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REGULATORY

NEWSLETTER N.33
January - March 2021

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

Contents

MEDICINAL PRODUCTS/DRUGS

Europe

News from the European Commission

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. The Commission publishes on its Public health website all updated guidance and relevant instructions for EU citizen, stakeholders and Members States. Latest updates include: EU Vaccine Strategy update informing of contracted doses for EU sites; launch new programmes, or expand existing ones, for the collection of plasma from donors recovered from COVID-19; and adopted a Communication outlining a balanced and common path to a safe and sustained re-opening of Europe.

The EC has also published three factsheets on COVID-19 vaccines: how do COVID-19 vaccines work; the health benefits of vaccination; and making sure COVID-19 vaccines are safe.

On 17 March 2021, the European Commission proposed to create a Digital Green Certificate to facilitate safe free movement inside the EU during the COVID-19 pandemic. The Digital Green Certificate will be a proof that a person has been vaccinated against COVID-19, received a negative test result or recovered from COVID-19.

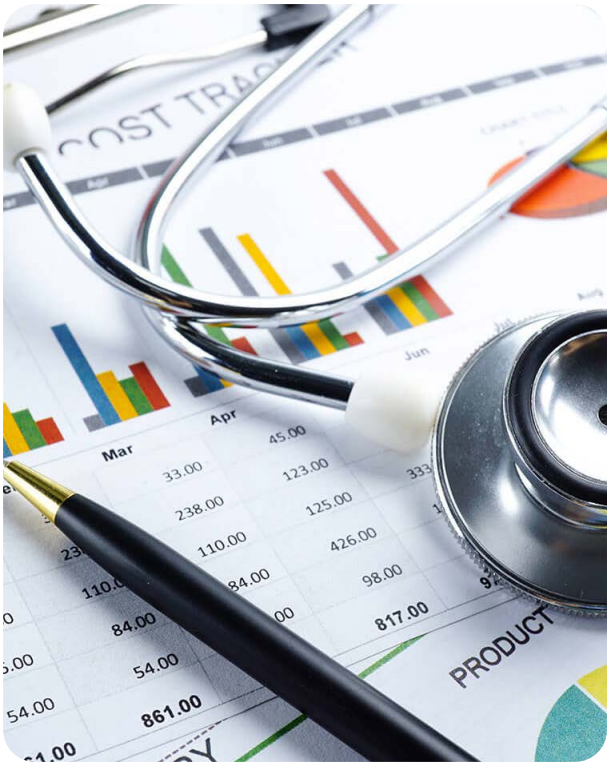
Trainings on CTR and CTIS Offered by European Commission and European Medicines Agency (EMA)

In March 2021, the EMA's Management Board agreed to revise the go-live date of the Clinical Trials Information System (CTIS), which is a main step of Clinical Trials Regulation (EU) No. 536/2014 (CTR) implementation in the European Union (EU). A new date of the go-live date of CTIS and at the same CTR application is 31 January 2022.

The Management Board informed that the new plan considers adding some very limited additional functionality in the CTIS, whilst continuing to focus on the technical robustness and quality of the system and the user experience, both at the time of go-live and after.

In order to support Member States with implementation of CTR, DG SANTE of the European Commission, the EMA and the Clinical Trials Facilitation and Coordination Group (CTFG) of the Heads of Medicines Agency jointly organized a training on 9-10 March 2021 for National Competent Authorities (NCAs) assessors, inspectors and ethics committee members from each EU/European Economic Area (EEA) Member State. The presentations' slides are available on the Commission website. The recoding is also available for those who register at Vimeo website and purchase an access.

In addition, the EMA organized virtual master sections for pharmaceutical companies, including Contract Research Organisations (CROs). Presentations together with eLearning recordings are published on the EMA website. The EMA sets up also a network of master trainers for sponsors and CROs.



Revision of the EU Legislation on Blood, Tissues and Cells

The European Commission launches a public consultation on the EU legislation on blood and tissues and cells. A current legislation is covered by Evaluation of the Union legislation on blood, tissues and cells dated 10 October 2019. The process will take into account a number of lessons learned from the COVID-19 pandemic. The Commission plans to propose a revision to this legislation at the end of 2021.

Pharmaceutical Strategy for Europe-Roadmap

On 30 March 2021, the European Commission published its Roadmap on the revision of the general pharmaceutical legislation. The main aim is to ensure a timely access to new medicines in the EU. It will be opened for feedback until 27 April 2021.

ePrivacy Regulation Draft Proposal

The Council of the European Union (EU) published a Proposal for a Regulation of the European Parliament and of the Council concerning the respect for private life and the protection of personal data in electronic communications. (ePrivacy Regulation). The ePrivacy Regulation will repeal the existing ePrivacy Directive.

In this context, the European Data Protection Board (EDPB) adopted a statement on the latest Council proposal.

News from the European Medicines Agency (EMA)

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

EMA Latest Updates on the COVID-19 Pandemic

The European Medicines Agency (EMA) provides support to medicine developers researching and developing potential COVID-19 medicines, helps pharmaceutical companies to speed up medicine and vaccine development and approval for COVID-19, and on how they should address the regulatory challenges arising from the COVID-19 pandemic. All news, press releases, dedicated guidance, rapid procedures and a contact point are available at COVID-19: latest updates.

EMA initiatives for acceleration of development support and evaluation procedures for COVID-19 treatments and vaccines guidance has been updated on 25 March 2021. The total review time for rapid scientific advice has been reduced to 20 days, compared to the regular 40/70 days' timeframe.

Latest updates also include: safety updates for Comirnaty, COVID-19 Vaccine Moderna and Vaxzevria (COVID-19 Vaccine AstraZeneca); extension of the availability of free scientific advice for potential COVID-19 treatments and vaccines to 15 September 2021; advice on the use of regdanvimab in COVID-19 patients not requiring oxygen and at high risk of progressing to severe disease; advice on the use of monoclonal antibody combination bamlanivimab/etesevimab and/or casirivimab/imdevimab to treat COVID-19; the authorisation of the fourth COVID-19 vaccine in the EU, COVID-19 Vaccine Janssen; rolling review of Sputnik V (Gam-COVID-Vac).

Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic

On 04 February 2021, the EMA updated the Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic, version 4. Additional flexibility and clarification have been added on the role of centralised monitoring and central review of data collected. The guidance expands the use of life-threatening

conditions; where the absence of SDV for critical data may likely pose unacceptable risks to participants' safety or the reliability/integrity of trial results; involving particularly vulnerable participants such as children or those temporarily (e.g. trials in emergency situations) or permanently (e.g. trials in patients with advanced dementia) incapable of giving their informed consent or in pivotal trials."

Common Commentary-EMA and FDA

The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have published a new Common Commentary document providing their recommendations for sponsors to use when planning clinical trials for paediatric cancer drugs. The Common Commentary gives a framework for seeking scientific advice from both the EMA and the FDA on new Paediatric Investigation Plans (PIPs) and initial Paediatric Study Plans (iPSPs).

EMA Revision on GVP Modules

On 01 February 2021, the EMA has launched two consultations on good pharmacovigilance practice (GVP) modules. The first consultation is a revision of Module XVI, Risk minimisation measures: selection of tools and effectiveness indicators. The second consultation is a new addendum to Module XVI, Methods for effectiveness evaluation, which provides marketing authorisation holders and competent authorities with additional information on data sources and managing risk minimisation measures. Both consultations close on 28 April 2021.

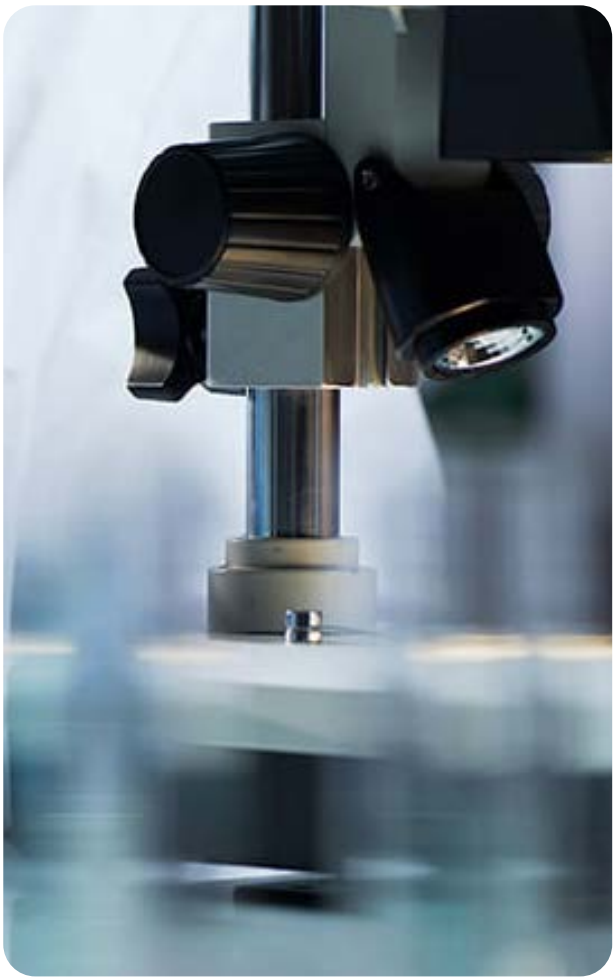
EMA's Q&As GCP-Update

EMA's questions and answers (Q&As) on good clinical practice (GCP), have been updated. New Q&A number 15 has been added: "Do GCP inspectors from regulatory authorities of an EU/EEA Member State have the authority to inspect trial participants' medical records and other data, even if there is no statement in the ICF establishing that trial participants consent to the review of their medical records and other personal data by EU inspectors?"

Revision of Q&As on Consultation Procedure for Ancillary Medicinal Substances in Medical Devices

On 30 March 2021, the EMA revised the Questions & Answers on the consultation procedure to the EMA by notified bodies (NBs) on an ancillary medicinal substance or an ancillary human blood derivative incorporated in a medical device. Regulation EU 2017/45 (MDR) requires NBs to seek an opinion from a competent authority or the EMA on the quality and safety of medicinal substances incorporated in medical devices that have an action that is ancillary to the action of the device. The NB should give due consideration to the scientific opinion when taking its certification decision.

In parallel, the EMA updated an applications forms templates to be submitted to the EMA by NBs for consultation on an ancillary medicinal substance or an ancillary human blood or plasma derivative used in the medical devices.



News from Individual Countries

The United Kingdom

MHRA Patient Involvement in New Applications-Pilot Project

The Medicines and Healthcare products Regulatory Agency (MHRA) informed about a pilot project that puts patient involvement in new applications of clinical trials. From 23 March 2021, when new applications for selected medicines (new active substances and new indications) are received, the applicant company will be asked for evidence on the patient involvement activities they undertook when developing their product. "For clinical trials, whilst additional information won't be requested at this early exploratory stage of the pilot, the MHRA will be documenting in medical assessment reports if there is evidence of patient involvement in clinical trial applications in order to better understand the current scope of activities." the MHRA writes.

The pilot project will help the MHRA to learn from any patient-related activities that take place during development and use this knowledge to improve the quality of clinical drug development and health outcomes in the future.

"During the pilot project, the information provided by the applicants will be voluntary and will not alter the outcome of their application. However, in future, the MHRA hopes that a successful pilot will lead to patient involvement playing a greater role in the final assessment process, when clinical trials are approved, or medicines are licensed."

Changes Related to Submitted Amendments

As of 25 March 2021, all amendments to Clinical Trial Investigational Medicinal Products (CTIMPs) that require notification to the MHRA will no longer require the submission of a European Commission Substantial Amendment Notification Form "Annex 2" form. The MHRA will now accept a copy of the completed Amendment tool when notifying amendments to a single CTIMP. The Annex 2 form, which is available on the MHRA website, can still be completed and submitted to the MHRA for 'bulk' amendments, where the same change will affect many trials simultaneously.

Moreover, the Health Research Authority (HRA) informed that the addition of a new National Health Service/Health and Social Care (NHS/HSC) site, and the addition or change of a Principal Investigator (PI) in the NHS/HSC for CTIMPs studies, will now be classified as non-substantial amendments. These changes should still continue to be classified as substantial when relating to a non-NHS/HSC setting.

Denmark

Home-Based Clinical Trials

The Danish Medicines Agency (DMA) has started a project to enable researchers and pharmaceutical companies to conduct so-called decentralised clinical trials which by means of new technologies make it easier for people to participate in clinical trials. The DMA is working together with patients, researchers and the patient industry and others to find ways for more elements of clinical trials to be home-based in the development of medicines in Denmark.

The Netherlands

CCMO Note on Transfer of Subject Data Outside EEA for Future and Ongoing Clinical Studies

On 16 July 2020, the Court of Justice of the European Union (CJEU) issued a judgment invalidates the EU-U.S. Privacy Shield. This means that organizations in the EU can no longer pass on personal data to the United States (US) based on the EU-U.S. Privacy Shield. Following that judgment and the European Data Protection Board (EDPB) recommendations on the consequences thereof, the CCMO published a note indicating the implications of this judgment for future and ongoing clinical studies and provides clarity about the transfer of data from test subjects to countries outside the European Economic Area (EEA).

France

New National Pharmacovigilance Application Tool

The National Agency for the Safety of Medicine and Health Products (ANSM), the French competent authority informed about a development of new national pharmacovigilance application for reporting adverse events. New features have been added to new tool, including implementation of the international standard for data exchange according to the ICH-E2B (R3) format which will become mandatory from 30 June 2022.

In addition, on 18 March 2021 the ANSM launched its new website.

Italy

Clinical Trials Contracts Update

The National Coordination Centre of Ethics Committees, established by AIFA, the Italian Medicines Agency published the updated version of the Contract for the conduct of clinical trials on medicinal products, in which the words "where appropriate" have been added to Article 4.2., namely: 4.2. The Sponsor undertakes to make the drug object of the clinical trial available at the end of the trial, beyond the observation period, for patients who have obtained a favourable clinical response for whom it is deemed appropriate, based on clinical judgment, to continue until the drug is made available through ordinary dispensing channels, in order to ensure therapeutic continuity, **where appropriate.**

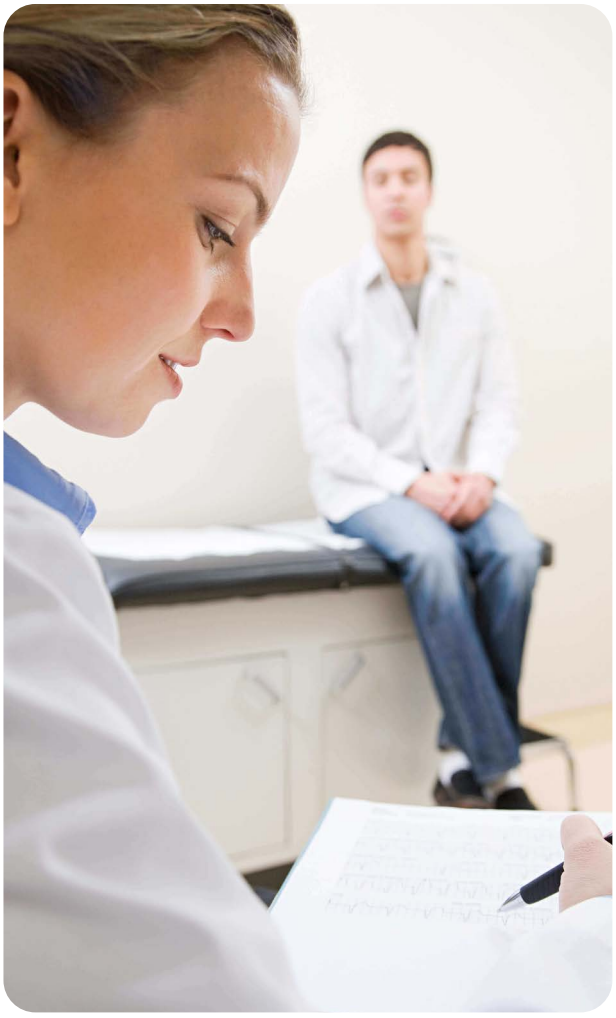
In addition, the National Coordination Centre updated version of the Contract for non-profit clinical trials on medicines, currently in consultation, to include Annexes A and B, respectively relating to the budget and the glossary for the protection of personal data.

Other Initiatives

CTFG Conclusion of the VHP Project

The Clinical Trials Facilitation and Coordination Group (CTFG), a working group on clinical trials of the Heads of Medicines Agencies has published a note informing the sponsors that the Voluntary Harmonization Procedure (VHP) project will be closed contextually with the implementation of the EU regulation 536/2014 on clinical trials (EU CTR). Sponsors are therefore informed that, starting 60 days before the effective date of the new regulation, initial clinical trial applications and substantial modifications applications via VHP will no longer be accepted and processed by the VHP administrator.

It is foreseen, if no unexpected issue with Clinical Trials Information System, the EU CTR will be fully applicable on 31 January 2022.



North America

United States of America

FDA Issues Much Anticipated Pandemic Remote Inspections Guidance

More than a year after the COVID-19 pandemic forced the US Food and Drug Administration (FDA) to halt most on-site inspections, the agency on 14 April 2021 issued guidance detailing its approach to remote interactive evaluations of drug and biomedical research facilities during the public health emergency.

Teleconferencing, livestreaming video and screen-sharing technologies are among the tools FDA says it will use when it determines that a remote interactive evaluation is appropriate for a particular facility. Remote interactive evaluations will be considered for all of FDA's drug inspection programs including preapproval and prelicense inspections, post-approval inspections, surveillance inspections and follow-up and compliance inspections.

After determining a remote interactive evaluation is appropriate, FDA says it will notify the facility or applicant and request confirmation of their willingness and ability to facilitate the technological aspects of the remote review.

Facilities may decline to undergo a remote interactive evaluation, but FDA warns that such decisions could lead to regulatory delays. "Declining FDA's request to perform a remote interactive evaluation could impede our ability to make a timely regulatory decision (e.g., regarding adequacy of a clinical trial used in support of a pending application or adequacy of a drug manufacturing operation described in the application)," the agency writes.

FDA will also take a risk-based approach to remote interactive evaluations of bioresearch monitoring (BIMO) inspections, including clinical trials being managed by CRO's and that information obtained from such evaluations will generally "be used to assess the facility's conduct, including data reliability and human subject protections to determine the acceptability of BIMO studies for FDA's application decision-making."

FDA, Guidance

Canada

Health Canada Issues Policy on Accessing the Premises of a Regulated Party Remotely to Verify Compliance

On 01 March 2021, Health Canada issued an updated policy to inform stakeholders of the legislative provisions for accessing a regulated party's place remotely. Entering a place remotely (using telecommunication) is known as "remote entry."

This policy explains: remote entry; the general conditions for conducting a remote entry; the rights and responsibilities of parties, including regulated parties, including drug and medical device companies and CRO's; and the consequences for parties that obstruct, hinder, provide false information, or fail to provide reasonable assistance during a remote entry.

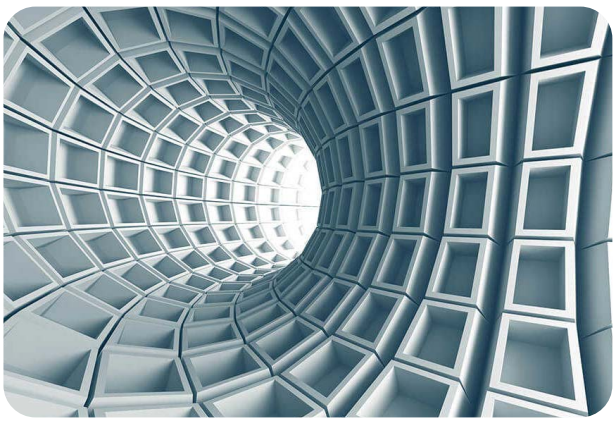
Health Canada's Regulatory Operations and Enforcement Branch (ROEB) has two directorates that are responsible for compliance and enforcement activities related to health products. These are the Health Product Compliance Directorate (HPCD) and the Medical Devices and Clinical Compliance Directorate (MDCCD).

Health Canada, Download the alternative format

Incident Reporting for Medical Devices

This guidance clarifies the new amended Medical Device Regulations that deal with incident reporting, in effect as of 23 June 2021. The guidance clarifies the Medical Devices Regulations that are currently in effect.

Download in PDF format



MEDICAL DEVICES

EUROPE

News from the European Commission

COVID-19 Tests-Guidance Issued by the European Commission

In February 2021, the Commission published a Question & Answer (Q&A) guidance on in vitro diagnostic medical device conformity assessment and performance in the context of COVID-19. The Commission explains what types of COVID-19 tests are available: "There are broadly two types of COVID-19 in vitro diagnostic tests performed on specimens from the human body in terms of the scientific rationale: those detecting the SARS-CoV-2 virus (e.g. the RT-PCR tests detecting the viral genetic material, or antigen tests detecting the viral protein) and those detecting the immune response of the human body to the infection (e.g. antibody tests)." In addition, the document informs of the legal framework for COVID-19 in vitro diagnostic medical devices, and the roles and responsibilities of various authorities in the COVID-19 testing process.

Guidance on State of the Art of COVID-19 Rapid Antibody Tests

The European Commission's Medical Device Coordination Group (MDCG) published guidance on state of the art of COVID-19 rapid antibody tests. For this guidance "state of the art is the developed stage of current technical capability and/or accepted clinical practice with regard to products, processes and patient management, based on the relevant consolidated findings of science, technology and experience." This guidance explains a legal requirements of Directive 98/79/EC on device performance in the context of COVID-19 rapid antibody tests and what kind of performance evaluations studies should be done to get tests suitable for intended purpose, taking into account the generally acknowledged state of the art.

European Commission Guidance on COVID-19

The Commission informed also that self-tests for COVID-19 (both self-swabbing and self-testing kits) are now starting to enter the EU market.

The Commission created the database contains publicly available In Vitro Diagnostics Medical Devices for COVID-19. The database is being updated periodically.

News from Individual Countries

Austria

New Validation Process in Preparation for MDR

The Austrian Federal Office for Safety in Health Care (BASG), informed about new validation process in preparation for Medical Device Regulation (EU) 2017/745 (MDR) from 01 April 2021.

To get validation of clinical investigation from 01 April 2021, an applicant should submit an application form in the new format and final favourable opinion of EC with documents in the versions listed in the final ethics committee opinion. The BASG undertakes to confirm that the notification is valid or to send a deficiency letter within 14 days. The applicant is then also granted a period of 14 days for correction or submission of documents. Once corrected documents received, BASG will complete the validation within one week. For clinical investigations with class I medical devices (MDs) or class IIa and IIb non-invasive MDs, class IIa/IIb medical devices: use under 30 days and invasive, once BASGs validation assessment confirmed, the study can be indicated. For other MDs, the 60-day period for the scientific and regulatory review will apply.

The BASG informed that the following rules for validation will apply to clinical investigations of medical devices as well as performance studies of in-vitro diagnostics to harmonise processing procedure.

Belgium

Submission Processes of Clinical Investigations According to MDR

Federal Agency for Medicines and Health Products (FAMHP), the Belgian Competent Authority (CA) published Guideline Submission Processes of Clinical Investigations according to MDR in Belgium. The new timelines and new regulatory pathways described in the guidance will be applicable from 26 May 2021. All applications submitted before that date will be handled in accordance with current Directives 90/385/EEC or 93/42/EEC (MDD) and their dedicated Belgian laws. The guidance provides clear instructions how and what kind of clinical investigations with medical devices should be submitted only to the Ethics Committee (EC); which must be only validated by the CA and submitted for favourable opinion to the EC; or get both CA approval and EC favourable opinion; or need a separate opinion from CA and EC.

Spain

Guidance on Clinical Investigations Under MDR

The Spanish Agency of Medicines and Medical Products (AEMPS) published guidance document related to the authorisation of clinical investigations under upcoming Medical Device Regulation (EU) 2017/745 (MDR). The MDR will come into force in the EU on 26 May 2021.

The AEMPS informs that from 05 April 2021, all clinical investigation authorization requests sent to the AEMPS must comply with the requirements of the MDR. Submissions of applications must be done in the same way as is currently done, due to the lack of EUDAMED module for clinical investigations. Clinical investigations with class I investigational medical devices (MDs) or class IIa and IIb non-invasive MDs, which may start after validation date completed by CA and EC favourable opinion in accordance with MDR will follow a national requirement. Clinical investigations with class III and implantable MDs, will need to follow 45 days evaluation period after validation. The guidance underlines that for safety reporting of serious adverse events (SAE), MEDDEV 2.7/3, revision 3, May 2015 should be followed until 25 May 2021. Since 26 May 2021 will be mandatory to follow up, MDCG 2020-10/1 "Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745."

Switzerland

New Requirements and Changes to the Submission Process of Clinical Investigations

The Swissmedic, the Swiss competent authority informed about new requirements and changes to the authorisation submission process of clinical investigations with medical devices from 01 May 2021 due to the upcoming Medical Device Regulation (EU) 2017/745 (MDR) which has been implemented into the Swiss Law. As of 01 May 2021, submissions (including any subsequent submissions) must be sent on the same day both to Swissmedic and to the responsible cantonal ethics committee. Starting from 01 May the new revised forms and the new folder structure must be submitted. For ongoing authorisation procedures, where authorisation will only take place after 26 May 2021, the missing documentation must be submitted.

The United Kingdom

Revision of Guidance for Manufacturers Regarding Clinical Investigations of Medical Devices

In January 2021, the UK's Medicines and Health products Regulatory Agency (MHRA) released, the 6th version of their Guidance for manufacturers regarding Clinical Investigations of Medical Devices. The revision provides instruction how to prepare a submission/notification of application for clinical investigations with medical devices to the MHRA in the context of current UK regulations.

Other Initiatives

IMDRF's Proposed Update to Guidance on Post-Market Clinical Follow-Up Studies

A proposed document on Assessment and Decision Process for the Recognition of a Conformity Assessment Body (CAB) Conducting Medical Device Regulatory Reviews has been released by the International Medical Device Regulators Forum (IMDRF) Good Regulatory Review Practices Working Group. The document explains the assessment process and outcomes, including the method to "grade and manage" nonconformities resulting from a recognizing Regulatory Authority's assessment of a CAB; and to document the decision process for recognizing a CAB or cessation of recognition.

The consultation closed on 19 April 2021.

North America

United States of America

Examples of Real-World Evidence (RWE) Used in Medical Device Regulatory Decisions

FDA has long said that it would consider real-world evidence (RWE) in making regulatory decisions related to medical devices. Those in industry know that FDA can be very critical of RWE, however, and it is not always clear why RWE was (or was not) acceptable in a particular submission.

On 16 March 2021, FDA released a summary document describing 90 instances in which RWE was used in medical device decision making (see report here). Interestingly, the examples in the report span between fiscal years 2012 and 2019, making it difficult to identify whether there has been any kind of shift in FDA acceptance of RWE following issuance of the 2017 guidance.

The report is helpful, however, in giving sponsors examples of where FDA has been accepting of clinical data in recent history. In the press statement announcing release of the report, FDA stated, "When reviewing the use of RWE to support a regulatory decision, the FDA relies on scientifically robust methods and approaches to determine whether the submitted RWE is of sufficient quality to support the regulatory decision."

The 90 examples come from the full continuum of clinical and device areas throughout all seven Offices of Health Technology in Centre for Devices and Radiological Health (CDRH) and across the medical device total product life cycle.

Canada

Health Canada Introduces New Reporting Requirements to Reduce Shortages

In an effort to prevent device shortages during the COVID-19 pandemic, Health Canada has introduced new reporting requirements COVID-19 guidance for reporting medical device shortages (GUI-0137) for device makers.

The agency said it will continue to allow certain products to be sold in Canada that may not fully meet Canadian regulations, but reports of any anticipated supply shortages are now required for such products, and the reports must be submitted in English and French.

Medical devices governed by the agency's "exceptional importation and sale interim order" may be imported or sold in the country provided the importer or manufacturer has a medical device establishment license. To import or sell such devices, companies must first submit a request to add a medical device to the authorized list. Once a product is on the list, companies must notify the agency at least five business days before they import a designated device.

OTHER "HOT" TOPICS IN EUROPE

Medical Device Regulation (MDR) and In Vitro Diagnostic Medical Devices Regulation (IVDR): Latest Status

The application of the Medical Device Regulation (EU) 2017/745 (MDR) will come into force in the EU on 26 May 2021 and In Vitro Diagnostic Medical Devices Regulation (EU) 2017/746 (IVDR) on 26 May 2022.

Article 33 of MDR requires the Commission to set up a European database on medical devices (EUDAMED.) According to Article 33(2) of the MDR, EUDAMED will be composed of six different electronic systems, called modules: first module the EUDAMED Actor registration module (launched on 01 December 2020), the module on Unique Device Identifier (UDI)/device registration (second module) and the module on Certificates and Notified Bodies (third module) will become available by May 2021. Modules: certain aspects of conformity assessment, clinical investigations, vigilance and market surveillance as well as post-market surveillance will be made available on a gradual basis as soon as they are functional. EUDAMED will be fully functional in May 2022.

Guidance related to procedures of clinical investigations with medical devices issued by the European Commission's Medical Device Coordination Group (MDCG) are expected to be published before 26 May 2021. In the meantime, some of the EU competent authorities published instructions for manufacturers and sponsors to be followed up for clinical investigation submissions until 25 May 2021 or after 26 May 2021. These guidance documents are discussed within the relevant sections of this Regulatory Newsletter.

Guidance on Harmonised Administrative Practices and Alternative Technical Solutions until EUDAMED is Fully Functional

The European Commission's Medical Device Coordination Group (MDCG) last week issued guidance on administrative practices and alternative technical solutions on the application of certain Medical Device Regulation (MDR) provisions in the absence of a fully functional EUDAMED system.

The Commission underlines that "the MDR stipulates that the corresponding provisions of Directives 90/385/EEC and 93/42/EEC shall continue to apply for the purpose of meeting the obligations laid down in the provisions of Article 123(3)(d) regarding the exchange of information."

Accordingly, the MDCG provides alternative solutions to fulfil the requirements for submitting or exchanging information as required under the MDR and during the absence of EUDAMED. In case of application for clinical investigations, its amendments and clinical investigations regarding devices bearing the CE marking (Post Market Clinical Follow up investigation) the application "should take place via the respective national procedures applicable to clinical investigations."

Medical Device Coordination Group (MDCG) New Guidance or Revisions of Guidance

- MDCG 2021-3 Questions and Answers on Custom-Made Devices & considerations on Adaptable medical devices and Patient-matched medical devices; March 2021
- Infographic. Is your software a Medical Device? Decision steps to assist qualification of Medical Device Software (MDSW)

Management of Legacy Devices-MDR EUDAMED

The European Commission published a document contains the details of how Legacy Devices (LDs) will be identified in EUDAMED and the way the different Unique Device Identifiers (UDIs) for the LDs will be generated or assigned. The document outlines the need for generated EUDAMED DI codes for devices that do not already have UDI DIs. The European Commission document explains exactly how to create this generated EUDAMED DI code. For devices that have an existing UDI DI, EUDAMED requires some small changes to this DI code. For devices that do not have an existing UDI DI then a generated EUDAMED DI is required. The Basic UDI component will have EUDAMED as the issuing entity.

Registry of LDs in EUDAMED by manufacturers will be mandatory in case a serious incident occurs or there is a field safety corrective action to apply, which requires registration as soon as possible and at least before a follow up or final vigilance report is submitted.

Members to MDR/IVDR Expert Panels Appointed by the European Commission

In January 2021, the Commission published list of the expert panels, established under the MDR and IVDR.

The experts will provide scientific, technical and clinical input to the Commission, Medical Device Coordination Group (MDCG), member states, notified bodies and manufacturers. Notified bodies are required to consult with expert panels on the clinical evaluations of certain high-risk medical devices and performance evaluations of some high-risk IVDs.

Remote Audits by Notified Bodies

Under the MDR and IVDR a Member States authorities obligation is to monitor notified bodies established on their territory and notified bodies are obligated to do audits on the manufacturer's premises and, if appropriate, on the premises of the manufacturer's suppliers and/or subcontractors to verify the manufacturing and other relevant processes. The Commission issued a notice where due to the "exceptional and unforeseen circumstances caused by the COVID-19 crisis," remote audits are allowed. Remote audits are limited to the period of time when such measures are "strictly necessary."

Updates of new officially designated notified bodies under the MDR and the IVDR are available in the European Commission NANDO database.

Key Brexit Updates

The Trade and Cooperation Agreement between the European Union (EU) and the United Kingdom (UK) of Great Britain and the Northern Ireland was reached on 24 December 2020 and came into force on 01 January 2021, following the end of the transition period on 31 December 2020.

The Council of the European Union (EU) adopted a Decision on 29 December 2020, which paved the way for the signing and provisional application of the EU-UK Trade and Cooperation Agreement and EU-UK Agreement on Security Procedures for Exchanging and Protecting Classified Information. The EU applied the agreement from 01 January 2021, pending ratification. The deal will not be fully operational until it is ratified by the EU which is now expected by the end of April 2021.

New rules and regulations around clinical trials and the approval of new medicines in the UK, forced the pharmaceutical and biotech industries the need to decipher added regulatory complexities to Great Britain (England, Scotland and Wales) and the Northern Ireland requirements. The Northern Ireland will follow EU rules for medicinal products and medical devices according to the Northern Ireland Protocol.

The UK's Medicines and Healthcare products Regulatory Agency (MHRA) has released plenty of guidance documents for industry and organisations explaining how clinical trials, drugs, medical devices and importation will be regulated as of 01 January 2021. Some of the following guidance have been recently updated:

- Guidance on qualified person responsible for pharmacovigilance (QPPV) including pharmacovigilance system master files (PSMF) updated to be easier to understand and clarified certain points, February 2021
- Guidance for retailers: supplying medical devices to Northern Ireland has been updated by a new section on customs requirements, 05 March 2021
- Importing medicines into Northern Ireland before 31 December 2021, Industry must notify the MHRA if they will not be using these flexibilities, published on 09 March 2021
- Exporting active substances manufactured in Great Britain for use in EEA and Northern Ireland, updated Register of Written Confirmations for UK active substance manufacturers, last update on 02 March 2021
- Medical devices: EU regulations for MDR and IVDR (Northern Ireland), a new section on importer requirements has been added, 05 March 2021
- List of approved countries for authorised human medicines, updated the information about acceptance of batch testing from EEA countries, which will be reviewed before 31 December 2022. A two-year notice period

will be given in the case of changes. This change is to allow the sector to continue to focus on the pandemic, and to protect the supply of medicines to UK patients, 16 March 2021

- Pharmacovigilance requirements for UK authorised products recorded webinar, 13 February 2021
- Registering an IVD for Performance Evaluation recorded webinar 2021.

MHRA Guidance on Borderline Products

On 06 January 2021, the MHRA published a guidance informing how the MHRA makes decisions on when a product is a medical device (borderline products) after Brexit and in the context with pandemic. The guidance underlines that it should be always considered the fact that if a product is considered a medical device in countries outside the UK that it will be a medical device in the UK as well. Decisions about whether a product is a medical device are based on the intended purpose of the product and its mode of action.

EMA Questions & Answers (Q&A) Guidance on Implementation of Northern Ireland Protocol Update

The European Medicines Agency (EMA) updated a practical guidance on the applicable rules in Northern Ireland after the transition period with respect to EMA activities.

Revision 3 dated 05 March 2021 updates the response to question 14.3 considering the Trade and Cooperation Agreement between the EU and UK (in particular, its Annex on Medicinal Products). In addition, a reminder under question 2.1 is added to consider also the guidance in question 2.2.

Explanatory Memorandum to Human Medicines Act

The MHRA published the Explanatory Memorandum to the Human Medicines (amendment etc.) (EU exit) Regulations 2020 and at the same confirmed that the UK remains an active member of the European Pharmacopoeia Commission through the British Pharmacopoeia (BP). This requirement remains the same after the transition period in accordance with the Human Medicines Regulations (Regulation 251).

Personal Data Transfer from EEA to the UK-Adoption Process Launched

On 19 February 2021, the European Commission launched the process towards the adoption of an adequacy decision for transfers of personal data from the European Economic Area (EEA) to the United Kingdom (UK). Until adopting the final adequacy decisions for the UK, data flows between the EEA and the UK continue and remain safe thanks to a conditional interim regime that was agreed in the EU-UK Trade and Cooperation Agreement. This interim period expires on 30 June 2021.

Data flows in the other direction-from the UK to the EEA-are regulated by UK legislation, which applies since 01 January 2021. The UK decided that the EEA ensures an adequate level of protection and that therefore data can flow freely from the UK to the EEA.

OTHER "HOT" TOPICS FROM UNITED STATES

FDA: Master Protocols have Value in COVID-19 and Beyond

On 14 April, 2021, an official from the US Food and Drug Administration (FDA) recommended that developers of COVID-19 drugs and therapeutics consider using master protocols to assess the benefits and the risks of potential COVID-19 treatments and outlined ways to ensure the integrity of the data generated from these protocols.

Gregory Levin, the deputy director of the Division of Biometrics III in the FDA's Office of Biostatistics, described how master protocols can be leveraged to evaluate the safety and effectiveness of COVID-19 drugs at the 14 April DIA/FDA Biostatistics Industry and Regulator Forum.

FDA's 2018 guidance defines master protocols as "a protocol designed with multiple sub-studies, which may have different objectives and involves coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure." These protocols have often been used to boost statistical power in trials with small sample sizes.

Master protocols have been most frequently implemented in oncology to generate evidence for multiple drugs or multiple diseases and are increasingly being used by drug developers for other types of treatments.

Janet Woodcock, Acting Commissioner of the U.S. Food and Drug Administration has also long advocated for the benefit of master protocols.

More recently, Woodcock pointed to some of the missed opportunities of investigational use of COVID-19 therapeutics during the early days of the pandemic, when early adoption of master protocols and platform trials could have allowed investigators and regulators to acquire more comprehensive and useful data.

DIA/FDA Biostatistics Industry and Regulator Forum (Reference: Download)

FDA/CDER Releases 2021 Guidance Agenda

The US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) released a list of the new and revised draft guidances it plans to release in 2021.

The agenda, while oftentimes aspirational, provides insights as to what the agency's drug center's new guidance priorities are for the coming year. However, the list does not include draft or revised guidances the agency plans to finalize in 2021.

Many of the planned guidances on the list were included in previous years' agendas, such as the proposed clinical pharmacology draft guidance "Assessing the Effects of Food on Drugs in INDs or NDAs – General Considerations", and updated guidance on "Pharmacogenomic Data Submission" and others. In total, there are 105 guidances included on the agenda, 42 of which are new for 2021.

Some of the notable new guidances include a guidance on meeting the standard for substantial evidence based on a single adequate and well-controlled clinical trial plus confirmatory evidence and a guidance aimed at class-specific recommendations for biosimilars and interchangeable products. In the new biostatistics category, CDER was planning three new draft guidances in 2020 on: "Adjustment for Covariates in Randomized Clinical Trials for Drugs and Biologics Using Nonlinear Models," "Multiple Endpoints in Clinical Trials and Statistical Aspects of the Design."

However, the 2021 agenda does include, but not limited, to guidances such as "Meeting the Substantial Evidence Standard Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence" guidance, "Expanded Access to Investigational Drugs for Treatment Use – Questions and Answers," and "Regulatory Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drugs and Biological Products."

Several of the guidances on the agenda are aimed at providing recommendations for individualized antisense oligonucleotides (ASO), including guidance on clinical recommendations to support investigational new drug application (IND) submissions, nonclinical testing, and on chemistry, manufacturing and controls (CMC) considerations for the so-called "n of 1" therapies.

FDA

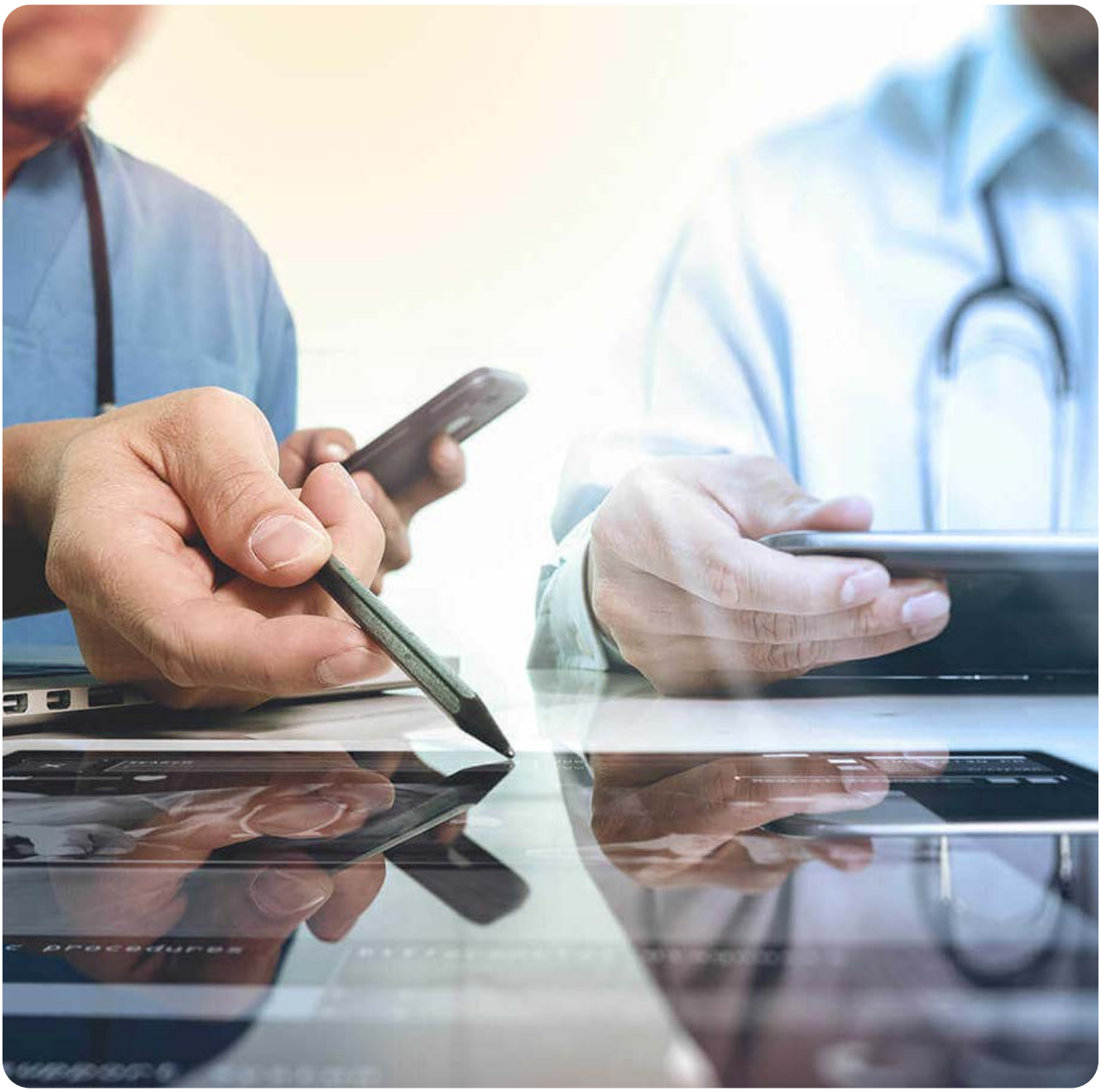
FDA Issues Final Rule Removing Certain Software from Medical Device Regulations

The US Food and Drug Administration (FDA) has issued a final rulemaking on 19 April 2021 that eliminates certain software intended to transfer, store or display clinical laboratory tests from being regulated as medical devices.

This action was taken to conform to the medical software provisions of the 21st Century Cures Act, enacted on 13 December 2016. The law amended the definition of a device in the Federal Food, Drug, and Cosmetic Act (FD&C Act) to exclude such software; the law also removes software that encourages a healthy lifestyle from medical device regulations.

The agency issued guidance on changes to existing medical software policies resulting from the 21st Century Cures Act in September 2019.

Federal Register



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