Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

GMP/GDP Consultative Committee
Note of Meeting

12 November 2018, 10 South Colonnade, Canary Wharf, London.

Representatives from the following organisations were present at the GMP-GDP Consultative Committee meeting held on the 12 November 2018:

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)
NHS Pharmaceutical QA Committee
Healthcare Distribution Association (HDA)
Joint Pharmaceutical Analysis Group (JPAG)
BioIndustry Association (BIA)
National Office of Animal Health (NOAH)
Proprietary Association of Great Britain (PAGB)
British Association of European Pharmaceutical Distributors (BAEPD)
Veterinary Medicines Directorate (VMD)

1. Introduction

MHRA welcomed current and new representatives to the meeting.

MHRA recognised the contribution of Mike Murray (ABPI) to the committee following his retirement.

2. Minutes of the last meeting and Matters Arising.

The minutes of the last meeting held on 02 May 2018 were agreed. There were no matters arising.

3. Brexit

3.1 Agency update

MHRA reported that the UK's position on medicines and medical devices regulation remains clear. The Government firmly believes it is in the interests of both the EU and

the UK to strike a deal, and it remains confident we will agree a mutually advantageous deal with the EU.

It is however the duty of a responsible Government to prepare for a range of potential outcomes. As such, extensive work to prepare for a 'no deal' scenario has been under way for almost two years and the Government is taking necessary steps to ensure the country continues to operate smoothly from the day we leave. This includes the publication of a number of technical notices earlier this year.

The MHRA consultation on the EU Exit no-deal legislative proposals was published on 04 October and closed on 01 November. The consultation asked for views on how the MHRA's legislation and regulatory processes would have to be modified in the event of the UK not securing a deal with the EU after the UK's exit, with no Implementation Period. Around 170 responses have been received and we are currently reviewing these. We'll be publishing further information and instructions in the coming months on Gov.uk:
https://www.gov.uk/government/consultations/mhra-consultation-on-eu-exit-no-deal-legislative-proposals

MHRA reported that work continues on the IT systems project – the replacement of EU systems for the submission and publishing of information with UK national systems. Stakeholder user-testing is planned for early 2019.

MHRA also reported that work is being carried out with DHSC to facilitate access to medicines stockpiles. In addition, the Inspectorate are drafting guidance on medicines transported by airfreight as an increase in airfreight is anticipated in a no-deal scenario.

3.2 Members update

MHRA responded to queries from members regarding how GMP certificates issued to 3rd country sites by the MHRA would be viewed by the EMA in a no-deal scenario. MHRA understands that the EMA would view MHRA-issued GMP certificates as third country information although they could still be used for MA applications and individual member states would be able to take a pragmatic view on the acceptance of the certificate and need for inspection.

MHRA also responded to queries regarding the licensing requirements to import medicines from the EEA in a no-deal scenario. MHRA confirmed that within the consultation document it had proposed that an import authorisation with the potential to name a QP from EU27 would be required. However, this does not appear to work for all organisations and therefore MHRA is looking at the possibility of a compromise position between the current wholesaling model and the model proposed in the consultation document. [***Post-meeting note*** – it is confirmed that as a result of the consultation feedback, MHRA will permit importation of finished products from the EEA under a UK wholesale dealer's licence. The activity will require supervision by a new person type, a 'Responsible Person for Import', who will be responsible for ensuring

that authorised medicines have been QP certified in the EEA prior to supply to the UK. Further guidance on this system will be published in due course.]

4 Agency update

4.1 Changes within MHRA

MHRA reported that two new non-executive directors - Amanda Calvert and Anne-Toni Rodgers were appointed to the Agency board in September 2018. In addition, Michael Whitehouse, another non-executive director will be joining the board with effect from 01 December 2018.

4.2 New senior post appointments

MHRA reported that James Pound has been appointed permanently as the Group Manager of the BP and Laboratory Services. Andrew Gray has been seconded to the role of Inspectorate Unit Manager following Mark Birse's secondment to the Devices division. David Churchward has taken over responsibility for coordinating the IE&S division's Brexit efforts.

4.3 Operational Transformation

4.3.1 *Agency level*

MHRA reported on the Operational Transformation programme. The programme has been formed to respond to the needs of the Agency's customers, to replace legacy technologies, and to improve the Agency's services.

The business case has been through the MHRA internal governance process and is now being considered by the Department of Health and Social Care (DHSC).

It is a programme business case designed for highly complex, integrated and uncertain environments. The Agency plans to update the programme in the Spring, when we have greater certainty about the post-Brexit landscape.

Between now and then the Agency will be focusing its energy on preparing for Brexit and on building Agency capability for change.

4.3.2 *Inspectorate update*

MHRA reported on Inspectorate participation within the Operational Transformation programme workstreams. This includes involvement in the Customer workstream, enhancing guidance and making it readily available on the website.

With regards to the Assurance workstream, there are 3 initiatives that the Inspectorate are looking to prioritise: reducing administrative burden on inspectors to allow them to focus on inspection activities, including using non-inspector staff to carry out certain pre-inspection activities; increase in desk-based inspections; formalising a process to charge additional fees in relation to serious non-compliance cases.

5. Inspectorate update

5.1 Operational

5.1.1 *GMP staff changes & recruitment*

As indicated at the last Consultative Committee meeting, the GMP Inspectorate recruitment campaign that was run in December 2017 resulted in 3 offers being made. Lewis Corbett, Julie Goodliff and Shirley Stagg started as GMDP Inspectors during the months of June and July 2018.

Unfortunately, Saima Ahmad (Senior GMDP Inspector) left the agency in August for a role in industry. Andrew Hopkins is also leaving the agency in January 2019 although with annual leave he will realistically stop working in December.

As a result, the team have vacancies for GMDP Inspectors and will be running another recruitment round, starting imminently and closing in early January. The agency is in the process of adopting the new Civil Service 'Success Profiles' approach to recruiting. This provides more details to potential candidates about the ability, behaviours, experience, technical skills and strengths that we are looking for.

Over the last few years the GMDP Inspectorate has experienced resource difficulties which has impacted on the risk-based inspection programme. As part of the team's efforts to address these resource issues and monitor compliance at an appropriate frequency, the team have been exploring new ways of working with recruitment to a new role of 'Healthcare Inspectors'. These inspectors will be recruited to inspect in the specials and blood sectors. Initially the team will be aiming to recruit two to three candidates with relevant experience, with the advert being posted around the start of November and closing in early January 2019. We would therefore hope to have Healthcare Inspectors in post by around the middle of 2019.

5.1.2 *Divisional restructuring and PCL Team merger*

MHRA reported that following a divisional restructure, the Process Licensing team (PCL) have joined the Inspectorate to become the Inspectorate & Process Licensing Group. The move is a natural fit as the key functions of the team are carried out to support the GMP and GDP Inspectorate. Asif Janjua has replaced Sean Kaiser as manager of the Process Licensing team. Further information can be found on the MHRA blog:
https://mhrainspectorate.blog.gov.uk/2018/08/01/process-licensing-office-joins-the-inspectorate/

5.1.3 *GDP team update and changes*

Mariam Naquesh-Bandi joined the team in October 2018. However, following the departures of Jacqui Masayi and Shahbaz Sarwar to take up new roles in industry, there remain vacancies and the GDP Inspectorate are currently running a recruitment exercise with an assessment centre taking place imminently.

5.1.4 *Operation PANGEA / GDP vigilance*

MHRA Enforcement Group reported on the recent Operation Pangea XI, an international operation coordinated by INTERPOL targeting the illegal supply of illicit

medicines and medical devices. The MHRA seized over £2 million worth of falsified and unlicensed medicines and medical devices as part of the operation. Further information on the operation can be found on the MHRA website: https://www.gov.uk/government/news/uk-seizes-more-than-2-million-of-fake-medicines-as-part-of-international-crackdown

5.1.5 *Manufacturers Licences - Licence variation and application*

MHRA reported on a project looking at the variations and applications process for manufacturers licences.

The GMP Inspectorate's internal metrics show that the statutory deadlines of 30 days (no inspection) or 90 days (inspection required) are not always being met and the team are not therefore delivering the level of service hoped for. A review was carried out to understand why this was the case:

What we did

In October last year all variations and applications submitted relevant to GMP (all manufacturing authorisation related submissions) were sent to the project lead – Christine Gray.

The purpose of the review was to:

- Assess the quality of applications received;
- Assess the error rate throughout the process and causes of errors;
- To identify any actions that would improve internal processes;
- To identify any actions that would improve applicant compliance.

Submissions were then tracked and assessed post closure (i.e. issue of licence).

Outcome

84 variations were received into the GMP queue and 88% were processed within the statutory timeframe. Whilst this is broadly acceptable as there are always some complications with some applications we wanted to look at how we could improve things.

60 variations were complete and accurate when received into the GMP queue. The remaining 24 (29%) could not be processed immediately because either there was an issue with the content of the submission itself or there was an issue with the entry in our system.

In some cases, the discussions with applicants were lengthy. Application issues were the highest root cause factor for late closure and contributed to 60% of missed statutory deadlines.

Failure to approve in a timely manner resulted in variations missing the statutory deadline. A delay in inspection and closure also resulted in a further variation missing the deadline however there were also IAG related issues with the site.

What are we doing about it?

Issues with the actual submission were the biggest contributor to missed statutory deadlines. We published a blog back in January 2017 titled “Helping us to Help You” as around 30% of applications were giving rise to RFIs. We still need to provide more guidance to enable our stakeholders to submit the right information.

This could be improved by:

- Improved guidance on submission and review of the forms for submission. This will include identification of mandatory fields, clarity within the forms regarding what can and cannot be applied for;
- Improving Guidance Note 5 and possibly embedding aspects of it into the application form or providing a link;
- Ensuring it is clear which roles are required for the different types of licence;
- We’ve been looking at other regulators’ websites to see what their processes and guidance look like.

We are working on this across teams and understanding how each part of the process works. Training of data processing unit (DPU) staff could allow earlier identification of incomplete forms or applications that are not suitable for submission. This would allow them to be returned to applicants ahead of the data entry process and gain efficiencies. Applicants would know sooner there was a problem and time would not be spent entering applications that won’t be processed to completion. This training can be provided by the inspectorate and include the content of Guidance Note 5, an overview of the named roles on licences, what those people do and what various licences are for to strengthen background knowledge. We can also develop in-house guidance for the DPU team.

Our systems can be modified to reduce error. The data entry screens do not mirror the structure of the application forms increasing the probability of human error. We are in the process of looking at this from within the DPU team.

Inspectors did not always deal with variations promptly. Under the system at the time, inspectors would only know something was in their work queue if they looked at it as there was no alerting system. Inspectors are also out inspecting and may not have the ability to deal with something. We have implemented a system change that triggers an email telling an inspector when something has been transferred to them. This email also tells them the basics of the variation giving them an idea of the likely time required to deal with it.

Historically all variations have gone to the last inspector of the site. This is not always necessary - depending on the nature of the change. This process has now changed and variations are now initially sent to someone with the correct technical sign-offs who has office availability within the week. More complex sites may still require the last inspector to get involved but early evaluation of the variation helps to shorten the processing timeframes.

Going forward

Timelines have improved but there is more work to be done. The Process Licencing team and Inspectorate continue to work on this to improve the service provided. We continue to work with the DPU team with a specific aim of evaluating processes there

and will use this to build on what we think the modifications to our system are and the training we need to provide.

Hopefully in time applicants will see a swifter turn-around on submissions made concerning manufacturing authorisations.

5.2 Providing Authoritative Information

5.2.1 *The GMP Symposium agenda / The GDP Symposium agenda*

The 2018 GMP and GDP Symposia will take place from 19 to 22 November 2018 at the Novotel London West, Hammersmith, London. A further GDP day will take place in Glasgow on 27 November 2018.

Regarding the GMP days, the event will have a similar style as before. This year there are several key areas of significant change which form the core of the agenda, namely Brexit, Annex 1 and the Falsified Medicines Directive. Other topics have been selected in response to developments in the industry, such as the application of GMP to new technology and the session on Importation. As usual there will also be a session on deficiency data which this year will include information on the team's new approach to recording and trending deficiency data, and the additional clarity this will give.

The panel session, offering an opportunity for delegates to put questions to MHRA inspectors, will be expanded by offering two general panel sessions during the day. There will also be a specialist panel session on the topic of the Falsified Medicines Directive.

There will also be optional 'lunch and learn' opportunities for delegates who are interested in niche topics or don't want to spend all their time networking. These will be in the form of narrated slide decks showing in the main auditorium.

Regarding the GDP days, the theme of the symposium this year is 'change in an ever-changing world' which reflects the challenges faced by the industry in respect of the role out of the safety features element of the Falsified Medicines Directive and Brexit.

5.2.2 *Labs team Symposium*

The MHRA Laboratories team will be holding a symposium on 13 March 2019 at the Novotel London West, Hammersmith, London. The event is aimed at labs performing regulatory work across GLP, GMP and GCP.

Agenda items include: Practical Applications of Data Integrity for Laboratories; Quality Assurance & Quality Control; Parallel Sessions: Bioanalytical Method Validation & Quality Pick 'n' Mix - GXP laboratory hot topics; Forward Look & Inspectorate Updates. Panel Session and inspector surgery slots will also available.

More info can be found on the MHRA website https://mhralabs.co.uk

5.2.3 *Inspectorate Blog*

MHRA reported that the IE&S Inspectorate blog is one of the most subscribed blogs on the government platform with over 9000 subscribers and it had now surpassed one million views.

MHRA requested delegates to promote the blog within their networks and welcomed feedback and ideas for future blogs which delegates would find useful.

6. British Pharmacopoeia Update

6.1 Brexit

Reassurance was provided that the BP will continue to be part of MHRA's public health role. For background, the UK was a founding member of the Convention on the Elaboration of a European Pharmacopoeia and will continue to be a member of the European Pharmacopoeia (Ph. Eur) in any EU Exit scenario, as the UK will continue to be a member of the Council of Europe (CoE) in its own right. More specifically, the standards of the Ph. Eur will continue to be adopted in the BP and the UK, and we will continue to reproduce the Ph. Eur in the BP for the convenience of our users. Whatever the outcome, the BP will continue to add value to users in the UK, Europe and in the rest of the world through the provision of authoritative and high-quality standards.

6.2 Publication & reference standards

The BP 2019 was published on 1st August 2018, maintaining the earlier publication date to give users an additional month to prepare for implementation. It becomes legally effective on the 1st January 2019. The BP 2019 contains 33 new monographs including 6 specifically for the BP Vet.

This year, the majority of new BP chemical reference standards for monographs in the BP 2019 were available at the publication date, allowing users additional time to prepare for compliance ahead of the legally effective date.

6.3 Innovation & change projects

- Biological medicines: The BP biologicals team have been busy progressing actions since the biological strategy was published in October 2017. A working party has been established to explore alternative approaches, including class-based monographs, and the establishment of a further two working parties is on the horizon, for ATMPs and for raw materials.
- AQbD: The BP is nearing the end of an initial feasibility study to investigate the application of Quality by Design (QbD) principles to analytical methods. The aims of this project are to understand the principles in question and whether there was scope for application to the pharmacopoeia. A key aspect of this work has been the practical evaluation of QbD concepts in the laboratory. On completion of the study, the team involved will be making recommendations to the BP Commission. Following this, the intention is to publish the work and findings externally.
- New Analytical Technologies: One recently established project aims to improve how new analytical technologies are introduced into the BP, both in terms of supporting texts in the Appendices to facilitate adoption of techniques, and into the tests of the monographs.

7. Support for Innovation

- The number of enquiries received by the Innovation Office / Regulatory Advice Service for Regenerative Medicine (RASRM) (One Stop Shop) has continued to increase, now at approximately 680 with approximately 80 for RASRM. This has resulted in over 130 meetings. https://www.gov.uk/government/groups/mhra-innovation-office

- A Government call for innovative regulation initiatives has been made and an announcement is expected in December on the first anniversary of the life science sector deal. There will be initiatives from across the MHRA. In manufacturing, there will be a focus on point of care manufacture.
- links with others include:
  - MHRA/BP strategy (specialised ATMP working party), link with US on standards (and the Standards Co-ordinating Body etc)
  - Accelerated access – pathway / collaborative, Advanced Therapy Treatment Centres
  - EU: developments are taken forward to the
    - Innovation Network, an HMA working group
    - EMA's GMDP Inspector's Working Group, however meetings will be reduced and focused on key topics – see item 9.1.
  - ICMRA – MHRA is closely linked to the new work area on innovation which focuses on Horizon Scanning.
- MHRA continues to participate in the Medicines Manufacturing Industry Partnership (MMIP), the Regulatory workstream lead is changing from Andy Tudor (Pfizer) - the name of the new lead is to be confirmed.

8. Diversion of CDs - Update on Z drugs

MHRA Enforcement Group reported that its efforts to crack down on the diversion of Prescription-Only Medicines (POMs) onto the black market continued to be effective.

Review of the latest data collected from wholesalers suggests that diversion from the legal supply chain is decreasing. However, it is still occurring, particularly for Zopiclone. Illegal websites controlled by Organised Crime Groups appear to be the key driver.

Analysis completed on medicines available on the Dark Web suggests that dark web websites do not appear to be a threat to the licensed supply chain as UK licensed products are not widely available.

Diversion of medicines used to make 'Purple drank' remains an issue.

As due diligence has been tightened there has been a corresponding increase in Social Engineering, Phishing and email-spoofing to try and obtain products. MHRA encouraged members to remain vigilant especially regarding direct theft of medicines during transport which also appears to be on the rise.

9. Feedback from the EMA

9.1 GMP/GDP Inspectors Working Group (IWG)

MHRA discussed the current work of the Inspectors Working Group:

As part of their relocation to Amsterdam, the EMA has implemented phase 3 of its business continuity plan, focussing on legal requirements and core public health functions.

The EMA inspection programme will continue, as it is linked to legal obligations and product focussed.

EMA activities 'on hold' until June 2019 will include face to face working group meetings and most EMA coordinated guidelines work. There are exceptions for issues related to Brexit, serious public health issues and seven key guidelines across all working groups. Three of the seven relate to the GMDP IWG, and the UK is continuing to support this work:

- Annex 1
    - 6200 comments from 140 contributors
    - Revision to be considered by IWG in December
- Annex 21
    - Technical content has been drafted, but consultation cannot take place until the Commission has confirmed the position regarding the definition of importation.
- GMP for MAH reflection paper
    - Draft circulated to IWG and QWP for comment

Any documents currently under consultation will be extended to June 2019. The impact to GMDP IWG is as follows:

– There will be no face to face meetings until at least Sept 2019;

- Some meetings may take place as teleconferences, limited to work continuing under the business continuity plan;
- The Compliance Group will be continued in a virtual (TC) environment; the audit programme will continue to support the completion of the US-EU MRA;
- Work listed in the 2018 and 2019 IWG work plan on guidelines other than Annex 1, Annex 21 and the GMP for MAH document may continue without EMA coordination, provided that individual National Competent Authorities have resources to coordinate the drafting groups independently. There would be no adoption (Compilation of Community Procedures or changes to GMP) until EMA recommences support to this activity post-relocation.

9.2 Work on the continuous supply of medicines

MHRA reported on the work coordinated by EMA/HMA regarding the availability of authorised medicinal products. A 2-day workshop was held on 08-09 November 2018, the third such workshop in recent years, which brought together the National Competent Authorities and various stakeholders. Concrete proposals were put forward including guidance for MAHs and a harmonised definition for what is meant by a 'medicines shortage'. The implications of Brexit on the continuous supply of medicines were also discussed and further work in this area will need to be carried out. A video recording of the meeting along with the presentations can be found on the EMA website: https://www.ema.europa.eu/en/events/heads-medicines-agencies-european-medicine-agency-workshop-availability-authorised-medicines

MHRA also encouraged members to review the robustness of supply lines and challenge them where necessary, making sure that contingency plans are in place to ensure continuity of supply.

10. Falsified Medicines Directive (FMD)

MHRA reported on matters relating to the FMD:

Safety Features

The public consultation on the flexibilities within the Delegated Regulation on Safety Features closed on 23 September, with more than 50 responses received from a wide range of stakeholders. Analysis of all consultation responses is currently underway with the aim to publish the final Government response later this year.

All stakeholders impacted by the implementation will be able to find guidance related to their position in the supply chain of medicines in the UK, whether produced by the Government or stakeholder-led, through Gov.uk: https://www.gov.uk/government/consultations/implementing-safety-features-under-the-falsified-medicines-directive

Further guidance will be issued by the Government in the coming weeks.

MHRA responded to queries from members including whether it would be possible for a manufacturer (either MIA holder under contract, or MS holder) to decommission whole over-labelled packs on behalf of the NHS hospital/pharmacy they carry out the activity for. MHRA confirmed post meeting that Article 23 which provides the flexibility to accommodate decommissioning for others refers to persons authorised or entitled to supply medicinal products to the public who do not operate within a healthcare institution or within a pharmacy. Hence the manufacturer that over labels the original licensed pack would not be able to decommission the pack in this scenario.

11. International Interactions

MHRA reported on the Inspectorate's recent international activities:

11.1 *EU-USA Mutual Recognition Agreement*

The Compliance Group (CG), continues to coordinate the EU GMP inspectorate audits through the Joint Audit Programme (JAP) which the FDA observe as part of the assessment of National Competent Authorities (NCAs). The CG also provides the US with the audit reports, CAPAs and other information in capability packages for FDA to assess. All audits are now complete of human-only and combined NCAs.

Currently 15 NCAs are confirmed as equivalent and which the FDA can rely on, a further 6 NCAs are due to be added on 1st Dec 2018 and a further 8 by July 2019.

Vet-only agencies' JAP audits have started with the UK's VMD and the French NCA being the first to be audited.

Periodic meetings between the EU and US continue where a key focus is the development of metrics on the progress of the MRA.

11.2 *International Coalition of Medicines Regulatory Authorities (ICMRA)*

MHRA confirmed that the GMP workstream - which had been looking at whether increased reliance can be placed on other Inspectorates' inspection outcomes as part of risk-based inspection programmes - had now been transferred to PIC/S. An SOP was issued in June earlier this year. See also item 7 for ICMRA's new work area on innovation focusing initially on horizon scanning.

11.3 *Pharmaceutical Inspection Co-operation Scheme (PIC/S)*

Involvement with PIC/S has continued through chairing various working groups and Expert circles and attendance at the Annual seminar in Chicago where MHRA ran a workshop on risk related to raw material and contract services and gave presentations on Inspector safety. This latter topic has also been a focus within the Inspectorate and wider Agency this year with all GMP Inspectors attending a 3-day hostile environment awareness training course.

12. Any other business

None to report.

13. Date of next meeting

To be confirmed.