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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.

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CORONOVIRUS (COVID-19) OUTBREAK – LATEST UPDATES

WHO Notice to Stakeholders Addresses Regulatory Expectations During the Pandemic

The World Health Organization (WHO) has published a notice to manufacturers, laboratories and contract research organizations (CROs) on regulatory expectations and flexibility during the COVID-19 pandemic. The notice addresses questions related to inspections, quality management systems (QMSs), facilities and equipment, personnel, material, production and quality control laboratories. The guidance underlines that due to a different stage of the pandemic in each country, national measures and guidance should also be considered. The aim is to ensure the quality, safety, efficacy and continuity in the supply of products and services in order to attain a high level of public health.

The WHO website with a technical guidance and publications on COVID-19 topic are updated daily.

Availability of Potential COVID-19 Treatments and Progress on COVID-19 Vaccine

On 2 April 2020, the International Coalition of Medicines Regulatory Authorities (ICMRA) held a virtual, global regulatory workshop convening experts from medicines regulatory authorities, the WHO and the European Commission. During the meeting these experts discussed the progress on COVID-19 medicine development. Regulators emphasised that, "within the current COVID-19 disease pandemic, no specific medicinal product has yet clearly demonstrated efficacy." In this forum, the experts gave updates and information about the ongoing and planned clinical trials. They mentioned various therapeutic candidates like remdesivir, lopinavir/ritonavir with or without interferon-ß, and chloroquine/hydroxychloroquine. It has been said that "other antivirals (e.g. monoclonal antibodies, hyperimmune sera) and immunomodulating agents such as IL-6 and IL-1 inhibitors are likewise considered for development." The experts also discussed compassionate and off-label use of medicines in the context of COVID-19. The meetings are ongoing at regular intervals and the European Medicines Agency (EMA) and Food and Drug Administration (FDA) are taking it in turns to chair these meetings.

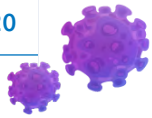
As of May 2020, the EMA was with interaction with many developers of potential COVID-19 treatments and vaccines. Since 3 July 2020, remdesivir has obtained conditional marketing authorisation for the treatment of COVID-19 in patients with pneumonia (adults and adolescents from 12 years of age) who require supplemental oxygen in the European Union under the name Veklury. Remdesivir should also be used in compassionate use programmes across Europe.

Apart looking for a potential COVID-19 treatment, worldwide researchers work to find a vaccine against SARS-CoV-2, the virus causing the COVID-19 pandemic. The Oxford scientists said that with an emergency approval from regulators, "the first few million doses of their vaccine could be available by September, if it proves to be effective''. Marco Cavaleri, the Head of Office, Anti-infectives and Vaccines in the Human Medicines Evaluation Division, responsible for scientific oversight and coordination of EMA activities for anti-infective and vaccines said that "a vaccine against SARS-CoV-2 could be approved in the European Union in about a year".

On 17 June 2020, the European Commission published European strategy to accelerate the development, manufacturing and deployment of vaccines against COVID-19.

Regulatory Affairs Professionals Society (RAPS) created COVID-19 vaccine tracker. RAPS updates this tracker once new information about COVID-19 vaccine candidates, pre-clinical stages of development or research is available.

In addition, the EMA has published an overview of how the Agency will accelerate its regulatory procedures to deliver marketing authorizations of COVID-19 related medicines and vaccines in the shortest possible timeframes, while ensuring robust scientific opinions are reached.



Europe

European Commission Guidance on COVID-19

The European Commission takes every measure to ensure availability of medical supplies and equipment and support Member States in their efforts to address the COVID-19 pandemic. They publish the recommendations on health systems resilience, testing strategies and for community measures. The EC gives access to National information resources on COVID-19, which provides an easy link to the up-to-date news and guidance of COVID-19 pandemic from each EU country.

The European Commission has published a list of essential medical devices and in vitro medical in the context of the COVID-19 pandemic.

On 2 April 2020, the European Commission issued guidance on medical devices, active implantable medical devices (AIMDs) and in vitro diagnostic medical devices (IVDMD) in the COVID-19 context. The guidance is in a 'questions and answers' format and explains, among other topics, the legal requirements for placing such medical devices on the EU market during COVID-19 outbreak and how standards can be used under the current legislation.

EMA's Governance During COVID-19 Pandemic

On 24 April 2020, the European Medicines Agency (EMA) published the third version of the Guidance on the management of Clinical Trials during the COVID-19 (Coronavirus) pandemic. This updated version provides additional flexibility and clarification for stakeholders on:

- "The distribution of medicines to trial participants. This takes into account social-distancing measures and possible limitations in trial site and hospital resources;
- The remote verification of source data (SDV) in the context of social distancing measures. This aims to facilitate activities that support the approval of COVID-19 and other life-saving medicines;
- Notifying authorities of urgent actions taken to protect trial participants against an immediate hazard, or of other changes taken to support patient safety or data robustness."

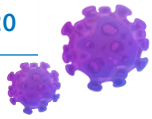
In May 2020, the guidance Questions and Answers on Regulatory Expectations for Medicinal Products for Human use during the COVID-19 pandemic has been updated, adding a new section with questions and answers, laying out flexibilities for good manufacturing practice (GMP) and good distribution practice (GDP), and a new section on the suspension of on-site inspections of plasma collection centres. It has been updated to answer questions on changes in the manufacturing and supply chain areas. It covers the need for a swift update of the supply chain to ensure continuity of supplies to the EU of crucial medicines for treatment of COVID-19 patients.

On 29 June 2020, the EMA adapted revision of the guidance Implications of coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials. The revisions to the guidance offer new recommendations for sponsors.

The EMA publishes the latest updates on COVID -19 guidance and press releases at the COVID-19: What's new.

The EMA has strengthened the mandate for the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), creating a COVID-19 Response Group working within ENCePP to strengthen the capacity of the regulatory network and clinicians to monitor and evaluate the benefit-risk balance of medicinal products used in the pandemic. The activities of ENCePP COVID-19 Response Group include, among others, the review of protocols and reports of COVID-19 studies posted in the European Union electronic Register of Post-Authorisation Studies (EU PAS Register) in order to analyse research topics and study designs and to develop/identify and disseminate relevant methodological guidance for pharmacoepidemiology (PE) studies on medicines and vaccines. This role gives ENCePP centres high visibility and recognition as key players in the fight against COVID-19 and for public health protection.

In addition, the EMA experts, together with European Commission and the Clinical Trials Facilitation and Coordination Group (CTFG) members recently held a WebEx conference, inviting organisations representing academia and patients' organisations. During the conference experts brought a range of topics related to the changes to ongoing clinical trials, informed consent, distribution of investigational medicinal products (IMP), monitoring, GCP inspections and communication with authorities during COVID-19 pandemic. The slides from the conference are available on EudraLex - Volume 10 - Clinical trials guidelines.



The Clinical Trials Facilitation and Coordination Group (CTFG) published Link to National guidance on CT management during the COVID-19 pandemic. The links connect directly to the EU countries guidance on recommendations for the conduct of clinical research at the time of restrictive measures due to the COVID-19 or the instruction for the (re)start the clinical research.

Recent Updates from EU Individual Countries Regarding COVID-19 Pandemic

Belgium

Federal Agency for Medicine and Health Product (AFMPS/ FAGG/FAMHP) has published an Addendum to the Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic, Version 2.0, dated 29 April 2020.

Denmark

Updated Extraordinary Measures for Clinical Trials due to COVID-19, English 5.1 version, dated 23 April 2020.

France

National Agency for the Safety of Medicine and Health Products (ANSM) has updated information on its website relating to COVID-19 - Ongoing Clinical Trials, dated 20 May 2020.

Portugal

The National Authority of Medicines and Health Products (INFARMED) has issued guidelines on the Management of Clinical Trials during the COVID-19 (Coronovirus) Pandemic, dated 15 April 2020.

Germany

Information on the authorisation and conduct of clinical trials of medicinal products during the COVID-19 pandemic (Version 2.3) updated on 27 May 2020.

The Netherlands

The Central Committee on Research Involving Human Subjects (CCMO) has updated information on its website by adding guidance on Conditions for (re)starting clinical research, 25 June 2020.

The United Kingdom

The Medicines & Healthcare products Regulatory Agency (MHRA) has updated the guidance Exemptions from Devices regulations during the coronavirus (COVID-19) outbreak, 17 June 2020.

The MHRA also launched COVID-19 Yellow Card reporting site for healthcare professionals, patients, and caregivers to report easily suspected side effects associated with any medicine used in patients with confirmed or suspected COVID-19 and incidents involving medical devices used in relation to COVID-19, including adverse incidents with equipment, diagnostic testing kits and software/apps.

North America

United States of America

The U.S. Food and Drug Administration (FDA) has issued guidance - COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products, May 2020.

FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency has been updated in July 2020.

FDA recognizes that the COVID-19 pandemic may impact the conduct of bioequivalence studies intended for submission in Abbreviated New Drug Applications (ANDAs). FDA has published guidance on Bioequivalence Studies for Submission in ANDAs during the COVID-19 Pandemic.

FDA Protects Patients and Consumers from Fraud During COVID-19

Throughout the pandemic, the U.S. Food and Drug Administration has found many nefarious actors seeking to exploit consumers during the pandemic by selling unproven medical products often with fraudulent claims. The emergence of fraudulent medical products is a common phenomenon during crisis situations.

For example, in 2013, the FDA issued ten warning letters to firms selling unproven medical products with false or misleading claims to protect against influenza. In 2014, seven warning letters were issued for unproven and fraudulent Ebola products.

Once COVID-19 reached the U.S., the FDA received complaints from U.S. consumers about unproven cures, illegitimate test kits, and substandard or counterfeit respirators being offered for sale on the internet, and the agency identified thousands of new "high-risk" internet domain names that were registered in early 2020. To proactively identify and neutralize these threats to consumers, the FDA launched Operation Quack Hack in March 2020.

As of June 2020, the FDA has identified more than 700 fraudulent and unproven medical products related to COVID-19. The Operation Quack Hack team has reviewed thousands of websites, social media posts, and online marketplace listings, resulting in over 90 warning letters to sellers, more than 150 reports sent to online marketplaces, and more than 250 abuse complaints sent to domain registrars to date. Operation Quack Hack initiatives have led domain registrars to investigate and take down numerous websites illegally selling unproven products and retailers to remove hundreds of unlawful products from the marketplace.

Canada

New Guidance Documents to Streamline Clinical Trials Related to COVID-19

Health Canada Wednesday issued two guidance documents designed to streamline clinical trials for medical devices and drugs that are related to COVID-19.

The guidance documents support an interim order (IO) that reduces the administrative burden of clinical trials and promotes efficient investigation of drugs and medical devices to treat, prevent, mitigate or diagnose COVID-19.

The IO has dropped administrative requirements for non-significant changes during a clinical trial; only changes that are significant now need approval. Also, trials may now engage a broader range of investigators and obtain informed consent in a variety of ways.

Health Canada's IO also reduces the administrative requirements for trials that involve new uses of drugs and medical devices that are already being marketed.

These adjustments, said HC, will be of particular benefit for such complex clinical trials as multi-site, multi-arm and remote trials, and those that involve repurposing drugs and devices.

Required clinical trial reviews by Health Canada and a Research Ethics Board (REB) have also been prioritized for COVID-19 related drugs and devices but must still take place.

The scope of the two guidance documents, one for drug clinical trials and one for medical devices, includes trials related to COVID-19 for pharmaceutical and biologic drugs, including blood and blood components; medical devices and combination products are also included. The IO and guidance documents apply to clinical trials in phases I-III.

The guidance documents for COVID-19-related clinical trials of drugs and medical devices are effective for one year from the date posted.

Management of Clinical Trials During the COVID-19 Pandemic

Health Canada has updated the guidance Management of Clinical Trials during the COVID-19 pandemic: Notice to Clinical Trial Sponsors, 3 April 2020.

MEDICINAL PRODUCTS/DRUGS

Europe

News from the EMA

Notice to Sponsors on Validation and Qualification of Computerised Systems Used in Clinical Trials

On 7 April 2020, the EMA has published the Notice to sponsors on validation and qualification of computerised systems used in clinical trials. The guidance has been issued due to the recent inspection findings and the implications they had on the integrity, reliability, robustness and acceptability of data in the context of clinical trials data submitted to support marketing authorisation applications (MAAs). Most clinical trial data supporting MAAs are collected through computerised data collection tools e.g. electronic case report forms (eCRFs) or clinical trial management systems (CTMSs). Failure to document and therefore, demonstrate the validated state of a computerised system, is likely to pose a risk to data integrity, reliability and robustness, which depending on the criticality of the affected data, may result in a recommendation from the GCP Inspectors Working Group (IWG) to the Committee for Medicinal Products for Human Use (CHMP), not to use the data to support MAAs.

News from Individual Countries

Austria

Non-Interventional Studies (NIS) Reporting Update

The Austrian Federal Office for Safety in Health Care (BASG) has informed that in accordance with §11 of the NIS MeldeVO, the final report and a lay summary in German should be submitted to the Federal Office via the BASG NIS Register 12 months after the end of the NIS. The NIS Register sends automatic reminders after 12 months. The basis of this reminder is the originally stated planned end of the NIS, not the actual end date.

Germany

Update of Radiation Protection Ordinance

The German Radiation Protection Ordinance of November 19, 2018 has been changed and came into force on 2 April 2020. The Ordinance sets up limits of radioactive substances and regulates protective measures to keep human population and the environment from damaging ionising radiation.

Italy

New Bank Details and Fees

The Italian Medicines Agency (AIFA) has informed of change on its bank details and fees. From 1 Apr 2020, the agency's cash service will be managed by the new Cashier Banco BPM SpA, VAT number 09722490969 with registered office in Milan, Piazza Filippo Meda no. 4.
The payments of the tariffs referred to in the Ministerial Decree of 6 December 2016 must be made to the new IBAN bank account:
IT49-E-05034-03200-000000010448
(SWIFT code: BAPPIT21060).

For payments made from abroad, the main BIC/SWIFT code of the BancoBPM SpA bank is BAPPIT22.

The Competent Authority fees from 1 April 2020 are as follows:

- Evaluation of clinical trials phase II and III **€ 9498,43**
- Evaluation of clinical trials phase IV **€ 5699,06**
- Evaluation of substantial amendment **€ 2234,93**
- System inspections concerning the recognition of eligibility of health institutes to conduct phase I studies **€ 2217,61.**

The United Kingdom

New Online Submission of Amendments and Amendments Tool to HRA/REC

From 2 June 2020, all applicants making a clinical trial project-related amendment for medicinal products and/ or medical devices to Health Research Authority (HRA)/ Research Ethics Committee (REC) will need to complete the amendment tool and submit their amendment via new online submission gateway instead of submission via e-mail. The tool replaces the Substantial Amendment Notification Form, and Notification of Non-Substantial/Minor Amendments(s) for NHS Studies.

The Research Tissue Banks and Research Databases amendments must also be submitted online from 2 June 2020, but will not need the amendment tool.

New Online Booking Service Procedure to HRA/REC

In May 2020, the HRA has changed an online booking service procedure to HRA/REC in the UK for all project-based studies in the National Health Service (NHS)/ Health and Social Care (HSC) in Northern Ireland, tissue banks, databases and health research taking place outside of the NHS/HSC except clinical trials related to COVID -19. For COVID-19 studies the previous booking service by phone is applicable.

The online booking service is available 24 hours a day, 7 days a week.

Updated Model of Clinical Trial Agreement for England, Scotland, Wales and Northern Ireland

In March 2020, the HRA published the revised commercial model Clinical Trial Agreement (mCTA) and Clinical Research Organisation model Clinical Trial Agreement (CRO-mCTA). The new models have been published on IRAS Help. The contracts are designed to be used without modification for industry-sponsored trials in NHS/HSC patients in hospitals throughout the UK Health Service. These model CTAs replace the 2018 versions.

Poland

Regulation on the Types, Scope and Templates of Patients Medical Documentation

On 15 April 2020, the New regulation of the Minister of Health of 6 April 2020 on the types, scope and templates of medical documentation and the method of its processing came into force. It introduces numerous changes regarding electronic documentation and keeping medical records in electronic form at sites. It underlines that patients medical records can be kept at sites only in one form - electronic or paper.

New Bank Account for Administrative Payments

The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, the Polish Competent Authority (CA) informed about the new bank account for administrative payments required for the authorization for the specific person from Contract Research Organisation (CRO) performing regulatory submissions activities on behalf of sponsor to the CA or other administration organisations. This administration payment, stamp duty, covers the number of persons mentioned on the Power of Attorney.

North America

United States of America

FDA Proposes New Rule on Reporting Requirements

On 23 July 2020, the U.S. Food and Drug Administration (FDA) published the proposed rule, Annual Summary Reporting Requirements Under the Right to Try Act, that when finalized, will implement a statutory requirement for sponsors and manufacturers to provide an annual summary to the FDA for any eligible investigational drug they provide to eligible patients under the Right to Try Act.

"The FDA is dedicated to achieving the goals that Congress set forth in the Right to Try Act, so that patients facing terminal conditions have another avenue to access investigational medicines," said Anand Shah, M.D., Deputy Commissioner for Medical and Scientific Affairs. "Today's proposed rule builds on the FDA's long-standing dedication to enhancing access for patients who are facing life-threatening diseases or conditions and our continued commitment to transparency."

The Right to Try Act, or the Trickett Wendler, Frank Mongiello, Jordan McLinn and Matthew Bellina Right to Try Act of 2017, provides a pathway for patients who have been diagnosed with life-threatening diseases or conditions who have tried all approved treatment options and who are unable to participate in a clinical trial, to access certain unapproved treatments. Ultimately, the sponsor or manufacturer who is developing the drug or biologic, not the FDA, is responsible for determining whether to make their product available to patients who qualify for access under the Right to Try Act.

US Regulations for Regenerative Medicine Advanced Therapies

Regenerative medicine is a rapidly expanding field, offering the potential to treat serious and life-threatening conditions by replacing, or "regenerating," human cells, tissues, or organs that have been damaged by disease, trauma, or congenital defects. With more than 200 investigational new drug (IND) applications anticipated by the US Food and Drug Administration (FDA) in 2020, regenerative medicine should yield many new therapies with enormous benefits to patients, especially those with unmet medical needs.

Navigating the complex regulatory environment of regenerative medicine requires companies to engage with the FDA early and often throughout the drug development process to identify and overcome potential obstacles to approval. Many of these therapies are developed by scientific institutions and medical research groups with limited in-house regulatory resources, so it is advisable to seek external regulatory support early in the planning process.

Regenerative medicines, as defined by the FDA, include cell therapies (non- and genetically modified), therapeutic tissue-engineering products, human cell and tissue products, and combination products using these biologic components, which lead to a sustained effect on cells and tissues.

In addition, a combination product (biologic device, biologic drug, or biologic device-drug) can be eligible for regenerative medicine advanced therapy (RMAT) designation when the biological product constituent part is a regenerative medicine therapy and provides the greatest contribution to the overall intended therapeutic effects of the combination product (i.e., the primary mode of action of the combination product is conveyed by the biological product constituent part). In January 2020, the FDA released six final guidance documents on gene therapy manufacturing and clinical development of products and a draft guidance.

The FDA's policy to advance the development of safe and effective cell and gene therapies can be found here: www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products.

FDA Finalizes Guidance on Broader Cancer Trial Eligibility

In four final guidance documents published on 10 July 2020, the US Food and Drug Administration (FDA) outlines cancer trial eligibility criteria considerations for individuals with several specific clinical conditions. Another guidance addresses minimum age considerations for inclusion of paediatric patients in cancer clinical trials.

The guidance, issued jointly by FDA's Centres for Drug Evaluation and Research and Biologics Evaluation and Research (CDER and CBER), provide considerations for balancing the importance of including children and those with some serious health conditions in cancer clinical trials against ethical and data quality considerations.

"Unnecessarily restrictive eligibility criteria may slow patient accrual, limit patients' access to clinical trials, and lead to trial results that do not fully represent treatment effects in the patient population that will ultimately use the drug," said FDA in its guidance for inclusion of paediatric patients. "Broadening cancer trial eligibility criteria can maximize the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice and should be considered to avoid jeopardizing patient safety."

The FDA issued these four final guidance documents after publishing them as drafts in March 2019. After public consultation, clarification and some additional condition-specific details were added to the guidances. Separately, a final guidance issued in 2019 addresses inclusion of adolescents in cancer clinical trials.

Guidance documents can be accessed at:

- https://www.fda.gov/media/121318/download
- https://www.fda.gov/media/121317/download
- https://www.fda.gov/media/121319/download
- https://www.fda.gov/media/123745/download

U.S. Clinical Trials Taking Longer Despite FDA Efforts to Accelerate Drug Development

The average time needed to complete clinical development of a new drug in the U.S. is increasing, outpacing the FDA's efforts to accelerate drug approval and lengthening the overall amount of time needed to bring a new drug to market, according to a new report.

The average combined clinical trial and approval timeline increased by almost five months between 2008 and 2018, an analysis by the Tufts Centre for the Study of Drug Development (CSDD) shows. At the same time, the clinical trial timeline grew by nearly seven months, while the approval phase dropped by nearly two months.

Drugs that fell under the FDA's expedited review program, however, were brought to market 11 percent faster than those without expedited review. And the trial-to-approval timeline for orphan drugs decreased 12 percent.

The duration of clinical trials increased across all phases, the study shows, with the greatest increase (9.2 percent) in phase 2. To read a summary of the results, click here: https://bit.ly/32t9vj7

Canada

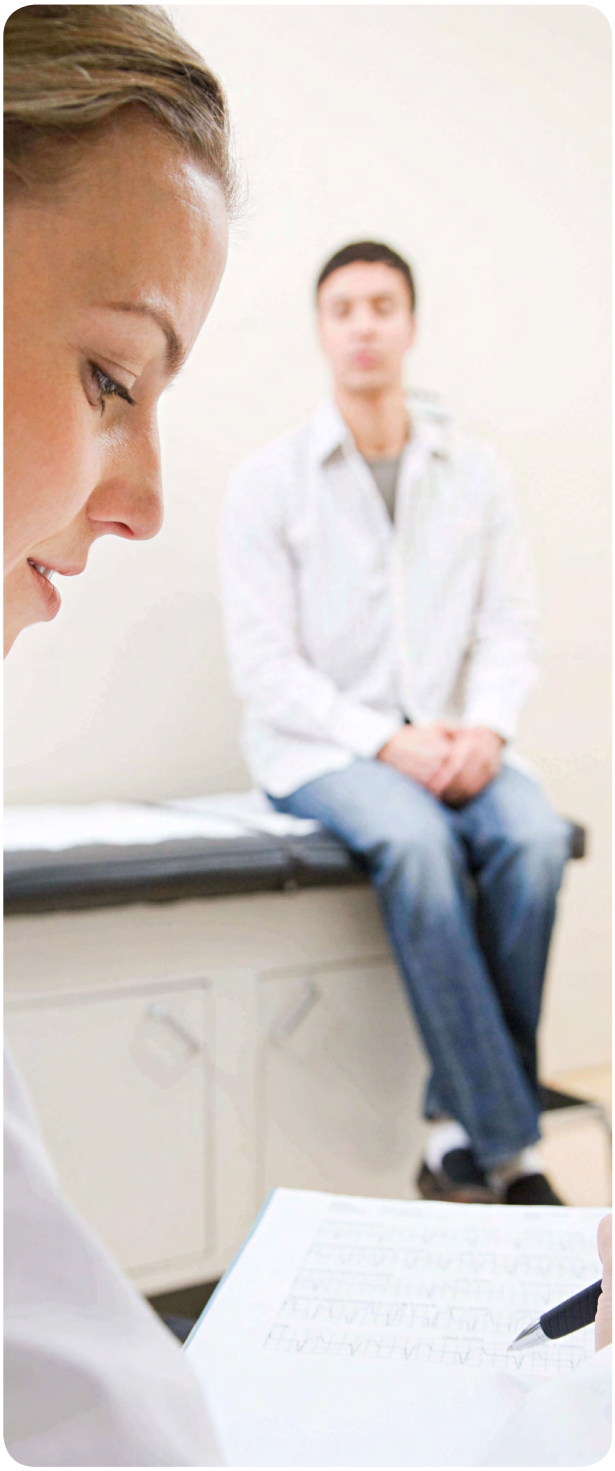
Confirmation of the Mandatory Use of the Regulatory Enrolment Process (REP) as of 1 October 2020

By way of this update, Health Products and Food Branch (HPFB) is reminding sponsors that the mandatory date for use of the Regulatory Enrolment Process (REP) and the Common Electronic Submissions Gateway (CESG) is 1 October 2020 applicable to pharmaceutical, biologic and radiopharmaceutical drugs for human use as well as disinfectants, pursuant to Part C, Division 1 and Division 8 of the Food and Drug Regulations.

The HPFB is implementing a single window for transmission of regulatory transactions in electronic format which is considerably faster and more efficient than courier services and which provides secure transmission of transactions which email does not offer. To facilitate the use of this single window, also known as the CESG, HPFB has created the REP.

The REP is a method HPFB uses to collect information from sponsors related to their company, dossiers, products, regulatory activities and transactions. It consists of a set of web-based templates that upon completion generate REP Extensible Mark-up Language (XML) files. The REP XML files are sent to HPFB via the CESG.

The REP will replace the processes for the existing Health Canada 3011: Drug Submission Application Form and the Drug Submission - Application Fee Form for Human and Disinfectant Drugs.



MEDICAL DEVICES

EUROPE

News from the European Commission

Implementation of Medical Devices Regulation (MDR) Postponed until 26 May 2021

The European Commission approved delaying the MDR application date by one year until 26 May 2021. The delay will allow the medical device industry to maintain maximum focus on helping healthcare systems to combat COVID-19, and on addressing the pandemic's impact on the whole healthcare ecosystem.

New Medical Devices Website Launched

The European Commission has launched a new Medical Devices website, hosted on the portal of the Directorate-General for Health and Food Safety (DG SANTE). Previously the website was hosted on the Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs (DG GROW).

The website contains information on current legislation and new Regulations and provides advice for all stakeholders in the medical devices and in vitro medical devices value chain by giving access to latest news, press releases, guidance and newsletters.

News from Individual Countries

Germany

BfArM and DMDI Merged

Since 26 May 2020, the Federal Institute for Drugs and Medical Devices (BfArM) and essential functional units of the German Institute for Medical Documentation and Information (DIMDI) were brought together under the umbrella of the BfArM to form one authority for medical devices in Germany. The former DIMDI employees can be reached under new email addresses and telephone numbers. Calls are automatically transferred during a transition period.

The DIMDI website (www.dimdi.de) is still functioning to access the full range of services. However, after a transition period (26 May 2021), all content will be transferred to the BfArM website.

North America

United States of America

Final Guidance for Electronic Submissions for Medical Devices

A new final guidance from the US Food and Drug Administration (FDA) lays the framework for electronic submissions for medical devices. The agency advised that more specifics about the nuts and bolts of electronic submissions, as well as the timing of implementation, will be provided in upcoming guidance.

One guidance document is insufficient for describing and implementing electronic formats for all types of submissions covered under the statutory requirements, said FDA in the newly issued guidance, which delineates the agency's plans for implementing the requirements of section 745A(b)(3) of the FDA Reauthorization Act of 2017 (FDARA). The newly issued final guidance follows a draft guidance issued in September 2019.

The guidance does clarify the types of guidance that must be submitted electronically. These include premarket notification submissions (510(k) submissions); De Novo submissions; premarket approval applications (PMAs), including transitional and modular PMAs; product development protocols, investigational device exemption applications of all types; humanitarian device exemptions, Emergency Use Authorizations; and certain investigational new drug (IND) applications such as those intended for use in screening donor blood.

Also included are biological license applications (BLAs) regulated by CBER as biological products, regardless of whether an IND submission is required before the BLA submission. Though Q-submission types aside from pre-submissions are not required to be in electronic format, "FDA recommends that all Q-submissions be submitted in electronic format to facilitate efficient review," according to the guidance.

Other Initiatives

IMDRF Finalized Guidance Covering Cybersecurity, Personalized Devices and Conformity Assessment Bodies

In April 2020, the International Medical Device Regulators Forum (IMDRF) published principles and practices for medical device cybersecurity guidance document. This document considers cybersecurity in the context of medical devices that either contain software, including firmware and programmable logic controllers (e.g. pacemakers, infusion, pumps) or exist as software only (e.g. Software as a Medical device (SaMD)).

It outlines recommendations for medical device manufacturers, healthcare providers, regulators, and users to: minimize cybersecurity risks that could arise from use of the device for its intended purposes; and to ensure maintenance and continuity of device safety and performance. All guidance documents are available here.

OTHER "HOT" TOPICS IN EUROPE

Medical Device Regulation: MDR-latest status

The application of the Medical Device Regulation (MDR) is now postponed until 26 May 2021. The European Commission updated its "rolling plan" for adopting implementing acts and other measures ahead of the MDR and In Vitro Diagnostic Regulation (IVDR).

Safety Reporting in Clinical Investigations of Medical Devices under The MDR

The new Medical Device Coordination Group (MDCG) guidance issued in May 2020, provides instructions of safety reporting requirements in clinical investigations (CIs) of medical devices performed in line with the Regulation (EU) 2017/745 – Medical Device Regulation (MDR) Article 80. The guidance explains the process of safety reporting for CIs in the absence of EUDAMED and when the platform is available; provides guidance when, by whom and to whom safety reporting must be done; informs how to proceed in case of Post-Market Clinical Follow Up (PMCF) investigations.

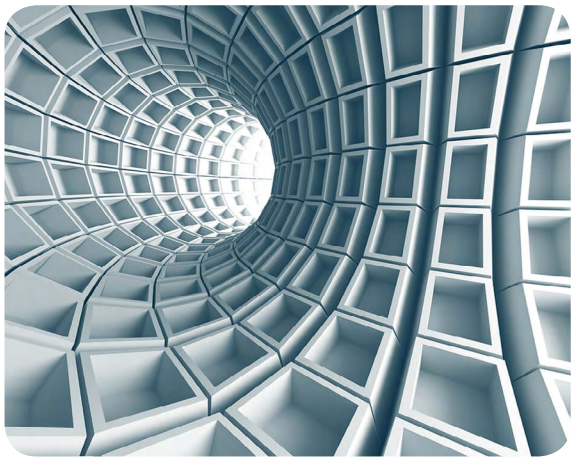
"Due to the transitional provisions in MDR Article 120(11) this guidance also covers clinical investigations which have started to be conducted in accordance with Article 10 of Directive 90/385/EEC (AIMDD) or Article 15 of Directive 93/42/EEC (MDD) prior to 26 May 2021. These investigations may continue to be conducted after date of application of the MDR, but the reporting of serious adverse events and device deficiencies shall be carried out in accordance with the MDR requirements from 26 May 2021 and onwards."

Guidelines on the Adoption of Union-Wide Derogations for Medical Devices in Accordance with Article 59 of Regulation (EU) 2017/745

In response to the COVID-19 pandemic, and with patient health and safety as a guiding principle, the European Parliament and the Council on 23 April 2020 adopted Regulation (EU) 2020/561. This new regulation eased the process for renewing notified body designations prior the new date of application of the Medical Devices Regulation (MDR) 26 May 2021.

Medical Device Coordination Group (MDCG) offers new guidance and templates documents to medical device manufacturers assess in implementing the MDR.

- Clinical Evaluation - Equivalence. A guide for manufacturers and notified bodies
- Regulation (EU) 2017/745: Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC. A guide for manufacturers and notified bodies
- Post-market clinical follow-up (PMCF) Plan Template. A guide for manufacturers and notified bodies
- Post-market clinical follow-up (PMCF) Evaluation Report Template. A guide for manufacturers and notified bodies
- Regulatory Requirements for Ventilators and Related Accessories
- Guidance on temporary extraordinary measures related to medical device Notified Body audits during COVID-19 quarantine orders and travel restrictions
- Interpretation of Article 54(2)b rev1
- Transitional provisions for consultations of authorities on devices incorporating a substance which may be considered a medicinal product [...] as well as on devices manufactured using TSE susceptible animal tissues
- Clinical evaluation assessment report template, July 2020



EUDAMED

The European Commission sets timeline for rolling out EUDAMED Models. The Commission said that the actor registration module will be made available at the latest by March 2021. After this date, the modules for unique device identification (UDI)/device registration and certificates/notified bodies will be online "as soon as functional," which the Commission said could be complete by May 2021.

Medical Devices: Latest Notified Body Designations

Germany's MDC Medical Device Certification GmbH was designated as the 13th notified body and under the Medical Devices Regulation (MDR). Sweden's Intertek Medical Notified Body AB became the 14th notified body designated under the MDR.

France's GMED became the 15th notified body designated under the MDR in the EU and first in France.

Germany's TÜV SÜD Product Service GmbH Zertifizierstellen became the fourth notified body designated under the In Vitro Diagnostic Regulation (IVDR).

CE Certificates-TEAM-NB Survey

The European notified body group Team-NB has published an annual survey from 23 notified bodies and TEAM-NB members from 27 EU member states at the end of 2019. Team-NB noticed an important increase in certificates issued in the 2019 with a jump of nearly 50% after 30% jump in the preceding year 2018. It showed that industry rushed to obtain the certificates before the application of the EU Medical Device Regulation (MDR).

Key Brexit Updates

Getting Ready for Changes

On 9 July 2020, the European Commission published document on Communication on readiness at the end of the transition period between the European Union and the United Kingdom. The document describes the current situation of negotiation on a new partnership with the EU and the UK and the procedures which have already been negotiated. In accordance with the Withdrawal Agreement, EU law continues to apply within the United Kingdom for a 'transition period' lasting until 31 December 2020. During the coronavirus pandemic the subsequent three rounds of negotiations had to be held by video conference. The Commission states that negotiations have shown little progress so far but discussions are intensified over the summer, with negotiation rounds and/or specialised sessions scheduled each week from 29 June 2020.

Both sides consider October as the latest point that a deal could be agreed upon, to allow implementation and ratification before the end of the year.

Joint Letter on the Need for a Mutual Recognition Agreement between the EU and UK

The European Commission has published the joint letter from the pharmaceutical and biotechnology sector to the Commission Presidents, Commissioner and Negotiators for constructive negotiation on Mutual Recognition Agreement between the EU and UK. They say: "we are extremely concerned about the lack of progress with only 6 months until the end of the Transition Period, which could lead to a failure to reach a negotiated outcome on the future EU-UK relationship." Industry representatives calls for negotiation to prioritize health and patients' access to medicines in the EU-UK, to ensure simplified and rational rules of origin and smooth import clearance processes.

Notice to Stakeholders Withdrawal of the United Kingdom and EU Rules in the Field of Clinical Trials- Update

The European Commission has released the Notice to Stakeholders dated 7 May 2020. The notice replaces the documents from 6 September 2018. The European Commission reminds clinical trial sponsors that they must comply with EU clinical trial rules following the Brexit transition period that expires on 31 December 2020 especially that the deadline to extend the transition period now passed, "There is no possibility for further extension beyond that date," the agencies write. The document explains supply process of investigational medicinal products (IMPs) between the EU and the UK, Legal representative and Qualified person role.

OTHER "HOT" TOPICS FROM UNITED STATES

FDA Announces First of Its Kind Pilot Program to Communicate Patient Reported Outcomes from Cancer Clinical Trials

On 23 June 2020, the U.S. Food and Drug Administration (FDA) launched Project Patient Voice, an initiative of the FDA's Oncology Centre of Excellence (OCE). Through a new website, Project Patient Voice creates a consistent source of publicly available information describing patient-reported symptoms from cancer trials for marketed treatments. While this patient-reported data has historically been analysed by the FDA during the drug approval process, it is rarely included in product labelling and, therefore, is largely inaccessible to the public.

"Project Patient Voice has been initiated by the Oncology Centre of Excellence to give patients and health care professionals unique information on symptomatic side effects to better inform their treatment choices," said FDA Principal Deputy Commissioner Amy Abernethy, M.D., Ph.D. "The Project Patient Voice pilot is a significant step in advancing a patient-centred approach to oncology drug development. Where patient-reported symptom information is collected rigorously, this information should be readily available to patients."

Patient-reported outcome (PRO) data is collected using questionnaires that patients complete during clinical trials. These questionnaires are designed to capture important information about disease- or treatment-related symptoms. This includes how severe or how often a symptom or side effect occurs.

Patient-reported data can provide additional, complementary information for health care professionals to discuss with patients, specifically when discussing the potential side effects of a particular cancer treatment. In contrast to the clinician-reported safety data in product labelling, the data in Project Patient Voice is obtained directly from patients and can show symptoms before treatment starts and at multiple time points while receiving cancer treatment.

The www.fda.gov/about-fda/oncology-center-excellence/project-patient-voice (Project Patient Voice website) will include a list of cancer clinical trials that have available patient-reported symptom data. Each trial will include a table of the patient-reported symptoms collected.

In the first phase of this pilot website, only one trial will be included while the FDA seeks public feedback on how the information is presented. The FDA will use this feedback to consider improvements to the website in order to make the information as user-friendly as possible.

The visualizations and data included on the website are voluntarily provided by the drug companies that conducted the clinical trials. AstraZeneca is the first company to provide patient-reported outcome data for one of their FDA-approved drugs and has collaborated with the FDA to identify methods to display the information in a way that is informative to health care professionals and patients.

Project Patient Voice is not meant to replace the clinician-reported safety information that is available as part of a drug's labelling. Data from Project Patient Voice should not substitute for advice from a health care professional. Rather, Project Patient Voice serves as a complement to FDA patient labelling and patient information, not a sole source of information on which to make decisions about medical care.

The FDA will seek public feedback regarding the Project Patient Voice pilot effort at a virtual public workshop co-sponsored with the American Society of Clinical Oncology on July 17. The "Clinical Outcome Assessments in Cancer Clinical Trials" workshop will include health care providers, patients, health outcomes researchers, industry, advocacy groups and other stakeholders interested in rigorous measurement of symptom and functional outcomes. In addition to discussing trial design considerations to obtain patient-reported symptomatic side effects, the FDA will obtain feedback on the presentation of PRO symptomatic side effect data on the Project Patient Voice website to further ensure that the information is clear and meaningful to health care professionals and patients.

FDA Puts Spotlight on Decentralized Clinical Trials

Decentralized clinical trials (DCTs) offer opportunities to optimize efficiencies in clinical trials, a number of U.S. Food and Drug Administration (FDA) officials, including Dr. Isaac R. Rodriguez-Chavez, officer for clinical research methodology, regulatory compliance & policy development within FDA's, Centre for Drug Evaluation and Research have said at recent public conferences. Dr. Rodriguez-Chavez and others believe DCTs will make it more convenient for individuals to participate in trials.

They will help the clinical trial industry do a more thorough job accessing diverse populations by reducing geographical barriers—increasing enrolment and retention of trial participants—and bringing trials to the local environments where trial participants reside, thus expediting trial conduct and hopefully decreasing costs.

Advocates of DCTs also hope leveraging them with local healthcare providers and digital health technologies will accelerate medical product development and speed delivery of therapies to patients. FDA is following the regulatory framework approved by Congress regarding the 21st Century Cures Act and the modernization of clinical research while protecting public health.

Meantime, FDA recognizes the need to guide the clinical research field at large about DCTs, and its Centre for Drug Evaluation and Research recently announced plans to release a guidance sometime by end of 2020.

Decentralizing clinical trials is no longer a 'nice-to-have' feature to reduce clinical trial times and improve participant engagement. The COVID-19 outbreak has shattered this illusion and placed the spotlight on the imperative to have better, faster access to new drugs, meaning clinical trials can no longer languish in a tedious, paper-based approach.

"At the Agency, 'decentralized trials' refers to the decentralization of technologies. These clinical trials use digital technologies to have remote interactions with real participants. In contrast, virtual trials are preclinical trials conducted in silico or on models. Both examples use digital technology, but their application is different. "Hybrid trials combine elements of traditional and centralized approaches," Rodriguez-Chavez continued. Here, some patient consultations or tests may be performed remotely and others in person at a trial site.

Normalization will be more likely after the FDA issues its decentralized guidance, tentatively scheduled for later this year. "It represents an expansion of clinical research from traditional to decentralized trials," Rodriguez-Chavez said. It will include hybrid trials, as well.

Telehealth "is up and coming in clinical research," he added, noting that the COVID-19 pandemic has expedited the expansion of telehealth. The Code of Federal Regulations governs the conduct of medical research, so he cautioned that those seeking to use telehealth in clinical research should ensure they meet local, state and federal regulations governing telehealth and telemedicine.

In addition to the communications ease of telehealth options, technology such as wearables can facilitate decentralized clinical trials. What could this like in the near future? Things to consider could include: Real-time patient data insights; Enrolment insights-dashboards show what is/not working and when to stop recruitment ; De-risk trials in real-time-compliant patients, fewer patients needed, faster database lock; Enhanced patient safety-clinical team alerted to adverse events as soon as they occur, direct to patient notification; Patient-centricity and empowerment-informed and educated patients know what to expect and are more compliant; On-demand support-click-2-call, live chat, telemedicine, home healthcare, travel considerations and more.

Resource:
www.fda.gov/media/134778/download

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