Regulatory & Pharma News Update May 2018

REGULATORY NEWS

MHRA Publishes GCP Inspection Metrics Report

On 11 May 2018 the Medicines and Healthcare products Regulatory Agency (MHRA) published their GCP inspection metrics report covering the period from 01 April 2016 to 31 March 2017. During this period, a total of 99 GCP inspections were undertaken by the MHRA GCP Inspectorate as follows:

Type of organisation inspected	No. of inspections reported	No. with ≥ 1 critical finding	Critical finding categories	No. with ≥ 1 major finding	Major finding categories (>10%)
Non-commercial	8	1 (12.5%)	• Oversight of CTIMP	7 (87.5%)	• Quality system • Monitoring
Commercial sponsors	15	7 (46.7%)	• Pharmacovigilance • Record keeping/essential documents • Monitoring • Data management • Data integrity	All (100%)	• Pharmacovigilance • Record keeping/essential documents • Data integrity
Contract Research Organisations (CROs)	8	2 (25%)	• Computer systems validation • Record keeping/essential documents	7 (87.5%)	• Record keeping/essential documents • Quality Assurance • Project/Trial management • Computer systems validation
Investigator Sites	24	1 (4.2%)	• Subject eligibility	14 (58.3%)	• CRF data/source data • Quality system • Medical/Principal Investigator oversight
Phase I Units	12	0	N/A	5 (41.7%)	• Quality system

Author: Karen Martin

Date of Issue: 16 May 2018

					• Training • Medical/Principal Investigator oversight • Medical oversight • Insurance • Dose escalation • Computer systems validation
UK Lab Facilities	15	No data	No data	No data	No data
Non-UK Bioequivalence & EMA Inspections	15	No data	No data	No data	No data

A summary of critical inspection findings is detailed below:

Commercial sponsors – 10 critical findings were reported from 7 organisations, as follows:

- Pharmacovigilance (4)
    - Use of unapproved Reference Safety Information (RSI)
    - The MHRA approved RSI in effect at the time of occurrence of a serious adverse event (SAE) was not being used to perform expectedness assessments as required by CT-3 guidance, resulting in under-reporting of SUSARs and inaccurate information being reported in the DSUR
    - The pharmacovigilance processes used by the sponsor resulted in a failure to comply with the terms of the Clinical Trial Authorisation (CTA).
    - There was significant potential for SUSARs to go unreported through several failing processes.
- Record keeping/essential documents (2)
    - The TMF was presented in paper but did not contain all essential documents required to enable reconstruction of trial events and demonstrate compliance with the regulations and the organisation's own quality system. Several essential documents were retained within different electronic systems which were not defined as part of the TMF and to which the inspectors were not provided direct access.
    - Requested documents could not be located in the eTMF, documents were not filed consistently, many documents were missing from the eTMF, and audit trails revealed that a large number of documents had been uploaded following receipt of the inspection notice.
- Monitoring (2)
    - The sponsor failed to ensure sufficient and robust monitoring leading to data integrity issues.
    - Monitoring had failed to identify the recruitment of ineligible subjects.
- Data Management (1)

- Electronic Patient Reported Outcome (ePRO) devices did not have an audit trail to verify when entries were made and by whom; incorrect data in the ePRO could not be changed but was being used for the analysis.

- Data Integrity (1)
    - Questionnaires that were to be completed for the trial for eligibility and endpoint data contained language and medical terms that were not easily understood by patients. There were deficiencies with electronic health records (EHRs) and paper source data. For example, it was not possible to verify who completed them, when they were completed, who had been making changes and why. The EHR audit trails had not been reviewed by the monitor or sponsor prior to the trial start date and there was only evidence that the monitor had logged into the system on one date.

CROs – 2 critical findings were reported from 2 organisations, as follows:

- Computer Systems Validation
    - Lack of validation documentation of a key eCRF software release
- Record Keeping/Essential Documents
    - It was not clearly defined in agreements with the Sponsors the scope of the TMF that was required to be held by the CRO; the TMF was found to be significantly incomplete; the eTMF lacked essential functionality; issues were found with the accuracy and reliability of the TMFs, e.g. misfiling, duplication, documents named incorrectly.

Non-commercial organisations –1 critical finding was reported from 1 organisation, as follows:

- Oversight of Clinical Trial Investigational Medicinal Product (CTIMP)
    - There was a lack of adequate Corrective and Preventative Action (CAPA) following the last MHRA GCP inspection (2013). For example, there was no copy of RSI held on file by R&D, hence, prior to SUSAR reporting, there was no process for the Trust to check that expectedness assessments had been made appropriately, or that the correct version of RSI had been used.

Investigator Sites – 1 critical finding was reported for 1 investigator site, as follows:

- Subject Eligibility:
    - Systemic inclusion by the investigator of ineligible subjects. Approximately 20% of subjects enrolled by the investigator (16/78 across several studies) were deemed ineligible.

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/706356/GCP_INSPECTIONS_METRICS_2016-2017__final_11-05-18_.pdf

Updated Guidance Published on Eudralex Volume 10

On 20 April 2018 a Questions and Answers (Q&A) document on the new Clinical Trial Regulation No. 536/2014 was published under Chapter V (Additional Documents) of Eudralex Volume 10. Eudralex Volume 10 provides guidance documents applicable to clinical trials. A number of these documents are being revised to bring them in line with the new EU Clinical Trials Regulation No. 536/2014, while new guidance documents are being prepared to cover new aspects introduced by the Regulation. Certain sections of this Q&A document are not yet complete and updated versions of the document will be published progressively. Additionally, two new guidance documents have been produced under Chapter IV (Inspections) of Eudralex Volume 10. These include:

- Annex III – to guidance for the conduct of good clinical practice inspections – computer systems (March 2018). EU GCP inspectors have agreed to use as a reference for inspection of computer systems the PIC/S Guidance on Good Clinical Practice for Computerized Systems in Regulated "GXP" Environments (PI 011-3). Hence this guidance includes a hyperlink to the PIC/S guidance. PIC/S (Pharmaceutical Inspection Co-operation Scheme) is a non-binding, informal co-operative arrangement between Regulatory Authorities in the field of Good Manufacturing Practice (GMP) of medicinal products for human or veterinary use. It aims to harmonise the inspection procedures worldwide by developing common standards in the field of GMP and by providing training opportunities to inspectors.
- Guidance for coordination of GCP inspections requested in the context of marketing authorisation applications for mutual recognition and decentralised procedures and cooperation between Member States (March 2018). This guidance document applies to the coordination of GCP inspections carried out by EU/EEA inspectors in connection with the marketing authorisation of medicinal products in the mutual recognition procedure and decentralised procedure whether it involves inspection activity in more than one Member State or not, since information will be shared with concerned Member States.

https://ec.europa.eu/health/documents/eudralex/vol-10_en#fragment1

EMA Publishes Annual Report for 2017

The European Medicines Agency (EMA) published its annual report for 2017 this month. The report provides an overview of the work of the EMA and highlights the EMA's major achievements in 2017. Some of these achievements include: the launch of the new and improved version of the EudraVigilance system; the first public hearing which allowed EU citizens to participate in the evaluation of a medicine (valproate) by responding to questions to complement the available scientific evidence; the launch of a new framework and action plan with academia, setting out a clear path to further develop interactions with this important stakeholder group; the first anniversary of PRIME – the PRIority Medicines scheme, which facilitates and promotes drug development for patients in need of new treatments. In addition, in 2017 the EMA recommended 92 medicines for marketing authorisation, of which 35 had a new active substance (i.e. one which had never previously been authorised in the EU). The report also highlights the challenges that have been faced with regard to Brexit and provides an overview of key Brexit-related dates and shows the steps taken by the EMA to prepare for Brexit.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002951.jsp&mid=WC0b01ac058004d5c1

Changes to Application for a Clinical Investigation for a Medical Device

On 18 April 2018, the application forms for notifying the Medicines and Healthcare products Regulatory Agency (MHRA) of a clinical investigation for a medical device changed. There is now only one form called Clinical Investigation Application Form. The MHRA is in the process of updating its guidance documents, but in the meantime, they still refer to the old forms (PCA1 and PCA2). The new form identifies key aspects of the devices under investigation and the study. This will help ensure the relevant information necessary for validation is included in the notification when submitted. The main changes are: significantly more detail about the investigational devices; incorporation of sterilisation questions and software questions within one form; significantly more detail about the study bringing MHRA and IRAS forms closer into alignment; and electronic sign-off.

https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device#history

FDA Adopts ICH Q7 Guidance

Last month, the FDA issued a final guidance for industry titled "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, Questions and Answers". This guidance adopts the ICH Q7 guideline of the same title, which was released by ICH in 2015 and adopted in the EU in Feb 2016. Since the implementation of the ICH Q7 guideline in 2000, it became apparent that some uncertainties related to the interpretation of some sections existed. Hence, this associated guidance, in the form of a questions and answers document was generated to remove ambiguities and uncertainties and to harmonise inspections of both small molecules and biotech active pharmaceutical ingredients (APIs).

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM605076.pdf

PHARMA NEWS

Takeda and Shire Reach Agreement on Acquisition

Japanese pharmaceutical company, Takeda, and Irish-based pharmaceutical company, Shire, announced on 08 May 2018 that they had reached agreement on the terms of an offer under which Takeda will acquire Shire. The deal, worth around £46 billion, has been approved by both companies' boards of directors, is expected to close in the first half of the calendar year 2019, and will be the largest overseas takeover by a Japanese company to date. Takeda shareholders will own approximately 50% of the combined group. Takeda's president and chief executive officer stated "Shire's highly complimentary product portfolio and pipeline, as well as experienced employees, will accelerate our transformation for a stronger Takeda. Together we will be a leader in providing targeted treatments in gastroenterology, neuroscience, oncology, rare disease and plasma-driven therapies".

CRO Market to Reach $44.4bn by 2021

The global contract research organisation (CRO) market is forecast to grow 12% year on year through 2021, according to a report published by The Business Research Company. IQVIA is currently the largest player in the CRO market with a 12.4% share, followed by LabCorp, ICON, Parexel and PPD. The report also showed that drug discovery was the largest segment by service type in 2017, accounting for about 33% of the market share, while oncology was the largest segment by therapeutic area, with approximately 25% of the total market. North America is the largest region for the production of CRO services, at $18.8 billion. This can be attributed to the large number of pharmaceutical companies and the extensive drug development activity in the region.

Novartis Launches New App for Ophthalmology Clinical Trials

Novartis has launched a new app – FocalView – that aims to allow researchers to track ophthalmic disease progression by collecting real-time data from patients. FocalView gives patients the ability to self-report data through the app's assessments. These measurements include visual acuity and contrast sensitivity and will also provide feedback on their visual function as well as changes over time. FocalView is available for download in the Apple Store in the US, with Novartis planning to launch in additional markets in the future. Users must consent to contribute to research data before interacting with the tool.

Bracket Partners with Uber Health

Bracket – a clinical trial technology and speciality services provider – has partnered with Uber Health to make clinical research more convenient for patients. One of the challenges that research patients face is access to reliable, affordable and pre-paid transportation to the clinic for their regular study visits. Via Uber Health, Bracket can offer research patients the ability to request a ride from their Patient Engagement app, with payment covered directly by the pharmaceutical company sponsoring the clinical trial.