Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

GMP/GDP Consultative Committee
Note of Meeting
7th October 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 7th October 2016:

MHRA (Inspection, Enforcement & Standards Division)
Scottish Lifesciences Association (SLA)
Proprietary Association of Great Britain (PAGB)
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)
NHS Pharmaceutical QA Committee
National Assembly for Wales
Healthcare Distribution Association (HDA)

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 18th April were agreed.

3. Brexit

3.1 Agency update

MHRA updated members on the work the agency has carried out following the outcome of the EU Referendum:

A cross-agency taskforce has been set up which meets regularly to provide input and direction for the agency's Corporate Executive Team. The agency's current position statement is available at the following link:
https://www.gov.uk/government/news/medicines-and-healthcare-products-regulatory-agency-statement-on-the-outcome-of-the-eu-referendum

Various scenarios have been worked through and there has been wider stakeholder communication sent to key stakeholders in recent weeks explaining the work the agency is doing. In addition, the agency is liaising with other international regulators that act as sovereign regulators to better understand how they operate.

For each of the scenarios the group are exploring how the agency would be affected and how to move forward once the Government decides the direction of travel to take.

MHRA confirmed that there are no routine activities that have been put on hold as a result of Brexit.

3.2 Members update

Members reported on the respective positions of their associations and work carried out.

Numerous associations represented at the meeting had attended a series of life science workshops covering all aspects of Brexit, including manufacturing, quality and regulatory aspects.

One major concern for distributors is around the value of the pound in relation to import and export activities. In particular, the effect on parallel imports.

4 Agency update

4.1 Changes within MHRA

MHRA reported that the agency is close to agreeing a lease for a building in Canary Wharf with a view to moving there in Q1 2018.

4.2 Changes within I,E&S

MHRA reported on the Digital Service Transformation project.

MHRA's computer system known as sentinel is being replaced. This is part of an agency wide IT refresh project to transform the way IT supports the work of the agency, as the IT systems in some areas are no longer fit for purpose and will be unsupported going forward. Within I,E&S, we want to use this opportunity to understand our end to end process and question why we do things the way we do, in order to identify and implement improvements and efficiency gains. The IT kit we have available such as laptops and windows applications are also being updated which will make it easier to create, manage and access information. I,E&S are keen to engage with key stakeholders to receive feedback on how we can embrace technology more, in order to "future proof" the new systems and operating processes being developed. Members were asked to consider whether they would be willing to take part in a brainstorming workshop or survey monkey questionnaire as a means of capturing stakeholder input.

5. Inspectorate update

5.1 Operational

5.1.1 ***Inspectorate staff changes & recruitment***

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

GDP

The team still have a full complement of 18 inspectors. The 3 new inspectors mentioned at the last meeting are Newaj Khan, Peter Brown and Bernadette Wilson.

GMP

3 GMDP inspectors have been recruited since the last meeting - Kevin Bailey, Ian White and George Collins. In addition a specific GMP QC labs inspector has been recruited - Lisa Ottowell. Furthermore, the GMP Inspectorate are working closely with another new recruit - Saila Hanif - who recently joined the Business Support team. She has been helping with risk assessments for overseas inspections.

3 GMDP inspector vacancies remain. The next campaign will begin in December.

5.2 Providing Authoritative Information

5.2.1 ***Agency Symposia***

MHRA reported on the GMP and GDP symposia.

This year's symposium will begin with a one day GDP event on 23rd November 2016 in Glasgow and will be followed by a four day event taking place 6th – 9th December 2016 at the Novotel West, Hammersmith. The London 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.

GDP delegates should note that the GDP days of the London event will be a repeat of the material presented at the Glasgow event. Registration was initially restricted to those on the waiting list from previous years but is now open to all. Further details are available on the MHRA website: https://www.gov.uk/government/collections/mhra-conferences-and-events

5.2.2 ***Publications***

The Orange Guide

MHRA reported that it is on track to publish the 2017 editions of both the Orange Guide and Green Guide in January.

The Orange Guide has been updated with revised sections on:

- qualification of suppliers and customers;
- parallel importation and parallel distribution;
- temperature control and monitoring;
- UK legislation; and
- matters relating to unlicensed medicines.

There are also new MHRA sections on:

- GMP for Excipients;
- Guidance on revised Annex 16 of GMP; and
- MHRA Data Integrity definitions and guidance for Industry.

Revised Annex 15 and 16 are included.

Also included is new Commission guidance on;

- principles and guidelines of Good Manufacturing Practice for active substances;
- principles of Good Distribution Practice of active substances;
- setting health based exposure limits; and
- formalised risk assessment for ascertaining the appropriate GMP for excipients.

The EU regulation on safety features for medicines is added together with two Commission Q&As on:

- importation of active substances; and
- safety features for medicinal products.

There is also a new appendix on sources of useful information.

<u>The Green Guide</u>

The Green Guide has revised sections on:

- qualification of suppliers and customers;
- controls on certain medicinal products;
- parallel importation and parallel distribution;
- the application and inspection process for new licences “what to expect”;
- updated UK legislation; and
- temperature control and monitoring.

There are also new sections on:

- the guidelines on principles of Good Distribution Practice of active substances for medicinal products for human use (2015/C 95/01);
- matters relating to unlicensed medicines;
- sourcing and exporting medicinal products – non-EEA countries;
- data integrity; and
- the EU regulation on safety features for medicines.

Two Commission Q&As have been added:

- importation of active substances; and
- safety features for medicinal products.

There are also two new appendices on:

- sources of useful information; and
- licensing requirements for import into the UK and export from the UK including introduced medicine – wholesale supply only.

5.2.3 ***Data Integrity Guidance***

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

There are a number of guidance documents currently in the public domain written by various regulatory authorities:

- MHRA guidance
- WHO guidance
- FDA draft Q&As
- EMA Inspector's Working Group Q&As

Whilst the documents cover different areas, they are convergent in their expectations.

MHRA co-chairs the PIC/S group on data integrity. The group have published a guideline in draft format which is primarily focused on Inspectorates. It has been published with a view to greater harmonisation and the possibility of having a single harmonised document in future. The guideline is however, incomplete and it will be added to and amended over time.

MHRA currently has a GxP-focused data integrity guidance document at consultation stage. The guidance extends across the different GxP areas and is of particular relevance given the recent issues identified with some GCP data. MHRA reminded members that the deadline for comments is 31 October and endeavoured to provide an update at the next meeting on the outcome of the consultation.

5.2.4 ***GDP Projects Update***

MHRA reported on the various GDP projects that are ongoing.

There are 11 active projects linked to the I,E&S divisional business plan - internal projects for better ways of working, process improvements and a number of external projects.

External projects include ensuring closer co-operation and improved working with the Enforcement group and their new supply chain investigation team, ensuring the complexity of the UK supply chain is fully appreciated and considered when developing the FMD delegated act, working with other regulators, developing trending

on deficiency data and providing authoritative advice to exporters who are new to GDP.

5.2.5 ***Behavioural Insight***

MHRA's Head of Economics updated members on the Behavioural Insight project – a proposed project exploring what factors affect levels of compliance with regulators generally and more specifically, which of those factors affect the level of compliance by wholesalers with UK regulations. See Annex 1.

Members wishing to volunteer to be interviewed as part of the project can contact MHRA. Interviews will be conducted anonymously.

5.2.6 ***Stakeholder Engagement***

MHRA provided an update on Stakeholder Engagement. The Inspectorate place great importance on enhancing the methods they use to engage with stakeholders. To this end they have initiated a project which is designed to look at external stakeholder management and engagement. The primary objectives will be to help the Inspectorate better understand the needs of stakeholders, remove cross inspectorate duplication of effort and to provide greater focus in the Inspectorate's approach to engagement. A further update on progress will be provided at the next meeting.

6. Support for Innovation

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

- Innovation Office:
- applies to all 3 areas of MHRA,
- working very successfully
- now received approximately 360 enquiries (approx. 60% relating to medicines, 40% devices), a high proportion of those enquiries are GMP related.

- One Stop Shop:
- effectively a mini Innovation Office for Advanced Therapies.
- now received 30 enquiries.
- involves all UK regulators relevant to Advanced Therapies, not just MHRA.

- Providing input to the Medicines Manufacturing Industry Partnership (MMIP), principally on the Regulatory workstream.
- a workshop on regulatory flexibility is being held later in the month with the aim of having a position paper in place by the end of the year.

- Supporting the ATMP taskforce
- due to publish their report in November
- MHRA feeds into all three subgroups – (international competitiveness, manufacturing, and people & skills)

- House of Commons enquiry on ATMPs.

- our CEO will be giving evidence.

- GMP for ATMPs
- the Commission's consultation is now closed. MHRA has provided its comments back to the Commission.

7. Diversion of Controlled Drugs

7.1 MHRA's Enforcement group updated members on an issue that has come to light since the last meeting regarding the diversion of controlled drugs from the licensed supply chain. Specifically, Benzodiazepines and 'Z drugs' such as Zopiclone and Zolpidem – all in tablet form.

These medicines have been leaking from the licensed supply chain and made available for sale on the black market and on illegal websites. These products are Schedule 4 controlled drugs under the Misuse of Drugs Act. Significant amounts of genuine licensed packs of these products from various manufacturers have been seized and recovered throughout the UK and Ireland.

A number of scenarios have been encountered, including:

- Retail pharmacies ordering amounts much larger than can be dispensed.
- pharmacy places order with wholesaler for unusually large amounts, far more than they would need to meet normal demand.
- product delivered to pharmacy and immediately supplied to criminals.

- Fraudulent use of someone else's WDA(H)
- criminals placing orders using another company's details.
- deliveries made to the criminal's warehouse, not the WDA(H) address.
- supplier only realises after the delivery has been made.

- Orders placed for export to non-EEA countries
- criminals place order, purporting to be a company in non-EEA country.
- shipping is arranged by the customer and their agent picks up the medicines and delivers to the criminal in the UK

The majority of the investigations that the MHRA has opened concern the first model, i.e. diversion at pharmacy level. MHRA is working with wholesalers to gather data and to encourage them to report any unusual or suspicious activity, especially in relation to the products in question.

MHRA are also working closely with the GPhC and Regional CD liaison officers across the UK to address the matter.

MHRA asked members, both manufacturers and wholesalers, to be especially vigilant if receiving unusual orders for the products in question.

8. EFPIA Survey

8.1 ABPI presented slides regarding the most recent European Federation of Pharmaceutical Industries and Associations (EFPIA) survey. The scope of the survey is to identify the number, duration and expense (resource implications) of GMP/GDP inspections conducted at manufacturing sites of member companies and affiliates inside and outside the Regulatory Authority's own borders – with a view to identifying potential efficiencies that could be suggested in future. See slides at the following link for further information:
http://www.efpia.eu/uploads/EFPIA_2015_Regulatory_Inspections_survey-webpage_version_v1-short.pdf

In addition, the 2014 position paper on 'Enhanced Good Manufacturing and Good Distribution Practices (GMP/GDP) Inspection Efficiency' can be found at the following link:
http://www.efpia.eu/uploads/documents/EFPIA_Enhanced%20Inspection%20Practice%20-%20Final_v8a_19May2014.pdf

9. International Interactions

MHRA reported on the Inspectorate's recent international activities:

9.1 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 FDA are continuing to assess each EU regulator. The UK assessment has been finalised and the decision is now awaiting ratification. The current proposal is that the initiative would come into force at the end of this year on a voluntary basis for inspections carried out in member territories, with a view to making it a permanent requirement in two years including third country inspections within the scope.

9.2 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. The phase 1 implementation phase has now been completed and phase 2 will be starting later this year to expand the number of countries involved.
The proposal longer-term is for the operational phase to be transferred to PIC/S.

9.3 PIC/S

As part of MHRA's chairmanship of PIC/S in 2016/17, the UK hosted the annual PIC/S training seminar held in Manchester. Further information can be found on the Inspectorate blog:

https://mhrainspectorate.blog.gov.uk/2016/08/01/pics-press-release-and-news-of-mhra-hosted-meetings-and-seminar-july-2016/

9.4 Benchmarking of European Medicines Agencies (BEMA)

MHRA reported that a BEMA assessment of the agency will be carried out later in the month. 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 or inspection designed to identify non-compliance.

10. Qualified Persons

10.1 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 been looking at the data held internally on active UK QPs named on MHRA licences to try and ascertain what the current state of play is. Various issues have been explored including the 'QP retirement cliff' and whether or not QPs are being named on multiple sites due to a lack of available QPs.

See Annex 2 for slides.

Whilst there is no significant evidence from the data that a shortage of QPs exists, the matter requires further investigation. MHRA will report further at the next meeting.

11. Falsified Medicines Directive (FMD)

MHRA reported on matters relating to the FMD:

11.1 Safety Features

Post Meeting Note:

- The Agency in collaboration with the Department of Health is currently working to transpose the Delegated Regulation in the most pragmatic way, aiming for an overall solution which keeps burden to a minimum whilst realising the benefits of a more secure medicines supply chain.
- MHRA and DH are working with stakeholders to understand the challenges facing different elements of the UK supply chain and to take account of these views both within the Impact Assessment being developed and the corresponding legal instructions. We expect to go out to public consultation in early 2017. We understand that the new system brings additional costs to businesses, but are committed to working with all across the supply chain, to minimise these where possible, while delivering the FMD.

- Under the FMD provisions, manufacturers and marketing authorisation holders (MAHs) have to establish, fund and manage the verification system via a non-profit legal entity, an organisation they have called SecurMed in the UK. DH and MHRA have a supervisory, non-voting role on the board of SecurMed who are close to concluding the tender process to identify which of the three "blue print service providers" – companies pre-assessed at an EU level as having the capacity and skills to build national repositories – they would like to build the UK hub.

- Brexit: The UK remains a full member of the EU and for the immediate future it remains business as usual. We continue with our plans for full implementation of the FMD Safety Features.

12. Feedback from the EMA

12.1 GMP/GDP Inspectors Working Group

MHRA presented slides on the current work of the Inspectors Working Group. See Annex 3.

13. Any other business

13.1 Desktop Assessments

MHRA reported that GDP desktop assessments are ongoing. Currently only multiple pharmacy WDA(H) sites are within the scope of the project. It may in future be extended to some GSL only sites.

13.2 Publication of Inspection Findings

MHRA reported that the Inspectorate are considering publishing all inspection findings (redacted) on the MHRA website.

14. Date of next meeting

March**/**April 2017