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Committees and Inspections

Annual report of the Good Manufacturing and Distribution Practice Inspectors Working Group 2016

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1. Introduction

This document is the annual report of the GMP/GDP Inspectors Working Group (GMDP IWG) for the year 2016. This group was established at EMA in 1996.

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

The GMDP 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 2016 work plan.

2. Meetings

The plenary GMP/GDP IWG meetings took place on:

- 2-4 February 2016
- 11-13 May 2016
- 21-23 September 2016 (Joint with QWP on 21 September)
- 22-24 November 2016 (meeting with interested parties 23 November)

In addition, drafting group meetings have been 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 2016 in the margins of the above mentioned plenary meetings.

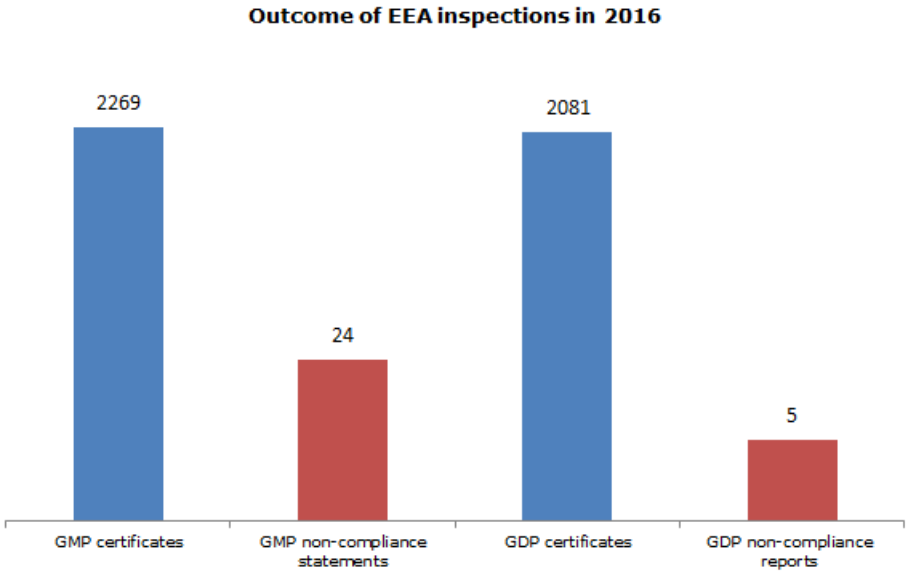
The Agency's Meeting Management Documents System (MMD) was introduced for GMP/GDP IWG meetings in 2016.

3. GMP and GDP inspections in 2016

The number of sites inspected for GMP in 2016 by EEA authorities was 2293. Out of these, 2269 sites received GMP certificates whereas 24 sites received non-compliance statements.

In addition, EEA authorities issued 2081 GDP certificates and 5 GDP non-compliance reports concerning GDP inspections conducted in 2016.

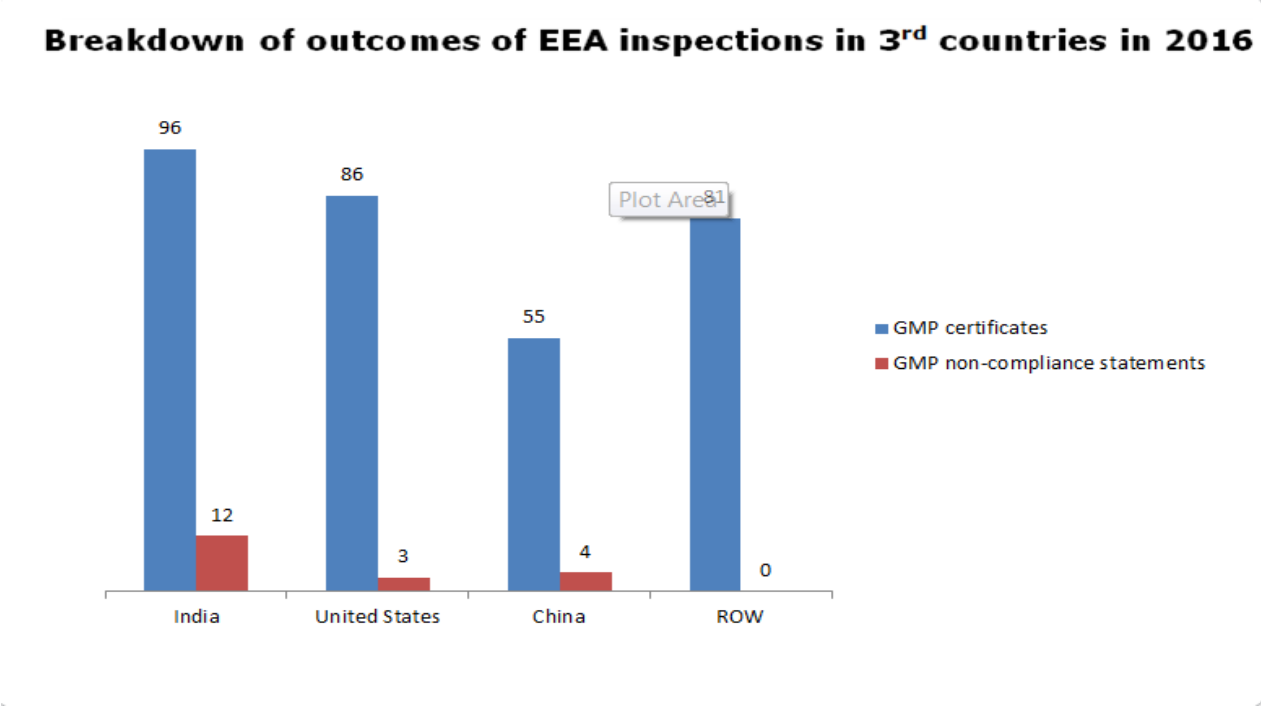
Inspection outcomes 2016	
GMP certificates	2269
GMP non-compliance statements	24
GDP certificates	2081
GDP non-compliance reports	5



A breakdown of the figures corresponding only to third countries where EEA authorities conducted the highest number of GMP inspections in 2016 is given below. They have been split according to their outcome (i.e. GMP certificates vs. non-compliance statements).

Country	GMP certificates	GMP non-compliance statements
China	55	4
India	96	12
United States	86	3
ROW*	81	0

**ROW includes the following countries: Argentina, Bangladesh, Bosnia and Herzegovina, Brazil, Canada, Ecuador, Indonesia, Israel, Jordan, Republic of Korea, Mexico, Monaco, Montenegro, Morocco, Occupied Palestinian Territory, Philippines, Russian Federation, Serbia, Singapore, South Africa, Taiwan, Thailand, Turkey, Ukraine, Uruguay and Vietnam.*



Note: The data presented above was extracted from EudraGMDP on 13th January 2017.

The Agency's draft re-inspection programme 2017 was discussed regularly with GMP/GDP IWG throughout 2016 in view of the anticipated MRA between EU and USA which has a significant impact on the plan. The final programme, still subject to change, was agreed at the November 2016 meeting of the GMP/GDP IWG.

The GMP/GDP Inspectors' Working Group was briefed on the various initiatives underway designed to achieve earlier access to medicines. The IWG pointed out the importance of applicants and/or manufacturers establishing an early dialogue with supervisory authorities and EMA in order to avoid later problems connected with possible pre-authorisation GMP inspections.

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

4.1. MRA general

A joint MRA partners meeting took place in Manchester in July 2016 in the margins of the PIC/S Committee of Officials meeting.

4.2. MRA with United States

Over 2016 a lot of work in the context of the EU–US mutual recognition agreement was done to support the finalisation of the negotiations allowing the final agreement to be signed in 2017.

In this framework, the GMDP IWG provided the forum to discuss and clarify the practical aspects for the implementation of the MRA when questions arose during the negotiation.

The IWG also supported the JAP audit programme providing resources to both, making the inspectorates available for the outstanding audits and providing auditors to complete the audit teams, allowing that all JAP audits took place as planned meeting the deadlines for the US capability assessment. Please see further details under point 5.1.

4.3. MRA with Japan

3 Japanese observers attended the February 2016 GMP/GDP IWG meeting.

Work on the MRA extension to all Member States, active substances, sterile and biological products continued throughout 2016 with significant progress.

4.4. MRA with Canada

A representative from Health Canada attended the May 2016 GMP/GDP IWG meeting.

Work on the MRA extension to include new Member States continued in 2016.

Technical input to the Comprehensive Economic Trade Agreement (CETA) was finalised in 2016.

4.5. MRA with Switzerland

Swiss observers attended all four GMP/GDP IWG meetings in 2016 and proactively shared the minutes of the Swiss Inspectorates Coordinating Committee (ICC).

4.6. MRA with Australia

A representative from the Therapeutic Goods Administration attended the GMP/GDP IWG meeting in September 2016. There were no changes to the existing MRA co-operation with Australia throughout 2016.

4.7. MRA with New Zealand

A representative from the Ministry for Primary Industries attended the GMP/GDP IWG meeting in May 2016. There were no changes to the existing MRA co-operation with New Zealand throughout 2016.

4.8. ACAA with Israel

There were no changes to the existing ACAA co-operation with Israel in 2016.

4.9. Other international collaborations on GMP

EDQM attended all four GMDP IWG meetings in 2016 as an observer.

UNICEF participated in the GMP/GDP IWG meeting in November 2016 in order to explore ways of sharing information on quality defects and GMP non-compliance since these may impact UNICEF programmes.

Two representatives from WHO participated in the GMP/GDP IWG meeting in May 2016 in order to explore closer working between GMP/GDP IWG and WHO on GMP guidance development and harmonisation.

In 2016, Japan became party to the international collaboration project on inspections of manufacturers of active substances.

Work was re-initiated on the development of a plan for the supervision of the heparin supply chain in collaboration with US-FDA. The working group has been elaborating criteria for risk ranking of manufacturers involved in the supply chain of heparin active substance. Additionally, with support from the CMDh, the group is working on building a list of crude heparin manufacturers for heparin

containing products or derivatives registered in the EU, which could be used to identify manufacturing sites for the purpose of inspection.

5. Harmonisation topics

5.1. Joint Audit Programme (JAP)

JAP audits of inspectorates in Austria, Czech Republic V, Estonia, Iceland, Lithuania H, Malta H, Romania and Spain, took place in 2016. With the exception of the audits of the Icelandic and Czech veterinary inspectorate, US FDA observed these audits in the context of the EU-US MRA.

The rolling plan to complete the JAP audits of all EU inspectorates for human or human and veterinary medicines in 2017 to support the EU-US MRA was prepared and finalised in 2016.

In the EU-US MRA negotiations over 2016, the FDA established the observation of the audits organized in the framework of the JAP programme as one of the pillars of their capability assessment of each EU MSs inspectorate. Thus, the observation of audits has been a key element in the US FDA's capability assessment for mutual recognition of GMP inspectorates and has allowed the signature of the current MRA between EU and US in 2017.

Both the JAP audit conducted in Lithuania H and Romania were a joint JAP and MRA audit in order to support the MRA extension with Canada.

The JAP audit schedule 2017-2021 was adopted in November 2016 by GMP/GDP IWG.

5.2. Compilation of Union procedures on inspections and exchange of information

Although the new Union procedure for handling GDP non-compliance was finalised in 2016 submission to the European Commission for adoption was put on hold depending on the outcome of discussions on improving the analogous procedure for GMP non-compliance.

- A modification was agreed to the aforementioned GMP procedure to address the situation where a non-compliance statement could appear indefinitely in the EudraGMDP database for a third country manufacturer no longer linked to a valid EU marketing authorisation.
- Proposals 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 remain under discussion.

GMP/GDP IWG agreed that there was no need for a specific procedure on dealing with non-compliance in the context of inspections connected with excipients manufacture. Cases can be managed on their own merits based on the general procedure adapted as necessary to fit the specific circumstances.

Work was very close to completion at the end of 2016 on a procedure for compliance management. The aim of this procedure is to identify and manage manufacturers at risk of becoming subject to a statement of non-compliance with a view to avoiding such an outcome. The document aims also to establish harmonised principles for the issuance of warning letters.

A way forward for managing the update of GMP certificates that list active substances was identified and will be progressed through an update of the procedure for the issue and update of GMP Certificates in the compilation of Union procedures.

Extensive discussion took place on a common interpretation of the “validity period” of GMP certificates paving the way for a further update of the procedure for the issue and update of GMP Certificates in the compilation of Union procedures.

A procedure outlining an EU/EEA programme for maintenance of equivalence in supervision of the pharmaceutical industry was agreed and adopted and will be included in the compilation.

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)

In light of the upcoming EU Clinical Trial Regulation (EU) No 536/2014, guidelines on GMP for IMPs will be separated from the basic requirements for GMP and the supplementary annexes (including Annex 13). The new guideline will however cross-refer to the basic requirements.

The European Commission has coordinated the drafting of the new guidance with input from GMP/GDP IWG and GCP IWG and sought input while developing the delegated regulation laying down the principles and guidelines on GMP for IMPs.

The Commission has also advised that references to the responsibilities of sponsors in the context of GMP are not appropriate for the GMP guideline as it is addressed solely at manufacturers and it has suggested that a reflection paper be developed on this topic.

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

The European Commission has coordinated the development of stand-alone guidance seeking input from GMP/GDP IWG and the Committee for Advanced Therapies (CAT). See also item 6.6.

6.3. GMP Guide: Chapter 1 (pharmaceutical quality system)

Minor additions related to shortage mitigations were agreed for public consultation but are currently on hold.

6.4. GMP Guide: Chapter 3 (premises and equipment) and Chapter 5 (production)

A multi-disciplinary team was established with input from Safety Working Party and Veterinary Safety Working Party in order to support a harmonised approach to the implementation of updated GMP guidance and complementary toxicological guidance on the manufacture of different products in shared manufacturing facilities. Questions and answers were agreed to be published for public consultation.

6.5. GMP Guide: Annex 1 (manufacture of sterile medicinal products)

Work began on drafting a revision of Annex 1. To align with changes to the relevant monograph of the European Pharmacopoeia, the new annex will also address the use of non-distillation methods for the

production of water for injections (WFI). Advance questions and answers were published on this topic for public consultation which ended in November 2016.

In addition, questions and answers on the impact of the updated ISO 14644 on Annex 1 were published.

6.6. GMP Guide: Annex 2 (manufacture of biological substances and medicinal products for human use)

The European Commission has proposed some deletions to the annex consequential to the development of stand-alone guidance for ATMPs (see item 6.2).

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

Work continued on drafting the updated annex in response to comments received during the public consultation in 2015.

6.8. GMP for importers of medicinal products (Annex 21)

Work commenced on drafting this new annex.

6.9. GMP and marketing authorisation holders (MAHs)

A concept paper was published in view of a perceived need to develop guidance, most likely in the form of a reflection paper, on the role of the MAH in GMP compliance.

6.10. EudraGMDP database

A change was implemented to allow for information of third country manufacturers to be made confidential in the API registration module.

Work to improve the data quality of the entries in the database continued in 2016.

Training on the use of EudraGMDP, including how to upload information into the planning module, was provided to US FDA in October 2016.

6.11. Questions & Answers (Q&A)

Work was carried out on a number of Q&A with a view to harmonising interpretation and expectations on a number of GMP topics. In addition to the Q&A already referred to in connection with the implementation of updated guidance on shared manufacturing facilities, the use of non-distillation methods for the production of water for injections (WFI) and the impact of the updated ISO 14644 on Annex 1, the following were also published on the EMA website in 2016:

- Q&A on reporting of quality defects and definition of “placed on the market” in this context.
- Q&A on data integrity.

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.

In view of the need, as a consequence of the Clinical Trial Regulation, to develop a new delegated regulation laying down the principles and guidelines of GMP to replace Directive 2003/94/EC, the GMP/GDP IWG has proposed that this opportunity is taken to update the principles in line with today's manufacturing environment.

8. Liaison with other groups

The GMDP 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 was consulted on a number of topics in connection with the development of ICH Q12 (lifecycle management).

8.2. Interested parties

The GMP/GDP IWG has established a joint working group with representatives of the existing associations comprising its interested parties 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 2016: AESGP (Association of the European Self-Medication Industry), APIC (Active Pharmaceutical Ingredients Committee), EFPIA (European Federation of Pharmaceutical Industries and Associations), Medicines for Europe (formerly EGA: European Generic and Biosimilar medicines Association), EIPG (European Industrial Pharmacists Group), EQPA (European QP Association), IFAH-Europe (International Federation for Animal Health Europe), ISPE (International Society for Pharmaceutical Engineering) and PDA (Parenteral Drug Association).

8.3. Quality Working Party

In addition to the annual joint meeting and regular exchanges on matters of joint interest, a joint subgroup was established 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. The subgroup will also respond to questions from CMDh on conflicts of interest in connection with the audits behind these declarations.

The GMP/GDP Inspectors Working Group continued supporting the Process Analytical Technology (PAT) team through their membership.