Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

GMP/GDP Consultative Committee
Note of Meeting

10th October 2017, 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 10th October 2017:

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)
Veterinary Medicines Directorate (VMD)
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)

1. Introduction

MHRA welcomed current and new representatives to the meeting.

2. Minutes of the last meeting and Matters Arising.

Minutes

The minutes of the last meeting held on 31st March were agreed.

Matters Arising

> *5. Members enquired if the Inspectorate organogram is available on the MHRA website. MHRA explained that since the move to GOV.UK, the organogram has not been available. MHRA agreed to check the policy regarding organograms internally with the Comms division and publish a blog or circulate the organogram if possible.* ***ACTION: MHRA***

MHRA reported that the Inspectorate organogram is now available on the MHRA Blogg.

5.2.6 Members of the MHRA Inspectorate and industry members provided support for the proposal and it was agreed that MHRA would set up a meeting in around 3 months' time to discuss the matter in more detail. JPAG suggested they would try and engage with other industry members of the committee prior to such a meeting. ***ACTION: MHRA/JPAG***

MHRA reported a meeting has been held with JPAG and an update is on the agenda.

3. Brexit

Agency update

MHRA updated members on the Agency's position following the triggering of Article 50. UK medicines and device legislation flows from EU regulation. Going forward the main goal is to have a negotiated deal staying with the current system. Jeremy Hunt and Greg Clarke's July 2017 letter to the Financial Times called for a close alliance.

Leaving the EU will be a two parts process. The first part is withdrawal and progress is slow. This will be followed by a two-year transition period, where both sides will have to make the separation work. Currently there is lack of clarity. Consequently, government is working on a no deal position as a worse scenario.

The Withdrawal Bill, which is designed to ensure that the UK exits the EU with maximum certainty, continuity and control is moving to Committee phase. Withdrawal impacts placing on the market, movement of goods and people. Deep dive meetings have been held with industry. The purpose of these meetings is to try and work matters out. However, the lack of clarity remains.

Committee members advised that industry needs clarification and timings and is pushing in the EU arena to try to get the activity of lobbying concerns started.

The Agency continues to proceed with the implementation of the EU Clinical Trials Regulations and the Safety Features aspect of the Falsified Medicines Directive. However, both will depend on the outcome of negotiations.

4 Agency update

4.1 *Changes within MHRA*

MHRA reported Gerald Heddell Director of IE&S Division is to retire at the end of March 2018.

4.2 *Reappointment of MHRA Chairman*

Professor Sir Michael Rawlins has been re-appointed as Chairman of MHRA for a second three-year term commencing 1 December 2017.

4.3 *Move and operational transformation*

Move

MHRA reported that it is to move office to 10 South Colonnade Canary Wharf in the first half of 2018.

Operational Transformation

MHRA reported that it had embarked on an Agency-wide Operational Transformation programme, driven by its desire to explore how it can deliver more value within its remit of safeguarding and improving public health, both in the UK and internationally. In addition, the Agency needs to refresh its digital platform to achieve this ambition.

This will enable the Agency to reposition and shape its services in response to the changes in the regulatory, political, and economic environment, as well as ongoing technology developments.

The Operational Transformation programme's aim is to revolutionise the way the Agency works to maximise public health impact and to optimise its role in the health system. The aim is to deliver the following objectives:

- To deliver superior products and services across every journey our customers experience
- To improve the experience of our customers
- To provide flexibility to meet changing customer requirements
- To ensure services are delivered in a way that demonstrates best value for money

The Operational Transformation programme team has been working with stakeholders to see how they interact with the Agency. The MHRA thanked committee members that had constituents that took part in the process.

5. Inspectorate update

5.1 Operational

5.1.1 *GMP staff changes & recruitment*

John Clarke retired from the GMP Inspectorate in August 2017. George Collins, Ian White and Kevin Bailey have been successfully accredited to conduct inspections.

Ana Boban has joined the GMP Inspectorate. Ana Boban came from the Halmed, the Croatian medicines agency where she was head of the inspectorate group and an active inspector. Amongst her accomplishments she headed the team from Croatia for the successful PIC/S assessment process.

5.1.2 *Stakeholder engagement*

Diane Leakey has retired from the role of Inspectorate L&D Manager.

Sara Berry, GDP inspector has been newly appointed into an expanded role of Inspectorate Learning, Development and Stakeholder Engagement Manager.

This role has been created to support & co-ordinate the significant inspectorate effort/resource that is put in to working with stakeholders. The purpose of the role is to develop strategies for stakeholder engagement and the coordination of stakeholder interactions with the view to promoting and increasing regulatory compliance. The key responsibilities are to:

- Co-ordinate and manage Stakeholder engagement on behalf of the Inspectorate.
- Identify and implement strategies for improving compliance (to supplement the inspection process).
- Facilitate the delivery of GxP symposia.
- Educate and train stakeholders using multimedia tools i.e. through management of the Inspectorate blog.
- Manage the Inspectorate Speaker request process to ensure pro-active engagement.

5.1.3 *GDP team update and changes*

Steve Todd GDP inspector has retired. Phillip Neale Operations Manager is to retire in November 2017.

Sara Berry who has taken on the role of Training Manager has given up 50% of her role as a GDP inspector.

The GDP Inspectorate is in the process of advertising positions for two new Operations Managers. The GDP teams currently have 16 GDP inspectors.

5.1.4 *Inspections in high risk third countries*

The GMP Inspectorate introduced a new risk assessment system for inspectors in 2016 following the July 2016 terrorist attacks in Dhaka Bangladesh and following some staff nervousness after the previous incidents in Tunisia and India.

Inspectors have attended a one day Foreign safety and security awareness travel (FSSAT) course. However, this gave rise to more questions especially concerning some incidents the inspectors had witnessed first-hand and a want for better understanding in the event of an accident such as an RTA whilst in remote locations.

The Good Practice Inspectorate has been using an intelligence system to collate the risk assessments which dictates travel mitigation measures and planning for certain times of the year.

Following engagement with MHRA insurers the Agency became aware of their services for intelligence alerting, training and webinar services.

Many countries that the MHRA inspect in are considered high risk and the Inspectorate use some mitigation such as sending two inspectors or times of the flight arrival to be in daylight.

The Inspectorate also, following advice, sent inspectors on Hostile Environment Awareness Training (HEAT), tailored made to the needs of the Inspectorate.

For those countries in the 'elevated' high risk destinations the Inspectorate continues to evaluate the need for a physical inspection and the need to travel and if this could be fulfilled by an alternative method. Where this is not possible the Inspectorate is looking at new mitigation measures such as having a security expert accompany inspectors on inspection, which has occurred in Bangladesh recently where some facilities had already had their GMP certificate re-issued based on desktop inspections (permissible under the Compilation of Community Procedures) and were producing significant quantities of medicines on the DH list of medicines that are critical to patients.

5.1.5 *Periodic update meeting with VMD*

MHRA reported that it has a SLA between MHRA and VMD. The Veterinary Medicines Regulations (VMR) requires manufacturers, wholesalers and importers of veterinary medicines to be authorised and regularly inspected by the regulatory authority. Similar legal provisions apply to human medicines.

To minimise cost to the industry through possible duplication of effort, the MHRA undertakes certain authorisation and inspection activities on behalf of the VMD. These are where a site holds, or submits applications for, both human and veterinary authorisations. These sites are referred to as 'Combined Sites' throughout this SLA.

This SLA primarily deals with the VMD and the MHRA's responsibilities for authorisations and inspections carried out under the VMR. It also sets out arrangements for sharing expertise and information between the parties.

Six monthly reviews are carried out. MHRA and VMD met at end of August to discuss the SLA and its operation. No issues were identified and VMD recognised work conducted by the Inspectorate. The discussions included joint inspections forthcoming training activity and technical meetings and health and safety of inspectors when travelling.

5.2 <u>Providing Authoritative Information</u>

5.2.1 *Agency Symposia W/C 20 November.*

MHRA reported on the GMP and GDP symposia.

This year's GMP symposia will have a similar style as before. Risk management will be core to the event but it retains the core subjects that delegates want such as the regulatory updates. Whilst some delegates at previous events felt the breaks were too long, the networking opportunity was important to many delegates. To facilitate this there will be the optional 'lunch and learn' videos available.

This year's event will be held on the 21st to 24th November 2017 (GDP, GMP, GDP, GMP) at the Novotel London. There will be general sessions to help delegates develop understanding of:

- Organisational behaviour.
- Knowledge management.
- Critical thinking.
- Quality risk management.

There will be focussed sessions looking at application:

- Production (cross contamination, sterility assurance).
- Wider supply chain (material suppliers, contract laboratories).

There will also be:

- Regulatory Updates.
- Panel Q&A.
- Short video presentations during lunch on a range of topics.
- An updated interactive app which should be easier to use, with all interactive questions in the same place.

GDP Symposium

This year's GDP symposium will be based around two themes - Risk management and Transportation with updates on Enforcement trends, FMD and a look at the top five deficiency areas identified on inspections.

Risk Management and Transportation cover many different types of operations in the wholesaling world and are two areas which have shown significant levels of poor compliance. They were also identified as two subject areas which delegates at previous symposiums had asked questions about and also suggested as possible topics for future symposia.

As usual the Inspectorate will provide updated information and guidance on topical matters through a mixture of presentations, highly interactive workshops and inspector surgeries to address concerns and improve compliance in GDP matters.

5.2.2 *Data Integrity Guidance – Update*

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

Work on the draft guidance is ongoing. This has been a considerable amount of work due to the volume of comments made, some of which were conflicting depending on what GXP the comments came from. The expected delivery for the internal review is now by the end of November 2017, due to availability of the inspectors.

5.2.3 *Inspectorate Blog*

MHRA provided an update concerning the Inspectorate blog: (https://mhrainspectorate.blog.gov.uk/).

The Inspectorate blog now has 6800 subscribers. This is the most in Government and has seen a 15% to 20% growth rate.

MHRA welcomed feedback and ideas for future blog items including items on any joint MHRA-industry work.

5.2.4 *Behavioural Insight*

MHRA provided an update on the Agency's Behavioural Insight project – a project exploring the factors that affect wholesalers' levels of compliance with UK regulations.

The analysis of the literature review has identified three main types of non-compliers:

- Amoral calculators who are motivated only by profit. To influence this group MHRA would have to seek to reduce the expected cost of compliance, increase the expected risk of being caught during noncompliance, and/or increase the expected size of the penalty if caught.

- Moral objectors who disagree with the principle of regulations. To influence this group MHRA would examine the reasonableness of its rules or guidelines, the degree of trust in the MHRA and the extent to which responsible entities in the supply chain are believed to be doing their part in addressing the problem. The MHRA can also use trade associations to influence this group.

- Organisationally ineffectual businesses who do not have the knowledge or systems to comply. To influence this group MHRA should seek to understand the barriers to compliance within these businesses, and ensure that the MHRA itself is giving out clear and adequate information to enable compliance.

Work by HMRC provides an example of how the MHRA could conduct analysis on its own customer base. MHRA could look to develop a segmentation model using the following factors:

- awareness of obligations;
- motivation to comply with obligations;
- ability to comply with obligations; and
- opportunity not to comply with obligations.

Next steps - MHRA analysts will conduct semi-structured interviews with experts within MHRA, such as GDP inspectors. These interviews will be analysed to give an insight in to MHRA's customer base, and to explore to what extent the lessons in this literature review are applicable to MHRA.

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

JPAG's proposal for industry and MHRA to collaborate to refine and evolve existing compliance guidance or identify areas where guidance is required and can be developed is to be taken forward. MHRA met with JPAG in June to discuss. The next meeting will follow the Consultative Committee meeting to develop this further.

6. British Pharmacopoeia Update

The British Pharmacopoeia (BP) 2018 has been published. The new edition was released a month earlier than previous editions, giving a lead time of four months to the legally effective date. The planning is in place for an early August release date year on year. This 2018 edition contains 41 new and 191 revised monographs, including 6 new BP(Vet) and 4 new unlicensed medicines monographs.

BP Stakeholder engagement activities:

Members of this committee and their organisations where thanked for contributions to the BP customer insight survey and dissolution consultations, and to the Agency consultation on biological standards. The BP customer insight follow-up survey has been completed and the responses are under analysis. Outcomes from the first survey included improvements in the BP website; and earlier availability and improved stock levels of British Pharmacopoeia Chemical Reference Substance (BPCRS). The responses received during the BP public consultation on dissolution testing for solid oral dosage forms have been analysed. A future strategy has been drawn up as an outcome and the official response is planned for early 2018.

The MHRA biological standards consultation:

A good response has been received through the consultation on the MHRA strategy for pharmacopoeial public quality standards for biological medicines and the official Agency response is due for release towards the end of October. Stakeholders recognised the value of standards and innovation, and the unique position of the Agency with NIBSC, the regulatory function and the Innovation Office under one roof and the on-going collaboration between the centres.

The strategy is aligned with Government initiatives such as the Early Access to Medicines Scheme, the Regulatory Advice Service for Regenerative Medicines and the implementation of the Advanced Therapies Manufacturing Action Plan & Taskforce (ATMT). It is also aligned and complementary to UK Government proposals as outlined in the Strategy for UK Life Sciences and the Life Sciences Industrial Strategy. There will be further engagement and meetings once the official outcomes have been published and offers to collaborate will be followed up.

7. Support for Innovation

MHRA reported that it continues to support innovation.

The Innovation Office is MHRA's front door for innovation discussions with industry. Over 100 meetings have been held with industry to help innovative products move forward.

The Innovation Office applies to all 3 areas of MHRA. The little sister to the Innovation Office is the One Stop Shop for Advanced Therapies. This forum involves all UK regulators relevant to Advanced Therapies i.e. HTA NICE and Defra. This is like the FDA's OTAT Learn (Office of Tissues and Advanced Therapies; previously OCTGT

Learn), the Centre for Biologics, Evaluation and Research's (CBER) for industry education.

The Innovation Office and One Stop Shop for Advanced Therapies both feed into horizon scanning.

8. Diversion of Controlled Drugs Update

MHRA's GDP Inspectorate provided an update regarding the diversion of controlled drugs from the supply chain. Investigations currently occupy the special team set up in Enforcement and involves GDP inspectors when a WDA(H) holder may be inspected with a focus on known excessive ordering or sales figures for the drugs in question.

There are currently 19 active investigations covering 12 WDA(H) holding companies and 7 internet company enquiries. Most enquiries involve looking at over ordering issues for large quantities of the Z drugs compared to what is viewed as normal levels for the types of companies under investigation.

E mails were sent to all WDA(H) holders with the condition included for handling Narcotics/Psychotropic, with a request for sales figures. Out of approximately 600 Emails sent out, there is one third (200) who have not responded – which is causing some concern.

There are 3 prosecutions underway and a possible 4-6 planned in the future.

9. Feedback from the EMA

GMP/GDP Inspectors Working Group (IWG)

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

There was no further update to give on most of the items reported on at the last meeting, the majority of which are still subject to the completion of Union procedure.

Annex1 (Sterile products) is not at an acceptable standard for consultation.

Work on Annex 21 is still ongoing. Issues around fiscal importation which are open to different interpretation need to be resolved before it can be finalised.

The Q&A on the production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies is now available on the EMA website:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/08/WC500232814.pdf

10. Qualified Persons update

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 reported that it has been looking at the data generated by liaising with relevant stakeholders and the QP population via surveys and questionnaires to see how many new QPs are being registered and how many were leaving the industry and contributory factors. So far numbers of registered QPs have remained even.

Specific niche areas e.g. ATMP manufacturer may be an issue particularly for QP training and more focus is needed to look at niche areas.

The perception of a person starting their career as a QP, the barriers within an organisation and the ability to keep QPs when trained will be a contributing factor for developing QPs.

11. Falsified Medicines Directive (FMD)

MHRA reported on matters relating to the FMD:

Safety Features

The safety feature element of FMD is to apply by the 9 February 2019. The Agency is continuing with the implementation of the safety features element in parallel with any Brexit negotiations.

The UK Medicines Verification Organisation, SecurMed, is concerned with the cost for building the UK repository and wants the UK to underwrite any money spent should the need for the system be dropped.

SecureMed has held a FMD Communications Strategy workshop at the beginning of October and is to hold a further IT System Solution Provider web-cast workshop in November.

MHRA continues to work on the Consultation document.

Members of the committee involved with the supply of medicines advised that the member they represent are already investing in new technology to work with the safety features requirements despite their being a no deal. In addition, more emphasis needs to be put into communication as there are some stakeholders that are still not aware of the requirements.

12. International Interactions

MHRA reported on the Inspectorate's recent international activities:

12.1 *EU-USA Mutual Recognition Agreement*

The Mutual Recognition Agreement with the USA will come into voluntary force in three weeks' time (November). The US needs to have assessed each member state Inspectorate, by July 2019 for the agreement to come into full effect.

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

MHRA reported on the latest developments around the GMP project carried out within the International Coalition of Medicines Regulatory Agencies (ICMRA). The project aims to determine if it is feasible to take a risk-based approach to international

inspections, placing reliance on data provided by the site and by their national regulator to carry out desktop assessments rather than inspecting the site.

ICMRA's proposed framework document has been taken to PIC/S and is to be worked up into a PIC/s document by a PIC/S working group for consideration and agreement by the full PIC/S Committee. The finish PIC/S document will be voluntary for each PIC/S country to use.

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

A new PIC/S Chairman, Mr Boon Meow Hoe, from the HSA Singapore has been elected for 2018/2019. In addition, The PIC/S Committee elected Ms Anne Hayes HPRA Ireland as Deputy Chairperson for the same period.

The PIC/S Committee has invited the following countries to join the Scheme as from 1 January 2018:

- Mexico's Federal Commission for the Protection from Sanitary Risks (COFEPRIS).
- The Turkish Medicines and Medical Devices Agency (TMMDA).
- The Iran Food and Drug Administration (IFDA).

13. Any other business

None

14. Date of next meeting

TOA 2018