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Annual report of the Good Manufacturing and Distribution Practice Inspectors Working Group 2021

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1. Introduction

This document is the annual report of the GMP/GDP Inspectors Working Group (GMP/GDP IWG) for the year 2021. This group was established at EMA in 1996.

There was no annual report from 2018 to 2020 as a result of the EMA Business Continuity Plan (BCP) due to the effects of the UK withdrawal from the European Union. The BCP was extended in 2020 due to the public health emergency due to COVID-19. The impact of the BCP on the work of the GMDP IWG has meant a prioritisation in activities and shorter meetings, although the meeting frequency has been maintained. The GMDP IWG currently meets virtually via remote meeting platforms.

The GMP/GDP IWG provides input and recommendations on all matters relating directly or indirectly to Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP).

The GMP/GDP IWG focuses on harmonisation and co-ordination of GMP and GDP related activities at EU level and maintains close co-operation with international partner authorities. The group's role and activities are described in more detail in its mandate, which was revised in 2013.

This annual report is set out in line with the format and objectives of the 2021 – 2023 3 year work plan.

2. Meetings

The plenary GMP/GDP IWG meetings took place on:

- 2-4 March 2021 (WebEx meeting) ;
- 22-24 June 2021 (WebEx meeting);
- 20-22 September 2021 (Joint QWP- IWG on 22 September) (WebEx meeting);
- 23-25 November 2021 (WebEx meeting)

In addition, two ad hoc meetings of the GMDP IWG were held during 2021 to discuss the progress of work on EudraGMDP and review regulatory flexibilities for COVID-19;

- 04 June 2021 (WebEx meeting) ;
- 21 July 2021 (WebEx meeting) ;

Drafting group meetings were held by teleconference or through other virtual meeting technology.

The Compliance Group, managing the Joint Audit Programme (JAP) on behalf of HMA, also met on four occasions in 2021 in the margins of the above mentioned plenary meetings.

3. GMP and GDP inspections in 2020 and 2021

The current COVID-19 public health emergency has a considerable impact on the work of GMP and GDP inspectors. Travel restrictions and hygiene measures has led to the suspension of on-site inspection as the primary means of verifying compliance with requirements. In 2020, the IWG adopted temporary measures to facilitate on-going compliance verification through use of "distant assessment" and agreed to the automatic extension of validity dates of EU GMP Certificates entered into EudraGMDP database. These measures were incorporated into questions and answers on regulatory expectations

for medicinal products for human and for veterinary use that were published by the European Commission[1].

During 2021, the GMDP IWG agreed to extend these temporary measures until end of 2022 and monitored the impact of the public health emergency on the conduct of inspections and on pharmaceutical supply chains.

4. Mutual recognition agreements (MRAs) and other agreements on GMP

4.1. MRA General

Despite the pandemic MRA related work was maintained in 2021.

4.2. MRA with US

Work continued on the inclusion of veterinary medicines in the operational scope e of the EU – US Mutual Recognition Agreement. Preparatory work on the modalities and scope of an assessment of FDA for the expansion of the MRA operation to vaccines and plasma derive products has started. Work on the inclusion of pre-approval inspections was put on-hold.

The GMP/GDP IWG continued to provide the forum to discuss and clarify the technical and practical aspects for the implementation of the MRA.

A representative from US FDA attended GMP/GDP IWG meetings throughout 2021.

4.3. MRA with Japan

There were no changes to the existing MRA with Japan throughout 2021.Representatives from the Pharmaceuticals and Medical Devices Agency (PMDA) attended GMP/GDP IWG meeting September 2021.

4.4. MRA with Canada

The Comprehensive Economic Trade Agreement (CETA) entered into provisional application in September 2017 pending ratification by all EU member states.

The provisions of the existing MRA have been integrated into the CETA with the addition of voluntary recognition of third country inspections.

The EU assessment of Canada towards "API Listing" and inclusion of APIs in the MRA progressed during 2021.

The mutual recognition of GMP inspections conducted outside of the territories of the Parties was implemented in April 2021.

Health Canada observed the JAP audit of EOF (Greece).

Representatives from Health Canada attended GMP/GDP IWG meetings throughout 2021.

[1] guidance_regulatory_covid19_en.pdf (europa.eu) and ah_vet-med_covid-19_qandas.pdf (europa.eu).

4.5. MRA with Switzerland

No changes were made to the MRA with Switzerland during 2021.

Representatives from Switzerland attended GMP/GDP IWG meetings throughout 2021 and proactively shared the minutes of the Swiss Inspectorates Coordinating Committee (ICC).

4.6. MRA with Australia

There were no changes to the existing MRA with Australia throughout 2021.

A representative from the Australian Pesticides and Veterinary Medicines Authority (APVMA) attended the June, September and November 2021 GMP/GDP IWG meetings. A representative from the Therapeutics Goods Administration (TGA) attended September 2021 GMP/GDP meeting.

4.7. MRA with New Zealand

There were no changes to the existing MRA with New Zealand throughout 2021.

4.8. ACAA with Israel

There were no changes to the existing ACAA co-operation with Israel in 2021.

A representative from the Ministry of Health attended September and November 2021 GMP/GDP meetings.

4.9. Other international collaborations on GMP

The EU-UK Trade and Cooperation Agreement concluded between the EU and the UK provisionally applies since 1 January 2021, pending the completion of ratification procedures.

The agreement contains a specific annex on medicinal products which covers the recognition of good manufacturing practice (GMP) inspection outcomes carried out by EU and UK authorities

The United Kingdom attended all four GMP/GDP IWG meetings in 2021 as an observer.

EDQM attended all four GMP/GDP IWG meetings in 2021 as an observer and informed the GMDP IWG during the year on a number of topics of common interest including the progress of sampling and testing programmes, the proceedings of the annual OMCL meeting, the EDQM reinspection programme and the CEP Steering Committee.

5. Harmonisation topics

5.1. Joint Audit Programme (JAP)

During 2021 the GMDP IWG endorsed a revision of the JAP Procedure to include distant assessments so that at time of crisis when a regular on-site audit is not possible, a distant assessment can be performed to determine the level of equivalence.

During 2021 the GMDP IWG endorsed an amended mandate for the Compliance Group and endorsed a new Chair of the Compliance Group and confirmed the renewal of the membership and as well confirmed the renewal of the membership of a number of members.

Due to the impact of the pandemic only two JAP audits were conducted on-site. One audit was conducted virtually.

With view to the changing pandemic and travel situation November 2021 a decision was taken to generally postpone routine JAP audits by a year to allow them to take place as on-site audits.

Throughout the year the Compliance Group monitored the implementation of CAPAs from 13 audits and closure of 5 JAP audits.

5.2. Compilation of Union Procedures on Inspections and Exchange of Information

Work on the compilation of union procedures was suspended in 2018 as a result of the Agency BCP. During 2021, work resumed by introducing the procedures that had been adopted by the GMDP IWG prior to the BCP. The new version (Version 18) was published by the Agency at the end of 2021 with significant updates including:

- A new procedure for compliance management, aiming at identifying and managing manufacturers at risk of becoming subject to a statement of non-compliance with a view to avoiding such an outcome.
- A revised procedure for dealing with serious GMP non-compliance information originating from third country authorities or international organisations.
- Revised procedures for handling reports of suspected quality defects and issuing rapid alerts.
- A revised procedure for Risk Based Planning for Inspections of Pharmaceutical Manufacturers.
- A modification was made to the procedure "Outline of a Procedure for Co-ordinating the Verification of the GMP Status of Manufacturers in Third Countries" to take into account the temporary measures introduced to deal with COVID and to include procedures for acceptance of third country inspections performed by MRA partners implementing parts of the PIC/S Mutual Reliance SOP.

In addition changes were made to interpretation guides or formats;

- A new interpretation document for the Union format for a wholesale distribution authorisation (medicinal products for human use)
- Union Format for a GMP Certificate
- Interpretation of the Union format for GMP certificate
- The issue and update of GMP certificates
- Statement of Non-compliance with GMP
- Interpretation of the Union Format for Manufacturer/Importer Authorisation

References to Directive 2001/20/EC were updated to Regulation 536/2014.

The new version was published on the Agency website : Good manufacturing practice | European Medicines Agency (europa.eu) and will enter into force in July 2022.

6. GMP and GDP guidance

GMP guidelines are developed in collaboration with PIC/S in accordance with the EMA-PIC/S co-operation agreement.

6.1. GMP Guide: Annex 1 (Manufacture of Sterile Medicinal Products)

A revised draft Annex 1 was finalised by the drafting group in December 2021 and is planned for adoption in 2022.

6.2. GMP for importers of medicinal products ("Annex 21")

Annex 21 was finalised and provided to the European Commission for publication in 2021.

6.3. GMP and Marketing Authorisation Holders (MAHs)

The reflection paper on Good Manufacturing Practice and Marketing Authorisation Holders was finalised and published in July 2021.

Reflection Paper on Good Manufacturing Practice and Marketing Authorisation Holders final version July 2021 (europa.eu)

6.4. Manufacture of Veterinary Medicinal Products Other Than Immunological Veterinary Medicinal Products (Annex 4).

A concept paper for the update of Annex 4 was finalized and published for stakeholder consultation in October 2021.

6.5. Annex 11 and chapter 4 of the guidelines on good manufacturing practice –computerised systems and documentation

Work has started on a concept paper for the update of Chapter 4 and Annex 11.

6.6. Manufacture Of Immunological Veterinary Medicinal Products (Annex 5)

A concept paper for the update of Annex 5 was finalized and published for stakeholder consultation in October 2021.

6.7. Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice"

Work on the guideline was paused in 2018 due to the BCP but was resumed during 2021 in readiness for the entry into force of the Clinical Trial Regulation in January 2022. The Guideline was adopted by the GMDP IWG in December 2021 and provided to the European Commission for publication.

6.8. Questions & Answers (Q&As)

Work was carried out on a number of Q&As with a view to harmonising interpretation and expectations on various GMP topics. The following were published during 2021.

- Q&A on the principles of GMP for starting materials of biological origin for Gene therapy products;
- Q&A on the GMPs applicable to the early manufacturing steps for comminuted plants and herbal extracts used as active substances.

7. Inspections, Non-compliance, Quality Defects and Referrals

7.1. Nitrosamine contamination and Sartans Lessons Learnt

General agreement was reached on the inclusion of risk-based selected Centrally Authorised Products (CAPs) in the sampling and testing programme for non-compliant CAPs. The list of products will be extracted from the CAPs in scope of the call for review exercise recommended by CHMP Article 5 (3) Scientific Opinion on presence of nitrosamine impurities in human medicines. This is also an action arising from the Sartans Lessons Learnt exercise.

In addition, a drafting group was formed in order to review all recommendations concerning GMP arising from the LLE assigned to the IWG.

8. EudraGMDP database

The new regulatory framework for veterinary medicines[2] requires the following changes to the EudraGMDP database which will come into effect from 28 January 2022:

- Integration of EudraGMDP with EMA's Organisation Management Service (OMS);
- Extension of the two following modules of EudraGMDP to the veterinary domain:
    - Wholesale Distribution Authorisations (WDA)
    - Active Pharmaceutical Ingredients Registration (API-Reg).

The GMP/GDP IWG has reviewed the proposed changes to the EudraGMDP database, providing technical input and direction as needed, as well as ensuring national systems are updated accordingly and that there was appropriate communication to stakeholders.

The GMP/GDP IWG agreed to a number of routine maintenance changes to the database during the year.

9. Collaboration with the European Commission

New legislative developments were monitored to assess and advise on the potential impact on GMP, GDP, inspections or inspection-related activities. In particular, attention was paid to developments related to the Joint Audit Programme, the Revision of the Pharmaceutical Legislation for human and veterinary medicinal products.

10. Liaison with other groups

The GMP/GDP IWG maintained dialogue and monitored developments involving external groups in areas of common interest. The aim was to communicate the work of the Group and to assess the impact of other groups' activities on GMP/GDP guidance, the Compilation of Union Procedures and other inspection-related activities.

[2] Regulations 2019/6 and 2021/16, Article 9(h)

10.1. Pharmaceutical Inspection Co-operation Scheme (PIC/S)

The GMP/GDP IWG continued the close collaboration with PIC/s on the harmonisation of guidance and procedures, training events and the (re) assessment of inspectorates as topics of strategic importance. The IWG and PIC/s liaisons have participated attended each other's meetings and working groups.

10.2. International Conference on Harmonisation for Registration Of Pharmaceuticals For Human Use (ICH)

The GMP/GDP IWG continued to be consulted on a number of topics in connection with the revisions to specific chapters and annexes and developing specific training material for ICH guidelines including Q9 (Quality Risk Management), ICH Q12 (lifecycle management), ICH Q13 (Continuous Manufacturing), Q14 (Analytical Procedure Development).

10.3. International Conference on Harmonisation For Registration Of Veterinary Products (VICH)

The GMP/GDP IWG were consulted on the development of a GMP for veterinary active pharmaceutical ingredients.

10.4. Interested Parties

Formal interested parties meetings were suspended as part of the EMA BCP. Nevertheless information continued to be exchanged in 2021 through an informal meeting of the Chair and a number of IWG members and representatives from interested parties,

The following organisations participated in the informal meeting with Interested Parties in 2021: AESGP (Association of the European Self-Medication Industry), APIC (Active Pharmaceutical Ingredients Committee), EFPIA (European Federation of Pharmaceutical Industries and Associations), Medicines for Europe, EIPG (European Industrial Pharmacists Group), EQPA (European QP Association), Animal Health Europe (formerly IFAH-Europe), ISPE (International Society for Pharmaceutical Engineering), PDA (Parenteral Drug Association), GIRP (European Healthcare Distribution Association, EAEPC (European Association of Euro-Pharmaceutical Companies representing Europe's licensed parallel distribution industry) and EBE (European Trade Association representing biopharmaceutical companies). GIRP, EAEPC and EBE attended the Interested Parties meeting for the first time.

10.5. Quality Working Party

In addition to the annual joint meeting held in September 2021 and regular exchanges on matters of joint interest and formed a joint IWG-QWP subgroup on how best to make adaptations for co-processed excipients.

The work of the Process Analytical Technology (PAT) Team was suspended in 2021 due to the BCP.

10.6. Innovation Task Force (ITF)

The GMDP IWG agreed to take part in relevant ITF meetings in order to provide a platform for early interactions with companies in relation to new technologies and they reviewed a small number of case studies on innovative manufacturing technologies during 2021.