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GMP/GDP Inspectors Working Group (GMP/GDP IWG)

Concept paper on the revision of the guidelines on Good Manufacturing Practice for medicinal products - Annex 15 - Qualification and Validation

Agreed by EMA GMP/GDP IWG	30 November 2025
Agreed by PIC/S	14 January 2026
Start of public consultation	9 February 2026
End of consultation (deadline for comments)	9 April 2026

The proposed guideline will replace:

- Eudralex Volume 4: Annex 15 Qualification and validation

Keywords	GMP, Medicinal Product, active substance, Annex 15, Qualification and validation

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1. Introduction

Annex 15 is currently **intended to be used by active substance manufacturers as an optional supplementary** guidance to the requirements already outlined in EudraLex, Volume 4, Part II, as reported in the chapter "Principles": "*may also be used as supplementary optional guidance for active substances without introduction of additional requirements to EudraLex, Volume 4, Part II*"[1].

In June 2020 the report Lessons learnt from presence of N-nitrosamine impurities in sartan medicines was published. The report **outlines the findings and recommendations arising** from the network's lessons learnt exercise initiated after the identification of N-nitrosamine in sartans medicines in mid-2018. By analysing the achievements and gaps identified during the sartans case management, the report provides a set of recommendations aimed at promoting prevention of the presence of unexpected impurities in human medicines in addition to better manage any future cases and ensure protection of public health. The experience gained from GMP inspections of active substance manufacturers is reported in chapter 4 "Improving market surveillance" of the report. Paragraph 4.2.2 outlines how one reason for the presence of N-nitrosamines in sartans was the lack of sufficient process and product knowledge during the development stage and GMP deficiencies by active substance manufacturers, including inadequate investigation of quality issues and insufficient contamination control measures, among other points on behalf of the active substance manufacturers inspected. The **chapter recommends making annex 15 mandatory for active substance manufacturers** in order to address the shortcomings identified and ensure quality and safety of medicines.

During the 115th meeting of the GMDP IWG (September 2024) it was **agreed that the implementation of the sartans lessons learnt recommendations should be addressed by a targeted revision of Annex 15** and a drafting group was formed to initiate the process. In addition, during this meeting the GMDP IWG also agreed that the revision of Annex 15 should be updated following ICH Q9 R1 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline Q9 (R1) on quality risk management - Step 5 - Revision 1. The revised Annex 15 will be applicable to manufacturers of chemical and biological active substances. EU and PIC/S inspectorates will ensure its implementation and compliance during regulatory inspections of the facilities manufacturing chemical and biological active substances.

During the 115th meeting of the GMDP IWG (September 2024) it was also agreed that a comprehensive review of Annex 15 should be initiated in the future, once the current targeted revision is finished.

2. Discussion

The proposal is to extend the scope of the annex to active substance (AS) manufacturers and amend the text in selected areas supplementing and linking with guidance provided in EudraLex, Volume 4, Part II and other guidance relating to active substances (e.g. GDP):

[1] https://health.ec.europa.eu/system/files/2016-11/2015-10_annex15_0.pdf

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- To reflect in the scope of the annex the extension to AS manufacturers.
- To extend the concept of the "Validation Master File", the concept of "Qualification and Validation policy" and change control. These extensions are expected to improve AS manufacturers practice of defining and documenting the qualification and validation activities when drafting the validation protocol referred in paragraph 12.20 of EudraLex Volume 4, Part II. The control of a change will be also emphasised as an important part of knowledge management.
- To extend the expectations for validation by third party contractors enabling AS manufacturers to have more control over outsourced activities.
- To also extend the need to perform an investigation of results failing to meet pre-defined acceptance criteria. This extension will promote AS manufacturers to have a more in-depth knowledge of their processes.
- In terms of qualification stages, to extend the concept of User Requirements Specifications, Factory Acceptance Testing/Site Acceptance Testing to AS manufacturing and link with the expectations on design qualification, installation qualification, operational qualification, performance qualification. Such extensions are expected to strengthen AS manufacturers control over their processes.
- To provide emphasis on having a robust process development and clarify expectations on the concurrent validation approach. Provisions on supplier qualification will be also emphasised. The extension of process validation activities to process recovery of materials and solvents will be highlighted. It will focus the attention on the variables that impact critical quality attributes when drafting process validation protocol and provides guidance on continuous process verification and hybrid approach. Emphasis on periodic review will be also provided.
- In terms of implementing the principles of Good Distribution Practices of active substances for medicinal products for human use, to provide more guidance on verification of transportation extending in this way Part II chapter 10 and emphasising the need to include in product knowledge also consideration on the impact of transportation to the quality of AS.

The proposal will also include targeted revisions of the text to consider the ICH guideline Q9 (R1) on quality risk management.

- The use of QRM in the design and validation/qualification of monitoring systems will be underlined in the general section. Guidance on QRM approach will be complemented with the provision for risk review activities to support validation and qualification in Annex 15. This will link with the guidance provided in chapter 2 of EudraLex Volume 4, Part II.
- Annex 15 will also provide emphasis on QRM in the context of traditional process.

Other relevant topics and related changes may be considered by the drafting group during the revision process, and will consult GMDP IWG, PIC/S in case required.

3. Recommendation

The EMA GMP/GDP Inspectors Working Group and the PIC/S Sub-committee on GMDP Harmonisation jointly recommends that the current version of Annex 15, Qualification and validation, be revised according to this concept paper.

4. Proposed timetable

Preparation of draft concept paper / draft guideline – from November 2024

Approval of draft concept paper by EMA GMP/GDP IWG – November 2025

Release for consultation of concept paper (2-month consultation) – February 2026

Deadline for comments on concept paper – April 2026

Discussion in EMA GMP/GDP IWG and PIC/S Committee drafting group – from April 2026

Release for consultation of draft guideline (3-month consultation) – April 2026

Deadline for comments on draft guideline – June 2026

Endorsement by EMA GMP/GDP IWG – July 2026

Publication by European Commission – by December 2026

Adoption by PIC/S Sub-committee on GMDP Harmonisation – by December 2026

5. Resource requirements for preparation

A drafting group has been established by EMA GMP/GDP Inspectors Working Group and the PIC/S Sub-committee on GMDP Harmonisation with a rapporteur and supporting experts from other EU member regulatory authorities and from non-EU PIC/S participating authorities. It is expected that most of the work will be completed by email and by teleconference.

The guideline will be discussed at GMP/GDP IWG and the PIC/S Committee as necessary and at other involved working parties and groups. Further discussions are expected with interested parties.

6. Impact assessment (anticipated)

Although annex 15 is not currently mandatory for AS manufacturers, the applicability of its principles in this sector is **generally recognised**. **Making annex 15 formally mandatory to active substance manufacturers is expected to further enhance public health safety by promoting manufacturers to have more oversight and knowledge about their processes and products**.

Although the change in scope of the annex from optional to mandatory is not expected to have a critical impact on companies, stakeholders should be adequately consulted. The application of effective quality risk management tools and principles throughout the lifecycle of a medicinal product including in validation and qualification activities leads to better, more informed, and timely decisions. Similarly, although the change resulting from the ICH guideline Q9 (R1) on quality risk management is not expected to have a critical impact on companies, stakeholders should also be consulted. The proposed questions to stakeholders are:

1. What is the current level of use of annex 15 principles in active substance manufacturing in the different sections of the guideline (process validation, cleaning validation, transport validation, investigations, qualification, change control) as well as usage of retrospective or concurrent validation approach?
2. What would be the impact of making annex 15 mandatory for active substance manufacturers in the different sections of the guideline (process validation, cleaning validation, transport validation, investigations, qualification, change control)?
3. What is the current level of understanding and use of ICH guideline Q9 (R1) on quality risk management in active substance manufacturing?
4. What would be the impact of the change resulting from ICH guideline Q9 (R1) on quality risk management?

7. Interested parties

- EMA GMP/GDP Inspectors Working Group.
- PIC/S Committee, Sub-committee on GMDP Harmonisation.
- National competent authorities of EU/EEA Member States.
- PIC/S participating authorities.
- Pharmaceutical industry.
- International societies and interest groups within pharmaceutical industry.

8. References to literature, guidelines, etc.

- Annex 15 - EudraLex The Rules Governing Medicinal Products in the European Union Volume 4 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use
- Part II - EudraLex The Rules Governing Medicinal Products in the European Union Volume 4 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use
- Good Distribution Practices of active substances for medicinal products for human use