European Medicines Agency
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GMP/GDP Inspectors Working Group (GMP/GDP IWG)

Concept paper on revision of the guidelines on Good Manufacturing Practice for medicinal products - Annex 6 Manufacture of Medicinal Gases.

Agreed by EMA GMP/GDP IWG	26 November 2025
Agreed by PIC/S	14 January 2026
Start of public consultation	11 February 2026
End of consultation (deadline for comments)	11 April 2026

The proposed guideline will replace:

- Eudralex Volume 4: Annex 6, Manufacture of Medicinal Gases

Keywords	GMP, Medicinal Product, Annex 6, Medicinal Gases

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1. Introduction

This concept paper addresses the need to update Annex 6, Manufacture of Medicinal Gases, of the Good Manufacturing Practice (GMP) guide. Annex 6 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 last revision of Annex 6 was adopted by the European Commission in 2010, and an update is necessary to take into account changes in current practice and taking into account stakeholder recommendations made to the Agency following the Covid-19 pandemic which are further detailed in the section "2. Discussion".

2. Discussion

The objective is to carry out a limited review and update of the guideline to reflect industry's current practices and the use of new technologies and computerised systems in their operations.

The following areas are in the focus of the revision:

- Requirements for premises: The extent to which the general EU GMP requirements for the manufacturing environment are applied for medicinal gases will be assessed taking into account positive pressurisation in the closed manufacturing process and in the containers used for storage of raw materials and finished products.

- Technological advances in production of medicinal gases should be taken into account; for example, the exclusive use of gas-specific couplings, and the complete elimination of containers without residual pressure valves are measures helping to reduce the risk of contamination and ensure drug safety. In this context, the current requirements to check valves and remove residual gases before refilling containers with residual pressure valves must also be evaluated.

- In the case of gas cylinders fitted with valves that have an integrated pressure regulator flowmeter, the requirements for inspections before and after refilling should be checked to see if they need adjusting. In addition, the requirements for defining the frequency of the flow checks of the integrated flowmeter for cylinders as well as cryogenic containers will be established.

- Documentation of manufacturing activities: Medicinal liquid oxygen is supplied to hospitals to ensure an adequate oxygen supply. Filling the hospital's tank evaporation units is therefore an important part of the supply chain for treating patients in this area. The requirements for documentation and quality assurance in this area are to be supplemented.

- The industry has pointed out that the release of medicinal liquid oxygen to hospitals should be regulated in a more practical manner, taking into account the procedures, process risks and availability of the qualified person. The revision of Annex 6 will consider if there should be specific considerations for medicinal gases in relation to the batch release process as described in Annex 16 (e.g. remote and/or retrospective certification).

- Some specificities of modern medicinal gas production may not be adequately addressed in the current EU GMP guidelines, for example, in relation to the Qualification of manufacturing facilities, mobile and stationary storage tanks, and reusable containers.

- Other relevant topics and related changes may be considered by the drafting group during the revision process.

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 6, Manufacture of Medicinal Gases, be revised according to this concept paper.

4. Proposed timetable

Preparation of draft concept paper – from January 2025

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

Release for consultation of draft concept paper (2 months 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

Proposed release for consultation of draft guideline (3 months consultation) – November 2026

Deadline for comments on guideline – February 2027

Endorsement by EMA GMP/GDP IWG – September 2027

Publication by European Commission – November 2027

Adoption by PIC/S Sub-committee on GMDP Harmonisation – December 2027

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)

The updated Annex 6 is intended to benefit both industry and regulators by clarifying expectations to areas already covered, by broadening these two areas not yet covered, and by pushing the adoption of a common approach between EU and non-EU regulatory authorities.

No unnecessary adverse impact on industry with respect to either resources or costs is foreseen, although there is always a cost associated with being in compliance (or quality). The revision may require some systems and processes to be modified over a period of time.

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, e.g. European Industrial Gases Association (EIGA).

8. References to literature, guidelines, etc.

- CPMP/QWP/1719/00 Rev 1 - Guideline on Medicinal Gases: Pharmaceutical documentation (including recommendation on non-clinical safety requirements for well established Medicinal Gases)
- Annex 6 - EudraLex The Rules Governing Medicinal Products in the European Union Volume 4 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use
- PIC/S PI 025-2 Aide Memoire on Medicinal Gases