Variazioni: inquadramento normativo e criticità nelle applicazioni- Focus sulle variazioni di qualità

Elisabetta Tribulato

MASTER UNIVERSITARIO DI II LIVELLO IN TECNOLOGIE FARMACEUTICHE E ATTIVITA' REGOLATORIE

Università di Pavia

28/04/2023

Dichiarazione di trasparenza/interessi*

Le opinioni espresse in questa presentazione sono personali e non impegnano in alcun modo l'AIFA

Interessi nell'industria farmaceutica	NO	Attualmente	Da 0 a 3 anni precedenti	oltre 3 anni precedenti
INTERESSI DIRETTI:				
1.1 Impiego per una società: Ruolo esecutivo in una società farmaceutica	X	☐	☐	☐ obbligatorio
1.2 Impiego per una società: Ruolo guida nello sviluppo di un prodotto farmaceutico	X	☐	☐	☐ obbligatorio
1.3 Impiego per una società: altre attività	X	☐	☐	☐ facoltativo
2. Consulenza per una società	X	☐	☐	☐ facoltativo
3. Consulente strategico per una società	X	☐	☐	☐ facoltativo
4. Interessi finanziari	X	☐	☐	☐ facoltativo
5. Titolarità di un brevetto	X	☐	☐	☐ facoltativo
INTERESSI INDIRETTI:				
6. Sperimentatore principale	X	☐	☐	☐ facoltativo
7. Sperimentatore	X	☐	☐	☐ facoltativo
8. Sovvenzioni o altri fondi finanziari	X	☐	☐	☐ facoltativo
9. Interessi Familiari	☐	X	☐	☐ facoltativo

* Elisabetta Tribulato, secondo il Regolamento per la disciplina dei conflitti di interesse all'interno dell'Agenzia Italiana del Farmaco approvato dal CdA AIFA con Delibera n. 37 del 13 ottobre 2020.

N.B. Il compenso ricevuto per questo intervento è regolato dalla contrattazione collettiva.

- Decreto Legislativo n. 2019 del 24 aprile 2006
- Regolamento n. 1234/2008 e s.m.i
- Classification Guideline
- Best Practice Guides –CMDh
- Question & Answers – CMDh & EMA
- European Pharmacopoeia Certificate of suitability (CEP)
- Qualified Person declaration

DECRETO LEGISLATIVO 24 aprile 2006, n. 219
Attuazione della direttiva 2001/83/CE (e successive direttive di modifica) relativa ad un codice comunitario concernente i medicinali per uso umano, nonché della direttiva 2003/94/CE.

→ *Articolo 6, comma 1)*
Nessun medicinale puo`essere immesso in commercio sul territorio nazionale senza aver ottenuto ***un'autorizzazione*** *dell'AIFA o un'autorizzazione comunitaria a norma del regolamento (CE) n. 726/2004 in combinato disposto con il regolamento (CE) n. 1394/2007.*

→ *Articolo 6, comma 2)*
Quando per un medicinale e' stata rilasciata una AIC ai sensi del comma 1, ogni ulteriore dosaggio, forma farmaceutica, via di somministrazione e presentazione, nonche' le ***variazioni*** *ed estensioni sono ugualmente soggetti ad autorizzazione ai sensi dello stesso comma 1; le AIC successive sono considerate, unitamente a quella iniziale, come facenti parte della stessa autorizzazione complessiva, in particolare ai fini dell'applicazione dell'articolo 10, comma 1.*

Registrazione prodotti medicinali: il processo di valutazione

Dossier registrativo azienda

Autorità Competenti

Output

Assessment Report A.R.

Risorse

Assessor (Esperti) –

Interni / Esterni

Legislazione e linee-guida interpretazione armonizzata

Informazioni sul prodotto

S P C

P L

. . . .

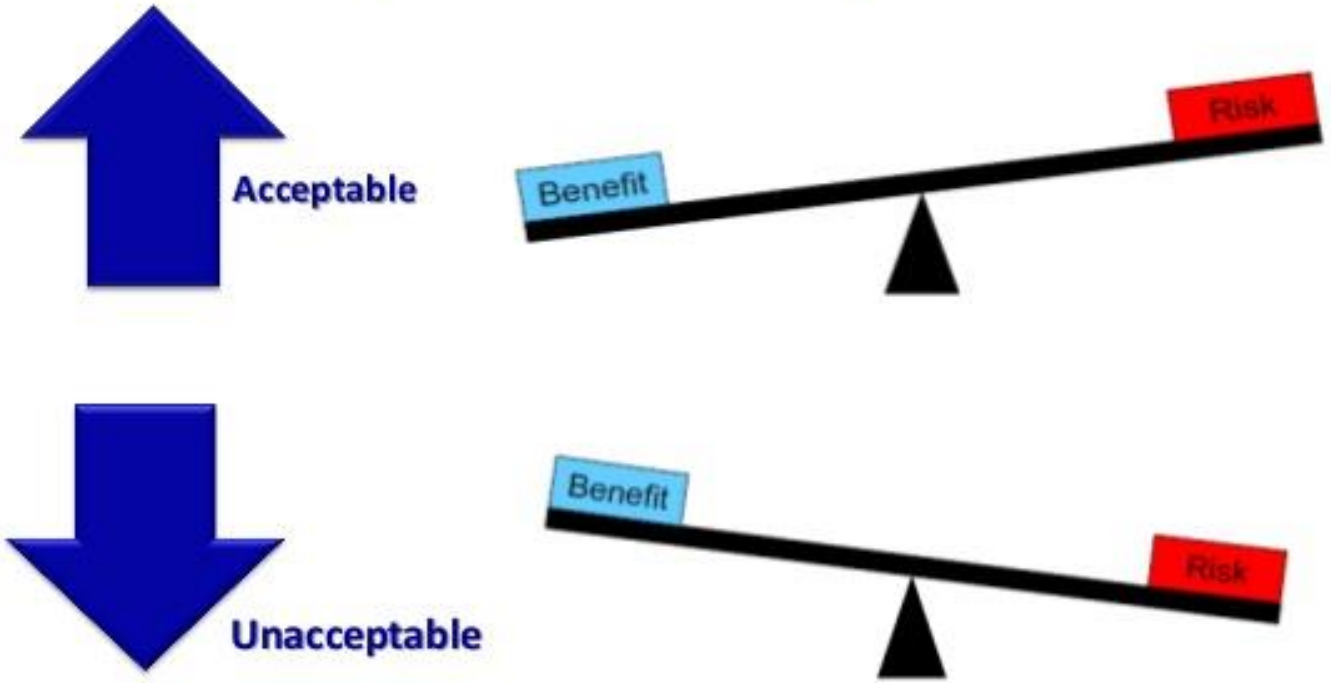
Criteri per l'autorizzazione all'immissione in commercio

MA is granted when the Benefit-Risk balance of a product is positive, meaning that benefits from use of this product outweigh risks associated with its use

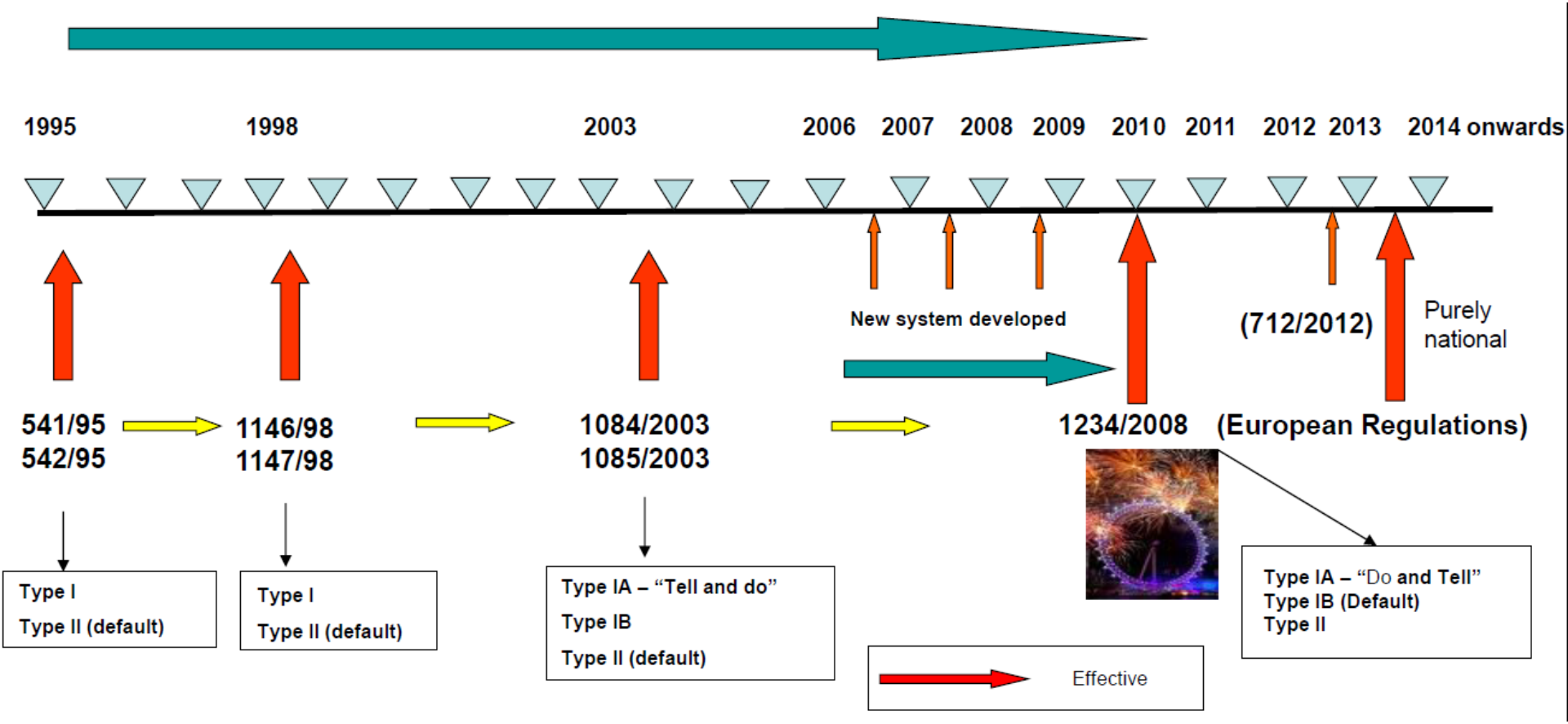
Benefits

Risks

VARIAZIONI al dossier di registrazione



European Variations System - Evolution



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New Variation Regulation

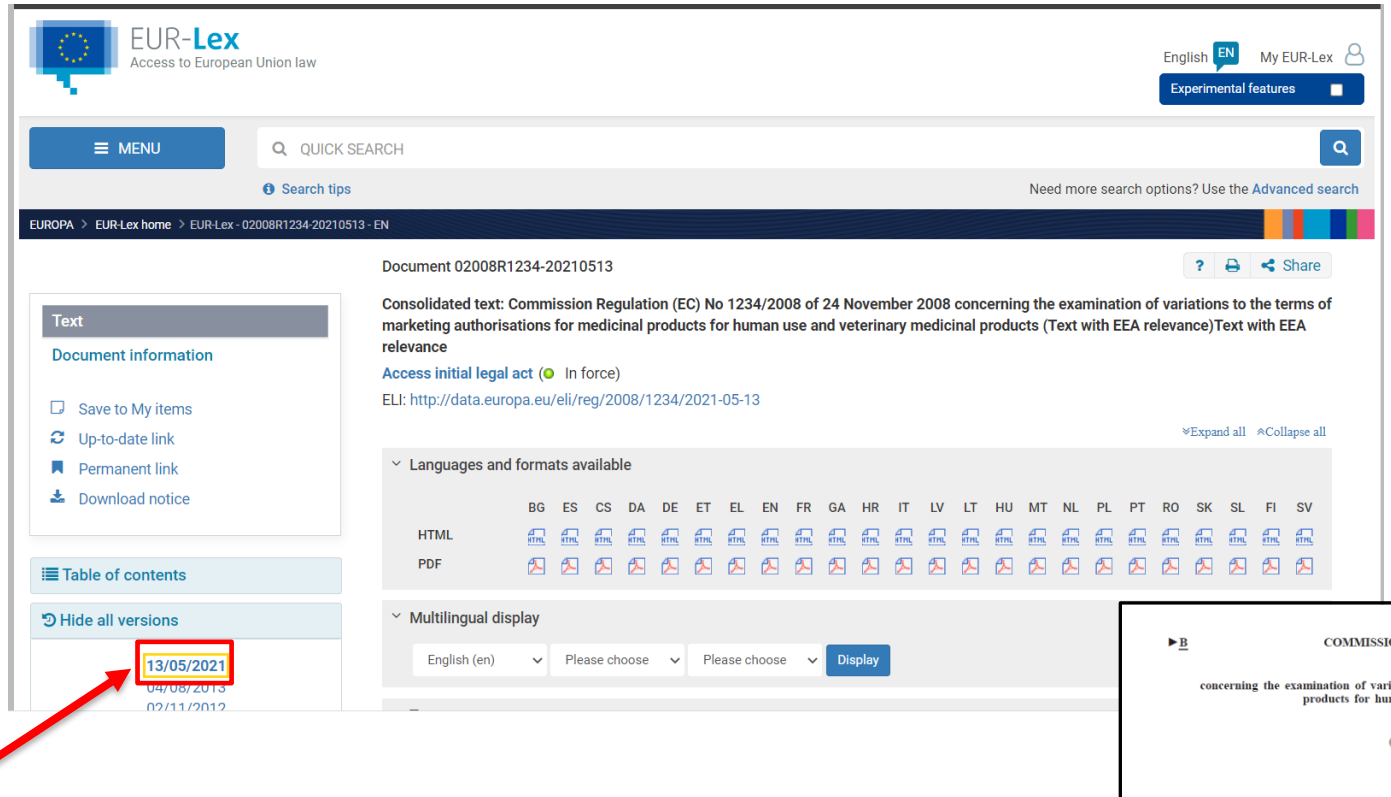
Regulation (EC) No 1234/2008

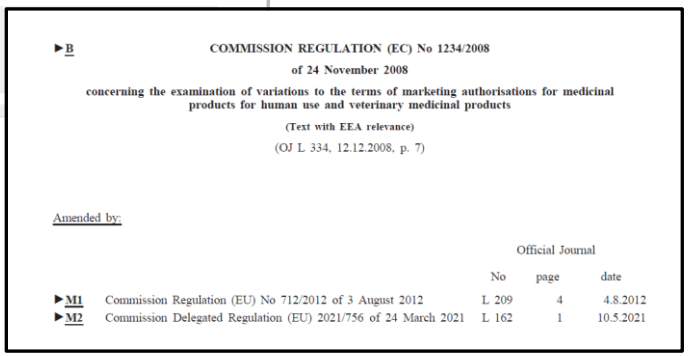
amended by EC/712/2012 (3 August 2012) and
by EU 2021/756 (24 march 2021)

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)

New Variation Regulation





►B

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

(Text with EEA relevance)

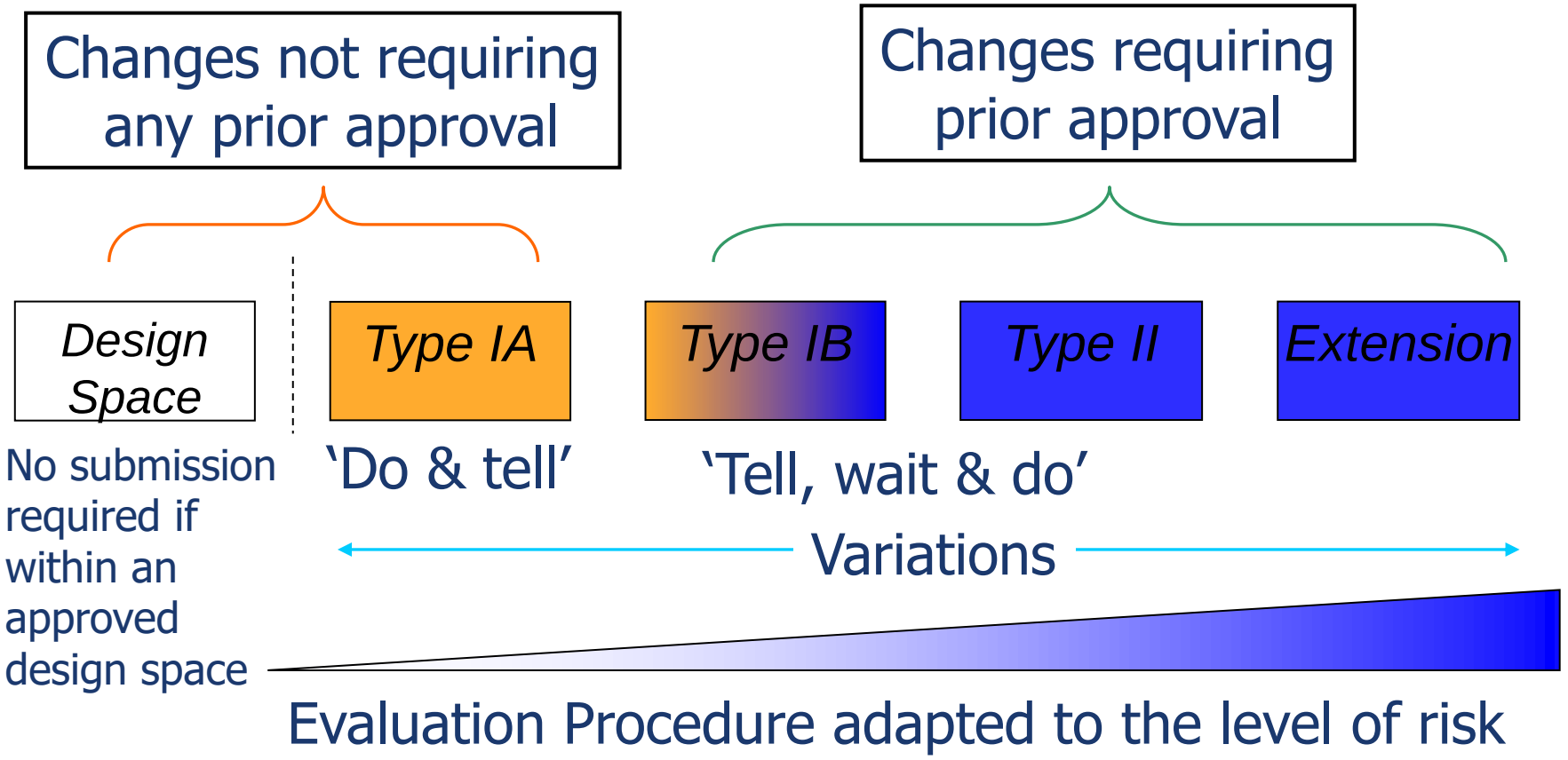
(OJ L 334, 12.12.2008, p. 7)

Amended by:

		Official Journal		
		No	page	date
►M1	Commission Regulation (EU) No 712/2012 of 3 August 2012	L 209	4	4.8.2012
►M2	Commission Delegated Regulation (EU) 2021/756 of 24 March 2021	L 162	1	10.5.2021

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02008R1234-20210513

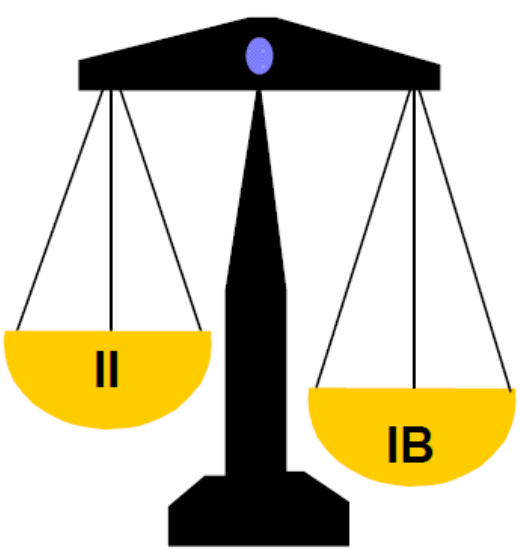
Summary - Types of Variations

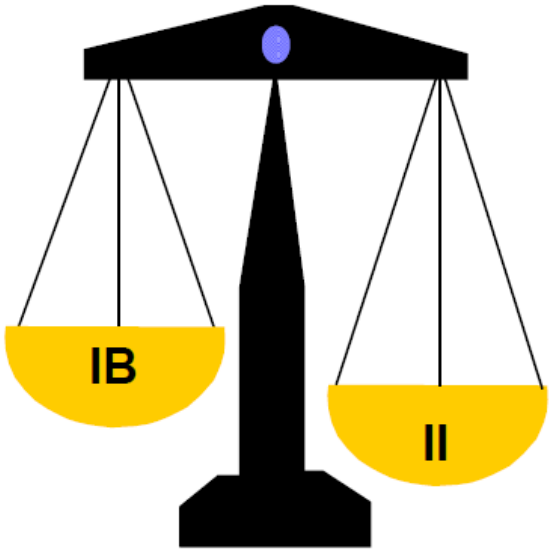


Regulation - Classification Rules

- 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.

Things to consider by applicant before submitting a “Type IB default” change as either Type IB or Type II ?





- Complexity of change
- Urgency – time to approval
- Confidence in supporting package/risk
- Timescale for response (IB (30 days),not negotiable)

Classification Guideline (key document)

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 – Structure

TOPIC / SCOPE OF CHANGES	VARIATION
A. ADMINISTRATIVE CHANGES	1-7
B. QUALITY CHANGES	
I. Active Substance	
a) Manufacture	1-5
b) Control of active substance	1-2
c) Container closure system	1-3
d) Stability	1
e) Design Space and post approval change management protocol	1-5
II. Finished Product	
a) Description and composition	1-6
b) Manufacture	1-5
c) Control of excipients	1-5
d) Control of finished product	1-3
e) Container closure system	1-7
f) Stability	1
g) Design Space and post approval change management protocol	1-5
h) Adventitious Agents Safety	1

III. CEP/TSE/monographs	1-2
IV. Medical Devices	1-3
V. Changes to a marketing authorisation resulting from other regulatory procedures	
a) PMF/VAMF	1-2
b) Referral	1
c) Other changes to the quality dossier requested by the competent authority	1
C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES	
I. Human and Veterinary medicinal products	1-12
II. Veterinary medicinal product – specific changes	1-7
D. PMF / VAMF	1-23

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	IAIN
b)	Primary packaging site	1, 2, 3, 4, 5	1, 2, 3, 4, 8, 9	IAIN
c)	Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/ immunological medicinal products, or for pharmaceutical forms manufactured by complex manufacturing processes			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 (including those that are aseptically manufactured) excluding biological/ immunological medicinal products		1, 2, 3, 4, 5, 6, 7, 8	IB

Biological/ immunological

Sterile/ non-sterile

Example – finished product manufacturer

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	IAIN
b) Primary packaging site	1, 2, 3, 4, 5	1, 2, 3, 4, 8, 9	IAIN
c) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/ immunological medicinal products, or for pharmaceutical forms manufactured by complex manufacturing processes			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 (including those that are aseptically manufactured) excluding biological/ immunological medicinal products		1, 2, 3, 4, 5, 6, 7, 8	IB

Conditions	
1.	Satisfactory inspection in the last three years by an inspection service of one of the Member States of the EU/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.

Example – finished product manufacturer

	Documentation
1.	Proof that the proposed site is appropriately authorised for the pharmaceutical form or product 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.
2.	Where relevant, the batch numbers, corresponding batch size and the manufacturing date of batches (≥ 3) used in the validation study should be indicated and the validation data presented, or validation protocol (scheme) to be submitted.
3.	The variation application form should clearly outline the "present" and "proposed" finished product manufacturers as listed in section 2.5 of the application form.
4.	Copy of approved release and end-of-shelf life specifications if relevant.
5.	Batch analysis data on one production batch and two pilot-scale batches simulating the production process (or two production batches) and comparative data on the last three batches from the previous site; batch data on the next two production batches should be available on request or reported if outside specifications (with proposed action).

Example – Active Substance manufacturer

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
a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	1, 2, 3	1, 2, 3, 4, 5, 6, 7	IAIN
b) Introduction of a manufacturer of the active substance supported by an ASMF			II
c) The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability			II
d) New manufacturer of material for which an assessment is required of viral safety and/or TSE risk			II
e) The change relates to a biological active substance or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product			II

Example – Active Substance manufacturer

B.I.a.1.a)

Conditions	
1.	For starting materials and reagents the specifications (including in process controls, methods of analysis of all materials), are identical to those already approved. For intermediates and active substances the specifications (including in process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved.
2.	The active substance is not a biological/immunological substance or sterile.
3.	Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current *Note for Guidance on Minimising the Risk of Tra* *Encephalopathy Agents via Human and Veterinary Medicinal Pr*

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), if applicable.
2.	A declaration from the marketing authorisation holder or the ASMF holder, where applicable, that the synthetic route (or in case of herbal medicinal products, where appropriate the method of preparation, geographical source, production of herbal drug and manufacturing route) quality control procedures and specifications of the active substance and of the starting material/reagent/intermediate in the manufacturing process of the active substance (if applicable) are the same as those already approved.
3.	Either a TSE Ph. Eur. Certificate of Suitability for any new source of material or, where applicable, documentary evidence that the specific source of the TSE risk material has previously been assessed by the competent authority and shown to comply with the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*. The information should include the following: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).
4.	Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the active substance from the current and proposed manufacturers/sites.
5.	The variation application form should clearly outline the "present" and "proposed" manufacturers as listed in section 2.5 of the application form for marketing authorisation.
6.	A declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a
7.	Where relevant, a commitment of the manufacturer of the active substance to inform the MA holder of any changes to the manufacturing process, specifications and test procedures of the active substance.

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 changes, which should be available at the time of implementation
B.I.a.2.z	17/12/2012	Deletion of one manufacturing process of the drug substance manufacturing processes	IA	1. There should at least remain one manufacturing process, as previously authorised. 2. The deletion should not be due to critical deficiencies concerning manufacturing
B.I.a.4.z	09/04/2013	Minor change of an analytical procedure for an in-process control.	IA	See corresponding change for the active substance: B.I.b.2.a
B.I.b) Control of active substance				
B.I.b.1.z	23/09/2019	Change in the testing frequency of specification parameter, from routine testing to skip or periodic testing	IB	N/A
		If information on the level of testing performed by the finished product manufacturer on receipt of the drug substance batches is already present in the approved registration dossier, the applicant is advised to apply for a type 1B (B.I.b.z) variation to remove this information from the dossier		

New!

B.III.2.z) CEP/TSE/MONOGRAPHS				
B.III.2.z.	23/05/2011	To reflect compliance with the Ph.Eur. and remove reference to the internal test method and test method number for active substances, excipients, active substance starting materials and immediate packaging materials *(Updated on 23/11/2015)*	IA	
B.III.2.z.	13/09/2022	Change from "novel excipient" (3.2.P.4.6) to EU Pharmacopoeial excipient (3.2.P.4.1)	IA	1. The specification of the excipient fully complies with the Ph. Eur. Monograph and all the tests in the specification correspond to the pharmacopoeial standard 2. Additional specifications to the pharmacopoeia for product specific properties are unchanged (e.g. particle size profiles, polymorphic form or, e.g. bioassays, aggregates) 3. The excipient must remain the same 4. Additional validation of a new or changed pharmacopoeial method is not required 5. The excipient was already considered not novel for the use in relation to the specific route of administration.

Grouping

Article 7

Grouping of variations

1. Where several variations are notified or applied for, a separate notification or application in accordance with Chapters II, III, or Article 19 as appropriate shall be submitted in respect of each variation sought.

2. By way of derogation from paragraph 1, the following shall apply:

(a) where the same minor variation(s) of type IA to the terms of one or more marketing authorisations owned by the same holder are notified at the same time to the same relevant authority, a single notification as referred to in Article 8 or 14 may cover all such variations;

Grouping

(b) where several variations to the terms of the same marketing authorisation are submitted at the same time, a single submission may cover all such variations provided that the variations concerned fall within one of the cases listed in Annex III;

(c) where several variations to the terms of the same marketing authorisation are submitted at the same time and the variations do not fall within one of the cases listed in Annex III, a single submission may cover all such variations provided that the competent authority of the reference Member State in consultation with the competent authorities of the Member States concerned or, in the case of a centralised marketing authorisation, the Agency agrees to such single submission.

❑ **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

- **Type IB notifications** – Key points

  - «Tell, Wait and Do» - implementantion after approval
  - 30 day procedure: scientific assessment
  - The NCA can request clarification, additional information or documentation from the MAH

- **Type II variations** – Key points
  - «Tell, Wait and Do» - implementantion after approval
  - 60 day procedure (usually): scientific assessment
  - The NCA can request clarification, additional information or documentation from the MAH

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- COVID-19
- BREXIT
- **Procedural Guidance**
  - General Info
  - Application for MA
  - eSubmissions
  - Generics

VARIATION PROCEDURE

In order to view some of the documents on this website you need **Acrobat Reader** (click here to download)

- **Best Practice Guides (BPGs) for the Submission and Processing of Variations in the Mutual Recognition Procedure**
  - **Chapter 1: CMDh BPG for the allocation of the mutual recognition variation number for Type I Notifications, Type II Variations, Grouping and Worksharing** (January 2020) [*Track version*]
  - **Chapter 2: Procedure for automatic validation of Mutual Recognition Procedures for Variations** (December 2022) [*Track version*]
  - **Chapter 3: CMDh BPG for the processing of Type IA Minor Variations (Notifications) in the Mutual Recognition Procedure** (December 2022) [*Track version*]

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

December 2022
CMDh/293/2013/Rev.25

Chapter 3 - CMDh Best Practice Guide for the processing of Type IA minor variations (notifications) in the Mutual Recognition Procedure

According to the Regulation minor variations of Type IA do not require prior approval but are 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 IAIN in the guideline.

It is possible for a MAH to include a Type IA variation in the submission of a Type IAIN 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 the CMDh 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 CMDh Best Practice Guide.

Type-IA variations: questions and answers

Share

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 (PDF/2.48 MB)

1.1. When shall I submit my Type IA/IA$_{IN}$ variation(s)? Rev. Dec 2016

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 Classification 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 which 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 ('IA$_{IN}$')

The Classification Guideline specifies which Type IA variations must be notified (submitted) **immediately** to the National Competent Authorities/European Medicines Agency ('the Agency') following implementation, in order to ensure the continuous supervision of the medicinal product.

Type IA variations NOT requiring immediate notification ('IA')

Variations which do not require immediate notification may be submitted by the marketing authorisation holder (MAH) **within 12 months** after implementation or may be submitted earlier should this facilitate dossier life-cycle maintenance or when necessary e.g. to ensure that the latest product information is reflected in Certificates of Pharmaceutical Products.

The 12 months 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 which have been implemented during the previous twelve months.

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

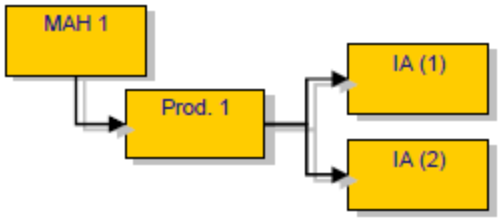
There are no recommended submission dates for Type IA. However, MAHs are encouraged to avoid submitting Type IA notifications shortly before or during the Agency holiday periods (e.g. end July and Christmas).

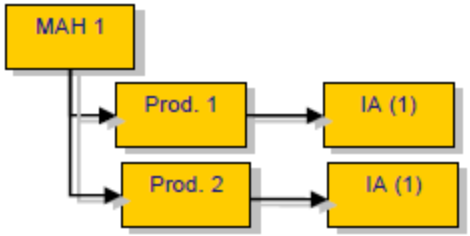
1.2. Can I group the submission of Type IA/IA$_{IN}$ variations? Can they be grouped with other types of variations? Rev. Sep 2014

Article 7(2)(a) of the Variations Regulation sets out the possibility for a MAH to group several Type IA/IA$_{IN}$ variations under a single notification to the same relevant authority, or to group them with other types of variations.

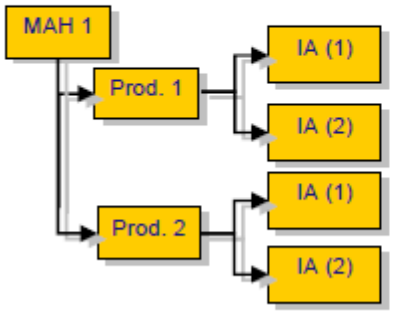
Possible grouping of Type IA/IA$_{IN}$ changes only:

- 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/IA_{IN} with other types of variations:

- Type IA/IA_{IN} 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/ IA_{IN} variations as part of a group, the legal deadlines for submission of each variation should be respected i.e. a Type IA_{IN} should always be submitted immediately, whether or not it is grouped with other variations, and any Type IA variation should always be submitted within 12 months following its 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 01/01/2022 and this site is deleted again (IA n° A.7) on 01/10/2022: 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

CMDh/132/2009, Rev.58
May 2022

Q&A - List for the submission of variations for human medicinal products according to Commission Regulation (EC) 1234/2008

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 IA_{IN} 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 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 should normally be used in the next packaging run.

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.

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.

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.

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 far as the Type IB variation is concerned, the applicant should confirm that stability data was generated in the same packaging material as was stated in the CEP dossier provided to EDQM. In addition, for those CEPs issued before 1st Sept 2011 and where no packaging material is stated in the CEP, details of the packaging materials used in the stability studies should be provided (description of the immediate container closure system, including the identity of materials of construction and if appropriate a brief description of any non-functional secondary packaging components).

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.

Chiarimenti sulla presentazione di variazioni all'AIC

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*

Accesso al farmaco >

Accesso precoce e u

Autorizzazione dei f

Farmaci carenti >

Farmaci antibiotici >

Farmaci biologici >

Vaccini >

Emoderivati >

Farmaci equivalenti

Farmaci biosimilari

Questions & Answers sui processi autorizzativi relativi a procedure Nazionali, di Mutuo Riconoscimento e Decentrate

L'Area Autorizzazioni Medicinali rende disponibile per gli stakeholders un documento contenente domande e risposte a quesiti di carattere regolatorio inerenti alle domande di AIC, di variazione e di rinnovo dell'AIC e ad altre tipologie di richieste gestite a livello nazionale, per medicinali autorizzati con procedure nazionali, di mutuo riconoscimento e decentrate, inclusa la fase nazionale di autorizzazione alla distribuzione parallela.

Il documento è concepito per essere aggiornato nel tempo quando emergono nuovi quesiti di comune interesse ai vari stakeholders o quando alcune Q&A risultano obsolete.

Published on: 08 marzo 2022

Related documents

Questions & Answers sui processi autorizzativi relativi a procedure Nazionali, di Mutuo Riconoscimento e Decentrate [0.99 Mb] [PDF] >

Related links

Access to medicinal products >

Early access and off-label use >

Authorisation of medicinal products >

Shortages and unavailability >

Antibiotic medicinal products >

Biological medicinal products >

Vaccines >

Blood derivatives >

Generic medicinal products >

Biosimilar medicinal products >

Other sources of useful information

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

May 2022
CMDh/173/2010/Rev.21

Examples for acceptable and not acceptable groupings for MRP/DCP products

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

- The update of an ASMF – including changes of the open as well as the restricted part – or Module 3.2.S can be submitted as a grouped application according to the highest type of the single changes, if condition 5 or 6, respectively, of Annex III of the Variation Regulation applies. However, in case of substantial changes in the updated version of the ASMF or Module 3.2.S it is recommended to submit a single variation of type II under category B.I.z. However, it is a prerequisite for the validation of these single variations that the section "present/proposed" is filled out completely and correctly.
- 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.

3. ACCEPTABLE AS SINGLE CHANGE INSTEAD OF GROUPING

- 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.

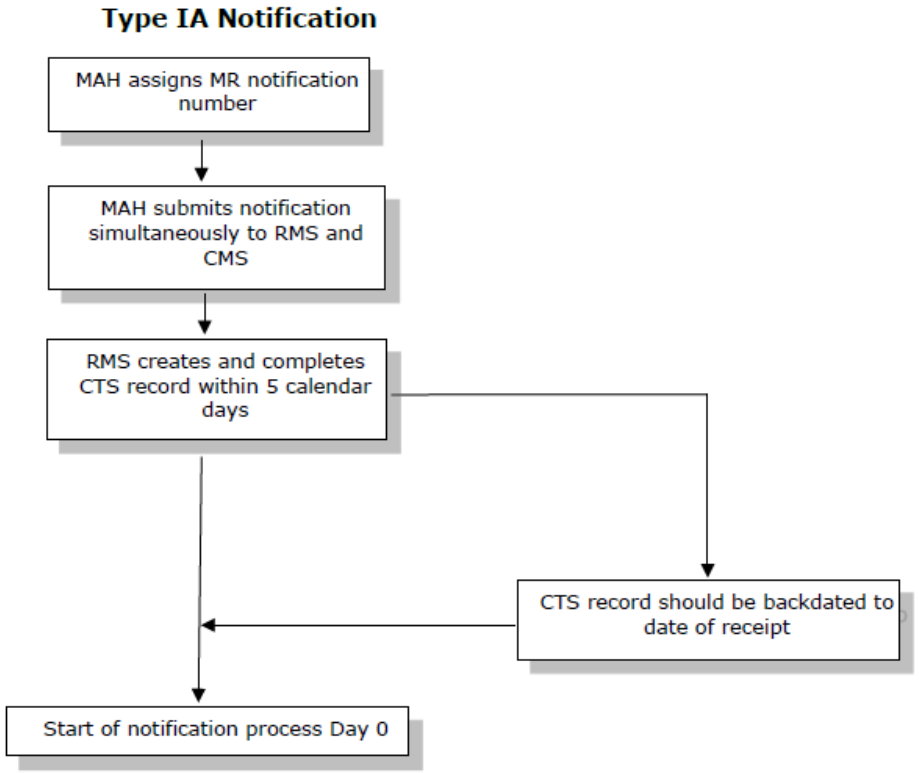
New!

- Considering "related substances" as one specification, even if including different limits for each impurity, a single type IB variation may be acceptable for the introduction of the full impurity profile of the finished product (if missing), under category B.II.d.1.c, if the analytical method is the same for all the impurities. If the approved limits for several impurities in the specification are changed, a single type II B.II.d.1.z variation is acceptable, provided that the impurities are related to the same active substance and all proposed changes are detailed in the Application Form. If several minor changes are proposed simultaneously (i.e. tightening, addition, etc.), a type I grouping of variations may be submitted, including variations under codes B.II.d.1.a/c/d/g as appropriate, depending on the type of changes (one variation per single change). A similar approach could be followed in case of 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 (B.I.b.1).

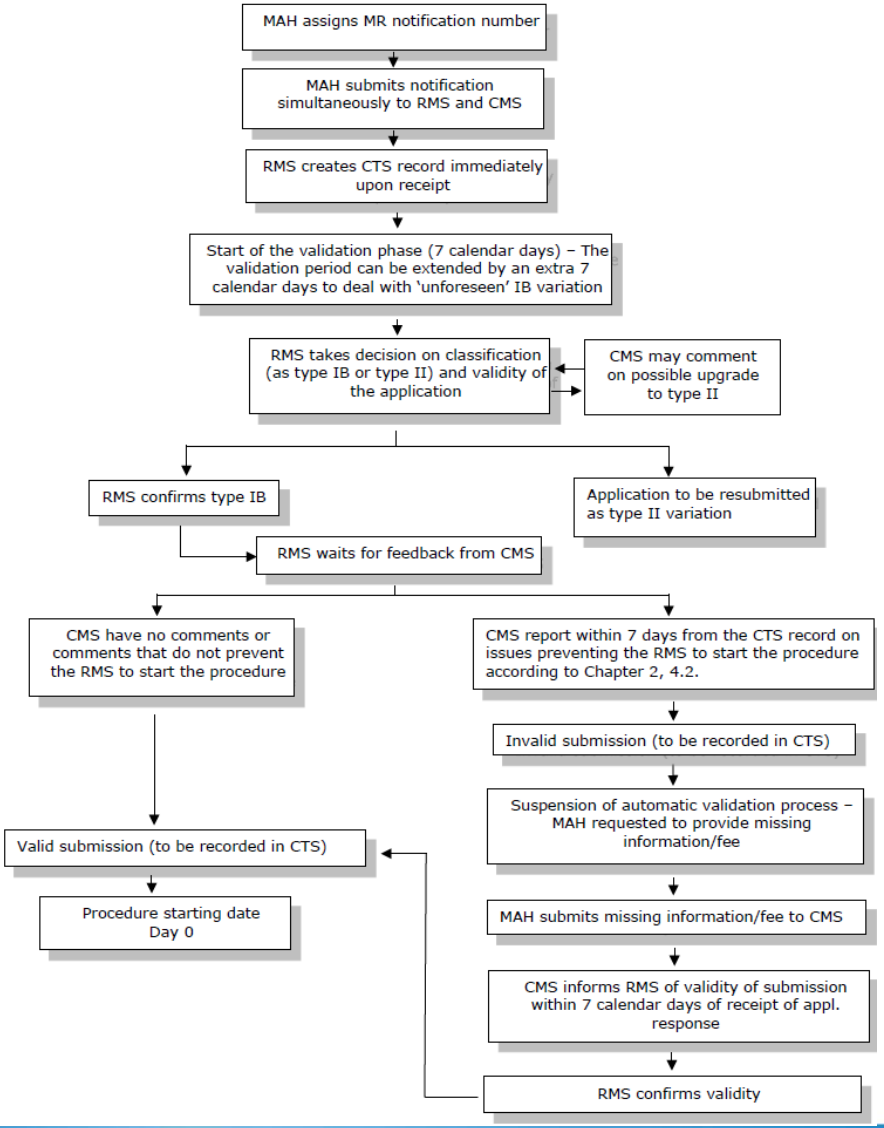
TIME-TABLES (validation)

ANNEX I

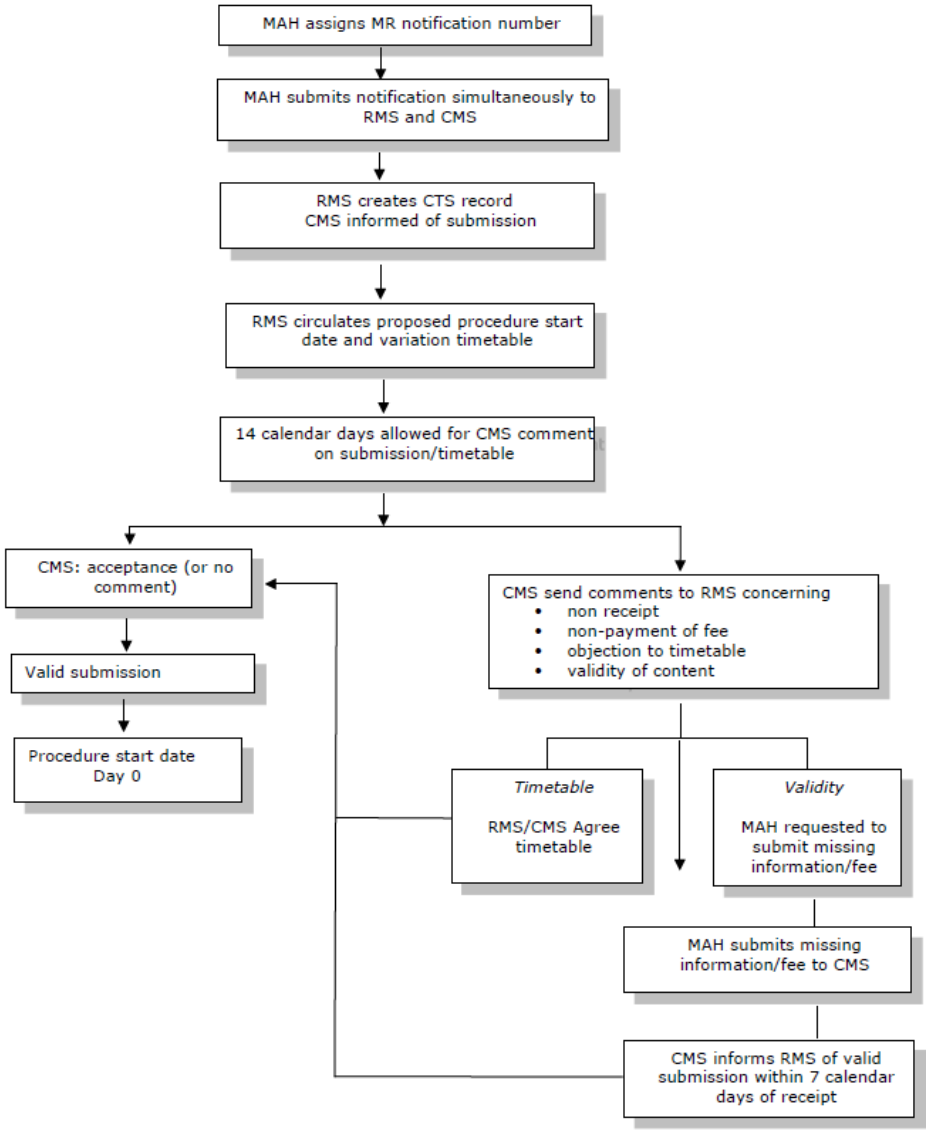
Flowchart for automatic validation: Starting the notification or variation procedure.



Type IB Notification



Type II Variation



TIME-TABLES (assessment)

ANNEX II

Type IA

Submission phase	To the RMS and CMS the MAH submits the application accompanied by supporting documentation as appropriate.
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 the product information is affected, the clean documents have to be uploaded to CTS for transfer to the MRI index. In case conditions to the marketing are affected by the outcome of the variation, the RMS will communicate the outcome via email to the CMSs and explicitly indicates in the email that the respective condition has now been fulfilled and can be deleted from the MA or, in case of a new condition to the marketing authorisation, needs to be included in the MA.
Within 6 months after acceptance	Competent authorities should implement the decision nationally within six months.

Type IB

Annex II

Submission	• MAH submits variation to the RMS and CMS. • 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. Where the product information is affected, the clean documents have to be uploaded to CTS for transfer to the MRI index. In case conditions to the marketing are affected by the outcome of the variation, the RMS will communicate the outcome via email to the CMSs and explicitly indicates in the email that the respective condition has now been fulfilled and can be deleted from the MA or, in case of a new condition to the marketing authorisation, needs to be included in the MA.

Type IB

Clock stop	Within 30 days of receipt of the 'Notification with Grounds', the MAH submits an amended notification to the RMS and CMS. 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.
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 and the procedure ends.

Type II

Annex II

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	Where applicable, the MAH provides 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. The clean documents have to be uploaded to CTS for transfer to the MRI index. In case condition(s) to the marketing authorisation are affected by the outcome of the variation, the RMS will explicitly indicate in the email that the respective condition(s) has(have) now been fulfilled and can be deleted from the MA or, in case of a new condition to the marketing authorisation, needs to be included in the MA. Please see Sample texts in Annex I.

Type II

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	Where applicable, the MAH provides 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. The clean documents have to be uploaded to CTS for transfer to the MRI index. In case condition(s) to the marketing authorisation are affected by the outcome of the variation, the RMS will explicitly indicate in the email that the respective condition(s) has(have) now been fulfilled and can be deleted from the MA or, in case of a new condition to the marketing authorisation, needs to be included in the MA. Please see Sample texts in Annex I.

Type II

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	Where applicable, the MAH provides 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. The clean documents have to be uploaded to CTS for transfer to the MRI index. In case condition(s) to the marketing authorisation are affected by the outcome of the variation, the RMS will explicitly indicate in the email that the respective condition(s) has(have) now been fulfilled and can be deleted from the MA or, in case of a new condition to the marketing authorisation, needs to be included in the MA. Please see Sample texts in Annex I.

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

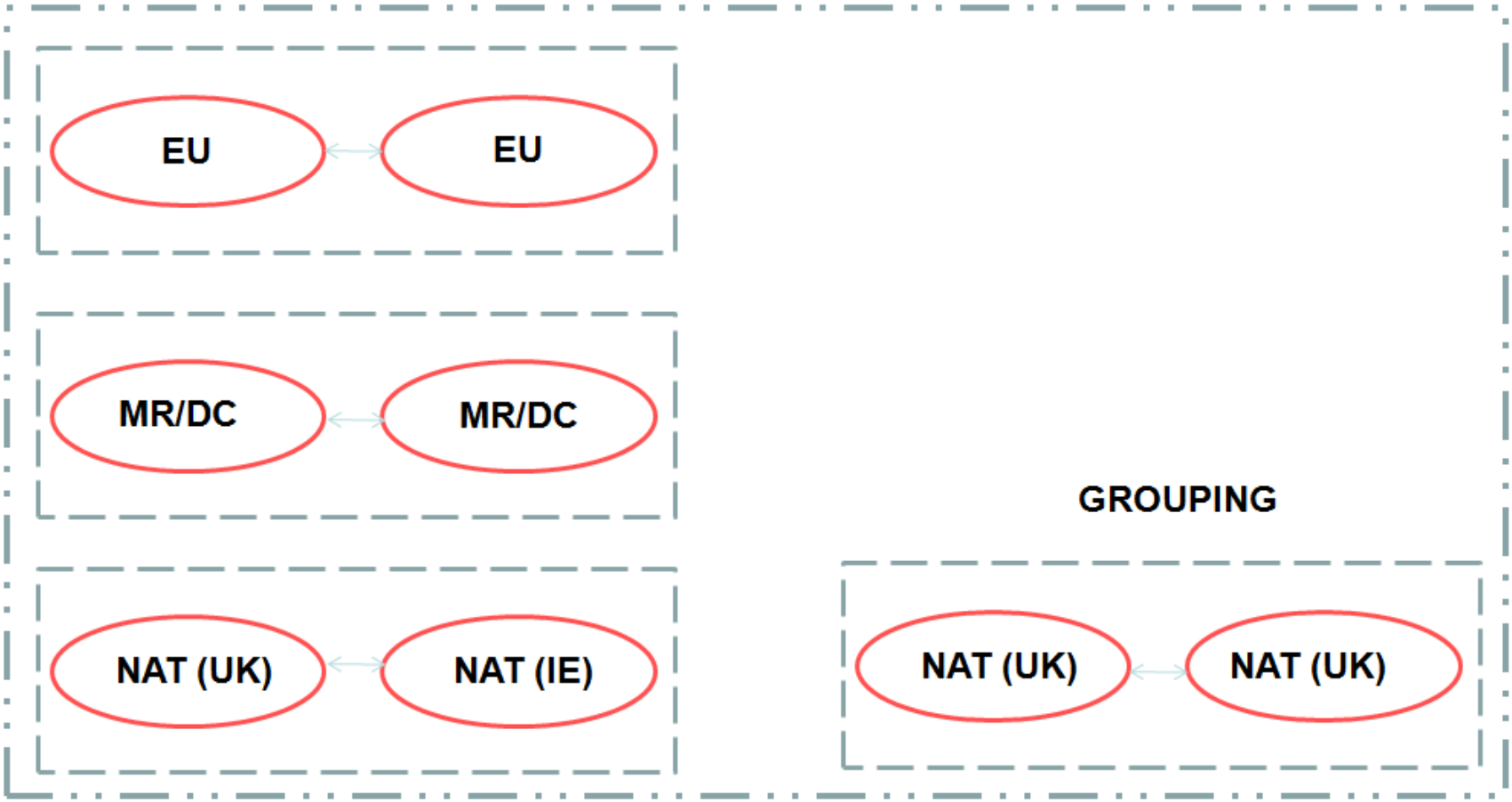
The group may not include a line extension

– 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.*"

WorkSharing

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 CMSs by CTS and to the MAH by email
Day 15	Reference authority circulates the PVAR to the CMSs and to the MAH
Day 20	CMSs 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 CMSs, 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 CMSs and to the MAH
Day 25	CMSs 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 CMSs 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. Where the product information is affected, for marketing authorisations granted via MRP/DCP the clean documents have to be uploaded to CTS for transfer to the MRI index.
Day 30	If not referred to CMDh, the final opinion is considered approved by CMS and changes not affecting PI may be immediately implemented.

WorkSharing

60-day procedure	
Day 0	Start of the procedure, the reference authority notifies the timetable to the CMSs by CTS and to the MAH by email
Day 40	Reference authority circulates the PVAR to the CMSs and to the MAH
Day 55	CMSs 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 CMSs, 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 CMSs and to the MAH
Day 75	The possible break-out meeting
Day 80	CMSs 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 CMSs 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. Where the product information is affected, for marketing authorisations granted via MRP/DCP the clean documents have to be uploaded to CTS for transfer to the MRI index.
Day 90	If not referred to CMDh, the final opinion is considered approved by CMS and changes not affecting PI may be immediately implemented.

WorkSharing

90-day procedure	
Day 0	Start of the procedure, the reference authority notifies the timetable to the CMSs by CTS and to the MAH by email
Day 70	Reference authority circulates the PVAR to the CMSs and to the MAH
Day 85	CMSs 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 CMSs, 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 CMSs and to the MAH
Day 105	The possible break-out meeting
Day 110	CMSs 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 CMSs 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. Where the product information is affected, for marketing authorisations granted via MRP/DCP the clean documents have to be uploaded to CTS for transfer to the MRI index.
Day 120	If not referred to CMDh, the final opinion is considered approved by CMS and changes not affecting PI may be immediately implemented.

WorkSharing
New!

30-day timetable for quality changes of type IB only or groupings with type IB as the highest variation type

Day 0	The reference authority 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 reference authority notifies the CMS on its position in a reduced assessment report or minimum assessment via email
Until Day 27	CMS notify the reference authority about their comments (CAVE: for quality changes of type IB usually there are no CMS comments foreseen, only in case of translation issues if SmPC changes are concerned)
Day 30	If the variation cannot be accepted by the reference authority, taking into account the CMS comments the reference authority sends the request for supplementary information to the CMS and MAH and stops the clock. If the variation can be accepted by the reference authority, taking into account the CMS comments, the reference authority 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.

WorkSharing New!

Clock stop	Within 30 days of receipt of the request for supplementary information, the MAH submits an amended notification to the reference authority and CMS. Where applicable, national translations updated in accordance with requests for amendment raised in the request for supplementary information, have to be submitted in the amended notification.
New Day 0	The reference authority restarts the clock, updates CTS and sends an email informing the MAH that the procedure has restarted. The CMS are informed via CTS.
Until New Day 20	The reference authority notifies the CMS on its position.
Until New Day 27	CMS notify the reference authority of their comments (if any despite the fact that for IB quality changes CMS comments are usually not foreseen).
New Day 30	The reference authority circulates the final opinion to the CMSs 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. Where the product information is affected, for marketing authorisations granted via MRP/DCP the clean documents have to be uploaded to CTS for transfer to the MRI index.

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 and/or 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 coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine;

   — 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].

3. Other changes specific to veterinary medicinal products to be administered to food-producing animals: change or addition of target species.

EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems and products
Medicinal products

AIFA AGENZIA ITALIANA DEL FARMACO

Revision 4

NOTICE TO APPLICANTS

VOLUME 2C
Regulatory Guidelines

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

July 2019

This guideline will be included in The Rules governing Medicinal Products in the European Union
The Notice to Applicants - Volume 2C – Regulatory Guidelines

B. PARENTERAL PREPARATIONS				
Liquid ready-to-use – Single-dose, total use				
11. Solution for injection (pre-filled syringe)	*from* *to*	100 mg/1 ml 200 mg/1 ml	100 mg 200 mg	EA
	from *to*	100 mg/1 ml 200 mg/2 ml	100 mg 200 mg	EA
	from *to*	100 mg/1 ml 100 mg/0.5 ml	100 mg 100 m	Variation
Liquid ready-to-use – Multi-dose or Single-dose, partial use				
12. Solution for injection (vial)	*from* *to*	500 mg/50 ml 1000 mg/50 ml	10 mg/ml 20 mg/ml	EA
	from *to*	500 mg/10 ml 1000 mg/20 ml	50 mg/ml 50 mg/ml	Variation
	from *to*	50 mg/5 ml 100 mg/10 ml	10 mg/ml 10 mg/ml	Variation

Parenterals – change of container only				
14. Solution for injection	*from* *to*	vial pre-filled syringe*(same concentration)*		**EA**[8]
	from *to*	vial pre-filled pen *(same concentration)*		**EA**[9]
	from *to*	pre-filled syringe pre-filled pen *(same concentration)*		**EA**[10]
15. Solution for injection	*from* *to*	vial ampoule *(same concentration)*		Variation

[8, 9, 10] For the purpose of the centralised procedure as the marketing authorisation covers different pharmaceutical forms and strengths, introduction of pharmaceutical forms that differ only with respect to the container/administration device or addition/deletion of a solvent may be handled as a variation. Applicants are advised to confirm with the Agency before submission.

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;

CTD (Common Technical Document)

Format approvato a livello internazionale utilizzato:

- per la presentazione di domande di registrazione dei prodotti medicinali in Europa, USA e Giappone (regioni ICH)
- per tutte le tipologie di domande di registrazione (sia "full" che "abridged")
- per tutte le categorie di prodotti medicinali (inclusi radiofarmaci, vaccini, herbals etc...)

Scopo del suo utilizzo è armonizzare le differenti filosofie regolatorie e i diversi approcci alla revisione dei dati salvaguardando tempo e risorse e facilitando la revisione da parte delle agenzie regolatorie migliorandone la comunicazione

- *Rif. Notice to Applicants vol. 2B - Presentation and content of the dossier*

European Commission

EN English

Search

Public Health

Home > Medicinal products > Eudralex > EudraLex - Volume 2

EudraLex - Volume 2 - Pharmaceutical legislation on notice to applicants and regulatory guidelines for medicinal products for human use

PAGE CONTENTS

Volume 2 of the publications "The rules governing medicinal products in the European Union" contains a list of regulatory guidelines related to procedural and regulatory requirements such as renewal procedures, dossier requirements for Type IA/IB variation notifications, summary of product characteristics (SmPC), package information and classification for the supply, readability of the label and package leaflet requirements.

The Notice to Applicants below has been prepared by the European Commission, in consultation with the competent authorities of the Member States and the European Medicines Agency (EMA) . This Notice has no legal force and does not necessarily represent the final views of the Commission. In case of doubt, therefore, reference should be made to the appropriate Union Directives and

https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-2_en#volume-2b---presentation-and-content-of-the-dossier

PAGE CONTENTS

Volume 2B - Presentation and content of the dossier

Notice to Applicants, Volume 2B EN incorporating the Common Technical Document (CTD) (May 2008).

Electronic Application Forms

The use of the electronic Application Forms (eAF) is mandatory for all procedures from 1 January 2016. The eAFs must be used for all applications: authorisations, variations and renewals.

- eSubmission : EU Electronic Application Forms (Module 1.2 application, variation and renewal forms)
- Questions and Answers EN (February 2008)
- **User guide for the electronic application form**
  - The User guide for the electronic application form is available on both CMDh website and eSubmission website.
    To be noted that this guide is not a NTA document anymore and hyperlinks are available on this page for information. Regular update of this common document (for centralised and decentralised applications) will be available directly on these websites.
- **Electronic Common Technical Document (eCTD)**
  - EU Module 1 Specification
- **Change Control Process for European eCTD Standards**
  - Change Control Process for European eSubmission Standards
  - Electronic Submission Change Request Q&A Form

Content and requirements of application forms

From 1 January 2016 the paper (Word) application forms are not to be used for submissions

Volume 2B

Notice to Applicants

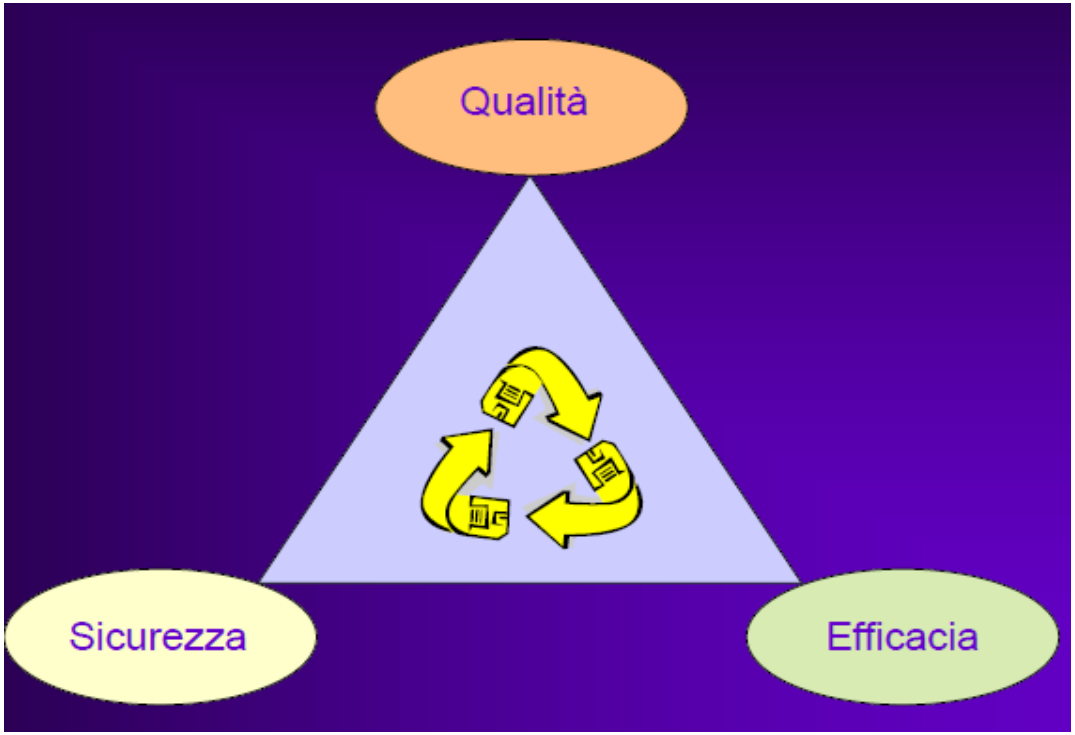
Medicinal products for human use

Presentation and format of the dossier

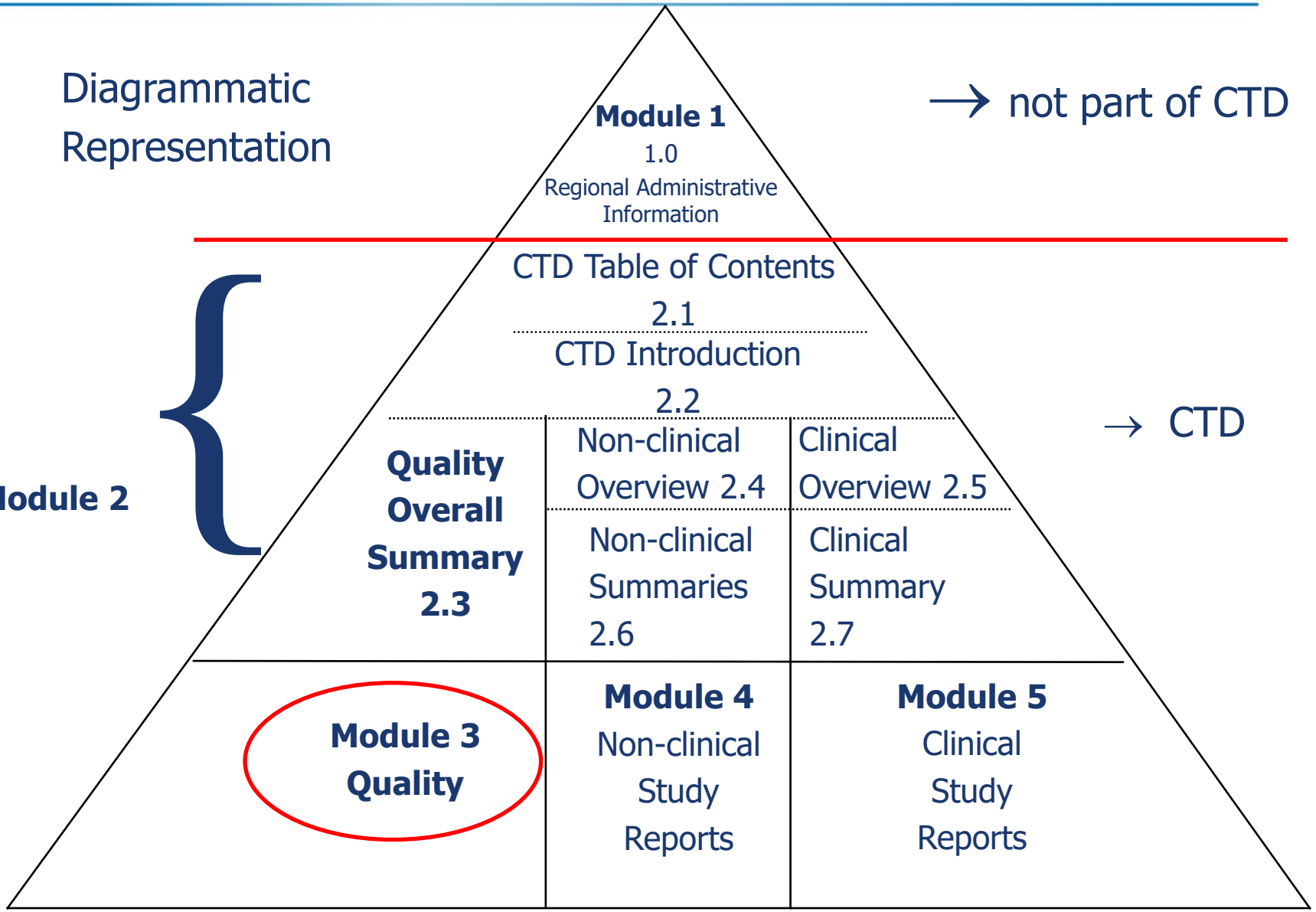
Common Technical Document (CTD)

Introduction	Edition June 2006
Module 1	Edition May 2008
Module 2	Edition July 2003
Module 3	Edition July 2004
Module 4	Edition July 2004
Module 5	Edition July 2004
Herbals	Edition July 2003

Dati da presentare nel dossier registrativo



Diagrammatic Representation

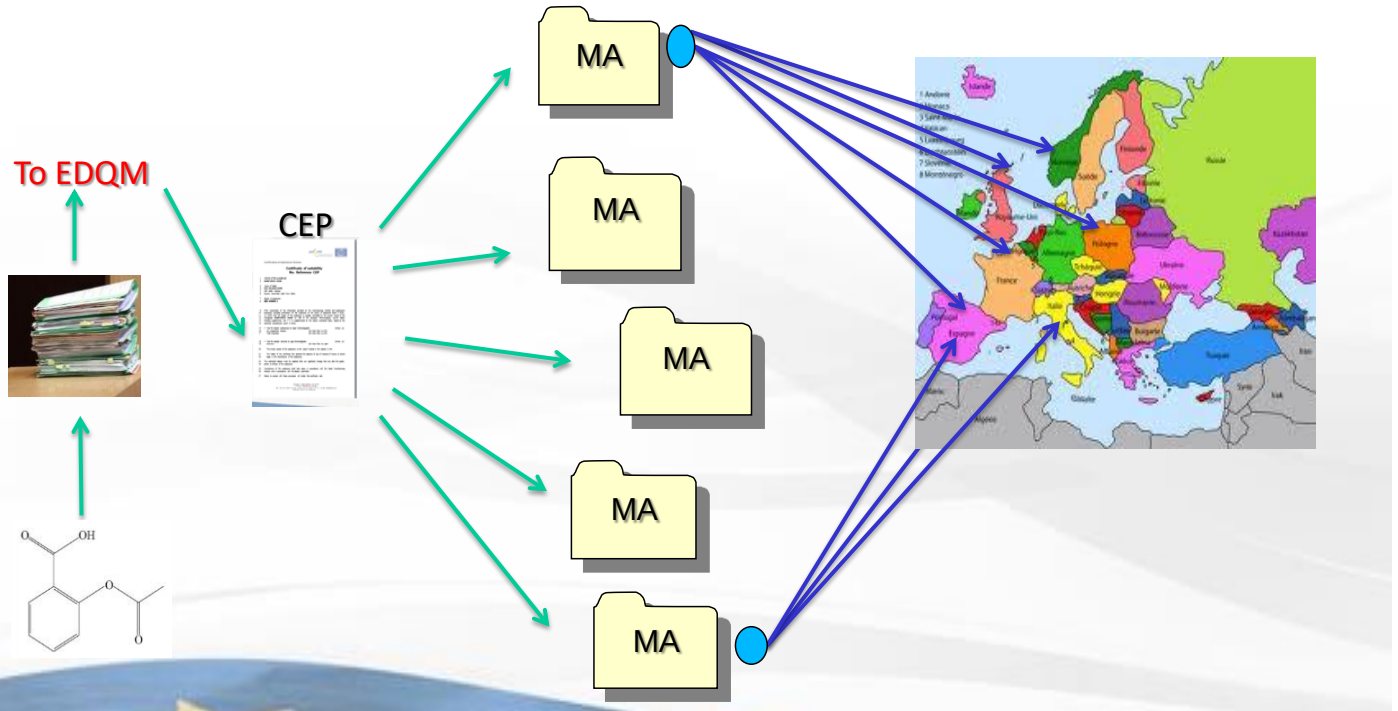


TOPIC / SCOPE OF CHANGES	VARIATION
A. ADMINISTRATIVE CHANGES	1-7
B. QUALITY CHANGES	
I. Active Substance	
a) Manufacture	1-5
b) Control of active substance	1-2
c) Container closure system	1-3
d) Stability	1
e) Design Space and post approval change management protocol	1-5
II. Finished Product	
a) Description and composition	1-6
b) Manufacture	1-5
c) Control of excipients	1-5
d) Control of finished product	1-3
e) Container closure system	1-7
f) Stability	1
g) Design Space and post approval change management protocol	1-5
h) Adventitious Agents Safety	1
III. CEP/TSE/monographs	1-2
IV. Medical Devices	1-3
V. Changes to a marketing authorisation resulting from other regulatory procedures	
a) PMF/VAMF	1-2
b) Referral	1
c) Other changes to the quality dossier requested by the competent authority	1

Esempio: impatto sulle variazioni all'AIC
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):

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

The substance is sterile and shall comply with the test for sterility (2.6.1.) of the European Pharmacopoeia. The method used for sterilisation is a sterile filtration and the sterilisation 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):

edqm
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

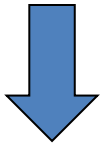
B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of specification limits for medicinal 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.

key document: QP declaration

Directive 2001/83/EC as amended (Directive 2001/82/EC for veterinary medicinal products) states that manufacturing-authorisation holders are obliged to use, as starting materials, only active substances that have been manufactured in accordance with the detailed guidelines on GMP for starting materials. Thus the legislation puts the responsibility on the manufacturing-authorisation holders using the active substance and does not foresee mandatory routine inspections of active-substance manufacturers.

eAF (updated September 2021):

☐ 5.22 **For each active substance, attach a declaration(s) from the Qualified Person of the manufacturing authorisation holder in Section 2.5.1 and from the Qualified Person of the manufacturing authorisation holders (i.e located in EEA) listed in Section 2.5.2 where the active substance is used as a starting material that the active substance is manufactured in compliance with the principles and guidelines of good manufacturing practice for starting materials. Alternatively, such declaration may be signed by one Qualified Person on behalf of all QPs involved (provided this is clearly indicated). The declaration should refer to an audit and the date of the audit.**

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"

QP Declaration Template

- QP Declaration Template and Guidance were published in May 2014

•http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/06/WC500167852.pdf

•http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500167853


Non-GMP
GMP
Raw Material
Intermediates
Regulatory Starting Material
Intermediates
API
Sponsor
Regulator
Starting materials
Drug substance
Formulated drug
Finished goods
Upstream
Downstream

QP Declaration Template

QP Declaration Template and Guidance useful to:

- harmonize the format for the declaration
- prevent questions during assessment
- enhance the efficiency of the regulatory process
- provide clear requirements

The template is not mandatory; but if not used the same information is necessary

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)."

QP Declaration highlights

- QP declaration is mandatory for any Marketing Authorization to confirm that the API is manufactured in accordance with GMP
- A QP declaration is signed by the QP working for the manufacturing and/or importing site located in EEA
- It is generally based upon an on site audit of the active substance manufacturer(s)

  "Off-site" audit as exceptional case (e.g. atypical API , travel difficulties)
- The outcome of the audit confirms that the manufacturing complies with the principles and guidelines of GMP

QP declaration highlights

- It should be based on an on-site audit of the API manufacturer:

- The auditor may be a third party contractor (written agreement)
- Suitably trained and experienced person(s)
- The audit cannot be replaced by GMP certificates from a relevant competent authority

- When more than one holder of a Manufacture/importation authorization is involved, it may be acceptable to provide a single declaration signed by one QP, provided that:

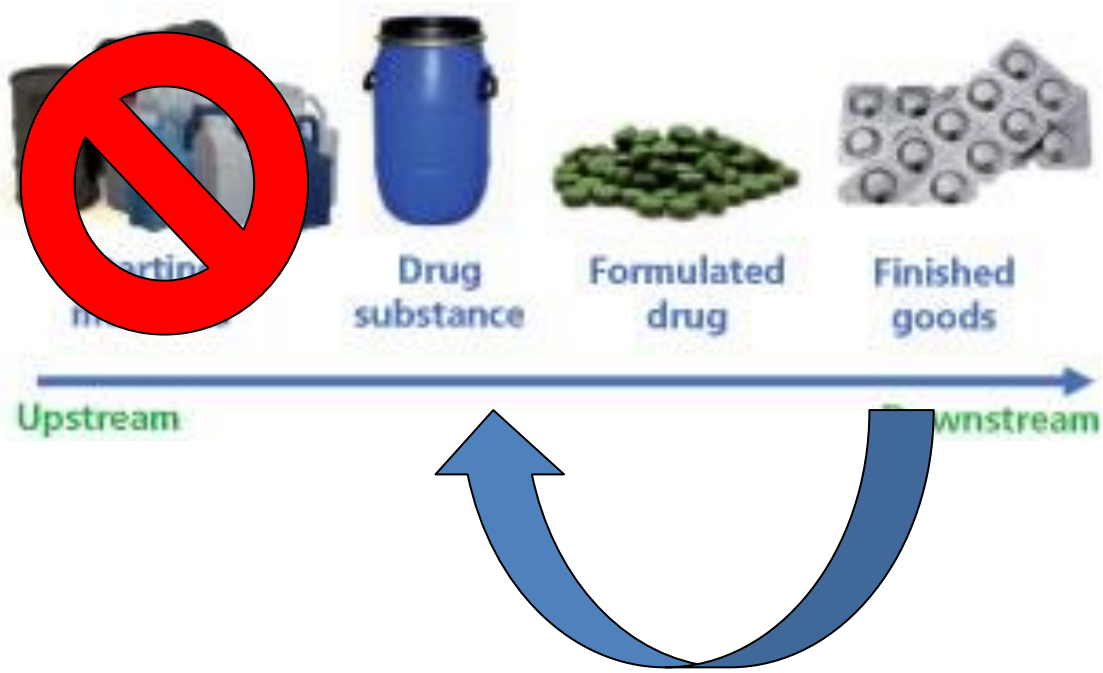
- it is signed on behalf of all the involved QPs
- the arrangements are covered by a technical agreement

QP Declaration and Marketing Authorizations

Requested for:

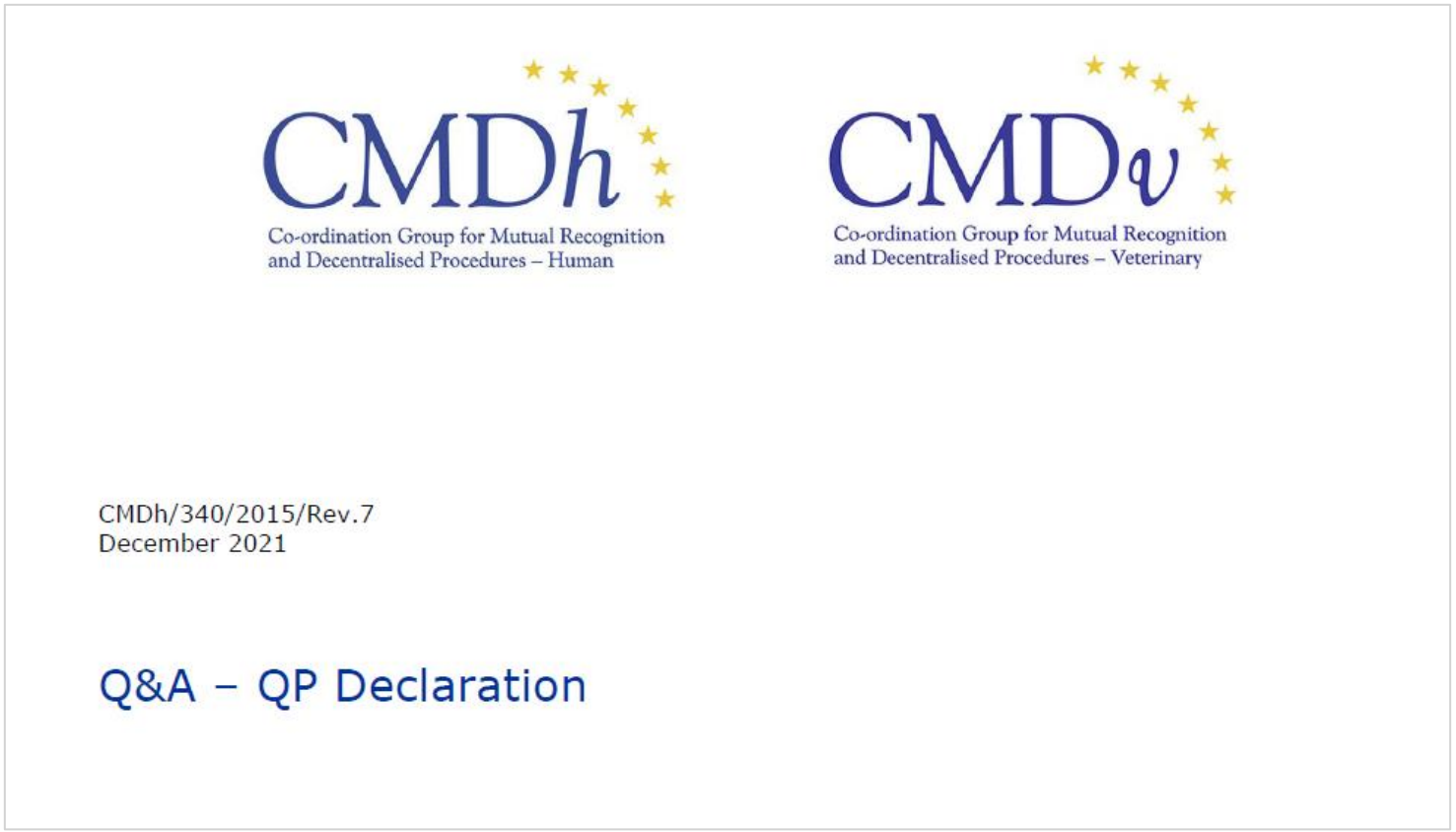
- All new MA applications
- All MA renewals
- Relevant variations
    - Addition or replacement of API manufacturer
    - Addition or replacement of finished product manufacturing site
    - Addition or replacement of the Batch Release site

Irrespective of API data submission – CEP, ASMF or 3.2.S.

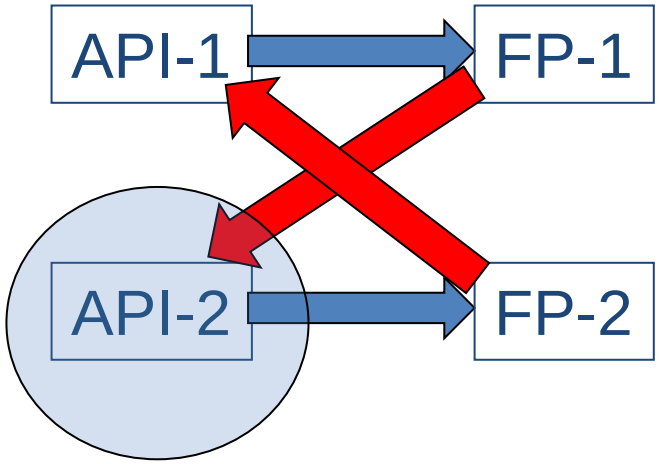


SM → API → FP

Sources of useful information




Starting materials
Drug substance
Formulated drug
Finished goods
Upstream
Downstream


API-1
FP-1
API-2
FP-2

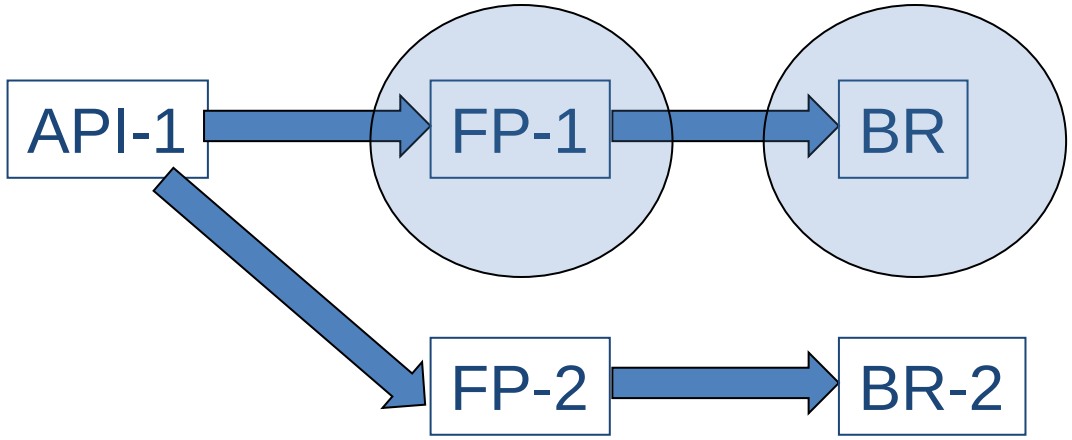
7. Which Qualified Person declaration(s) are required in support of individual types of changes to a Marketing Authorisation, to confirm that the active substance is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union?

Answer (Human & Veterinary):

Active substance manufacturer:

In case of addition of a new active substance manufacturer or updating of information about an already approved API manufacturer which involves a new site, supported by a CEP (B.III.1 - all relevant sub-categories, including z), ASMF and Module 3 data (human) or part II (veterinary) (B.I.a.1 – all relevant sub-categories, including z), QP declarations should be provided from each of the registered finished product manufacturing and batch release sites located in the EU/EEA. The declarations should cover all new intermediate and API manufacturers, as reported in the 3.2.S section of the dossier (human) or in the section 2.C (veterinary).


Starting materials
Drug substance
Formulated drug
Finished goods
Upstream
Downstream

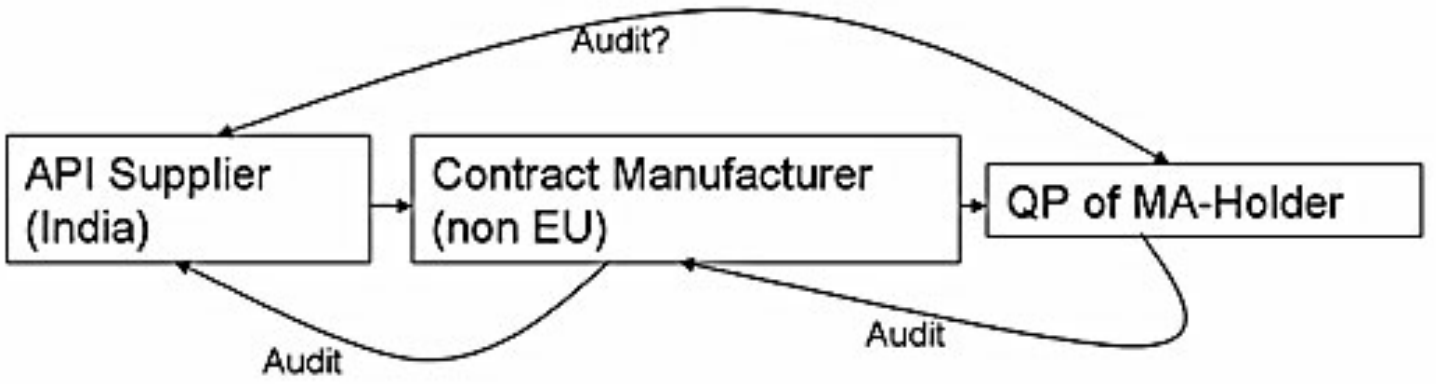

API-1
FP-1
BR
FP-2
BR-2

Finished product manufacturer:

In case of addition of a new finished product manufacturer (B.II.b.1.c, B.II.b.1.d, B.II.b.1.e, B.II.b.1.f or B.II.b.1.z), as a minimum QP declarations should be provided from the proposed new finished product manufacturer (if located within EU/EEA), as well as at least one of the registered EU/EEA batch release sites. In fact, as reported in the note of the classification guideline to variations under category B.II.b.1, as the QP responsible for batch certification takes overall responsibility for each batch, a further declaration from the QP responsible for batch certification is expected when the batch release site is a different site from the site which is added with the proposed variation. The declarations should cover all registered drug substance manufacturing sites (main and intermediate manufacturing sites).

In case of addition of a new finished product manufacturer which is also responsible for batch release or simultaneous addition of a new finished product manufacturer and a new batch release site (grouping of variations including at least one variation under both categories B.II.b.1 and B.II.b.2.c), as a minimum QP declarations should be provided from the new batch release site, as well as the proposed new finished product manufacturer (when located within EU/EEA, if different from the former).


Starting materials
Drug substance
Formulated drug
Finished goods
Upstream
Downstream


Audit?
API Supplier (India)
Contract Manufacturer (non EU)
QP of MA-Holder
Audit
Audit

5. A CEP or ASMF has 2 manufacturing sites A and B (both sites perform complete manufacture of the API). The MAH wishes to approve only manufacturing site A. Is it acceptable to register only manufacturing site A and therefore submit a QP declaration only for site A?

Answer (Human & Veterinary):

This situation is considered acceptable as long as it is clearly stated in relevant parts of the dossier that only API batches from site A will be used.

Therefore, in module 1 (human) or part I (veterinary) the QP declaration, annex 5.8 and application form should report this information, along with a commitment to only use API batches from site A.

Module 3 e.g. S.2.1 and S.4.4 (Part IIC for Veterinary Products) should specify only the information related to site A.

In case the manufacturing site B is ever added to the authorization, a valid QP declaration needs to be provided for both sites (A and B) in the frame of the corresponding variation to be submitted.

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A voi GRAZIE per l'attenzione!

... ci sono domande?

CONTACTS
Dr.ssa Elisabetta Tribulato
Ufficio Procedure Post Autorizzative
Post-Authorisation Procedure Office.
Italian Medicines Agency
Via del Tritone, 181 - 00187 Roma
e.tribulato@aifa.gov.it