STATEMENT ON THE NEW GMP ANNEX 1
Use of safety cabinets for the preparation of parenterals in pharmacies

Thomas Hinrichs and Michael Klein, Germany-Elmshorn
30.09.2022

On 25.08.2022, the final version of the new Annex 1 of the EU GMP Guideline was published [1]. Over several years, the previous version [2] was completely revised in collaboration between the European Medicines Agency (EMA), the World Health Organization (WHO) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S). Some of the changes have raised the question of whether safety cabinets may continue to be used for aseptic, patient-specific preparation of medicinal products in light of the requirements formulated therein. The question is based primarily on a statement in Section 4 (Premises) of the new annex, which states:

"Restricted Access Barrier Systems (RABS) or isolators are beneficial in assuring required conditions and minimizing microbial contamination associated with direct human interventions in the critical zone. Their use should be considered in the CCS [Contamination Control Strategy]. Any alternative approaches to the use of RABS or isolators should be justified."

Section 8 (Production and Specific Technologies) adds:

"Where possible, the use of equipment such as RABS, isolators or other systems, should be considered in order to reduce the need for critical interventions into grade A and to minimize the risk of contamination."

The description of appropriate barrier technologies in the new EU GMP Annex 1 also specifically highlights RABS and isolators.

Does this mean that parenterals-producing pharmacies or similar facilities will have to switch to isolators in the future to meet regulatory requirements?

Our position:

The EU GMP Guideline [3] is a standard designed to ensure product quality in the industrial manufacture of pharmaceuticals. It therefore corresponds to the PIC/S GMP Guide PE 009-16 [4], which has identical requirements. This also applies to PIC/S PE 009-16 Annex 1 [5], which was recently adapted to the new EU GMP Annex 1.

The intended identical wording of both sets of regulations is significant in that there is a further PIC/S standard that is explicitly distinct from the specifications for industry. This guideline, designated PE 010-4 [6], describes requirements for the manufacture of medicinal products in health care establishments. Products prepared there are intended for individual use and direct supply to patients. The main addressees are pharmacies. Regulations for the devices to be used there are consequently to be taken from PIC/S Guide PE 010-4 and not from PIC/S GMP Guide PE 009-16 or the EU GMP Guide. They will therefore remain unaffected by the revision of Annex 1.

Which requirements regarding the devices to be used have to be considered?

PIC/S Guide PE 010-4 states that

"handling and filling of aseptically prepared products [...] should be performed in a grade A environment in a laminar flow cabinet (LFC) or a positive pressure pharmaceutical isolator."

These specifications are in line with the recommendations of the German Federal Chamber of Pharmacists as published in the commentary of the corresponding guideline [7]:

"All critical work steps must be performed in a cleanroom grade A area (safety cabinet/isolator). For the production of ready-to-use parenterals with CMR properties of category 1A or 1B, a safety cabinet or an isolator according to [the German standard] DIN 12980 must be used."

The German Pharmacy Operations Regulation [8] does not include any specifications on this aspect. With regard to the preparation of medicinal products for parenteral use (§ 35), it merely adopts the definition of the required cleanroom grades from Annex 1 of the EU GMP Guidelines, but does not include specific requirements with regard to suitable devices.

For the manufacture of medicinal products in facilities with manufacturing authorization according to Section 13 of the German Medicines Act [9], the requirements of the EU GMP Guidelines must be comprehensively observed. But even here, the use of an isolator is not mandatory, as the above quotes from the new EU GMP Annex 1 show. Alternative systems, primarily safety cabinets, are permitted if their use is justified. This is also required in manufacturing facilities wherever the individuality of the manufactured drug preparations makes extensive automation technically and economically difficult or even impossible. As mentioned at the outset, the systems used must be integrated into a contamination control strategy in order to identify and minimize risks from contamination with microorganisms, endotoxins/pyrogens and particles (information on this, for example, in [10] and [11]).

Conclusion

The new EU GMP Annex 1 as well as the PIC/S PE 009-16 Annex 1 applies to industrial manufacture. These requirements do not apply to the preparation of sterile medicinal products as part of normal pharmacy operations. It is therefore not affected by the amendments. Corresponding work can therefore continue to be carried out in a safety cabinet, provided that the framework conditions specified in the in the PIC/S Guide PE 010-4 are complied with. Safety cabinets also continue to be the method of choice for comparable activities in manufacturing facilities, as they cannot usually be replaced by complex, automated systems. The new EU GMP Annex 1 recognizes this as an alternative to closed systems, but in future it requires a justification for their use as well as their integration into corresponding CCS measures.

Dipl.-Ing. Thomas Hinrichs
Managing Partner
Berner International GmbH

Dipl.-Biochem. Michael Klein
Head of Research
Berner International GmbH

References:

[1] European Commission. 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. Annex 1. Manufacture of Sterile Medicinal Products. Stand: 22.08.2022, https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf.

[2]. Eurpoean Commission. The Rules Governing Medicinal Products in the European Union. Volume 4. EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use. Annex 1. Manufacture of Sterile Medicinal Products. Stand: 25.11.2008, https://health.ec.europa.eu/system/files/2016-11/2008_11_25_gmp-an1_en_0.pdf.

[3] European Commission. 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, https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_de.

[4] PIC/S. Guide to good manufacturing practice for medicinal products. Part I. PE 009-16 (Part I). Stand: 01.02.2022, https://picscheme.org/docview/4588.

[5] PIC/S. Revised Annex 1 (Manufacture of sterile medicinal products) to Guide to good manufacturing practise for medicinal products. Stand: 09.09.2022, https://picscheme.org/docview/4737.

[6] PIC/S. Guide to good practices for the preparation of medicinal products in healthcare establishments. PE 010-4. Stand: 01.03.2014, https://picscheme.org/docview/3443.

[7] Kommentar zur Leitlinie der Bundesapothekerkammer zur Qualitätssicherung. Aseptische Herstellung und Prüfung applikationsfertiger Parenteralia. Stand der Revision: 13.11.2019, https://www.abda.de/fuer-apotheker/qualitaetssicherung/leitlinien/leitlinien-und-arbeitshilfen/.

[8] Verordnung über den Betrieb von Apotheken (Apothekenbetriebsordnung - ApBetrO). Stand: 28.06.2022, https://www.gesetze-im-internet.de/apobetro_1987/BJNR005470987.html.

[9] Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG). Stand: 04.06.2022, https://www.gesetze-im-internet.de/amg_1976/.

[10] ECA Foundation. ECA Task Force on Contamination Control Strategy. How to Develop and Document a Contamination Control Strategy. Stand: 01/2022, https://www.eca-foundation.org/news/eca-foundation-ccs-task-force-guidance.html.

[11] Sandle, T. (2021), An Anatomy Of A Contamination Control Strategy For Sterile Manufacturing. GMP Review 25(2):1-10. https://www.researchgate.net/publication/350441966_An_Anatomy_Of_A_Contamination_Control_Strategy_For_Sterile_Manufacturing.