EMA
EUROPEAN MEDICINES AGENCY

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

New Variations Guidelines webinar for MAH (human)

Tuesday, 13 January 2026

Welcome & introduction

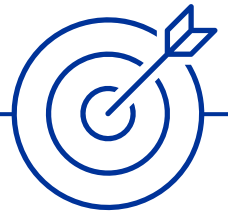
Alberto Gañan Jimenez

- Head of Committees and Quality Assurance Department, EMA

Susanne Winterscheid

- CMDh member and VRWP chair, BfArM, Germany

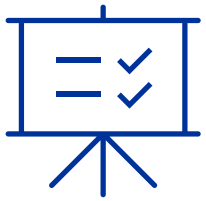
Aim of this webinar



To support stakeholders on the upcoming changes resulting from the EC Variations Guidelines (2025) that apply from 15 January 2026.

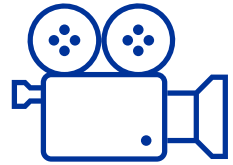
You can ask questions at slido.com #variations2026 passcode: variations

Housekeeping notes – Webinar materials



Presentation will be available at:

- EMA Event Web Page



Recording will be available at:

- EMA Event Web Page
- EMA YouTube Channel

You can ask questions at slido.com #variations2026 passcode: variations

Housekeeping notes – Q&A

You can ask questions or give your input via the audience interaction tool **Slido**.

1. **Join at slido.com** with the code #**variations2026** by scanning the QR code here:

2. **Send or upvote the questions** you want to have answered
3. **Some questions will be** addressed informally in writing on slido or **verbally addressed** in the live Q&A session

Interaction via Slido is voluntary, and you may opt to remain anonymous. If you chose to use Slido, ***you consent to the processing of your personal data*** *as explained in the EMA Data Privacy Statement for Slido.*

Agenda

- 13:00 Welcome and introduction
- 13:10 Overview of the new EC Variation Guidelines
  - Procedural aspects
  - Chapter E (Administrative changes)
  - Chapter Q & M (Quality & PMF/VAMF)
  - Chapter C (Safety, Efficacy, Pharmacovigilance changes)

- 14:00 EMA/CMDh Q&A and Guidance
- 14:35 Q&A session and closing remarks
- 15:00 End of session

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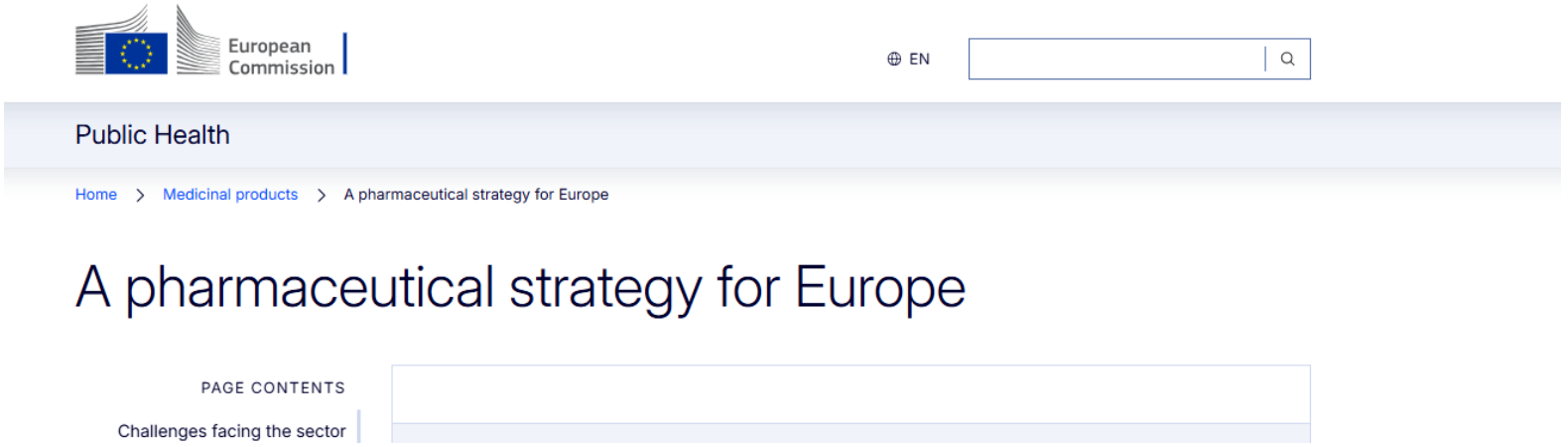
Overview of the revision of EC Variations Guidelines

Susanne Wintersheid, CMDh member and VRWP chair, BfArM, Germany

Background



- Revision of the variation's framework included in the **2020 pharmaceutical strategy for Europe**.
- **Amended Variation Regulation** (Regulation (EU) 2024/1701) was published on 17 June 2024 and became **applicable on 1 January 2025.**
- **New EC Variations Guidelines** were published on 22 September 2025 and will **apply from 15 January 2026.**
- **Second revision** of the variations framework is expected once the revision of the basic acts (Regulation/Directive) is complete

Revision of EU variations framework

- Aim to **improve the existing system** by incorporating experience gained and make the lifecycle management of medicines more:
  - **Efficient** for regulators and MAHs
  - **Future proof** with scientific and technological progress

- **Simplify** and enable an **agile review** of classification guideline and operational procedures.

- **Short-term measures** which can be done independently from the review of basic legislation.

Revision of Variations Guidelines - principles

- All categories of variations were reviewed based on **experience** acquired, the **scientific and technical progress**.
- Aim to **improve the efficiency** ensuring the protection of public health in the EU.
- When appropriate, **streamline the variation framework** (e.g. *decreasing, downgrading and simplifying the various categories of variations*).
- When possible, **future proof** the variations framework for the upcoming changes (e.g. *adapt/prepare for innovation*).
- The changes made are **compatible** with the revised Variation Regulation.

EMA/CMDh Q&As and guidelines to support implementation of revised variations guidelines

New & revised guidance:

- EMA/CMDh Guidance on the application of the revised variations framework (June/25 and Sep/25)
- Update of CMDh guidance documents to reflect new Variation Guidelines (Oct/25)
- Q&A on skip testing (Oct/25)
- Q&A on novel or complex manufacturing process (Nov/25)
- EMA's post-authorisation guidance e.g.:
  - Type IA/IB/II/Extension applications/grouping of variations (Nov/25)
  - Classification of changes: Q&A (Nov/25)
- Q&A regarding medicines used in combination with medical devices and consultation procedures by notified bodies (Nov/25)
- Guidance on stability testing for applications for variations (December 2025)
- Guidance on Post-Approval Change Management Protocol (PACMP) (December 2025)

Additional guidance upcoming:

- Guidance on Product Lifecycle Management document (PLCM) (expected in January 2026)

You can ask questions at slido.com #variations2026 passcode: variations

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Overview of the new Variations Guidelines (Procedural aspects)

Alex Correia, Regulatory Affairs Office, EMA

Main changes on procedural aspects (1/2)

- **Administrative***:
  - Updated of references to **Legislative frameworks**
  - Deletion of references to the **Veterinary Legislation**

- **Streamline of information/future-proof:**
  - Deletion of **information already covered** in the Variation Regulation or Directive 2001/83/EC
  - Deletion/shift of **practical information** to EMA/CMDh **guidance** (e.g. timetables)
  - **Reorganisation of information**: merge of repetitive information across sections (e.g. submission requirements, mutual recognition and purely national procedures,…)

* Also applicable to the Annex of the Variations Guidelines..

Main changes on procedural aspects (2/2)

- **New/updated information:**
  - **Cut-off date** set for 15 January 2026 (set by EC in June with the draft proposal).
  - List of **definitions** expanded on the Introduction section
  - Guidance on **grouping**, **super-grouping**, **annual update** of Type IA variations
  - Guidance namely on **annual update** of the EC Variations Guidelines, **influenza** and **coronovirus** vaccines, **public health emergency**
  - Change in the **coding system** from Chapter A, B, C, D to Chapter E, Q, C and M
  - Guidance on the need to **review quality documentation** in case of change in the therapeutic indication, posology or maximum daily dose

Super-grouping of Type IA variations

Super-grouping is currently possible in the following cases:

- One or several minor variations of Type IA listed in **chapters E and Q** in the MRP/DCP/purely nationally procedure if **several MSs** or **agreed with the concerned authorities**
- One or several minor variations of Type IA in the MRP/DCP if the **same RMS**
- One or several minor variations of Type IA in the **CP**

Additional cases may be identified in the future.

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Overview of the new Variations Guidelines (Annex)

Alex Correia, Regulatory Affairs Office, EMA

Elisa Pedone, Pharmaceutical Quality Office, EMA

Carmen Purdel, QWP member, Romania

Virginia Rojo, Procedure Office, EMA

Susanne Winterscheid, CMDh member and VRWP chair, BfArM, Germany

	Topic/Scope of changes	Variation
E.	ADMINISTRATIVE CHANGES	1-5
Q.	QUALITY CHANGES	
Q.I.	**Active Substance**	
	(a) Manufacture	1-6
	(b) Control of active substance	1-3
	(c) Container closure system	1-4
	(d) Stability	1
	(e) Additional regulatory tools	1-8
Q.II.	**Finished Product**	
	(a) Description and composition	1-6
	(b) Manufacture	1-5
	(c) Control of excipients	1-4
	(d) Control of finished product	1-3
	(e) Container closure system	1-8
	(f) Stability	1
	(g) Additional regulatory tools	1-8
	(h) Adventitious Agents Safety	1
Q.III.	**CEP/TSE/monographs**	1-2
Q.IV.	**Medical Devices**	1-3
Q.V.	**Changes to a marketing authorisation resulting from other regulatory procedures**	
	(a) PMF/VAMF	1-2
	(b) Referral	1
C.	SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES	1-12
M.	PMF/VAMF	1-16

Chapter E
Administrative Variations

E. Administrative Changes

E.1	Change in the (invented) name of the finished product	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	for centrally authorised medicinal products	1	1, 2	IA_{IN}
(b)	for nationally authorised medicinal products		2	IB
Conditions				
1.	The check by the EMA on the acceptability of the new name has been finalised and was positive.			
Documentation				
1.	Copy of the EMA letter of acceptance of the new (invented) name.			
2.	Revised product information.			

E.3	Change in ATC Code	Cond. to be fulfilled	Docum. to be supplied	Proced. type
		1	1, 2	IA
Conditions				
1.	Change following granting of or amendment to ATC Code by WHO.			
Documentation				
1.	Proof of acceptance (by WHO) or copy of the ATC Code list.			
2.	Revised product information.			

- **No** actual **changes** on conditions and documentation:

- Indent **E.1** (formerly A.2), concerning change in the name of the finished product.

- Indent **E.3** (formerly A.6), concerning change in ATC code.

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E. Administrative Changes

E.2	**Change in name of the active substance, excipient, medical device (part), or packaging component**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
		1	1, 2, 3	IA_{IN}
	Conditions			
	1. The active substance/excipient/medical device/packaging component must remain unchanged.			
	Documentation			
	1. For active substance and excipients, proof of acceptance by WHO or copy of the INN list. If applicable, proof that the change is in line with the Ph. Eur. For herbal medicinal product, declaration that the name is in accordance with the guideline on declaration of herbal substances and herbal preparations in (traditional) herbal medicinal products. For medical devices, updated CE certificate and/or declaration of conformity, if available.			
	2. Revised product information, as appropriate.			
	3. Amendment of the relevant section(s) of the dossier.			

E.5	**Deletion of manufacturing sites for an active substance, intermediate or finished product, storage of master and/or working cell bank, primary and/or secondary packaging site, manufacturer responsible for batch release, site where quality control takes place, and/or supplier of a packaging component, medical device (part), starting material, reagent and/or excipient (when mentioned in the dossier)**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
		1, 2	1	IA
	Conditions			
	1. There should at least remain one site/manufacturer, as previously authorised, performing the same function as the one(s) concerned by the deletion. Where applicable, at least one manufacturer responsible for batch release that is able to certify the product testing for the purpose of batch release within the EU/EEA remains in the EU/EEA.			
	2. The deletion should not be due to critical deficiencies concerning manufacturing.			
	Documentation			
	1. Amendment of the relevant section(s) of the dossier, including revised product information as appropriate.			

- **Adjusted indents**:

- Indent **E.2** (formerly A.3), concerning change in the name of the active substance or excipient, had "**medical device (part), or packaging component" added**.

- Indent **E.5** (formerly A.7) concerning deletion of sites, had the list of **explicitly referenced manufacturing activities broadened** and the **reference to medical device added**.

E. Administrative Changes

E.4	**Change in the name and/or address of the marketing authorisation holder, ASMF holder, storage site of the master and/or working cell bank, manufacturing site for an active substance, intermediate or finished product, primary and/or secondary packaging site, manufacturer responsible for batch release, site where quality control takes place, and/or supplier of a packaging component, medical device (part), starting material, reagent and/or excipient (when mentioned in the dossier)**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	(a) The change in the name and/or address concerns the marketing authorisation holder	2	1, 2	IA_{IN}
	(b) The change in the name and/or address concerns a manufacturer(s) whose activities include batch release of the finished product	1	1, 2	IA_{IN}
	(c) The change in the name and/or address does not concern a manufacturer(s) whose activities include batch release of the finished product nor the marketing authorisation holder	1	1, 2, 3	IA
	Conditions			
	1. The physical location of the concerned manufacturing site and all manufacturing operations must remain the same.			
	2. The marketing authorisation holder must remain the same legal entity.			
	Documentation			
	1. A formal document from a relevant official body (e.g. Chamber of Commerce, or if not available, from a competent authority) in which the new name and/or address is mentioned, or a copy of the modified manufacturing authorisation, if available.			
	2. Amendment of the relevant section(s) of the dossier, including revised product information as appropriate.			
	3. In case of change in the name of the holder of the Active Substance Master File, updated 'letter of access'.			

- **Consolidated / merged indents**:

- Former indents A.1, A.4 and A.5 have been combined under indent E.4, and the **list** of explicitly referenced **manufacturing activities was broadened**. The current scope is intended for changes to the name and/or address of the MAH, ASMF Holder or any of the supplier / manufacturing sites.

Chapter Q & M
Quality & PMF/VAMF

Q.I.a.1- Manufacturing site

		Cond. to be fulfilled	Docum. to be supplied	Proced. type
Q.I.a.1	**Change in the manufacturing site of a starting material/intermediate used in the manufacturing process of the active substance or change in the manufacturing site (including where relevant quality control testing sites) of the active substance**			
Manufacturing site of an active substance or starting material or intermediate				
(c)	Addition or replacement of a manufacturing site of a starting material used in the manufacture of the active substance or reagent required to be mentioned in the dossier	1, 2, 3	1, 2, 3, 4, 6	IA
(d)	Addition or replacement of a manufacturing site of — a biological active substance or — a biological starting material/reagent/raw material/intermediate used in the manufacture of a biological active substance which may have a significant impact on the quality, safety or efficacy of the finished product or — a material for which an assessment is required of viral safety and/or TSE risk			II
Other				
(k)	Addition or replacement of a storage site of the Master Cell Bank and/or Working Cell Banks	7	1	IA

Conditions

2. The active substance is not a biological or sterile substance.

Proportional risk-based approach to biologicals

(c) site for **starting material** or **reagent** requ by dossier IA or IB (cond 2-biological or sterile substance)

(d) revised scope to define when a type II is required; examples of biological starting materials, reagents, raw material, intermediate for biological **AS impacting Q, S, E** (type II)
(e.g. cell banks, pegylation reagents, cytotoxic payload of ADCs, cytokines in ATMP manuf)

(k) Storage site for MCB/WCB **(downgraded to IA)**

Q.I.a.1- Manufacturing site

Q.I.a.1	**Change in the manufacturing site of a starting material/intermediate used in the manufacturing process of the active substance or change in the manufacturing site (including where relevant quality control testing sites) of the active substance**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
Manufacturing site of an active substance or starting material or intermediate				
(a)	Addition or replacement of a manufacturing site of an active substance or intermediate	1, 2, 3	1, 2, 3, 4, 5, 6	IA_{IN}
(b)	Addition or replacement of a manufacturing site of an active substance or intermediate that requires significant update to the relevant active substance section of the dossier, e.g. where a substantially different route of synthesis or manufacturing conditions is used, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability			II
(f)	Addition of a manufacturing site of the active substance that is supported by an Active Substance Master File (ASMF)			II
(g)	Addition or replacement of a manufacturing site responsible for sterilisation of the active substance using a Ph. Eur. method		1, 2, 4, 9	IB
(h)	Addition or replacement of a manufacturing site responsible for micronisation of the active substance	2, 4	1, 4, 5	IA

Proportional risk-based approach to Chemicals:

scope (a) site for an **active substance** or **intermediate** broaden scope which was restricted to sites in **'same pharmaceutical group'.**

revised scope (b) **merge** the type II scopes for **substantially different route** and **significant dossier update**

Q.I.a.1- QC testing site

Proportional risk-based approach to biologicals:

Quality control testing arrangements for the active substance or starting material or intermediate				
(i)	Addition or replacement of a batch control/testing site of the active substance or starting material/intermediate used in the manufacturing of a biological active substance, applying a biological/immunological/immunochemical analytical procedure		1, 9, 10	IB
(j)	Addition or replacement of a batch control/testing site of the — the active substance or — intermediate of an active substance or — starting material of a biological active substance applying physicochemical and/or microbiological analytical procedures	5 6	1	IA

scope (i) site performing a biological/immunological/immunochemical analytical procedure (**downgraded** from type II to **IB**)

- ✓ scope (j) site performing a **physicochemical and/or microbiological** analytical procedure (**downgraded** from IB to **type IA**)
- ✓ Cond. 6 related to the **method** not to the biological AS

Changes to analytical procedure?
→ add relevant scope under Q.I.b.2

Similar approach in Q.II.b.2 for FP QC sites

In section Q.I.a.1
Condition & documentation requirements were reworded, added or deleted to clarify / strengthen requirements for IA, IB

Q.I.a.2 Change in AS manufacturing process

Q.I.a.2	Change in the manufacturing process of the active substance, intermediate of an active substance or starting materials for biological active substance	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Minor change in the manufacturing process	1, 2, 3, 4, 5	1, 2, 3, 4	IA
(b)	Major change to the manufacturing process which may have a significant impact on the quality, safety or efficacy of the finished product			II
(c)	Change in the geographical source of a herbal starting material and/ or production of a herbal substance		1, 2, 3, 4, 5	IB
(d)	Minor change to the restricted part of an Active Substance Master File		1, 2, 3, 6	IB
(e)	Deletion of a manufacturing process	6, 7	1	IA

a) Removed Cond. excluding **biologicals** and **ASMF** from submitting IA for minor changes even if little or no risk to quality;
cond. 2 and **4** ensure that these are minor changes and MAH has full visibility

b) Removed default type II for **biologicals** → it is a type II in case of major changes that **impact Q, S, E** of product for **biologicals and chemicals**

e) Add new category for deletion of a manufacturing process (art 5)

2. For chemical active substance: the synthetic route remains the same, i.e. intermediates remain the same and there are no new reagents, catalysts or solvents used in the process.

   For herbal active substances: the geographical source, production of the herbal starting material/herbal substance and the manufacturing process of the herbal active substance remain the same.

   For biological active substance/starting material/intermediate: the manufacturing steps remain the same and there are no changes to the manufacturing parameters (critical and non-critical PPs and IPCs) or to the specifications of the starting materials, intermediates, or active substance.

   For all: there are no changes to the finished product.

4. The change is fully described in the open ('applicant's') part of an Active Substance Master File, if applicable.

New documentation requested for minor change (4).
MAH to confirm the minor changes do not impact FP/AS.
Documentation 6 requirement revised:
'or' was replaced by 'and' to put emphasis on MAH/FPM responsibilities.

Q.I.a.3 Change in batch size of AS

Q.I.a.3	Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	An increase to the originally approved batch size	1, 2, 3, 4, 5, 6, 7	1, 2, 3	IA
(b)	Downscaling of the approved batch size	1, 2, 3, 4, 5, 6, 8	1, 2, 3	IA
(c)	The change in batch size of a biological active substance/intermediate requires assessment of the comparability			II
(d)	The scale for a biological active substance/intermediate is increased/ decreased without process change (e.g. duplication of line)		1, 2, 4	IB

a) & b) **chemicals**: remove the arbitrary "10-fold" threshold not relevant for active substance (upscaling more than 10-fold compared to the originally approved batch size – **IA**)

The entire category applies to **AS and intermediates**

- ✓ Doc requirements for **biologicals**:
  2- batch analysis data (3 for biologicals)
  4- justification on comparability assessment

5.	The change is fully described in the open ('applicant's') part of an Active Substance Master File, if applicable.
6.	The specifications of the active substance/intermediates remain the same and the control strategy for impurities has been reviewed and remains appropriate.

New conditions: 5 and 6.
Control strategy for impurities should be reviewed.

2.	Batch analysis data (in a comparative tabulated format) on a minimum of two production batches of the active substance or intermediate, as appropriate, manufactured to both the currently approved and the proposed sizes. Batch analysis data of 3 batches (unless otherwise justified) for biological active substance, should be available for the proposed batch size.
4.	For biological active substance, a justification that an assessment of comparability is not required.

Doc 2: requirements for **chemicals** : batch analysis data: (**2 batches** instead of 1)
Doc 3: MAH AND ASMF Holder declaration. To put emphasis on MAH/FPM responsibilities

Q.I.a.4 Change to in-process controls

Q.I.a.4	Change to in-process controls applied during the manufacture of the active substance, intermediate of an active substance or starting materials for biological active substance	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Minor change of in-process control limits	1, 2, 3, 4, 5	1, 2	IA
(b)	Addition of new in-process control and limits with its corresponding analytical procedure	1, 2, 5, 6	1, 2, 3, 4, 5	IA
(c)	Deletion of a non-significant or obsolete in-process control	1, 2, 5, 7, 8	1, 2, 6	IA
(d)	Widening of the approved in-process control limits, which may have a significant effect on the overall quality of the active substance			II
(e)	Deletion of an in-process test which may have a significant effect on the overall quality of the active substance			II
(f)	Change of an analytical procedure for an in-process control	2, 4, 5, 9, 10	1	IA
(g)	Replacement of an in-process control with its corresponding analytical procedure		1, 2, 3, 4, 5	IB

5.	The change is fully described in the open ('applicant's') part of an Active Substance Master File, if applicable.
8.	The change is not related to a revision of the control strategy with an intention to minimise testing of parameters and attributes (critical or non-critical).
9.	The new analytical procedure is not a biological/immunological/immunochemical procedure.
10.	Appropriate studies have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the former analytical procedure.

Broaden scope to **intermediates** of AS and **starting material** for **biologicals**

a) 'Minor' change instead of 'tightening'

b***) Addition of new ICP – low risk (IA)*** if all cond fulfilled [remove **biological** method condition (9)]
g) Replacement of IPC → **higher risk (IB)**

c) Deletion of IPC- new cond 8

f) minor change of analytical procedure for **IPC (IA),** except for biological method (IB) (art 5)

Deleted subcategory for ''addition/replacement of new in-process test(s) and limits as a result of a safety or quality issue'' as it can be covered by the existing subcategory with a modification to condition 2 (text ''or as a result of a safety or quality issue'').

→ New and reworded condition to strengthen requirements for IA/IB

Q.I.b.1 change in specification attribute of AS

	Change in the specification attribute and/or acceptance criteria of an active substance, starting material/reagent/intermediate used in the manufacturing process of the active substance	Cond. to be fulfilled	Docum. to be supplied	Proced.
(a)	Change within the specification acceptance criteria for finished product subject to Official Control Authority Batch Release	1, 2, 3	1, 2	IA_{IN}
(b)	Change within the specification acceptance criteria	1, 2, 3, 4	1, 2	IA
(c)	Addition of a new specification attribute with its corresponding analytical procedure and acceptance criteria	1, 2, 4, 5, 6	1, 2, 3, 4, 5	IA
(d)	Deletion of a non-significant or an obsolete specification attribute	1, 2, 4, 7, 8	1, 2, 6	IA
(e)	Deletion of a specification attribute which may have a significant effect on the overall quality of the active substance and/or the finished product			II
(f)	Change outside of the specification acceptance criteria for the active substance			II
(g)	Change outside of the specification acceptance criteria for starting material/reagent/intermediate which may have a significant effect on the overall quality of the active substance and/or the finished product			II
(h)	Change outside of the specification acceptance criteria for starting material/reagent/intermediate		1, 2, 4, 5	IB
(i)	Change in specification attribute for the active substance from in-house to a non-official Pharmacopoeia/Pharmacopoeia of a third country where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State		1, 2, 3, 4, 5	IB
(j)	Change of the analytical marker or widening of the acceptance criteria of the analytical marker (other extracts) for a herbal active substance		1, 2, 3, 4, 5	IB
(k)	Change in the testing of specification attribute of the active substance, from routine to skip/periodic testing and vice versa		1, 2, 7	IB
(l)	Replacement of a specification attribute with its corresponding analytical procedure		1, 2, 3, 4	IB

"change within/outside" instead of "tightening/widening" to allow more flexibility

Proportional Risk based approach:

c) addition of new spec is low risk (IA), no bio method condition;
l) replacement of spec is a IB (higher risk)

f) **Widening spec for AS**: high risk→ type II

g) **Widening spec for critical SM/I/R with impact on Q**: high risk→ type II

h) **Widening spec for SM/I/R**: lower risk → type IB

k) New scope for change in testing from routine testing to skip/periodic testing and vice versa (art 5) → **refer to published Q&A**

Q.I.b.2 change in analytical procedure of AS

Q.I.b.2	**Change to analytical procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance**	Cond. to be fulfilled	Docum. to be supplied	Proced.
Change to analytical procedure for the active substance				
(a)	Minor change to an analytical procedure for the active substance	1, 2, 3, 4	1, 2	IA
(b)	Deletion of an analytical procedure for the active substance if an alternative procedure is already authorised	4, 5	1	IA
(c)	Introduction, replacement or substantial change to a biological/immunological/immunochemical analytical procedure for an active substance			II
(d)	Other change to an analytical procedure (including replacement or addition) for the active substance		1, 2	IB
Change to analytical procedure for starting material/reagent/intermediate used in the manufacturing process of the active substance				
(e)	Minor change to an analytical procedure for starting material/reagent/intermediate	1, 2, 3, 4	1, 2	IA
(f)	Deletion of an analytical procedure for a starting material/reagent/intermediate, if an alternative analytical procedure is already authorised	4, 5	1	IA
(g)	Introduction, replacement or change to a biological/immunological/immunochemical analytical procedure for starting material /reagent /intermediate, used in the manufacturing process of an active substance		1, 2	IB
(h)	Other change to an analytical procedure (including replacement or addition) for a starting material/reagent/intermediate	1, 2, 4, 6, 7	1, 2	IA

7. The analytical procedure is not a biological/immunological/immunochemical procedure.

Proportional risk-based approach with

- ✓ Split section in two parts:
  - → higher risk for AS
  - → lower risk for SM/R/I

Conditions & Documenting updated

Example:

- ✓ Introduction/substantial change for **biological method** is a type II for AS and a IB for SM/R/I
- ✓ Other changes is a type IB for AS and IA for SM/R/I (unless IB for biological method, cond 7)
- ✓ Minor change can be IA also for biological method if all cond are fulfilled

You can ask questions at slido.com #variations2026 passcode: variations

Q.I.b.3 change to in-house reference standard/ preparation for biological AS/FP

Q.I.b.3	Change to an in-house reference standard/preparation for a biological active substance	Condition to be fulfilled	Documen-tation to be supplied	Procedure type
(a)	Replacement of an in-house reference standard/preparation not covered by an approved qualification protocol (1)			II
(b)	Replacement of an in-house reference standard/preparation not covered by an approved qualification protocol, where comparability test results using current and proposed reference standard/preparation material are available		1, 2	IB
(c)	Introduction of a qualification protocol for the preparation/ replacement of an in-house reference standard or preparation (2)			II
(d)	Substantial change to the qualification protocol for the preparation/ replacement of an in-house reference standard or preparation which may have a significant impact on the quality, safety or efficacy of the active substance			II
(e)	Other change to the qualification protocol for the prepartation/ replacement of an in-house reference standard or preparation		1	IB

(1) *Note:* Other changes to or with respect to an in-house reference standards/preparations, not covered by an approved protocol, should be classified in analogy to respective changes affecting the biological active substance/finished product.

(2) *Note:* Upon approval of the variation for the qualification protocol, the introduction of a new reference standard for a biological active substance/finished product or the extension of its re-test period/storage period, according to the approved qualification protocol will be covered by the existing quality assurance system and hence, there will be no need to file a variation as long as all approved acceptance criteria are met.

New section

- ✓ In current annex these changes are classified under B.I.b.2 (+guidance in Q&A)
- ✓ This new section is in line with the practise indicated in the PAG **Q&A (Q 2.8)**, which is now **obsolete and will be removed**

Notes:

- ✓ how to classify other changes to ref std where there is no protocol
- ✓ If there is a protocol then no need to file a variation

For FP this category can be used (see **note after Q.II.d.3**)

Q.I.c.1 change in immediate packaging of the AS

Q.I.c.1	Change in immediate packaging of the active substance	Cond. to be fulfilled	Docum. to be supplied	Proced.
(a)	Change in immediate packaging of non-liquid active substance	1, 2, 3	1, 2, 3, 4	IA
(b)	Change in immediate packaging of sterile liquid active substance			II
(c)	Change in immediate packaging of nonsterile liquid active substance		1, 2, 4, 5	IB
(d)	Deletion of one of the authorised immediate packagings of the active substance	4	1	IA

Conditions

1. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.
2. Relevant stability studies have been started under ICH conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging, the three months' stability data do not yet have to be available. These studies must be finalised and the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the shelf life/retest period (with proposed action).
3. The active substance is not a sterile active substance or biological active substance.
4. There should be at least one remaining packaging adequate for the storage of the active substance at the authorised conditions.

Proportional risk-based approach:

Risk for change in CCS is mostly related to E&L (→ higher for semisolids and liquids) and CCI (→ for sterile AS)

a) Non-liquid AS → low risk → type IA
if sterile or biological → type IB

b) Sterile liquid AS (independently from biological) → higher risk → type II

c) Nonsterile liquid AS → medium risk → type IB

d) New for deletion (art 5)

Q.I.c.2: alignment with similar categories AS spec

Q.I.c.3: remove biological condition as not relevant for analytical procedure on CCS

Q.I.c.4: secondary packaging when mentioned in dossier – new category from art 5

Q.I.d.1 change in retest/storage period of the AS

Q.I.d.1	Change in the re-test period/storage period or storage conditions of the active substance or intermediates used in the manufacturing process of the biological active substance	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Re-test period/storage period			
1.	Reduction of re-test period/storage period	1	1, 2, 3, 4	IA
2.	Introduction of re-test period/storage period		1, 2, 3	IB
3.	Extension of the re-test period/storage period based on extrapolation or stability modelling not in accordance with relevant stability guidelines			II
4.	Extension of re-test period/storage period supported by real time data not in accordance with an approved stability protocol or an extension based on extrapolation of stability data in accordance with relevant stability guidelines		1, 3	IB
5.	Extension of a re-test period/storage period supported by real time data fully in line with the stability protocol	2	1, 2, 3	IA
(b)	Storage conditions			
1.	Change to more restrictive storage conditions	1, 3	1, 2, 3	IA
2.	Change in storage conditions		1, 2, 3	IB
(c)	Change to an approved stability protocol	1, 4	1, 4	IA

Conditions

1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
2. Stability studies have been performed in accordance with a currently approved stability protocol. Real time data are submitted. All batches meet their pre-defined specification at all time points. No unexpected trends have been observed.
3. The physical state of the active substance has not changed.
4. The changes do not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.

Proportional R-B approach, remove biological specific wording/downgrading, and future proofing

a)
1. **reduction**: doc added to justify change
2. new scope **introduction** retest period
3. **Extension** based on extrapolation or modelling (not in accordance with GL) → high risk → **type II**

4. Extension based on extrapolation or modelling (in accordance with GL) → medium risk → **type IB** (**downgrade** for biologicals)

5. Extension based on real time data (in line with protocol) → low risk → **type IA (downgrade)**

b)
1. Change to more restrictive storage condition – type IA (new cond 3, no change in physical state)
2. Change to storage condition- **type IB** (downgrade for biologicals)

New conditions
Doc requirements: real time data on **3 batches**

Q.I.e & Q.II.g: Additional regulatory tools: DSp & PACMP

Q.II.g.1	**Introduction of a new design space or extension of an approved design space for the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	New design space for one or more unit operations in the manufacturing process of the finished product including the resulting in-process controls and/or analytical procedures		1, 2, 3	II
(b)	New design space for an analytical procedure for an excipient/ intermediate and/or the finished product		1, 2, 3	IB
(c)	Changes to, or extension of, an approved design space for the finished product and/or an analytical procedure for excipients/ intermediates and/or the finished product		1, 2, 3	IB

Q.I.e.5	**Implementation of changes foreseen in a post-approval change management protocol (PACMP)**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Implementation of changes foreseen in a PACMP via Type IA notification	1	1, 2, 3	IA
(b)	Implementation of changes foreseen in a PACMP via Type IA_{IN} notification	2	1, 2, 3, 4	IA_{IN}
(c)	Implementation of changes foreseen in a PACMP via Type IB notification		1, 2, 3, 4	IB

Q.I.e.1/Q.II.g.1

a) New DSp analyt proc: **downgraded to IB**

b) Changes/extension DSp: **new category IB**

Q.I.e.3/Q.II.g.3: Deletion of PACMP: **type IA** instead of IAin

Q.I.e.5/Q.II.g.5: Implementation of PACMP: **IA, IAin or IB** depending on risk also for **biologicals** (as agreed at the time of PACMP approval)

Conditions /documentation requirements strengthen.

Questions and answers on post approval change management protocols (PACMP)

Q.I.e & Q.II.g- Additional regulatory tools- PLCM

Q.I.e.6	Introduction of a product lifecycle management document (PLCM) related to the active substance	Cond. to be fulfilled	Docum. to be supplied	Proced. type
			1, 2, 3	II

Q.I.e.7	Changes related to the active substance in line with an approved product lifecycle management document (PLCM)	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Major change to the active substance in line with an approved PLCM		1, 2, 3	II
(b)	Minor change to the active substance in line with an approved PLCM	1	1, 2, 3	IA
(c)	Minor change to the active substance in line with an approved PLCM	2	1, 2, 3	IA_{IN}
(d)	Minor change to the active substance in line with an approved PLCM		1, 2, 3	IB

Q.I.e.8	Changes to an approved product lifecycle management document (PLCM) related to the active substance	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Major changes to an approved PLCM			II
(b)	Minor changes to an approved PLCM		1, 2, 3	IB

New scopes for use of PLCM document in AS/FP

✓ **Q.I.e.6/ Q.II.g.6:**
Introduction of PLCM

✓ **Q.I.e.7/ Q.II.g.7:**
Changes to AS/FP in line with PLCM

✓ **Q.I.e.8/ Q.II.g.8:**
Changes to PLCM

Upcoming Q&A

You can ask questions at slido.com #variations2026 passcode: variations

Q.II.a Changes to description and composition of FP

Q.II.a.3	Change in the composition (excipients) of the finished product	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(b)	Other excipients			
1.	Any minor adjustment of the quantitative composition of the finished product with respect to excipients	1, 2, 4, 8, 9, 10	1, 2, 6	IA
2.	Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the finished product (for example, biological excipients or a new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk)			II

Q.II.a.3 → removal of biological product type II and modification of scope b.2 to focus on **excipient that may have impact on S, Q, E** (e.g. biological excipient or excipient with viral safety/TSE risk)

Q.II.a.4	Change in coating weight of oral dosage forms or change in weight of capsule shells	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Solid oral pharmaceutical forms	1, 2, 3, 4	1, 2	IA
(b)	Gastro-resistant pharmaceutical forms where the coating or capsule shell is a critical factor for the release mechanism		1, 3, 4, 5, 6	IB
(c)	Modified or prolonged release pharmaceutical forms where the coating or capsule shell is a critical factor for the release mechanism			II

Q.II.a.4 → downgrade gastroresistant to IB; all other modified or prolonged release remain type II

Q.II.b Change to manufacturing/QC sites of FP

Q.II.b.1	**Change in the manufacturing site for part or all of the manufacturing process of the finished product (except for batch release and batch control testing sites)**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Addition or replacement of a site responsible for secondary packaging	1, 2	1, 7	IA_{IN}
(b)	Addition or replacement of a site responsible for immediate packaging	1, 2, 3, 4	1, 2, 7, 8	IA_{IN}
(c)	Addition or replacement of a site responsible for any manufacturing operation(s) of finished product manufactured by novel or complex manufacturing processes			II
(d)	Addition or replacement of a site which requires an initial or product specific GMP inspection			II
(e)	Addition or replacement of a site responsible for any manufacturing operation(s) of a finished product		1, 2, 4, 5, 6, 7, 8	IB
(f)	Addition or replacement of a site responsible for the assembly of a finished product containing an integral medical device		1, 2, 3, 4, 7	IB

b) Remove bio condition, but cond if sterile remains

c) now single category for all FP manufactured by **novel or complex manufacturing process** → type II (**refer to updated Q&A)**

e) Remove default type II for sterile and biological FP → type IB (unless falls under scope c or d)

f) **New scope** for site of assembly for integral MD

Q.II.b.2: ***similar approach as in Q.I.a.1 for FP QC testing sites***

Novel or complex manufacturing process in Q.II.b.1 and Q.II.b.4

What is understood by "manufactured by novel or complex manufacturing process" in category Q.II.b.1 (replacement or addition of finished product manufacturing site) and in category Q.II.b.4 (change in batch size of the finished product)? H November 2025

Q.II.b Change to FP manufacture

Q.II.b.3 **Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a) Minor change in the manufacturing process	1, 2, 3, 4, 5, 6, 7, 8	1, 2, 3, 4, 5, 6, 7, 8, 9	IA
(b) Major change to a manufacturing process of the finish product that may have a significant impact on the quality, safety and efficacy of the finished product			II
(c) Introduction of a non-standard terminal sterilisation method			II
(d) Introduction of, or change in, an overage that is used for the active substance			II
(e) Change in the holding time and/or storage conditions of an intermediate or bulk product used in the manufacture of the finished product		1, 6, 10	IB

7. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batch. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Q.II.b.4 **Change in the batch size (including batch size ranges) of the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(d) The change relates to all other pharmaceutical forms manufactured by novel or complex manufacturing processes			II

Q.II.b.3

a) minor changes (cond 1 remove bio but still IB if sterile); **cond 7** modified stability studies initiated but not required to submit 3 months data upfront

b) Remove default type II for **biological FP** → same categories for biologicals and chemical FP (major changes)

e) new category for change in hold time/ storage conditions for intermediate

Q.II.b.4

Similar categories as before

d) term of 'novel or complex manufacturing process' used → type II

see updated Q&A

Q.II.b.5 (IPC)

Section aligned with corresponding AS (Q.I.a.4)

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Q.II.c Control of excipient

Q.II.c.3	Change in source of an excipient or reagent with TSE risk, which is used in the manufacture of an active substance or in a finished product	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Change in the source of an excipient or reagent from a TSE risk material to a material of vegetable or synthetic origin	1	1, 2, 3	IA
(b)	Change in the source of an excipient or reagent which is unlikely to present any risk of TSE contamination	1, 2	1, 3	IA
(c)	Change in the source of a TSE risk material, or introduction of a TSE risk material, not covered by a European Pharmacopoeial TSE certificate of suitability			II

Q.II.c.4	Change in synthesis, manufacturing or recovery of an excipient (when described in the dossier)	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Minor change in synthesis, manufacturing or recovery of an excipient	1, 2, 3	1, 2, 3, 4	IA
(b)	Change in the manufacturing site, synthesis, manufacturing or recovery of the excipient which may affect the quality, safety or efficacy of the finished product			II
(c)	Deletion of one manufacturing process of an excipient	4, 5	1	IA
(d)	Addition or replacement of a site responsible for the manufacture or testing of an excipient, when required to be described in the dossier		1, 2	IB

Q.II.c.1- Change in the specification attribute and/or acceptance criteria of an excipient

✓ Aligned with similar sections for AS/FP

Q.II.c.2- Change in analytical procedure for an excipient

✓ Aligned with similar sections for AS/FP

Q.II.c.3- Change in source of an excipient or reagent with TSE risk, which is used in the manufacture of an active substance or in a finished product
✓Categories reworded according to **TSE risk** rather than used to manufacture biological product

Q.II.c.4- Change in synthesis, manufacturing or recovery of an excipient (when described in the dossier)
- Term novel excipient is removed
a) Remove terms of pharmacopeial/novel excipient; add biological excipient condition (3)
b) Overarching type II for all **critical excipients**, not just biologicals
c) new category with new conditions
d) new category

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Q.II.d Control of finished product

Q.II.d.1	Change in the specification attribute and/or acceptance criteria of the finished product	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Change within the specifications acceptance criteria	1, 2, 4	1, 2	IA
(b)	Change within the specification acceptance criteria for finished products subject to Official Control Authority Batch Release	1, 2, 4	1, 2	IA_{IN}
(g)	Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur (*).	1, 2, 4, 6	1, 2	IA_{IN}
(i)	Change in the testing of specification attribute, from routine to skip/periodic testing and vice versa		1, 2, 7	IB
(j)	Replacement of a specification attribute with its corresponding analytical procedure		1, 2, 3, 4, 6	IB

(*) *Note:*
There is no need to notify the competent authorities of an updated general monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that reference is made to the 'current edition' of Ph. Eur. in the dossier of an authorised medicinal finished product. This variation therefore applies to cases where no reference to the updated monograph of the pharmacopoeia was contained in the technical dossier and the variation is made to make reference to the updated version.

Q.II.d.3	Variations related to real-time release testing in the manufacture of the finished product	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	Introduction, replacement, or substantial change of a real-time release testing procedure			II

Note: For changes to in-house reference standard/preparation for a biological finished product, refer to category Q.I.b.3 Change to an in-house reference standard/preparation for a biological active substance.

Q.II.d.1

Alignment with corresponding sections (see Q.I.b.1)

i) New category for change from routine to skip/periodic testing (art 5) → **Q&A**

New **Note** for category (g)

Q.II.d.2 (analytical procedures)

-Alignment with corresponding sections (see Q.I.b.2)

Q.II.d.3
Rewording of scope

-Additional note to refer to **Q.I.b.3** for changes to ref standards/preparations

You can ask questions at slido.com #variations2026 passcode: variations

Q.II.e Container closure system of finished product

Q.II.e.1 Change in immediate packaging of the finished product	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a) Change in qualitative and quantitative composition of an approved container			
1. Solid pharmaceutical forms	1, 2, 3, 5, 6	1, 2, 3, 5	IA
2. Semi-solid and non-sterile liquid pharmaceutical forms		1, 2, 4, 5	IB
3. Sterile liquid finished products			II
4. The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life			II
(b) Change in type of container or addition of a new container			
1. Solid, semi-solid and non-sterile liquid pharmaceutical forms		1, 2, 4, 5	IB
2. Sterile finished products			II
(c) Deletion of a container			
Deletion of an immediate packaging container that does not lead to the complete deletion of a strength or pharmaceutical form	4	1, 6	IA

Q.II.e.2 Change in shape or dimensions of the container or closure (immediate packaging) of the finished product	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a) Non-sterile finished products	1, 2, 3	1, 3	IA
(b) Sterile finished products		1, 2, 3	IB

Risk related to E&L (→ higher for semisolids and liquids) **and CCI** (→ for sterile FP)

Composition

a.1) solid → low risk → IA (if sterile / biological → IB)

a.2) semisolid → medium risk → type IB

a.3) sterile liquid → higher risk → Type II

a.4) less protective CCS → higher risk → Type II

New container

b.1) solid, semisolid, nonsterile liqu → medium risk → Type IB

b.2) Sterile liqu → higher risk → Type II

If device is affected refer to Q.IV

Q.II.e.2
Deletion of existing type II for change in part that affects delivery as now is covered in Q.IV

Q.II.e.3 - Change in any part of the (primary) packaging material not in contact with the finished product formulation – no change, except wording of 'needle shield' deleted

Q.II.e Container closure system of finished product

Q.II.e.4 - Change in the specification attribute and/or acceptance criteria of CCS

-align with corresponding AS category, + **Doc deleted**: No need to request batch analysis for CCS

Q.II.e.5- Change in test procedure for CCS

-align with corresponding AS category, + **Deletion** of bio **condition** for (b) as it is not relevant for CCS

Q.II.e.6- Change in pack size of the finished product

c) **Fill volume of parenteral**: delete specific wording of biological FP- type II

e) new category for calendar pack (IAin) (art 5)

Q.II.e.7 - Change in manufacturer, sterilisation process or supplier of packaging components (when mentioned in the dossier)

b) **New** category for sterilisation site / process (IB)

-Remove reference to devices suppliers from this category (now in Q.IV)

Q.II.e.8 - Change of a **secondary packaging component** of the finished product (including replacement or addition or deletion), when mentioned in the dossier

- New section (type IA)

Q.II.f.1 change to shelf life/storage condition of FP

Q.II.f.1	Change in the shelf life or storage conditions of the finished product	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Reduction of the shelf life of the finished product			
1.	As packaged for sale	1, 6	1, 2, 3, 4	IA_{IN}
2.	After first opening	1, 6	1, 2, 3, 4	IA_{IN}
3.	After dilution or reconstitution	1, 6	1, 2, 3, 4	IA_{IN}
(b)	Extension of the shelf life of the finished product			
1.	As packaged for sale (supported by real time data, fully in line with the stability protocol)	3, 4, 5	1, 2, 3	IA_{IN}
2.	After first opening (supported by real time data)		1, 2, 3	IB
3.	After dilution or reconstitution (supported by real time data)		1, 2, 3	IB
4.	Extension of the shelf life of the finished product based on extrapolation or stability modelling not in accordance with relevant stability guidelines			II
5.	Extension of the shelf life of the finished product based on extrapolation of stability data in accordance with relevant stability guidelines		1, 2, 3	IB
(c)	Change in storage conditions of a biological finished product			II
(d)	Change in storage conditions of the finished product or the diluted/ reconstituted product		1, 2, 3	IB
(e)	Change to an approved stability protocol of the finished product	1, 2	1, 4	IA

a) Reduction of shelf life via type IA only if new cond/doc requirements are fulfilled

b) Extension shelf life

1. packaged supported by real time data / fully in line with protocol **downgraded to type IA only** for immediate release film coated tablets, type **IB** for others **Chem**, **biological**, **herbals** (cond 3,4)
2. no change – IB
3. no change – IB
4. Extension based on extrapolation or modelling (not in accordance with GL) → high risk → type II
5. Extension based on extrapolation or modelling (in accordance with GL) → medium risk → **type IB** (downgrade for biologicals)

c) Storage conditions

1. for biologicals – still type II (remove wording about protocol)

d) for other FP/diluted FP- IB as before

New conditions (3, 4, 5, 6)
Doc 1: real time data on **3 batches** to support var

Note on **extrapolation** not allowed for biologicals **deleted**

Q.III.1 CEP

		Cond. to be fulfilled	Docum. to be supplied	Proced. type
Q.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**			
(a)	European Pharmacopoeial certificate of suitability to the relevant Ph. Eur. Monograph (*)			
1.	New certificate of suitability (CEP) (including replacement or addition)	1, 2, 3, 4, 5, 6, 9	1, 2, 3, 4,	IA_{IN}
2.	Update of an approved certificate of suitability (CEP)	1, 2, 3, 4, 5, 9	1, 2, 3, 4,	IA
3.	Deletion of certificate(s) of suitability (CEP)	8	2	IA
4.	New certificate of suitability (CEP) for a non-sterile active substance that is to be used in a sterile finished 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	IB
5.	New or updated certificate of suitability (CEP) for a herbal active substance		1, 2, 4, 6	IB

(*) *Note:* For active substances supported by a certificate of suitability (CEP), a separate variation is required under category Q.I. scope in the following scenarios:
- to register or amend sites (e.g. micronisation or control/testing sites) if these sites are not included on the CEP (Q.I.a),
- to register or amend in-house analytical procedures used by finished product manufacturer if these analytical procedures are not included on the CEP (Q.I.b),
- to register or amend a re-test period if the re-test period is not included on the CEP (Q.I.d).

No upgrading of variation scopes by default, they are still type IA 'do & tell'.

Merging of scopes to simplify and improve readability.

A **Note** has been included to explain situations in which additional variations are required.

Condition 1: strengthened to put emphasis on MAH/FPM responsibilities and include reference to change in composition(API-Mix).
Conditions 2&3: revised for better clarity.

Doc 1: Letter of access for CEP 2.0 is included in documentation 1.
Doc 2: Added more detailed explanation (CTD dossier sections expected), in line with QWP Q&A on how to use a CEP in the context of a MAA or a MAV.
Doc 5: Reference to the active substance itself included.

Q.III.1 TSE certificate

Q.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**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(b)	European Pharmacopoeial TSE certificate of suitability for an active substance/starting material/reagent/intermediate/or excipient			
1.	New TSE certificate for an active substance (including replacement or addition)	4, 7	1, 2, 3, 4	IA_{IN}
2.	New TSE certificate for a starting material/reagent/ intermediate/excipient (including replacement or addition)	4, 7	1, 2, 3, 4,	IA
3.	Update of an approved TSE certificate	4, 7	1, 2, 3, 4	IA
4.	Deletion of TSE certificate(s)	8	7	IA
5.	New/updated TSE certificate using materials of human or animal origin for which an assessment of the risk with respect to potential contamination with adventitious agents is required			II

Conditions

4. 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, or if it does, the update of the CEP/TSE Certificate is only due to administrative changes.

6. The active substance/starting material/reagent/intermediate/excipient is not sterile.

Documentation

Condition 4 revised for updates

Condition 6 deleted for new certificates_"sterile AS" could be **IA variations**

Q.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State

Q.III.2	**Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State for active substances, reagents, intermediates, excipients, immediate packaging materials and active substance starting materials (*)**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Change of specification(s) of a former non-EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State			
1.	Active substance	1, 2, 3, 4	1, 2, 3, 4	IA_{IN}
2.	Excipient/active substance starting material/reagent/ intermediate/immediate packaging material	1, 2, 3, 4	1, 2, 3, 4	IA
(b)	Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	1, 2, 4	1, 2, 3, 4	IA
(c)	Change in specifications from a national pharmacopoeia of a Member State to the Ph. Eur.	1, 4	1, 2, 3, 4	IA
(d)	Change related to a herbal active substance or herbal starting material		1, 2, 3, 4, 5	IB

Conditions

4. Suitability of the new or changed pharmacopoeial analytical procedure has been confirmed under the actual condition of use.

Documentation

Category title and Q.III.2.a.2 scope were revised to include reference to reagents, intermediates, excipients, immediate packaging materials and active substance starting materials.

Changes in FP should not be submitted under this category but as Q.II.d.

Condition 4 revised
"Suitability of the method has been confirmed" instead of "additional validation of the method is not required"

Q. Quality Changes – Herbal medicinal products

- Herbal active substances are multi-component mixtures
- Herbal medicines have complexity and variability, which is reflected in how variations are notified and assessed
- THMPs are not within the scope of the EC Regulation 1234/2008
- Variations guideline does not include THMPs.
- CMDh agreed to apply the Variation Regulation by analogy, in case MRP/DCP had been used for registration of a THMP (CMDh/287/2013/Rev.1).
- The same risk-based approach with CHE/BIO: downgraded when it was scientifically justified

Q.I.a.1- AS Manufacturing site

(a)	Addition or replacement of a manufacturing site of an active substance or intermediate	1, 2, 3	1, 2, 3, 4, 5, 6	IA_{IN}
(b)	Addition or replacement of a manufacturing site of an active substance or intermediate that requires significant update to the relevant active substance section of the dossier, e.g. where a substantially different route of synthesis or manufacturing conditions is used, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability			II
(c)	Addition or replacement of a manufacturing site of a starting material used in the manufacture of the active substance or reagent required to be mentioned in the dossier	1, 2, 3	1, 2, 3, 4, 6	IA

- (a) and (c): **Type IA IN /IA only if** **Condition 1 (new updated with herbal substance)**

1. For starting materials, the specifications and analytical procedures are identical to those already approved. For intermediates and active substances the specifications (including in process controls, analytical procedures), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved.
For herbal active substances, the geographical source, production of the herbal starting material/herbal substance and the manufacturing process of the herbal active substance are the same as those already approved.

- **Same** geographical source of herbal substance
- **Same** manufacturing process for the herbal substance

Documentation 2 :

…..For herbal active substances, a **declaration** that the geographical source, production of the herbal starting material/herbal substance and the manufacturing process of the herbal active substance are the same as those already approved.

otherwise Type IB

Q.I.a.1- AS Manufacturing site

(e)	Addition or replacement of a new herbal starting material supplier or of a new herbal active substance manufacturing site using the same or different plant production (i.e. cultivated or wild collection)	1, 4, 5, 6, 7, 8	IB

- (e): specific scope for **herbal** starting material or active substance, with **two additional documentation requirements** (**type IB**)
- New term: plant production (updated GACP)
- Documentation requirements: 1,4,5,6,**7,8 (new):**

New herbal substance supplier
- comparison of specification, critical quality attributes
- GACP-confirmation

New herbal active substance manufacturer
- comparison of specification, critical quality attributes
- detailed comparison of physical state, extraction solvent, DER and manufacturing process covering all steps
- QP-declaration for all manufacturers involved

7.	For herbal starting material, a detailed comparison regarding specifications and critical quality attributes of the herbal starting material. For herbal active substance, a detailed comparison regarding specifications and critical quality attributes (e.g. for extracts: reference to the herbal starting material (incl. scientific binominal name and plant part), physical state, extraction solvent (nature and concentration), drug extract ratio (DER) and manufacturing process (including a stepwise comparison of all manufacturing steps in tabular format).
8.	For herbal starting material supplier, a GACP declaration from the new supplier (and updated QP declaration if the new supplier is also involved in the herbal active substance manufacture).

Q.I.a.2 Change in AS manufacturing process

Q.I.a.2	Change in the manufacturing process of the active substance, intermediate of an active substance or starting materials for biological active substance	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Minor change in the manufacturing process	1, 2, 3, 4, 5	1, 2, 3, 4	IA
(b)	Major change to the manufacturing process which may have a significant impact on the quality, safety or efficacy of the finished product			II
(c)	Change in the geographical source of a herbal starting material and/ or production of a herbal substance		1, 2, 3, 4, 5	IB
(d)	Minor change to the restricted part of an Active Substance Master File		1, 2, 3, 6	IB
(e)	Deletion of a manufacturing process	6, 7	1	IA

- (a) classification unchanged – IA; **Condition 2** updated for more clarity: "….the geographical source, production of the herbal starting material/herbal substance and the **manufacturing process** of the herbal active substance remain **the same"**

- (c) Downgraded to IB instead of II
- Documentation requirements: 1, 2, 3, **4, 5 (new)**

4.	A declaration from the marketing authorisation holder that an evaluation has been performed and the minor changes do not impact the quality, safety or efficacy of the active substance/finished product (e.g. minor amendments to process description without actual process change, such as details of reagents (e.g. buffers, media preparation). For herbal starting materials/active substances, this evaluation should include a detailed comparison regarding quality determining process characteristics (e.g. for extracts: extraction time, temperature, pressure).
5.	In the case of herbal starting materials, an updated GACP declaration and a declaration from the marketing authorisation holder that the manufacturing process of the herbal active substance remains the same.

Q.I.b.1 Change in AS control

Q.I.b.1	**Change in the specification attribute and/or acceptance criteria of an active substance, starting material/reagent/intermediate used in the manufacturing process of the active substance**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(h)	Change outside of the specification acceptance criteria for starting material/reagent/intermediate		1, 2, 4, 5	IB
(i)	Change in specification attribute for the active substance from in-house to a non-official Pharmacopoeia/Pharmacopoeia of a third country where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State		1, 2, 3, 4, 5	IB
(j)	Change of the analytical marker or widening of the acceptance criteria of the analytical marker (other extracts) for a herbal active substance		1, 2, 3, 4, 5	IB

- (j) new specific scope for **herbal** active substance (applicable for other extracts); type IB
- Documentation requirements: 1,2,3,4,5 (≈ CHE)

Q.II.f.1Change in the shelf-life or storage conditions of the FP

Q.II.f.1	Change in the shelf life or storage conditions of the finished product	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Reduction of the shelf life of the finished product			
1.	As packaged for sale	1, 6	1, 2, 3, 4	IA_{IN}
2.	After first opening	1, 6	1, 2, 3, 4	IA_{IN}
3.	After dilution or reconstitution	1, 6	1, 2, 3, 4	IA_{IN}
(b)	Extension of the shelf life of the finished product			
1.	As packaged for sale (supported by real time data, fully in line with the stability protocol)	3, 4, 5	1, 2, 3	IA_{IN}

- **New condition 4 :** Product is not a biological or **herbal finished product**

Therefore variation would be a Type IB

Q.III.1. CEPs

Q.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	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	European Pharmacopoeial certificate of suitability to the relevant Ph. Eur. Monograph (*)			
	5. New or updated certificate of suitability (CEP) for a herbal active substance		1, 2, 4, 6	IB

- (a.5) new specific scope for **herbal CEPs**
- **Type IB ≠** type IA (CHE)
- Documentation requirements: 1, 2, 4, **6 (new)**

6.	For herbal active substances a detailed comparison regarding specifications and critical quality attributes (e.g. for extracts: reference to the herbal starting material (incl. scientific binominal name and plant part), physical state, extraction solvent (nature and concentration), drug extract ratio (DER) and manufacturing process (including a stepwise comparison of all manufacturing steps in tabular format).

Q.III.2. Monograph

Q.III.2	Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State for active substances, reagents, intermediates, excipients, immediate packaging materials and active substance starting materials (*)	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Change of specification(s) of a former non-EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State			
1.	Active substance	1, 2, 3, 4	1, 2, 3, 4	IA_{IN}
2.	Excipient/active substance starting material/reagent/ intermediate/immediate packaging material	1, 2, 3, 4	1, 2, 3, 4	IA
(b)	Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	1, 2, 4	1, 2, 3, 4	IA
(c)	Change in specifications from a national pharmacopoeia of a Member State to the Ph. Eur.	1, 4	1, 2, 3, 4	IA
(d)	Change related to a herbal active substance or herbal starting material		1, 2, 3, 4, 5	IB

- (d) new specific scope for **herbal API or SM**
- **Type IB ≠** type IA (CHE)
- Documentation requirements: 1, 2, 3, 4, **5 (new)**

5.	For herbal active substances/herbal starting materials a detailed comparison regarding their characteristics (e.g. for extracts: reference to the herbal starting material (incl. scientific binominal name and plant part, physical state extraction solvent (nature and concentration), drug extract ratio (DER) and the manufacturing process) should be provided.

Q.IV.1 Changes to a device co-packaged with the medicinal product or referenced in the product information

Q.IV.1	Changes to a device co-packaged with the medicinal product or referenced in the product information	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Addition or replacement of a co-packaged device or referenced device	1, 2, 3, 5	1, 2, 3	IA_{IN}
(b)	Addition, replacement or other changes of a co-packaged or referenced device that may have a significant impact to the delivery, quality, safety and/or efficacy of the medicinal product			II
(c)	Deletion of a co-packaged or referenced device	3, 4, 5	1, 4	IA_{IN}
(d)	Minor change for a co-packaged device or referenced device that does not impact the delivery, quality, safety and/or efficacy of the medicinal product or the usability of the device	3, 5	1	IA
	Conditions			
1.	The change does not have a significant impact on the delivery, quality, safety and/or efficacy of the medicinal product or the usability of the device.			
2.	Compatibility studies have been finalised and the device is compatible with the medicinal product.			
3.	The change should not lead to substantial amendments of the product information.			
4.	The medicinal product can still be safely and accurately delivered.			
5.	There is no impact to the Risk Management Plan of the medicinal product.			
	Documentation			
1.	Amendment of the relevant section(s) of the dossier, including description, drawing and composition of the device material, compatibility and usability studies as appropriate.			
2.	For the addition or replacement of a co-packaged medical device, evidence that relevant standards have been met e.g. EU declaration of conformity or, where applicable, EU certificate, or other appropriate documentation such as summary information confirming compliance with relevant General Safety and Performance Requirements.			
3.	Data to demonstrate performance, safety and compatibility of the device, as appropriate.			
4.	Justification for the deletion of the device.			

To be used for addition, replacement, deletion or changes to co-packaged or referenced devices.

If conditions are not met, or if the change does have a potential impact on the delivery, quality, safety, efficacy or usability, it should be submitted as IB

It does not apply for referenced devices. More information in the Q&A

Q.IV.2 Changes to an integral medical device (part)

Q.IV.2	**Changes to an integral medical device (part)**	Cond. To be fulfilled	Docum. To be supplied	Proced. Type
(a)	Addition or replacement of an integral device (part) or major change to the materials and/or design and/or performance characteristics of an integral device which may have a significant impact on the delivery or the quality, safety, or efficacy of the medicinal product			II
(b)	Addition or replacement of an integral device (part) which does not have a significant impact on the performance, delivery, quality, safety or efficacy of the medicinal product		1, 2	IB
(c)	Deletion of an integral medical device (part) that does not lead to the complete deletion of a strength or pharmaceutical form	1, 2	1	IA_{IN}
(d)	Change of a material of a device (part) not in contact with the medicinal product	3, 4	1, 2	IA
(e)	Change of a material of a device (part) in contact with the medicinal product that does not have a significant impact on the performance, safety, quality or efficacy of the medicinal product and does not contain materials of human or animal origin for which assessment is required of viral safety data or TSE risk		1, 2, 3, 4	IB
(f)	Addition or replacement of a supplier/manufacturer of an existing device (part)	5, 6	1, 2	IA
(g)	Addition or replacement of a site responsible for sterilisation of the device (part) and/or change to the sterilisation process of the device (part) when supplied as sterile		1, 2, 5, 6	IB
(h)	Other minor change to an integral device (part)	3, 4	1, 2	IA

To be used for addition, replacement, deletion or any other change excluding changes in specification attributes or analytical procedures that have its own scopes in Q.IV.3.

Site responsible for the assembly of the device should be submitted under Q.II.b.1.f

→ Deletion of supplier is under E.5

→ When the sterilization is done by the manufacturer of the medicinal product as part of the manufacturing process, a scope under Q.II.b should be used

Q.IV.2 Changes to an integral medical device (part)

Conditions	
1.	The medicinal product can still be safely and accurately delivered.
2.	The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.
3.	The change has no impact on the performance, delivery, safety or quality of the finished product. The functionality must remain the same.
4.	There is no substantial amendment of the product information.
5.	There is no change to the device (part).
6.	The supplier/manufacturer does not perform sterilisation.

In case of minor changes to the device with no significant impact on the medicinal product, a justification for the absence of a NBOp/EU certificate based on the impact assessment can be acceptable.
See Q&A

Documentation	
1.	Amendment of the relevant section(s) of the dossier, including revised product information as appropriate.
2.	Justification for the absence of a Notified Body opinion/EU certificate/EU declaration of conformity, based on the risk-assessment performed, which concluded that the proposed change has no significant impact on the medicinal product.
3.	The results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
4.	Where appropriate, proof must be provided that no interaction between the medicinal product and the device (part) occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the device), including confirmation that the material complies with relevant pharmacopoeial requirements or legislation of the Union on plastic material and objects in contact with foodstuffs. Comparative data on permeability e.g. for O_2, CO_2 moisture should be provided as appropriate.
5.	Evidence that the sterilisation has been conducted and validated in accordance with GMP and/or relevant ISO standards, as per guideline on the sterilisation of the medicinal product, active substance, excipient and primary container.
6.	Description of the sterilisation method and sterilisation cycle. Validation of the sterilisation cycle should be provided if it does not use the reference conditions stated in Ph. Eur..

Q.IV.3 Changes to the dimensions, specification attributes and/or acceptance criteria or analytical procedures for an integral medical device (part)

Q.IV.3	**Changes to the dimensions, specification attributes and/or acceptance criteria or analytical procedures for an integral medical device (part)**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Minor change to the dimensions of a medical device (part)	1, 2, 3	1	IA
(b)	Change to the specification for a medical device (part) that is not part of the final product specifications			
1.	Change to the specification acceptance criteria, including amendments to more accurately describe the appearance	1, 2, 4, 5	1	IA
2.	Addition of a new specification attribute with its corresponding analytical procedure	1, 2, 8	1, 2, 3	IA
3.	Replacement of a specification attribute with its corresponding analytical procedure		1, 2, 3	IB
4.	Change outside of a specification acceptance criteria or deletion of a specification attribute that has a significant impact on the quality, safety, performance or usability of the device			II
(c)	Change to an analytical procedure for the medical device (part)			
1.	Addition, replacement or other change to an approved analytical procedure	1, 6	1, 2, 4	IA
2.	Deletion of an analytical procedure if an alternative an analytical procedure is already authorised	1, 7	1	IA

Major change in dimensions would be a change in design under Q.IV.2.a (type II)

Q.IV.3 is only applicable to specifications and analytical procedures for the medical device (3.2.P.7).
Analytical procedures and specifications that are part of the final product specification and control strategy (3.2.P.5) should be classified under the appropriate Q.II.d category.

General principles

- Changes to medical devices should be submitted under the appropriate Q.IV classification, even if the medical device also acts as container closure system.
- For clarification in which cases an EU certificate/Notified Body Opinion is needed, please consult the Q&A for applicants, marketing authorisation holders of medicinal products and notified bodies regarding medicines used in combination with medical devices and consultation procedures for certain medical devices
- For dossier requirements please consult QWP-BWP Guideline on medicinal products used with a medical device. **Any information that is not a requirement should not be included in the dossier.** If included, it would need to be maintained through the appropriate variations.

Q&A on combination products

The Q&A has been updated to include the reference to the updated Variations guidelines and clarify in which cases a EU certificate/Notified Body Opinion is needed. Those are listed under section 4 Lifecycle management:

- **Question 4.1** Will I need to provide a (new or updated) EU declaration of conformity/certificate of conformity issued by a notified body/notified body opinion if there are changes to the device (or device part) after the initial marketing authorization
- **Question 4.2** How should I submit changes to the terms of the Marketing Authorisation following changes to the device (or device part)?

For **minor changes** to the integral device (or device part) that **do not impact** the quality, safety or performance of the device (part) or the intended use of the device, the MAH should assess and provide a **justification (based on a risk-assessment)** whether the change has no significant impact on the device to justify the absence of a NB opinion; otherwise, proof of compliance with the MDR should be provided.

In case of groupings of **multiple minor changes** to the device, the accumulation of changes may have a greater impact and warrant the request of a NBOp.

Q&A on combination products

As a guiding approach, a new or revised notified body opinion (or for class I (excluding Im and Is), MAH's GSPRs compliance statement for the device part of an iDDC) is:

1. required when a **new device** is introduced with a line extension or variation;
2. expected when **major changes** are introduced to an existing device, such as:
   - change to its **design**
   - **addition or replacement** of an integral device (part)
   - change to its **performance characteristics**
   - change to its **intended purpose** such as a different patient population and/or new user (e.g. home versus hospital setting) and/or new usability study, and/or significantly different instructions for use.

   which may have a significant impact on the delivery or the quality, safety, or efficacy of the medicinal product.
3. expected in case of changes to the medicinal product which may impact the **performance** or **safety** of a device, for example the introduction of a new finished product formulation resulting in different viscosity significantly affecting device performance.

Q.V & M - Changes to PMF variations

Q.V.a.1 Inclusion of a new, updated or amended PMF (Plasma Master File)

- d) PMF 2nd step procedure from IA_{IN} to IA when changes do not affect the properties of the finished product – New doc 5: Updated product information if required by national legislation

Change from D. to M and reduction from 23 categories to 16. NO CHANGES TO VAMF (Viral Antigen MF) scopes.

M.4 Addition or relocation of a blood/plasma collection centre within a blood establishment already included in the PMF	a) Relocation downgraded from IB to IA, with 3 new conditions (same legal entity, inspected, same quality system)
M.5 Deletion or change of status (operational/non-operational) of establishment/centre(s) used for blood/plasma collection or in the testing of donations and plasma pools	c) Change from non-operational to operational: new scope type IB when epidemiological data has not been annually submitted or there have been other than administrative changes in blood centres
M.7 Addition or relocation of a centre/laboratory for testing of donations and/or plasma pools within an establishment already included in the PMF	a) Relocation downgraded from Type IB to IA with 3 new conditions (same legal entity, inspected, same quality system)
Combined D.10 to D.13 in **M.9**: Changes of an establishment or centre in which storage of plasma is carried out or organization involved in the transport of plasma	a) Relocation downgraded to Type IA, with 3 new conditions (same legal entity, inspected, same quality system)
Combined D.14 - D.16 into **M.10**: Addition or replacement of blood and plasma tests	b) New scopes for Minipools (NAT) → CE-marked (Type IA) & non CE-marked (Type II)
Combined categories D.17-D.18 into **M.11**: Change of inventory hold procedure	Removal of inventory hold period or reduction in its length: from type IB to IA
M.12 Addition or replacement of blood containers (e.g. bags, bottles)	b) New scope IB: non CE-marked, no impact on quality. Doc.: proof of equivalent Quality and anticoagulant solution complies w/ Ph. Eur

Chapter C
Clinical (Safety/Efficacy/PhV)

C. Safety, Efficacy, Pharmacovigilance Changes

- Mainly minor revisions
- Clarifications, incorporation of Article 5 recommendations
- Redundant categories deleted
- Section C.II for veterinary products removed
- Roman numeral ”I” removed for human products, resulting in new classification codes for all variation categories

New category	Old category
C.1	C.I.1
C.2	C.I.2
C.3 (revised)	C.I.3
C.4	C.I.4
C.5	C.I.5
C.6	C.I.6
C.7	C.I.7
C.8	C.I.8
C.9 (revised)	C.I.11
C.10	C.I.12
C.11 (new)	
C.12 (revised)	C.I.13

News and revisions (1)

C.3

- Clarifications made that this category also covers PRAC recommendations and other joint recommendations of the EU competent authorities
- Type IB classification (C.3.b) added for implementation of changes that require minor assessment – previously widely used ”z” classification

		Cond. to be fulfilled	Docum. to be supplied	Proced. type
C.3	**Change(s) in the summary of product characteristics, labelling or package leaflet intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Article 45 or 46 of Regulation (EC) No 1901/2006, or the outcome of a PRAC signal recommendation, or to adapt to a joint recommendation of EU competent authorities (e.g. a Core SmPC, or following the assessment of an Urgent Safety Restriction etc.)**			
(a)	Implementation of the agreed wording	1	1, 2	IA_{IN}
(b)	Implementation of the agreed wording that requires additional minor assessment (e.g. translations are not yet agreed upon)		1, 2	IB
(c)	Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH			II

News and revisions (2)

C.9

- Type IA classification clarified to emphasize that the scope is to implement a previously conducted assessment (in previous guideline: "agreed wording")
- Type IB classification added for various changes that require minor assessment

C.9	**Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Implementation of changes to reflect the outcome of previous assessment	1	1, 2	IA_{IN}
(b)	Implementation of changes which require additional minor assessment (e.g. change to the due date of obligations and conditions of a marketing authorisation and required pharmacovigilance activities in the risk management plan, including changes to the due date of study milestones, and template updates)		2	IB
(c)	Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the holder where significant assessment by the competent authority is required			II

News and revisions (3)

C.11

- New type IB category for Package Leaflet user test, based on art 5 recommendation.

C.12

- Bioequivalence studies explicitly mentioned in the scope for clarification
- Further clarification made that this category is intended for variations where no product information revision is *proposed* by the MAH

C.12 **Other variations not specifically covered elsewhere in this Annex which involve the submission of studies, including bioequivalence studies, to the competent authority**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
			II

Note: This variation scope includes the submission of studies where no changes to the summary of product characteristics, labelling or package leaflet are initially proposed by the MAH.
In cases where the assessment by the competent authority of the data submitted leads to a change of the summary of product characteristics, labelling or package leaflet, the relevant amendment to the summary of product characteristics, labelling or package leaflet is covered by the variation.

EMA
EUROPEAN MEDICINES AGENCY

EMA/CMDh Q&As and Guidance

Susanne Winterscheid, CMDh member and VRWP chair, BfArM, Germany

Brian Dooley, Pharmaceutical Quality Office, EMA

Gernot Hirn, QWP member, Austria

EMA/CMDh Q&As and guidance to support implementation of revised variations guidelines

New & revised guidance:

- EMA/CMDh Guidance on the application of the revised variations framework (June/25 and Sep/25)
- Update of CMDh guidance documents to reflect new Variation Guidelines (Oct/25)
- Q&A on skip testing (Oct/25)
- Q&A on novel or complex manufacturing process (Nov/25)
- EMA's post-authorisation guidance e.g.:
  - Type IA/IB/II/Extension applications/grouping of variations (Nov/25)
  - Classification of changes: Q&A (Nov/25)
- Q&A regarding medicines used in combination with medical devices and consultation procedures by notified bodies (Nov/25)
- Guidance on stability testing for applications for variations (December 2025)
- Guidance on Post-Approval Change Management Protocol (PACMP) (December 2025)

Additional guidance upcoming:

- Guidance on Product Lifecycle Management document (PLCM) (expected in January 2026)

You can ask questions at slido.com #variations2026 passcode: variations

Guidance on the application of the revised variations framework - Type IB/II variations

- **Type IB/II variations**:
  - If submitted **before 15 January 2026**, the current eAF should be used and the procedure will follow the current EC Variations Guidelines (2013) until its conclusion.
  - If submitted **as of 15 January 2026** the updated eAF should be used and the new EC Variations Guidelines (2025) followed.

Guidance on the application of the revised variations framework - Type IA variations

- **Type IA variations**:
  - The **date of implementation** should be taken as the **point of reference** for the application of the current/new EC Variations Guidelines.
  - All Type-IA variations **implemented before 15 January 2026** should be **submitted before 15 January 2026.**
    - If no annual update is due before 15 January 2026, the MAH should submit an earlier annual update/individual notification(s) outside the annual update.
  - The **first type-IA variation** implemented **as of 15 January 2026** will start a **new cycle for the annual update**.

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

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(...)

EMA and CMDh have prepared updates of relevant guidance documents in order to adapt to the revised variations guidelines. They will be applicable from 15 January 2026, however, they are published already now for giving early advice to stakeholders to prepare future variation applications adequately. Some minor updates may still be necessary in the next weeks.

Stakeholders should monitor the webpages on EMA and CMDh websites mentioned at the Variations framework section. They should also take the necessary measures to prepare their systems, processes, procedures and documentation for compliance with the revised variation framework.

In case of doubt, MAHs should contact the relevant competent authority.

- Summary of the Pharmacovigilance System and Risk Management Plan in the Mutual Recognition and Decentralised Procedures (October 2025) - [*Track version*]
- Extension applications in Mutual Recognition and Decentralised Procedures (October 2025) - [*Track version*]
- Recommendations on informed consent applications in Mutual Recognition and Decentralised Procedures (October 2025) - [*Track version*]
- CMDh Recommendation on Implementation of Article 30 Decisions cf. Directive 2001/83/ec, as amended for Generic/Hybrid/Biosimilar Medicinal Products Approved through MRP/DCP (October 2025) - [*Track version*]
- Position paper common grounds seen for invalidation/delaying day 0 for variations (October 2025) - [*Track version*]
- Urgent Safety Restriction Member State Standard Operating Procedure (October 2025) - [*Track version*]
- Standard Operation Procedure for Article 61(3) Changes to Patient Information (October 2025) - [*Track version*]
- Q&A - List for the submission of variations for human medicinal products according to Commission Regulation (EC) 1234/2008 as amended (October 2025, correction December 2025) - [*Track version*]
- Recommendation on the classification of an unforeseen variation to the terms of the marketing authorisation (Template Art. 5) (October 2025) - [*Track version*]
- Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008 (October 2025)
- Examples for acceptable and not acceptable groupings for MRP/DCP products (October 2025) - [*Track version*]

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Home > Human regulatory: overview > Post-authorisation > Variations including extensions of marketing authorisations

Variations including extensions of marketing authorisations

Share

A variation is a change to the terms of a marketing authorisation. This section provides guidance for marketing authorisation holders on the regulatory requirements and procedures for the different types of variations.

Human | Regulatory and procedural guidance

Page contents

In this section

Current variations framework:

- Type-IA variations: questions and answers
- Type-IB variations: questions and answers
- Type-II variations: questions and answers
- Worksharing: questions and answers
- Grouping of variations: questions and answers
- Article 5 procedure: Regulatory and procedural guidance
- Extensions of marketing authorisations: questions and answers

Revised variations framework:

- Guidance on the application of the revised variations framework

Using the IRIS platform

From January 2025, marketing authorisation holders should use the IRIS platform when managing variations including extensions of marketing authorisations after the original submission.

Further guidance on the use of the IRIS platform and how to prepare submissions is available on the dedicated IRIS website:

- IRIS: A secure online platform for handling product-related scientific and regulatory procedures with EMA

IRIS does not replace the current submission gateway; they coexist serving different functions.

Related content

You can ask questions at slido.com #variations2026 passcode: variations

EMA

Q&A on classification of changes

1. Administrative changes
2. Quality changes
3. (Non-) Clinical changes
4. Editorial changes

On 19/11/2025, EMA published updated guidance on classification of changes for changes submitted and implemented from 15/01/2026.

New Q&As developed

Updated Q&As

- to align with the updated classification guideline and classification codes
- some clarification added or wording slightly modified

Q&As removed when no longer relevant

Q&A on classification of changes

New Q&As developed:

- **Administrative changes:** How to apply for a change in name and/or address of a marketing authorisation holder or manufacturing site?
- **Quality changes:** Which variation category should be used to remove/replace the Rabbit Pyrogen test from the marketing authorisation dossiers? (reference to the QWP Q&A added)
- **(Non-) Clinical changes:** What should I consider in relation to the quality documentation in case of a change in the clinical use of marketed products meaning change in therapeutic indication, posology or maximum daily dose (MDD)?
- **(Non-) Clinical changes:** When is the submission of assessments carried out on target patient groups in order to comply with Article 59(3) of Directive 2001/83/EC and any resulting change(s) to the Package Leaflet a stand-alone variation?

Q&A on Skip Testing

Q.I.b.1	**Change in the specification attribute and/or acceptance criteria of an active substance, starting material/reagent/intermediate used in the manufacturing process of the active substance**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(k)	Change in the testing of specification attribute of the active substance, from routine to skip/periodic testing and vice versa		1, 2, 7	IB

7. Justification from the marketing authorisation holder or the ASMF holder for the change in the testing of specification attribute. A change from routine testing to skip/periodic testing is warranted when the manufacturing process is under control and supported by sufficient amount of historical data compliant with the specification or as foreseen by relevant guidelines.
A change from skip/periodic testing to routine testing should be supported by analytical data demonstrating failure to meet the approved acceptance criteria for the skip tested specification.

Q.II.d.1	**Change in the specification attribute and/or acceptance criteria of the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(i)	Change in the testing of specification attribute, from routine to skip/periodic testing and vice versa		1, 2, 7	IB

8. Justification from the holder for the change in the testing of specification attribute.

A change from routine testing to skip/periodic testing is warranted when the manufacturing process is under control and supported by a sufficient amount of historical data compliant with the specification.

A change from skip/periodic testing to routine testing should be supported by analytical data demonstrating failure to meet the approved acceptance criteria for the skip tested specification.

New variation scopes added to Variation Guidelines

Both are classified as Type IB

Documentation 1,2 and 7
- Amendment(s) to relevant sections of the dossier
- Comparative table
- Justification (see Q&A)

A small error in Q.II.d.1.i:
Doc 8 is indeed doc 7

Q&A on Skip Testing

- **Why a Q&A on skip testing?**
  - QWP noticed the misunderstanding / confusion between ‘skip testing’ and ‘reduced testing’ for assessors and applicants/MAH
  - Clarification requested from IWG on responsibilities of assessors and inspectors ➔IWG clarified that decision on skip testing is under the remit of assessors
  - A Q&A on ‘reduced testing of starting materials’ is already available at the EMA website, under QWP Q&As
- Decision to initiate the work on a new Q&A on Skip testing taken in December 2023
- Six questions prepared, Q6 proposed and drafted under the remit of IWG
- Text adopted by QWP (March 2025) and IWG for Q6 (September 2025)
- Q&A published under QWP Q&As, Part 2, October 2025
  Quality of medicines questions and answers: Part 2 | European Medicines Agency (EMA)
- Q&A on ‘reduced testing of starting materials’ will be amended in 2026

Q&A on Novel or Complex Manufacturing Process

To help the **interpretation** of finished products and/or pharmaceutical forms manufactured by *novel or complex manufacturing processes* in the context of categories **Q.II.b.1.c** and **Q.II.b.4.d**

Clarify in which situations the addition of FP sites and changes in batch size should be submitted as a **type II variation** (independently from the PV data requirements) in line with a risk-based approach

Revision into a single Q&A

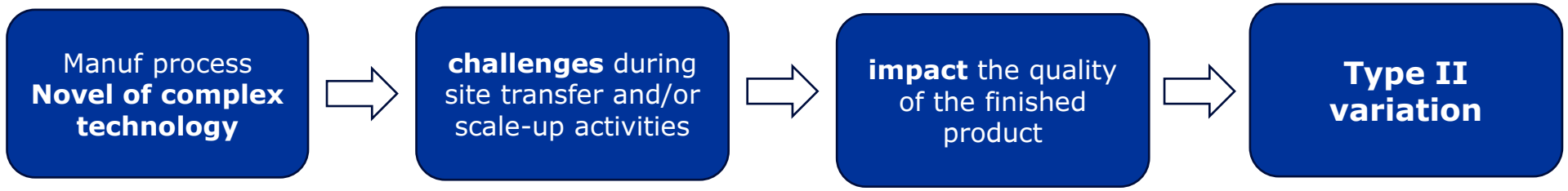
Applicable to FP including Biological and Chemical AS

Addition of list of examples

Quality of medicines questions and answers: Part 1 | European Medicines Agency (EMA)

Q&A on Novel or Complex Manufacturing Process

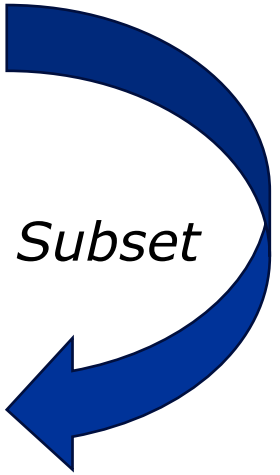
What is understood by "manufactured by novel or complex manufacturing process" in category Q.II.b.1 (replacement or addition of finished product manufacturing site) and in category Q.II.b.4 (change in batch size of the finished product)? H November 2025



- Not all **non-standard processes** should be considered **complex** (i.e. require type II variation)
- **Annex II** of the Guideline on process validation for finished products - information and data to be provided in regulatory submissions) direct applicants to **PV data requirements,** not variation classification

Examples of **products manufactured by processes** that could be **considered complex (require type II):**

- ✓ Advanced Therapy Medicinal Products (ATMPs)
- ✓ Liposomal preparations
- ✓ Nanoparticulate preparations (e.g. Lipid nanoparticles)
- ✓ Parenteral modified release preparations
- ✓ Metered-dose preparations for inhalation and inhalation powders
- ✓ Multilayer tablets



Q&A on Novel or Complex Manufacturing Process

Examples of Novel or Innovative manufacturing processes:

- ✓ Continuous manufacturing
- ✓ Decentralized manufacturing
- ✓ Additive manufacturing (3D printing)
- ✓ Use of process models in the control strategy
- ✓ Manufacture of personalised medicines
- ✓ Other advanced manufacturing approaches

- **Type IB** variation? → applicants must provide a **justification** if they consider that the manufacturing process is not novel or complex.
- If the justification is not accepted, the competent authority may upgrade the variation to type II or ask the applicant to withdraw and resubmit as Type II variation.
- Appropriate variation categorisation can also be anticipated using Post Approval Change Management Protocols.
- If there is any uncertainty, applicants may consult the relevant authority before submitting the variation.

You can ask questions at slido.com #variations2026 passcode: variations

Finished products that are not considered complex or non-standard by default (Q.II.b.1/Q.II.b.4)

- Specialised dosage forms
  - Sterile suspensions or emulsions
  - All modified release preparations
  - Low content dosage forms (≤ 2% of composition)
- Specialised processes or established processes known to be complex
  - Lyophilisation processes, microencapsulation
  - Aseptic processing
- Non-standard methods of sterilisation (other conditions than Ph.Eur. 5.1.1 “standard process”)
  - Moist heat – F_0 concept
  - irradiation < 25 kGy

Ref: Annex II to EMA Process validation GL

These are not always high-risk in relation to changes to scale or manufacturing site
=> Type 1A/1B by default

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Q&A on use of PLCM

Additional Regulatory Tools

Revised Variation Regulation

(7) the following Article 6a is inserted:

'Article 6a

Additional regulatory tools

For certain changes to the chemical, pharmaceutical and biological information for a medicinal product a holder may rely on a range of process parameters, quality attributes, protocols or summary documents, upon agreement of the relevant authority and subject to the conditions referred to in the Annexes and the guidelines referred to in Article 4(1) with regard to the specific regulatory tool.';

Revised Variation Guidelines

Chapters *Q.I.e* & *Q.II.g Additional Regulatory Tools*:

- Design Space – ICH Q8/Q11/Q14
- Post-Approval Change Management Protocol (PACMP) - ICH Q12
- Product Lifecycle Management document (PLCM) - ICH Q12

* These tools usually rely on enhanced pharmaceutical development approaches (QbD) and increased product and process understanding.

Product Lifecycle Management document (PLCM)

- Defined in ICH Q12 guideline (chapter 5)
- Global tool for harmonised lifecycle management
- Located in eCTD module 3.2.R
- Serves as a central repository of the legally binding elements considered necessary to assure product quality (e.g. quality attributes, manufacturing process parameters, analytical parameters, acceptance criteria)
- Enables planning and implementing future changes in a predictable manner
- Provides transparency and facilitates continual improvement

Product Lifecycle Management document (PLCM)

Q.II.g.6

Q.II.g.6 **Introduction of a product lifecycle management document (PLCM) related to the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
		1, 2, 3	II
Documentation			
1. The content of the product lifecycle management document has been developed in accordance with the relevant European and international scientific guidelines. Results from product, process and analytical development studies (including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic understanding of how material attributes and process parameters impact the critical quality attributes of the finished product has been achieved.			
2. The product lifecycle management document includes a description of the material attributes, quality attributes and process parameters (or analytical procedure parameters), their proposed limits and ranges, and future variation reporting categories, in a tabular format.			
3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

Q.II.g.7

Q.II.g.7 **Changes related to the finished product in line with an approved product lifecycle management document (PCLM)**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a) Major change to the finished product in line with an approved PLCM		1, 2, 3	II
(b) Minor change to the finished product in line with an approved PLCM	1	1, 2, 3	IA
(c) Minor change to the finished product in line with an approved PLCM	2	1, 2, 3	IA_{IN}
(d) Minor change to the finished product in line with an approved PLCM		1, 2, 3	IB

Q&A on use of PLCM

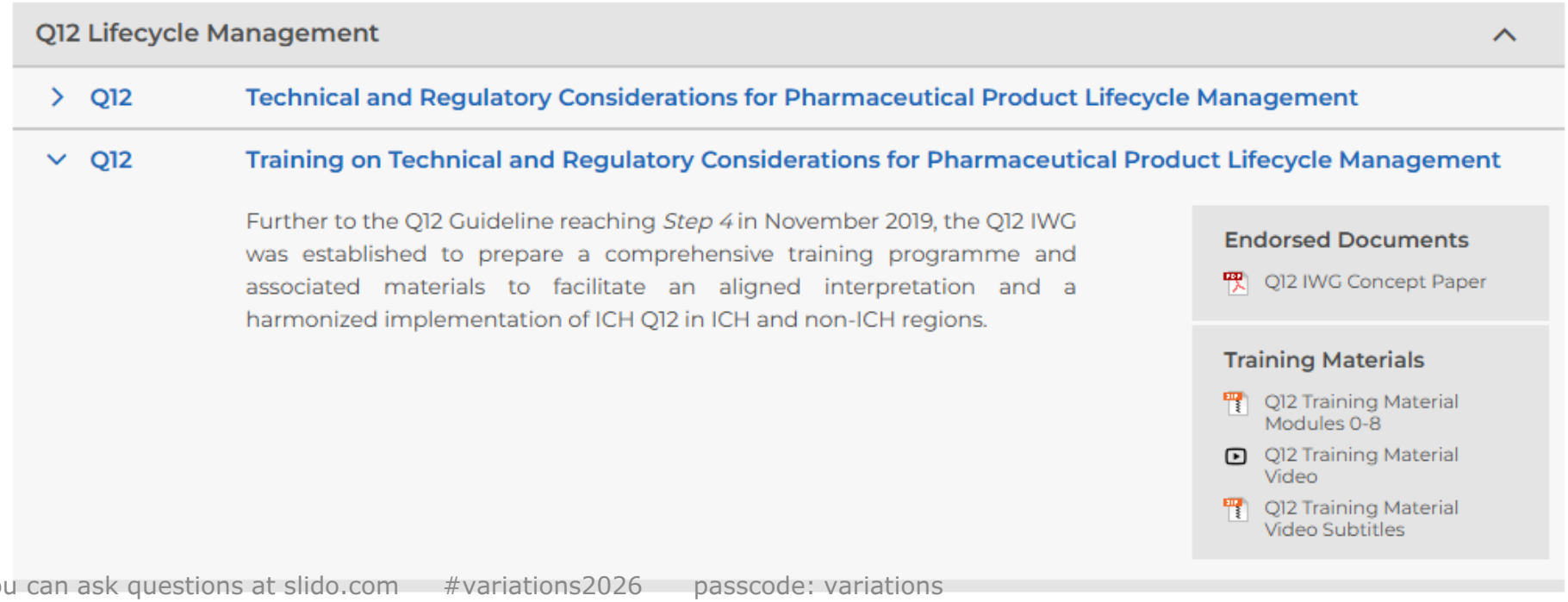
Key points

- PLCM is a tool to facilitate global harmonisation
- PLCM to be submitted and assessed via Type II variation procedure
- PLCM to apply to specific manufacturing process step(s) or analytical procedure(s)
- PLCM to apply to specific manufacturing and/or testing site(s)
- Future variation types/categories to follow the EU variations guidelines
- GMP compliance & PQS effectiveness of the site(s) to be confirmed prior to approval*

*Note: GMP inspections pilot on PQS effectiveness in planning

References – examples and training material

- ICH Q12 guideline on technical and regulatory considerations for pharmaceutical product lifecycle management - annexes (Step 5) EMA/CHMP/ICH/831751/2017
- ICH Quality Guidelines https://www.ich.org/page/quality-guidelines



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Q&A on use of PLCM

Steps taken

- Draft Q&A presented to QWP/BWP in December 2025
- MS comments
- Drafting group reviewed comments and revised the Q&A text

Next steps

- QWP/BWP adoption
- CHMP adoption
- Publication of final Q&A – **tbc (January 2026)**

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Revised Q&A on PACMP

Q&A on PACMP

What is a PACMP?

- Protocol for **specific planned quality change(s)**
  - Cannot be used, if (non-)clinical data are required or if change results in a line extension
  - Concrete plans to implement change in the foreseeable future (otherwise discouraged)
    - e.g. PACMP in MAA for not yet identified new manufacturing sites
  - Sufficiently detailed and specific enough (otherwise refusal)
- Unequivocally defines change(s), studies, supporting data and acceptance criteria
  - Adequate knowledge to manage the implementation of the change(s) to be demonstrated
  - Relevant information should be included in the PACMP itself
    - References to other sections are not sufficient as those could be changed after approval of the PACMP (would need to be reevaluated)

Q&A on PACMP

How can a PACMP be submitted, updated or deleted?

- Submitted via Type II variation: Q.I.e.2 / Q.II.g.2 (or MAA, not recommended)
- May be updated prior to implementation of change(s) described in PACMP
  - Minor change (no change to overall strategy) -> Type IB (Q.I.e.4.b or Q.II.g.4.b)
    - e.g. replacement of analytical procedure with an orthogonal method
  - Major change -> Type II (Q.I.e.4.a or Q.II.g.4.a)
    - e.g. removal/addition of tests and studies
- Deletion -> Type IA (Q.I.e.3, Q.II.g.3), conditions:
  - Not a result of unexpected events or out of specification results during implementation
  - No effect on the already approved information in the dossier

Q&A on PACMP

How will the change(s) in the PACMP be implemented?

- Implementing variation (Q.I.e.5 / Q.II.g.5) has to comply with PACMP
  - All studies performed as described
  - Results comply with predefined acceptance criteria
  - Minor deviations (no change to overall strategy of PACMP) may be justified -> Type IB VAR
- Typically, implementing variation type one level lower (Type IA / IAin / IB)
  - To be proposed as part of PACMP; subject to approval
  - Type II implementing VAR could be required in exceptional cases, e.g.
    - certain complex changes (e.g. complete redesign of DS manufacturing process)
    - multi-use PACMPs that require product / site-specific adaptations

Q&A on PACMP

Multiple Changes / Multiple Times / Multiple Products

PACMP covers more than one change

- Changes need to be interrelated
- Changes can and will be implemented together via a single Type IA / IAin / IB variation
- Justification to be provided in the protocol

PACMP designed to be used repeatedly, applying the same principles (`multi-use´)

- Conditions and acceptance criteria need to be sufficiently specific
- Strategy and acceptance criteria should be relevant over the planned multi-use timeframe
- Product or site-specific adaptations not acceptable
- Feasibility of multi-use approach to be demonstrated

PACMP covers multiple products

- Protocol and change(s) have to be applicable to all products in scope
- Can only be submitted via Type II WS variation
- All products covered by PACMP should be in scope of the variation

You can ask questions at slido.com #variations2026 passcode: variations

Q&A on PACMP

How is oversight of PACMPs maintained?

Listing (table of contents) of PACMPs provided and maintained in Module 3.2.R

- Unique PACMP identifier/name
- Procedure number in which PACMP was submitted
- Brief description of change(s) covered by the PACMP
- Proposed reporting category of implementing variation
- Overview of Module 3 section(s) expected to be impacted
- Status of PACMP (pending implementation / implemented – procedure number)

Implementing variation

- Reference to the approved PACMP and the precise scope of the change(s) in eAF
- Overview with high level description of the proposed change and supporting data
- Module 3 documents self-standing

Q&A on PACMP

Impact of revision of the EU Variation GL on already approved PACMPs

- Approval of PACMP before, BUT submission of implementing variation after 15 Jan 2026
  - Submission of implementing variation according to the agreed variation type in the PACMP
  - Corresponding change category in new EC Variations Guideline (2025) to be used (B.I.e.5 = Q.I.e.5 and B.II.g.5 = Q.II.g.5)
- Approval of PACMP after 15 Jan 2026, refer to the new Variations Guideline (2025).

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New Variations Guidelines Q&A session

Alberto Ganan Jimenez, Committees and Quality Assurance Department, EMA

Questions and Answers session

Moderators

- Alberto Ganan Jimenez (EMA)

Submit your questions:

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New Variations Guidelines Conclusion and final remarks

Susanne Winterscheid, CMDh member and VRWP chair, BfArM, Germany

Alberto Ganan Jimenez, Committees and Quality Assurance Department, EMA

Next Steps

New Variations Guidelines take effect

- 15 January 2026

Ongoing monitoring of implementation

- CMDh / CMDh Variation Regulation Working Party
- EMA
- Interested Parties meeting(s)

EMA/CMDh Q&As and guidelines to support implementation of revised variations guidelines

New & revised guidance:

- EMA/CMDh Guidance on the application of the revised variations framework (June/25 and Sep/25)
- Update of CMDh guidance documents to reflect new Variation Guidelines (Oct/25)
- Q&A on skip testing (Oct/25)
- Q&A on novel or complex manufacturing process (Nov/25)
- EMA's post-authorisation guidance e.g.:
  - Type IA/IB/II/Extension applications/grouping of variations (Nov/25)
  - Classification of changes: Q&A (Nov/25)
- Q&A regarding medicines used in combination with medical devices and consultation procedures by notified bodies (Nov/25)
- Guidance on stability testing for applications for variations (December 2025)
- Guidance on Post-Approval Change Management Protocol (PACMP) (December 2025)

Additional guidance upcoming:

- Guidance on Product Lifecycle Management document (PLCM) (expected in January 2026)

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Thank you

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