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Concept paper on the revision of annex 5 of the guidelines on good manufacturing practice for medicinal products – manufacture of immunological veterinary medicinal products

Agreed by GMP/GDP IWG and PIC/S	September 2021 (IWG) October 2021 (PIC/S)
Start of public consultation	9 November 2021
End of consultation (deadline for comments)	9 January 2022

The proposed guideline will replace:

- Eudralex Volume 4: Annex 5 manufacture of immunological veterinary medicinal products
- for PIC/S participating authorities: PE 009-14: annex 5 - manufacture of immunological veterinary medicinal products

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

Keywords	GMP, veterinary medicinal product, annex 5

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1. Introduction

This concept paper addresses the need to update Annex 5 (manufacture of immunological veterinary medicinal products) of the Good Manufacturing Practice (GMP) guide. Annex 5 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 original version has not been revised since it was originally issued in 1992. Since that time, there has been extensive progress in the use of new technologies, significant changes in GMP following the adoption of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q8, Q9, Q10 and Q11 guidelines, International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) guidelines. Additionally, there have been development of new products (e.g. Advanced Therapy Medicinal Products, Blood products, Cell therapy products, Gene therapy products, Biotechnology products, Animal extracted products, Tissue engineered products, Allergen products …) .

The revision of the current text of Annex 5 is considered a priority for the following main reasons:

- to facilitate the implementation of the principles in these aforementioned ICH guidelines and ad hoc VICH guidelines;
- to extend the underlying concepts to include new areas of technology (e.g. novel therapy products), new processing, new products not previously covered;
- to clarify areas that have been highlighted as ambiguous due to the age of the document.

As the existing Annex is focused solely on the manufacture of immunological veterinary medicinal products to this day, there is no source of guidance in EU-PIC/S GMP for the conditions of manufacture of other veterinary biological products and for the early stages in the manufacture of a range of these products (GMP Part I vs GMP Part II).

Moreover, since the update and split of GMP Part I and II in 2005, a number of Annexes have been revised (e.g. Annex 2 and 15) or are under revision (Annex 1). This revision has provided the opportunity to indicate if specific requirements are applicable to those described in GMP Part I and II. The current Annex 5 does not similarly indicate if requirements are applicable to Parts I and II.

2. Discussion

The current Annex does not reflect the advances in the manufacture of immunological veterinary medicinal products; the revised text will embrace the application of new technologies which have been developed since publication of the original Annex and therefore are not currently addressed by it.

The current guidance deals solely with immunological products. However in absence of other standards, is often consulted in relation to the manufacture of veterinary biological products. To fill this gap, the revised Annex should also be extended to address the conditions of manufacture for a full range of veterinary medicinal substances including products which are defined as biological products. Moreover, the revised guideline will also provide supplements to GMP Part I and GMP Part II. The scope and title of the guideline should therefore be broadened to encompass this evolution.

Since Annex 5 was published, introduction of relevant ICH concepts, adoption of VICH guidelines, consequential regulatory changes and technological advancements have occurred which are not reflected in the current GMP Annex. In addition, with the aim of maintaining a globalized approach and in keeping with greater international convergence, opportunities will be taken where appropriate to align this guidance with international requirements. The opportunity will also be taken to ensure maintenance of coherence with other EU or PIC/S pharmaceutical guideline documents.

The current GMP Annex on the manufacture of immunological veterinary medicinal products was established before the development of the ICH Q8, Q9 and Q10 guidelines and main VICH guidelines. Specifically, ICH Q9 (i.e. EU GMP Part III and PIC/S GMP Annex 20) provides principles and examples

of tools for quality risk management that can be applied to different aspects of pharmaceutical quality, while ICH Q10 describes a modern pharmaceutical quality system in order to establish and maintain a state of control, the realisation of product quality and facilitation of continual improvement over the entire product life cycle. The revised Annex will clarify to what extent principles of Q8, Q9 and Q10 and VICH guidelines should be followed in the design and implementation of facilities, equipment and processes for the manufacture of veterinary biological products.

Other changes that may require GMP guidance update include those for harmonization with international pharmacopeia (USP, Ph. Eur. monograph) (e.g. oral, nasal or auricular vaccine) or other international standards relating to specific infectious diseases (OIE, EFSA, ECDE, FAO and EUFMD minimum biorisk management standards for laboratories working with foot-and-mouth disease virus[1]).

A change is also necessary in order to make clear that this annex 5 is applicable to both medicinal product manufacturers and biological substance manufacturers.

Finally, the revision of Annex 5 will correct inaccuracies and areas of ambiguity contained in the existing "outdated" document and will offer a higher level of clarity for effective interpretation of GMP expectations.

3. Recommendation

The GMP/GDP Inspectors Working Group and the PIC/S WG on VMP jointly recommend that the current version of Annex 5, on the manufacture of immunological veterinary medicinal products, should be revised to reflect changes in the regulatory environment (e.g. enforcement of new EU Veterinary Medicines Regulation - Regulation (EU) 2019/6) and technological progress and to cover the manufacture of veterinary medicinal substances and products included in the definition of biological veterinary medicinal products (including novel therapy products).

The revised Annex should clarify how manufacturers can take advantage of new possibilities derived from the application of an enhanced process understanding by using innovative tools as described in the ICH Q8, Q9 and Q10 guidelines and VICH guidelines.

The scope of the project will be limited to Annex 5 but the revision of Annex 5 should also take into account related changes in other GMP chapters and annexes as well as in other regulatory documents. It should also state its applicability to GMP guidelines part I and II.

4. Proposed timetable

Preparation of draft concept paper – June 2021
Approval of draft concept paper – September 2021
Release for consultation –2 month
Deadline for comments – December 2021
Discussion in PIC/S Committee – March 2022
Discussion in EMA GMDP IWG - March 2022
Discussion with other Working Parties - during 2022 & 2023
Proposed date for release of draft guideline – March 2023
Deadline for comments – 3 months from above date
Re-discussion in EMA GMDP IWG – November 2023
Re-discussion in PIC/S Committee – November 2023

5. Resource requirements for preparation

A drafting group will be established by GMP/GDP Inspectors Working Group and the PIC/S WG on VMP representing the PIC/S committee with a rapporteur and supporting experts from other EU member regulatory authorities and from non-EU PIC/S participating authorities.

[1] FAO-EUFMD Minimum Biorisk Management Standards for laboratories working with FMDV - http://www.fao.org/3/ca5709en/ca5709en.pdf#page=226

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 5 is intended to benefit both industry and regulators by incorporating new regulatory concepts, clarifying requirements and taking the opportunity to adopt a common approach between EU and non-EU regulatory authorities. Revision of the Annex will facilitate a better understanding of expectations which will lead to more consistent and improved manufacture of veterinary biological products, thereby enhancing the continuity of supply.

No adverse impact on industry with respect to either resources or costs is foreseen, although clarification of the use of new systems may require some facilities, equipment and processes to be modified over a period of time.

7. Interested parties

- EMA (GMP/GDP Inspectors Working Group, Quality Working Party, Biologics Working party Veterinary Novel Therapies and Technologies working Party (NTWP) and Immunological Working party (IWP))
- PIC/S (Committee, Sub-committee on GMDP Harmonisation, WG on VMP)
- National competent authorities of EU/EEA member states
- PIC/S participating authorities
- EDQM
- Pharmaceutical Industry

8. References to literature, guidelines, etc.

- ICH Q8 (R2) Pharmaceutical development
- ICH Q9 Quality Risk Management
- ICH Q10 Pharmaceutical Quality System
- ICH Q11 Development and manufacture of drug substances
- EU GMP guide to good manufacturing practice for medicinal products: Eudralex volume 4 / PIC/S GMP guide: PE 009-14
- OIE, EFSA, EDE, FAO-EUFMD Minimum Biorisk Management Standards for laboratories working with FMDV
- VICH Guidelines
- REGULATION (EU) 2019/6 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC
- Pharmacopeia