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Annual report of the Good Manufacturing and Distribution Practice Inspectors Working Group 2017

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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 2017. This group was established at EMA in 1996.

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. 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 2017 work plan.

2. Meetings

The plenary GMP/GDP IWG meetings took place on:

- 14-16 February 2017;
- 30 May–1 June 2017;
- 25-27 September 2017 (Joint with QWP on 27 September);
- 5-7 December 2017 (meeting with Interested Parties 6 December);

In addition, 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 2017 in the margins of the above mentioned plenary meetings.

A new chairman, Brendan Cuddy, was appointed by EMA as of the May 2017 meeting.

3. GMP and GDP inspections in 2017

The number of sites inspected for GMP in 2017 by EEA authorities was 2493. Out of these, 2476 sites received GMP certificates whereas 17 sites received GMP non-compliance statements.

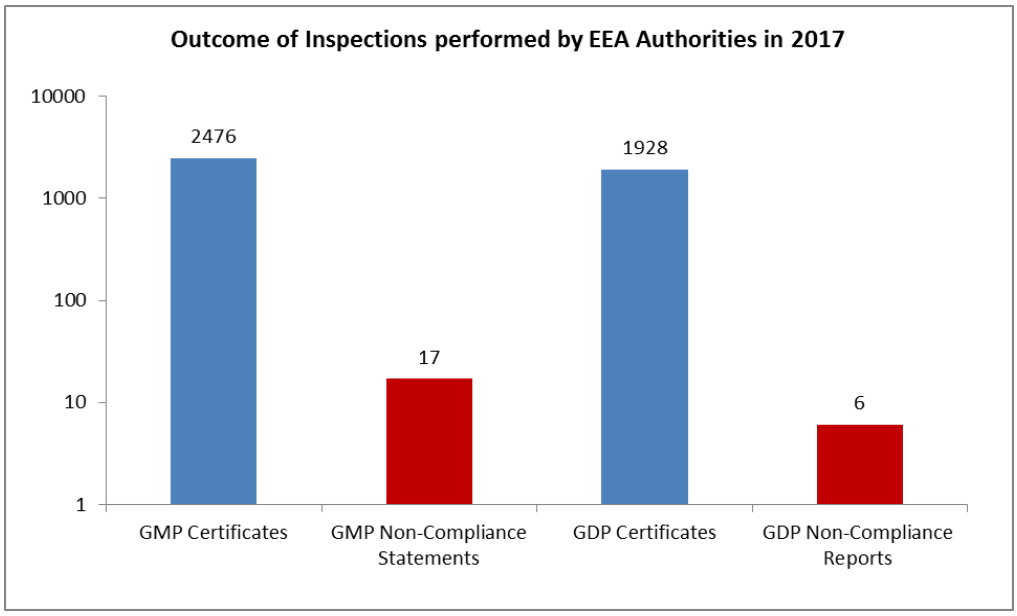
In addition, EEA authorities issued 1928 GDP certificates and 6 GDP non-compliance reports concerning GDP inspections conducted in 2017.

Figure 1: Inspection outcomes following EEA inspections performed in 2017 (tabular format)

Inspection outcomes 2017	
GMP Certificates Issued	2476
GMP Non-Compliance Statements Issued	17
GDP Certificates Issued	1928
GDP Non-Compliance Reports Issued	6

Note: The data presented above was extracted from EudraGMDP on 9th January 2018.

Figure 2: Inspection outcomes following EEA inspections performed in 2017 (graphical format)



A breakdown of the figures corresponding only to third countries where EEA authorities conducted the highest number of GMP inspections in 2017 is given below. They have been split according to their outcome (i.e. GMP certificates vs. GMP non-compliance statements).

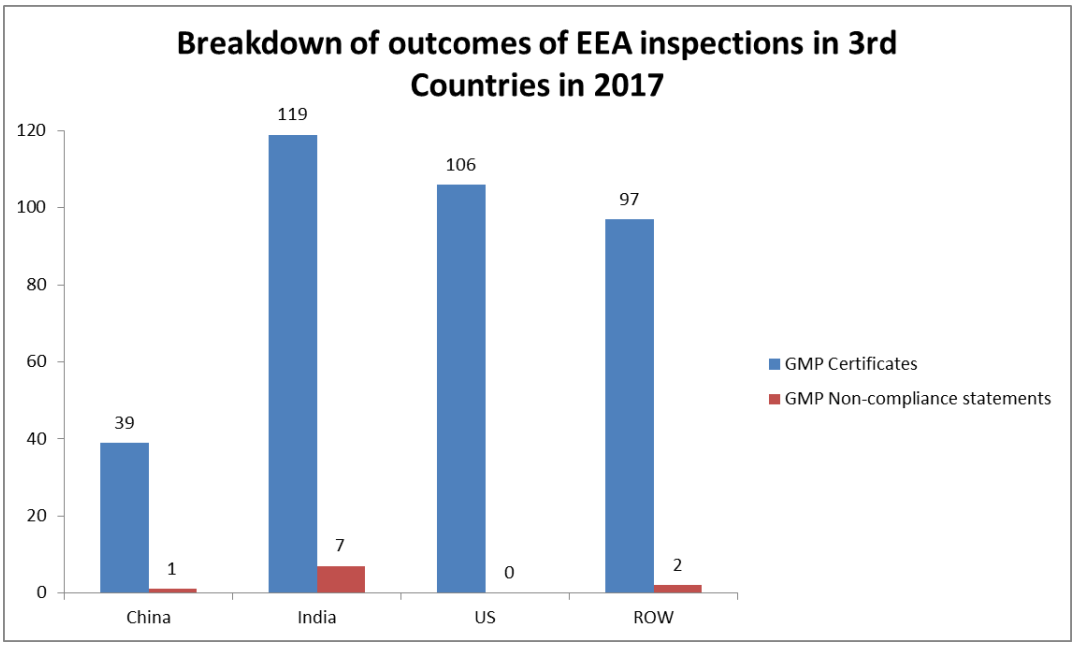
Figure 3: Inspection outcomes following EEA inspections performed in third countries in 2017 (tabular format)

Country	GMP Certificates	GMP Non-compliance Statements
China	39	1
India	119	7
United States	106	0
ROW*	97	2

Note: The data presented above was extracted from EudraGMDP on 9th January 2018.

**ROW includes the following countries: Argentina, Bangladesh, Brazil, Canada, Chile, Egypt, Iran, Japan, Jordan, Republic of Korea, Lebanon, The former Yugoslav Republic of Macedonia, Malaysia, Mexico, Monaco, Montenegro, Morocco, Oman, Pakistan, Russia, San Marino, Serbia, Singapore, South Africa, Taiwan, Thailand, Turkey, Ukraine, United Arab Emirates, Vietnam.*

Figure 4: Inspection outcomes following EEA inspections performed in third countries in 2017 (graphical format)



The draft 2018 EMA re-inspection programme was discussed regularly with the GMP/GDP IWG throughout 2017 in view of the impact of the MRA between EU and USA. The final programme, still subject to change, was agreed at the December 2017 GMP/GDP IWG meeting.

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

4.1. MRA General

A joint MRA partners meeting took place in Taipei, Taiwan in September 2017 in the margins of the PIC/S Committee of Officials meeting.

4.2. MRA with US

Work continued to support the preparation for and the entry into force of the EU – US Mutual Recognition Agreement during 2017. The Agreement, signed on 1 March 2017, entered into force on 1 November 2017. Further details can be found in this press release and on the United States section of the Agency's MRA webpage.

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

The GMP/GDP IWG also supported the JAP audit programme by making the inspectorates available for the outstanding audits and providing auditors to complete the audit teams, ensuring that all JAP audits took place as scheduled and meeting the deadlines for the US capability assessments as set out in the MRA agreement. Please see further details under point 5.1.

A representative from US FDA attended the December 2017 GMP/GDP IWG meeting.

4.3. MRA with Japan

Work on the MRA expansion to cover active substances, sterile and biological products continued throughout 2017.

2 representatives from the Pharmaceuticals and Medical Devices Agency (PMDA) attended the February 2017 GMP/GDP IWG meeting.

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.

A representative from Health Canada attended the May 2017 GMP/GDP IWG meeting.

4.5. MRA with Switzerland

The MRA with Switzerland was amended to include recognition of inspections of third country manufacturers carried out by either party, recognition of control testing done in Switzerland if the product comes from a third country manufacturer inspected by Switzerland or EU authorities and the use of EudraGMDP.

Swiss observers attended all four GMP/GDP IWG meetings in 2017 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 2017.

A representative from the Therapeutic Goods Administration attended the September 2017 GMP/GDP IWG meeting.

4.7. MRA with New Zealand

There were no changes to the existing MRA with New Zealand throughout 2017.

4.8. ACAA with Israel

There were no changes to the existing ACAA co-operation with Israel in 2017.

A representative from the Institute for Standardization and Control of Pharmaceuticals attended the December 2017 GMP/GDP meeting.

4.9. The Instrument for Pre-accession Assistance

The Instrument for Pre-accession Assistance[1] allowed for the attendance of representatives from EU candidate countries and from potential candidate countries in the Western Balkans throughout 2017.

Representatives from the Agency for Medicinal Products and Medical Devices of Bosnia and Herzegovina, the Agency for Medicines and Medical Devices of Montenegro, the Ministry of Health of

[1] https://ec.europa.eu/neighbourhood-enlargement/instruments/overview_en

the Republic of Serbia, the Ministry of Health of the Republic of Macedonia, the Kosovo Medicines Agency and the Turkish Medicines and Medical Devices Agency attended GMP/GDP IWG meetings in 2017.

4.10. Other international collaborations on GMP

EDQM attended all four GMP/GDP IWG meetings in 2017 as an observer.

Work continued on developing a plan for the supervision of the heparin supply chain in collaboration with US-FDA and international partners. An inspection plan for crude heparin manufacturers was adopted by the GMP/GDP IWG as part of the EMA re-inspection programme for 2018/2019.

5. Harmonisation topics

5.1. Joint Audit Programme (JAP)

JAP audits of inspectorates in Belgium, Bulgaria-H, Cyprus-H, Denmark, Finland, Ireland, Latvia-H, Netherlands-H, Poland, Portugal-H, Slovakia-H and Slovenia took place in 2017. In addition, a JAP audit of the inspectorate in Norway took place in 2017.

In the EU-US MRA negotiations, the FDA established the observation of the audits organised in the framework of the JAP programme as one of the pillars of their capability assessment of each EU Member State inspectorate. Thus, the observation of audits has been a key element in the US FDA's capability assessment for mutual recognition of GMP inspectorates. US FDA observed the above audits of EU inspectorates in the context of the EU-US MRA.

The Compliance Group monitored the planning of JAP audits, reviewed and adopted JAP audit reports and followed up on outstanding corrective and preventive actions stemming from the audits and updated the GMP/GDP IWG on progress.

The rolling plan to complete the JAP audits of all EU inspectorates for human or human and veterinary medicines in 2018 and to include JAP of EU inspectorates for veterinary medicines in 2018 and 2019 to support the EU-US MRA and its possible extension of the scope to veterinary medicinal products was prepared and finalised in 2017.

The JAP audit schedule 2016-2021 was adopted at the December 2017 GMP/GDP IWG meeting.

The mandate of the Compliance Group was revised in December 2017 and the composition of the Compliance Group was confirmed at the December 2017 GMP/GDP IWG meeting.

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

A 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 was finalised and provided to the European Commission for adoption in 2017.

Discussions around a common interpretation of the "validity period" of GMP certificates led to the agreement of changes to: "The outline of a procedure for co-ordinating the verification of the GMP status of manufacturers in third countries", "The issue and update of GMP certificates", "A model for risk-based planning for inspections of pharmaceutical manufacturers" and the "Union format for a GMP certificate" in 2017.

Work for managing the update of GMP certificates that list active substances continued in 2017.

Guidance notes on how to complete the GMP non-compliance statement and supervisory risk assessment templates were agreed.

Work to improve the overall process that leads to the continued supply of "critical" medicines where a site in the manufacturing chain is subject to a statement of non-compliance continued in 2017. In this context, a proposal for a revised GMP non-compliance statement template was agreed for public consultation.

Work on the procedure for handling GDP non-compliance continued to be on hold pending the outcome of discussions on the analogous procedure for GMP non-compliance.

Work on the revision of the procedure for dealing with serious GMP non-compliance information originating from third country authorities or international organisations started in 2017.

Work on the interpretation of the Union format for a wholesale distribution authorisation was resumed in 2017.

Clarifications around the classification of QC testing, to be incorporated in the interpretation of the Union formats for manufacturing authorisations and GMP certificates were agreed.

Work on the revision of the procedures for handling reports of suspected quality defects and rapid alerts continued in 2017.

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. Detailed guidelines on GMP for Investigational Medicinal Products (IMPs)

The guidelines, which will replace Annex 13 as from the date of entry into application of Regulation (EU) No 536/2014 on Clinical Trials, were finalised and published in December 2017.

In addition, a draft guideline on sponsor-manufacturer responsibilities was agreed for public consultation.

6.2. Detailed Guidelines on GMP for Advanced Therapy Medicinal Products (ATMPs)

This stand-alone guidance, developed by the European Commission in collaboration with the GMP/GDP IWG and the Committee for Advanced Therapies (CAT), was finalised and published in November 2017.

6.3. GMP Guide: Chapter 3 (Premises and Equipment) and Chapter 5 (Production)

A draft Questions and Answers document, developed by a multi-disciplinary team established to oversee the implementation of the updated GMP guidance on shared manufacturing facilities, was released for public consultation between January and April 2017.

In addition, a workshop to develop understanding of the use and application of health-based exposure limits (HBEL) in the context of the quality risk management of cross contamination during the manufacture of different products in the same manufacturing facilities was held in June 2017.

As a result of the workshop, work continued on finalising the questions and answers during 2017.

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

A revised draft Annex 1 was finalised and released for public consultation in December 2017.

In addition, the final version of a Questions and Answers (Q&As) document addressing the use of non-distillation methods for the production of water for injections (WFI) was published in August 2017. The aim of these Q&As is to provide preliminary guidance in light of the changes to the relevant monograph of the European Pharmacopoeia until such time the ongoing revision of Annex 1 is complete.

6.5. GMP Guide: Annex 2 (Manufacture of Biological substances and Medicinal Products for Human Use)

Work continued on adapting this annex following the development of stand-alone guidance for ATMPs (see item 6.2).

6.6. GMP Guide: Annex 17 (Real Time Release Testing)

Annex 17 was finalised and provided to the European Commission for publication in 2017.

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

Work continued on drafting this new Annex.

6.8. GMP and Marketing Authorisation Holders (MAHs)

Work continued on drafting the reflection paper on Good Manufacturing Practice and Marketing Authorisation Holders.

6.9. EudraGMDP database

A change request was implemented to change the access rights of US FDA to MRA partner authority.

Work to improve the data quality of the entries in the database continued in 2017.

Training on the use of EudraGMDP, including how to upload information into the planning module, was provided to Health Canada in January 2017.

6.10. 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. In addition to the Q&As already referred to in connection with the implementation of the updated guidance on shared manufacturing facilities and the use of non-distillation methods for the production of water for injections (WFI), the following were also published on the Agency's website in 2017:

- Q&A on formulated active substances;
- Q&A on the validity of manufacturing authorisations and GMP certificates in EudraGMDP;
- Q&A on how a GMP non-compliance statement can be lifted.

7. 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 clinical trials, advanced therapy medicinal products and veterinary medicinal products.

8. 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.

8.1. International Conference on Harmonisation (ICH)

The GMP/GDP IWG continued to be consulted on a number of topics in connection with the development of ICH Q12 (lifecycle management).

8.2. Interested Parties

A working group consisting of representatives from the GMP/GDP IWG and its interested parties continued their dialogue with a view to finding ways to add mutual value to the annual interested parties meetings.

The following organisations participated in the meeting with Interested Parties in 2017: 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.

8.3. Quality Working Party

In addition to the annual joint meeting held in September 2017 and regular exchanges on matters of joint interest, a joint IWG-QWP subgroup continued to look at ways of increasing regulators' confidence in the "QP declarations" submitted with marketing authorisation applications and some variations to confirm the GMP status of active substance manufacturers associated with the relevant submission. In 2017, the joint subgroup focused on consulting stakeholders and initiated three surveys in order to gather information and identify areas for improvement in the current process. A questionnaire was sent to selected marketing authorisation holders and in parallel, a targeted questionnaire was sent to interested parties. In addition, a survey of national inspectorates carrying inspections focused on supplier qualification was undertaken.

The GMP/GDP IWG continued supporting the Process Analytical Technology (PAT) Team through their membership.