TMQA Regulatory News Update May 2017

MHRA Publishes Guidance on Common Issues with Clinical Trial Applications

The Medicines and Healthcare products Regulatory Agency (MHRA) receives more than 1000 clinical trial authorisation (CTA) applications each year. The majority of these are approved (up to 95%) but more than half of all applications require additional information to be submitted before they are considered approvable. Many of the requests for further information or grounds for non-acceptance (GNA) are avoidable if the available guidance is followed or if a satisfactory justification for not following the guidance is provided. The timeframe for initial assessment of a CTA is 30 days with an MHRA target of 14 days for phase I applications. Currently the MHRA conducts an initial assessment within approximately 22 days and 12 days for phase I applications. However, when GNA are raised it can add up to 23 days for final approval or 21 days for phase 1 applications. The MHRA has published guidance to assist applicants in understanding the common reasons for the MHRA requiring additional information and directs applicants to where further information can be found. Every trial will have its own peculiarities and is assessed on a case by case basis, which may lead to questions needing to be asked on specific areas. The guidance provides common issues related to validation, non-clinical, clinical, and pharmaceutical aspects of the CTA application. From a clinical aspect, the most common GNA relate to lack of an acceptable reference safety information section. GNAs are also often raised because of lack of information about appropriate risk mitigation strategies (including contraceptive requirements, dose escalation stopping criteria and appropriate eligibility criteria) as well as unacceptable unblinding procedures in case of a medical emergency.

https://www.gov.uk/government/publications/common-issues-identified-during-clinical-trial-applications

MHRA Inspectorate Blog on Computer Systems Validation

A recent topic posted on the MHRA Inspectorate Blog in April 2017 was that of computer systems validation. The blog provides a combination of a case study seen at a single organisation and some of the common computer systems validation findings that GCP inspectors have seen across a number of recent inspections. The post provides some guidance on the type of validation activities that should be considered. The case study highlights the importance of having final versions of functional specifications and user requirements from which inspectors can assess if the system is in a validated state, as well as having documented evidence of testing such as completed test scripts with the outcomes of the testing and evidence demonstrating that any errors have been corrected. Advice is provided on what to look for in a validation report and what to be aware of with regards to contracts with eSystem vendors. The blog highlights the point that system validation does not stop with the systems development but the user aspect of validation should also be considered. Common findings relating to the user aspect of validation are provided and include:

- The product being released to the customer before training material has been developed and released
- Users being given access to the system with no training
- Users being given inappropriate (higher level) access such as the ability to make data changes
- User material not being reviewed or updated following the release of a new version with new functionality
- Users not being notified of system updates that included changes to functionality
- Internal processes and SOPs are not followed and as a result the formal review and approval of key documents such as validation plans, test scripts and reports are not completed.

https://mhrainspectorate.blog.gov.uk/2017/04/20/computer-system-validation-gcp/

MHRA Publishes Inspectorate Organogram

The MHRA inspectorate organogram has been published by the MHRA and can now be accessed on the MHRA website. The decision to publish the MHRA inspectorate organogram was made at a meeting held in March 2017. Names of GCP/GLP/GPvP/GMP/GDP inspectors, as of May 2017, can be found on the organogram.

https://mhrainspectorate.blog.gov.uk/wp-content/uploads/sites/151/2017/05/MHRA-Inspectorate-Organogram-May-17-1.pdf

EMA Publishes Draft Guidance on GCP Compliance in Relation to Trial Master Files

The European Medicines Agency (EMA) published a draft guidance in April 2017 for public consultation, entitled "Guideline on GCP Compliance in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials". This guidance has been prepared to assist sponsors and investigators to comply with the requirements of the new Clinical Trials Regulation (EU) No. 536/2014 which has yet to come into effect. According to recital 52 of this Regulation, "in order to be able to demonstrate compliance with the protocol and with this Regulation, a clinical trial master file, containing relevant documentation to allow effective supervision (monitoring by the sponsor and inspection by Member States), should be kept by the sponsor and investigator". Articles 57 and 58 of the Regulation make this mandatory. The same applies to the legal representatives and CROs or any third party to the extent of their assumed trial related duties and functions. The guideline aims to collate and explain the requirements of the Regulation and ICH E6 to assist organisations in maintaining a TMF that facilitates trial management, GCP compliance and inspection. The guidance also addresses archiving of the TMF, clarifying retention times, in particular, expectations in case of digitisation and consecutive destruction of paper documentation.

http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500225871&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

EMA Publishes Draft Guideline for the Notification of Serious Breaches

While the reporting of serious breaches of GCP or the trial protocol is a requirement of UK Statutory Instrument (SI) 2004 No.1031 as amended by SI 2006 No. 1928, it is not a requirement of EU Directive 2001/20/EC, as amended. However, reporting of serious breaches is a requirement of the new Clinical Trials Regulation No. 536/2014, which has yet to come into effect, and is defined in Article 52 of the Regulation, which states: "The sponsor shall notify the Member States concerned about a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach". A serious breach is defined by the Regulation as "a breach that is likely to affect to a significant degree: (a) the safety and rights of a subject; (b) the reliability and robustness of the data generated in the clinical trial". Given this new requirement of the Clinical Trials Regulation, the EMA has published a draft guideline on the notification of serious breaches of Regulation No 536/2014 or the clinical trial protocol. The guideline has been issued for public consultation with the end of the consultation period being 22 August 2017. The guideline outlines practical arrangements for notification of serious breaches and possible actions that may be taken by the EU/EEA Member States concerned in response to notifications of serious breaches, and provides advice on what should and should not be classified as a serious breach. Serious breaches are to be notified via the EU Clinical Trial portal and any serious breach occurring outside the EU/EEA that might have an impact of data integrity of a clinical trial already authorised or being conducted in the EU/EEA territory should be reported. Similarly, serious breaches of the protocol of an EU/EEA authorised clinical trial occurring exclusively outside the EU/EEA that are likely to affect the safety and the rights of a subject and/or the benefit risk balance of a clinical trial already authorised or being conducted in EU/EEA territory, should be notified. Sponsors should have a formal process in place to cover the legislative requirements of serious breach notifications including: receipt and assessment; investigation including a root cause analysis; corrective and preventative action; reporting to the EU Clinical Trial portal; and compliance with the 7 calendar day reporting timeline.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/05/WC500228199.pdf

EMA to Launch a New Version of Eudravigilance

The EMA is to launch a new and improved version of Eudravigilance – the European information system of suspected adverse reactions to medicines that are authorised or being studied in clinical trials in the European Economic Area (EEA) – following an independent audit of the new version which confirmed that the system achieved full functionality and met functional specifications. This new version will go live on 22 November 2017 and will have enhanced functionalities for reporting and analysing suspected adverse reactions. Users of the system (i.e. Competent Authorities, Marketing Authorisation Holders and sponsors of clinical trials) will need to ensure that their processes and local IT infrastructure are compatible with the new system and the internationally agreed format. Expected benefits of the new system include:

- Simplified reporting of individual case safety reports (ICSRs) and the re-routing of ICSRs to Member States. Marketing authorisation holders will no longer have to provide these reports to national competent authorities, but will report directly to Eudravigilance, reducing duplication of effort.
- Better detection of new of changing safety issues, enabling rapid action to protect public health.

- Increased transparency based on broader access to reports of suspected adverse reactions by healthcare professionals and the general public via the adrreports.eu portal, the public interface of the Eudravigilance database.
- Enhanced search and more efficient data analysis capabilities.
- Increased system capacity and performance to support large volumes of users and reports (including non-serious adverse reactions originating from the EEA).
- More efficient collaboration with the World Health Organisation (WHO) as EMA will make the reports of individual cases of suspected adverse reactions within the EEA available to WHO Uppsala Monitoring Centre directly from Eudravigilance; Member States will no longer need to carry out this task.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/05/news_detail_002752.jsp&mid=WC0b01ac058004d5c1

EMA Updates to GVP Guidances

Good pharmacovigilance practices (GVP) are a set of measures drawn up to facilitate the performance of pharmacovigilance in the EU. The guideline on GVP was a key deliverable of the 2010 pharmacovigilance legislation and is divided into chapters that fall into two categories: modules covering major pharmacovigilance processes; and product or population-specific considerations. GVP modules I to XVI cover major pharmacovigilance processes and the development of this set of guidance is concluded. However, module II (Pharmacovigilance system master file), module V (Risk management systems) and module XVI (Risk minimisation measures: selection of tools and effectiveness measures) were updated on 30 Mar 2017 and revision 2 of these modules became effective on 31 Mar 2017. Modules XI, XII, XIII and XIV stay void as these planned topics have been covered by other guidance documents. The chapters on product or population-specific considerations have been developed for vaccines and biological medicinal products. Three additional chapters are planned as follows: P III Pregnancy and breast-feeding; P IV Paediatric population; and P V Geriatric population. The planned date of release of these modules for public consultation is Q4, 2017 for P III and Q3, 2017 for P IV and P V.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c

EMA and Heads of CAs Discuss Consequences of Brexit

On 29 March 2017, the UK notified the European Council of its intention to leave the EU. The implications of Brexit on the location of the EMA (the EMA is currently located in London, UK) and its operations will depend on the future relationship between the UK and EU, which is unknown at this time.

The EMA issued a press release in April 2017 stating that it had organised an information meeting with members of its Management Board and heads of the national Competent Authorities (CAs) of the EU/EEA Member States. The goal was to start discussing how the work relating to the evaluation and monitoring of medicines will be shared between Member States in view of the UK's withdrawal from the EU. Work will start on the basis of the scenario that foresees that the UK will no longer participate in the work of the EMA and the European medicines regulatory system as of 30 March 2019. It is expected that all CAs will contribute to EMA activities as per the capacity and capability of each authority, to ensure an optimised and robust allocation of the workload across the network. The envisaged working methology will include a mapping of current and future capacity and expertise in

the network and the identification of potential gaps. The EMA, its scientific committees and working parties, together with the national CAs will now assess the different options for workload distribution.

On 2 May 2017, the EMA and European Commission published a notice to marketing authorisation holders of centrally authorised medicines to remind them of their legal obligations in preparation for Brexit which include: EU law requires that marketing authorisation holders are established in the EU (or EEA); and some activities must be performed in the EU (or EEA), related for example to pharmacovigilance, batch release etc. Marketing authorisation holders may therefore be required to adapt processes and consider changes to the terms of the marketing authorisation to ensure its continued validity once the UK leaves the EU.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/04/news_detail_002738.jsp&mid=WC0b01ac058004d5c1

EMA Publishes Annual Report for 2016

The EMA published its annual report for 2016 this month, which focused on the agency's key achievements in the areas of medicines evaluation, support to research and development of new and innovative treatments and the safety monitoring of medicines in real life. In 2016, the EMA recommended a marketing authorisation for 81 medicines for human use, including 27 new active substances. As a result of the safety monitoring of all medicines marketed in the EU, the product information for over 300 medicines for human use was updated on the basis of new safety information. Some of the EMA's main projects, initiatives and achievements in 2016 were also highlighted. These include: the launch of PRIME (PRIority MEdicines), an initiative to support the development of medicines that address unmet medical needs in order to get breakthroughs in medicines to patients more quickly; and the policy on the publication of clinical trial data for new medicines, a ground-breaking new initiative that turned the EMA into one of the most transparent medicines regulators worldwide. Other developments detailed in the report include new ways to collect data on medicines such as big data, patient registries and real world data, and the EMA's contribution to addressing public health challenges, including antimicrobial resistance and the Zika virus outbreak. The consequences of Brexit were also discussed in the annual report and the EMA has set up a task force to assess the likely impact of Brexit on EMA operations, and to identify the parameters that are essential to continue operations efficiently in a new location.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/05/news_detail_002743.jsp&mid=WC0b01ac058004d5c1

FDA Publishes Updated Compliance Program Guidance Manual

Since the Investigational New Drug (IND) Regulations went into effective in 1963, the FDA has exercised oversight of the conduct of clinical trials involving FDA-regulated products. Compliance programs were established by the FDA to provide uniform guidance and specific instructions for inspections of clinical investigators, sponsors, in-vivo bioequivalence facilities, institutional review boards and non-clinical laboratories. The Bioresearch Monitoring (BIMO) program is one such compliance program whose purpose is to provide instructions to FDA personnel for conducting inspections of sponsors, CROs and monitors, and recommending associated administrative/enforcement actions. The program covers both domestic and foreign inspections of sponsors, CROs, and monitors. The objectives of the BIMO are to: protect the rights, safety and welfare of subjects involved in FDA-regulated clinical trials; verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications; and assess compliance with FDA's regulations governing the conduct of clinical trials. An updated Compliance Program Guidance

Manual covering FDA inspections of sponsors, CROs and monitors was recently published by the BIMO with an implementation date of 19 April 2017. This guidance manual has been updated to incorporate the Final Rule detailing the requirements for submitting registration and summary results information to ClinicalTrials.gov (the clinical trial registry and results database operated by the National Library of Medicine (NLM) of the National Institutes of Health (NIH)), which became effective in January 2017.

https://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133777.htm