitted as single type II variation under B.II.b.1 according to the indent of the main change but updated to type II. Complex related changes submitted under a single type II should always be clearly identified in the application form as following: a clear description of all the consequential changes should be provided in the precise scope. All the related changes should be listed in the present/proposed table. Changes affecting the FP and not only related to the introduction of the new manufacturing site such as changes in excipients, specification parameters /limits for the FP, container closure system including suppliers should be submitted as additional scopes in a grouped application.

Worksharing (Article 20)

Sharing of assessment across multiple Marketing Authorisations (MAs)

The same Type IB or II, or the same group of variations affecting > 1 MA, from the same MAH, involving different NCA

The group may also contain IA changes

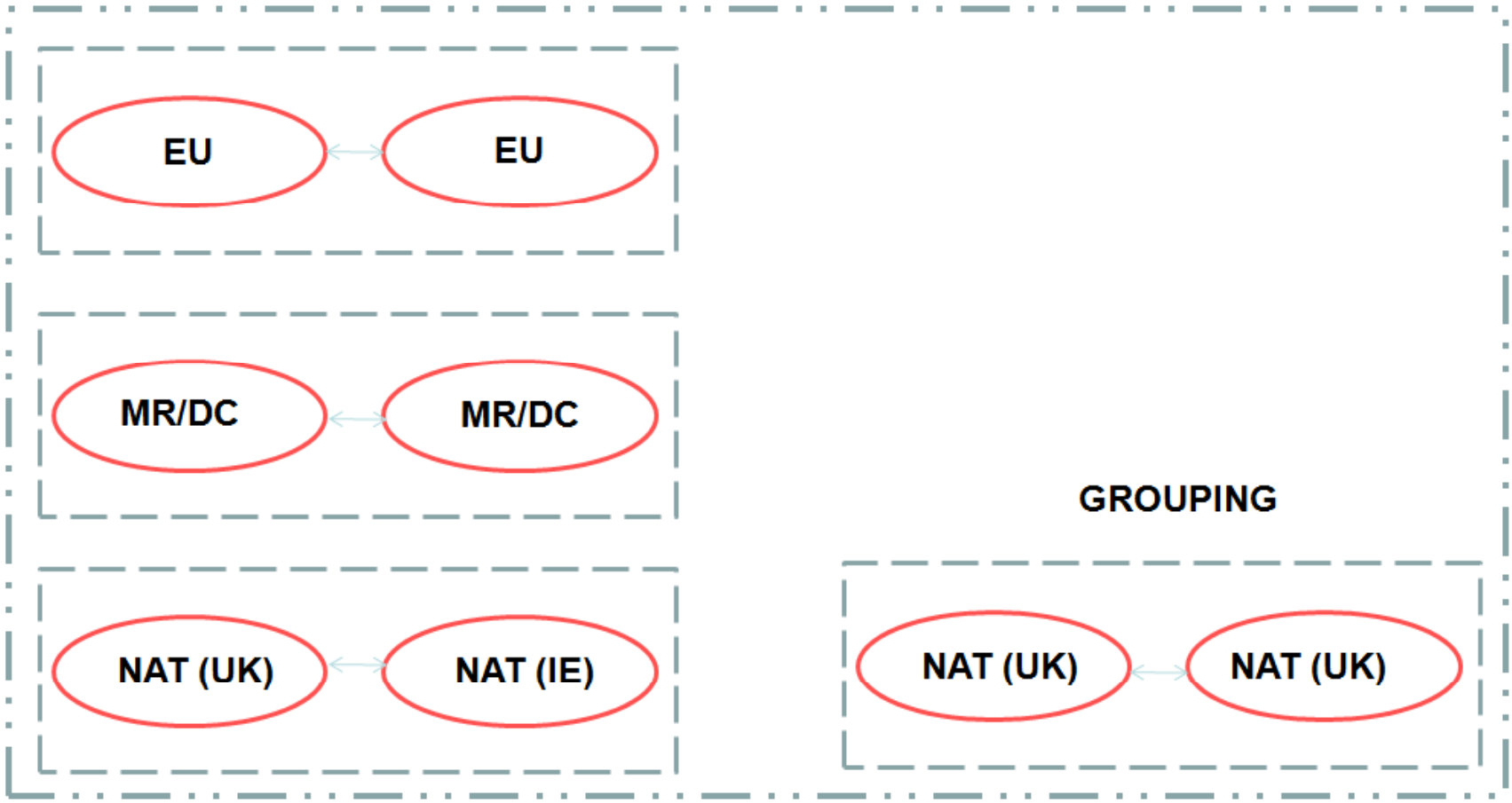
The group may not include a line extension

– The ‘same’ change should not necessitate any product specific assessment

Worksharing (Article 20)

- ‘Same MA’ includes all strengths/pharm forms of a certain product. For MRP/DCP, ‘same MAH’ rules apply to different companies as MAH in RMS and CMS
- Where appropriate CMD(h) agrees the Reference Authority
- BPG details procedures – principles for Type II variation apply

TYPE OF WORKSHARING



Some critical points about worksharing procedures

Worksharing procedures may be efficiently time-saving and enforce collaboration among European regulatory authorities. In the relative BPG they are considered similarly to type II variations in terms of time-table and procedural steps. Nevertheless, it should be underlined that they may include purely nationally authorized products and therefore the involvement of each NCA should be highly guaranteed in all phases of the procedure.

Some critical points about worksharing procedures

- Time-table: importance of sharing among MSs and applicant
- Supporting documentation: further documentation should not be sent after day0 and before the clock-stop
- Additional documentation: during the procedure, the applicant sent to IT only the additional documentation related to the points raised by IT. We reminded several times to the applicant that all MSs should received all the updated documents for all the raised points, as clearly stated in the BPG (chapter 7): "*The MAH shall submit the application and any identical subsequent documentation for the worksharing procedure to all relevant authorities, i.e. the reference authority and all Member States where the products concerned are authorised.*"

Application of articles 23 and 24 of COMMISSION REGULATION (EC) No 1234/2008 as amended by Commission Regulation (EU) No 712/2012

SECTION 2

Amendments to the decision granting the marketing authorisation and implementation

Article 23

Amendments to the decision granting the marketing authorisation

1. Amendments to the decision granting the marketing authorisation resulting from the procedures laid down in Chapters II and IIa shall be made:

(a) in the case of major variations of type II, within two months following receipt of the information referred to in Article 11(1)(c) and Article 13e(a), provided that the documents necessary for the amendment of the marketing authorisation have been transmitted to the Member States concerned;

(b) in the other cases, within six months following receipt of the information referred to in Article 11(1)(c) and Article 13e(a), provided that the documents necessary for the amendment of the marketing authorisation have been transmi tted to the Member States concerned.

Article 24

Implementation of variations

1. Minor variations of type IA may be implemented any time before completion of the procedures laid down in Articles 8, 13a and 14.

Where a notification concerning one or several minor variations of type IA is rejected, the holder shall cease to apply the concerned variation(s) immediately after receipt of the information referred to in Articles 11(1)(a), 13e(a), and 17(1)(a).

2. Minor variations of type IB may only be implemented in the following cases:

(a) for variations submitted in accordance with the procedures laid down in Chapter II, after the competent authority of the reference Member State has informed the holder that it has accepted the notification pursuant to Article 9, or after the notification is deemed accepted pursuant to Article 9(2);

(b) for variations submitted in accordance with the procedures laid down in Chapter IIa, after the relevant authority has informed the holder that it has accepted the notification pursuant to Article 13b, or after the notification is deemed accepted pursuant to Article 13b(2);

3. Major variations of type II may only be implemented in the following cases:

(a) for variations submitted in accordance with the procedures laid down in Chapter II, 30 days after the competent authority of the reference Member State has informed the holder that it has accepted the variation pursuant to Article 10, under the condition that the documents necessary for the amendment to the marketing authorisation have been provided to the Member States concerned. Where an arbitration procedure has been initiated in accordance with Article 13, the holder shall not implement the variation until the arbitration procedure has concluded that the variation is accepted;

(b) for variations submitted in accordance with the procedures laid down in Chapter IIa, after the competent authority has informed the holder that it has accepted the variation pursuant to Article 13c;

ANNEX I

Extensions of marketing authorisations

1. Changes to the active substance(s):

   (a) replacement of a chemical active substance by a different salt/ester complex/derivative, with the same therapeutic moiety, where the efficacy/safety characteristics are not significantly different;

   (b) replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer), where the efficacy/safety characteristics are not significantly different;

   (c) replacement of a biological active substance with one of a slightly different molecular structure where the efficacy/safety characteristics are not significantly different, with the exception of:

   — changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

   — replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue;

   — replacement of a strain for a veterinary vaccine against equine influenza;

   (d) modification of the vector used to produce the antigen or the source material, including a new master cell bank from a different source, where the efficacy/safety characteristics are not significantly different;

   (e) a new ligand or coupling mechanism for a radiopharmaceutical, where the efficacy/safety characteristics are not significantly different;

   (f) change to the extraction solvent or the ratio of herbal drug to herbal drug preparation where the efficacy/safety characteristics are not significantly different.

2. Changes to strength, pharmaceutical form and route of administration:

   (a) change of bioavailability;

   (b) change of pharmacokinetics e.g. change in rate of release;

   (c) change or addition of a new strength/potency;

   (d) change or addition of a new pharmaceutical form;

   (e) change or addition of a new route of administration ([1]).

DRAFT Proposal to the European Commission to update the Guideline on the Categorisation of Extension Applications (EA) vs. Variations Applications (V)

May 2017/June 2018

EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market, implementation and legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

Brussels,
F2/AW D(2002)

Final – Revision 3

NOTICE TO APPLICANTS

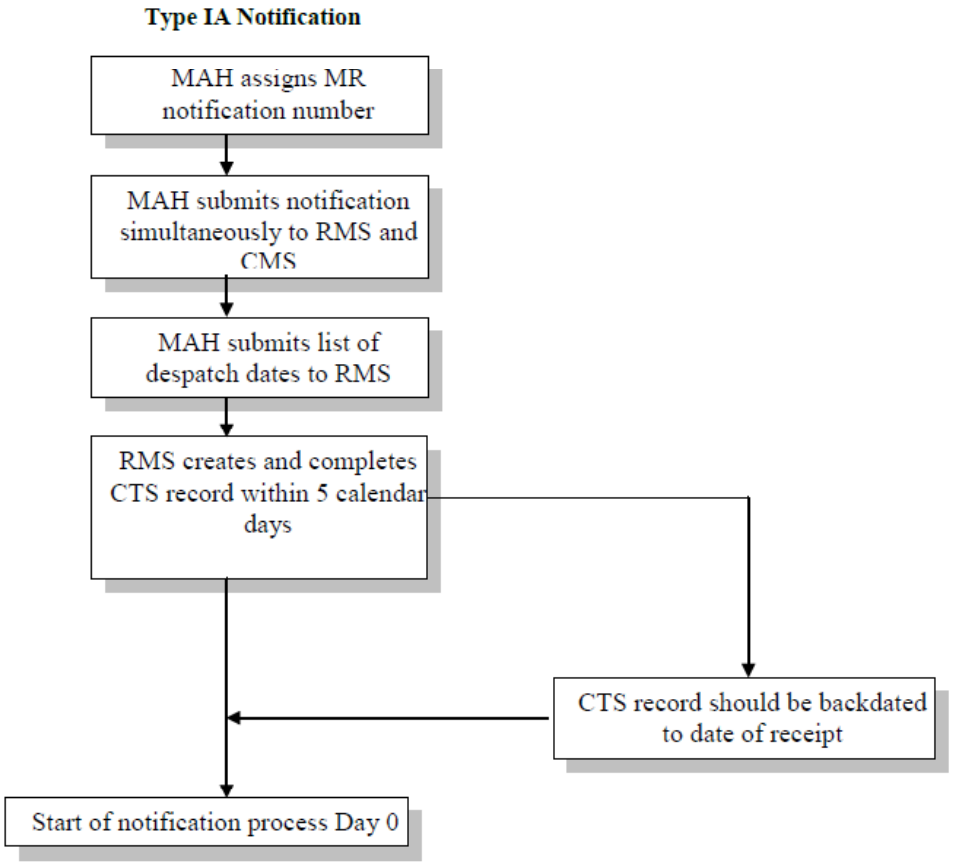
GUIDELINE ON THE CATEGORISATION OF EXTENSION APPLICATIONS (EA) versus VARIATIONS APPLICATIONS (V)

OCTOBER 2003

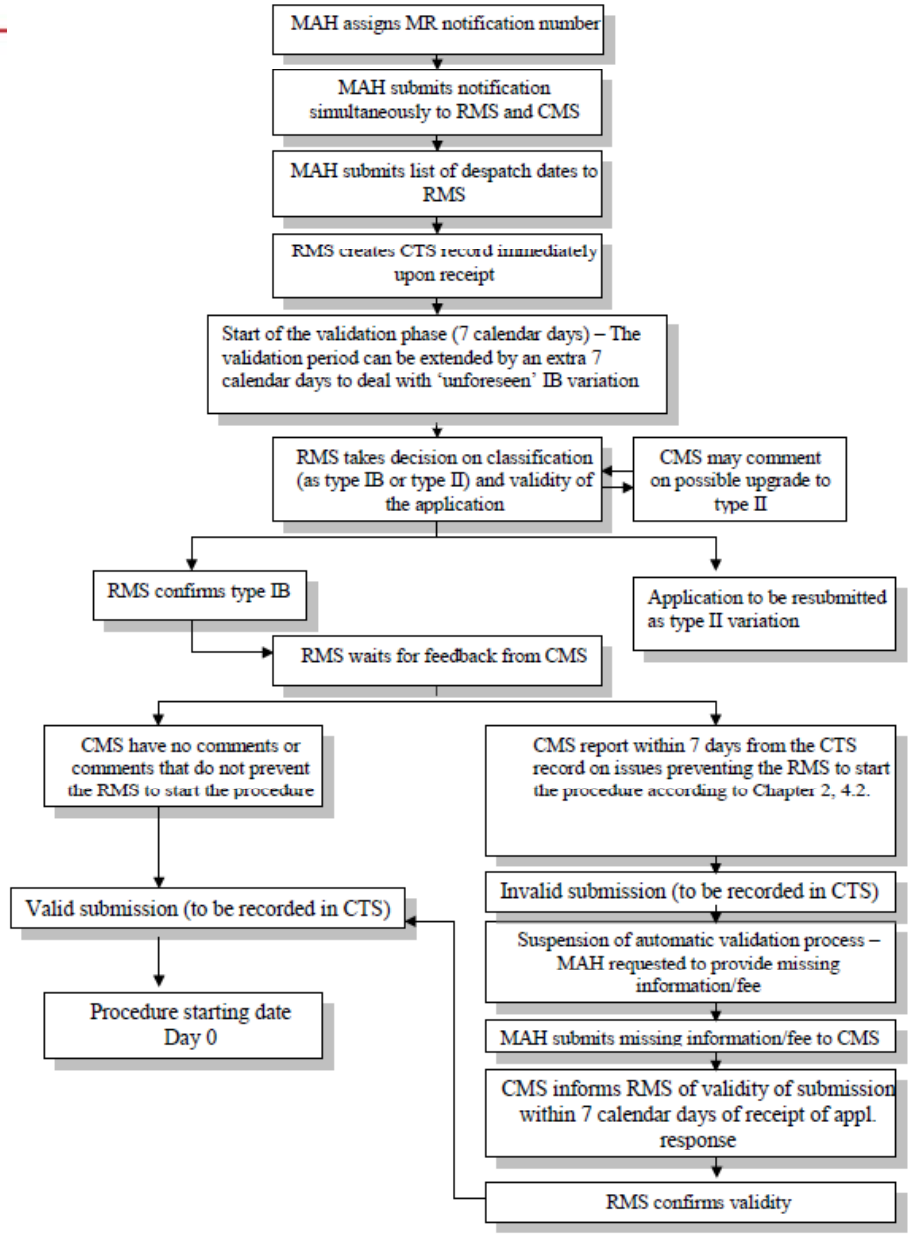
TIME-TABLES (validation)

ANNEX II

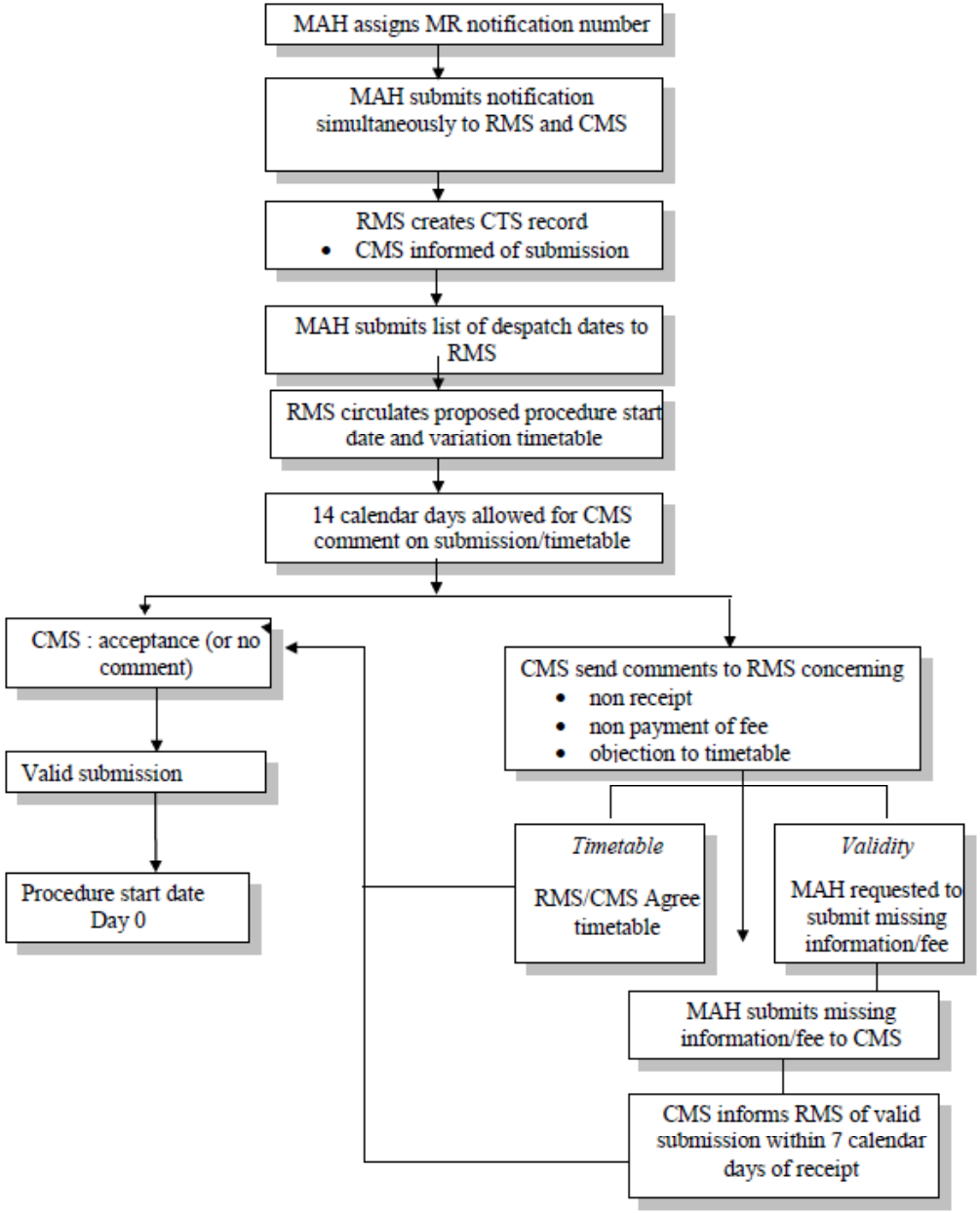
Flowchart for automatic validation: Starting the notification or variation procedure.



Type IB Notification



Type II Variation



TIME-TABLES (assessment)

Type IA

Submission phase	To the RMS and CMS the MAH submits the application accompanied by supporting documentation as appropriate. The MAH submits list of dispatch dates to the RMS.
Day 0	The RMS starts the procedure and completes the CTS record. The CMS are only informed via CTS, there will be no additional mail
Until Day 30	The RMS checks if the notification can be accepted. The CMS only checks if the notification has been received and if the fee has been paid as appropriate.
Day 30	The RMS will inform the MAH on behalf of the CMSs of the outcome of the variation notification. CMS are informed accordingly via the updated CTS record. Where applicable, the MAH provided the RMS during the procedure highlighted and clean versions of the SmPC, labelling or package leaflet in electronic format. The RMS checks the highlighted (changed) text, and circulates these documents together with a statement that it has endorsed the changes made, to the MAH and CMSs. All changes in the text, in comparison with the previously approved version of product information, should be marked with track-changes in the highlighted versions circulated at the end of procedure *or the RMS should confirm that these are unchanged since submission*. It is recommended to upload the clean documents to CTS for transfer to the MRI index."
Within 6 months after acceptance	Competent authorities should implement the decision nationally within six months.

Type IB

Submission	• MAH submits variation to the RMS and CMS and a list of dispatch dates to the RMS only. • The RMS creates a CTS record.
Day 0	The RMS starts the procedure after validation, completes the CTS record and sends an e-mail informing the MAH of the procedure start date. The CMS are only informed via CTS, there will be no additional mail.
Until Day 20	The RMS notifies the CMS on RMS position in cases of changes to the product information acc. to the C-section categories.
Until Day 27	CMS notify RMS of their comments in case of changes to the product information acc. to the C-section categories, product name and pack size.
Day 30	• If the variation cannot be accepted by the RMS, taking into account the CMS comments the RMS circulates the 'Notification with Grounds' to the CMS and MAH and the clock stops. • If the variation can be accepted by the RMS, taking into account the CMS comments, the RMS circulates an acceptance notification to the MAH and informs the CMS by updating CTS and the procedure ends. Where applicable, the MAH provided the RMS during the procedure highlighted and clean versions of the SmPC, labelling and/or package leaflet in electronic format, The RMS checks the highlighted (changed) text, and circulates these documents together with a statement that it has endorsed the changes made, to the MAH and CMS. All changes in the text, in comparison with the previously approved version of product information, should be marked with track-changes in the highlighted versions circulated at the end of procedure. It is recommended to upload the clean documents to CTS for transfer to the MRI index.
Clock stop	Within 30 days of receipt of the 'Notification with Grounds', the MAH submits an amended notification to the RMS and CMS and a list of dispatch dates to the RMS only. Where applicable, national translations updated in accordance with requests for amendment raised in the 'Notification with Grounds', have to be submitted in the amended notification.

Type IB

New Day 0	The RMS restarts the clock, updates CTS and sends an email informing the MAH that the procedure has restarted. The CMS are only informed via CTS, there will be no additional mail.
Until New Day 20	The RMS notifies the CMS on RMS position in case of changes to the product information acc. to the C-section categories.
Until New Day 27	CMS notify RMS of their comments in case of changes to the product information acc. to the C-section categories, product name and pack size.
New Day 30	• If the variation can be accepted by the RMS, taking into account the CMS comments the RMS circulates an acceptance notification to the MAH and informs the CMS by updating CTS the procedure ends. Where applicable, the MAH provided the RMS highlighted and clean versions of the SmPC, labelling and/or package leaflet in electronic format, The RMS checks the highlighted (changed) text, and circulates these documents together with a statement that it has endorsed the changes made, to the MAH and CMS. All changes in the text, in comparison with the previously approved version of product information, should be marked with track-changes in the highlighted versions circulated at the end of procedure. It is recommended to upload the clean documents to CTS for transfer to the MRI index.
	• If the variation cannot be accepted by the RMS, taking into account the CMS comments, the RMS circulates a rejection notification to the CMS and MAH and the procedure ends.
Within 6 months after acceptance	Competent authorities should implement the decision nationally within six months.

Flow-charts of the type II variation procedures:

Recommended reduced (30-day) procedure for type II variations

Day 0	Start of the procedure, RMS notifies the timetable to the CMS's by CTS and to the MAH by email
Day 15	RMS circulates the PVAR to the CMS's and to the MAH
Day 20	CMS's send the possible comments on the PVAR to the RMS
Day 21	RMS sends the request for supplementary information to the MAH and the CMS's, clock stop
Clock off period	Should not be longer than 10 + 10 days (10 days for the MAH to provide the responses and 10 days for the RMS to prepare the FVAR)
Day 22	RMS circulates the FVAR to the CMS's and to the MAH
Day 25	CMS's send the possible comments on the FVAR to the RMS
Day 30	End of the procedure, the RMS notifies the completion of the procedure and, when applicable, circulates both highlighted and clean versions of the endorsed, finalised SmPC/PL/labelling to the CMS's and the MAH

60-day procedure for type II variations

Day 0	Start of the procedure, RMS notifies the timetable to the CMS's by CTS and to the MAH by email
Day 40	RMS circulates the PVAR to the CMS's and to the MAH
Day 55	CMS's send the possible comments on the PVAR to the RMS
Day 59	RMS sends the request for supplementary information to the MAH and the CMS's, clock stop
Clock off period	Should not be longer than 60 + 60 days (60 days for the MAH to provide the responses and 60 days for the RMS to prepare the FVAR)
Day 60	RMS circulates the FVAR to the CMS's and to the MAH
Day 75	The possible break-out meeting
Day 80	CMS's send the possible comments on the FVAR to the RMS
Day 90	End of the procedure, the RMS notifies the completion of the procedure and, when applicable, circulates both highlighted and clean versions of the endorsed, finalised SmPC/PL/labelling to the CMS's and the MAH

90-day procedure for type II variations

Day 0	Start of the procedure, RMS notifies the timetable to the CMS's by CTS and to the MAH by email
Day 70	RMS circulates the PVAR to the CMS's and to the MAH
Day 85	CMS's send the possible comments on the PVAR to the RMS
Day 89	RMS sends the request for supplementary information to the MAH and the CMS's, clock stop
Clock off period	Should not be longer than 90 + 60 days (90 days for the MAH to provide the responses and 60 days for the RMS to prepare the FVAR)
Day 90	Re-start of the procedure. RMS circulates the FVAR to the CMSs and to the MAH
Day 105	The possible break-out meeting
Day 110	CMS's send the possible comments on the FVAR to the RMS
Day 120	End of the procedure, the RMS notifies the completion of the procedure and, when applicable, circulates both highlighted and clean versions of the endorsed, finalised SmPC/PL/labelling to the CMS's and the MAH

Flow chart - Worksharing Procedure
where the reference authority is the competent authority of a member state

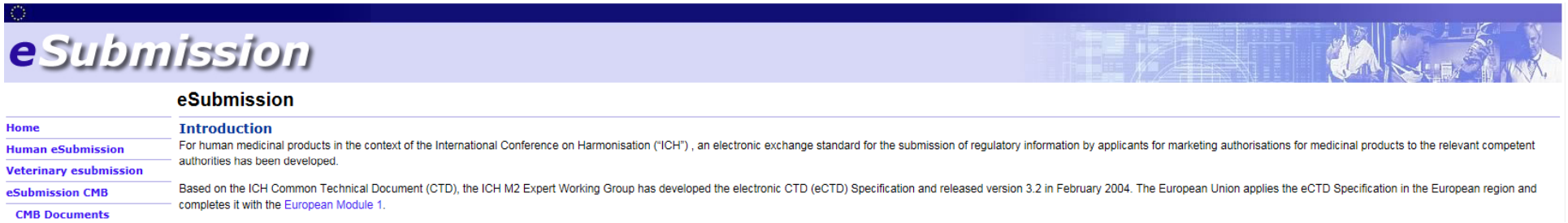
Recommended reduced (30-day) procedure	
Day 0	Start of the procedure, the reference authority notifies the timetable to the CMS's by CTS and to the MAH by email
Day 15	Reference authority circulates the PVAR to the CMS's and to the MAH
Day 20	CMS's send the possible comments on the PVAR to the reference authority
Day 21	Reference authority sends the request for supplementary information to the MAH and the CMS's, clock stop
Clock off period	Should not be longer than 10 + 10 days (10 days for the MAH to provide the responses and 10 days for the reference authority to prepare the FVAR)
Day 22	Reference authority circulates the FVAR to the CMS's and to the MAH
Day 25	CMS's send the possible comments on the FVAR to the reference authority
No later than day 30	If a CMS does not agree with the final opinion of the reference authority on grounds of potential serious risk to public health, the reference authority is requested to refer the application to CMDh.
Day 30	The reference authority circulates the final opinion to the CMS's and the MAH. If applicable, it is the responsibility of the applicant to provide the updated SmPC/PL/labelling (both annotated version in which all changes approved during the procedure have been marked, and clean versions to the RMSs/MSs involved in the WS procedure
Day 30	If not referred to CMDh, the final opinion is considered approved by CMS

60-day procedure	
Day 0	Start of the procedure, the reference authority notifies the timetable to the CMS's by CTS and to the MAH by email
Day 40	Reference authority circulates the PVAR to the CMS's and to the MAH
Day 55	CMS's send the possible comments on the PVAR to the reference authority
Day 59	Reference authority sends the request for supplementary information to the MAH and the CMS's, clock stop
Clock off period	Should not be longer than 60 + 60 days (60 days for the MAH to provide the responses and 60 days for the reference authority to prepare the FVAR)
Day 60	Reference authority circulates the FVAR to the CMS's and to the MAH
Day 75	The possible break-out meeting
Day 80	CMS's send the possible comments on the FVAR to the reference authority

No later than day 90	If a CMS does not agree with the final opinion of the reference authority on grounds of potential serious risk to public health, the reference authority is requested to refer the application to CMDh.
Day 90	The reference authority circulates the final opinion to the CMS's and the MAH. If applicable, it is the responsibility of the applicant to provide the updated SmPC/PL/labelling (both annotated version in which all changes approved during the procedure have been marked, and clean versions to the RMSs/MSs involved in the WS procedure
Day 90	If not referred to CMDh, the final opinion is considered approved by CMS

90-day procedure	
Day 0	Start of the procedure, the reference authority notifies the timetable to the CMS's by CTS and to the MAH by email
Day 70	Reference authority circulates the PVAR to the CMS's and to the MAH
Day 85	CMS's send the possible comments on the PVAR to the reference authority
Day 89	Reference authority sends the request for supplementary information to the MAH and the CMS's, clock stop
Clock off period	Should not be longer than 90 + 60 days (90 days for the MAH to provide the responses and 60 days for the reference authority to prepare the FVAR)
Day 90	Reference authority circulates the FVAR to the CMS's and to the MAH
Day 105	The possible break-out meeting
Day 110	CMS's send the possible comments on the FVAR to the reference authority
No later than day 120	If a CMS does not agree with the final opinion of the reference authority on grounds of potential serious risk to public health, the reference authority is requested to refer the application to CMDh.
Day 120	The reference authority circulates the final opinion to the CMS's and the MAH. If applicable, it is the responsibility of the applicant to provide the updated SmPC/PL/labelling (both annotated version in which all changes approved during the procedure have been marked, and clean versions to the RMSs/MSs involved in the WS procedure
Day 120	If not referred to CMDh, the final opinion is considered approved by CMS

key document: eCTD



An **eCTD** is the electronic submission of registration files that are organized according to the version 3.2 of the ICH eCTD specifications and the current version of the EU Module 1 specifications. In other words, an eCTD is the submission of (mostly) PDF leaf documents, stored in the eCTD directory structure, crucially accessed through the XML backbone (index.xml) and with the files integrity guaranteed by the MD5 Checksum.

http://esubmission.ema.europa.eu/index.htm

Use of eCTD for centrally authorised products

This step can be considered completed since all dossiers in the Centralised Procedure (CP) are handled in eCTD format.

Use of eCTD for new MAA in DCP by 1 July 2015

This step can be considered completed since applications for marketing authorisation within the Decentralised Procedure (DCP) are submitted in eCTD format since 1 July 2015. No major problems with this step have been identified.

Use of eCTD for new MAA in MRP by 1 January 2017

This step can be considered completed since applications for marketing authorisation within the Mutual Recognition Procedure (MRP) are submitted in eCTD format since 1 January 2017. No major problems with this step have been identified.

Use of eCTD for all regulatory activities in European procedures (DCP/MRP) by **1 January 2018**

This refers to all submission types for a dossier such as variations, renewals, PSURs, ASMFs and so on.

Use of eCTD for new MAA in NP by **1 July 2018**

This step has been added to the updated version of the eSubmission Roadmap to strive for a harmonised approached within the EU and in consultation with all NCAs.

Use eCTD for all regulatory activities in National Procedures (NP) by **1 January 2019**

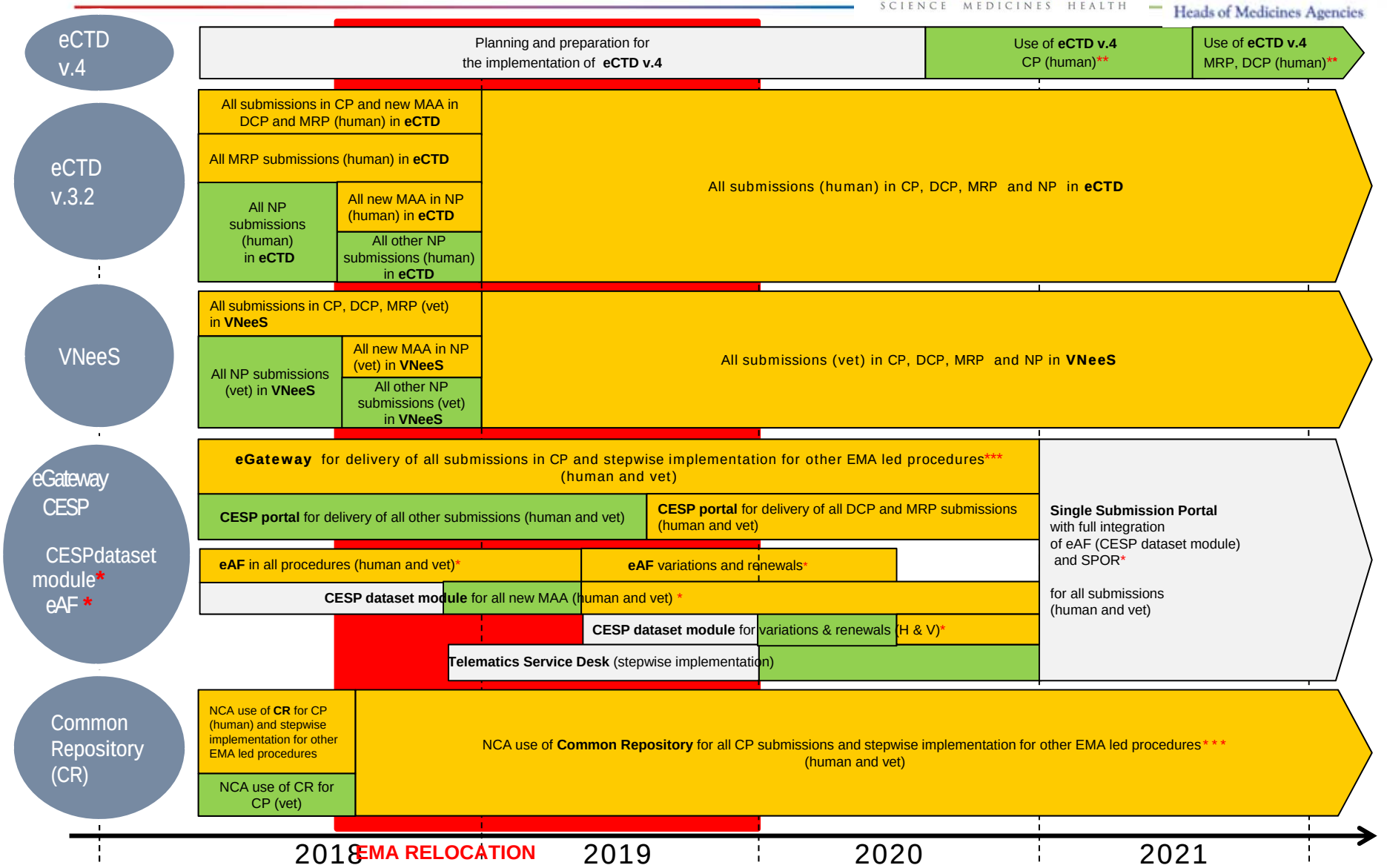
This step has been added to the updated version of the eSubmission Roadmap to have the same stepwise approach as for MRP submissions.

eSubmission Roadmap - timelines

(reflecting version 2.1 dated 28 February 2018)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HMA
Heads of Medicines Agencies



Planning in progress
Ongoing or optional
Mandatory

*) The SPOR project will stepwise (see specific Roadmap) deliver master data services (RMS, OMS, SMS, PMS) to be integrated with the eAF and CESP dataset module. Currently, the mandatory use of OMS is planned for Q4 2018, subject to outcomes of further planning exercise.

) Timelines subject to planning *) Some procedure types are excluded

key document: QP declaration

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 May 2014
EMA/196292/2014
Compliance and Inspections Department

Guidance for the template for the qualified person's declaration concerning GMP compliance of active substance manufacture "The QP declaration template"

21 May 2014
EMA/334808/2014
Compliance and Inspections Department

Qualified Person's declaration concerning GMP compliance of the active substance manufacture "The QP declaration template"

Reference Number _____

PART A: Concerned active substance manufacturing sites

Name of Active Substance:

Name and Address of Active Substance Manufacturing Site[1,2]	**Manufacturing Operation / Activity**[3]

1. List each site involved in the synthesis of the active substance beginning with the introduction of the designated active substance starting material, include intermediate manufacturing sites / part–processing sites.
2. State the site name and address in detail, including the building numbers (if applicable).
3. For example – Full or partial manufacture of the active substance, micronisation.

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	**MIAH Number**	**Manufacturing Activity**

"This declaration is made on behalf of all the involved QPs named on the relevant MIAH(s) specified in Part B"

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) ☐ 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]

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

"In the case of third party audit(s), I have evaluated each of the named contract acceptor(s) given in Part C and that technical contractual arrangements are in place and that any measures taken by the contract giver(s) are documented e.g. signed undertakings by the auditor(s)."

Sources of useful information

CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

CMDh QUESTIONS & ANSWERS
QP DECLARATION

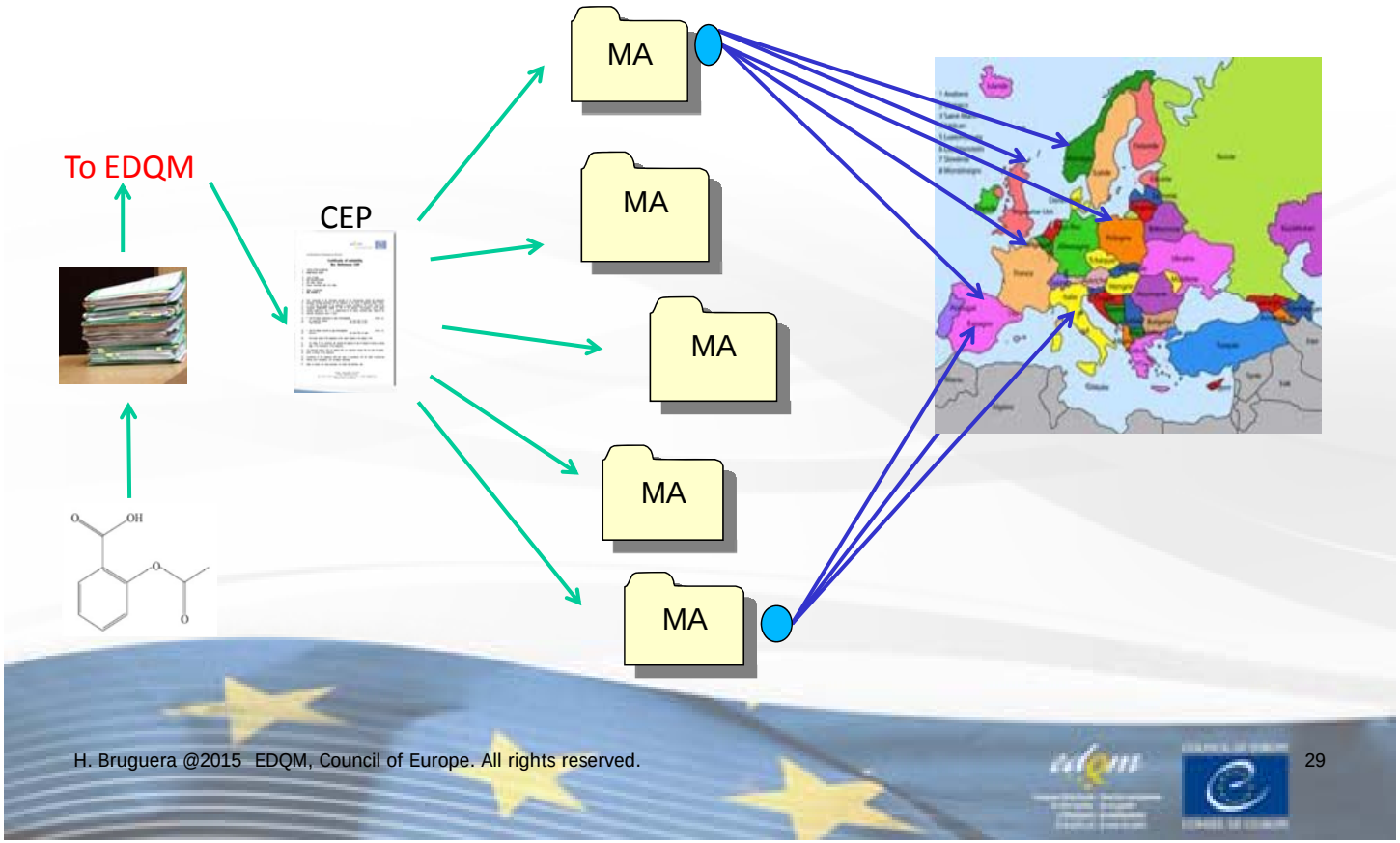
Doc. Ref.: CMDh/340/2015, Rev.1
December 2015

Examples of critical cases where a “simple” Type IA variation may not be sufficient to cover the proposed change(s)

B.III.1 Submission of a new or updated Ph. Eur. Certificate of suitability

an example of a “simple” type IA variation, where MAHs often do not consider the possibility that some relevant aspects (i.e. micronization, particle-size distribution, dilution, potential viral safety, sterilization) are not covered by CEP procedure and therefore other variations could be necessary to add the new API manufacturer into the Dossier.

CEP



CEP and Module 3

- Retest period is optional
  - If mentioned on the CEP, stability data have been assessed
  - If NOT mentioned => stab data not assessed. Either the substance is tested just before use, or stability data may be submitted in the Marketing Application.
- Sterility: IF mentioned in a subtitle
  - The validation of the sterilisation process has been submitted and assessed
  - This is mentioned on the CEP
  - The site is under a systematic inspection programme
  - Anyway, sterilisation information should be included in the Marketing Application

CEP and Module 3

- Grades (eg. Micronised) are optional
  - If approved, mentioned as subtitle + specification + method
  - If NOT mentioned on the CEP => not assessed. May be submitted in the Marketing Application
- Polymorphism:
  - Some substances show polymorphism. Often mentioned in the monograph
  - If the company claims a specific form: mentioned as subtitle + specification + method
  - If NOT mentioned on the CEP => not assessed. To be checked in the Marketing Application

What may be covered (or not)

- Production Section
  - In some monographs
  - Compliance must be ensured, but generally not by a routine test
  - For a chemical test: assessed at the Certification level
  - For criteria related to viral safety, etc, NOT assessed at the Certification level
- Use of materials of animal or human origin:
  - For information to users and authorities.
- Compliance of individual batches are not covered by a CEP and batch data are needed

What should be addressed at the level of the MAA ?

- EDQM assessment is performed taking into account the ‘general’/common use of the substance,
- specific uses should be addressed at the level of the MAA
- And a CEP may not address all parameters relevant for the specific use in the finished product e.g. physico-chemical characteristics, Production section, stability data for a retest period (only if absent on CEP).... additional data needed

B.III.1 Submission of a new or updated Ph. Eur. Certificate of suitability

Examples (where specific details are given):

European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R0-CEP

1 *Name of the substance:*
2 **AMOXICILLIN SODIUM**
3 Sterile

4 *Name of holder:*

B.III.1 Submission of a new or updated Ph. Eur. Certificate of suitability

Examples (where specific details are given):

31 The re-test period of the substance is 2 years if stored in depyrogenated aluminium canister
32 sealed with chlorobutyl rubber stopper and with aluminium tear off seal.

33 The substance is sterile and shall comply with the test for sterility (2.6.1.) of the European
34 Pharmacopoeia. The method used for sterilisation is a sterile filtration and the sterilisation
35 process has been assessed and approved.

B.III.1 Submission of a new or updated Ph. Eur. Certificate of suitability

Examples (where specific details are given):

European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R0-CEP

1 *Name of the substance:*
2 **AMOXICILLIN TRIHYDRATE**
3 Compacted

4 *Name of holder:*

32 — Test for particle size (Annex 3)
33 0% of particles ≥ 850 µm (20 mesh)
34 not less than 75% of particles < 850 µm and > 180 µm (20-80 mesh)
35 not more than 25% of particles ≤ 180 µm (80 mesh)

B.III.1 Submission of a new or updated Ph. Eur. Certificate of suitability

Examples (where some details are missing):

- In case the re-test period is not stated in the CEP and MAH wants to include a re-test period for the API: grouping (IB) of B.III.1.a Submission of a new or updated European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph (active substance, IA) and B.I.d.1.a.4 Change in the re-test period/storage period (or storage conditions) of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier: Extension or introduction of a re-test period/storage period supported by real time data (IB).

B.III.1 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: **For an active substance** **For a starting material/reagent/intermediate used in the manufacturing process of the active substance** **For an excipient**	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.			
1. New certificate from an already approved manufacturer	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA_{IN}**
2. Updated certificate from an already approved manufacturer	**1, 2, 3, 4, 8**	**1, 2, 3, 4, 5**	**IA**
3. New certificate from a new manufacturer (replacement or addition)	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA_{IN}**

B.III.1 Submission of a new or updated Ph. Eur. Certificate of suitability

Conditions	
1.	The finished product release and end of shelf life specifications remain the same.
2.	Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3.	The manufacturing process of the active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
4.	For active substance only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier.
5.	The active substance/starting material/reagent/intermediate/excipient is not sterile.

B.III.1 Submission of a new or updated Ph. Eur. Certificate of suitability

Examples:

- Micronization [and particle-size distribution] or sterilization: grouping of B.III.1.a Submission of a new or updated European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph (active substance, IB if condition 2 or 5 is not met) and what?

B.III.1 Submission of a new or updated Ph. Eur. Certificate of suitability

B.I ACTIVE SUBSTANCE

B.I.a) Manufacture

B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
h) Addition of an alternative sterilisation site for the active substance using a Ph.Eur. method		**1, 2, 4, 5, 8**	**IB**
i) Introduction of a new site of micronisation	**2, 5**	**1, 4, 5, 6**	**IA**

5.	The particle size specification of the active substance and the corresponding analytical method remain the same.

micronization

	declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances - see the note under variation no. B.II.b.1.

sterilization

8.	Proof that the proposed site is appropriately authorised for the pharmaceutical form or product or manufacturing operation concerned, i.e.:
	For a manufacturing site within the EU/EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMP database will suffice.
	For a manufacturing site outside the EU/EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority.
	For a manufacturing site outside the EU/EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EU/EEA. A reference to the EudraGMP database will suffice.

particle-size distribution (when relevant)

- In case it is necessary to set or modify particle-size specification:

B.I.b) Control of active substance

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release	1, 2, 3, 4	1, 2	IAIN
b) Tightening of specification limits	1, 2, 3, 4	1, 2	IA
c) Addition of a new specification parameter to the specification with its corresponding test method	1, 2, 5, 6, 7	1, 2, 3, 4, 5, 7	IA
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	1, 2, 8	1, 2, 6	IA
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product			II
f) Change outside the approved specifications limits range for the active substance			II

5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.

B.III.1 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance For a starting material/reagent/intermediate used in the manufacturing process of the active substance For an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.			
1. New certificate from an already approved manufacturer	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA_{IN}**
2. Updated certificate from an already approved manufacturer	**1, 2, 3, 4, 8**	**1, 2, 3, 4, 5**	**IA**
3. New certificate from a new manufacturer (replacement or addition)	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA_{IN}**

Pay particular attention to the new condition n. 11

11.	If the active substance is a not a sterile substance but is to be used in a sterile medicinal product then according to the CEP it must not use water during the last steps of the synthesis or if it does the active substance must also be claimed to be free from bacterial endotoxins.

5.	New certificate for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free		**1, 2, 3, 4, 5, 6**	**IB**

6.	Suitable evidence to confirm compliance of the water used in the final steps of the synthesis of the active substance with the corresponding requirements on quality of water for pharmaceutical use.

Attività

- Registrazione
- Sicurezza
- Difetti di qualità
- PCA - Programma di controllo annuale
- Carenze e indisponibiltà
- Batch Release per i medicinali immunologici e i medicinali derivati dal sangue e dal plasma (umano)
- Revoche di AIC su rinuncia del Titolare
- Contrasto al crimine farmaceutico
- Ispezioni
- Negoziazione e rimborsabilità
- Consumi e spesa farmaceutica
- Informazione indipendente
- Sperimentazione e ricerca
- Registri Farmaci sottoposti a monitoraggio
- Rapporti Internazionali
- Affari amministrativi

Questa notizia è disponibile anche in ...

Attualità area Azienda
Ambiti di attività - Registrazione
Tutte le attualità

Precisazioni AIFA sulla presentazione di variazioni all'AIC - tipologia B.III.1. (23/01/2015)

Avviso alle aziende farmaceutiche

23/01/2015

Si porta all'attenzione di tutte le aziende farmaceutiche che, nell'ambito delle variazioni di tipologia B.III.1.a, deve essere attentamente valutato il rispetto della condizione 11 ove prevista, considerando quanto espressamente indicato negli "Orientamenti del 16.05.2013 riguardanti i particolari delle diverse categorie di variazioni". Pertanto si evidenzia che nell'ambito delle variazioni dei termini delle autorizzazioni all'immissione in commercio di medicinali, ai sensi del Regolamento (CE) n. 1234/2008 della Commissione e successive modificazioni, la presentazione di un nuovo Certificato di conformità alla Farmacopea Europea (per un produttore nuovo o già autorizzato) per una sostanza attiva non sterile da utilizzare in un medicinale sterile, nei casi in cui, in base a quanto riportato nel CEP, l'acqua è utilizzata nelle ultime fasi della sintesi e nel Certificato stesso la sostanza non è indicata essere priva di endotossine, non può essere presentata come tipo IAin per il mancato rispetto della condizione 11. Pertanto in tale situazioni la modifica deve essere sottomessa come variazione di tipo IB, preferibilmente come tipologia B.III.1.a.5, specifica per questi casi citati. In tutti i casi la documentazione a supporto della variazione dovrà contenere anche il documento previsto al punto 6 della relativa check-list (prove opportune che attestino la conformità dell'acqua utilizzata nelle fasi finali della sintesi del principio attivo ai corrispondenti requisiti in materia di qualità delle acque per uso farmaceutico - si veda a tal proposito la linea-guida CPMP/QWP/158/01 Rev. 1 Quality of Water for Pharmaceutical Use).

Quality of Water

- By default the minimum acceptable quality of the water is potable water (see CPMP/CVMP NfG on quality of water for pharmaceutical use (CPMP/QWP/158/01 Revision & EMEA/CVMP/115/01 Revision).
- Only when a special grade/quality for the substance (e.g. sterile and/or free from bacterial endotoxins) is mentioned as sub-title on the CEP, or when only one route of administration is known, will a specific quality of water be expected & assessed.
- When water is used in the lasts steps, this is mentioned on the CEP

AIFA AGENZIA ITALIANA DEL FARMACO
Tutela Ricerca e Sviluppo per la Salute

edqm European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R1-CEP

1 *Name of the substance:*
2 **APROTININ**
3
4 Bacterial endotoxin free

36 In the last steps of the synthesis water for injections is used as solvent.

B.III.1 Submission of a new or updated Ph. Eur. Certificate of suitability

Conditions	
1.	The finished product release and end of shelf life specifications remain the same.
2.	Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3.	The manufacturing process of the active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
4.	For active substance only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier.
5.	The active substance/starting material/reagent/intermediate/excipient is not sterile.

CEPs & animal derived material

- when a product of animal origin is used for the manufacture of a non-biological substance (eg. Use of a peptone in a fermentation medium, preparation of amino acids from poultry feather, etc). The following applies :
- If there is a TSE risk, this is assessed within Certification, 'double CEP', (references to specific & TSE general monograph);
- If non-ruminant material, Viral safety is not considered, and the CEP carries a sentence "the holder of the certificate has declared the use of substance of human or animal origin in the manufacture". Viral safety data is not assessed by EDQM even if data is provided.
- In such situations, each national licensing authority which receives the CEP in a marketing authorisation application has to consider if viral safety should be evaluated.

B.III.1 Submission of a new or updated Ph. Eur. Certificate of suitability

Certification of Substances Division

Certificate of suitability
No. R0-CEP

1 *Name of the substance:*
2 **AMOXICILLIN SODIUM**

3 *Name of holder:*

37 The holder of the certificate has declared the use of material of human or animal origin in the
38 manufacture of the substance.

B.III.1 Submission of a new or updated Ph. Eur. Certificate of suitability

European Directorate for the Quality of Medicines & HealthCare

COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Certification of Substances Division

Certificate of suitability
No. R0-CEP

1 *Name of the substance:*
2 **URSODEOXYCHOLIC ACID**

3 *Name of holder:*

13 After examination of the information provided on the manufacturing method and
14 subsequent processes (including purification) for this substance on the site(s) of
15 production mentioned above, we certify that the quality of the substance is suitably
16 controlled by the current version of the monograph **URSODEOXYCHOLIC ACID**
17 no. 1275 of the European Pharmacopoeia, current edition including supplements, only if
18 it is supplemented by the test(s) mentioned below, based on the analytical procedure(s)
19 given in annex.

B.III.1 Submission of a new or updated Ph. Eur. Certificate of suitability

After examination of the information provided on the origin of raw material(s) and type of tissue(s) used and on the manufacturing process for this substance on the site(s) of production mentioned above, we certify that the substance **URSODEOXYCHOLIC ACID** meets the criteria described in the current version of the monograph Products with risk of transmitting agents of animal spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

- countries of origin of source materials: Argentina, Australia, Brazil, Canada, Colombia, Costa Rica, Paraguay, Uruguay, USA, Mexico, South Africa and India
- nature of animal tissues used in manufacture: Bovine bile

B.III.1 Submission of a new or updated Ph. Eur. Certificate of suitability

What information are necessary?

- Since viral safety is not assessed during CEP release procedure, all the necessary information assessing the risk with respect to potential contamination with adventitious agents should be provided in section 3.2.A.2 “Adventitious Agents Safety Evaluation”, as detailed in Volume 2B “Notice to Applicants” - Medicinal products for human use. This must include not only information regarding TSE risk but also any other information related to Viral Safety according to monograph Ph.E. 5.1.7.

B.III.1 Submission of a new or updated Ph. Eur. Certificate of suitability

B.II.h Adventitious Agents Safety

B.II.h.1 Update to the "Adventitious Agents Safety Evaluation" information (section 3.2.A.2)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Studies related to manufacturing steps investigated for the first time for one or more adventitious agents			**II**
b) Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier			
1) with modification of risk assessment			**II**
2) without modification of risk assessment		**1, 2, 3**	**IB**
Documentation			
1. Amendment of the relevant section(s) of the dossiers including the introduction of the new studies to investigate the capability of manufacturing steps to inactivate/reduce adventitious agents.			
2. Justification that the studies do not modify the risk assessment.			
3. Amendment of product information (where applicable).			

Also note that updated section 3.2.A.2 with essential information (Ph.E. 5.1.7.) may be acceptable within type IB variation if new viral inactivation studies are not necessary.

B.III.1 Submission of a new or updated Ph. Eur. Certificate of suitability

Other issues related to CEP presentation:

- Is it acceptable that some of the sites reported in the CEP are not included in the Dossier?

- How to find information about possible sites of production of intermediates, which should be subjected to QP declaration for GMP compliance (document 5 of the check-list)?

CEP & sites of manufacture

- Content of CEPs was changed in July 2013
- All CEPs (new and revised) granted since then carry:
  - Holder details on the CEP
  - Sites involved in the manufacture of a substance, after the introduction of starting materials
    - Annex 1 to CEPs

CEPs granted before...

- They contain:
  - Holder
  - Manufacturer of the final substance
  - Manufacturer of crude, last intermediate before salification, etc
- Users of CEP/customers need to obtain more detailed information from CEP holder

(in the new certificates, now in Annex 1)

Certification of Substances Division

Certificate of suitability
No. R0-CEP

Name of the substance:
AMOXICILLIN SODIUM

Name of holder:

Site(s) of production:
(last intermediate) (final substance)

(last intermediate)

(last intermediate)

AGENZIA ITALIANA DEL FARMACO
Tutela Ricerca e Sviluppo per la Salute

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 May 2014
EMA/196292/2014
Compliance and Inspections Department

Guidance for the template for the qualified person's declaration concerning GMP compliance of active substance manufacture "The QP declaration template"

Thank you for your attention!

CONTACTS
Dr. Marco Franceschin
Ufficio Procedure Post Autorizzative
Medicinal Products Authorization Dept.
Italian Medicines Agency
Via del Tritone, 181 - 00187 Roma
m.franceschin@aifa.gov.it