Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

GMP/GDP Consultative Committee
Note of Meeting

2nd May 2018, 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 2nd May 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)
The Cogent Group
BioIndustry Association (BIA)
Association of Pharmaceutical Specials Manufacturers (APSM)
National Office of Animal Health (NOAH)
Proprietary Association of Great Britain (PAGB)
British Association of European Pharmaceutical Distributors (BAEPD)

1. Introduction

MHRA welcomed current and new representatives to the meeting.

2. Minutes of the last meeting and Matters Arising.

The minutes of the last meeting held on 10th October 2017 were agreed. There were no matters arising

3. Brexit

Agency update

MHRA reported that the UK's position on medicines and medical devices regulation remains clear. The Agency aims to retain a close working partnership with the EU to ensure patients continue to have timely access to safe medicines and medical innovations. The Agency is committed to continuing a close working relationship with the European Medicines Agency (EMA). This was reiterated further by the Prime Minister in her Mansion House speech of 2nd March 2018, where she confirmed that

the Government would like to explore with the EU the terms on which the UK could remain part of EU agencies, such as the EMA.

The three principles that underpin negotiations for the UK's future relationship are that patients are not disadvantaged, industry is able to get their products into the UK market as quickly and simply as possible and the UK continues to play a leading role in promoting public health. These were set out by the Health Secretary, Jeremy Hunt, and Business Secretary, Greg Clark, in their letter published in the Financial Times on 4th July 2017.

Furthermore, on 19th March 2018, David Davis confirmed that the UK and EU have agreed a fixed implementation period of 21 months, lasting until December 2020.

During this time, access to each other's markets will continue on current terms, providing certainty for businesses and citizens across the EU and UK and time to prepare for the future. Industry can continue to operate and invest with confidence, as the design of our future partnership with the EU becomes clear.

4 Agency update

4.1 Changes within MHRA

MHRA reported that Dr Sam Atkinson has been appointed as Director of IE&S Division following the retirement of Gerald Heddell at the end of March 2018.

4.2 Accommodation move

MHRA reported that the current offices at BPR is to move to 10 South Colonnade, Canary Wharf, London E14 4PU in June 2018.

4.3 Operational transformation

MHRA reported that as part of the continued commitment to deliver a high-quality service to our customers, stakeholders and partners, the Agency is embarking on a major Operational Transformation Program (OTP) across all three of our expert centers – the MHRA regulatory centers, the National Institute for Biological Standards and Control (NIBSC) and the Clinical Practice Research Datalink (CPRD). This includes significant investment in our digital capabilities and infrastructure.

Since embarking on the program, the Agency has carried out a series of awareness campaigns such as asking stakeholders to take part in a Customer Survey held in September 2017, has held presentations at the MHRA Symposia as well as organised stakeholder meeting or engagement workshop with the Medicines Industry Liaison Group (MILG).

The MHRA reported on the aim of the Operational Transformation Program (OTP), the Case for change, Strategy into action, Mapping our processes, Progress so far, and the Next steps.

MHRA reported that it is currently facing a period of unprecedented change at the Agency linked to Brexit, relocation of our head office to Canary Wharf, and a major

upgrade to its IT and operating systems. The OTP is designed to ensure the MHRA retains its position as a leading Agency at a time of considerable change and are best placed to meet developing customer needs. The aim of OTP is to revolutionise the way it works by redesigning, realigning and improving its functions and operations to maximise public health impact and to optimise its role in the health system. The objective is to ensure services are delivered in a way that demonstrates best value for money, in terms of cost, service quality and ultimate impact on public health, based on a broad external understanding of the opportunities, challenges and capabilities on which to base the Agency's future direction.

Whilst there are specific activities and deliverables required by the OTP, the Inspectorate are using the program as an opportunity to identify and review all key Inspectorate business processes with the aim of harmonising the way the Inspectorate works and to implement best practice across all areas of GXP.

The Inspectorate have published a recent blog on OTP. A full report can be found on https://mhrainspectorate.blog.gov.uk/2018/03/22/operational-transformation-programme-an-inspectorate-view/

5. Inspectorate update

5.1 Operational

5.1.1 *GMP staff changes & recruitment*

The GMP Inspectorate recruitment campaign that was ran in December 2017 has resulted in 3 offers being made with the possibility of a further 2 which are yet to undertake the assessment centre. The new recruits start during the months of June and July 2018.

5.1.2 *Stakeholder engagement*

The IE&S Division supports 46% of all speaker requests that they receive. Specifically, for GMDP, the Division has received 56 speaker requests over the last financial year (April 2017- April 2018) and supported 46 of those. Going forward, the Agency will be looking at processes in which it can manage the inspectorate requests to ensure pro-active engagement.

Inspectorate questionnaire Feedback

The MHRA reported that the Inspectorate questionnaire Feedback was last conducted in 2010 - 2012, and questionnaires were emailed to those organisations recently inspected with questions requesting specific feedback from the inspection process.

The Inspectorate questionnaire Feedback will be re-implemented across the inspectorate. Tools such as Survey-Monkey will be used to keep responses anonymous and results, actions and improvements will be communicated to stakeholders through the Inspectorate blog.

5.1.3 *GDP team update and changes*

The GDP Inspectorate is in the process of advertising positions for new GDP inspectors.

Richard Andrews has taken the role of Unit Manager Inspectorate Operations, and two vacant positions for GDP Operations Manager have been filled by Bernadette Wilson and Claire Glenister.

5.1.4 *GDP Working with Enforcement*

The MHRA responded to questions from the delegates about current enforcement issues such as unusual sale patterns, mainly focusing on the rising trend of the purchase of Codeine Linctus and the use of it in the product referred to as “Purple drank”, also known as ‘LEAN’ or Sizzurp’.

Codeine Linctus is being mixed with other liquid medicinal products such as promethazine or dextromethorphan, purchased over the counter from a pharmacy or via prescription and online, as well as mixed with soft drinks and fruit-flavoured sweets to improve taste, and is being used recreationally by young people.

When these medicines are mixed together to create ‘purple drank’, users can easily lose track of how much of the active drug they have consumed as the liquid is masked by pleasant or familiar flavours from soft drinks. The effects will vary depending on the contents of the drink. However, users have reported euphoric and dissociative effects. The ability to drive may be also be impaired, and young people have complained of ‘memory problems’ after taking the drink. There is a risk of overdose particularly due to the use of codeine, which may be increased when taken in combination with alcohol.

5.1.5 *Specials manufacturers, short notice inspection programme*

In March 2018 MHRA announced that 7 days notice would be given for all holder of MS licences. Inspectors have noticed an increasing trend of sites not implementing corrective actions or completing commitments previously given to the agency until they had received notification of an inspection. The reduction in the notice period is intended to prevent this type of behaviour.

The 7 day notice period applies to all licence holders where the majority of their work is conducted under the MS licence. Sites which predominantly operate under and MIA or MIA(IMP) but also hold an MS licence will continue under the existing notice periods. However, it was re-emphasised that the Agency has the right to inspect any licence holder at short or no notice.

5.1.6 *Specials Q&A*

The Specials Q&A is currently under revision. When this process is completed a decision is to be made regarding the level of consultation with stakeholders.

5.2 Providing Authoritative Information

5.2.1 *Agency Symposia W/C 20 November.*

The GMP Symposium agenda / The GDP Symposium agenda

MHRA reported on the GMP and GDP Symposia.

The 2018 GMP and GDP Symposia will take place from 19 to 22 November 2018 at the Novotel London West, Hammersmith, London. This year the event days are Monday to Thursday rather than Tuesday to Friday – the sequence of GDP, GMP, GDP, GMP is not changing.

It was reported that both GMP and GDP are at the early stages of planning the event, however at this stage GMP is planning to cover a range of regulatory updates including Brexit, FMD and updates to EU GMP. The theme of the event is planned to be Global Supply Chains, incorporating a range of related topics.

In response to delegate feedback some minor changes are planned for the format of the event relating to the lunch and learn sessions, targeting of case studies to different sectors, and inspectors' surgery.

As for the GMP event, the GDP agenda is likely to include regulatory updates on Brexit and FMD, as well as exploring a range of current trends and topics incorporating feedback from the 2017 Symposium. No significant changes are planned to the format of GDP days as feedback indicated that delegates were satisfied with the current arrangements.

Labs team Symposium

The MHRA Laboratories Symposium event took place in Leeds on the 27th February 2018 and had a total of approximately 220 attendees. It covered GLP, GCP and GMPQC labs with generic applicable to all GxP in the morning and GxP specific streams in the afternoon. The GMPQC session was run by Christine Grey and Lesley Graham and included critical thinking for OOS investigations with a workshop aspect.

The labs team within the inspectorate are responsible for inspections of all commercial independent GMP testing labs alongside the GLP programme for pre-clinical testing and stand-alone laboratories performing analysis of clinical trial samples.

This was the first time the labs team have run their Symposium to include GMP labs with previous large events only catering for GLP and GCP.

It was reported that 62 delegates opted for the GMP stream. In addition to attendance by delegates from the independent QC testing labs, the session was attended by manufacturers from big pharma, consultancy firms, the NHS and the Welsh Blood Service.

The GMP stream rated highest on feedback of the 3 streams. The plan is to include a GMPQC stream at future events.

5.2.2 *Data Integrity Guidance – Update*

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

The Agency issued the GXP DI Guide earlier this year in March 2018. Comments received to date have been favourable and now the team are also concentrating on other data submitted to the Agency and working with Licensing Division on systems and training regarding how to identify data fraud.

Pharmaceutical Inspection Co-operation Scheme (PIC/S)

MHRA reported that the PIC/S guidance is for inspectors, however the Committee is conscious that the industry will have access to this and is considering consultation.

5.2.3 *Inspectorate Blog*

MHRA reported that the IE&S Inspectorate blog is the most subscribed blog on the government platform with approximately 7000 subscribers. The most popular posts have approximately 20,000 hits. The Division has published 112 posts since June 2015 and aims to publish one post every two weeks.

Posts in the pipeline include:

- RP assessment
- Transport security
- Risk based decisions on temperature excursions and manufacturer stability data
- Primary packaging
- Licence changes
- Sterile manufacturing
- QP use of remote certification
- Testing – inappropriate locations

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

5.2.4 *Proposal for industry-MHRA collaboration to refine and evolve compliance guidance – JPAG update*

It was agreed that prior to the next Consultative Committee meeting a request would be made to see if there was any topic of value that would benefit from a collaborative discussion amongst the interested parties to assist with any guideline/standard/monograph drafting.

5.2.5 *GDP transport issues*

MHRA reported that although in the past there has been some ambiguity for a number of years now it has been a requirement that medicines travel within the conditions referred to on the label.

Considerable work has been done by all main line UK wholesalers to introduce temperature-controlled vehicles to deliver both cold chain and ambient products. This has involved considerable investment but the fleets are achieving a high level of GDP compliance.

During the cold spell in December it was identified on inspection that uncontrolled trunking units were being used to move medicines when external temperatures were around minus 6 degrees C. The conditions inside the vehicles were unknown as they were not monitored however subsequent tests revealed that temperatures were unlikely to be substantially different to external conditions. Some products being transported were “do not refrigerates” with a minimum temperature range of 8 degrees C. Some of these products were subsequently recalled as a result of the potential impact of the low temperatures encountered during transport. Due to the necessary rapid re-organisation of delivery networks there were some reports of shortages in NHS facilities.

In response to this a six week study at one distribution centre has demonstrated deliveries from manufacturers and wholesalers arriving on uncontrolled and unmonitored transport on more than 250 occasions.

The GDP team have now put a project team together to consider the issues associated with the UK pharmaceutical transportation network both from a perspective of potential temperature issues but also of security. It is the intention that the team will initially do more work to more fully understand the issues and risks surrounding transportation and their potential impacts with a longer term view to work with industry to improve compliance in this area.

6. British Pharmacopoeia Update

MHRA reported that the content for the British Pharmacopoeia (BP) 2019 is being finalised. This is expected to be released in August 2018, 4 months prior to its legally effective date. The 2019 edition will contain 30 new and 117 revised monographs, including 1 new and 10 revised BP(Vet) monographs.

6.1 <u>Stakeholder engagement activities</u>

MHRA reported that the official response to the Agency public consultation on the strategy for pharmacopoeial public quality standards for biological medicines was published in October 2017 and is now in the process of being implemented.

The consultation and responses emphasised the value of pharmacopoeial public quality standards and the valuable contribution the MHRA is able to make through its incorporation of regulatory, BP documentary and NIBSC physical standard setting functions.

The strategy laid out collaborative and knowledge building approaches to be used to achieve this, recognising the importance of industry stakeholders as well as other international regulatory and peer organisations.
https://www.gov.uk/government/consultations/strategy-for-pharmacopoeial-public-quality-standards-for-biological-medicines

An official response to the BP consultation on dissolution testing in finished product monographs is expected in July 2018, following consideration of the responses by the Pharmacy Expert Advisory Group and BP Commission. This response will summarise the proposed actions which will be taken in response to this consultation.

6.2 BP Expert Membership

The membership of BP Expert Advisory Groups, Panels of Experts and Working Parties includes representation from a wide range of stakeholders in the public sector, industry and academia.

Serving four-year terms, members support the development of the BPs technical content, collaborating in its development and providing challenge where appropriate.

The current terms of office for all members of BP groups will end on 31st December 2018 and a comprehensive review of expert membership will take place this autumn.

In advance of this, an announcement will be made inviting expressions of interest from stakeholders to joining specific groups, who will supplement members wishing to be reappointed.

Historically, the BP has made these announcements via its website and through its members, but this year it will also use additional channels built up by the Agency, including this committee, with a view to reaching as many interested parties as possible.

MHRA encouraged delegates to consider if this would be something of interest and to circulate the invitation to any members who may be interested.

7. Defective Medicines Report Centre (DMRC)

7.1 Staff changes

Sandra Bax (DMRC manager) has recently retired from the team. Her post is being advertised and members of the committee or relevant contacts are encouraged to apply. The team currently consist of Alison Bunce, Graham Matthews and Catherine Pitt.

7.2 Feedback from members/stakeholders about DMRC Guide to defective medicines and reports received.

DMRC was involved in activities at a European level to harmonise approaches for assessment of defective medicines reports by competent authorities.

7.3 Feedback on harmonisation on EMA

As part of this work a harmonised template for pharmaceutical companies to use to report defects to competent authorities and the EMA was being rolled out across Europe. The template has not been formally adopted in the UK but this might form part of a wider revision to the MHRA website Guide to Defective Medicinal Products https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/403210/A_guide_to_defective_medicines.pdf.

An email will be sent to members of the committee to request feedback on the current Guide to Defective Medicinal Products, to be taken into consideration as part of this revision.

8. Support for Innovation

MHRA reported that it continues to support innovation and gave an overview on activities and enquiries for the MHRA's Innovation Office and the UK Cross-Agency 'One Stop Shop' where the total number of enquiries exceeds 600.

MHRA Innovation Office provides a single point of access to expert regulatory information, advice and guidance that helps organisations of all backgrounds and sizes develop innovative medicines, medical devices or novel manufacturing processes.

The Innovation Office celebrated its 5-year anniversary in March 2018.

The links to other innovation support mechanism was also noted – principally the EU's Innovation Network and ICMRA's recent new work programme on innovation.

9. Diversion of CDs Update on Z drugs

MHRA reported that its efforts to crack down on the diversion of Prescription-Only Medicines (POM) onto the black market are working, as recent figures highlight a drop in large scale orders of prescription medicine.

MHRA has analysed bulk orders of diverted medicines between January - May 2017 compared to January – May 2016. The figures show:

- trading of Diazepam is down by 64%
- trading of Nitrazepam is down by 24%
- trading of top strength Temazepam is down by 20%
- trading of Zolpidem is down by 14%.

The Enforcement Unit is running 17 active investigations, and it is disrupting organised criminal networks diverting medicines from the legitimate supply chain onto the illegal market. 44 arrests have been made so far, for offences such as possession with intent to supply a controlled drug, and offences under the Proceeds of Crime Act.

10. Feedback from the EMA

10.1 GMP/GDP Inspectors Working Group (IWG)

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

- Annex 1 (Sterile products) the consultation is closed. 140 responses were received and over 5000 comments were given.

- Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) 536/2014 of the European Parliament and of the Council by specifying principles and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections is applicable as from the date of entry into application of Regulation (EU) No 536/2014 on Clinical Trials.

- Commission Directive (EU) 2017/1572 of 15 September 2017 supplementing Directive 2001/83/EC of the European Parliament and of the Council as regards the principles and guidelines of good manufacturing practice for medicinal products for human use is applicable as from the date of entry into application of Regulation (EU) No 536/2014 on Clinical Trials.

- Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products. ATMP manufacturers should comply with these Guidelines no later than 22 May 2018.

- Revised Q&A on shared facilities (HBEL guidance) have been published http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/01/WC500219500.pdf

- The Q&A on Annex 16 'unexpected deviations' is to be considered for:

    - Defining 'registered specifications' and 'unexpected'
    - Multiple batch certification

- GMP will be considered for changes regarding shortage mitigation.

- Continuity of supply following GMP non-compliance – the consultation regarding SNC format is available now (3/4/18-15/5/18)
http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500246646&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

- Work on GDP serious non-compliance will follow a common approach

11. Qualified Persons project update

It was considered that the work already conducted had answered the original questions posed in the project charter. The data indicated that the existing number of QPs and training pathways were appropriate were able to meet current industry demands. However, it is acknowledged that certain niche areas such as ATMP and

NHS may have specific issues. It was suggested that if it was considered necessary separate projects to look at these niche areas may be considered.

12. Falsified Medicines Directive (FMD)

MHRA reported on matters relating to the FMD:

Safety Features

The UK is obligated to implement the Delegated Regulation on safety features because the deadline for doing so falls before the UK's exit from the EU.

MHRA expects to publish a consultation in the coming weeks and appreciates this has been eagerly awaited by stakeholders across the sector, many of whom have been engaging actively with DHSC and MHRA for several years. This time has been used to better inform the positions contained within the consultation.

MHRA reported that the consultation only focuses on a small number of flexibilities within the Delegated Regulation; stakeholders impacted by these changes should have been able to develop their implementation plans. MHRA reported that they are conducting a focused impact assessment as the Agency are only consulting on those areas where the UK has legal flexibility to make policy decisions. All other parts of the Delegated Regulation must be implemented regardless.

13. International Interactions

MHRA reported on the Inspectorate's recent international activities:

13.1 *EU-USA Mutual Recognition Agreement*

An update was given on the EU-USA Mutual Recognition Agreement (MRA) and that 12 Member States have been fully assessed by the US-FDA.

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

A brief update was provided on the work of ICMRA. In particular this focussed upon the finalising of the GMP project and the handover of this work to PIC/S.

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

An update following the last PIC/S committee meeting was given. Fuller details on this are available at the MHRA Inspectorate blog- https://mhrainspectorate.blog.gov.uk/2018/05/09/pic-s-press-release-following-april-2018-meeting/

14. Any other business

GDP Inspectorate reported that it would be canvassing the members to review the structure of the meeting with a view to making it more relevant to all attendees and to

raise and/or separate out the GDP element.

15. Date of next meeting

TOA 2018