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REGULATORY

NEWSLETTER N.27
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CROMSOURCE is an international provider of outsourced services to the pharmaceutical, biotechnology and medical device industries, specialised in clinical development and staffing solutions.

SUMMARY

Abbreviations

Acronym	Definition
AIFA	Agenzia Italiana del Farmaco (Italy)
ANDA	Abbreviated New Drug Application
ANSM	National Agency for the Safety of Medicine and Health Products (France)
ATMP	Advanced Therapy Medicinal Product
BfArM	Federal Institute for Drugs and Medical Devices (Germany)
BLA	Biologic License Application
CA	Competent Authority
CAB	Conformity Assessment Bodies
CCMO	Central Committee for Research Involving Human Subjects (The Netherlands)
CDRH	Centre for Devices and Radiological Health (US)
CE	(Conformité Européenne) (European Conformity)
CESP	Common European Submission Portal
CI	Clinical Investigation
CNIL	Commission Nationale de l'Informatique et des Libertés (France)
CPP	Human Protection Committee (France)
CRO	Contract Research Organisation
CTA	Clinical Trials Application
DMA	Danish Medicines Agency (Denmark)
DMF	Drug Master File
DSUR	Development Safety Update Report
EC	European Commission
EEA	European Economic Area
Enpr-EMA	European Network of Paediatric Research at the European Medicines Agency
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (United States)
FD&C Act	Food, Drug, and Cosmetic Act
FY	Fiscal Year
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
GVP	Good Pharmacovigilance Practice
HMA	Heads of Medicines Agencies
ICTRP	International Clinical Trials Registry Platform
IGJ	Healthcare and Youth Inspectorate (The Netherlands)
IMDD	Investigational Medical Device Dossier
IMP	Investigational Medicinal Product

Acronym	Definition
IMPD	Investigational Medicinal Product Dossier
IMDRF	International Medical Device Regulators Forum
ISO	International Standardisation Organisation
IVDR	In Vitro Diagnostics Regulation, EU 2017/746
MAD	Mutual Acceptance of Data
MAH	Marketing Authorisation Holder
MD	Medical Device
MDCG	Medical Devices Coordination Group
MDR	Medical Device Regulation, EU 2017/745
MDUFA	Medical Device User Fee Amendments
MDVS	Medical Device Vigilance System
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MIR	Manufacturer Incident Report
MR	Méthodologie de reference (Reference methodology)
MS	Member State
MREC	Medical Research Ethics Committee (The Netherland)
NB	Notified Body
NCA	National Competent Authority
NCAR	National Competent Authority Report
NDA	New Drug Application
OECD	Organisation for Economic Co-operation and Development
OOS ATMP	Out of Specification Advanced Therapy Medicinal Products
OsSC	Osservatorio Nazionale per la Sperimentazione Clinica (Italy)
PDUFA	Prescription Drug User Fee Act
PEI	Paul Ehrich Institut (Germany)
PHS Act	Public Health Service Act (US)
PRRC	Person Responsible for Regulatory Compliance
SMS	Substance Management Services
SRN	Single Registration Number
UDI	Unique Device Identifier
UK	United Kingdom
WHO	World Health Organization
XEVMPD	EudraVigilance Medicinal Product Dictionary

NEWS FROM EUROPE: MEDICINAL PRODUCTS

News from the European Commission

Update of the End of the Trial Notification Form

The European Commission (EC) made a revision to the Declaration of the End of the Trial Form, submitted for early termination or the end of a clinical trial.

The update covers the instruction for sponsors, added to the footer, and explaining what should be completed and how.

The Results of EU Trials To Be Made Publicly Available through the EU Clinical Trials Register – Reminder to Stakeholders

The EC in cooperation with the European Medicinal Agency (EMA) and Heads of Medicines Agencies (HMA), published joint letter to all sponsors of clinical trials conducted in the European Union reminding them of their obligation to make results of concluded trials publicly available through the EU Clinical Trials Register.

The data from April 2019 showed that only 27,093 (47%) clinical trials from 57,687 clinical trials in total were completed in EudraCT Clinical Trials Database.

The EC reminds that as of July 2014, a commercial and non-commercial sponsors are required to post positive and negative results of the clinical trials within one year after the end of a clinical trial or six months after the end of trial for paediatric studies. The joint letter underlines that sponsor responsibility is to ensure that the protocol information and the results of clinical trials are submitted to EudraCT Clinical Trials Database. Once the sponsor submits the results, the information is automatically fed to EU Clinical Trials Register and visible two weeks after the posting date. The information publicly available is also shared with the World Health Organization's (WHO) International Clinical Trials Registry Platform (ICTRP).

In addition, the EC published an updated list of the concrete data fields and sections to be made public in the EU Clinical Trials Register.

News from the European Medicines Agency

The source of each news item below is the EMA website: https://www.ema.europa.eu/

Enpr-EMA Opened a Public Consultation on a Draft Framework for Paediatric Clinical Trial Preparedness

The European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) opened a public consultation on clinical trial preparedness in paediatrics.

The consultation discusses what should be done by the paediatric community (sponsors, Contract Research Organisations and sites) to improve the landscape for medicines research over the next five to ten years.

Trial preparedness is defined "as a structured assessment of the key factors that could increase the likelihood of a smooth and timely course of a paediatric clinical trial, integrating information from multiple stakeholders on what is possible within a development plan and/or individual studies."

In addition, guidance is given on how to collect relevant information, involve relevant contributors, follow a structured process, and use appropriate resources.

"Sites, and networks of sites, should be involved as early as possible in those aspects of study preparation that they can contribute to." and "Early consultation with patients' advocacy groups, ideally consultation with patient/parent panels, should be considered since they may improve the communication with the target population and allow to identify potential practical barriers for the conduct of the study."

The Enpr-EMA invites stakeholders including clinical trial sites, investigators, networks, sponsors and patients to respond by 15 November 2019.

EMA Service Desk Portal Extended for Registration of Substances to the Clinical Trial Sponsors

In July 2019, the EMA delivered Substance Management Services (SMS) to support EU-wide regulatory activities in accordance with the EudraVigilance Operational Plan (2018-2020).

The EMA extended the use of the EMA Service Desk portal for registration of substances to the clinical trial sponsors. This means that starting from July 2019 sponsors need to request a new substance in advance, if they want to submit a Clinical Trial Application or to submit an IMP in the EudraVigilance Medicinal Product Dictionary (XEVMPD).

New substances will be registered in XEVMPD as approved substances. The confidentiality will be kept and new substance will be not available for any other public EMA systems. The next transition phase is planned in 2020 where products, referentials and organisations will also need to pre-register via the EMA Service Desk portal. The transition process is to implement the ISO Identification of Medicinal Products standards.

News from Individual Countries

The United Kingdom

MHRA Strategy for Pharmacopoeial Public Quality Standards for Biological Medicines

The Medicine and Healthcare products Regulatory Agency (MHRA), the British National Competent Authority provided update on their biologics pharmacopoeial quality strategy for the next 12 months.

The MHRA declared to work "on alternative approaches for biotechnologically produced proteins" to develop and carry out laboratory work to developer deeper understanding of performance and class-based concepts." For Advance Therapy Medicinal Products (ATMPs) the MHRA wants to "establish a working party to provide guidance and direction on the development of standards that support quality and innovation."

Additionally, the MHRA will carry on engagement through workshops and conferences to continue knowledge building and support for manufacturers and healthcare system.

France

Update of MR-001 and MR-003 Declarations by CNIL

The Commission Nationale de l'Informatique et des Libertés (CNIL), the French independent authority that exercises its functions with accordance to the French Data Protection Act updated two declarations Méthodologie de référence MR-001 and Méthodologie de référence MR-003.

MR-001 is for interventional research, including minimal risk and constraint research, clinical trials of drugs, and research that requires a review of genetic characteristics. The data controller undertakes to collect only data that is strictly necessary and relevant to the objectives of the research.

Reference methodology MR-003 covers biomedical research data without obtaining consent, such as personal data, covering treatments that include health data and are of a public interest, carried out in the context of human research for which the person concerned does not object to participate after having been informed. MR-003 is for non-interventional research and clinical trials which involves no risk or constraint, in which all acts are performed and products are used in the usual way.

In France the data controller (sponsor, investigator, and site) to comply with the General Data Protection Regulation (GDPR) submits a declaration attesting compliance with a reference methodology to the CNIL.

The proper declaration must be sent online to the CNIL. For a notification of declaration, green light approval is given within one week. For a request for opinion or authorisation the approval is issued in two months.

Germany

Changes of Submissions and Notifications to PEI and BfArM

The Paul-Ehrlich-Institut (PEI), the German NCA for sera, vaccines, blood preparations, bone marrow preparations, tissue preparations, allergens, ATMPs, xenogeneic cell therapeutics and genetically engineered blood components announced that since 8 August 2019 the initial submission of clinical trials authorisation needs to be submitted exclusively online via the Common European Submission Portal (CESP). Moreover, the mandatory online submission will be applicable for the reply to formal letters of deficiency (validation), reply to letters with justified objections, substantial amendments, temporary halt notifications, summary of study results and Development Safety Update Report (DSUR). Submission via Eudralink or e-mail will not be accepted by the PEI.

In addition, the Federal Institute for Drugs and Medical Devices (BfArM), the German NCA for chemical and some biological medical products also has begun accepting applications to run clinical trials via CESP. Use of the CESP for applications to BfArM will provide an alternative to the submission of paper applications and physical media such as DVDs/CD-ROMs.

Italy

New Requirements for Documents to Be Submitted to AIFA and ISS for Clinical Trials.

The Agenzia Italiana del Farmaco (AIFA) i.e. the Italian Medicines Agency, sent a communication about the implementation of new templates for the transmission letters and about the documentation to be provided by the applicants (sponsor or CRO) to AIFA and to the "Istituto Superiore di Sanità" (ISS) at the time of initial submission and for substantial amendments. New requirements are applicable from 1 August 2019.

In Italy for phases I, I/II, I/III initial submission has to be done to the AIFA, the ISS and relevant Ethics Committee(s) i.e. ISS supports the AIFA in case of phase I studies. The announcement informs what kind of documents should be submitted in paper version. In case the submission will be done via "Osservatorio Nazionale per la Sperimentazione Clinica" (OsSC) online system, the applicant must ship specific paper copies, after e-submission via OsSC, to AIFA with one CD-ROM containing the whole submitted documents.

The form to be used to prepare transmission letter is available at AIFA website in the "modulistica" section.

In case the submission of phase I studies will not be done via OsSC, the specific paper copies like transmission letter, Clinical Trial Application (CTA) form = Appendix 5 (originally signed), Amendment form = Appendix 9 (originally signed), checklist, receipt of the bank transfer payment, must be submitted to AIFA and ISS with two CD-ROMs including whole packages, for each.

Similar requirements are presented for clinical trials for phases II, III and IV where the initial submission dossier and substantial amendments have to be submitted to AIFA and relevant Ethics Committee (no ISS involved).

The AIFA announcement lists the documents to be submitted for phases II, III and IV in paper and on CD-ROM in case the submission will be done either via OsSC or in paper version.

For every submissions to AIFA, originally signed transmission letter with the stamp duty (costing 16 Euro, one stamp every four pages) must be submitted.

In addition, the AIFA underlined that the paper submission is allowed only for those cases that are described in the AIFA communication dated 20 December 2018.

The Netherlands

CCMO Instruction How to Proceed with Out of Specification ATMPs

Section on Out of Specification ATMPs added to standard research file submitted to recognized MREC (Medical Research Ethics Committee) or the Central Committee for Research Involving Human Subjects (CCMO).

The section has been added because in some cases, an ATMP does not meet the quality requirements as laid down in the specifications of the Investigational Medicinal Product Dossier (IMPD). For example, a cell therapy product can contain fewer cells than desired and therefore fall "outside the specifications." The CCMO informs that in exceptional cases OOS ATMP can still be administered, but must meet the following requirements:

- Get a positive benefit/risk assessment by the manufacturer/sponsor and the study doctor,
- The study protocol must contain a paragraph describing the OOS ATMP procedures,
- The protocol must specify how in such situations the data analysis deals with data obtained after the administration of an OOS ATMP,
- The information of OOS ATMP should be stated in the subject information sheet and informed consent,
- The participating subject in question must be informed in a timely and adequate manner about the product and agree to its administration.

In addition, the sponsor must inform the CCMO by notification that OOS ATMP has been delivered to the site and whether it has been administrated. If the OOS ATMP is produced and/or released in the Netherlands, a notification must also be sent to the Healthcare and Youth Inspectorate (IGJ). Both the CCMO and the IGJ must be notified within 48 hours.

NEWS FROM EUROPE: MEDICAL DEVICES

News from the European Commission

Additional Guidance Regarding the Vigilance System as Outlined in MEDDEV 2.12-1 rev. 8

"This document provides additional guidance in relation to the Medical Device Vigilance System (MDVS) that is currently in operation under the Medical Devices Directives. The guidance should complement and be used in conjunction with MEDDEV 2.12-1 rev. 8, 2013."

It highlights an updated version of the Manufacturer Incident Report (MIR) form that will become mandatory in January 2020.

The January version of the MIR introduces the use of the adverse event terminology/coding harmonized via the International Medical Device Regulators Forum (IMDRF) and the use of unique device identification (UDI). The new MIR also introduces the concept of a single registration number (SRN), which will pre-populate a manufacturer's details in the future Eudamed. The current version of the MIR must also be included in device manufacturers' databases. Introducing the use of UDI and the SRN via the MIR comes in preparation for the future regulatory system under the EU's medical device and in vitro diagnostic Regulations.

The EC's latest guidance for the MDVS also identifies a set of five circumstances for which coordinating NCA is needed and the four types of situations where information-under the National Competent Authority Report (NCAR) should be disseminated between NCAs. The EC clarifies differences between the IMDRF NCAR and the EU NCAR exchanges. Member States must have "the appropriate/necessary bilateral confidentiality agreements" for the IMDRF NCAR exchange.

MDR-latest status

European Commission Decision How New Medical Device Expert Panels will be Designated under MDR and IVDR

In the process of preparing for the implementation of the medical devices Regulations the EC published on 10 September 2019 the Commission Implementing Decision (EU) 2019/1396 (Decision) laying down rules on designation of expert panels in the field of medical devices. These expert panels are to be designated to provide scientific, technical and clinical assistance to the Commission, the Medical Device Coordination Group (MDCG), Member States, Notified Bodies (NBs) and manufacturers under the MDR (Medical Device Regulation) and the In Vitro Diagnostic Regulation (IVDR). These expert panels will also be consulted by NBs as part of the conformity assessment of high-risk medical devices.

The Decision provides 11 areas in which one expert panel will be designated:

1. Orthopaedics, Traumatology, Rehabilitation, Rheumatology;
2. Circulatory System;
3. Neurology;
4. Respiratory System, Anaesthesiology, Intensive Care;
5. Endocrinology and Diabetes;
6. General and Plastic Surgery and Dentistry;
7. Obstetrics and Gynaecology, including Reproductive Medicine;
8. Gastroenterology and Hepatology;
9. Nephrology and Urology;
10. Ophthalmology;
11. In-Vitro Diagnostic medical devices.

Advisors shall be appointed to the expert panels for a term of three years following a call for expression of interest and consultation with the MDCG. This should ensure the selection of highly qualified, independent advisors.

The call for experts will be launched later in 2019 and published in the Official Journal of the European Union.

Draft Implementing Acts on the Common Specifications for the Reprocessing of Single-Use Medical Devices under MDR.

The EC has outlined the common specifications for the reprocessing of single-use medical devices under the MDR. The common specifications have been issued via a draft implementing regulation in alignment with criteria in Article 17(3) of the MDR and shall apply from 26 May 2020.

Provided that the safety and performance profile of the reprocessed device is equivalent to that of the original device and that the reprocessing is performed in accordance with the common specifications, EU member states may decide not to apply rules relevant to manufacturers' obligations for single-use devices reprocessed and reused within health institutions. The EC discusses devices incorporating medicinal substances and implantable devices and notes that not all single-use devices are suitable for reprocessing.

Guidance Regarding a Person Responsible for Regulatory Compliance (PRRC)

European regulators have published new guidance documents addressing persons responsible for managing compliance with the MDR/IVDR. It explains that manufacturers, Authorized Representatives and micro and small manufacturers must designate at least one staff member responsible for ensuring compliance to the MDR and/or IVDR. PRRC qualifications are specific for each of these three operators.

Micro and small manufacturers and European Authorized Representatives will have the option to subcontract their PRRC functions to third parties provided their subcontractors meet stated qualifications.

Finally, the guidance explicitly forbids a single individual from serving as PRRC for both an Authorized Representative and a manufacturer based outside the EU.

Guidance on the Implant Card Required by MDR.

Medical Devices: Guidance document Implant Card relating to the application of Article 18 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices.

"This document provides guidance for Member States, concerned industry and other stakeholders on a blueprint of an implant card (IC) required by the MDR (Regulation (EU) 2017/745). It describes the intended use, content and information to be provided by the manufacturer together on the IC and a definition of fields to be completed by the implanting healthcare institutions or healthcare providers according to national law in Member States. Whereas the intended purpose and most of the data elements of the IC are already defined in Article 18 of the MDR, this document contains the description of other data elements which must be completed by the healthcare institution or healthcare provider and which must be considered by the individual Member State when implementing Article 18 MDR as required."

NOTIFIED BODIES (NBs)

Recently, three additional NBs have been designed to issue CE mark certification under the upcoming MDR:

- IMQ ISTITUTO ITALIANO DEL MARCHIO DI QUALITÀ S.P.A., the Italian certification firm,
- DEKRA Certification GmbH based in Stuttgart, and
- TÜV Rheinland LGA Products GmbH from Munich.

IMQ, DEKRA Certification GmbH and TÜV Rheinland joined BSI Assurance UK, TÜV SÜD as the NBs that can certify device makers for MDR compliance.

For the incoming IVDR, which is set to take effect in May 2022, only one NB has been designated until now, Stuttgart-based DEKRA Certification GmbH.

In addition, in September 2019 the BSI's UK notified body issued approval for the first device certified under MDR.

News from Individual Countries

Denmark

Regulatory Advice Regarding Upcoming MDR Offered by DMA

The Danish Medicines Agency (DMA) has launched a pilot project to offer regulatory advice especially for start-ups and small and medium-sized medical device manufacturers as well as educational and research units regarding upcoming EU Regulation for Medical Devices 2017/745 (MDR) on 26 May 2020. The pilot project includes one hour, one-to-one meeting at DMA or as a teleconference. The pilot project will be active until end of 2019. The advice will cover more detailed guidance on the applicable and coming rules, as well as guidance about requirements and processes regarding applications for clinical investigations in regard to specific products and general regulations about CE marking.

The United Kingdom

MHRA Updates Guideline on Clinical Investigation-Biological Safety Assessment

The United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) have updated the guideline on clinical investigations of medical devices regarding biological safety assessment in line with the EU MDR.

The guidance relates to the legislative provisions under Annex XV of the MDR that a biological safety evaluation needs to be carried out before any clinical investigation is commenced. The updated guidance refers also to Article 62 of the EU MDR and indicates that "the competent authority must be able to verify that an appropriate toxicological risk assessment has been carried out so that it can ensure that the anticipated benefits to the patients enrolled in the clinical trial justify the foreseeable risks."

The guidance refers also to the ISO 10993:2018 standard on the biological and clinical evaluation of medical devices. The revised section on the toxicological risk assessment states, "In all cases a complete chemical fingerprint of the final medical device after all raw materials have gone through the manufacturing process should be provided and such chemicals undergone sufficient toxicological risk assessment."

In addition, the guidance includes the conformity assessment requirements and provides the list of documentation of an evaluation for the purposes of a manufacturer's conformity assessment should normally include.

France

Pilot Phase for Medical Device Clinical Investigations in the Context of the Application of the New EU MDRA

On 16 September 2019, the National Agency for the Safety of Medicine and Health Products (ANSM), the French NCA launched the 'pilot phase' procedure relating to clinical trials conducted on medical devices to be prepared for upcoming MDR in May 2020. France is the first European country to launch a 'pilot phase'.

The 'pilot phase' concerns initial authorizations for clinical trials involving MDs of types Class III, implantable, invasive Class IIa or IIb. The MD must either be without a CE mark or be CE marked for a different purpose. All therapeutic areas are concerned and all sponsors (academic or private) can apply. The participation of sponsors is voluntary.

The sponsor is therefore free to choose between two options:

- To apply the provisions currently in force (known as Jardé Law)
- To choose to simulate application of the provisions set out in the MDR by taking part in the 'pilot phase'.

In addition, the ANSM published practical information guide for applicants in English and French. The document describes the very detailed submission process to both the ANSM and the CPP. The deadlines, timelines and contact emails depends on the situation the applicant meets. The document provides the processing times for Clinical Investigation (CI) in comparison with the MDR. The guide includes the list of documents mandatory for submission and the summary of the dialog between Sponsor, the ANSM and the CPP in case the sponsor decides to take part in the 'pilot phase' for CI with MDs in France.

The Netherlands

Investigational Medical Device Dossier Update

The Central Committee for Research Involving Human Subjects (CCMO) published updated the Investigational Medical Device Dossier (IMDD). The update is in line with the requirements of the MDR and starting from 20 September 2019 should be used for submitting clinical investigation with medical device to the review committee Medical Research Ethics Committee (MREC) or (CCMO).

Other initiatives

IMDRF

Requirements for Regulatory Authority Recognition of Conformity Assessment Bodies Conducting Medical Device Regulatory Reviews

International Medical Device Regulators Forum published on 27 June 2019, a draft document MDRF GRRP WG N59 – Requirements for Medical Device Conformity Assessment Bodies for Regulatory Authority Recognition. The purpose of this document is to define the requirements for Conformity Assessment Bodies (CABs) performing regulatory reviews and other related functions for medical devices, including IVD medical devices. Both the regulatory review process and the decisions made by a CAB may be subject to further review by the applicable Regulatory Authority (RA) in the countries and regions where the medical device is manufactured and/or placed on the market.

OTHER "HOT" TOPICS IN THE EU

Key Brexit updates

European Commission Notice on Withdrawal of the UK and EU Rules in the Field of Good Laboratory Practice (GLP)

The EC's notice explains that as of the withdrawal date from the European Union, the principle of mutual recognition set out article 50(1) of directive 2004/10/EC, will no longer apply to tests conducted in the United Kingdom.

Instead, the "Mutual Acceptance of Data" (MAD) system established under the auspices of the Organisation for Economic Co-operation and Development (OECD) will apply from the withdrawal date from EU. All Member States participating in the MAD system must accept data from OECD members, which are full adherents to the MAD system having passed a successful evaluation by OECD under the OECD GLP Compliance Monitoring Programme.

The United Kingdom (UK) is an OECD member and a full adherent to the MAD system, as are Austria, Belgium, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, the Netherlands, Poland, Portugal, the Slovak Republic, Slovenia, Spain and Sweden. Thus, from the withdrawal date the mutual acceptance under the MAD system will apply between the UK and these EU Member States.

MHRA will Accept Results from Batch Testing Performed in the United States and other Non-EEA Countries

The UK's MHRA has confirmed it will accept results from batch testing performed in the United States in the event of a no-deal Brexit. As such, the US is now added in the original list of countries authorized to perform batch testing.

The updated list can be found under the link: List of approved countries for authorised human medicines on exit day - GOV.UK

Further Guidance Note on the Regulation of Medicines, Medical Devices and Clinical Trials if There's No Brexit Deal – Update

In preparation for Brexit, the MHRA has published further guidance outlining the steps that need to be taken to allow the marketing of medicines and medical devices, and continuing clinical trials in the EU and European Economic Area (EEA) market after Brexit.

MHRA GVP Guidance Note

This guidance describes the aspects of the EU guidance on Good Pharmacovigilance Practices (GVPs) that will no longer apply to the MHRA and UK Marketing Authorisation Holders (MAHs) or are to be read subject to modification in a no-deal Brexit.

UK Statutory Instruments Updated for EU Exit

The UK prepared draft contingency legislation for human medicines and medical devices and a drafts have been laid in Parliament in January 2019. In the event of a no-deal Brexit, the regulation will be applicable and followed by MHRA.

- The Medical Devices (Amendment etc.) (EU Exit) Regulations 2019
- EXPLANATORY MEMORANDUM TO THE HUMAN MEDICINES AND MEDICAL DEVICES (AMENDMENT ETC.) (EU EXIT) REGULATIONS 2019
- The Human Medicines and Medical Devices (Amendment etc.) (EU Exit) Regulations 2019
- The Human Medicines (Amendment etc.) (EU Exit) Regulations 2019
- The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019

NEWS FROM THE UNITED STATES OF AMERICA – "HOT" TOPICS

The Fees for Fiscal Year 2020 (October 1, 2019 through September 30, 2020)

Food and Drug Administration (FDA) announced the fee rates and payment procedures for medical device user fees for fiscal year (FY) 2020. The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Medical Device User Fee Amendments of 2017 (MDUFA IV), authorizes FDA to collect user fees for certain medical device submissions and annual fees both for certain periodic reports and for establishments subject to registration.

FDA Issues 510(k) Guidance Documents with Aim to Modernize 510(k) Program

The US Food and Drug Administration's Centre for Devices and Radiological Health (CDRH) on September 13, 2019 released final guidance documents on the Special 510(k) Program, the Abbreviated 510(k) program, how to format Traditional and Abbreviated 510(k)'s and CDRH's refuse to accept policy for 510(k)s.

As part of a wider, ongoing push to modernize FDA's 510(k) program, the final guidance documents provide more clarity on several programs the agency has been working on for the last couple of years. The FDA plans to discuss these guidance documents during a webinar on 31 October 2019.

FDA Awards 12 Grants to Fund New Clinical Trials to Advance the Development of Medical Products for the Treatment of Rare Diseases

The U.S. Food and Drug Administration today announced that it has awarded 12 new clinical trial research grants totalling more than $15 million over the next four years to enhance the development of medical products for patients with rare diseases. The grants were awarded to principal investigators from academia and industry across the country.

The FDA awarded the grants through the Orphan Products Clinical Trials Grants Program, funded by Congress to encourage clinical development of drugs, biologics, medical devices and medical foods for the treatment of rare diseases. The grants are intended to substantially contribute to marketing approval of products to treat rare diseases or provide essential data needed for development of such products.

"For more than 35 years, the FDA has been providing much-needed financial support for clinical trials of potentially life-changing treatments for patients with rare diseases. To date, the Orphan Products Clinical Trials Grants Program's grants have supported research that led to the marketing approval of more than 60 treatments for rare diseases," said FDA Principal Deputy Commissioner Amy Abernethy, M.D., Ph.D. "We are encouraged by the amount of interest we continue to have in the grants program and are committed to working with researchers and industry to facilitate and support the study and development of treatments for patients with rare diseases." The FDA received 89 clinical trial grant applications that were reviewed and evaluated for scientific and technical merit by more than 100 rare disease experts, including members of academia.

"The majority of rare diseases still do not have approved therapies and the FDA is committed to fostering product development in areas of unmet need. The Orphan Products Grants Program is one of several ways that the FDA supports the development of products for rare diseases. Since its creation in 1983, the program has provided more than $400 million to fund more than 600 new clinical studies," said Janet Maynard, M.D., director of the FDA's Office of Orphan Products Development. "We are pleased to continue to support research for a variety of rare diseases that have little, or no, treatment options for patients. By helping to spark research, FDA hopes to speed the development of products for rare diseases, and ultimately, make needed treatments available to those patients who need them most."

FDA Informs Patients, Providers and Manufacturers about Potential Cybersecurity Vulnerabilities for Connected Medical Devices and Health Care Networks that Use Certain Communication Software

As of 1 October 2019, the U.S. Food and Drug Administration is informing patients, health care professionals, IT staff in health care facilities and manufacturers of a set of cybersecurity vulnerabilities, referred to as "URGENT/11," that-if exploited by a remote attacker-may introduce risks for medical devices and hospital networks. URGENT/11 affects several operating systems that may then impact certain medical devices connected to a communications network, such as Wi-Fi and public or home Internet, as well as other connected equipment such as routers, connected phones and other critical infrastructure equipment. These cybersecurity vulnerabilities may allow a remote user to take control of a medical device and change its function, cause denial of service, or cause information leaks or logical flaws, which may prevent a device from functioning properly or at all.

To date, the FDA has not received any adverse event reports associated with these vulnerabilities. The public was first informed of these vulnerabilities in a July 2019 advisory sent by the Department of Homeland Security. Today, the FDA is providing additional information regarding the source of these vulnerabilities and recommendations for reducing or avoiding risks the vulnerabilities may pose to certain medical devices.

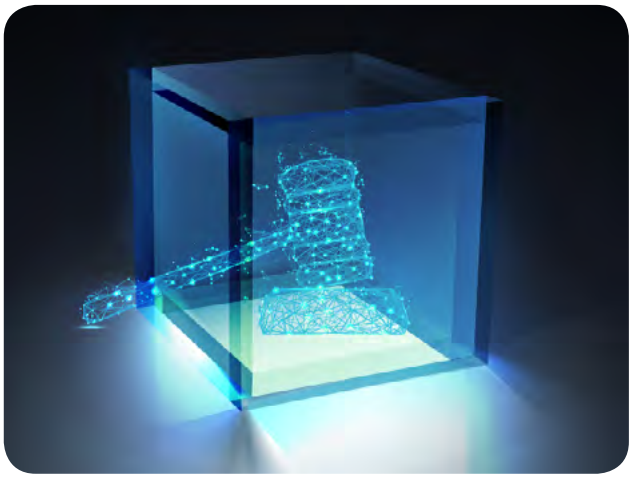
"While advanced devices can offer safer, more convenient and timely health care delivery, a medical device connected to a communications network could have cybersecurity vulnerabilities that could be exploited resulting in patient harm," said Amy Abernethy, M.D., Ph.D., FDA's principal deputy commissioner. "The FDA urges manufacturers everywhere to remain vigilant about their medical products-to monitor and assess cybersecurity vulnerability risks, and to be proactive about disclosing vulnerabilities and mitigations to address them. This is a cornerstone of the FDA's efforts to work with manufacturers, health care delivery organizations, security researchers, other government agencies and patients to develop and implement solutions to address cybersecurity issues that affect medical devices in order to keep patients safe."

The URGENT/11 vulnerabilities exist in a third-party software, called IPnet that computers use to communicate with each other over a network. This software is part of several operating systems and may be incorporated into other software applications, equipment and systems. The software may be used in a wide range of medical and industrial devices. Though the IPnet software may no longer be supported by the original software vendor, some manufacturers have a license that allows them to continue to use it without support. Therefore, the software may be incorporated into a variety of medical and industrial devices that are still in use today.

Some medical device manufacturers are already actively assessing which devices may be affected by URGENT/11 and are identifying risk and remediation actions. In addition, several manufacturers have already proactively notified customers of affected products, which include medical devices such as an imaging system, an infusion pump and an anaesthesia machine. The FDA expects that additional medical devices with one or more of the cybersecurity vulnerabilities will be identified.

The FDA will continue its work with manufacturers and health care delivery organizations-as well as security researchers and other government agencies-to help develop and implement solutions to address cybersecurity issues throughout a device's total product lifecycle.

The FDA will continue to assess new information concerning the URGENT/11 vulnerabilities and will keep the public informed if significant new information becomes available.



FDA Revises 1989 Guidance on Drug Master Files

The revised draft guidance from the US Food and Drug Administration (FDA) on drug master files (DMFs) deals with submissions on confidential information about facilities, manufacturing, processing, packaging and storing drugs. FDA said on 18 October 2019, that the update includes new procedures for DMFs referenced in abbreviated new drug applications (ANDAs), more detailed instructions on submitting original DMFs versus amendments, reference to the electronic submission requirements under section 745A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) that apply to certain DMFs, clarification and reorganization of material associated with Type III and Type IV DMFs and a change in FDA's contact person for the guidance.

A footnote on the second page says, "Although FDA's approach to the use of master files in BLAs under the PHS Act largely parallels its approach to the use of DMFs in applications under the FD&C Act, there is a significant difference: a BLA holder is generally expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license. For biological products in BLAs under the PHS Act, FDA has, as a scientific matter, generally not permitted applicants to incorporate information about drug substance, drug substance intermediate, or drug product by reference to a master file; rather, FDA generally expects such information to be submitted directly to the BLA."

In June, FDA proposed a new rule to allow certain biologics, originally approved under a new drug application (NDA), to continue relying on DMFs for certain information even after the NDA is deemed to be a license for a biological product on 23 March 2020.

The agency also further extended the implementation date for Type III DMF submissions in eCTD format to 5 May 2020.

FDA Finalizes Guidance on PDUFA Fee Waivers, Reductions and Refunds

The US Food and Drug Administration (FDA) on 16 October 2019 finalized guidance providing advice to drug and biologic sponsors looking to apply for Prescription Drug User Fee Act (PDUFA) fee waivers, reductions and refunds.

Specifically, the guidance explains the various types of fee waivers, reductions and refunds offered to industry, such as those for pressing public health needs, small business entities and when paying the fee would be a significant barrier to an applicant's ability to develop a drug.

The 29-page guidance finalizes a draft version released for comment in June 2018, which in turn was an update to the agency's previous final guidance on the topic from 2011. The guidance is nearly identical to the draft version with only a few minor additions and editorial changes.

On refund requests, the final guidance explains that the deadline for requesting a program fee refund is 180 calendar days from the date the fee is due, even if the applicant has submitted a citizen petition that may pertain to their claim for a refund.

FDA also explains that if a pending refund request "does not expressly cover a subsequent time frame for which an applicant wishes to claim a refund," the applicant would be required to submit another request for a refund that covers the subsequent timeframe.

"For example, if an applicant has a request for a FY 2020 program fee refund that is pending at the time of a program fee assessment for FY 2021, and the applicant believes it is also eligible for a refund for FY 2021 and wishes to claim a FY 2021 refund, a timely request for a refund for FY 2021 must be submitted," FDA writes.

Another change to the final guidance includes the addition of instructions for small businesses that are granted a fee waiver for an application they ultimately do not submit to contact the Division of User Fee Management and Budget Formulation within the Centre for Drug Evaluation and Research for further guidance on qualifying for a fee waiver on a future application.

The final guidance also adds a section with instructions for where and how to submit written requests for fee waivers, reductions and refunds, whether by email or by post.

Additionally, the final guidance includes an appendix containing Form FDA 3971, which is to be used by small businesses for requesting a fee waiver or refund.

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