Regulatory & Pharma News Update February 2018

REGULATORY NEWS

HMA Publishes Updated Guidance on Reference Safety Information

The Heads of Medicines Agency (HMA) Clinical Trial Facilitation Group (CTFG) acts as a forum for discussion to agree on common principles and processes to be applied throughout the European medicines regulatory network. It also promotes harmonisation of clinical trial assessment decisions and administrative processes across the national competent authorities. In November 2017, the CTFG published an updated Questions and Answers (Q&A) document on reference safety information (RSI) following detailed discussions between national competent authorities and sponsors, which arose from clinical trial application and substantial amendment procedures as well as GCP inspections. The primary purpose of the RSI is to serve as the basis for expectedness assessments of 'suspected' serious adverse reactions (SARs) by the sponsor for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) and annual safety reporting. The sponsor may use an approved Summary of Product Characteristics (SmPC) as RSI, though it is more common for RSI to be provided in the Investigator's Brochure (IB) for Investigational Medicinal Products (IMP). While the RSI section of an IB should only contain expected SARs to the IMP, a broader description of the safety profile of the IMP, in addition to the RSI, should be included elsewhere in the IB.

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf

UK and China Sign MoU on Medicine and Device Regulation

The UK's Medicines and Healthcare products Regulatory Agency (MHRA) has signed a memorandum of understanding (MoU) with the China Food and Drug Administration (CFDA). This new signing expands on a previous MoU signed in 2014 which focussed on the exchange of safety information on medicines and medical devices. The new agreement pledges new areas of cooperation such as an exchange of learning from the accelerated access review and how to effectively regulate the trading of medicines online.

https://www.gov.uk/government/news/uk-and-china-sign-memorandum-of-understanding-on-medicine-and-device-regulation

MHRA Opens Consultation on Exemption for IVDR/MDR

The MHRA is developing guidance for health institutions wishing to apply the exemption to the new in vitro diagnostic medical device regulation (2017/746) and the new medical device regulation (2017/745), in particular Article 5(5) of both regulations. As a result, it has opened a consultation,

ending 31 March 2019, which aims to gather views from a broad range of stakeholders and allow health institutions to test and model the guidance, hence the long consultation period. These new regulations entered into force in May 2017 and are subject to a three (for Regulation 2017/745) and five (for Regulation 2017/746) year transition period.

https://www.gov.uk/government/consultations/health-institution-exemption-for-ivdrmdr

MHRA Inspectorate Blog Provides Guidance to MAHs Using Pharmacovigilance Service Providers

Last month's MHRA Inspectorate Blog provided a guide to Marketing Authorisation Holders (MAHs) when considering agreements with pharmacovigilance system service providers. The pharmacovigilance systems of MAHs are often dependent on multiple third parties. Whilst the majority of service providers offer a valuable and compliant support to MAHs, the MHRA GPvP Inspectorate experience is that MAHs do not always include adequate text in written agreements to allow management of the outsourced activities and the risk of serious pharmacovigilance failures. Module III of Good Vigilance Practices (GVP) specifically lists risk factors for pharmacovigilance systems, accounting for mergers and acquisitions, subcontracting, safety database and contractual arrangement changes. The blog outlines issues identified through GPvP inspection experience and provides recommendations in support of compliant practices, particularly with regard to points to consider when producing contracts and agreements text. The blog highlights challenges faced by MAHs in relation to contracts with service providers. These challenges include the following:

- Data integrity and control – the ownership and provision of safety data, source records and derived datasets needs to be clearly allocated in agreements with service providers.
- Oversight and Supervision – MAHs and service providers need to share information about pharmacovigilance risk and compliance to assess impact and address deficiencies. The qualified person for pharmacovigilance (QPPV) must have authority over the pharmacovigilance system, though the MAH remains responsible for the delivery of pharmacovigilance.
- Contracts and Agreement Content – the MHRA recommends that MAHs and service providers work together to construct agreements that, in addition to describing specific pharmacovigilance tasks, limit the potential for pharmacovigilance failures arising from outsourcing services.

https://mhrainspectorate.blog.gov.uk/2018/01/22/mhra-gpvp-inspectorate-guide-to-marketing-authorisation-holder-considerations-for-agreements-with-pharmacovigilance-system-service-providers/

MHRA Provides Update to Pharma Companies on Brexit Preparations

The MHRA provided an update in January 2018 to pharmaceutical companies on preparations for exiting the EU. According to the update, the European Council agreed on 15 Dec 2017 that sufficient progress had been made to move onto the second stage of negotiations and adopted guidelines for that second phase. This followed the publication of a Joint Report on progress during the first phase, which is available on the MHRA website. The Joint Report makes clear that "goods placed on the market under Union law before the withdrawal date may freely circulate on the markets of the UK and the Union with no need for product modification or re-labelling; be put into service where provided in Union law, and that goods concerned should be subject to continued oversight." The EU guidelines acknowledge the proposal put forward by the UK for a time-limited implementation

period, based on the existing structure of EU rules and regulations. The aim is for access to one another's markets to continue on current terms throughout this period. The guidelines also reconfirm the EU's desire to establish a close future partnership with the UK. The MHRA is aware that companies who market pharmaceuticals in the EU and UK will need to plan and make decisions in advance of the UK's departure from the EU in March 2019. The UK's intention is to secure an implementation period based on the existing structure of EU rules and regulations as quickly as possible. The update emphasises that the UK's current regulatory relationship with the European network remains unchanged. Additionally, the update sets out UK regulatory requirements after March 2019 in the event of no ongoing relationship with European Medicines Agency networks.

https://www.gov.uk/government/news/mhra-update-to-pharmaceutical-companies-on-exit-preparations

EMA Provides Brexit-Related Guidance for Companies

Late last year, the European Medicines Agency (EMA) and European Commission provided guidance to help pharmaceutical companies responsible for human and veterinary medicines prepare for Brexit. This aims to ensure that companies are ready to take the necessary steps to ensure an undisrupted supply of their medicines, based on the assumption that the UK will no longer be a Member State of the EU as of 30 March 2019. Additional guidance, as well as updates to existing guidance published last year, have been recently published by the EMA. A new guidance was published on 28 Jan 2018 for procedures related to Brexit for medicinal products for human and veterinary use within the framework of the centralised procedure, while an update to the existing questions and answers document and to the notice to marketing authorisation holders was also published. Companies are advised to check this page of the EMA website regularly for guidance on Brexit, as the EMA and European Commission are preparing a series of guidance documents.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_001891.jsp&mid=WC0b01ac0580cb2e5b

EMA Surveys Pharma Companies on their Preparedness for Brexit

The EMA is launching a survey to gather information from companies on their Brexit preparation plans and identify any particular concerns with regard to medicines supply that may impact public or animal health. The survey is being sent directly to marketing authorisation holders of centrally authorised medicines that are located in the UK, or who have quality control, batch release, and/or import manufacturing sites or a qualified person for pharmacovigilance (QPPV) or pharmacovigilance system master file (PSMF) in the UK. The deadline for completion of the questionnaire is 9 February 2018. The aim of the survey is to identify those companies where there is a need for concerted action to address medicines supply concerns due to Brexit in order to protect human and animal health, and to help the EMA and the European Commission plan resources in the areas where these submissions will be processed. The survey will also serve to prompt those companies who have not yet taken any action to start planning for any regulatory steps required for their centrally authorised products to remain on the EU market post-Brexit in order to minimise disruption to medicines supply and avoid shortages. Findings and recommendations from the survey will be shared with the European Commission and presented to the EMA's Management Board. A high-level summary of the overall results of the survey will be published on the EMA website.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/01/news_detail_002890.jsp&mid=WC0b01ac058004d5c1

EMA Publishes Guidance on Follow-up and Risk Management for ATMP Developers

On 1 February 2018 the EMA released a revised draft guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products (ATMP). ATMPs offer new opportunities for the treatment of disease and injury based on innovative approaches and technologies. Because of this novelty, ATMPs may be associated with risks of a different nature to those generally encountered with more conventional medicines

The guideline is open for public consultation with the consultation period ending on 30 April 2018. The revision is part of the joint action plan published by the European Commission and EMA in October 2017 to streamline procedures and better address the specific requirements of ATMP developers. This is the first revision of the original ATMP guideline on safety and efficacy follow-up and risk management; the guideline has been revised to take into consideration the experience gained with the authorisation of these products and to define their risks and their risk minimisation measures. Additionally, guidance is provided on methodology in order to design post-authorisation safety and efficacy follow-up studies. It also provides advice on early detection of risks during development and provides a framework for the effective mitigation of their consequences for patients.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/02/news_detail_002897.jsp&mid=WC0b01ac058004d5c1

FDA Updates Guidance on Payment and Reimbursement to Research Subjects

The US FDA has updated its guidance to Institutional Review Boards (IRBs) and Clinical Investigators on paying research subjects for their participation in clinical trials. The new title of the guidance is "Payment and Reimbursement to Research Subjects – Information Sheet" and has been generated in response to enquiries received by the FDA from stakeholders about appropriate reimbursement practices. The guidance highlights that the FDA does not consider payment to research subjects for participation in studies a benefit that would be part of the weighing of benefits or risk; it considers it a recruitment incentive. The FDA does not consider payment for reimbursement of travel expenses to and from the clinical site and associated costs such as airfare, parking, and lodging to raise issues regarding undue influence. IRBs should be sensitive to whether other aspects of proposed payment for participation (other than reimbursement for reasonable travel and lodgings expenses) could present an undue influence, thus interfering with the subjects' ability to give voluntary informed consent. According to the guidance, any credit for payment should accrue as the study progresses and not be contingent on the subject completing the entire study. However, payment of a small proportion as an incentive for completion is considered acceptable by the FDA, providing that such incentive is not coercive.

https://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm

FDA Launches Clinical Trial Transparency Programme

The US FDA is launching a new pilot programme aimed at increasing clinical trial transparency. One place where they are evaluating how they can release information that may better inform scientists, providers and patients is clinical study reports (CSRs). A CSR is a portion of the drug file, related to a clinical trial, that contains detailed summaries of the methods and results of a clinical trial. Currently

when a drug is approved, the FDA releases certain information that the FDA uses when reviewing the new drug application (NDA). This includes summaries written by FDA medical reviewers that capture their assessment of the data, the proposed labelling or other requirements, and other important relevant data supporting safe and effective use. This information is included in the FDA's drug approvals database Drugs@FDA. The format of these summaries can make it difficult for external audiences to extract the detailed clinical evidence that supported the FDA's approval decisions. The new pilot programme will evaluate whether disclosing certain information included within CSRs following approval of a NDA improves public access to drug approval information. Nine recently approved NDAs whose sponsors volunteer to participate will be selected by the FDA for this pilot programme. It is expected that making a CSR publicly available after a drug's approval will provide stakeholders with more information on the clinical evidence supporting a drug application and more transparency into the FDA's decision-making process.

Additionally, the FDA has also announced plans to provide the ClinicalTrials.gov identification number (called the NCT #) to FDA materials for future drug approvals. This number will make it easier to associate the clinical trial listings on ClinicalTrials.gov to FDA communications about specific drugs. Members of the public can easily use this number to identify and track clinical research from a drug's development throughout the regulatory process. Including this number on FDA materials could greatly benefit all those interested in following the progress of specific clinical research. ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm592566.htm

Use of Form FDA 1572 for Clinical Trials in Europe

The Danish Medicines Agency published an interesting article in October 2017 relating to whether or not investigators participating in multinational trials in Europe should sign the Form FDA 1572 (Statement of Investigator) and whether it is in accordance with EU legislation to conduct a clinical trial in Europe under the US Investigational New Drug (IND) regulations. The article states that an investigator in Europe cannot comply with the requirements of the Form 1572 and that a trial conducted at a site in the EU cannot be conducted under any foreign country legislation. The trial must be conducted under the requirements of EU Directives 2001/20/EC, 2001/83/EC and 2005/28/EC (and Clinical Trials Regulation (EU) No 536/2014 when it comes into force). Clinical trials submitted to the US FDA for marketing approval must comply with the IND regulations found in Title 21 Code of Federal Regulations (CFR) Part 312. Compliance with 21 CFR Part 312 can be achieved:

1. By conducting trials either under IND or
2. Not under IND ("non-IND foreign clinical studies") or
3. As a combination of sites within the US as IND-sites and sites outside the US not under the IND application (non-IND sites), whatever is most appropriate.

If the sponsor choses option 1, then the sponsor and all investigators must meet all IND requirements. However, it is possible to apply for a waiver from FDA for any of the Institutional Review Board (IRB) requirements covered by the IRB regulations (21 CFR Part 56.105). The sponsor should submit the waiver request to the IND under which the trial will be conducted prior to initiating the study.

If the sponsor choses option 2, then the trial must be conducted in accordance with 21 CFR Part 312.120 – Foreign clinical studies not conducted under an IND. The requirements of 21 CFR Part 312.120 can be met if a clinical trial is conducted in compliance with international ethical and data

quality standards set forth by EU Directives 2001/20/EC, 2001/83/EC and 2005/28/EC (and Clinical Trials Regulation (EU) No 536/2014 when it comes into force). The Form FDA 1572 does not apply.

If the sponsor choses option 3, then the sponsor can choose not to have sites outside the US under the IND application. With this option the sponsor can submit one protocol to the FDA that clearly defines and describes IND and non-IND sites. The investigators at the non-IND sites do not need to sign the Form FDA 1572, but the sponsor must ensure that these sites comply with 21 CFR Part 312.120 "Foreign clinical Studies not conducted under an IND", which requires the trial to be conducted in accordance with Good Clinical Practice (GCP) and that FDA is able to validate the data from the trial through an on-site inspection. Alternatively, the sponsor can submit one protocol for sites under the IND and another protocol for foreign sites not under the IND. The Form FDA 1572 does not apply for the non-IND sites. If the intent is to pool the data from US and foreign sites for marketing approval, the protocols would normally be very similar or identical. For sites outside the US that are not included under the IND, the protocol does not need to be submitted to the IND. However, the FDA recommends that the sponsor discusses plans to pool the data from the different sites with the appropriate FDA review division before trial initiation.

https://laegemiddelstyrelsen.dk/en/licensing/clinical-trials/gcp-inspection/clinical-trials-under-us-legislation/

PHARMA NEWS

IQVIA Awarded FDA Contract to Expand Biological Safety Monitoring

IQVIA (Formerly Quintiles IMS) announced a novel alliance with the FDA Center for Biologics Evaluation and Research (CBER) this month to monitor and assist in the evaluation of safety and effectiveness of various CBER-regulated vaccines, blood products and other biologics. IQVIA was selected and awarded this alliance after an open and competitive contracting process. The agreement marks the launch of the CBER's Biologics Effectiveness and Safety (BEST) Initiative as a new component of the ongoing Sentinel Initiative, which is the FDA's electronic system for monitoring the safety of FDA-regulated medicinal products.

Charles River Gains Access to AstraZeneca's High-Throughput Screening

Charles River announced a collaborative agreement with AstraZeneca this month which gives them commercial access to AstraZeneca's high-throughput screening (HTS) and compound management infrastructure. Through this new agreement, Charles River will perform HTS programs for their clients using AstraZeneca's state-of-the-art HTS facility. This will enhance Charles River's existing capabilities by broadening assay platforms and increasing their ability to automate, ultimately allowing them to execute HTS projects with greater speed and accuracy. Charles River will place scientists-in-residence at AstraZeneca's Centre for Lead Discovery in Cambridge, UK to manage their compound collections and run drug discovery screens for clients

Almac Expands Capabilities in Ireland

In January 2017 Almac – a global contract pharmaceutical development and manufacturing organisation - confirmed that it had secured new premises in Dundalk, Ireland as part of its ongoing global expansion strategy, to meet client demand and to address any potential challenges that may arise due to Brexit. Last month it confirmed successful completion of inspections of Almac Clinical Services Ireland and Almac Pharma Services Ireland at its European campus in Dundalk by the Irish regulatory authority – Health Products Regulatory Authority (HPRA). Following these HPRA inspections, Almac will officially be able to conduct QP batch certification and release for clinical trial material and commercial drug product from the Dundalk campus. To ensure Almac meets current and future client needs in the EU marketplace, Almac has also announced further investment at the Dundalk campus, including a new QC laboratory and packaging facility for commercial drug products and a dedicated EU Distribution Centre for clinical trial supply. The £30 million investment will more than treble the GMP footprint at its European campus which is scheduled to be operationally ready by January 2019.