Regulatory & Pharma News Update December 2017

REGULATORY NEWS

EMA Headquarters Relocates to Amsterdam

After much speculation, it was announced last month that the European Medicines Agency (EMA) headquarters will relocate from London to Amsterdam following the UK's withdrawal from the European Union (EU). The EMA will take up its operations in Amsterdam on 30 March 2019 at the latest. The EMA received bids from 19 Member States, with Amsterdam narrowly winning over Milan. Surveys within the EMA showed that a large majority of EMA staff would be willing to relocate with the EMA to Amsterdam. Amsterdam's bid proposed a building with complete conference facilities – in line with the EMA's London site capabilities – to house the EMA headquarters. The city also proposed two options for temporary offices located close to the conference centre, which would ensure the continuity of operations until the construction of the EMA headquarters is completed. The EMA has been based in London, UK since its establishment in 1995 and employs nearly 900 people at its headquarters in Canary Wharf, London. The EMA and the Netherlands will establish a joint governance structure to steer and oversee the relocation project. A monitoring chart to track progress will be made available on the EMA website from early December.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/11/news_detail_002857.jsp&mid=WC0b01ac058004d5c1

EMA Publishes Guidance to Help Pharma Prepare for Brexit

The EMA has published additional guidance to help pharmaceutical companies to prepare for the UK's withdrawal from the EU. This follows the Notice to marketing authorisation holders (MAHs) of centrally authorised medicines products for human and veterinary use that was published in May this year, along with a list of Questions and Answers (Q&A) that is available on the EMA website. This new guidance document is one of a series of Brexit-related guidance which will be published on the EMA website in due course. The new practical guidance has been developed taking into consideration that as of 30 March 2019, the UK will become a third country. As a result, MAHs and applicants of centrally authorised products for human or veterinary use need to ensure that the necessary changes are made by 30 March 2019.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/11/news_detail_002862.jsp&mid=WC0b01ac058004d5c1

EMA Launches New Version of Eudravigilance

The EMA launched a new and improved version of Eudravigilance last month. Eudravigilance is the European system for managing and analysing information on suspected adverse reactions to medicines which have been authorised or are being studied in clinical trials in the European

Economic Area (EEA). The EMA operates the system on behalf of the EU. The enhancements and expected benefits of the new version of Eudravigilance are:

- Simplified reporting of individual case safety reports (ICSRs) and reduced duplication of effort, as marketing authorisation holders no longer have to provide these reports to national competent authorities, but can send them directly to Eudavigilance;
- Better detection of new or changing safety issues, enabling rapid action by regulators to protect public health;
- Enhanced interoperability based on the use of the ISO/ICH agreed standard for ICSRs;
- Better searchability and more efficient data analysis;
- Increased system capacity to support large volumes of users and reports;
- More efficient collaboration with the World Health Organization (WHO) as EMA will make the reports of individual cases of suspected adverse reactions within the EEA available to the WHO Uppsala Monitoring Centre directly from Eudravigilance; Member States will no longer need to carry out this task.

There will be no changes to the reporting of suspected unexpected serious adverse reactions during clinical trials until the application of the new Clinical Trials Regulation. Public access to data held in Eudravigilance will be provided through the adrreports.eu portal, which includes new features for data retrieval and presentation.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/11/news_detail_002858.jsp&mid=WC0b01ac058004d5c1

EU General Data Protection Regulation

In May 2018 a new General Data Protection Regulation (GDPR) will replace the existing EU Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data. The GDPR is the most important change in data privacy regulation in 20 years. The GDPR was approved by the EU Parliament on 14 April 2016 and was designed to harmonise data privacy laws across Europe and to protect all EU citizens from privacy and data breaches in an increasingly data driven world that is vastly different from the time in which the 1995 Directive was established. Some of the key changes in the GDPR are summarised below:

- The GDPR will now apply to all companies processing the personal data of people residing in the EU, regardless of the company's location, i.e. the processing may or may not take place in the EU. It also applies to the processing of personal data of data subjects in the EU by a controller or processor not established in the EU, where the activities relate to offering goods or services to EU citizens and the monitoring of behaviour that takes place within the EU. Non-EU businesses processing the data of EU citizens will have to appoint a representative in the EU.
- Organisations in breach of the GDPR can be fined up to 4% of global turnover or €20 million (whichever is greater). This is the maximum fine that can be imposed for the most serious infringements. There is a tiered approach to fines. Since the rules apply to both controllers and processors, "clouds" will not be exempt from GDPR enforcement.
- The conditions for consent have been strengthened and companies will no longer be able to use long terms and conditions full of legalese. The request for consent must be given in an intelligible and easily accessible form, using clear and plain language.

- Breach notification will become mandatory in all member states where a data breach is likely to "result in a risk for the rights and freedoms of individuals". This must be done within 72 hours of becoming aware of the breach.
- Data subjects will have to right to obtain confirmation from the data controller as to whether or not personal data about them is being processed, where and for what purpose. The controller will provide a copy of the personal data, free of charge, in an electronic format.
- The data subject has the right to have the data controller erase his/her personal data, cease further dissemination of the data, and potentially have third parties halt processing of the data. The conditions for erasure include the data no longer being relevant to original purposes for processing, or a data subject withdrawing consent. However, it should be noted that this right requires controllers to compare the subjects' rights to the "public interest in the availability of the data" when considering such requests.
- The GDPR introduces data portability, which is the right for a data subject to receive the personal data concerning them, which they have previously provided in a commonly used and readable format and have the right to transmit that data to another controller.
- Privacy be design, although a concept for many years, has only just become a legal requirement with the GDPR. It calls for the inclusion of data protection from the onset of the systems design rather than an add on.
- The appointment of Data Protection Officers will only be mandatory for those controllers and processors whose core activities consist of processing operations which require regular and systematic monitoring of data subjects on a large scale or of special categories of data or data relating to criminal convictions and offences. Instead, there will be internal record keeping requirements.

https://www.eugdpr.org/

MHRA Publishes Pharmacovigilance Inspection Metrics for 2016/2017

The MHRA published its Good Pharmacovigilance Practice (GPvP) inspection metrics for 2016/2017 on 01 Dec 2017. The report covers inspections conducted between 01 Apr 2016 and 31 Mar 2017. During this period, the MHRA GPvP Inspectorate conducted 36 inspections of MAHs and one inspection of a pharmacovigilance service provider. Of these, 13 were inspections of MAHs/organisations that had not previously undergone an MHRA GPvP inspection, 15 were routine re-inspections, and 9 were triggered inspections due to critical findings identified at previous inspections or in response to a specific issue.

A total of six critical, 150 major and 84 minor findings were identified during these inspections. The number of critical findings is down from 11 reported in the previous period. The largest proportion of critical findings was in relation to signal management (two in total), while a single critical finding was identified in each of the following areas: maintenance of reference safety information, supervision and oversight of the pharmacovigilance system, non-interventional programmes, and failure to establish a global pharmacovigilance system.

Of the 150 major findings reported, these were distributed across 18 topic areas. The largest proportion for a specific topic area was identified in relation to the quality system and quality assurance activities; together these findings represented 27% of all major findings. Findings related to reference safety information, case processing and signal management represented the next

largest proportion, each representing approximately 11% of all major findings. Other topic areas where major findings were identified included: Pharmacovigilance System Master File (PSMF), miscellaneous, MAH oversight, Periodic Safety Update Report (PSUR), Risk Management System, Safety Data Collection and Collation, Contracts and Agreements, Non-interventional Programmes, Clinical Trial Pharmacovigilance, Literature Searches, Post-authorisation Safety Studies (PASS), Qualified Person for Pharmacovigilance (QPPV), and Product Quality. Miscellaneous findings included failures in safety data management, supply of unlicensed medicines, MAH responsibilities with regard to the maintenance of the Article 57 database, management of company-sponsored websites and public communication.

The total number of major findings increased by approximately 60% from the previous reporting period. Major findings associated with quality managed increased by 82% from the previous period. The requirement for risk-based audits of the pharmacovigilance system and management of non-compliance have been poorly implemented by several MAHs. This includes failure to implement effective and timely CAPA following inspection findings. Another significant increase was in the number of findings relating to reference safety information which increased from seven to 17. These findings were characterised by failures and/or delays to submit safety variation applications to update the safety sections of the Summary of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs). Major findings in relation to signal management increased from 11 to 16 and included failures to comply with product-specific guidance (GVP Chapter P II) for biological medicinal products. Major findings in relation to oversight and supervision of the pharmacovigilance system increased significantly from one to seven findings. These included failures in the oversight of pharmacovigilance service providers, with subsequent impact on a variety of pharmacovigilance activities. Examples were also seen of failures by the MAH to support the EU QPPV, particularly where this role had been outsourced to a third-party service provider. Deficiencies in the maintenance of the PSMF and Article 57 database were also reported under this heading.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/664019/Pharmacovigilance_Inspection_Metrics_Report_2016-2017_Final.pdf

MHRA Publishes Guidance on to GMP/GDP Inspections

On 20 Oct 2017 the MHRA published guidance on responding to Good Manufacturing Practice/Good Distribution Practice (GMP/GDP) inspections, and information sheets on compliance management and regulatory action. Guidance is provided on responding to a GMP/GDP post inspection letter, while information sheets on both compliance management and regulatory action are provided for the following: Re-inspection of site under Compliance Management/Regulatory Action; Specials Manufacturers; UK MIA, MIA (IMP) and third country manufacture; Contract Laboratory; and Active Substance Manufacturer.

https://www.gov.uk/guidance/good-manufacturing-practice-and-good-distribution-practice

MHRA Updates List of Accredited Phase I Units

On 20 Oct 2017, the MHRA updated the list of accredited phase I units in the UK. The list now includes 13 phase I units, with 10 in England, one in Scotland, one in Northern Ireland and one in Wales. The MHRA phase I accreditation scheme is a voluntary scheme for organisations conducting phase I clinical trials, in particular for those conducting first-in-human trials. Accredited phase I units have to exceed the basic regulatory good clinical practice (GCP) standards by having additional procedures that include the highest standards for avoiding harm to trial subjects and for handling any medical emergencies.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/653674/List_of_accredited_units__20_October_2017_.pdf

FDA Improves Access to Adverse Drug Reaction Reports

On 28 Sep 2017, the US Food and Drug Administration (FDA) launched a new user-friendly search tool that improves access to data on adverse events associated with drug and biologic products through the FDA's Adverse Event Reporting System (FAERS). The tool is designed to make it easier for consumers, providers and researchers to access this information. The new dashboard enables users to search for and organize data by criteria such as drug/biological product, age of the patient, type of adverse event, year the adverse event occurred, or within a specific timeframe. As well as making it easier to search for adverse events, the FDA hopes the increased transparency will spur the submission of more detailed and complete reports for consumers, healthcare professionals and others by making it easier for people to see other reports that the FDA receives, and search the database for similar observations. The FDA uses FAERS for surveillance, such as looking for new safety concerns that might be related to a marketed product, evaluating a manufacturer's compliance with reporting regulations and responding to outside requests for information. The reports in FAERS are evaluated by clinical reviewers in the FDA's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research to monitor the safety of products after they are marketed. If a potential safety concern is identified in FAERS, further evaluation is performed.

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm578105.htm

New Indian Regulation Mandates the Inclusion of Indian Subjects in Clinical Trials

At a Technical Committee Meeting held on 25 Sep 2017 under the chairmanship of the Directorate General of Health Services (DGHS), India, a recommendation was made that any firm intending to market a new drug which is being developed outside India should include Indian subjects in the global clinical trial. At the same meeting it was determined that trials already approved in ICH countries, such as those in the US, Japan and Europe, will be reviewed on priority by the Drugs Controller General of India (DCGI). This new ruling will affect Contract Research Organisation's (CROs) recruitment procedures for drug trials intended for the Indian market.

http://cdsco.nic.in/writereaddata/technical%20committee%2042%2025_9_2017.pdf

RECENT FDA WARNING LETTERS

Investigator Dr Sohail Khan *10 Oct 2017*

Following an FDA inspection at the clinical site of Dr Khan on 14 Jul 2017, and following review of written responses to the form FDA 483, the FDA concluded that Dr Khan did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations as follows:

- Failure to retain records required to be maintained under 21 CFR Part 312 for a period of two years following the date a marketing authorisation is approved for the drug for the indication for

which the drug is being investigated; or, if no application is filed, or if the application is not approved for such indication, until two years after the investigation is discontinued.

  - Dr Khan failed to retain records of the disposition of the drug, including dates, quantity and use by subjects.
  - Dr Khan failed to retain adequate and accurate case histories, including signed and dated informed consent forms, case report forms, and all supporting data.

The objectional observations related to study records for two protocols. For one protocol, two years had not passed following approval of the indication under study, and for the other protocol, two years had not passed since the Sponsor had discontinued the study for the protocol at Dr Khan's site. During the inspection, Dr Khan stated that all study records related to the two protocols had been shredded or destroyed; no electronic or paper records remained for these studies. In his written response to the Form FDA 483, Dr Khan stated that his understanding was that study records were required to be retained for two years following study termination at a site.

Investigator Dr Laveeza Bhatti *04 Aug 2017*

Following an FDA inspection at the clinical site of Dr Bhatti between Oct 27 and Dec 16, 2016, and following review of written responses to the form FDA 483, the FDA concluded that Dr Bhatti did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations as follows:

- Failure to ensure that the investigation was conducted according to the investigational plan:
  - The investigational plan required that subjects be excluded if there was any clinically significant finding on screening or baseline ECG. QRS duration of >120 milliseconds (msec) and QTc interval >450 msec were specified as two such clinically significant findings in the protocol. However, two subjects had been randomized and received study drug despite meeting this exclusion criteria. In Dr Bhatti's written response to the Form FDA 483, he stated that, with regard to the first subject, he conferred with two other site clinicians as well as a cardiologist about the ECG finding, and while, abnormal, the finding was considered not clinically significant. Dr Bhatti notified the Sponsor after randomisation of the subject and the subject was allowed to remain on the trial.
  - The investigational plan required that subjects were enrolled who had not taken more than 10 days of prior therapy with any (b)(4) agent following a diagnosis of (b)(4). One subject was randomized and received study drug despite not meeting this requirement.
  - The investigational plan required that ECGs be performed at screening, on day 1, and at weeks 2, 4, 12, 24, 26, 28, 36 and 48, and every 12 weeks thereafter, up to and including withdrawal from the study. One subject missed ECGs at three of the required visits, and five subjects missed an ECG at one of the required visits.
  - The investigational plan required an ECG approximately two hours post-dose and just before the two-hour post-dose pharmacokinetic sampling at week 32. However, during the week 32 visit, one subject did not have a post-dose ECG performed, and another subject, who received study drug at week 32 visit at 12:40 and 12:42, had an ECG performed at 12:20.
- Failure to retain records required to be maintained under 21 CFR Part 312 for a period of two years following the date a marketing authorisation is approved for the drug for the indication for which the drug is being investigated; or, if no application is filed, or if the application is not approved for such indication, until two years after the investigation is discontinued.

- Dr Bhatti failed to retain case histories that included ECG tracings and the Columbia-Suicide Severity Rating Scale (C-SSRS). Specifically, ECG tracings at one or more required visits were not retained for seven subjects, and C-SSRS from one visit was not retained for one subject.

PHARMA NEWS

FDA Approves Sensor-Embedded Pill

The FDA has approved Otsuka Pharmaceuticals' sensor-embedded pill (Abilify MyCite (aripiprazole tablets with sensor)) that digitally verifies if a patient has taken their medication. The product has been approved for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder and for use as an add-on treatment for depression in adults. The system works by sending a message from the pill's sensor to a wearable patch. The patch transmits the information to a mobile application so that patients can track the ingestion of the medication on their smart phone. Patients can also permit their caregivers and physicians to access the information through a web-based portal.

ICON Tests Amazon's Echo Dot Assistant to Boost Recruitment in Clinical Trials

The global CRO, ICON, revealed last month that it is engaged in developments using the Amazon Echo Voice Assistant platform to enhance interactions with patients enrolled into clinical trials. ICON's proof-of-concept application uses a Voice Assistant to deliver a patient-reported outcome (PRO) instrument and collect patient responses. Initial testing of the application, which is launched using the command "Alexa, complete my diary", has indicated that the platform is able to operate robustly with multiple users and languages with minimal training. ICON's CIO commented that "the development of conversational applications may provide an effective way of interacting with patients in an engaging manner in future clinical trials". It is predicted that by 2020, 30% of web browsing sessions will be done using Voice Assistants or Virtual Reality. This is further demonstrated by the rapid increase in sales of voice-enabled devices like Amazon Echo and Google Home, which are predicted to rise 130% this year in the US.