AGENZIA ITALIANA DEL FARMACO

Common technical document (CTD and e-CTD) and module 3 Quality

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

Università di Pavia

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Dichiarazione di trasparenza/interessi*

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

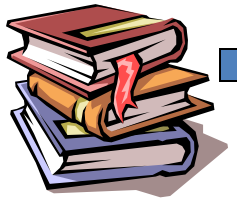
Interessi nell'industria farmaceutica	NO	Attualmente	Da 0 a 3 anni precedenti	oltre 3 anni precedenti
INTERESSI DIRETTI:				
1.1 Impiego per una società: Ruolo esecutivo in una società farmaceutica	☒	☐	☐	☐ obbligatorio
1.2 Impiego per una società: Ruolo guida nello sviluppo di un prodotto farmaceutico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

* Marco Franceschin, 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.

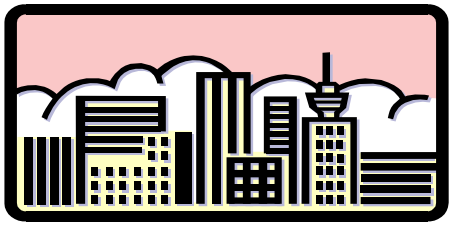
N.B. Per questo intervento non ricevo alcun compenso

Registrazione prodotti medicinali: il processo di valutazione

Dossier registrativo azienda



Autorità Competenti



Risorse

Assessor (Esperti) –

Interni / Esterni

Legislazione e linee-guida interpretazione armonizzata

Output

Assessment Report A.R.

Informazioni sul prodotto

S P C

P L

. . . .

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, nonche' della direttiva 2003/94/CE.

- Art. 1. Definizioni

nn-bis) **medicinale falsificato**: fatta eccezione per i prodotti con difetti di qualita' non intenzionali e delle violazioni dei diritti di proprieta' intellettuale, qualsiasi medicinale che comporta una falsa rappresentazione rispetto a: 1) la sua identita', compresi l'imballaggio e l'etichettatura, la denominazione o la composizione, in relazione a uno qualsiasi dei componenti, compresi gli eccipienti, e il relativo dosaggio; 2) la sua origine, **compresi il produttore**, il paese di produzione, il paese di origine e il titolare dell'autorizzazione all'immissione in commercio; 3) la sua tracciabilita', compresi i registri e i documenti relativi ai canali di distribuzione utilizzati;

DIRETTIVA 2011/62/UE DEL PARLAMENTO EUROPEO E DEL CONSIGLIO

dell'8 giugno 2011

che modifica la direttiva 2001/83/CE, recante un codice comunitario relativo ai medicinali per uso umano, al fine di impedire l'ingresso di medicinali falsificati nella catena di fornitura legale

(Testo rilevante ai fini del SEE)

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...)

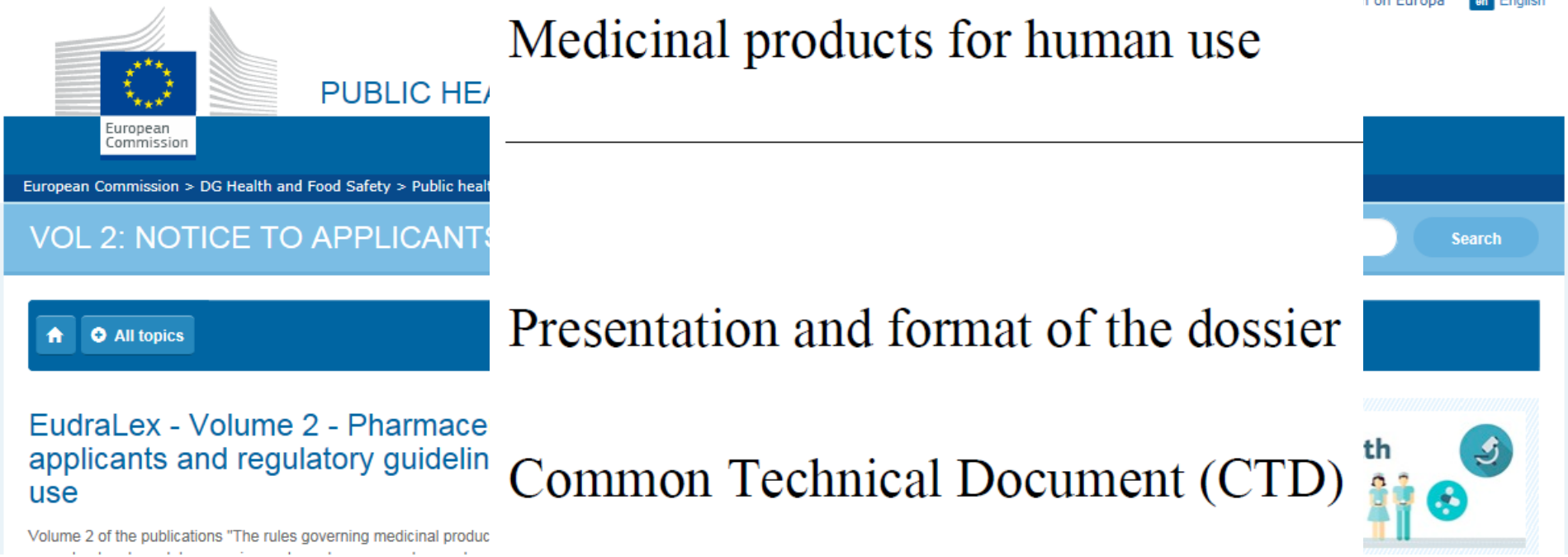
Scopo del suo utilizzo è armonizzare le differenti filosofie regolatorie e i diversi approcci alla revisione dei dati salvaguardando tempo e risorse e facilitando la revisione da parte delle agenzie regolatorie migliorandone la comunicazione

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

Volume 2B

Notice to Applicants

Medicinal products for human use

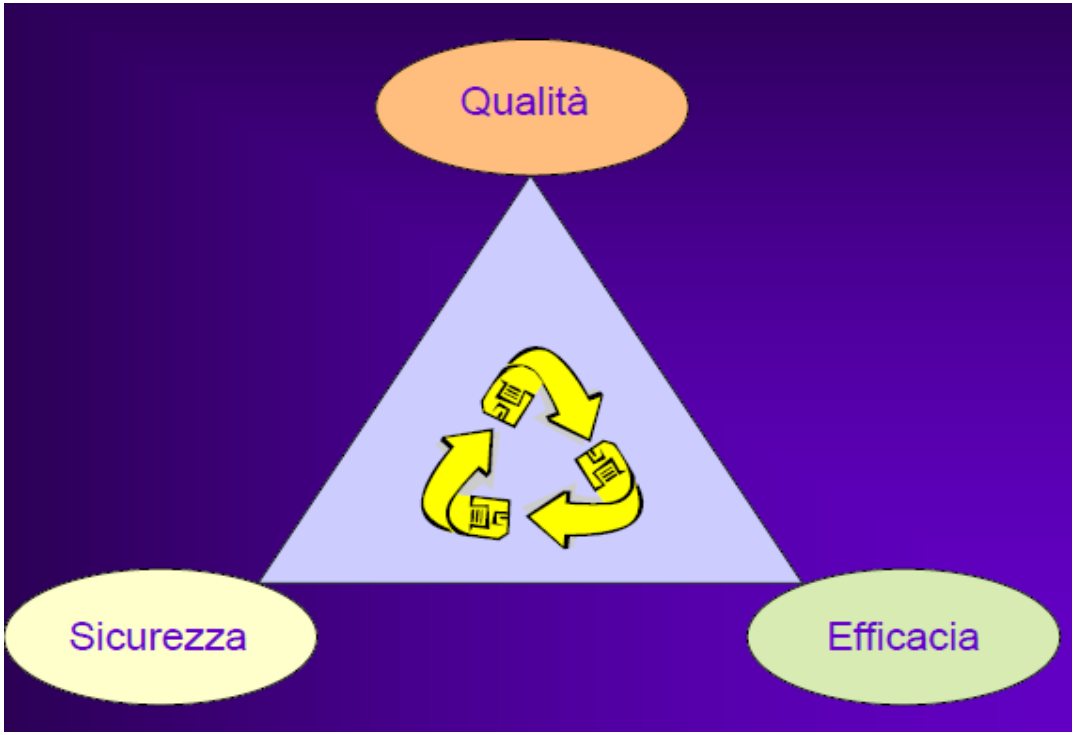


Presentation and format of the dossier

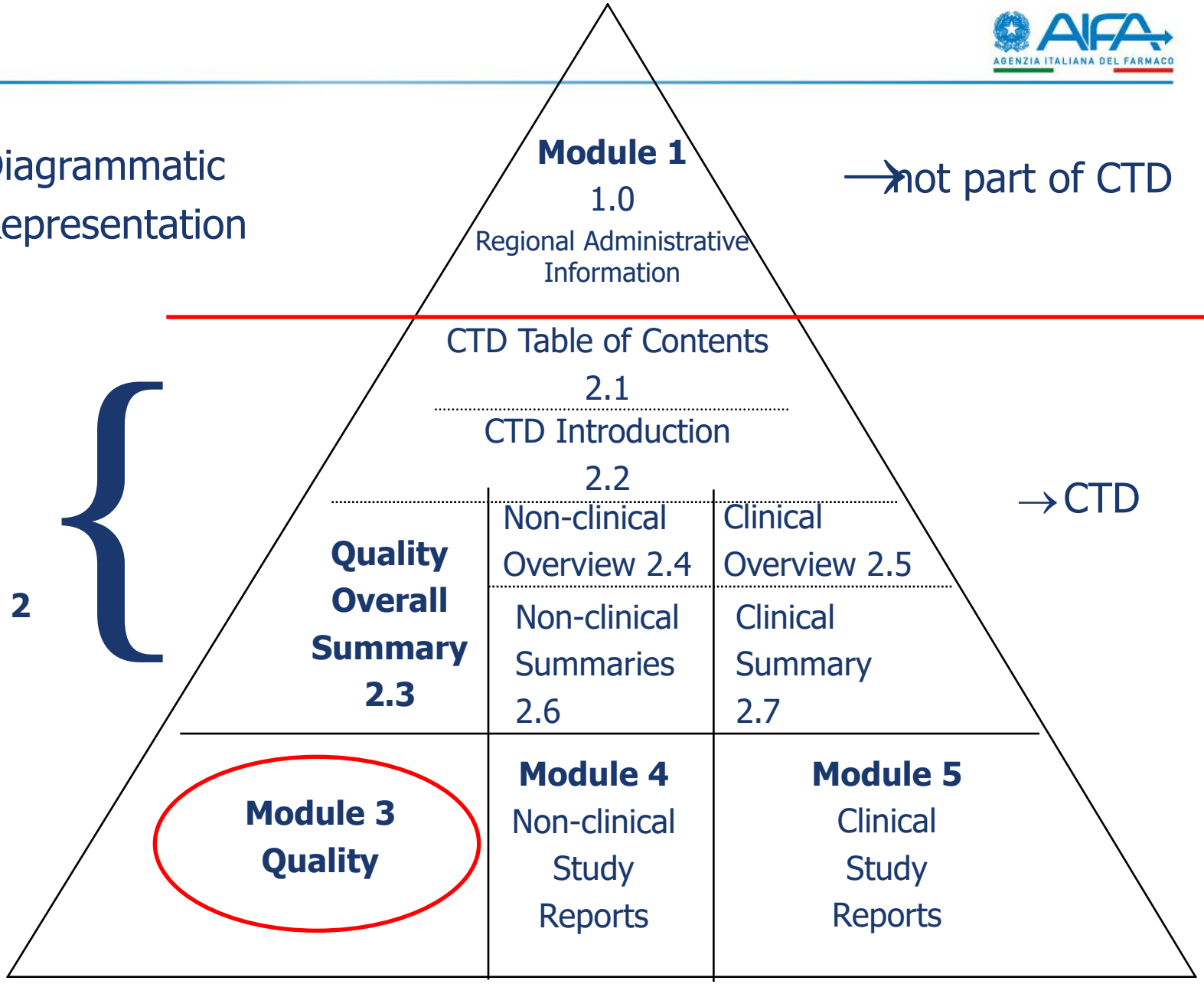
Common Technical Document (CTD)

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



→ not part of CTD

Module 2

→ CTD

3.1 Table of Contents of Module 3

A Table of Contents for Module 3 should be provided.

3.2 Body of Data

3.2.S DRUG SUBSTANCE[1] (NAME, MANUFACTURER)

Reference CPMP Guidelines:

"On summary of requirements for active substances in part II of the dossier",including the Certification of Suitability of monographs of the European Pharmacopoeia.(see also NTA, Vol. 2B – introduction).

"Active Substance Master File procedure"

3.2.S.1 General Information (name, manufacturer)

3.2.S.1.1 Nomenclature (name, manufacturer)

CTD-Q: due documenti principali

3.2.S Drug substance

3.2.S.1 General Information
3.2.S.2 Manufacture
3.2.S.3 Characterisation
3.2.S.4 Control of Drug Substance
3.2.S.5 Reference Standards or Materials
3.2.S.6 Container Closure System
3.2.S.7 Stability

3.2.P Drug Product

3.2.P.1 Description and Composition
3.2.P.2 Pharmaceutical Development
3.2.P.3 Manufacture
3.2.P.4 Control of Excipients
3.2.P.5 Control of Drug Product
3.2.P.6 Reference Standards or Materials
3.2.P.7 Container Closure System
3.2.P.8 Stability

3.2.S Principi attivi

I principi attivi possono essere classificati in:

- Nuovi principi attivi, usati per la prima volta in un prodotto medicinale per uso umano o veterinario
- Principi attivi esistenti, non descritti in Farmacopea Europea o in una delle Farmacopee degli stati membri UE
- Principi attivi esistenti, descritti in Farmacopea Europea o in una delle Farmacopee degli stati membri UE

3.2.S. Drug Substance

- 3.2.S.1 General Information
- 3.2.S.2 Manufacture
- 3.2.S.3 Characterisation
- 3.2.S.4 Control of Drug Substance
- 3.2.S.5 Reference Standards or Materials
- 3.2.S.6 Container Closure System
- 3.2.S.7 Stability

3.2.S.1 General Information

In tale sezione vengono riportate informazioni generali quali:

- Nomenclatura
- Struttura
- Proprietà generali del principio attivo (es. solubilità, polimorfismo, etc...)

3.2.S.1	General Information
3.2.S.1.1	Nomenclature
3.2.S.1.2	Structure
3.2.S.1.3	General Properties

3.2.S.2 Manufacture

3.2.S.2	Manufacture
3.2.S.2.1	Manufacturer(s)
3.2.S.2.2	Description of manufacturing process and process controls
3.2.S.2.3	Control of materials
3.2.S.2.4	Controls of critical steps and intermediates
3.2.S.2.5	Process validation and/or evaluation
3.2.S.2.6	Manufacturing process development

3.2.S.2 Manufacture (1)

Devono essere riportati:

- Nome, sede del(i) produttore(i)
- Descrizione del processo produttivo e relativi controlli in-process, i controlli dei materiali utilizzati, degli step critici e degli intermedi
- La convalida del processo produttivo (quest'ultima obbligatoria solo nel caso di produzione in asepsi e per la sterilizzazione). Generalmente viene fornito un riassunto dettagliato del rapporto di convalida (parametri critici, criteri di accettabilità e risultati ottenuti sui lotti di convalida)

3.2.S.2 Manufacture (2)

.....Devono essere riportati:

- Il processo produttivo e relativi controlli in-process devono essere descritti in maniera adeguata, ad esempio tramite un diagramma di flusso (riportante formule e pesi molecolari, rese, materie prime, reagenti, intermedi, condizioni operative) seguito da una descrizione narrativa dettagliata
- E' necessario che siano elencati tutti i materiali utilizzati nel processo produttivo, fornendo informazioni che dimostrino la loro qualità
- Particolare attenzione a: starting material (vedi ICH Q11) solventi e catalizzatori impiegati nella sintesi

ICH guideline Q3D on elemental impurities

EU GL Specification limits for residues of metal catalysts

- Catalysts and reagents
- Focused on drug substance contamination
- PDEs for 15 elements
- Does neither mention nor contradict the use of risk assessment

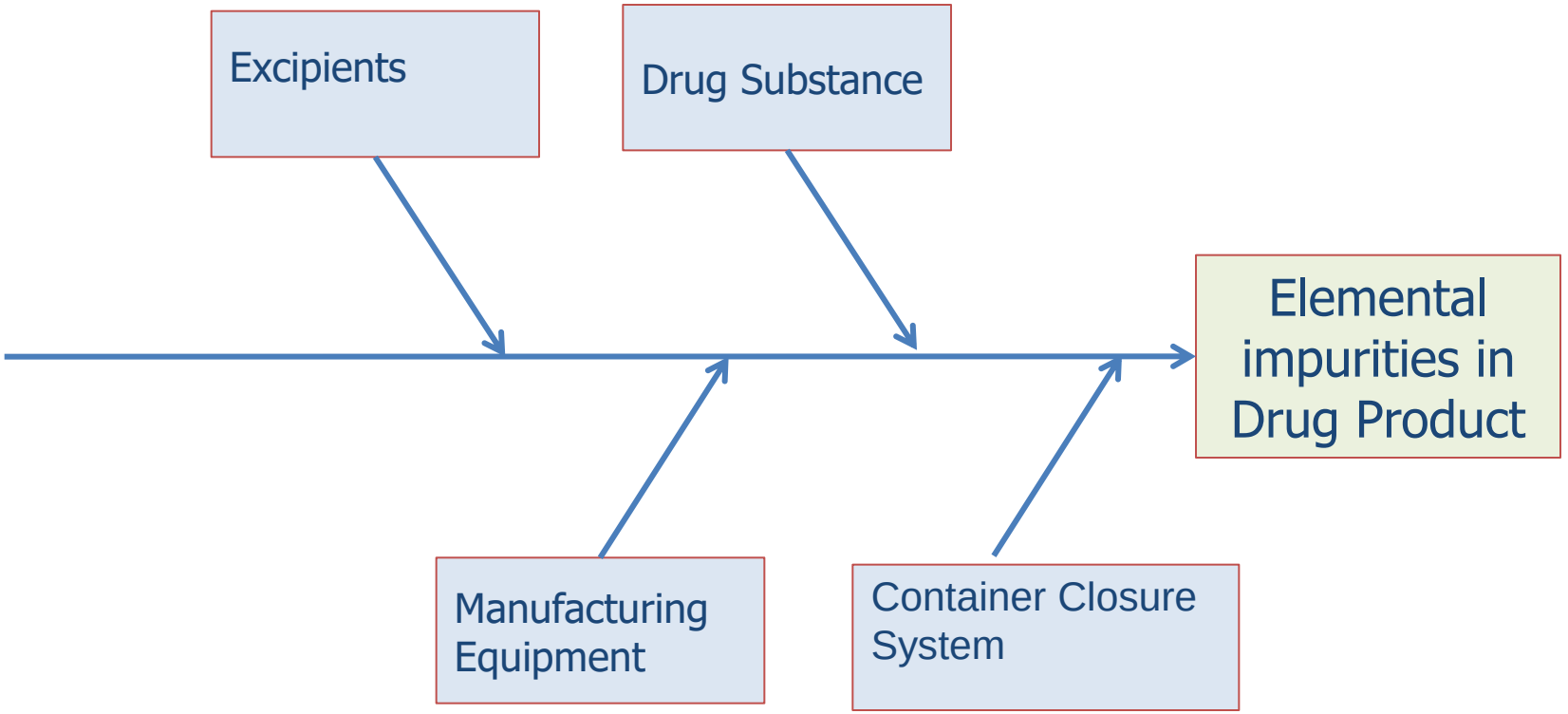
ICH Q3D

- All sources of elemental impurities
- Focused on drug product contamination
- PDEs for 24 elements
- Focused on risk management in line with ICH Q8-11

Implementation

- *For new marketing authorisation applications: June 2016*
- *For authorised medicinal products: December 2017*

Potential sources of elemental impurities



The product assessment should consider the potential of each of these categories to contribute elemental impurities to the drug product

Selection of API Starting Material

Ridefinizione dell'API SM indietro nella sintesi

Esperienza degli assessor

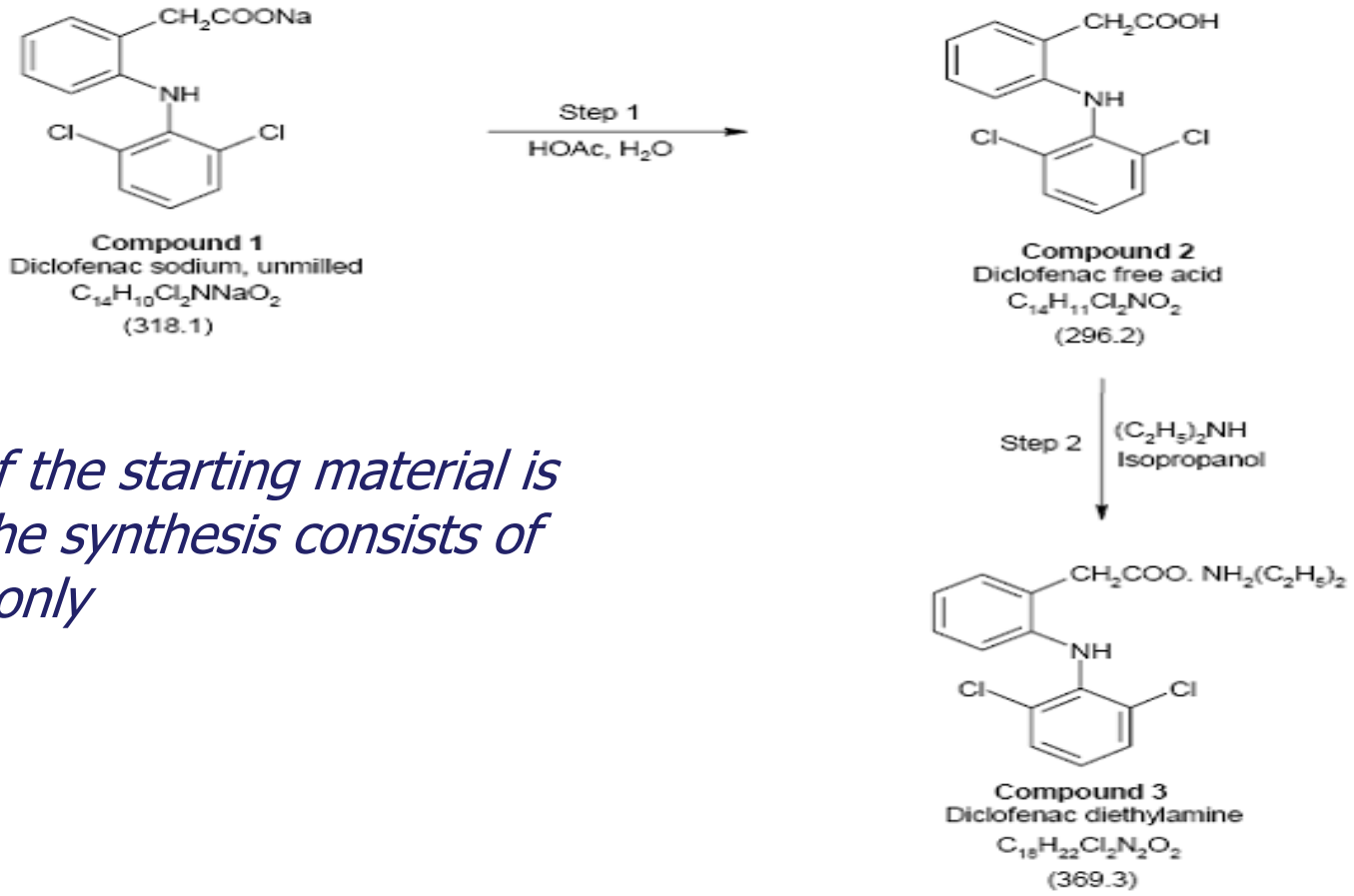
Dall'ingresso dello "starting material" (SM) nella sintesi dell'API il processo deve essere conforme alle GMP

Sempre più spesso produttori certificati GMP da corpi ispettivi europei acquistano intermedi avanzati o differenti sali della materia prima da produttori extra EEA non certificati ed eseguono solo pochi step di sintesi (o addirittura solo una purificazione o una differente salificazione)

Top ten deficiencies: SM proposto non accettato

Es. Starting material

1 Flow chart of manufacturing route



Compound 1
Diclofenac sodium, unmilled
$C_{14}H_{10}Cl_2NNaO_2$
(318.1)

Compound 2
Diclofenac free acid
$C_{14}H_{11}Cl_2NO_2$
(296.2)

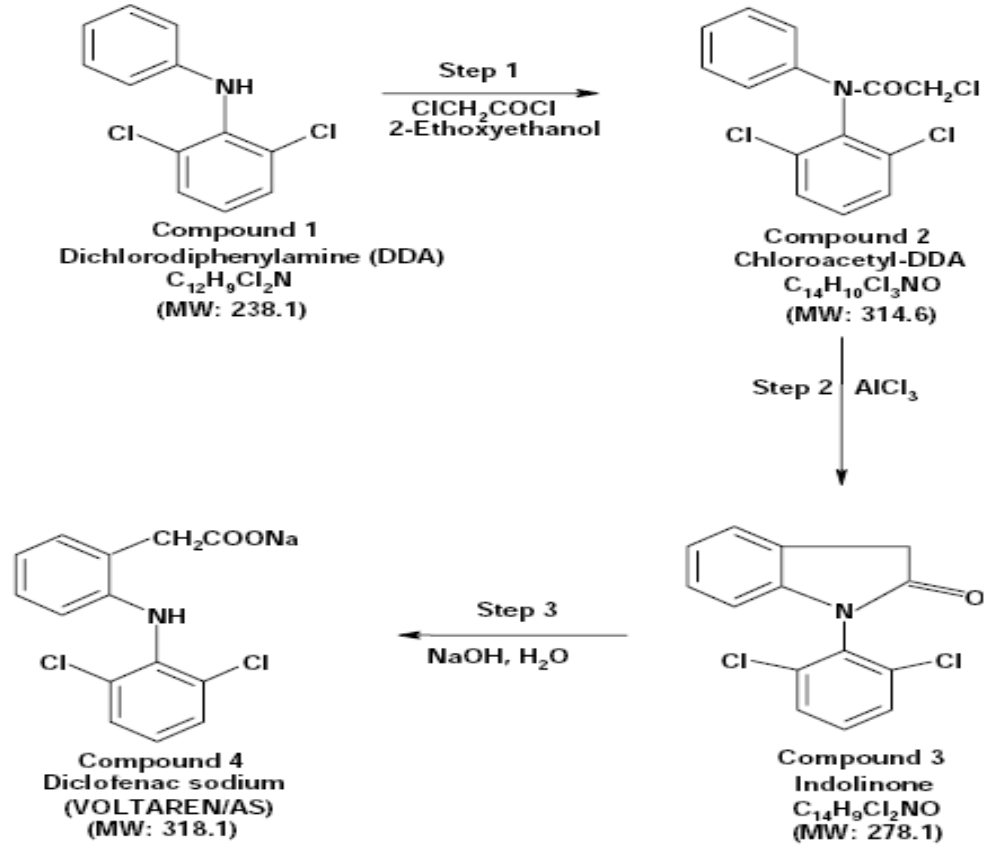
Compound 3
Diclofenac diethylamine
$C_{18}H_{22}Cl_2N_2O_2$
(369.3)

Re-definition of the starting material is requested as the synthesis consists of salt formation only

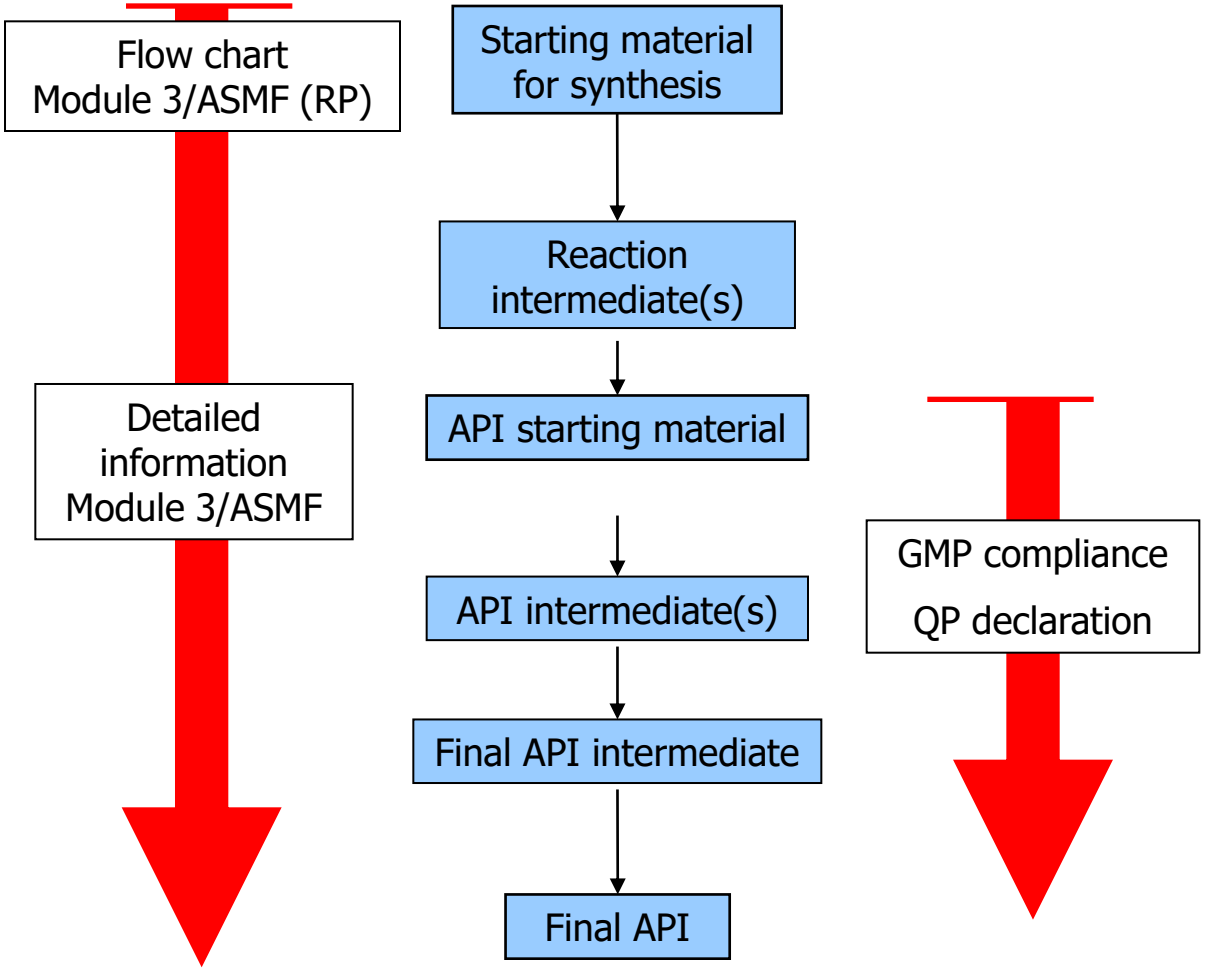
.....Es. Starting material (2)

Parte della sintesi non in GMP

1 Flow chart of manufacturing route



Selection of API Starting Material



Selection of API Starting Material

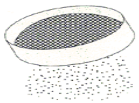
Quanti step ?

API starting material → API intermediate → ..... → Final API

n??

"A sufficient number of chemical transformation steps, as defined in the glossary of ICH Q11, need to be included so that the generation, fate and control of impurities can be understood."





'Neither recrystallization nor salt formations are considered chemical transformation steps, and neither are activities unlikely to have an impact on API purity such as milling or sieving."

Reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active substances 3 July 2017 EMA/CHMP/CVMP/QWP/826771/2016 Corr. 1

Guideline on the chemistry of active substances, EMA/454576/2016 in vigore dal 21/05/2017

ICH Q11 Development and manufacture of drug substances (chemical entities and biotechnological/biological entities) in vigore dal 01/11/2012

3.2.S.3 Characterisation (1)

Elucidation of Structure and other Characteristics

- Informazioni riguardo la struttura e altre caratteristiche del principio attivo
- La struttura chimica del principio attivo è confermata generalmente attraverso comuni analisi spettrometriche (IR, NMR, Massa)
- Informazioni relative al potenziale isomerismo, identificazione della stereochimica e caratteristiche fisico-chimiche, quali il polimorfismo

3.2.S.3	Characterisation
3.2.S.3.1	Elucidation of structure and other characteristics
3.2.S.3.2	Impurities

Polimorfismo

Polimorfismo definito come: " the ability of a compound to exist in more than one crystal form". Different crystal arrangements of the same chemical composition, the molecules are the identical with regards of atom types and covalent bonding sequence

Una fase solida cristallina può organizzarsi in un reticolo cristallino in modo diverso, dando luogo a forme cristalline dette polimorfe. Circa i 2/3 delle sostanze organiche presentano il fenomeno del polimorfismo (es. sulfatiazolo 4-5 polimorfi, progesterone 5…)

Le differenti forme cristalline possono provocare comportamenti diversi per l'assorbimento, la fusione, la solubilità, ecc. E' quindi prevedibile che una forma cristallina di un certo tipo possa influenzare l'attività di un farmaco nell'organismo (con particolare riferimento alle forme farmaceutiche solide)

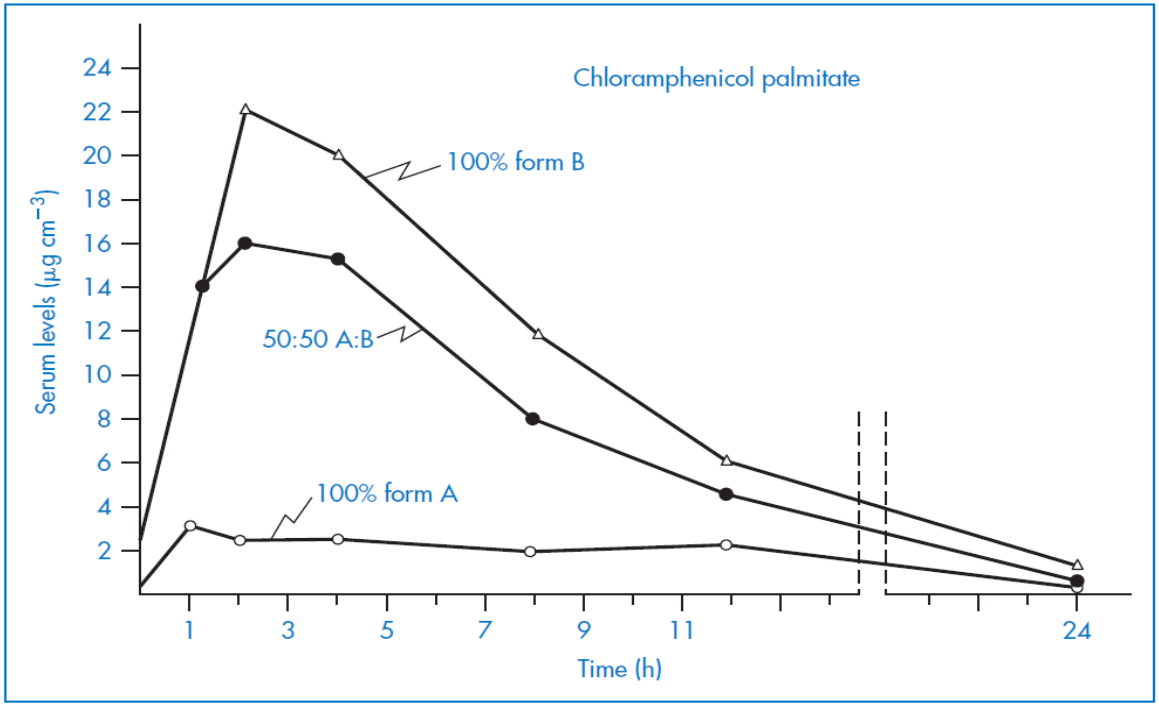
…..Polimorfismo

Possibile differenza nella biodisponibilità di diverse forme polimorfe di un farmaco

- In alcuni casi non è significativa
- In alcuni casi potrebbe avere un impatto, in particolare quando il farmaco è scarsamente solubile (in genere la forma più stabile ha la più bassa solubilità)

.....Polimorfismo

Absorption of polymorph B of chloramphenicol palmitate (prodrug) was significantly greater than absorption of polymorph A in humans, probably due to the higher solubility of form B [1]



3.2.S.3 Characterisation (2)

Maximum daily dose	Identification Threshold
< 1mg	1.0 %
1 mg – 10 mg	0.5 %
> 10 mg – 2 g	0.2 %

3.2.S 3.2 Impurities

- Specifiche linee guida trattano il tema delle impurezze di sintesi e di degradazione (*ICH Q3A-Q3B*), stabilendo i limiti di queste sulla base della dose giornaliera del farmaco, e i casi in cui è necessario identificare e qualificare le impurezze da un punto di vista tossicologico mediante specifici studi

3.2.S.4 Control of Drug Substance

3.2.S.4	Control of drug substance
3.2.S.4.1	Specification
3.2.S.4.2	Analytical Procedures
3.2.S.4.3	Validation of analytical procedures
3.2.S.4.4	Batch analyses
3.2.S.4.5	Justification of Specification

3.2.S.4 Control of Drug Substance (1)

- Devono essere descritte le specifiche del principio attivo, insieme con le procedure analitiche impiegate, le convalide di dette procedure e i risultati ottenuti sui lotti testati
- Le specifiche devono essere adeguate a controllare la qualità del p.a. (es. vedere 3.2.S.2 per solventi residui o catalizzatori)
- Ogni specifica proposta deve essere opportunamente giustificata (*ICH Q6A*)
- Le procedure analitiche utilizzate per il rilascio del principio attivo vanno descritte dettagliatamente e convalidate, ma nel caso di metodiche ufficiali di Farmacopea è sufficiente citare solo il relativo riferimento e non è necessario presentare la convalida del metodo

3.2.S.4 Control of Drug Substance (2)

Nel caso di un principio attivo descritto in Farmacopea Europea (o in un'altra Farmacopea Ufficiale, ove il p.a. non fosse presente in Ph.Eur.) **le specifiche da applicare sono quelle riportate nella relativa monografia**, con l'eventuale aggiunta di test specifici legati allo specifico processo di sintesi (es. ulteriori impurezze e solventi residui)

3.2.S.4 Control of Drug Substance (3)

Un aspetto importante da considerare, che assume particolare rilevanza nelle forme farmaceutiche solide o nelle sospensioni, è la granulometria del principio attivo (**particle size**), perché può influenzare la solubilità e, quindi, l'assorbimento del principio attivo. Una diminuzione della dimensione delle particelle produce quasi sempre un aumento della solubilità. Tuttavia, sono riportati in letteratura alcuni casi in cui la diminuzione del particle size porta ad una diminuzione della solubilità a causa di fenomeni di agglomerazione delle particelle. È evidente che la scelta della granulometria ottimale del principio attivo e la definizione delle specifiche devono essere valutate attentamente e, caso per caso, sulla base delle caratteristiche non solo del principio attivo, ma anche della forma farmaceutica del prodotto finito

Es. Specifiche

Sr. No.	Tests	Specifications	Reference to test method
1	Characters	Clear, colourless or very slightly yellow liquid	Ph.Eur. 1558
2	Solubility	Very slightly soluble in water for injections, miscible with hexane and methanol	Ph.Eur. 1558, general notice part
3	Identification by IR	IR spectrum of both standard and sample should exhibit maxima at the same wavelengths	Ph.Eur. 2.2.24
4	Refractive index	Between 1.5125 and 1.5145	Ph.Eur. 2.2.6
5	Related Substances by HPLC		Validated method
5.1	Impurity G	NMT 0.20%	
5.2	Impurity E	NMT 0.01%	
5.3	Individual unspecified impurity	NMT 0.05%	
5.4	Total impurities	NMT 0.30%	
6	Related substances by GC		Validated method
6.1	Impurity J	NMT 0.05%	
6.2	Impurity K	NMT 0.05%	
6.3	Impurity L	NMT 0.05%	
6.4	Impurity O	NMT 0.05%	
7	Assay	Between 98.0% w/w and 102.0% w/w	Ph.Eur. 2.2.29
8	Bacterial endotoxins	NMT 6 EU/g	Ph.Eur. 2.6.14
9	Water	NMT 0.20% w/w NMT 0.10% @	Ph.Eur. 2.5.12
10	Heavy metals	NMT 20 ppm	Ph.Eur. 2.4.8, method C
11	Residual solvents		Validated method / Ph.Eur. 2.2.28
11.1	Triethylamine	NMT 500 ppm	
11.2	Methanol	NMT 3000 ppm	
11.3	Isopropyl alcohol	NMT 5000 ppm	
11.4	Toluene	NMT 890 ppm	
11.5	Dimethyl acetamide	NMT 1090 ppm	
11.6	Ethanol	NMT 500 ppm	
12 **	Benzoic acid	NMT 0.10% w/w	Validated method, Ph.Eur. 2.2.29

3.2.S.5 Reference Standards or Materials

- Informazioni riguardanti gli standard di riferimento impiegati per l'analisi del principio attivo
- Gli standard di riferimento sono utilizzati per effettuare identificazione, titolo e purezza di un principio attivo; devono essere testati per dimostrarne l'idoneità allo specifico utilizzo
- Se non ottenuti da fonte ufficiale (Ph.Eur., USP), come nel caso degli "in-house" Reference Std, occorre fornire i dati per la loro caratterizzazione

3.2.S.6 Container Closure System

- Deve essere descritto il sistema di confezionamento e chiusura, inclusi dettagli sui materiali che compongono il confezionamento primario e le loro specifiche. Le specifiche devono includere: descrizione, identificazione, dimensioni
- Devono essere forniti dettagli sul confezionamento secondario, così come una giustificazione sulla scelta del tipo di confezionamento in base alla protezione che questo fornisce al principio attivo (luce, umidità) e alla sua compatibilità con lo stesso
- compliance dei materiali a quanto previsto dalla Famarcopea Europea (se presente) e al REGOLAMENTO (UE) N. 10/2011 della commissione riguardante i materiali e gli oggetti di materia plastica destinati a venire a contatto con i prodotti alimentari, come modificato dal REGOLAMENTO (UE) N. 202/2014 della commissione

3.2.S.7 Stability

- Riassunto degli studi di stabilità effettuati sul principio attivo e le conclusioni relative alle condizioni di conservazione e al "re-test period "
- Protocolli post -approval ed eventuali commitment
- Dati di stabilità inseriti in forma appropriata (forma narrativa e/o tabelle e/o grafici)

Re-test period: **"***The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be retested for compliance with the specification and then used immediately. A batch of drug substance can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification."*

Principi attivi: come sono presentate le informazioni?

In base al tipo di principio attivo è possibile presentare i dati seguendo una delle tre possibili opzioni indicate nella GL *CHMP/QWP/297/97/rev 1 corr:*

- **CEP** (Certificate of Suitability European Pharmacopoeia): solo in caso di p.a. riportati in Ph.Eur.
- **ASMF** – Active Substance Master File: in riferimento sia a nuovi principi attivi, sia a principi attivi esistenti non inclusi in Farmacopea Europea (o in una Farmacopea di uno stato membro), sia a principi attivi inclusi in Farmacopea Europea (o in una Farmacopea di uno stato membro)
- **Dati completi presenti sul modulo 3**

Qualsiasi sia la procedura seguita, i dati devono essere riportati secondo la struttura 3.2.S CTD

Principi attivi: come sono presentate le informazioni? ASMF

I dati sul p.a. (es. caratteristiche chimiche, processo produttivo, controlli durante la produzione, convalida di processo…) possono essere presentati in un ASMF. Le informazioni sono suddivise in due parti:

Restricted part (RP): **informazioni confidenziali** (es. descrizione dettagliata del processo di sintesi)

Applicant's part (AP): tutte le informazioni necessarie perchè l'Applicant possa assumersi le proprie responsabilità sul p.a. (es. schema della sintesi, specifiche, dati sui lotti, stabilità …)

Le Autorità competenti/EMA hanno pieno accesso alle informazioni complete (RP+AP), necessarie per la valutazione

Rif. Guideline on Active Substance Master File Procedure
CPMP/QWP/227/02/rev 3
(in vigore dal 1 ottobre 2012)

Valutazione ASMF

	EDQM → CEP	EU (MR/DC, NCA)
Incoming identical ASMF (same manufacturer,…)	once	Reference to several applications
Assessment ASMF	One assessment/ASMF Two assessors One LoQ	several assessment/identical ASMF several assessors several LoQ

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

19 May 2011
EMA/252320/2011
Working Group on Active Substance Master File Procedures

Mandate of the Working Group on Active Substance Master File Procedures

In order to harmonise assessment of ASMFs, reduce the frequent updates of ASMFs, and reduce the resource and regulatory burden on Competent Authorities, ASMF and MA holders, the Working Group on Active Substance Master File Procedures has established a worksharing procedure for the assessment of ASMFs, including a centralised EU numbering system for ASMFs and a centralised repository for the ASMF assessment reports.

CEP

Rilasciato dall'EDQM (European Directorate for the Quality of Medicines)

- Nel caso di p.a. descritti in Ph. Eur. l'Applicant può utilizzare il CEP per sostituire alcune delle informazioni necessarie sul modulo 3

- La presentazione del CEP è opzionale e non obbligatoria per i p.a. di Ph. Eur., tuttavia rappresenta l'opzione da preferire a dimostrazione che un p.a. utilizzato nella produzione di un prodotto medicinale è conforme ai requisiti di Ph. Eur.

- Il CEP sostituisce i dati delle corrispondenti sezioni del modulo 3 e pertanto non è necessario richiedere ulteriori informazioni eccetto quelle relative a quelle caratteristiche fisico-chimiche del p.a. non coperte dal CEP (es. particle size o polimorfismo) o i dati di stabilità ove il "retest period" non sia riportato sul CEP

    - Anche la compliance TSE può essere dimostrata tramite CEP

…CEP: informazioni riportate

- Nome della sostanza attiva
- Holder, siti di produzione
- Monografia di riferimento
- Data di validità (5 anni)

Se necessario:

- Impurezze/solventi/catalizzatori aggiuntivi con limiti e metodi
- Retest period, con condizioni di conservazione e contenitore
- Omissione di test riportati in monografia quando non pertinenti (TLC quando sostituita, solventi specifici…)

…CEP

- Omissione di Test

  Nel caso in cui la monografia di Ph. Eur. menzioni un test per una data impurezza (catalizzatore, reagente, solvente) che non è però impiegata dal produttore del p.a. oggetto del CEP, il test per questa impurezza può essere omesso dai controlli sul principio attivo: questa informazione deve essere chiaramente riportata sul CEP rilasciato

- Aggiunta test

  Se la monografia non controlla impurezze aggiuntive, gli assessor EDQM controllano se il produttore ha fornito test adeguatamente validati, queste vengono menzionate sul CEP e il metodo usato, non previsto dalla Ph. Eur. , aggiunto come annex

Es. CEP

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 2007-001-Rev 00

Name of the substance:
ZINC UNDECYLENATE

Name of holder:
EDQM
7 allée Kastner
France-67081 Strasbourg

Site(s) of production:
EDQM
7 allée Kastner
France-67081 Strasbourg

After examination of the information provided on the manufacturing method and subsequent processes (including purification) for this substance on the site(s) of production mentioned above, we certify that the quality of the substance is suitably controlled by the current version of the monograph **ZINC UNDECYLENATE** no. 539 of the European Pharmacopoeia, current edition including supplements, only if it is supplemented by the test(s) mentioned below, based on the analytical procedure(s) given in annex.

- Test for residual solvents by gas chromatography (Annex 1)
  Ethanol not more than 5000 ppm

The holder of the certificate has declared the absence of use of material of human or animal origin in the manufacturing of the substance.

The submitted dossier must be updated after any significant change that may alter the quality, safety or efficacy of the substance.

Manufacture of the substance shall take place in accordance with the Good Manufacturing Practice and in accordance with the dossier submitted.

Failure to comply with these provisions will render this certificate void.

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

This certificate is granted within the framework of the procedure established by the European Pharmacopoeia Commission [Resolution AP-CSP (93) 5 as amended] for a period of five years starting from **1 April 2007**. Moreover, it is granted according to the provisions of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.

This certificate has one annex of 3 pages.
This certificate has:
lines.

On behalf of the
Director of EDQM & HealthCare

Strasbourg, 1 April 2007

DECLARATION OF ACCESS *(to be filled in by the certificate holder under their own responsibility)*

EDQM, as holder of the certificate of suitability

R0-CEP 2007-001-Rev 00 for ZINC UNDECYLENATE

hereby authorises .....
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holder)*:

Address: 7, allée Kastner, CS 30026 - F - 67081 Strasbourg (France)
Telephone: 33 (0) 3 88 41 30 30 - Fax: 33 (0) 3 88 41 27 71 - e-mail: cep@edqm.eu
Internet : http://www.edqm.eu

… CEP

- Il riferimento al(i) CEP viene riportato nelle relative sezioni della parte 3.2.S
- Copia del(i) CEP viene fornita nel modulo 3.2.R (e nell'annex 6.10 dell'application form nel Modulo 1)
- Le informazioni non coperte dal CEP devono essere fornite nelle relative sezioni della parte 3.2.S
- CEP non sono equivalenti ai certificati di analisi che devono essere presentati per dimostrare compliance

…CEP and GMP

A CEP is neither equivalent to a GMP certificate nor does it replace it

- When submitting a CEP application, the manufacturer has to commit that the substance covered by the CEP is produced according to GMP requirements
- Sites inspected based on a risk evaluation → no routine inspection of all sites
- As a consequence, a CEP may be granted with, prior to or without an inspection of the manufacturing site being performed
- In case negative outcome: → CEP withdrawal or suspension

GMP API: QP declaration

According to the European Legislation the Manufacturing Authorization Holder is responsible to assure that only active substances manufactured according to the GMP and distributed according to the GDP are used to manufacture a medicinal product (*Directive 2011/83/EC, as amended; art. 46 f*)

The responsibility is taken on by the QP trough the QP Declaration

Sostanze attive: considerazioni riassuntive

La documentazione presentata deve essere conforme ai requisiti previsti da:

- Allegato I D.L.vo 219/2006
- EudraLex - Volume 2 "Notice to Applicants" (**CTD**)
- Farmacopea Europea, ove applicabile (*legally binding*)
- Linee guida europee (*Facilitates assessment approval and control*

  Alternative approaches may be taken – provided appropriate justification)

con particolare attenzione a:

- Processo di produzione (GMP/QP declaration, starting materials)
  - Caratteristiche chimico-fisiche che influenzano anche la qualità del prodotto finito con impatto su efficacia (es. particle size, polimorfismo) e sicurezza (es. profilo di impurezze, solventi residui)

3.2.P. Drug Product

- 3.2.P.1 Description and Composition
- 3.2.P.2 Pharmaceutical Development
- 3.2.P.3 Manufacture
- 3.2.P.4 Control of Excipients
- 3.2.P.5 Control of Drug Product
- 3.2.P.6 Reference Standards or Materials
- 3.2.P.7 Container Closure System
- 3.2.P.8 Stability

3.2.P.1 Description and Composition of the Drug Product

Descrizione generale del prodotto finito e la sua composizione. La descrizione include informazioni su:

- forma farmaceutica
- composizione (lista dei componenti con le relative quantità, incluso *overage* o *overfill*, funzione e standard qualitativo)
- descrizione dei diluenti per la ricostituzione (se pertinente)
- tipo di contenitore e sistema di chiusura

3.2.P.2 Pharmaceutical Development (1)

- Attraverso una corretta formulazione si rende il principio attivo “somministrabile” nelle quantità e nelle modalità più adatte ad espletare l’effetto farmacologico ricercato e a limitare gli effetti tossici

- Le indagini che portano allo sviluppo della formulazione più adeguata, con la scelta della qualità del principio attivo, degli eccipienti, del processo di produzione e del contenitore nel quale la forma farmaceutica sarà dispensata, rappresentano lo sviluppo farmaceutico

3.2.P.2 Pharmaceutical Development (2)

- 3.2.P.2.1 Components of the Drug Product
- 3.2.P.2.2 Drug Product
- 3.2.P.2.3 Manufacturing Process Development
- 3.2.P.2.4 Container Closure System
- 3.2.P.2.5 Microbial attribute
- 3.2.P.2.6 Compatibility

3.2.P.2 Pharmaceutical Development (3)

- Discussione compatibilità tra p.a. ed eccipienti. Nel caso di combinazioni fisse deve essere discussa anche la compatibilità dei p.a. tra loro
- Identificazione caratteristiche chimico-fisiche del principio attivo che influenzano la perfomance del prodotto finito: solubilità, polimorfismo, distribuzione della grandezza particellare (3.2.P.2.1)
- Deve essere descritto l'impatto degli eccipienti sulla perfomance del prodotto e <u>discussa e giustificata</u> la scelta e la funzione degli eccipienti
- In particolare, come riporta la GL sugli eccipienti: "….*inclusion of antimicrobial preservatives or antioxidants in a medicinal product needs special justification. Wherever possible the use of these substances should be avoided…*

3.2.P.2 Pharmaceutical Development (4)

Es. considerazioni assessor:

- nel caso di medicinali equivalenti, riportati profili di dissoluzione comparativi tra generico e prodotto di riferimento?
- il processo produttivo del prodotto finito influenza le proprietà chimico fisiche del p.a. (es. forma polimorfa)? (3.2.P.2.3)
- la scelta dei materiali del contenitore e chiusura è adeguata a supportare la stabilità e l'uso del prodotto? (3.2.P.2.4)
- nel caso ad es. di preparazioni iniettabili gli studi di compatibilità supportano quanto riportato nel §6.6. dell'SPC? (3.2.P.2.6)

3.2.P.3 Manufacture

3.2.P.3	Manufacture
3.2.P.3.1	Manufacturer(s)
3.2.P.3.2	Batch formula
3.2.P.3.3	Description of Manufacturing Process and Process Controls
3.2.P.3.4	Controls of critical steps and intermediates
3.2.P.3.5	Process validation and / or evaluation

3.2.P.3 Manufacture

- Produttori del prodotto finito (nome, indirizzo) corrispondenti Autorizzazione alla Produzione e/o certificati GMP in modulo 1
- Batch formula (componenti, le loro quantità per lotto, il riferimento allo standard qualitativo)
- Descrizione del processo produttivo e relativi controlli in-process (IPC)
- Controllo degli step critici e degli intermedi isolati durante il processo
- Convalida del processo produttivo (dimostrazione che un determinato processo sia ripetibile fornendo un prodotto le cui caratteristiche soddisfano le specifiche definite)

GL: Manufacture of the finished dosage form: Revision 1 into effect 14/02/2018

3.2.P.4 Control of Excipients

3.2.P.4	Control of excipients
3.2.P.4.1	Specifications
3.2.P.4.2	Analytical procedures
3.2.P.4.3	Validation of analytical procedures
3.2.P.4.4	Justification of specifications
3.2.P.4.5	Excipients of human or animal origin
3.2.P.4.6	Novel Excipients *(ref to A 3)*

3.2.P.4 Control of Excipients (1)

Informazioni relative agli eccipienti:

- specifiche (es. identificazione, caratteristiche fisiche, titolo, test di purezza)
- procedure analitiche
- convalida delle procedure analitiche
- giustificazione delle specifiche

Dati "ridotti" sono richiesti nel caso di eccipienti descritti in Ph.Eur. o in una Farmacopea di uno stato membro (*vedi GL EMEA/CHMP/QWP/396951/2006*)

3.2.P.4 Control of Excipients (2)

- eccipienti di origine umana o animale (es. gelatina utilizzata nelle capsule) devono essere fornite informazioni (o CEP) riguardo alla possibile presenza di agenti responsabili di TSE (Transmissible Spongiform Encephalopathie), per valutare il rischio rispetto alla potenziale contaminazione (vedi anche 3.2.A.2)
- nuovi eccipienti (dati completi di produzione, caratterizzazione e controlli, riferimento a studi tossicologici etc..., come se si trattasse di un nuovo p.a. (vedi anche 3.2.A.3)

3.2.P.4 Control of Excipients (3)

- Porre particolare attenzione alla composizione in eccipienti nel caso di formulazioni pediatriche
- Verificare se le relative sezioni del Foglio Illustrativo siano redatte conformemente all'annex alla GL "*Excipients in the label and package leaflet of medicinal products for human use*", vol. 3B NTA EMA/CHMP/302620/2017, pubblicato ed in vigore dal 9 ottobre 2017

Name	Route of Administration	Threshold	Information for the Package Leaflet	Commenti
Aspartame (E 951)	Oral	0	Questo medicinale contiene x mg di aspartame per <dose> equivalente a x mg/<peso><volume>. Aspartame e' una fonte di fenilalanina. Può esserle dannoso se è affetto da fenilchetonuria, una rara malattia genetica che causa l'accumulo di fenilalanina perche' il corpo non riesce a smaltirla correttamente.	Aspartame ingerito oralmente è idrolizzato nel tratto gastrointestinale. Fenilalanina è il principale prodotto della sua idrolisi. Informazione da considerare nel RCP: Non sono disponibili studi né non-clinici né clinici sull'uso di aspartame nei bambini al di sotto delle 12 settimane di età.

3.2.P.5 Control of Drug Product

3.2.P.5	Control of drug product
3.2.P.5.1	Specification(s)
3.2.P.5.2	Analytical Procedures
3.2.P.5.3	Validation of Analytical Procedures
3.2.P.5.4	Batch analyses
3.2.P.5.5	Characterisation of Impurities
3.2.P.5.6	Justification of specification(s)

3.2.P.5 Control of Drug Product

- specifiche del prodotto finito (rilascio e shelf-life) (3.2.P.5.1)
- procedure analitiche (3.2.P.5.2)
- convalida delle procedure analitiche (3.2.P.5.3)
- certificati di analisi dei lotti (3.2.P.5.4)
- caratterizzazione delle impurezze (ove non fosse già fornita in 3.2.S.3.2) (3.2.P.5.5)
- giustificazione delle specifiche (3.2.P.5.6) *Rif GL ICH Q6*

Es. Specifiche

Test	Specification	Method
Description	Viscous liquid, free from visible particles	In-house (Visual)
Colour of Solution	Colourless	Ph.Eur.
pH	8.0 to 11.0	Ph.Eur.
Identification		
Macrogol 3350	Chromatographic peak corresponds to the retention time of the standard	In-house (HPLC)
Potassium	Chromatographic peak corresponds to the retention time of the standard	In-house (Ion chromatography)
Sodium	Chromatographic peak corresponds to the retention time of the standard	In-house (Ion chromatography)
Chloride	White precipitate which dissolves in ammonia	Ph.Eur
Hydrogen carbonate	A pink/red colour produced	Ph.Eur
Assay (Active ingredient content per 25ml dose)		
Macrogol 3350	12.469 to 13.781g (95-105%)	In-house (HPLC)
Potassium	25.0 to 27.6mg (95-105%)	In-house (Ion chromatography)
Sodium	177.5 to 196.1mg (95-105%)	In-house (Ion chromatography)
Chloride	223.2 to 246.6mg (95-105%)	In-house (Titrimetric)
Hydrogen carbonate	123.2 to 136.2 mg (95-105%)	In house (Titrimetric)
Preservative Assay		
Benzyl alcohol	41.0 to 50.2mg (90-110%)	In-house (HPLC)
Methyl hydroxybenzoate	10.2 to 12.4mg (90-110%)	In-house (HPLC)
Ethyl hydroxybenzoate	5.0 to 6.2mg (90-110%)	In-house (HPLC)
Microbiological Contamination		
Microbiological Contamination	Complies with Ph.Eur. for microbiological quality of non-sterile pharmaceutical aqueous preparations for oral use	Ph.Eur.

3.2.P.5 Control of Drug Product

Es. considerazioni assessor:

- Sono inclusi i test previsti dalla Ph. Eur. per quella determinata forma farmaceutica?
- Sono inclusi test particolarmente significativi in quanto correlati a biodisponibilità/efficacia (es. dissoluzione) e sicurezza (impurezze o sterilità ed endotossine batteriche per prodotti sterili)?
- Le specifiche proposte sono adeguatamente giustificate?
- La convalida dei metodi analitici, ove necessaria, è stata condotta in accordo a quanto previsto dalla ***GL ICH Q2 (R1) Validation of analytical procedures: text and methodology***
- I risultati delle analisi confermano la consistency tra i lotti e l'uniformità del prodotto?

EMA/425645/2020
22 February 2021

European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) No 726/2004 for nitrosamine impurities in human medicines

February 2021
CMDh/412/2019, Rev.10

CMDh practical guidance for Marketing Authorisation Holders of nationally authorised products (incl. MRP/DCP) in relation to the Art. 5(3) Referral on Nitrosamines

3.2.P.6 Reference Standards or Materials

- Informazioni sugli standard di riferimento utilizzati per l'analisi del prodotto finito (per esempio standard del principio attivo o delle impurezze)

- Riferimento alla sezione 3.2.S.5.

3.2.P.7 Container Closure System

- Descrizione del contenitore e sistema di chiusura e del confezionamento secondario
- Informazioni sull'identità dei materiali di ciascuno dei componenti del confezionamento primario e relative specifiche: compliance alla Famarcopea Europea e ai Regolamenti europei per i prodotti alimentari
- Giustificazione della scelta del contenitore in base alle proprietà fisico-chimiche del prodotto (es. adeguata protezione dalla contaminazione microbica?)
- Eventuali studi di estrazione e/o di interazione per dimostrare che il contenitore scelto è sicuro e che non vi sia rilascio di sostanze o interazioni dei componenti con gli ingredienti del prodotto finito (in particolare per materiale plastico contenente formulazioni liquide)
  - Conferma che i contenitori descritti sono quelli utilizzati negli studi di stabilità

3.2.P.8 Stability

Lo scopo degli studi di stabilità è determinare la *shelf-life* (periodo di validità) e le condizioni di conservazione del prodotto medicinale

- Studi condotti, protocolli usati, risultati ottenuti (sia in condizioni long-term che accelerate) e conseguenti conclusioni relativamente alle condizioni di conservazione e periodo di validità sia nel confezionamento primario integro che, se necessario, dopo prima apertura (stabilità "in-use").
- Protocolli di studi di stabilità post-approval e commitment
- Dati di stabilità inseriti in forma appropriata (forma narrativa e/o tabelle e/o grafici).

Gli studi di stabilità devono essere condotti in accordo a quanto previsto dalle ICH e CHMP/QWP GL corrispondenti

Example of stability results

Stability Study started:	**16-May-05**								
Storage conditions:	**25°C/60%RH**								
Container:	**Blister: Alu/PVC/PVDC**								
Test Point (Month):	**0**	**3**	**6**	**9**	**12**	**18**	**24**	**36**	**48**
Appearance:	Complies	Complies	Complies	Complies	Complies	Complies			
Disintegration (min,sec):	01, 15	00, 52	00, 48	00, 36	00,55	01, 01			
Friability (%):	0,1	0,1	0,0	0,1	0,1	0,0			
Resistance to Crushing (N):	71 - 80	64 - 72	60 - 74	61 - 72	60 - 69	61 - 70			
Loss on Drying (%):	n.p.	4,9	4,7	4,6	4,7	4,1			
Identification:	Complies	n.p.	n.p.	n.p.	n.p.	n.p.			
Assay (mg):	24,7	25,1	24,6	25,4	24,9	24,9			
(% declared amount):	98,8	100,4	98,4	101,6	99,6	99,6			
Related substances:									
Captopril Disulphide (%):	0,16	0,23	0,28	0,33	0,38	0,48			
Single unidentified impurity (%):***	< 0.05	N.D.	N.D.	N.D.	N.D.	< 0.05			
Total unidentified impurities (%):	< 0.05	N.D.	N.D.	N.D.	N.D.	< 0.05			
Dissolution: (%Mean) Captopril dissolved after 20 min:	105,0	102,1	96,9	102,9	104,4	92,5			
Microbiological quality:	Complies	n.p.	n.p.	n.p.	n.p.	n.p.			

Storage conditions

Testing conditions where the product is stable	**Required labelling statement**	**Additional labelling statement*, where relevant** * *Depending on the pharmaceutical form and the properties of the product, there may be a risk of deterioration due to physical changes if subjected to low temperatures.*
25° C/60%RH (long term) 40° C/75%RH (accelerated) or 30° C/65%RH (long term) 40° C/75%RH (accelerated)	None *SPC and PL statements:* *This medicinal product does not require any special storage conditions*	Do not refrigerate or freeze
25° C/60%RH (long term) 30° C/60 or 65%RH (intermediate) or 30° C/65%RH (long term)	Do not store above 30° C or Store below 30° C	Do not refrigerate or freeze
25° C/60%RH (long term)	Do not store above 25° C or Store below 25° C Do not refrigerate or freeze	Do not refrigerate or freeze
5° C ± 3° C (long term)	Store in a refrigerator or Store and transport refrigerated *SPC and PL should include a reference to the temperature range e.g. (2° C to 8° C)*	Do not freeze
Below zero	Store in a freezer or Store and transport frozen	

3.2.P.8 Stability

Es. considerazioni assessor

- Gli studi sono condotti in accordo alle correnti ICH/CHMP GL?
- I metodi analitici usati sono uguali o differenti da quelli descritti in P.5? Sono validati?
- Le specifiche differenti da quelle al rilascio sono giustificate?
- Si può concludere che il periodo di validità proposto è giustificato dai risultati ottenuti? Presentati dati di analisi statistica a supporto di eventuale estrapolazione (*vedi ICH Q1E*)?
- Le condizioni di conservazione sono giustificate dai dati di stabilità?
- I contenitori usati negli studi di stabilità sono quelli proposti per il commercio?
- Sono condotti gli studi di stabilità "in use" ove necessario?
- I risultati degli studi di stabilità sul periodo di validità e le condizioni di conservazione (anche "in-use") sono "riflessi" nelle relative sezioni di SPC/PL/label?

Aspetti principali da considerare

Drug substance	Drug product
Compliance to • European Pharmacopoeia, if applicable • EU quality guidelines Focus on: • Manufacturing process (synthesis) (GMP, QP declaration, starting materials) • Chemical-physical characteristics with potential impact on efficacy (particle size, polymorphism) and safety (impurity profile, residual solvents, catalysts..)	Compliance to • European Pharmacopoeia • EU quality guidelines Focus on: • Pharmaceutical development (e.g. justification for the choice of excipients, compatibility studies …) • Manufacturing process (adequate validation) • Control test and specifications • Stability studies To set "safe" shelf-life (expiry date) and storage conditions

3.2. A Appendices

- **3.2.A.1 Officine di produzione e attrezzature utilizzate** (Biotech)

- **3.2.A.2 Adventitious Agents Safety Evaluation**

  Informazioni di valutazione del rischio di potenziale contaminazione con agenti avventizi non virali (TSE, bacteria, mycoplasma, fungi) o virali

- **3.2.A.3 Nuovi Eccipienti**, non presenti in alcun prodotto medicinale autorizzato in EU, considerati come nuovi p.a. (dati completi, vedi 3.2.P.4)

3.2.R Regional Information (EU)

Questa sezione prevede l'inserimento di informazioni regionali, il contenuto quindi non è armonizzato e può cambiare in base ai requisiti richiesti dal Paese di destinazione.

3.2.R Regional Information (EU)

Per i Paesi UE:

- schema della convalida del processo di produzione del prodotto finito
- Medical Device
- Copia del (i) CEP (Certificate(s) of Suitability Ph. Eur.)
- Prodotti medicinali contenenti (o per cui si utilizzano nel processo produttivo) materiali di origine umana o animale

  (l'Applicat deve dimostrare conformità con la "*Note for guidance on minimising the risk of TSE*" oppure, se disponibile, allegare il CEP TSE)

key document: eCTD

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

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

Use of eCTD for centrally authorised products

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

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

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

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

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

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

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

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

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

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

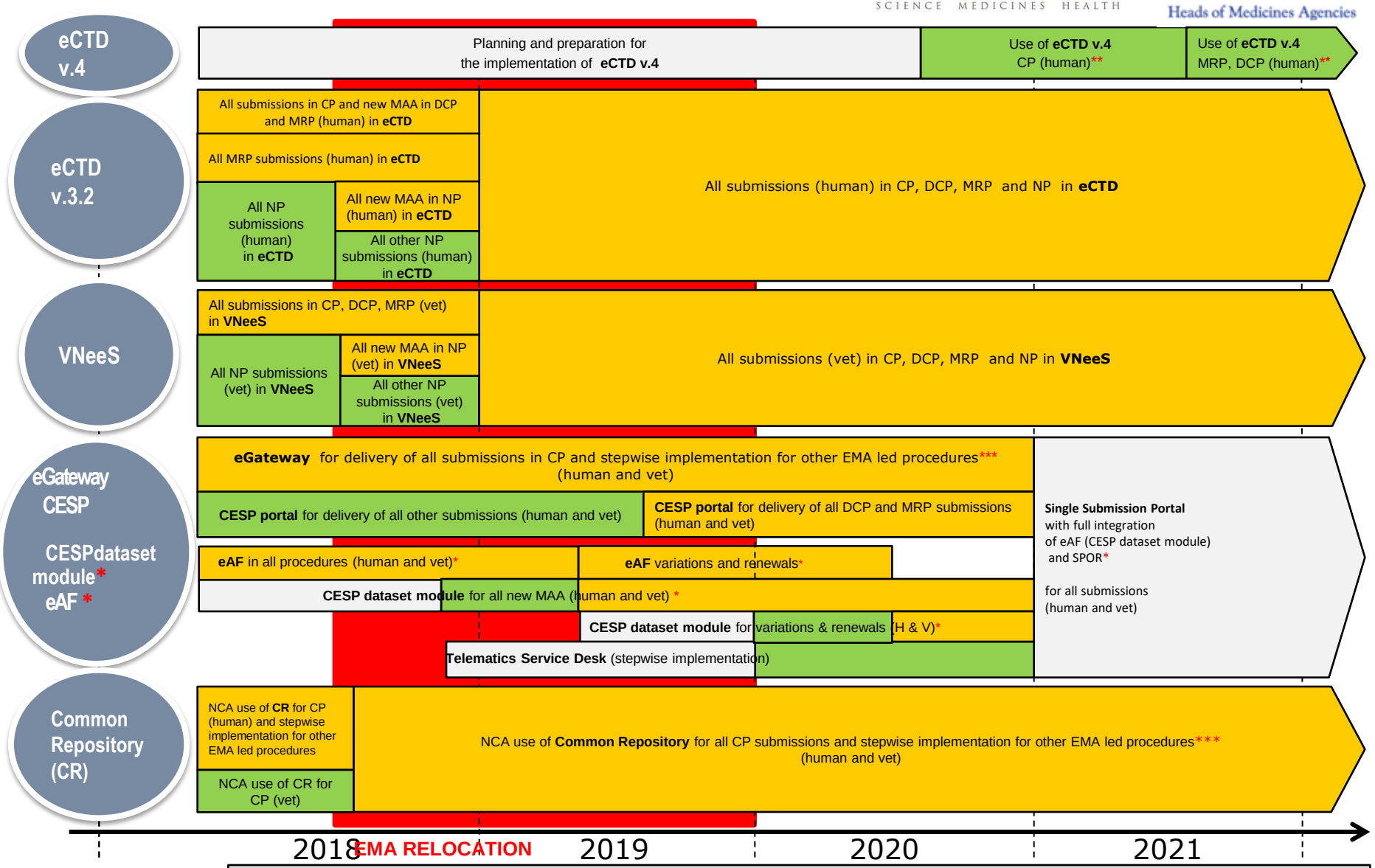
This step has been added to the updated version of the eSubmission Roadmap to have the same stepwise approach as for MRP submissions.

eSubmission Roadmap - timelines

(reflecting version 2.1 dated 28 February 2018)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HMA
Heads of Medicines Agencies



Planning in progress
Ongoing or optional
Mandatory

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

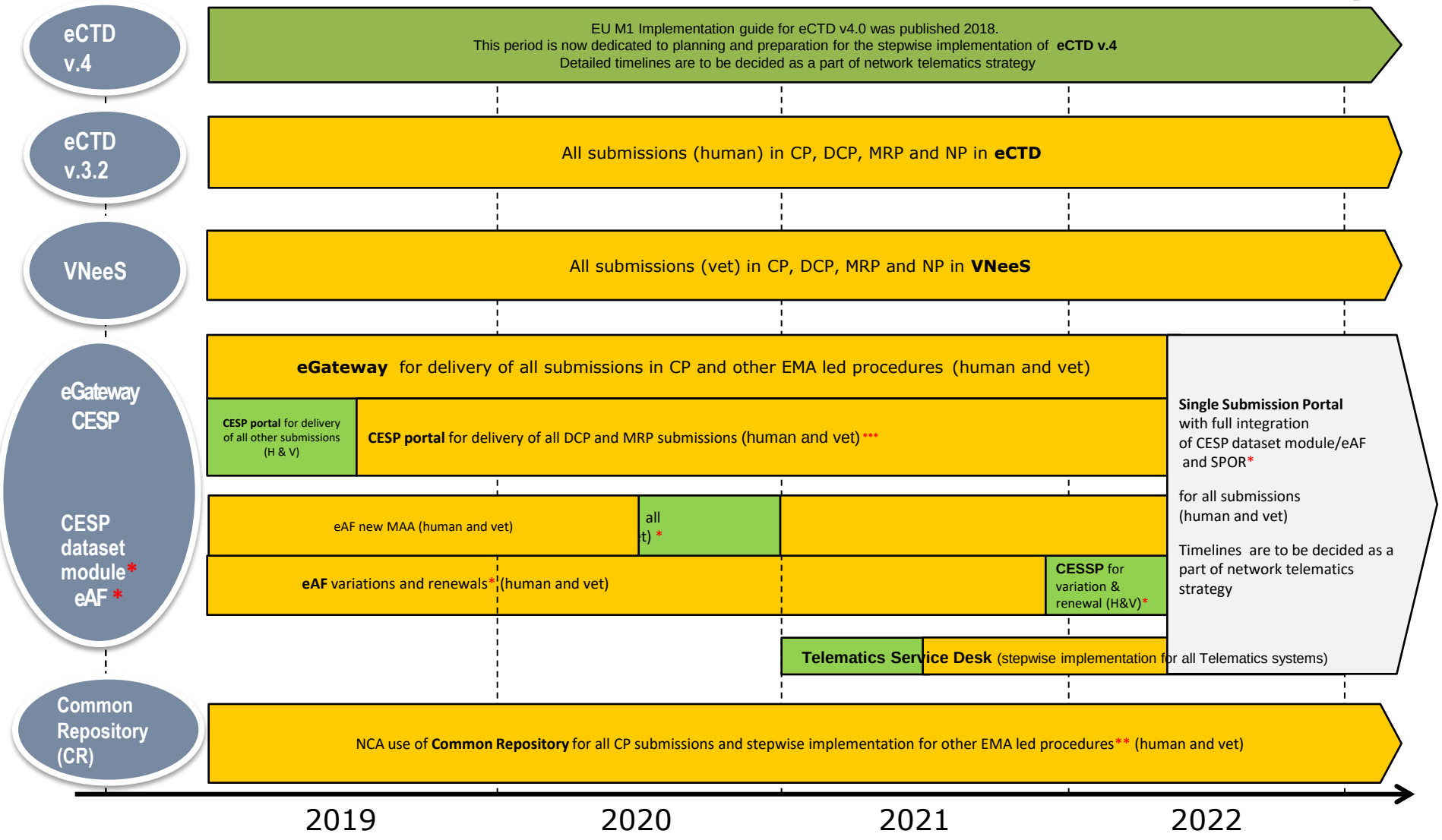
) Timelines subject to planning *) Some procedure types are excluded

eSubmission Roadmap - timelines

(reflecting version 2.2 June 2019)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HMA
Heads of Medicines Agencies



Planning in progress
Optional use
Mandatory use

*) The SPOR project stepwise (see specific Roadmap) delivers master data services (RMS, OMS, SMS, PMS) to be integrated with the eAF and CESP dataset module.
Development will follow the EU IDMP Implementation Guide and FHIR standards.
Currently, mandatory use of OMS is planned for Q2 2020, subject to outcomes of further planning exercise.

) Some procedure types are excluded *) NP: please see CMDh/CMDv websites

Esempi di impatto della parte chimico-farmaceutica del dossier sulle informazioni per il paziente ("stampati")

La Banca Dati Farmaci

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO

1. DENOMINAZIONE DEL MEDICINALE

Ceftriaxone 500 / 2 ml mg polvere e solvente per soluzione iniettabile per uso intramuscolare
Ceftriaxone 1 g / 3,5 ml polvere e solvente per soluzione iniettabile per uso intramuscolare

2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA

Ceftriaxone 500 mg/2 ml polvere e solvente per soluzione iniettabile per uso intramuscolare
Un flacone di polvere contiene:
Principio attivo: ceftriaxone bisodico 3,5 H_2O 596,5 mg pari a ceftriaxone 500 mg;

Ceftriaxone 1 g / 3,5 ml polvere e solvente per soluzione iniettabile per uso intramuscolare
Un flacone di polvere contiene:
Principio attivo: ceftriaxone bisodico 3,5 H_2O 1,193 g pari a ceftriaxone 1 g;

Per l'elenco completo degli eccipienti, vedere paragrafo 6.1.

3. FORMA FARMACEUTICA

500mg, 1 g polvere e solvente per soluzione iniettabile
Polvere e solvente per soluzione iniettabile.

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

6. INFORMAZIONI FARMACEUTICHE

6.1 Elenco degli eccipienti

Polvere:
saccarosio
sodio fosfato dibasico diidrato
sodio fosfato monobasico monoidrato
polisorbato 20
acido fosforico concentrato (per aggiustamento del pH)
sodio idrossido (per aggiustamento del pH)
L-metionina
azoto

Solvente:
acqua per preparazioni iniettabili.

6.2 Incompatibilità

Questo medicinale non deve essere somministrato con altri medicinali nella stessa siringa, ad eccezione della follitropina alfa.

6.3 Periodo di validità

3 anni.

6.4 Precauzioni particolari per la conservazione

Non conservare a temperatura superiore ai 25°C.
Conservare nella confezione originale per proteggere il medicinale dalla luce.

6.5 Natura e contenuto del contenitore

La polvere è confezionata in flaconcini da 3 mL in vetro neutro incolore (tipo I). I flaconcini sono sigillati con tappi in bromobutile protetti da ghiera e capsule di chiusura a strappo in alluminio.
Il solvente è confezionato in flaconcini da 2 o da 3 mL di vetro neutro incolore (tipo I) con tappo in gomma rivestito in Teflon o in fiale da 2 mL in vetro neutro incolore (tipo I)

Confezioni da 1, 3 e 10 flaconcini con il numero corrispondente di flaconcini di solvente o fiale. È possibile che non tutte le confezioni siano commercializzate.

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO

1. DENOMINAZIONE DEL MEDICINALE

60 mg/10 ml sciroppo

2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA

Una bustina da 10 ml di sciroppo contiene
Principio attivo: levodropropizina 60 mg

Eccipienti: saccarosio, metil-para-idrossibenzoato, propil-para-idrossibenzoato

Per l'elenco completo degli eccipienti, vedere paragrafo 6.1.

3. FORMA FARMACEUTICA

Sciroppo

4.4 Avvertenze speciali e precauzioni d'impiego

Questo medicinale contiene 4 g di saccarosio per dose (10 ml): i pazienti affetti da rari problemi ereditari di intolleranza al fruttosio, da malassorbimento di glucosiogalattosio, o da insufficienza di sucrasi isomaltasi, non devono assumere questo medicinale. Da tenere in considerazione per la somministrazione a soggetti affetti da diabete mellito.

Il medicinale contiene metil para-idrossibenzoato e propil para-idrossibenzoato, noti per la possibilità di causare orticaria. In generale i para-idrossibenzoati possono causare reazioni ritardate, tipo la dermatite da contatto e raramente reazioni immediate con manifestazione di orticaria e broncospasmo.

2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA

100 ml di soluzione contengono:
Principio attivo: latanoprost 0,005 g
Una goccia contiene circa 1,5 mcg di latanoprost.
Eccipiente: Benzalconio cloruro 0,02% come conservante.

Per l'elenco completo degli eccipienti vedere paragrafo 6.1.

3. FORMA FARMACEUTICA

Collirio, soluzione
La soluzione è un liquido trasparente incolore

6.3. Periodo di validità

2 anni
Dopo la prima apertura del flacone, il medicinale deve essere utilizzato entro 28 giorni: trascorso tale periodo il medicinale residuo deve essere eliminato.

6.4. Precauzioni particolari per la conservazione

Conservare in frigorifero (2°C - 8°C), nella confezione originale per riparare il medicinale dalla luce.
Dopo la prima apertura del flacone, il medicinale deve essere conservato a temperatura non superiore a 25°C.
Riportare la data di prima apertura nell'apposito spazio previsto sulla scatola.

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

Principi base

Comunicazione: L'assessment del dossier di qualità deve prevedere un dialogo con gli assessor preclinici e/o clinici e con gli ispettori

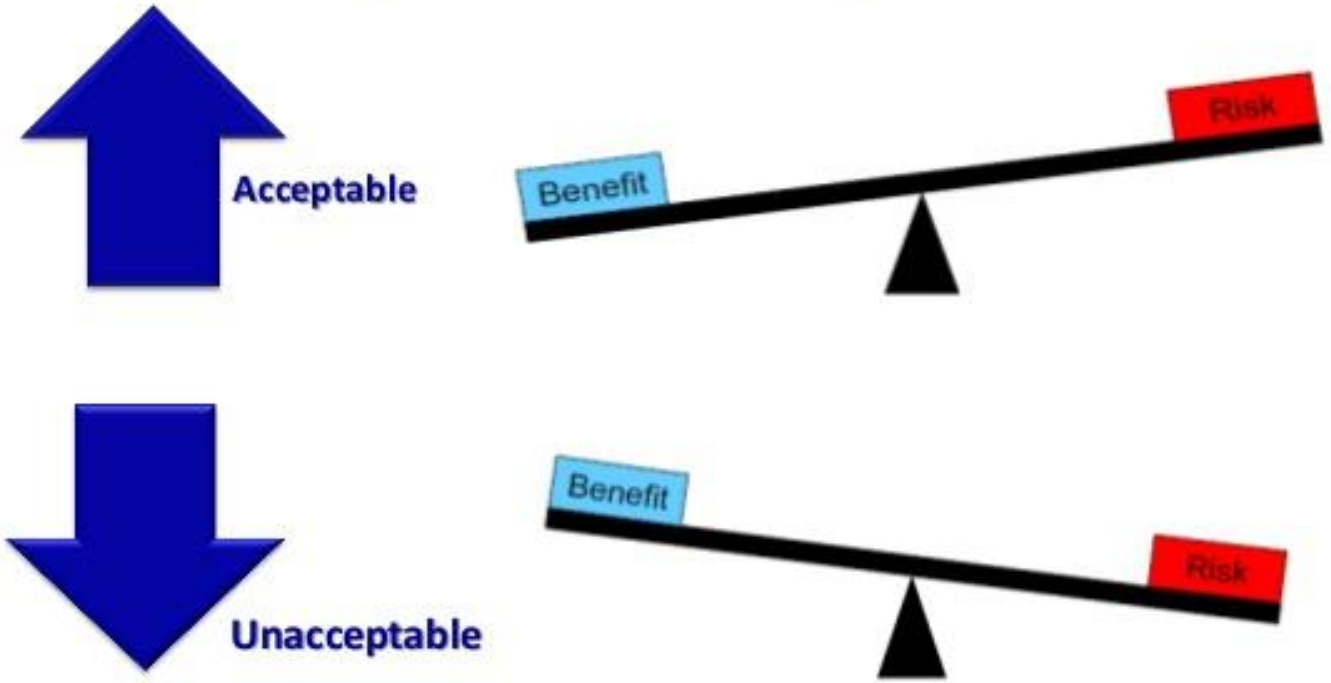
Risk-Based Pharmaceutical Assessment in relation to Efficacy and Safety: examples

Active ingredient	**Main Reason for concern (i.e. Q in relation to..**	**Links to other parts of dossier to be consulted to determine a valid 'weighting factor' for the concern**
Particle size	Bioavailability - Efficacy	Link size distribution/polimorph data to that of material used in bioavailability studies/clinical trials M5
Polymorphism	Bioavailability - Efficacy	Link polymorph data to that of material used in bioavailability studies/clinical trials, M5
Impurities	Safety	Link to toxicology studies M4 Check all impurities are qualified

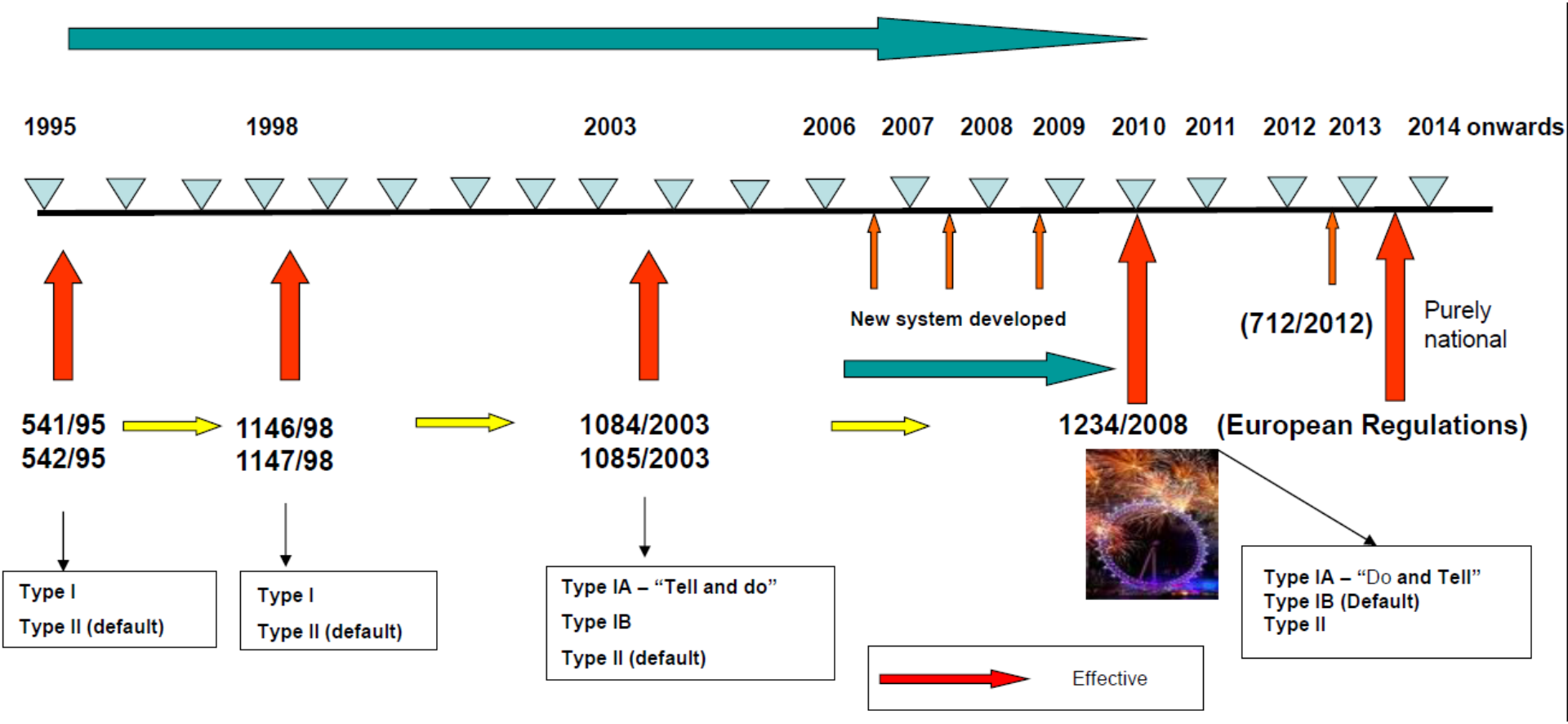
Risk-Based Pharmaceutical Assessment in relation to Efficacy and Safety: examples cont'd…

Finished product	**Main Reason for concern (i.e. Q in relation to..**	**Links to other parts of dossier to be consulted to determine a valid 'weighting factor' for the concern**
Manufacture - Sterilisation	Safety	No links – perceived risk of sterilisation failure is enough to recommend rejection of the application
Stability, degradation products	Safety	Link to tox studies - qualification of degradation products M4 Link to SPC – shelf-life and storage conditions
Compatibility with administration sets, other 'dosing devices', solvents, drugs	Safety - Efficacy	Link to SPC – check the advice given under 'administration' is correct, and in line with the compatibility studies results

VARIAZIONI al dossier di registrazione



European Variations System - Evolution



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New Variation Regulation

Regulation EC No 1234/2008

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

Implementation of specific changes:-

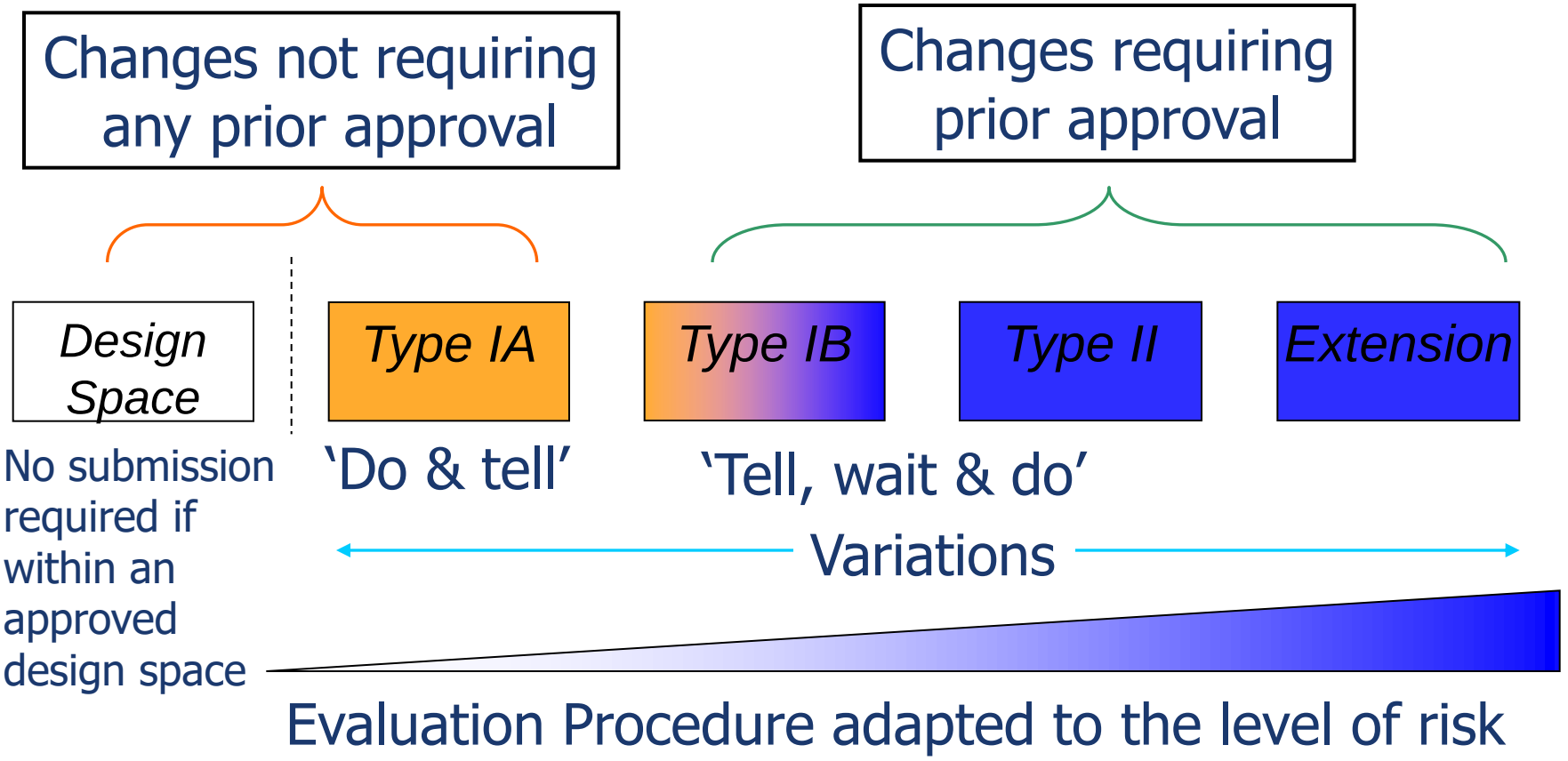
Within 90 days (2 November 2012)

Within 12 months (4 August 2013) – Purely National

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

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

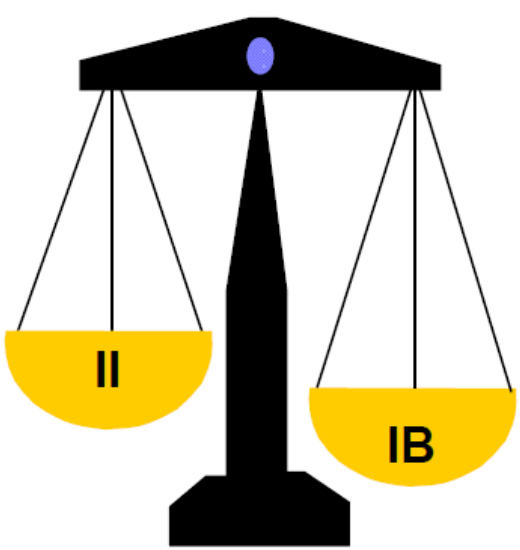
Summary - Types of Variations

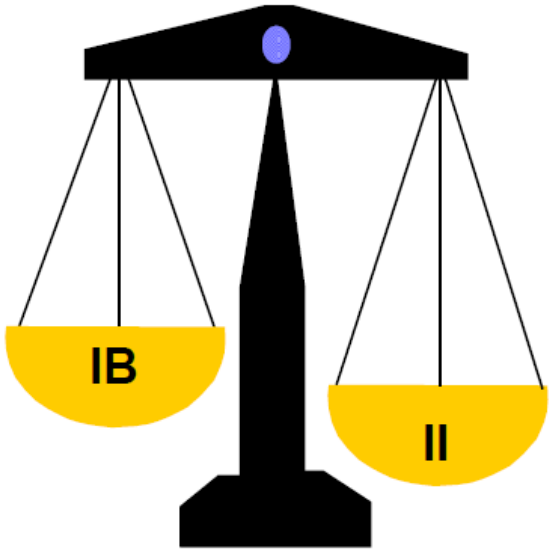


Regulation - Classification Rules

- 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	IA_{IN}
b) Primary packaging site	1, 2, 3, 4, 5	1, 2, 3, 4, 8, 9	IA_{IN}
c) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/ immunological medicinal products.			II
d) Site which requires an initial or product specific inspection			II
e) Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products.		1, 2, 3, 4, 5, 6, 7, 8, 9	IB
f) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products manufactured using an aseptic method excluding biological/ immunological medicinal products.		1, 2, 3, 4, 5, 7, 8	IB

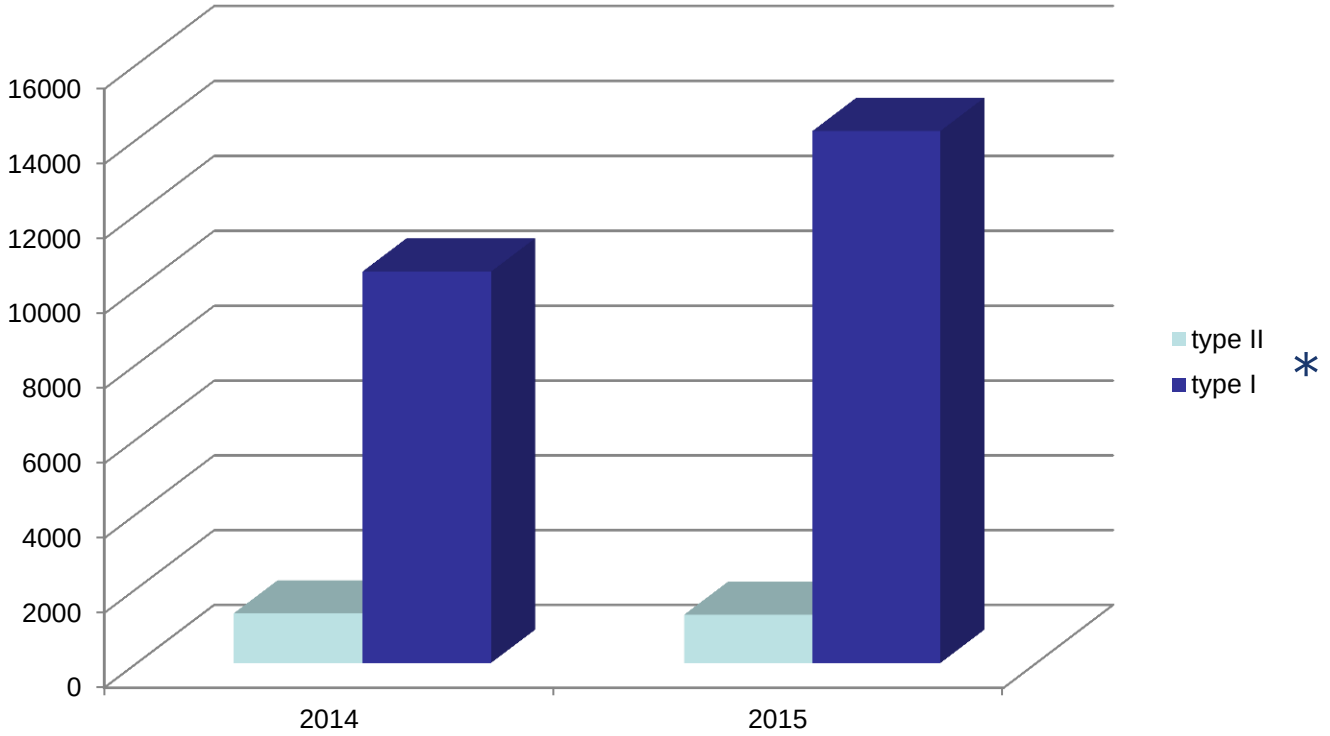
Conditions

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

Type II biological/immunological

Examples (IB)

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



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

Article 5

Recommendation on unforeseen variations

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

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

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

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

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

Type IA notifications - Key Points

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

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

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

Company should cease to apply a change if not acceptable.

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

CHAPTER 3

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

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

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

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

Type-IA variations: questions and answers

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

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

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

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

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

Back to top

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

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

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

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

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

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

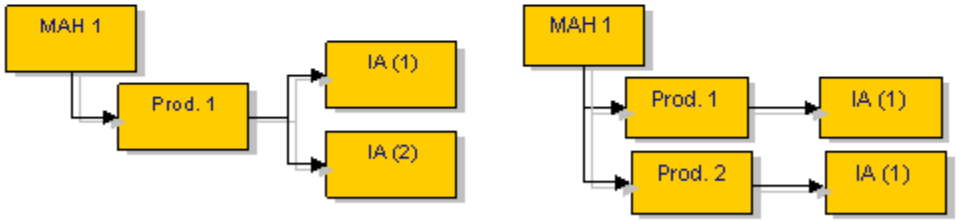
There are no recommended submission dates for type-IA variations.. However, MAHs are encouraged to avoid submitting type-IA notifications shortly before or during the Agency holiday periods (e.g. the end of July and Christmas).

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

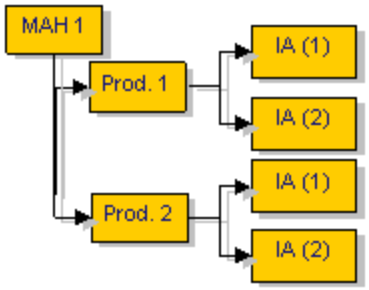
Article 7(2)(a) of the Variations Regulation sets out the possibility for a MAH to group several type-IA or -IAIN variations under a single notification to the same relevant authority, or to group them with other types of variation.

Possible grouping of type-IA and -IAIN changes only

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



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



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

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

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

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

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

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

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

Examples:

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

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

Type IA variations submitted after the 12 months following implementation:

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

please check with your NCA!

Sources of useful information

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

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

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

Question 5.2

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

Answer:

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

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

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

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

Question 5.3

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

Answer:

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

Question 4.11

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

Answer:

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

Question 3.2

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

Answer:

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

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

Question 3.10

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

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

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

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

Question 3.17

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

Answer:

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

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

Question 2.8

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

Answer:

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

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

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

Article 57

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

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

Documentation

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

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

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

Attività

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

Avviso alle Aziende Farmaceutiche

10/06/2014

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

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

In allegato:

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

Allegati

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

Link correlati

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

Argomenti correlati

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

B.II.d) Control of finished product

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

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

The previous version was:

7. The change does not concern a genotoxic impurity.

Other sources of useful information

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

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

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

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

1. ACCEPTABLE GROUPINGS

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

3. ACCEPTABLE AS SINGLE CHANGE INSTEAD OF GROUPING

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

New!

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

Worksharing (Article 20)

Sharing of assessment across multiple Marketing Authorisations (MAs)

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

The group may also contain IA changes

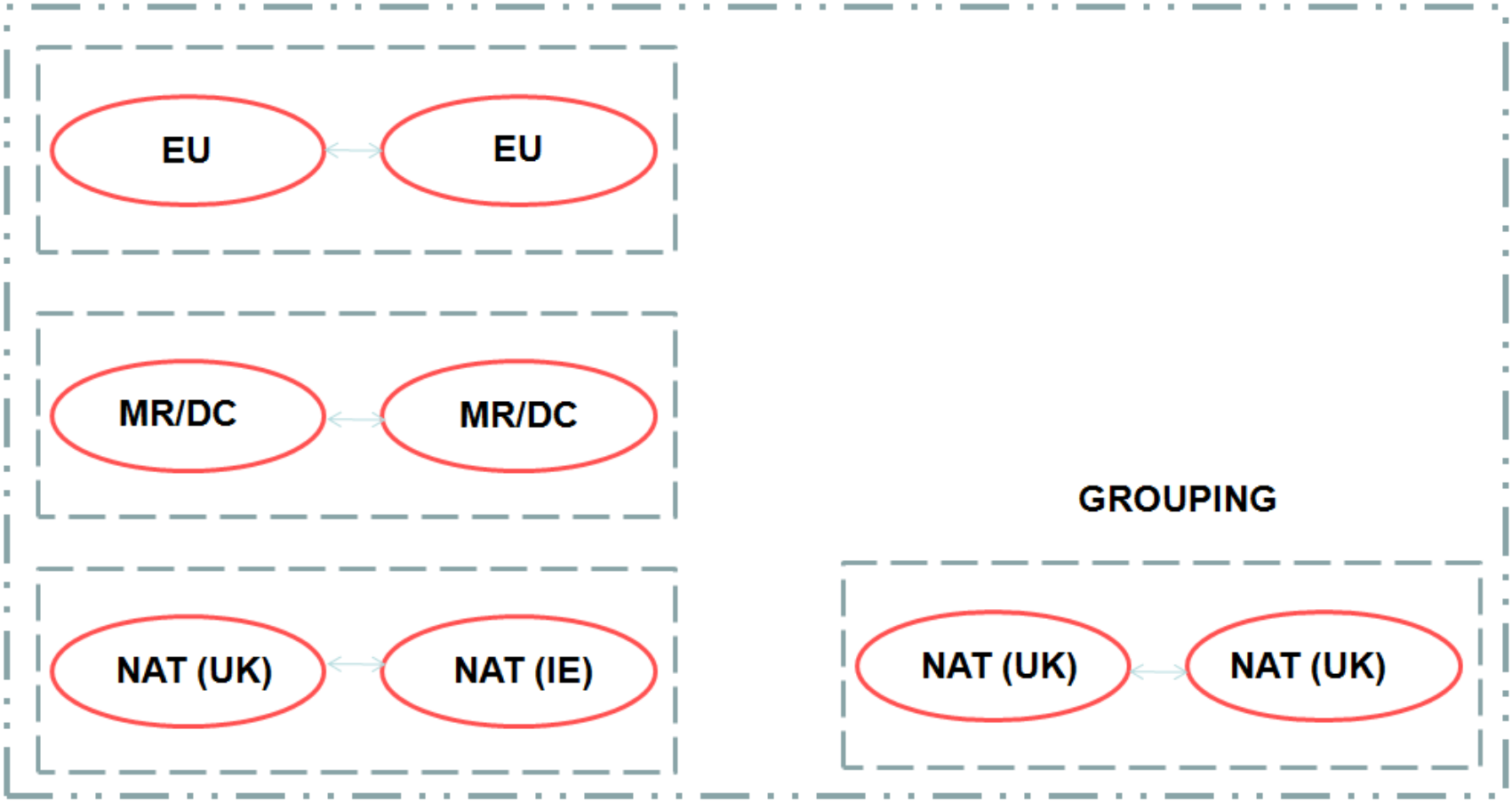
The group may not include a line extension

– The 'same' change should not necessitate any product specific assessment

Worksharing (Article 20)

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

TYPE OF WORKSHARING



Some critical points about worksharing procedures

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

Some critical points about worksharing procedures

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

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

SECTION 2

Amendments to the decision granting the marketing authorisation and implementation

Article 23

Amendments to the decision granting the marketing authorisation

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

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

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

Article 24

Implementation of variations

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

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

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

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

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

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

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

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

Extensions of marketing authorisations

1. Changes to the active substance(s):

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

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

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

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

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

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

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

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

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

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

   (a) change of bioavailability;

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

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

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

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

EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems and products
Medicinal products

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

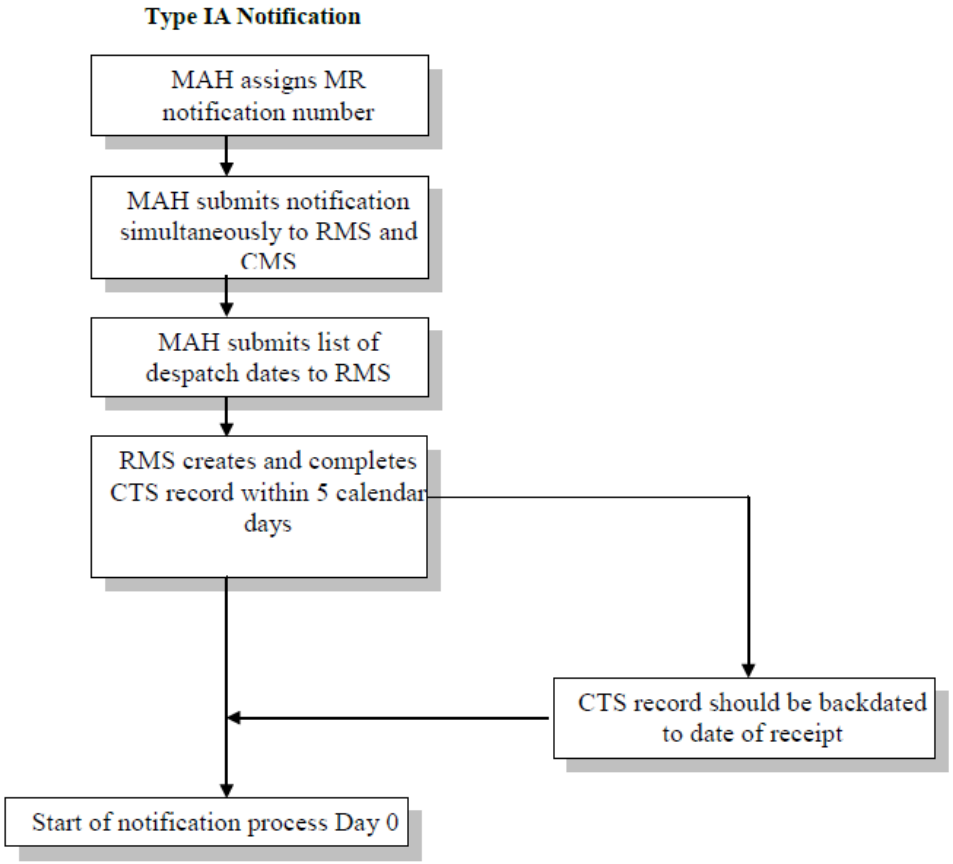
Parenterals – change of container only				
14. Solution for injection	*from* *to*	vial pre-filled syringe*(same concentration)*		**EA**[8]
	from *to*	vial pre-filled pen *(same concentration)*		**EA**[9]
	from *to*	pre-filled syringe pre-filled pen *(same concentration)*		**EA**[10]
15. Solution for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

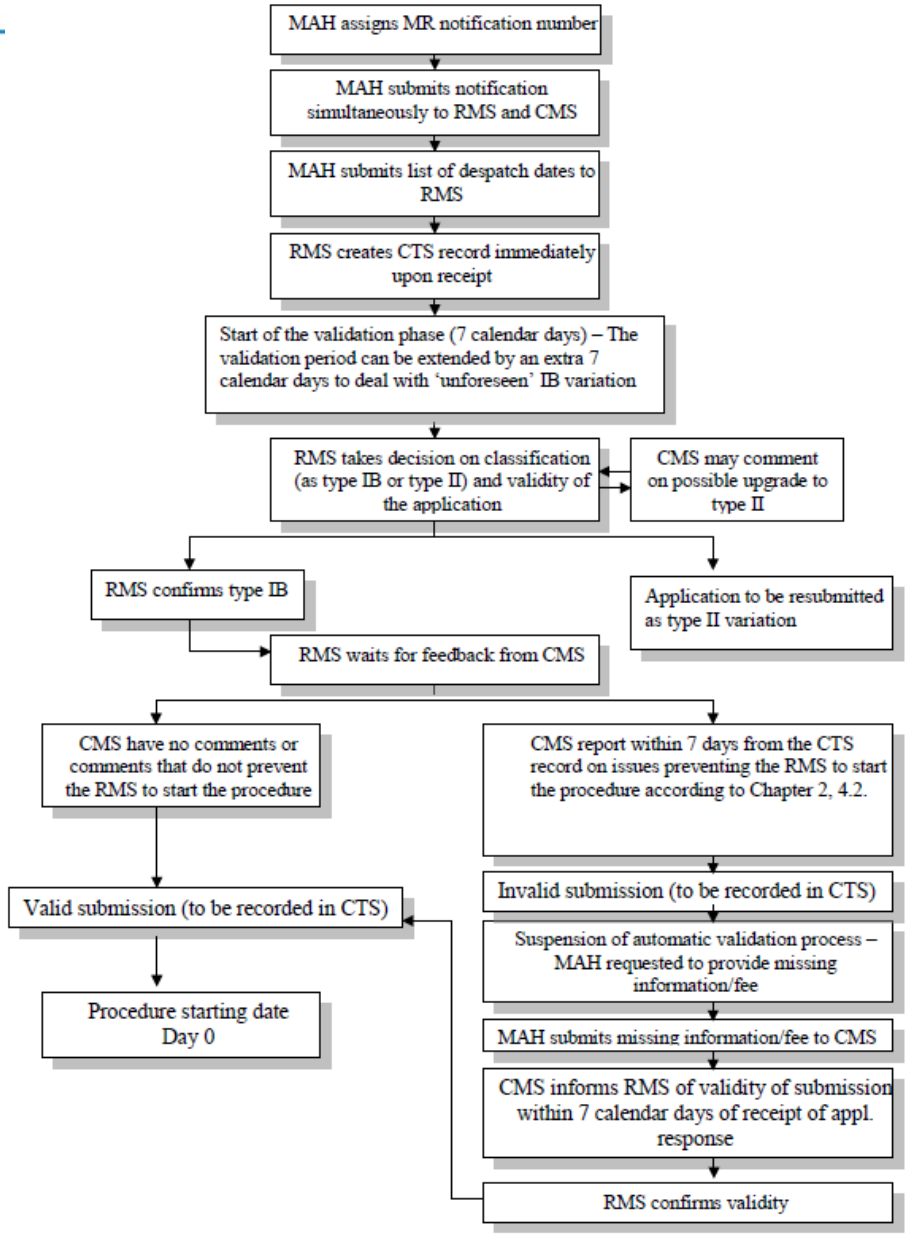
TIME-TABLES (validation)

ANNEX II

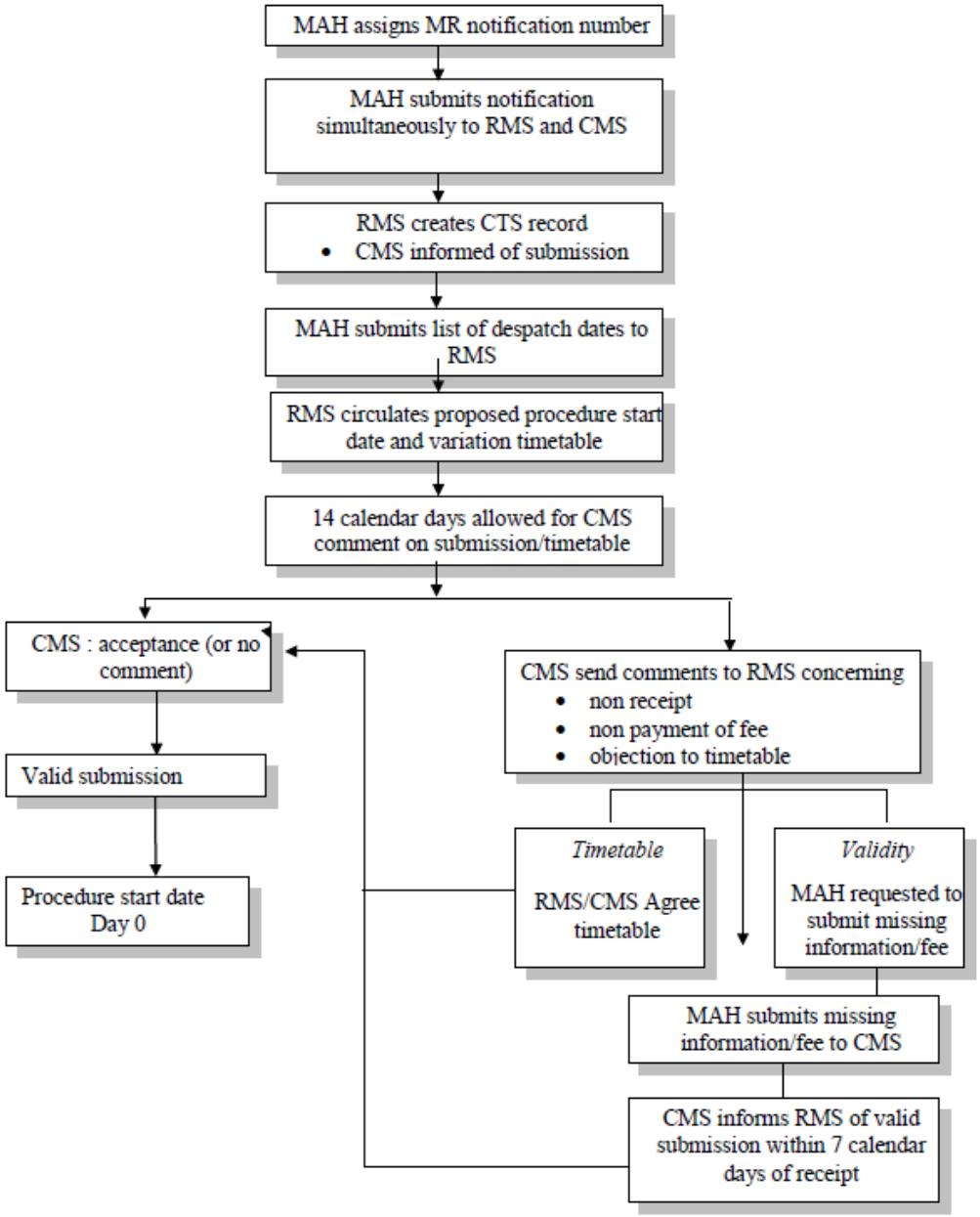
Flowchart for automatic validation: Starting the notification or variation procedure.



Type IB Notification



Type II Variation



TIME-TABLES (assessment)

Type IA

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

Type IB

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

Type IB

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

Flow-charts of the type II variation procedures:

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

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

60-day procedure for type II variations

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

90-day procedure for type II variations

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

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

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

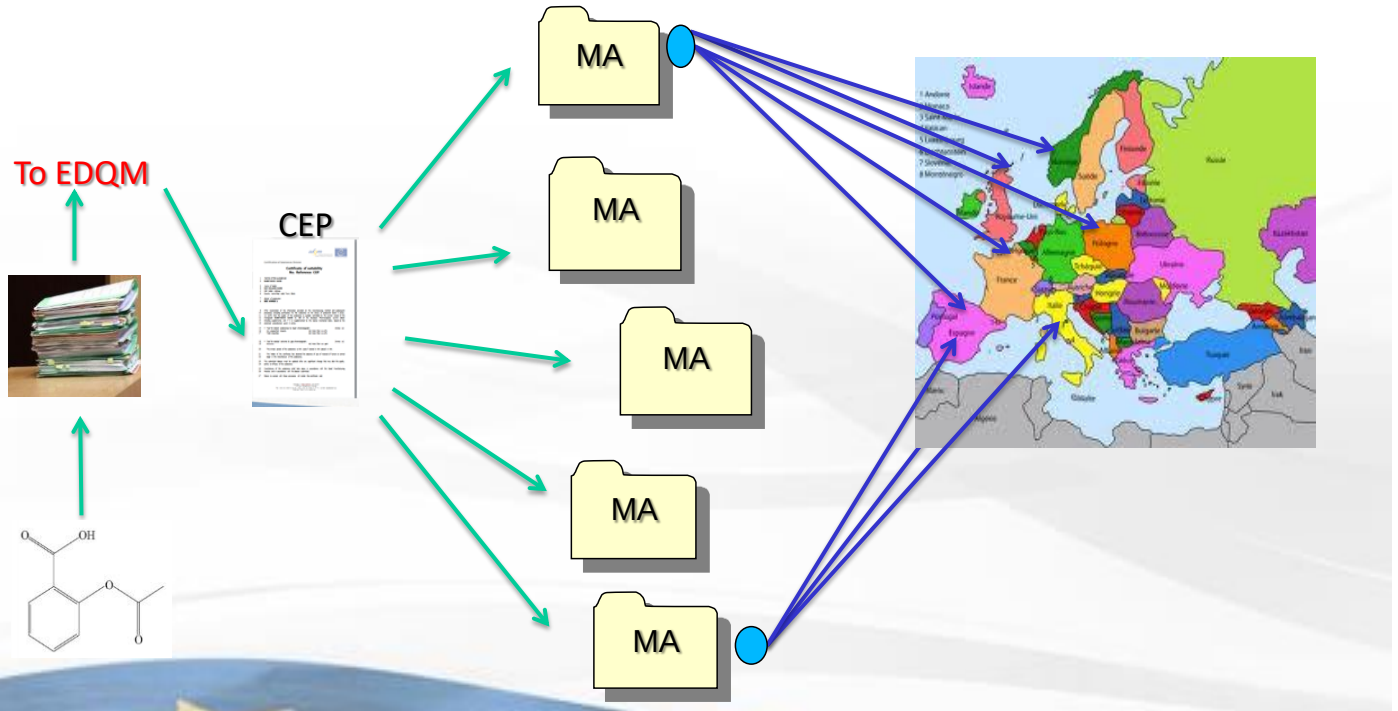
No later than day 90	If a CMS does not agree with the final opinion of the reference authority on grounds of potential serious risk to public health, the reference authority is requested to refer the application to CMDh.
Day 90	The reference authority circulates the final opinion to the CMS's and the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

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

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):

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

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

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

Examples (where specific details are given):

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

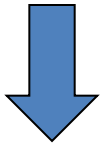
B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of specification limits for medicinal 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 February 2018):

☐ 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:

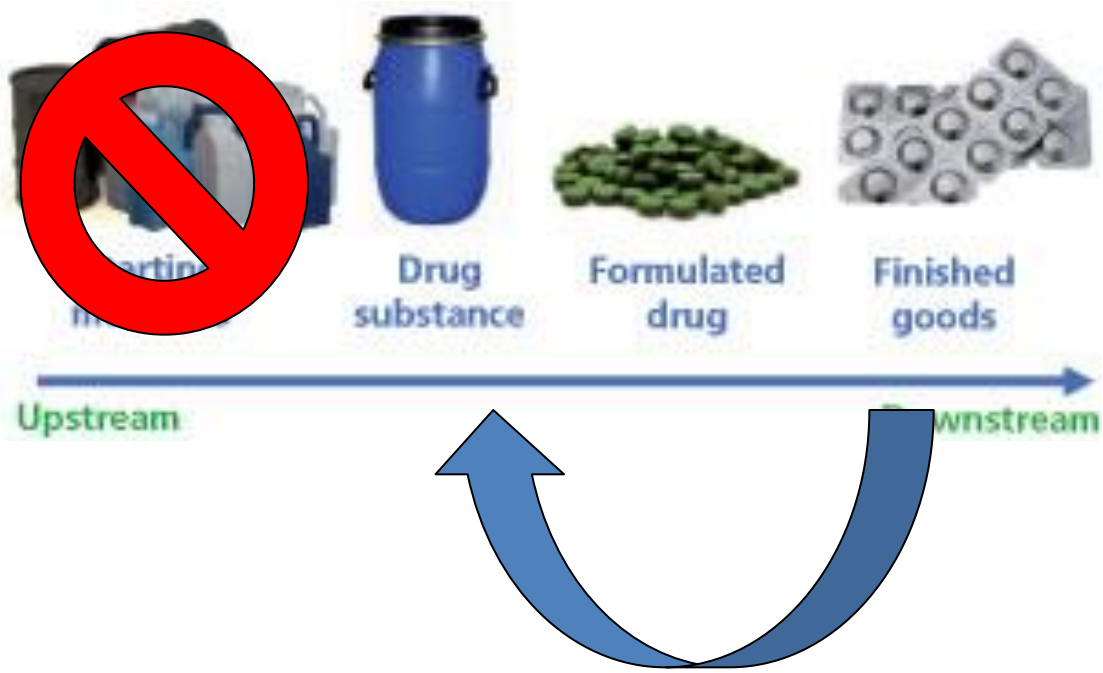
- it is signed on behalf of all the involved QPs
- the arrangements are covered by a technical agreement

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

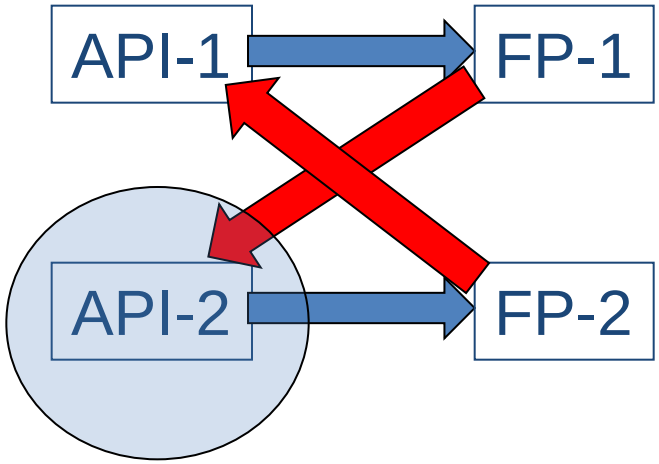
CMDh
Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

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

CMDh/340/2015/Rev.6
July 2020

Q&A – QP Declaration


Starting materials
Drug substance
Formulated drug
Finished goods
Upstream
Downstream


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

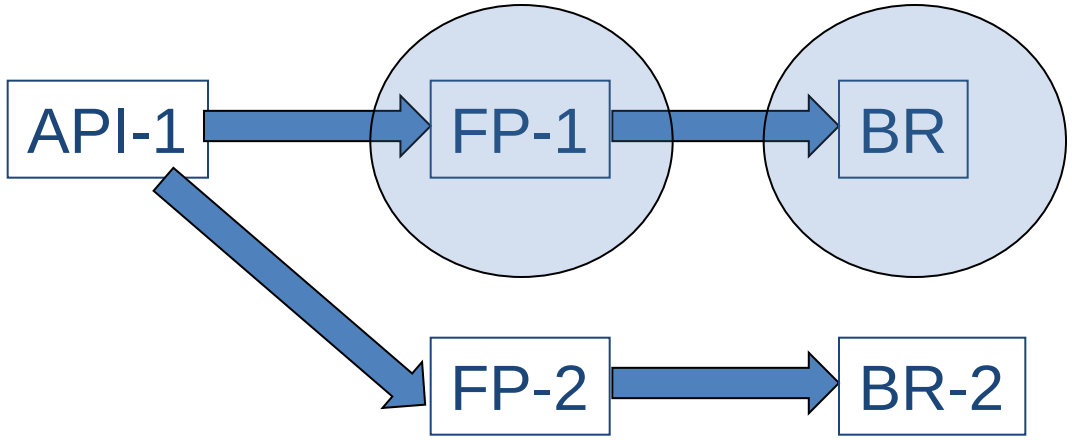
7. Which Qualified Person declaration(s) are required in support of individual types of changes to a Marketing Authorisation, to confirm that the active substance is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union?

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

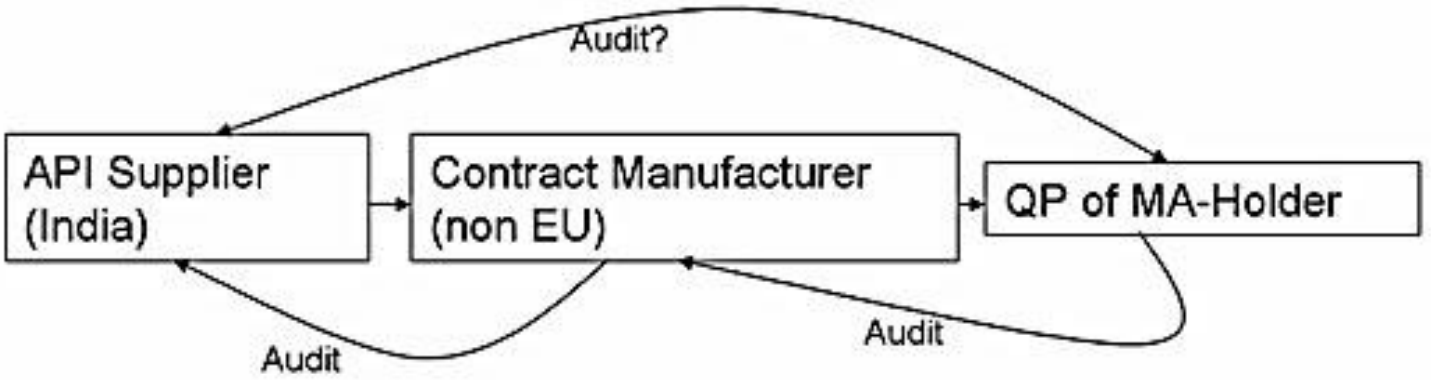

API-1
FP-1
BR
FP-2
BR-2

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.

Un ringraziamento particolare a Eugenia Cogliandro per il supporto formativo e per le slides e alla prof.ssa Carla Caramella per l'invito.

A voi GRAZIE per l'attenzione!

... ci sono domande?

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