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PHARMACEUTICAL INSPECTION CONVENTION
PHARMACEUTICAL INSPECTION CO- OPERATION SCHEME

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

# Concept Paper on the revision of Annex 3 of the guidelines on Good Manufacturing Practice for Radiopharmaceuticals

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| Agreed by EMA GMP/GDP IWG | 26 November 2025 |
| Agreed by PIC/S | 5 December 2025 |
| Start of public consultation | 15 December 2026 |
| End of consultation (deadline for comments) | 15 February 2026 |

The proposed guideline will replace:

- Eudralex Volume 4: Annex 3, Manufacture of Radiopharmaceuticals.
- for PIC/S participating authorities: PE 009-17: Annex 3 – Manufacture of Radiopharmaceuticals.

Comments should be provided using this template. The completed comments form should be sent to ADM-GMDP@ema.europa.eu.

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| Keywords | GMP, medicinal product, radiopharmaceuticals, radioactive generators, precursors, annex 3. |

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# 1. Introduction

This concept paper proposes to update Annex 3, Manufacture of Radiopharmaceuticals, of the Good Manufacturing Practice (GMP) guide. Annex 3 is common to the Member States of the European Union (EU)/European Economic Area (EEA) as well as to the Participating Authorities of the Pharmaceutical Inspection Co-operation Scheme (PIC/S). The current version was issued in 2008.

The aim of this revision is to provide guidance within some areas that were not covered in the current version, clarify some sections, and support innovative pharmaceutical manufacturing and control approaches, as better detailed in the following paragraph 3 "Discussion".

# 2. Problem statement

Since the release of the current version of Annex 3, several revisions of GMP, ICH, other EMA radiopharmaceutical relevant guidelines and of the EU legislation have been adopted, introducing new concepts that are not considered in the current version.

In addition, the experience gained during GMP inspections of radiopharmaceuticals indicates that a revision of Annex 3 is necessary to avoid inconsistent interpretations and to clarify sections in the current version. Furthermore, recent developments in the field of radiopharmaceuticals, e.g. analytical capabilities and radiosafety equipment, also need to be considered in the revision.

# 3. Discussion

The current version of Annex 3 was released in 2008. As mentioned in the problem statement section, changes in the EU legislation and the revision of the regulatory guidelines have subsequently occurred, as well as the importance to support innovation in radiopharmaceutical manufacturing and quality control, and to promote harmonised approaches in radiopharmaceutical manufacturing, highlighted the necessity to revise this Annex.

The following items have been identified as the key areas that need to be updated in the revision of the Annex 3 affecting its structure, content, wording and level of detail:

- Revise and update the sections regarding the GMP requirements for starting materials, active substances and finished radiopharmaceutical products, and for manufacturing process steps and quality control, considering the experience gained since the Annex 3 introduction, including the development of new radiopharmaceutical products, as well as to support innovation in manufacturing and quality control.
- Update the Annex to be aligned with the latest revisions of the GMP Chapters and Annexes since the release of this Annex in 2008, e.g. Chapter 1, Chapter 4, Chapter 6, Annex 1, Annex 11 and Annex 15.
- Update the Annex in light of the ICH quality guidelines, e.g. Q9 Quality Risk Management, Q10 Pharmaceutical Quality System and Q12 Lifecycle Management.
- Take into consideration, for further consistency and alignment, relevant EMA quality guidelines, such as the Guideline on Radiopharmaceuticals and the Guideline on Radiopharmaceuticals Based on Monoclonal Antibodies.
- Revise the Annex to be consistent with the Clinical Trial Regulation and the GMP guidelines for investigational medicinal products.
- Clarify the application of GMP requirements in the context of radiation protection and product short shelf-life.
- Clarify the multi-step release process, including the relevance of the OOS and/or deviations assessment on the batch release.
- Consider the requirements for importation of radiopharmaceuticals.
- Clarify the distribution process, including product recall.

- Where relevant, the revised Annex should include references to radioprotective measures set out in other guidelines that are under the scope of other regulatory bodies, i.e., IAEA (International Atomic Energy Agency).
- Revise the Glossary section accordingly, in order to support the revision of this Annex.

## 4. Recommendation

The EMA GMP/GDP Inspectors Working Group and the PIC/S Sub-committee on GMDP Harmonisation jointly recommend that the current version of Annex 3 is revised to reflect changes in regulatory and manufacturing environments, according to this concept paper.

## 5. Proposed timetable

Preparation of draft concept paper – June 2025
Approval of draft concept paper – November 2025
Release of concept paper for consultation – December 2025
Deadline for comments on concept paper – February 2026
First draft of the revised annex for discussion in EMA GMDP IWG and PIC/S Committee – March 2027
Proposed release for Stakeholder's consultation of the draft revised annex – September 2027
Deadline for comments – 3 months from the above date
Discussion in EMA GMP/GDP IWG and PIC/S Committee – June 2028
Endorsement by the GMDP IWG and PIC/s Committee – November 2028

## 6. Resource requirements for preparation

A joint drafting group has been established by EMA GMDP Inspectors Working Group (IWG) and the PIC/S Sub-committee on GMDP Harmonisation.

It is expected that most of the work will be completed by email and by teleconference.

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

## 7. Impact assessment (anticipated)

The update of Annex 3 is intended to benefit both industry and regulators by clarifying expectations to areas already covered or those areas not yet adequately covered, and contribute to a more harmonised interpretation, both for regulators and for industry.

No unnecessary adverse impact on industry with respect to either resources or costs is foreseen.

## 8. 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, e.g. EFPIA (European Federation of Pharmaceutical Industries and Associations), ISPE (International Society for

Pharmaceutical Engineering), PDA (Parenteral Drug Association), EANM (European Association of Nuclear Medicine) and NMEU (Nuclear Medicine Europe).

# 9. References to literature, guidelines, etc.


- The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use.
- PIC/S Guide to GMP for medicinal products.
- ICH Q9 Quality Risk Management, Q10 Pharmaceutical Quality System and Q12 Lifecycle Management.
- Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use.
- Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections.
- Concept paper on the revision of the EMA Guideline on Radiopharmaceuticals.
- EMA Guideline on Radiopharmaceuticals Based on Monoclonal Antibodies.
- European Pharmacopoeia (and other Pharmacopoeias from PIC/S participating authorities).
- International Atomic Energy Agency (IAEA)/WHO guidelines on good practices for quality control of radiopharmaceutical products (draft working document for comments).