Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

GMP/GDP Consultative Committee
Note of Meeting
18th April 2016, 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 18th April 2016:

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)
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)
Ethical Medicines Industry Group (EMIG)
The Cogent Group
NHS Pharmaceutical QA Committee
National Office of Animal Health (NOAH)

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 30th October were agreed.

3. Agency update

3.1 Changes within MHRA

MHRA reported that the government's lease is running down at 151 Buckingham Palace Road and the agency is examining options for relocation within the next few years.

3.2 Changes within I,E&S

MHRA reported that a new Quality Manager, Nicola Thomas had joined the Division.

MHRA then presented on the current quality strategy across the division:

The quality strategy sets out the direction for quality, innovation and engagement over the next 3 years.

Key elements:

- Maintain and improve the quality management system
- Engage with staff to embed a quality culture
- Co-ordinate external stakeholder engagement activities
- Have an overview of innovation work

Maintain and improve the quality management system

- Improve the internal audit programme to take a risk based approach to audit and involve staff from across the division – completed. New audit schedule based on risk and recently recruited team of internal auditors.
- Identify areas that would benefit from process improvement – some of this is done. Inspectorate processes are mapped out to allow us to see similarities/differences in processes between the GXPs with the aim of harmonising these.

Engage with staff to embed a quality culture

- Review of staff survey results and implementation of action plan – done, plan being implemented
- Promotion of L&D
- Promote benefits of QMS

Co-ordinate external stakeholder engagement activities

- Understand stakeholder engagement activities across the division. Improve consistency of approach, exploit new opportunities and identify new areas of collaboration and engagement.

Have an overview of innovation work

- Identify and understand innovation work across the division, co-ordinating and communicating activities.

To do all of this, there is a quality matrix made up of groups of staff within the division, looking at:

- Staff engagement
- External stakeholder engagement
- Quality and improvement (Innovation)

3.3 Heads of Medicines Agencies (HMA) Multi -Annual Work-Plan

MHRA reported on the HMA multi-annual work-plan. There are eleven work areas which are derived from the joint EMA/HMA 'EU Medicines Agencies Network Strategy to 2020'

There will be a separate EMA multi-annual work-plan on areas that they are responsible for.

The aim is to make the HMA more strategic with fewer more substantive topics being discussed.

Four of the eleven work areas have been allocated as high priority in 2016:

- Antimicrobial resistance
- Availability of appropriately authorised medicines
- Innovation and access to new medicines
- Optimisation of the regulatory operations

3.4 MHRA Annual Lecture

MHRA reported on the recent MHRA annual lecture which had been delivered by Dr Margaret Chan - Director General of the World Health Organisation. Further information on the lecture can be found at the following link: https://www.gov.uk/government/news/dr-margaret-chan-delivers-mhra-annual-lecture

A video of the lecture can be found on Youtube at the following link:

https://www.youtube.com/watch?v=rRPdMi8otdA&list=PLSFBoykD5J2Zz2v9kYHkwknX1XySFRIU5&index=2

4. Inspectorate update

4.1 Operational

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

MHRA reported with regards to staff changes and recruitment within the GDP and GMP teams:

GDP

The GDP team have recently recruited 3 new inspectors which are currently in the process of being signed off. The team now have a full complement of 18 inspectors.

GMP

4 GMDP inspectors have been recruited since the last meeting, 2 of which are re-joining the agency. Another assessment centre will be held in May to fill the 4 positions currently vacant.

In addition, another returning inspector has been appointed to the post of Risk Manager within the Inspectorate. They will be looking to take forward best practice for use of the risk-based inspections (RBI) system across GxPs.

4.2 Providing Authoritative Information

4.2.1 ***Inspectorate Blog***

At the last meeting MHRA committed to writing an item for the Inspectorate blog on the outcome of the Joint Audit Programme (JAP) audit carried out in October 2015. Due to unforeseen delays, the final report was only received in March. This found MHRA to be in compliance with JAP requirements. MHRA will now start drafting a blog on the matter.

MHRA again welcomed ideas from members on future blog topics. Suggestions can be made using the comments box on the webpage.

The Inspectorate blog now has over 3,500 subscribers putting it amongst the top 5 most popular subscribed blogs within government.

4.2.2 ***Agency Symposia***

MHRA reported on the GMP and GDP symposia.

The 2016 symposia will be taking place 6th – 9th December 2016 at the Novotel West, Hammersmith. 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.

Based on the popularity of last year's GDP event in Glasgow, a separate 1 day GDP event is also planned outside of London but the dates and location are still to be confirmed.

The agenda is being developed and will feature regulatory updates as well as 'hot topic' items. 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 inclusions.

4.2.3 ***Publications***

The Orange/Green Guide

MHRA reported that it is on track to publish the 2017 editions of both the Orange Guide and Green Guide in January. The new editions of the guides will have all the revised Commission guidance that is currently in the electronic versions on Medicines Complete.

For both guides, MHRA are looking to produce further guidance on the Inspectorate's expectations on various topics.

4.2.4 ***Office-Based Assessments***

MHRA reported on the latest developments regarding office-based assessments.

The GDP team started a programme of office-based assessments earlier this year and are currently working through some pharmacy chains, holding WDAs, with multiple collection-type sites. The WDA holder is sent a questionnaire which captures relevant information for the site to be assessed, and further email and telephone conversations may take place to achieve the level of information required to complete the assessment.

By September 2016 the team will have completed about 300 such pharmacy site assessments and the success of the process will then be reviewed before taking forward to look possibly at other types of business models, such as GSL only sites.

5. ***Bioequivalence Issues***

MHRA reported that an increasing number of issues are being seen with bioequivalence studies conducted in 3rd countries, in particular in India. MHRA are working with EMA to undertake additional surveillance and inspections. Additionally, MHRA are looking to utilise the relationship with the Indian authorities to explore how best to address the matter. The majority of issues identified are in relation to data integrity.

6. Support for Innovation

6.1 Accelerated Access Review

MHRA presented slides on the Accelerated Access Review. See Annex 1.

6.2 ABPI/MHRA conference

ABPI provided feedback from the joint MHRA/ABPI conference held in March. The conference was titled 'making the case for UK medicines manufacturing' and aimed to introduce the work done so far through the Medicines Manufacturing Industry Partnership (MMIP) and the MHRA Innovation Office to a wider stakeholder audience. Presentations were delivered by the MMIP chairman, MHRA and member companies that have brought their product development to the UK.

There was also an interactive session where questions were posed to the audience. 3 key areas were identified which would encourage companies to carry out more manufacturing in the UK:

- More innovation in innovative manufacturing and innovative supply chain activity in the UK
- Government encouragement through funding
- Increased availability of appropriate skills.

Skills were identified as having the biggest impact, both in the short-term and long-term, in particular in the ATMP sector (QPs and engineering skills).

A significant amount of work has been carried out in relation to skills leading to the publication of the Science Industry Partnership (SIP) skills strategy which forecasts the Sector's demand for skilled people up to 2025. The SIP Skills Strategy can be downloaded here:
http://scienceindustrypartnership.com/media/529053/5202fd_sip_skills_strategy_2015_final_low.pdf

The underpinning evidence document 'The Demand for Skills in the UK Science Economy' provides a comprehensive assessment of both the forecast scale of workforce demand across the science industries over the next 10 years, and the nature of skills needed in the future, driven by key enabling technologies; it can be downloaded here.
http://scienceindustrypartnership.com/media/529050/sip_science_industry_demand_for_skills_final.pdf

6.3 MHRA Update

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

- Working with the Catapult Programme on innovation in the following areas: high value manufacturing, precision medicines, cell and gene therapy and medicines discovery.

- Supporting various groups including the ATMP taskforce launched by MMIP, and the Continuous Manufacturing and Crystallisation (CMAC) partnership.

- Innovation Office:
- applies to all 3 areas of MHRA,
- now received approx. 270 enquiries

7. International Interactions

MHRA reported on the Inspectorate's recent international activities:

7.1 Mutual Reliance Initiative (MRI)

The Mutual Reliance Initiative is a strategic collaboration between EU regulatory authorities and the US-FDA to evaluate whether we have comparable regulatory and procedural frameworks for inspections of manufacturers of human medicines so that we can rely on each other's information. The EMA and Commission are visiting FDA

this week as part of the MRI discussions. The scope of any agreement is still being discussed.

7.2 ICMRA

MHRA reported on the latest developments around the GMP project carried out within the International Coalition of Medicines Regulatory Agencies (ICMRA). A pilot has now been completed to determine if it is feasible to take outcomes of other regulators' inspections (international) and make a decision based on those i.e. a desktop assessment. A phase 1 implementation phase is underway. MHRA have selected 2-3 facilities located in a PIC/S country and will carry out a desktop assessment to determine if a GMP certificate can be issued without a physical inspection. The process will be reviewed and will be followed by a phase 2 implementation.

7.3 India

MHRA have now met with the drug controllers in 5 key supply states within India. The controllers have been invited on the inspections MHRA carry out within those states. MHRA are now looking at how to strengthen the relationships and take forward any learning with them. A secondment/exchange program with CDSCO is also under consideration which will help each agency understand how the other works.

7.4 PIC/S

7.4.1 *Training Seminar 2016*

MHRA will chair PIC/S in 2016/17. As part of this, the agency will be hosting the annual PIC/S training seminar which will be held in Manchester. The focus of the seminar will be around 'Inspectorates of the future' looking at the direction of change in industry and working more closely in future to meet the challenges of new technologies. The 2-day committee meeting will be followed by a 3-day workshop which non-PIC/S regulators are invited to.

7.4.2 *Data Integrity*

MHRA are close to issuing a GxP wide guidance document on data integrity. The guidance will be circulated for comments in the near future. WHO have also produced a GxP wide guidance document which is close to publication. MHRA co-chairs the PIC/S working group on data integrity. This group will look to publish guidance harmonised across all PIC/S members.

7.5 Benchmarking of European Medicines Agencies (BEMA)

MHRA reported that a BEMA assessment will be carried out of the agency in October this year. The assessment is carried out by colleagues from other member states who will assess how the MHRA as a whole meets best practice standards regarding the systems and processes that the agency uses.

The assessment is an opportunity to identify strengths and best practices in agencies and any opportunities for improvement; it is not an audit designed to identify non-compliance.

The BEMA process applies to both Human and Veterinary medicines competent authorities.

8. Qualified Persons

8.1 MHRA reported on the action taken since the last meeting around a possible shortage of QPs following the report published by Cogent in 2014. MHRA have appointed an inspector to take the project forward. The first step will be to develop the scope of the project with input from key members of the committee. It will likely be a 1.5 – 2 year project. **Action: MHRA**

8.2 Transitional QPs for MIA(IMP) licences

MHRA reported on issues relating to TQPs for MIA(IMP) licences. An Inspectorate blog on the topic has been published https://mhrainspectorate.blog.gov.uk/2016/02/12/transitional-qps-for-investigational-medicinal-products-imps/

A further update will be published at the end of April 2016, to confirm the launch of the reassessment process and will include a link to the application form which will be made available on the MHRA website.

(*Post meeting note:* This has now gone live: https://www.gov.uk/guidance/good-manufacturing-practice-and-good-distribution-practice)

MHRA reported that representatives from both the GMP and GCP Inspectorate have been involved in providing training on behalf of EMA for the Member States on the new Clinical Trials Regulation by giving a presentation on the GCP and GMP aspects of the Regulation. The session included a panel discussion which highlighted the need for harmonisation of approach and visibility of how each Member State plans to implement national legislation for exempted activities under Article 61 (5) of EU Regulation No. 536/2014, due to the extended scope of the exemption which will mean that an MIA(IMP) is not required for:

- Re-labelling or re-packaging…carried out in health centres and clinics…by pharmacists or other persons legally authorised….used in hospitals, health centre or clinics taking part in same clinical trial in same Member State
- Preparation of diagnostic radio pharmaceuticals
- Preparation of prescriptions for individual patients

Such activities will however be subject to appropriate and proportionate requirements to ensure subject safety, and reliability and robustness of data and will be subject to regular inspections by Member States.

MHRA raised for awareness the possible implications for NHS sites who may consider surrendering MIA(IMP) licences, as this may lead to a reduction in opportunities for trainee QPs who need to gain relevant experience from working at sites that hold a manufacturing licence.

9. Falsified Medicines Directive (FMD)

MHRA reported on matters relating to the FMD:

9.1 Safety Features

MHRA explained that DH/MHRA are planning for implementation of the Safety Features elements of the Falsified Medicines Directive, with a unique identifier/2D barcode and tamper evident packaging required on all prescription medicines by February 2019. An industry led stakeholder group will be responsible for procuring and funding the UK medicines verification hub, with DH/MHRA oversight. The IT provider is due for selection by Q3 2016 with the hub build due by early 2018, ensuring sufficient time for testing. Meanwhile, a new DH/MHRA implementation advisory board has been set up to consider some of the policy questions raised by this legislation, how certain flexibilities would be addressed and its impact on different parts of the supply chain.

9.2 Excipients guidance

MHRA reported that the 'Guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use' which is published in EudraLex Volume 4 - Good manufacturing practice (GMP) Guidelines has now come into effect.

It can be found in Part III - GMP related documents. As a result, Chapter 5 of the EU GMP Guide has been revised.

A risk assessment as set out in the guidelines should be carried out for excipients for authorised medicinal products for human use by 21 March 2016.

The guidance covers 3 key areas:

- Determination of appropriate GMP based on type and use of excipient
- Determination of Excipient Manufacturer's Risk Profile
- Confirmation of Application of Appropriate GMP

The MHRA's expectations are:

- The excipient risk assessment/risk management procedure is incorporated in the Quality Management System.
- There is an on-going program of work to determine the appropriate level of GMP for the excipients being used and that application of those standards can be demonstrated.

- Importers of medicinal products have the risk assessment/management documentation available on site.

10. Feedback from the EMA

10.1 GMP/GDP Inspectors Working Group

MHRA presented slides on the work of the Inspectors Working Group. See Annex 2.

Additionally, MHRA are working with EMA and PIC/S on creating a group to discuss the practical implementation of the guidance within Chapters 3 and 5 of the GMP guide regarding the toxicological basis for cross-contamination control. MHRA invited members of the committee to provide case studies (these can be anonymous) on how companies have implemented the requirements. This will help the group in their discussions.

11. Any other business

11.1 The Inspectorate are still looking at how to streamline operations and make them more efficient. One area that has been identified is external stakeholder meetings where common topics may be repeated at separate meetings across GxPs. MHRA has held a Stakeholder Engagement day in the past for other GxPs in place of a joint committee meeting. The day is split in two with one part addressing common topics across the GxPs and the other addressing topics that are specific to each GxP.

11.2 MHRA reported that there has been no change to the situation regarding meeting GMP inspection timeframes. The inspection workload is being managed on RBI principles. The proposed inspection dates within GMP reports fit into a wider risk based inspection planning process within which the overall workload is prioritised based on risk. This process also accounts for the need to re-inspect facilities within 3 years to maintain “accepted currency” of GMP certificates. As such, whilst sites may not be re-inspected in line with the proposed dates within their reports, that is because there are facilities that are higher risk and therefore take priority.

The GMP Inspectorate’s aim is to maintain the 3 year re-inspection window for all UK based GMP sites, and in the main they have been successful in this regard.

12. Date of next meeting

October 2016