



GMP/GDP Consultative Committee Note of Meeting

31st March 2017, Room G-1, 151 Buckingham Palace Road, London.

Representatives from the following organisations were present at the GMP-GDP Consultative Committee meeting held at BPR on the 31st March 2017:

MHRA (Inspection, Enforcement & Standards Division)
British Generic Manufacturer's Association (BGMA)
Joint Professional Bodies QP Assessor Panel (JPB-QP)
Pharmaceutical Quality Group (PQG)
Association of the British Pharmaceutical Industry (ABPI)
Research Quality Association (RQA)
Veterinary Medicines Directorate (VMD)
NHS Pharmaceutical QA Committee
Healthcare Distribution Association (HDA)
Joint Pharmaceutical Analysis Group (JPAG)
The Cogent Group
BioIndustry Association (BIA)

1. Introduction

MHRA welcomed current and new representatives to the meeting.

2. Minutes of the last meeting and Matters Arising.

2.1 The minutes of the last meeting held on 7th October were agreed.

3. Brexit

3.1 Agency update

MHRA updated members on the Agency's position following the triggering of Article 50 earlier in the week.

As set out in the PM's letter, the government hopes to negotiate a 'deep and special partnership' with the EU. The Agency had been working on a range of potential scenarios, some of which included ongoing cooperation with EU regulatory procedures, others did not.

Members expressed their concern about the planning needed by industry to be able to operate on Day 1. MHRA stated that it appreciated that there are a number of areas

which are unknowns including QPs, import testing and movement of goods etc. However, the Agency is hopeful that it will receive an early indication if the option of ongoing cooperation is a possibility and this should help from a planning perspective for both industry and regulators.

The implementation of changes to EU GMP should not be affected as UK is a PIC/S member and PIC/S GMP is aligned with EU GMP.

The Agency is currently proceeding with the implementation of the Clinical Trials Regulation and the Safety Features aspect of the Falsified Medicines Directive: both will depend on the outcome of negotiations.

4 Agency update

4.1 Changes within MHRA

MHRA reported on recent changes including:

- the Agency is preparing for relocation to a building in Canary Wharf in Q2 2018. The building will act as a hub for various government departments.
- the Agency recently signed a Memorandum of Understanding (MoU) with the Swiss competent authority (Swissmedic). This will facilitate easier exchange of information. <https://www.gov.uk/government/news/improving-international-collaboration-mhra-and-swissmedic-sign-mou>
- the Agency has initiated a 'fake meds' campaign which has mainly been targeted through social media. Other activities have been carried out to support the campaign including TV appearances. <https://fakemedics.campaign.gov.uk/>
- the Agency now reports to a new Minister. Lord James O'Shaughnessy has been appointed as Parliamentary Under Secretary of State at the Department of Health.

5. Inspectorate update

5.1 Operational

5.1.1 *Inspectorate staff changes & recruitment*

MHRA reported that following review, the structure of the division will be restructuring to have both GMP and GDP reporting into one Unit manager (Richard Andrews) and GLP, GCP and GPvP reporting into another Unit Manager (Andrew Gray). This will allow the Inspectorate to meet future challenges and ensure we maximise our delivery along with offering opportunities for growth. Operationally, the changes will have no impact on inspections.

Members enquired if the Inspectorate organogram is available on the MHRA website. MHRA explained that since the move to GOV.UK, the organogram has not been

available. MHRA agreed to check the policy regarding organograms internally with the Comms division and publish a blog or circulate the organogram if possible.

ACTION: MHRA

MHRA went onto report with regards to staff changes and recruitment within the GMP team:

- Des Makohon retired after 18 years' service with the Agency.
- The advert for GMDP inspectors launched in December received a good response with 46 applicants.

5.2 Providing Authoritative Information

5.2.1 **Agency Symposia**

MHRA reported on the GMP and GDP symposia.

Both the GMP and GDP symposia in 2016 were very well supported with all the London events sold out.

As usual, MHRA requested feedback from delegates to inform and improve future events. Key messages from the 2016 events were; the new technology trialled last year which replaced iPads on tables with individual access from smart phones was well received - particularly in relation to accessibility, being able to contact other delegates easily, being able to provide individual responses and having the slide decks available to scroll through. Good feedback was received both on the content and style of presentations across all events.

There were a number of suggestions for this year's events including sessions on FMD, Brexit, best practice, more interactive sessions (although a minority wanted less), what's good and bad on inspection and a view from industry in relation to what it's like to be inspected.

The dates for this year's events will be w/c 20th November in London (probably at the same venue at the Hammersmith Novotel) for both GMP and GDP symposia with two days each spread throughout the week and a GDP-only symposia in Glasgow (also at the same venue of the Glasgow Hilton) straight after during w/c 27th November.

MHRA encouraged members to feedback any thoughts or ideas for the next symposia as the themes and outline structures will be developed for this years' events in the coming months.

5.2.2 **Publications**

The Orange Guide

MHRA reported following publication of the 2017 editions of both the Orange Guide and Green Guide in January.

The Orange Guide has been updated with revised sections on:

- qualification of suppliers and customers;
- parallel importation and parallel distribution;
- temperature control and monitoring;
- UK legislation; and
- matters relating to unlicensed medicines.

There are also new MHRA sections on:

- GMP for Excipients;
- Guidance on revised Annex 16 of GMP; and
- MHRA Data Integrity definitions and guidance for Industry.

Revised Annex 15 and 16 are included.

Also included is new Commission guidance on;

- principles and guidelines of Good Manufacturing Practice for active substances;
- principles of Good Distribution Practice of active substances;
- setting health based exposure limits; and
- formalised risk assessment for ascertaining the appropriate GMP for excipients.

The EU regulation on safety features for medicines is added together with two Commission Q&As on:

- importation of active substances; and
- safety features for medicinal products.

There is also a new appendix on sources of useful information.

The Green Guide

The Green Guide has revised sections on:

- qualification of suppliers and customers;
- controls on certain medicinal products;
- parallel importation and parallel distribution;
- the application and inspection process for new licences “what to expect”;
- updated UK legislation; and
- temperature control and monitoring.

There are also new sections on:

- the guidelines on principles of Good Distribution Practice of active substances for medicinal products for human use (2015/C 95/01);
- matters relating to unlicensed medicines;
- sourcing and exporting medicinal products – non-EEA countries;
- data integrity; and
- the EU regulation on safety features for medicines.

Two Commission Q&As have been added:

- importation of active substances; and
- safety features for medicinal products.

There are also two new appendices on:

- sources of useful information; and
- licensing requirements for import into the UK and export from the UK including introduced medicine – wholesale supply only.

Moving forward, MHRA will review the content to make sure it is still appropriate after Brexit. In the meantime, the electronic versions of the guides will be updated regularly to include any new and updated content.

5.2.3 **Data Integrity Guidance**

MHRA reported on the work being done in relation to publication of data integrity guidance.

At the time of the last meeting MHRA had published a GXP-focused data integrity guidance document for public consultation. Comments have since been received and are currently being reviewed. Due to the high volume of comments received (over 1500 lines) it is taking a considerable amount of time to carry out the review. The Inspectorate expect to complete the review by August.

The publication will be supported by a series of blogs for each GXP group.

5.2.4 **Inspectorate Blog**

MHRA provided an update concerning the Inspectorate blog (<https://mhrainspectorate.blog.gov.uk/>).

The team are obliged to produce 26 blog posts a year and are currently well ahead of this target. There has been a 50% increase in subscribers to the blog in the last year.

MHRA welcomed feedback and ideas for future blog items including items on any joint MHRA-industry work.

The agency has also launched another blog (MedRegs) which covers other regulatory matters from other parts of the Agency: <https://medregs.blog.gov.uk/>

Members of the committee were encouraged to help promote the Inspectorate blog widely within their networks so as to support the Inspectorates programme of compliance management and education.

5.2.5 **Behavioural Insight**

MHRA provided an update on the Agency's Behavioural Insight project – a project exploring the factors that affect wholesalers' levels of compliance with UK regulations.

A literature review has been completed and this will be shared internally with MHRA colleagues at the end of May when the MHRA expert interviews are completed.

The interviewees consist of GDP inspectors and others around the Agency who are not GDP inspectors but have relevant expertise, such as unit managers.

Each interview will consist of questions regarding the interviewee's thoughts on what drives decisions on whether to comply or not and how that might differ across different groups of wholesalers.

Following analysis of the literature review and expert interviews, the external interviews will be designed and arranged with wholesalers across the UK to better understand the decision that drives compliance and non-compliance. The agency's understanding of the decision making process of wholesalers can then be used to identify methods of driving up compliance levels.

5.2.6 ***Proposal for industry-MHRA collaboration to refine and evolve compliance guidance***

JPAG presented slides on a proposal for industry and MHRA to collaborate to refine and evolve existing compliance guidance or identify areas where guidance is required and can be developed. See Annex 1.

Members of the MHRA Inspectorate and industry members provided support for the proposal and it was agreed that MHRA would set up a meeting in around 3 months' time to discuss the matter in more detail. JPAG suggested they would try and engage with other industry members of the committee prior to such a meeting.

ACTION: MHRA/JPAG

6. **British Pharmacopoeia Update**

MHRA provided an update on activities in the BP:

The past few years has seen the BP deliver improvements including:

- a new website – www.pharmacopoeia.com which brought the online BP and the reference standards sales point on to one site, with added functionality benefits such as email alert subscription and, in direct response to stakeholder feedback, more visible posting of draft monographs for comment with regular, longer consultation periods
- new supplementary chapters on the Aseptic Preparation of Unlicensed Medicines and DNA Barcoding as a tool for Botanical Identification of Herbal Drugs
- 8 informally harmonized monographs between the BP and USP

Current activities:

- planned release date of BP 2018 a month earlier than normal (early Aug 2017), giving users an extra month to prepare ahead of legally effective date
- continuing support of the MHRA project investigating the concepts of Analytical Quality by Design
- outcomes of recent work around Inhaled Product monographs will begin to be introduced from BP 2018

Stakeholder engagement activities:

- BP heavily involved in the Agency public consultation on the strategy for pharmacopoeial public quality standards for biological medicines (deadline 10 April 2017)
<https://www.gov.uk/government/consultations/strategy-for-pharmacopoeial-public-quality-standards-for-biological-medicines>
- BP specific public consultation on how dissolution testing in BP finished product monographs for solid oral dosage forms could be improved (deadline 21 April 2017)
<https://www.pharmacopoeia.com/news/228>

Stakeholder engagement activities – upcoming:

- a follow-up to a customer insight research piece around the BP, carried out for the website redevelopment will be out soon
- there will be follow up with previous responders but new participants are sought too as well.

The BP would appreciate the survey being circulated around committee members networks so that a full range of responses from stakeholders with different relationships to the BP can be obtained.

7. Support for Innovation

7.1 MHRA firstly clarified that innovation doesn't just concern new products - it can also be for existing products made in different ways or in different locations.

MHRA went on to report on activities carried out by the agency in support of innovation. MHRA are involved in various areas including:

- Accelerated Access Review:
 - final report published on 24 October
 - MHRA implementing recommendations raised in the final report.
- Innovation Office:
 - applies to all 3 areas of MHRA,
 - working very successfully
 - now received approximately 422 enquiries (approx. 60% relating to medicines, 40% devices), a high proportion of those enquiries are GMP related.
- One Stop Shop:
 - effectively a mini Innovation Office for Advanced Therapies.
 - now received 40 enquiries.

- involves all UK regulators relevant to Advanced Therapies.
- Supporting the ATMP taskforce:
 - the taskforce published its Advanced Therapies Manufacturing Action Plan which has led to the BP consultation on the strategy for pharmacopoeial public quality standards for biological medicines.
 - knowledge sharing internally and also externally with FDA to understand issues they face regarding ATMPs.
 - ongoing support of other recommendations the taskforce has made.
- Providing input into the House of Commons inquiries on regenerative medicines, and on genomics/genome-editing.
- GMP for ATMPs
 - the Commission's consultation is now closed. MHRA has provided its comments back to the Commission and the process is still ongoing.

8. Diversion of Controlled Drugs

8.1 MHRA GDP Inspectorate provided an update regarding the diversion of controlled drugs from the supply chain.

As reported at the last meeting, a significant leakage of mainly class 4 controlled products in tablet form (specifically Diazepam, Nitrazepam, Zolpidem and Zopiclone) from the legitimate to the illegitimate supply chain has been identified.

The GDP team have been heavily involved in two aspects of the Agency's response to this situation. Firstly working in support of Enforcement colleagues inspecting a number of retail pharmacies which also hold WDAs and small wholesalers suspected of supplying products out of the legal supply chain. This work is still ongoing and may lead to a number of criminal prosecutions.

The other area where the team have undertaken a significant number of targeted inspections in collaboration with the Home Office involves larger wholesalers further back up the supply chain who have supplied very large quantities of controlled products to customers, who in turn are suspected of facilitating the supply into the illegal supply chain.

The circumstances which have allowed these very large supplies to have taken place are varied but include poor due diligence and oversight checks - particularly when supplying supposedly export customers, unlimited supply permitted through auto ordering systems, cultures which are predominantly focussed and incentivised towards sales and the ex-works supply of products - a concept which is not recognised within GDP. In all these cases there has been a significant breach of the requirements for wholesalers to monitor the sales of controlled products and to identify unusual trading patterns.

As a consequence of these inspections, processes have been significantly strengthened, particularly with the introduction of realistic maximum ordering levels for these products on automated systems and within telesales environments and there is

evidence that these actions have now been largely effective in helping to prevent supply from these sources.

9. Feedback from the EMA

9.1 GMP/GDP Inspectors Working Group (IWG)

MHRA presented on the current work of the Inspectors Working Group:

Legislation – Ongoing

- GMP Implementing Regulation for IMPs and detailed GMP guide for IMPs
- GMP Directive for authorised products
 - Awaiting publication; implementation aligned with CT Portal (~ end 2018)
- Annex 13 not included in revised GMP documents (distribution, sponsor involvement etc) will now be separate guidance in Eudralex Volume 10.

GMP Guide revisions – Ongoing

Stand-alone documents:

- GMP for IMPs
- GMP for AT(I)MPs

Volume 4 revisions:

- Annex 1 (Sterile products)
 - Aiming for public consultation June / July 2017
- Annex 17 (real time release testing) ongoing
- Annex 21 (importation) ongoing
 - Nearly ready for consultation although issues around fiscal importation need to be resolved before it can be finalised.

Q&As / guidance – Complete

- Data Integrity Q&A
- Considering GxP Q&A / guidance at EU level
- Chapter 8 Q&A
 - Includes the regulator's view of the meaning of 'placing on the market' and 'recall'
- Q&A on shared facilities; in conjunction with the Safety Working Party, and more to follow
- API registration information in EudraGMDP public view

Q&As / guidance – in progress

- Continuity of supply
 - GMP certificate validity – some member states currently interpret the certificate as expired if it has gone beyond its 3 year validity period.
 - Continuing supply of critical medicines following serious GMP non-compliance.

- IWG have issued some questions to be addressed by the European QP Association regarding certification of product where a statement of non-compliance is in place and they are requested to do so by the national competent authority. Similar questions will be sent to UK QP groups.
- Q&A on WFI by RO and biofilms
 - Due for publication shortly
- Audits and declarations in the active substance supply chain
 - Concern around perceived conflicts of interest difficulties and poor quality audits.
 - A questionnaire will be sent to MAHs and manufacturers on the matter.

Compilation of Union Procedures

- Compliance Management
 - Principles aligned with existing MHRA procedure
 - Developments at EU level, focusing on communication and ICH Q12 readiness
 - Likely implementation end 2017

IWG 2017 work plan

- GMP for MAHs
- Shortage mitigation through Chapter 1
- Chapter 4 and Annex 11 review (data integrity)
- Review of ICH Q12 practical application
- Continued support for MRA work
 - Joint Audit programme
 - 'GMP documents' for US-MRA.

10. Qualified Persons project

- 10.1 MHRA reported on the action taken since the last meeting around a possible shortage of QPs following the report published by Cogent in 2014.

At the last meeting MHRA presented data from which some preliminary conclusions were drawn. This was based on the data held within the MHRA's database which is limited to QPs named on licences. MHRA is now liaising with relevant stakeholders to utilise their networks to gain a better understanding of the picture across the whole QP/trainee QP population. The intention is to use surveys and questionnaires to capture information and data from which further conclusions may be drawn.

11. Falsified Medicines Directive (FMD)

MHRA reported on matters relating to the FMD:

- 11.1 Safety Features

- The Agency is continuing with the implementation of the safety features element of the FMD.
- Work is ongoing regarding the options on some of the flexibilities within the Regulation, including who will be decommissioning at the various points in the supply chain.
- The UK Medicines Verification Organisation, SecurMed, are close to reaching an agreement with a blueprint provider to build the UK repository.
- MHRA and DH are planning a consultation for release in May. This will address the flexibilities in the Delegated Act. *Post Meeting Note: The consultation will now not be published in May due to the General Election.*

12. International Interactions

MHRA reported on the Inspectorate's recent international activities:

12.1 EU-USA Mutual Recognition Agreement

The Mutual Recognition Agreement with the USA has now been signed and agreed. It will come into voluntary force in November. For the agreement to come into full effect, the US needs to have assessed each member state Inspectorate, in the main through observing the ongoing programme of Joint Audit Programme (JAP) audits by July 2019.

12.2 ICMRA

MHRA reported on the latest developments around the GMP project carried out within the International Coalition of Medicines Regulatory Agencies (ICMRA). The project aims to determine if it is feasible to take a risk-based approach to international inspections, placing reliance on data provided by the site and by their national regulator to carry out desktop assessments rather than inspecting the site. The work is currently in phase 2 implementation period. The proposal longer-term is for the operational phase to be transferred to PIC/S and work continues in this area.

12.3 PIC/S

MHRA continues to chair the PIC/S Committee and will do so for the rest of the year. The last meeting was held in February in Geneva. Further information can be found on the Inspectorate blog:

<https://mhrainspectorate.blog.gov.uk/2017/03/13/pics-meeting-february-2017/>

12.4 Benchmarking of European Medicines Agencies (BEMA)

MHRA reported following a successful BEMA assessment in October last year. The assessment was carried out by colleagues from other member states who assessed how the MHRA as a whole meets best practice standards regarding the systems and processes that the Agency uses. Further information can be found on the Inspectorate blog:

<https://mhrainspectorate.blog.gov.uk/2017/01/10/who-inspects-the-inspectors-part-ii/>

13. Any other business

13.1 Publication of Inspection Trend Data

MHRA reported that GMP inspection trend data is available on the blog:
<https://mhrainspectorate.blog.gov.uk/2017/01/12/2015-gmp-inspection-deficiency-data-trend/>

The 2016 data is due for publication shortly. This will include the raw data set so that companies can use the data to extract relevant data/trends relevant to their area of interest.

Post meeting note – this has now been published:
<https://mhrainspectorate.blog.gov.uk/2017/04/21/2016-gmp-inspection-deficiency-data-trend/>

14. Date of next meeting

October 2017