GMP/GDP Consultative Committee
Note of Meeting
8th May 2015, Room R-T-501/2, 151 Buckingham Palace Road, London.

Representatives from the following organisations were present at the GMP-GDP Consultative Committee meeting held at BPR on the 8th May 2015:

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)
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 17th October were agreed.

3. Agency update

3.1 Changes within MHRA

MHRA reported as follows:

- Professor Sir Michael Rawlins has been appointed as the agency's new chairman. Professor Sir Michael Rawlins had been chair of the National Institute of Health and Clinical Excellence (NICE) until recently, a role from which he stood down in 2013. He had been chairman of Biobank prior to joining the agency.

- MHRA have vacated the 3rd floor of 151 Buckingham Palace Road and now only operate from the 4th and 5th floors. This has posed challenges internally but should not have an impact externally. The 3rd floor will be leased out to the Care Quality Commission.

GOV.UK

MHRA presented on the transition to the GOV.UK website. See Annex 1.

Members were encouraged to provide feedback on the move to GOV.UK via the website, especially if any useful information that was previously on the old website has not been moved across. It is noted that FAQs were affected by this. MHRA are looking to create guidance documents from these FAQs so that the information can be added to GOV.UK.

3.2 Changes within I,E&S

MHRA reported as follows:

- The current editor-in-chief of the British Pharmacopoeia, Matilda Vallender, will be retiring by the end of May. James Pound will be taking over her role.

- Sandra Bax has been appointed as manager of the Defective Medicines Report Centre (DMRC).

4. Inspectorate update

4.1 Operational

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

MHRA reported that it was still actively recruiting new GMDP inspectors. There were no successful candidates at a recent assessment centre and the process will be repeated until the posts are filled. Regarding the GDP team, 3 additional inspectors will be recruited on 2-year fixed-term contracts. This will help address the current backlog within the team, especially with regards to GSL sites.

4.1.2 ***Compliance Reporting***

GMDP Compliance Reports

MHRA reported on the new GMDP Compliance Report requirements. At the last Consultative Committee meeting, MHRA reported on the upcoming changes to the Compliance Report format including new sections on data integrity and 'molecules handled'. These changes have now been implemented and accompanying guidance has been published. This can be found at the following link: https://www.gov.uk/good-manufacturing-practice-and-good-distribution-practice#complete-a-compliance-report

Broker and Active Substance Compliance Reports

MHRA reminded attendees that registered brokers of medicines and registered manufacturers, importers and distributors of active substances must fill in a yearly compliance report and submit this via the Portal if they had not done so already.

4.1.3 ***Office-based Assessments***

MHRA reported on plans to carry out office-based assessments for certain sites. The GDP Inspectorate are looking at how they can improve efficiency. One way of doing this is through office-based assessments.

The plan would initially be to use this process for pharmacy chain sites that are currently authorised with the agency but have not been inspected before. If this proves successful, the process would then be extended to GSL sites. Again, this would be applied to sites that are currently authorised with the agency but have not been inspected before.

The intention is not for office-based assessments to replace the inspection process, simply to help prioritise which sites require an inspection. Following the assessment process, if the risk appears to be low, then an inspection may be delayed by 2-3 years. The GDP Inspectorate intend to roll out the process later this year.

This should not impact on GDP certificates, as certificates are valid for 5 years, and those sites that are close to expiry would be re-inspected as normal.

4.2 Providing Authoritative Information

4.2.1 ***Agency Symposia***

MHRA reported that the 2015 GMDP symposium will be taking place 8th – 11th December 2015 at the Novotel West, Hammersmith. Based

on the popularity of last year's symposia, the four day event will start with a GDP day, followed by a GMP day and days three and four will then be a repeat of days one and two. The agenda is being developed and will feature regulatory updates such as Annex 16, Annex 1 and Annex 13, either as topics in their own right or as a general regulatory update session, depending on the timings and status of the updates at the time of the symposium. Positive feedback was received in relation to last year's data integrity workshop, and so this year's event will also feature interactive workshops where this format is particularly suited to the topic area. Although the post evaluation feedback from last year's event did include some suggested topics delegates would like to see covered, committee members were encouraged to provide further suggestions for inclusion.

4.2.2 ***Publications***

The Orange/Green Guide

MHRA reported on the latest revision of the Orange and Green Guides. The 2015 edition of Rules and Guidance for Pharmaceutical Manufacturers and Distributors (the "Orange Guide") has been successfully published in January 2015 along with the Rules and Guidance for Pharmaceutical Distributors (the "Green Guide").

As well as the print version, both guides are available electronically in the following formats:

- online via Medicines Complete
- eBook via Amazon Kindle
- eBook via Apple ITunes
- eBook PDF via ebooks.com
- also as eBook PDFs via several suppliers direct to libraries

Moving forward, the guides will need to be updated to include new or amended Commission text for the following:

- COMMISSION DELEGATED REGULATION (EU) No 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use.
- Guidelines Good Distribution Practice of active substances for medicinal products for human use (2015/C 95/01).
- Guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use (2015/C 95/02).
- Part III - Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities.

- Revised Annex 15: Qualification and Validation.

These updates will be available on Medicines Complete shortly.

Consideration is now being given to the next revision of the guides and whether or not to publish a 2016 edition. Currently there is not enough new content to warrant a 2016 edition of each guide therefore the next print version may be published in 2017.

4.2.3 ***GMP/GDP Deficiency Data***

MHRA reported that it continues to work with an industry stakeholder group to review the way in which deficiency trend data is presented. The next step is to look at how data is collected and use an IT tool to best present the findings. One of the requests coming out of the group was to provide more detail on deficiencies that have a significant impact such as those seen by the Compliance Management Team (CMT). MHRA made a presentation on the CMT statistics from the last year. See Annex 2.

MHRA are looking to expand the process across other GxPs over the next year. MHRA are also looking to work with the EMA in order to widen the process across other EEA competent authorities.

4.2.4 ***Data Integrity Guidance***

MHRA reported on the work the GMDP Inspectorate has carried out regarding data integrity. The team have taken the lead on this issue globally and are the first to issue guidance:
https://www.gov.uk/government/publications/good-manufacturing-practice-data-integrity-definitions
Other organisations are in the process of developing their own guidance. Moving forward, the intention is to make the guidance applicable across GxPs, with a GxP core and independent Annexes for each GxP where necessary. The Inspectorate are now looking to drive this forward at an EU level.

5. Support for Innovation

5.1.1 MHRA reported on activities carried out by the agency in support of innovation. The work falls under one of MHRA's strategic objectives – 'Bringing innovation and new products speedily and safely to patients'.

This includes:

- UK's Early Access to Medicines Scheme (EAMS)

- two-step process:
    - Promising Innovative Medicine (PIM) designation – 4 to-date,
    - scientific opinion - 1 product received opinion

- EMA's Adaptive Pathways MHRA involvement:
- early discussions that shaped communications and the pilot project
- review of submissions (>30) and 'safe harbour' discussions
- discussion on next phase of the project

- Innovation Office:
- applies to all 3 areas of MHRA, running for 2 years and now received approx. 180 enquiries,
- recent increased rate of submission – helpful effect of case studies published via MMIP or more confidence / familiarity to make submissions, 60/40 medicines/devices,
- for medicines, major areas are ATMP and novel manufacture at 11% each. All manufacturing related enquiries can be handled by current GMP, no 'disruptive' change enquiries seen.

- One Stop Shop via Innovation Office portal:
- for ATMP / Regenerative Medicines only
- for joint advice provided across all UK regulators as needed for the enquiry i.e. MHRA, HTA, HFEA, HRA (and HSE / DEFRA as required for GMO enquiries)
- relatively few enquiries received. Further marketing / promotion required to ensure wider awareness

6. International Interactions

MHRA reported on the Inspectorate's recent international activities:

- The GMDP Inspectorate have recently carried out two remote assessments of sites on behalf of the EMA. Based on the information provided by the sites and taking into account the sites' compliance history, the assessment allowed the Inspectorate to recommend inspection of the sites to be deferred.

- MHRA will chair PIC/S in 2016/17. Paul Hargreaves will be the chairperson representing MHRA. As part of this, the agency will be hosting the annual PIC/S training which will be held in Manchester. There are now 46 members of PIC/S with a further 13 countries undergoing assessment.

- 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. Papers have been submitted by these two groups. Subsequently there is now a group led by the UK looking to pull together a pilot study which could start later this year.

- The work with the TTIP (Transatlantic Trade and Investment Partnership) continues. FDA inspectors have accompanied various European competent authority inspections in recent months as part of the Joint Audit Programme (JAP) whereby European competent authorities audit each other. A European team of inspectors will go out to the US later in the year to reciprocate the process.

- MHRA are close to signing a Memorandum of Understanding (MoU) with India. It is hoped that this will be finalised later this year. The MoU will facilitate easier exchange of information and provide a mechanism for sharing understanding through exchange of personnel.

- MHRA have supported WHO training in India for both regulators and industry.

7. Qualified Persons

7.1 ABPI presented on developments since the last meeting following the publication of the Cogent report into the possible shortage of Qualified Persons. See Annex 3.

This prompted discussion between MHRA, ABPI and other members on how to move the matter forward. MHRA agreed that a project group may need to be set up, following formulation of a problem statement and data collection exercise held by MHRA and JPB-QP, to take the matter forward if an issue is identified. MHRA and JPB-QP agreed to liaise and report back at the next meeting. MHRA suggested that it may be appropriate for the group to sit within the Medicines Manufacturing Industry Partnership (MMIP) and that a steer from the MMIP and Science Industry Partnership (SIP) may be required. ABPI agreed to discuss the matter with MMIP and SIP.

Action: MHRA, JPB-QP, ABPI

8. Falsified Medicines Directive (FMD)

8.1 Safety Features

MHRA reported on the latest news regarding the delegated act for the safety features elements of the FMD. The European Commission has been engaging informally with Member State experts on the details to be included in a delegate act. The last scheduled meeting was held end of March.
The expectation is that the Commission will publish the act this summer which will then go to Council and European Parliament. They can reject the act but the barrier for this is high. If the act is not rejected, the final act will be published by the end of 2015. UK then has 3 years to implement. The agency is working with the Department of Health with regards to implementation of the act.

8.2 Common Logo

MHRA reported on the latest developments regarding the requirement for online sellers of medicines to display a common logo on their website. According to FMD all online sellers of medicines - pharmacies and retail - must have a logo on their website by 1 July. This is an EU obligation that agency has transposed through copy out (i.e. exactly as it says in EU legislation).

Details of the logo have been agreed at EU level through a Commission implementing act published in June 2014.
The agency is currently developing the processes to allow online sellers of medicines to apply for the logo by 1 July. IE& S division have the operational lead and are working closely with other colleagues such as IT. Once the agency's work is further developed, we intend to further engage with online sellers of medicines to ensure that the introduction of these requirements is as smooth as possible for affected stakeholders.

8.3 Publication of Guidance

MHRA reported that guidelines in relation to GDP for active substances and risk assessments to ascertain appropriate GMP for excipients have now been published on the Commission's website:
http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52015XC0321(01)&from=EN
(comes into force 21 Sep 2015)
http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52015XC0321(02)&from=EN
(comes into force 21 March 2016)

These updates will appear on the online version of the Orange Guide shortly.

Companies should conduct excipient risk assessments in accordance with the guideline, although if a company can demonstrate that the expectation of the guideline has been met and provide justification for adopting an alternative approach then this would be acceptable. MHRA encouraged members to provide feedback to the Inspectorate if they experience differences in how other Member States interpret the guidelines once implemented.

9. Feedback from the EMA

9.1 GMDP Inspectors Working Group

MHRA reported on the work of the Inspectors Working Group:

Legislative changes:

- GMP for APIs:
  - delegated Regulation 1252/2014 published 28 Nov - supplements 2001/83/EC, apply from 28 May 2015

- GMP for IMPs:
  - delegated Regulation - to be based on Directive 2003/94/EC
  - commission to adopt and publish detailed guidelines in line with the principles of GMP
  - update of Annex 13, may have to be stand-alone due to legislation

- Fate of 2003/94 (GMP for finished products):
  - repeal and replace or amend when 2001/20 no longer applicable

- Pharmaceuticals in the environment strategy:
  - study on the risks of environmental effects of medicinal products
  - report published in June 2014.
  - commission workshop held to develop approach to control of pollution by pharmaceutical substances and Commission developing their strategy

- Veterinary Directive 2001/82/EC under revision to become a regulation, Medicines Directive 2001/83/EC to be revised at a future point

GMP updates - published:

- Annex 15:
  - coming into effect 1 Oct 2015

- GDP for API:
  - published Mar 15, in Vol 4 ‘Other documents related to GMP’
  - coming into effect 21 September 2015

- GMP for Excipients:
  published in Part III EU GMP, published Mar 15, effect 21 March 2016

Ongoing GMP updates:

- Annex 16:
  - Adopted, subject to agreement on minor text details and with the Commission for legal review and translation:
  - aligned to ICH principles
  - includes changes to reflect increased global manufacturing and more complex supply practices
  - intended to harmonise expectations across EU
  - publication expected by the end of Q3 2015.

- Annex 17:
  - broaden from current release of terminally sterilised products to align with QWP guideline on real time release testing (RTRT)
  - draft text for public consultation to be published Q2/3 2015

GMP updates - starting:

- Revision of Annex 1:
  - complete revision to include ICH principles, improve clarification, address new technologies, guidance for WFI manufactured by technologies other than distillation
  - concept paper out Dec 2015

- Revision of Annex 13:
  - 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

- Drafting of Annex 21, ‘Importation of Medicinal products’:
  - concept paper to be published Q2 2015

- ATMP:
  - review following Commission report with GMP (IMP and FP) changes
  - it is possible that a parallel GMP guide will be created for ATMPs

- Compliance Management process and Data Integrity:
  - widen process across other member states
  - will fall under GMP but not certain which section as yet

9.2 Joint Audit Programme (JAP)

MHRA reported on the Joint Audit Programme (JAP). This is a Heads of Medicines Agencies programme. The programme covers 46 Inspectorates across the EEA and aims to ensure equivalence between Member States by way of audits carried out as part of the programme. Assessments are carried out every 5 years.

9.3 Medicines Shortages

MHRA reported on work initiated by the EMA, working with Member States and an inter-association task force to prevent shortages. Various guidance documents have been published in the last year by both EMA and industry associations such as ISPE. The next steps will be to form a plan on how to get the message across to stakeholders. There will be a workshop on the matter this summer co-chaired by MHRA and EMA.

10. Any other business

10.1 ABPI reported that sales of their GMP DVD entitled 'You'll Soon Feel Better' had been strong and foreign language versions are in production.

10.2 MHRA reported that the Responsible Person Training Standard had been signed off in recent weeks. Cogent and MHRA will liaise to agree a strategy to officially launch the Training Standard. Linked to this, the Inspectorate are looking to take a more educational role in line with other areas of the agency e.g. producing online learning packages. GDP would be the first area to be looked into.

10.3 MHRA confirmed that the expiry date on GMP and GDP certificates should be applied flexibly and does not necessarily mean that the certificate is not valid. JPB-QP reported that this was not the interpretation across other Member States, both in industry and other competent authorities. MHRA encouraged members to report any issues such as this to GMPinspectorate@mhra.gsi.gov.uk so that MHRA can raise a problem statement at the Inspector's Working Group.

11. Date of next meeting

October/November 2015