# GMP/GDP Consultative Committee
# Note of Meeting
## 17th October 2014, Room R-T-410, 151 Buckingham Palace Road, London.

Representatives from the following organisations were present at the GMP-GDP Consultative Committee meeting held at BPR on the 17th October 2014:

MHRA (Inspection, Enforcement & Standards Division)
Scottish Lifesciences Association (SLA)
Proprietary Association of Great Britain (PAGB)
Bio-Industry Association (BIA)
British Generic Manufacturer's Association (BGMA)
Association of Pharmaceutical Specials Manufacturers (APSM)
British Association of Pharmaceutical Wholesalers (BAPW)
Joint Professional Bodies QP Assessor Panel (JPB-QP)
Pharmaceutical Quality Group (PQG)
Association of the British Pharmaceutical Industry (ABPI)
Research Quality Association (RQA)
British Association of European Pharmaceutical Distributors (BAEPD)
Veterinary Medicines Directorate (VMD)
Ethical Medicines Industry Group (EMIG)
NHS Pharmaceutical QA Committee
The Cogent Group

**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 11th April were agreed.

*Matters Arising*

2.2 Publication of GDP deficiency data

BAPW reported that it had spoken to its members and had sent some ideas on how the data could be presented for the MHRA inspectorate to take forward.

**3. Agency update**

3.1 Changes within MHRA

MHRA reported as follows:

- There has been a change in the Minister that MHRA are responsible to. This has changed from Earl Howe, the Health Minister, to George Freeman, the Life Sciences Minister. This is a significant change as the ministerial post for life sciences is a new post, charged with making the UK the best place for industry in terms of science, design and adoption of 21st century medicines and healthcare innovations.

- The current chairman of the agency, Sir Gordon Duff, will be leaving the MHRA at the end of the year to take up a post as principal of St Hilda's College, Oxford University. A new chairman will be announced shortly.

- Dr Siu Ping Lam has been permanently appointed as Director of the MHRA Licensing Division.

- The MHRA office in Welwyn Garden City has been vacated and staff have been relocated to the MHRA (NIBSC) site in South Mimms.

3.2 Changes within I,E&S

MHRA explained that significant restructuring had taken place within the I,E&S division. The three major changes are as follows:

- The two inspectorate groups have been brought together as one with four different units within the group, two of which are Operations units. The remaining units are an Inspectorate Strategy and Innovation unit, and Inspectorate Risk, Control and Governance unit. There are also additional changes within these units. Changes have been made to ensure more consistent working across the group, driving forward innovation and risk-based methodologies, and providing a common strategy across the group.

- The creation of a third Enforcement Investigations unit following the incorporation of the Devices Division's enforcement team into the Enforcement group. This means the agency now has a consolidated Enforcement group looking across medicines and devices.

- The creation of a new Divisional Quality Standards Function in order to drive forward the quality standards within the division.

**4. Inspectorate update**

4.1 Operational

4.1.1 ***Inspectorate staff changes & recruitment***

MHRA reported that five additional inspectors have now joined the Inspectorate. MHRA are actively recruiting to fill the three remaining vacancies within the Inspectorate, to reach its full complement.

4.1.2 ***Compliance Management Project (EU)***

MHRA reported on the Compliance Management Project. MHRA launched a compliance management escalation process in 2013, to take proactive action in response to poor compliance which is yet to reach a level where regulatory action is warranted.
The team has seen positive outcomes from this escalation process:

- effective in achieving manufacturer and MAH prioritisation
- particularly useful in chronic compliance cases
- outcomes:
  - avoidance of regulatory action
  - minimising the risk of supply shortages as a direct result of avoiding regulatory action, although difficult to measure

As a result, MHRA presented this approach to the EMA during meetings in July and September, with a recommendation that similar principles be adopted by each national competent authority across the Community. This was received positively, and a working group will be formed to draft a compliance management procedure for the Community compilation.

4.1.3 ***GMDP Compliance Reports***

MHRA reported on changes to GMDP compliance reports. These have been in place since the launch of the Risk-Based Inspection (RBI) process in 2009. There is an expectation that information relating to site changes and certain quality indicators are provided prior to inspection, and that significant changes are notified as interim updates. The compliance report has recently been revised, with additional sections relating to:

- Background information to facilitate data integrity verification during routine inspections. Such verification may be made by:
  - data governance policy
  - confirm access to System Administrator staff
  - list of principal IT systems, including any changes
  - number of Out of Specification investigations that have been performed (phase I and II)

- Information on all active substances handled on site (to permit a more robust assessment of cross contamination risks)

- Information on corporate activities located at the site to be inspected.

In addition to the three main changes above, the guidance notes which were previously available as a separate document have now been embedded into the compliance report itself, to make reference easier. This does give the appearance of a more detailed document, however the additional information requested for data integrity verification should already be available as existing requirements of GMP, and the embedding of the guidance is intended to give a more consistent approach to completion of the required information.

Finally, the interim compliance report has been separated as a stand-alone document.

The majority of these changes will be presented at the upcoming GMDP Symposium. All changes will be rolled out at the beginning of January 2015.

4.2 Providing Authoritative Information

4.2.1 ***Agency Symposium***

MHRA reported that the GMDP symposium will be taking place on 9th – 12th December 2014 at the Novotel London West, London. In order to balance the high demand for places whilst still retaining a level of intimacy and opportunity to interact with inspectors, the same programme is being repeated on a second day for both GMP and GDP. Delegates were asked to complete a survey monkey questionnaire to identify topics of interest for the agenda. The final agenda features topics relating to recent changes to the EU GMP Guide including changes to Chapter 3, Chapter 5, Annex 15, Annex 16, the new Clinical Trial Regulations, and 'hot topic' issues seen on inspection such as data integrity. To date, three days of the symposium have completely sold out with only a few places available on the GMP day on 12th December 2014.

4.2.2 ***Publications***

*The Orange Guide*

MHRA reported on the latest revision of the Orange Guide. This is the first year that the agency are publishing an annual revision. This year the guide has been updated to incorporate changes made to European Community guidelines on Good Manufacturing Practice (Chapters 3, 5, 6, and 8) and the revised EC Guidelines on Good Distribution Practice.

In addition there are new sections on:

- the Gold Standard for Responsible Persons
- MHRA Innovation Office
- the application and inspection process for new licences "what to expect"
- MHRA Compliance Management and Inspection Action Group
- MHRA risk-based inspection programme
- naming contract Quality Control laboratories on a manufacturer's licence
- a new flow chart on registration requirements for UK companies involved in the sourcing and supply of active substances to be used in the manufacture of licensed human medicines.

For the Green Guide the principle is the same. It will have revised EC Guidelines on Good Distribution Practice along with the majority of the sections listed above. In addition, there are new sections on:

- UK Guidance on EU Guide Chapter 1 of GDP - Quality Management
- list of persons who can be supplied with medicines by way of wholesale dealing taken from the Human Medicines Regulations 2012
- EC Q&A on GDP guidelines
- controls on certain medicinal products
- sales representative samples
- handling returns of non-defective medicinal products
- reporting adverse reactions
- short-term storage of ambient and refrigerated medicinal products – requirements for a wholesale dealer's licence.

The new revisions of both the Orange Guide and Green Guide should be available from January 2015.

*Guidance Notes 5, 6 and 14*

MHRA reported that Guidance Notes 5, 6 and 14 have been updated and published on the MHRA website. The contents have been reordered and updated where necessary and some new sections have been added e.g. GN 6 which has new sections in relation to brokering.

4.2.3 ***Industry-led Quality Fora***

MHRA reported on its involvement at industry-led quality fora. Currently, MHRA attend a number of industry-led events related to quality issues. MHRA re-iterated that if organisations present hold a quality event and feel it would be beneficial for MHRA to have an input, MHRA would gladly consider any invitation to attend such an event.

*BGMA Quality Forum feedback*

BGMA presented feedback following the first BGMA Quality Forum held in June. See Annex 1.

4.2.4 ***GMP Deficiency Data***

MHRA reported that the inspectorate has been working with an industry stakeholder group over the last 18 months to review the way in which deficiency trend data is presented. The aim of this work has been to ensure that the inspectorate are providing information in a manner which is of most benefit to industry in learning from a wider deficiency data set.

Some of the identified improvements, particularly in regards to greater granularity in collected data, and possible incorporation of data from other inspectorates, will require an IT solution to achieve, and the team continue to work on this development.

In the meantime, and working with the data collection tools available at present, the inspectorate have compiled the report of 2013 inspection findings which implement as many requests from the group as possible within the limitations of the current data set.

The 2013 trend report is now published on the website at the following link: http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con464241.pdf

The report includes:

- 2013 trends
- 5 year trend of top issues:
  - Risk of cross contamination and quality systems issues remain most prevalent over the 5 year period
  - Number of majors per inspection generally consistent
  - Number of critical deficiencies per inspection has increased slightly (average of 0.08/inspection in 2008-2012; 2013 average of 0.13). This is aligned with a cluster of data integrity issues
- Areas for future focus:
  - Data integrity
  - Supply chain visibility (an on-going issue, with additional FMD requirements)
  - Investigation of anomalies
  - Contamination risks.

4.2.5 ***You'll Soon Feel Better***

ABPI presented an item on their GMP video 'You'll Soon Feel Better'. See Annex 2.

4.3 GDP Update

MHRA reported that the GDP team still consists of 16 inspectors with three on fixed term contracts, now extended.
600 inspections were completed from January to June 2014 involving 455 companies.

Deficiency statistics show 16 Criticals, 496 Majors and 1957 Others. The Criticals covered 6 companies. The inspectorate are still putting together deficiency data working with definitions based on the EU Guidance chapters as requested by BAPW. The inspectorate will present a summary of findings from the deficiency data at the upcoming Symposium and will eventually publish full information on the MHRA website. The following appear to be the most commonly observed deficiencies so far:

- Implementation of an adequate Quality System using Risk Management, Change Control and CAPA principles
- Maintenance of correct temperatures for storage and transportation
- Transportation validation
- Qualification checks on all customers
- Management of Returned product

A review of the deficiencies will provide a source of information by which the inspectorate can identify areas where greater guidance is required for industry as well as helping wholesalers identify opportunities to improve. The inspectorate can then respond using the Green Guide revisions and information on the MHRA website.

The team continue to address stakeholders through meetings and events based around newly regulated areas. They also receive training to inspect these new types of business. Some examples include marine compliance, freight forwarders working with exporters, API storage and distribution sites, Clinical Commissioning Groups and others.

Another area the team have looked at closely is desktop inspections and how these can be introduced into the GDP environment with the vast array of different types of companies which MHRA inspects. The ability to carry out desktop-based inspections is linked to the risk data available and the risk-based inspection process will be utilised to identify suitable sites. The team carried out the first such desktop inspection, which was successful in meeting the needs of the company and the MHRA.

4.3.1 ***RP Gold Standard update***

COGENT presented on the RP Gold Standard and updates following the last meeting. See Annex 3. The Gold Standard can be found at the following link:
http://www.thegold-standard.co.uk/job-details/?jobid=297

4.3.2 ***Process Licensing Portal update***

MHRA presented an update on the Process Licensing Portal - the new electronic system for submitting certain applications. See Annex 4.

4.3.3 ***EudraGMDP***

MHRA presented on the EudraGMDP database. See Annex 5.

**5. QP Survey Report**

COGENT presented a summary of their findings from the QP Survey Report. See Annex 6 for the summary and Annex 7 for the report itself.

Following the presentation, there was some discussion about how the matter would be taken forward. JPB QP stated they would be happy to support the initiative as they had not had any input into the report so far. ABPI stated that the MMIP group intended to review the report and have invited COGENT to participate in the process.

**6. International interactions**

MHRA reported on the inspectorate's recent international activities:

- The inspectorate have agreed to carry out another joint training programme with WHO for the Indian state and national regulators.

- The Director of IE&S recently accompanied the MHRA CEO on a visit to India to meet regulators and industry. India is a key supplier of medicines to the UK and such visits help build and maintain a good relationship.

- MHRA continues to lead on the GMP project carried out within the International Coalition of Medicines Regulatory Agencies (ICMRA). There have now been six meetings. The work is progressing in two work streams: one on how countries can build a network of being able to rely on each other through the work that is done; the other looks at how information can be shared with a view to building a reliance network to negate the need for an inspection or supplementing an inspection with existing information.

- The work with the TTIP (Transatlantic Trade and Investment Partnership) continues. Workgroups have been set up by the EMA to take forward. MHRA are one of four competent authorities involved.

- MHRA are looking at working more closely with the HPRA (formerly IMB) on inspections. Some MHRA inspectors are due to go to Ireland to help assist them with their Blood Programme as they currently have a shortage of inspectors in that area. They will look to reciprocate in future.

## 7. Falsified Medicines Directive

7.1 Safety Features

MHRA reported on the latest news regarding the delegated act for the safety features elements of the FMD. Work is underway by the European Commission to develop the delegated act, which the MHRA and DH have been heavily involved in. The latest round of Member State comments and proposals for the "black" and "white" lists will be submitted soon. MHRA expect a further Member State meeting in December followed by publication of the delegated act early in 2015.

7.2 Common Logo

The implementing act on the common logo was published in June and the provisions relating to distance selling will need to be implemented by July next year. Discussions are ongoing within the UK on how this will be implemented.

## 8. Feedback from the EMA

8.1 GMDP Inspectors Working Group

MHRA reported on the work of the Inspectors Working Group:

*Legislative changes*:

- Delegated act on GMP for APIs – due to be published soon.
- Delegated act on GMP for IMPs as a result of the new Clinical Trial regulation:
  - To be based on Directive 2003/94/EC
  - Commission to adopt and publish detailed guidelines in line with those principles of GMP
- Directive 2003/94/EC will be repealed, replaced or amended when 2001/20/EC is no longer applicable.

- Pharmaceuticals in the environment strategy:
  - Report published in June. Workshop held in September by Commission on the development of a strategic approach to pollution of water by pharmaceutical substances.
  - Pharmaceutical Committee: Commission to give presentation on state of play of the strategy to be delivered by September 2015, taking into account the study on environmental risks from medicinal products carried out for DG SANCO by BIO IS consultancy and other relevant information
- Veterinary Directive 2001/82/EC to be revised.

*Completed GMP updates:*

- Chapter 3 / 5: 'dedicated facilities' with improved guidance in 3.6 and 5.17-22 to prevent cross-contamination – coming into effect 1st March 2015.
- Chapter 5: starting materials controls on suppliers (5.27-30, 5.35-36). Also new text 5.71 on the notification of supply restrictions – coming into effect 1st March 2015.
- Chapter 8: use of QRM principles for defects / complaint investigations and for risk-mitigating actions, recall decisions and CAPAs. Also clarifies expectations and responsibilities in relation to the reporting of quality defects to the competent authorities – coming into effect 1st March 2015.
- Part II: new text to link Part 17 to the forthcoming GDP for APIs – came into effect 1st September 2014.
- GDP for API. The text is complete but yet to be published by the Commission.
  - guidance on distribution requirements relevant to APIs based on text in GDP for finished products and in Part II.
- GMP for Excipients. The text is complete but yet to be published by the Commission.
  - guidance on the appropriate GMP to be applied based on a formal risk assessment by the manufacturing authorisation
  - determine risk profile of excipient, document the GMP sections that need to be in place, conduct a gap analysis (audit etc) to show what is / is not in place, establish and maintain a control strategy

*Ongoing GMP updates:*

- Annex 15:
  - Amend text to link with Quality Working Party guideline on continuous process verification as an alternative to, or in a hybrid approach with, traditional process validation

- Updated text on cleaning validation to link with changes in Chapters 3 and 5
- Text on transport verification
- Include ICH principles
- Draft text been out to consultation and finalised text expected to be agreed at December IWG
- Publication expected by the end of Q1 2015

- Annex 16:
  - Include changes to reflect increased global manufacturing and more complex supply practices
  - Clarify requirements to harmonise expectations across EU
  - Include ICH principles
  - Draft text been out to consultation and finalised text expected to be agreed at December IWG
  - Publication expected by the end of Q1 2015.

- Annex 17:
  - Broaden from current release of terminally sterilised products to align with QWP guideline on real time release testing (RTRT)
  - Include ICH principles
  - Main text not yet been out for consultation

*Future developments:*

- Revision of Annex 1 – Manufacture of Sterile Medicinal Products
  - Complete revision to include ICH principles, improve clarification, capture new technologies, guidance for WFI manufactured by technologies other than distillation, align with PIC/S / international requirements where possible.
- Revision of Annex 13 – Manufacture of Investigational Medicinal Products
  - Partial revision to incorporate requirements of CT Regulation
  - CT Regulation not coming into effect until 6 months after EU portal/database is operational – expected Q1 2017
- Compilation of Community Procedures to be renamed and restructured.
- ATMP Report - discussed with Commission, relevant findings form the Regenerative Medicine Expert Group (RMEG) to be shared with the Commission.
  - GMP IWG – subgroup formed to gather EU-wide issues based on RMEG findings - MHRA will be rapporteur.
  - IWG sub-group will link with CAT on Quality issues
- Starting materials for ATMPs
  - revisions / clarification on classification at Commission's Tissue CA and Blood CA

8.2 Falsified GMP Certificates

MHRA reported that there had been an instance of a falsified GMP certificate reported to the MHRA by the Peruvian competent authority. The certificate was for a Chinese site that had allegedly been inspected by the MHRA but did not appear on the EudraGMDP database. MHRA reiterated that all genuine GMP certificates issued by the MHRA can be found on the EudraGMDP database.

**9. Industry Metrics**

MHRA reported that the inspectorate are looking to strengthen their RBI system using metrics obtained from industry. MHRA have met with four large pharmaceutical companies to discuss the governance systems they have and what information the agency can take from them to place more reliance on the work they do and therefore provide regulatory relief. Consideration is being given as to what metrics will help support the RBI system.

MHRA reported that the FDA are launching a quality metrics programme as part of their Office of Pharmaceutical Quality (OPQ). MHRA have discussed with FDA how they expect the quality metrics programme to work and will discuss further along with EMA on how metrics programmes can be aligned.

**10. Any other business**

MHRA suggested it may canvass members on whether they felt there would be value in joining a wider stakeholder engagement meeting which would address common aspects across the GxPs.
MHRA will discuss internally prior to contacting members on the matter.

**11. Date of next meeting**

April 2015