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REGULATORY

NEWSLETTER N.25

January - March 2019

CROMSOURCE is committed to sharing our expertise with our clients and future clients. This reflects the first part of our 'Advise Agree Deliver' motto! In this spirit we have pleasure in making available this issue of our Regulatory Newsletter. This newsletter is put together by our expert regulatory team and tracks the changes occurring in European and US regulations relating to clinical research performed in both medicinal products and medical devices.

The Newsletter is a quarterly publication distributed via email and posted on the CROMSOURCE website. We hope you find this information useful, and welcome feedback, questions and suggestions.

Contact us on cromsource@cromsource.com at any time.

Contents

Abbreviations

Acronym	Definition
AIFA	Agency of Medicines and Sanitary Products (Spain)
ANSM	National Agency for the Safety of Medicine and Health Products (France)
ATIMP	Advanced Therapy Investigational Medicinal Products
AxMPs	Auxiliary Medicinal Products
BSI	British Standard Institution
CA	Competent Authority
CAT	Committee for Advance Therapies
CCMO	Central Committee for Research Involving Human Subjects (The Netherlands)
CDER	Center for Devices and Radiological Health (United States)
CE	Conformité Européene (European Conformity)
CESP	Common European Submission Portal
CHMP	Committee for Medicinal Products for Human Use
CND	National Classification of Medical Devices
CPP	Comité de Protection des Personnes (French Ethics Committee)
CT	Clinical Trial
CTA	Clinical Trials Application
CTFG	Clinical Trials Facilitation and Coordination Group
CTR	Clinical Trials Regulation (EU): 536/2014
EC	European Commission
EDPB	European Data Protection Board
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FMD	Falsified Medicines Directive
FDA	Food and Drug Administration (United States)
FDARA	Food and Drug Administration Reauthorization Act
GDPR	General Data Protection Regulation
GMDN	Global Medical Device Nomenclature
GMO	Genetically Modified Organism
ICSR	Individual Case Safety Report
IMP	Investigational Medicinal Product
IVD	In Vitro Diagnostics
IVDR	In Vitro Diagnostics Regulation, EU 2017/746
MD	Medical Device
MDCG	Medical Devices Coordination Group
MDR	Medical Device Regulation ,EU 2017/745

Acronym	Definition
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MS	Member State
MREC	Medical Research Ethics Committee (The Netherland)
NANDO	New Approach Notified and Designated Organisations
NB	Notified Body
NCA	National Competent Authority
NDA	New Drug Application
PIP	Paediatric Investigation Plan
PQD	Pharmaceutical Quality Dossier
RSI	Reference-Safety Information
SIS	Subject Information Sheet
UI	Unique Identifier
UK	United Kingdom
VHP	Voluntary Harmonisation Procedure

NEWS FROM EUROPE: MEDICINAL PRODUCTS

News from the European Commission

Falsified Medicines Directive

The 9 February 2019 was the last day to implement the final part of the Falsified Medicines Directive 2011/62/EU (FMD) by all European member states.

Falsified medicines are defined by EMA as "fake medicines that pass themselves off as real, authorised medicines". The Directive 2011/62/EU refers to prescription medicines. They must bear the safety features for medicinal products. The FMD states that all new packs of prescription medicines placed on the European market will have to bear a 'unique identifier' (UI) in the form of a 2D barcode and must be verified whether the packaging has been tampered with 'tamper evidence'. The pharmaceutical manufacturer, or the marketing authorisation holder, must upload the information from the 2D data matrix barcode into the European data repository after certification and before the product is released for sale or distribution. The created FMD system will verify the product's authenticity and identify an individual product pack when the prescribed medicine is supplied to a patient in the EU.

Questions and Answers on the Interaction between the CTR and the GDPR

The European Data Protection Board (EDPB) has published their opinion on the interplay between the Clinical Trials Regulation (CTR) and the General Data Protection Regulation (GDPR) having regard to article 70.1.b of GDPR. The EDPB monitors and ensures the correct application of the GDPR, advises the European Commission on any issue related to the protection of personal data in the EU and issues guidelines, recommendations, and best practices on procedures. The opinion has been prepared on the legal basis for the processing of personal data in the context of clinical trials (primary use) and secondary use of clinical trial data for other scientific purposes. The Q&A on the interplay between CTR and GDPR addresses a number of topics and will become more relevant when the CTR becomes applicable. The topics included in the Q&A are the adequate legal basis, informed consent and its withdrawal, information of data subjects, transfers and secondary uses.

News from the European Medicines Agency

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

EMA First Guidance on New Rules for Medicinal Product with an Integral Medical Device

The EMA has published the Questions & Answers document on implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations with the close consultation of the European Commission.

The publication of such document has been issued due to Article 117 of the MDR, which amends Directive 2001/83/EC Annex I point 12, Section 3.2 and which sets out the dossier requirements for medicinal products which incorporate a device component as a single integral final product.

From 26 May 2020, when MDR will be fully applicable in the EU, the marketing authorisation applicants for medicinal product with an integral medical device must provide relevant additional documents for the device component.

If the device component of medicinal product will be CE marked the applicant is expected to provide a Declaration of Conformity and/or EU notified body certificate. If the Device component is a risk classification of sterile class I, measuring class I, class IIa, class IIb or class III medical device without a declaration of Conformity and EU notified body certificate, then the applicant must provide an opinion from a notified body to the National CA or EMA to comply with the MDR Article 117. The changes described above will lead to new or revised roles and responsibilities for the EMA and NCAs.

Article 117 of the MDR will not have impact on current authorized medicinal products with an integral medical device however, after 26 May 2020 and if such authorised products will get a substantial change to the design or intended purpose of the device component, or a new device is introduced the appropriate variation will need to be submitted to EMA/NCA.

Guideline on Quality, Non-clinical and Clinical Requirements for Investigational Advanced Therapy Medicinal Products in Clinical Trials

This guideline was published for consultation by the EMA on 21 February 2019. The consultation end date is **01 August 2019.** Comments should be submitted to: AdvancedTherapies@ema.europa.eu

The guideline provides guidance on the structure and data requirements for a clinical trial application for advanced therapy investigational medicinal products (ATIMPs). The guideline addresses development, manufacturing and quality control as well as non-clinical and clinical development of ATIMPs. This guideline does not address environmental aspects of ATIMPs that contain or consist of genetically modified organisms (GMO).

Other initiatives

CTFG Issues Recommendation Document on the Initiation and Conduct of Complex Clinical Trials

On 12 February 2019 the Clinical Trials Facilitation and Coordination Group (CTFG) - a working group of the Heads of Medicines Agencies on clinical trials issued the document highlighting differences between complex clinical trials and conventional clinical trials conducting in the EU/EEA. CTFG defines a complex clinical trial as a trials design with separate parts that could constitute individual clinical trials ('sub-protocols') and/or is characterised by extensive prospective adaptations such as planned additions of new Investigational Medicinal Products (IMPs) or new target populations. The complex clinical trials are usually designed as basket, umbrella, and platform trials and commonly used in oncology. "Basket trials generally investigate the safety/efficacy/effect of an IMP or combination of IMPs across a variety of populations. Umbrella trials investigate the safety/efficacy/effects of several IMPs in a single population. Whereas platform trials may test several IMPs in one or multiple populations in a highly dynamic design." CTFG explains. The CTFG recommends that complex clinical trials can be submitted to the NCAs as:

- One single complex clinical trial with sub-protocols. These trials should have one single EudraCT number and have one or more separate sub-protocols that must be linked together by an overarching hypothesis. Opening or closing of sub-protocols will require a substantial amendment request.

- Separate clinical trials. Such trials must be identified by individual EudraCT numbers. The individual trials can be linked by trial names/ titles and may share the same master protocol.

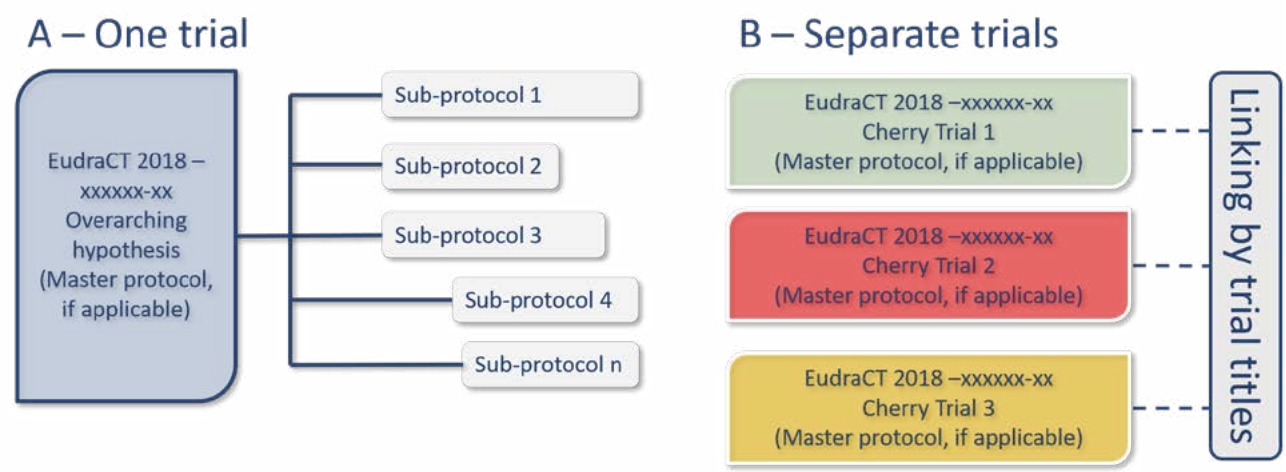


***Fig. 1**: Example of complex clinical trial design with separate parts. The separate parts can be submitted as one clinical trial with sub-protocols (A) or as separate trials (B). If the clinical trials have a master protocol and are submitted as separate clinical trials (B), the master protocol should be submitted with each trial application.*

In addition, the CTFG underlines that "Whereas trials with several sub-protocols can be submitted as one or separate trials, a complex clinical trial with several arms sharing a common control arm must be submitted as one trial".

The CTFG documents provides details recommendations to encourage sponsors to plan and initiate complex clinical trials in EU/EEA. The recommendations refer how to implement appropriate risk mitigation strategies; how to describe and justify the proposed design of complex clinical trials; what the sponsors of complex clinical trials investigating several IMPs and/or populations are expected to consider; how to assure quality of trial conduct, optimise clinical feasibility, ensure trial subject safety, maintain data integrity during conduct complex clinical trials and others.

The CTFG underlines that conducting the complex clinical trials could be a challenge for the sponsors but from another side presents potential opportunities and benefits of such trials.

National Pilot Projects and Participation in VHP-plus – the list of MSs

The CTFG has also published on their webpage an overview of national competent authorities that have set up CT Regulation pilots projects in order to prepare themselves for transition to the CT Regulation EU 536/2014 and declared participation in VHP-plus by Ethics Committees. From 1 March 2019 the VHP plus process has been a part of the Belgian CTR pilot project. In 2019 the Netherlands, Greece, Latvia, Norway, Czech Republic will be involved in VHP-plus. Denmark will be involved in VHP-plus only for clinical trials involving ATMPs and clinical trials involving children. Finland will start the pilot project in 2019.

News from Individual Countries

- **Italy**

Guide how to fill fields of the electronic Clinical Trial Application in the Italian submission portal Ossc

In January 2019, the Agenzia Italiana del Farmaco (AIFA), the Italian Regulatory Agency published guidance explaining the compilation of section D of the Clinical Trials Application (CTA). The AIFA created the detailed guidance to avoid the issues that have been identified during the assessment of clinical trials applications and to simplify the procedures to make them faster and more effective.

- **Switzerland**

Clinical Trial Application dossiers concerning clinical trials with medicinal products – update

On 01 January 2019, the Swiss Agency for Therapeutic Products (Swissmedic) has updated guidelines for Clinical Trial Application dossiers concerning clinical trials with medicinal products. The changes in the guideline mainly cover deletion of requirement for special import licence for immunological products, blood and blood product and clarifications regarding reference-safety information (RSI), auxiliary medicinal products (AxMPs) and the Pharmaceutical Quality Dossier (PQD) submission for market batches.

In addition, Swissmedic has also updated two forms for use in clinical trials:

- FO Submission of Changes to a Clinical Trial and Answer to Conditions. This form is to be used for amendments of a clinical trial
- FO Reporting Related to a Clinical Trial. This form is for notifications and reporting ongoing clinical trials.

- **The Netherlands**

New model of Subject Information and guidance

The Centrale Commissie Mensgebonden Onder (CCMO), the Dutch Competent Authority has published new model of Subject Information Sheet (SIS). The SIS applies from 1 April 2019 and can be used for any type of the study (clinical trials with medicinal product, medical devices or others). The template applies also to both interventional and observational studies. The wording in the SIS model will be used as a reference document for assessment by accredited MREC and CCMO for all submitted SIS after 1 April 2019 except sections 10 of the model: “Usage and storage of your data and body material”. The wording in the section is mandatory and any modifications to it made by applicants must be explained in the cover letter.

In addition, the CCMO published a Q&A document about the data included in section 10 of the template of SIS and the GDPR impact on the new template.

- **France**

Communication with the ANSM- mandatory obligations

As of 17 January 2019 all exchanges of information, responses and decisions between the National Agency for the Safety of Medicines and Health Products (ANSM), the French Competent Authority and the applicants or CPP (French Ethics Committee) are to be made only by e-mail.
The requirement concerns initial application of Clinical Trials (CT) (aec-essaiscliniques@ansm.sante.fr) and its amendments to the CA (ams-essaiscliniques@ansm.sante.fr); initial submissions of pilot projects to the CA (phasepilote.reglement@ansm.sante.fr); initial submission of clinical investigations with medical devices and in-vitro MDs and its amendments to the CA (EC.DM-COS@ansm.sante.fr).

NEWS FROM EUROPE: MEDICAL DEVICES

News from the European Commission

MDR - latest status

The new Medical Devices Regulation (MDR) and In-Vitro Diagnostic Medical Devices Regulation (IVDR) officially entered into force on 26 May 2017. For the MDR there are 13 months left before application (26 May 2020) and for the IVDR 36 months (26 May 2022). Some regulations already apply, such as the new requirements on Notified Bodies designated under the new Regulations. It is also already possible to place a MDR/IVDR compliant devices on the market.

New European Commission Portal to Medical Devices Regulations

To help smooth the transition to MDR and IVDR, the European Commission has launched a Medical Devices section on theirs website. The portal presents the new regulatory requirements for manufacturers, importers, health institutions, authorities in EU and non-EU countries.
The Medical Devices section is a large database of documents, guidance and links to websites with information dedicated separately for MD manufacturers and IVD manufacturers. The documents and information are provided in all European Union languages and some other non-European Union languages, such as Arabic, Chinese, Japanese and Russian.

The portal presents the list of the most recent relevant documents from the Library – an entry point to a comprehensive database of documents produced by stakeholders throughout the European Union.

First Corrigenda for MDR, IVDR

On 13 March 2019, the Council of the European Union release corrigenda to the MDR and the IVDR. The MDR includes 14 corrections and the IVDR 17 corrections. The corrigenda are not significant for changing transition deadlines, classifications of MDs or others impacting on the Regulations. The corrections are made to fix the mistakes (e.g. grammar), inconsistencies and dispel confusions in the areas where such could be met. For example in the MDR on page 148, Annex IX, Section 3 the corrigendum corrects the text from “Surveillance assessment applicable to class IIa, class IIb and class III devices” to just “Surveillance assessment.” In the IVDR has been made the similar. On page 308, Annex IX, Section 3 the text “Surveillance assessment applicable to class C and class D devices” has been corrected to “Surveillance assessment.”

The corrigenda have been prepared in every European languages.

Interpretation of Article 54(2)b by MDCG

Following the first corrigenda, the European Commission published the Medical Devices Coordination Group (MDCG) interpretation documents of the Article 54(2)b of the MDR. Article 54(2)b states the MDR exemption may apply to medium/high-risk or high-risk devices "where the device has been designed by modifying a device already marketed by the same manufacturer for the same intended purpose, provided that the manufacturer has demonstrated to the satisfaction of the notified body that the modifications do not adversely affect the benefit-risk ratio of the device." Interpretation of the word "marketed" is unclear and could be interpreted that "device already marketed" cannot be intended to refer to a device already marketed uniquely under the new Regulation. The issue has "raised questions from the public and from Member States." The MDCG informed that they are going to " launch the procedures for the establishment of expert panels, clarification of this issue is extremely urgent, notably due to its impact on the future workload of panels and hence on relevant budget and workload estimations."

First Designated Notified Body under MDR

In January 2019, the BSI (British Standard Institution) United Kingdom became the first officially designated notified body (NB) in the European Union under MDR. The designation under the IVDR will be set this year for the BSI. The European Commission will be listening the new designated NBs in the Notified and Designated Organizations (NANDO) database.

Eudamed and Medical Device Nomenclature System

The European Commission issued two essential documents MDR Eudamed Functional Specifications – draft and Medical Devices Nomenclature.

Article 34 of Regulation (EU) 2017/745 obliges the Commission to draw up the functional specifications for Eudamed in collaboration with the MDCG and to draw up a plan for the implementation of those specifications by 26 May 2018, which shall seek to ensure that Eudamed - the European database on medical devices- is fully functional, and considered as such by an independent audit report, by March 2020.

Eudamed Functional Specifications – draft covers the legal requirements taken from both applicable regulations as stated in the MDR Eudamed justification; the functional specification derived from the legal requirements for the MDR Eudamed Information system and the Non-Functional specifications. The functional specifications are divided between the restricted website and the public website, each contain their functional specifications grouped by the modules who make up the MDR Eudamed system.

Medical Devices Nomenclature document offers a summary of how the future nomenclature is expected to fulfill certain legal requirements and criteria. The European Commission in the cooperation with the Medical Device Coordination Group (MDCG) plans that the CND nomenclature to be mapped to the GMDN nomenclature and will be made available in the future Eudamed.

In addition, the correspondence between the nomenclatures will be visible to operators and incorporated in Eudramed. This will allow all operators registering their device to find CND nomenclature equivalent to a GMDN code.

OTHER "HOT" TOPICS IN THE EU

Key Brexit updates

As far as the latest on the Brexit extension the European Council agreed a further extension of the date for the UK's withdrawal from the EU at its meeting on 10-11 April. The extension will last as long as necessary and, in any event, no longer than **31 October 2019.**

The United Kingdom will still be a Member State on 23-26 May 2019 and will be under the obligation to hold the elections to the European Parliament in accordance with Union law.

Note: if the UK were to fail to hold European Parliament elections, it will leave the EU on **1 June 2019** and the deadline should be understood as 31 May 2019.

That the UK will leave the EU has not been changed. The British Government underlines that leaving the EU with a deal remains a top priority.

The MHRA has been preparing for every eventuality, including a hard Brexit scenario and has published guidance for stakeholders, manufacturers, sponsors and CROs, held a general overview webinars which covered all aspects of MHRA IT programme and the topics gaining access to new portal for submissions and safety reporting.

All Guidance and Publications Published by MHRA in One Place in case of No-deal Brexit

The MHRA has published a series of guidance documents covering their proposed arrangements for the regulation of medicines, medical devices and clinical trials, if the UK leaves the EU with no deal. The British Agency published the guidance in one place to simplify everyone the searching of applicable information. There are: marketing authorisations, variations and licensing guidance, Importing and exporting guidance for medicinal products and active substances manufactured in the UK; procedures for medicines for children (PIP and clinical trials); regulations of medical devices; regulatory submissions and vigilance activities; procedures for vaccines and blood products and others.

UK Created Equivalent of CESP and Other EU Portals after No-deal Brexit

If the UK leaves the EU without an agreement, the UK would no longer be part of the EU medicines and medical devices regulatory networks. Therefore, the MHRA has created new portals for submissions and safety reporting. Since November 2018 the MHRA held three webinars for stakeholders, manufacturers, sponsors and CROs.

- First covered all aspects of the MHRA IT Contingency programme
- A second webinar covered the instructions of gaining access to the new MHRA Submissions portal. The ability to gain access has been live since 4th March and every applicants were encouraged to register to use MHRA Submissions prior the Brexit.
- A third webinar focussed on the pharmacovigilance solutions and how to register for either the MHRA Gateway or ICSR Submissions. The ability to gain access to portal to submit and receive ICSRs/SUSARs after the Brexit have been opened from 11th March.

The European Medicines Agency Relocated from London to Amsterdam

From 4 March 2019, the official address of the EMA is that of its permanent building in Amsterdam Zuidas:

- ***European Medicines Agency, Domenico Scarlattilaan 6, 1083 HS Amsterdam, The Netherlands***

However, EMA will not physically occupy its permanent building until the latter part of 2019.

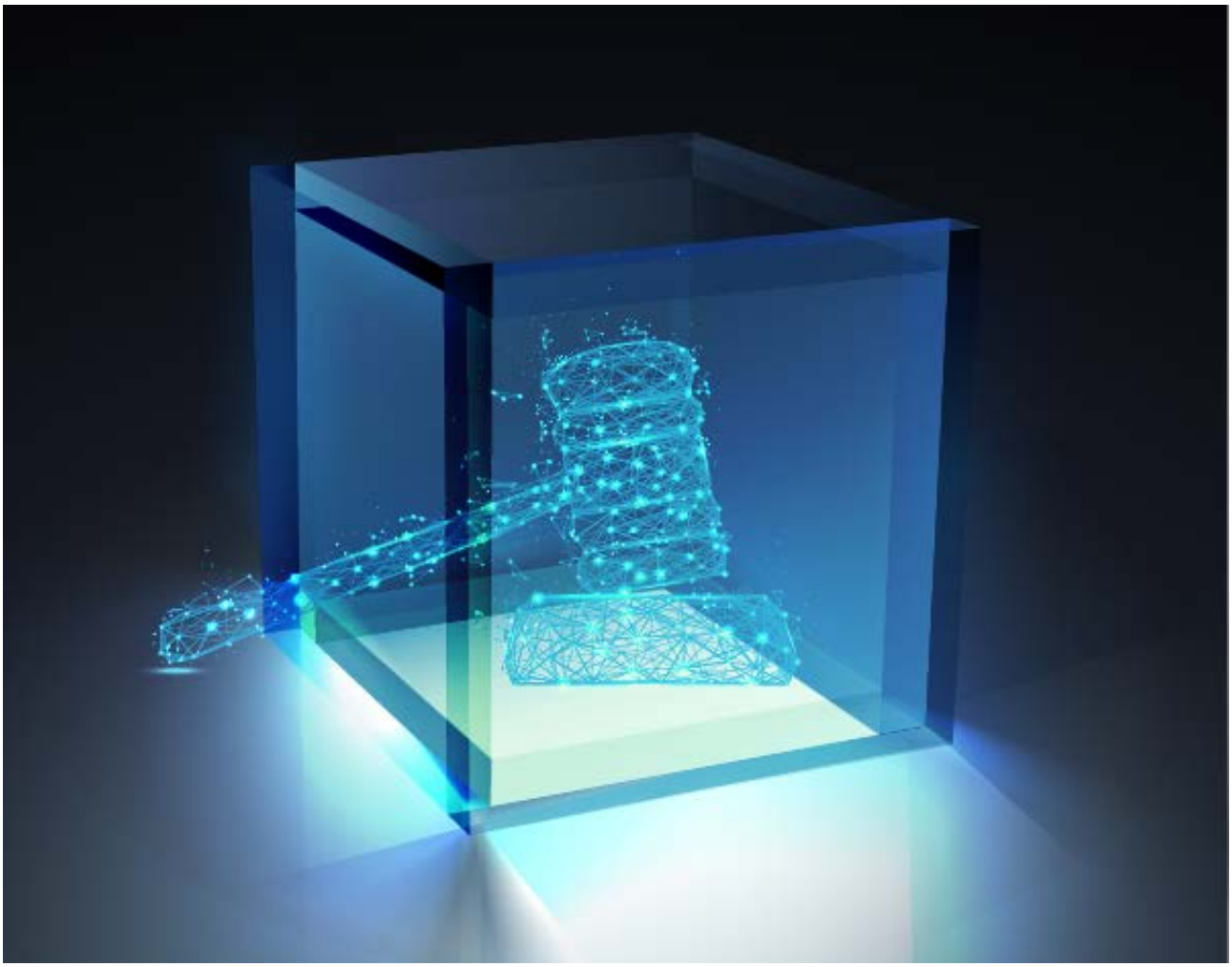
For EMA face-to-face meetings and visits to be used the EMA's temporary premises in Amsterdam, the Spark building, until EMA moves into its permanent building in Amsterdam Zuidas.

- ***European Medicines Agency, Orlyplein 24, 1043 DP Amsterdam, The Netherlands***

For postal deliveries or consignments must be used the Spark building's loading bay address below:

- ***European Medicines Agency, Loading bay, Piarcoplein 75, 1043 DW Amsterdam, The Netherlands***

The EMA has already started their regular meetings of the scientific committees, Committee for Medicinal Products for Human Use (CHMP), Committee for Advance Therapies (CAT) and Biologics Working Party.



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

New Clinical Review Guidance on FDA's 2019 Agenda

For the first time in 20 years, the FDA will update its guidance on how clinical investigators should conduct trials, Commissioner Scott Gottlieb told a key House appropriations subcommittee last month as the lawmakers begin the process of developing next year's budget.

The revised guidance is part of the FDA's efforts to modernize the way it looks at clinical evidence of a drug's effectiveness and safety, Gottlieb said. Much has changed in the science and data in the past 20 years, but the agency's approval standards remain unchanged, he said.

Now, Gottlieb said, "We have much more opportunity to use a broader array of data as confirmatory evidence to help support product review. This includes real-world evidence and real-world data."

In addition to the new guidance, Gottlieb said the FDA plans to "update our approach to drug review across every stage in the life cycle of a new innovation, from the time an investigator first asks the FDA for permission to begin the clinical testing of a new drug to how we continue to assess the safety and effectiveness of new medicines after they're approved by the agency."

Beginning in the next few months, CDER will adopt new standard templates for its 30-day IND (Investigational New Drug) safety reviews and protocol reviews, Gottlieb added. This will better integrate the work of clinical and scientific reviewers and will improve the consistency of the IND reviews. It will also provide greater predictability to product developers, he said.

And the agency will expand its Adverse Event Reporting System to contain premarket safety data, including IND safety reports on serious unexpected adverse reactions in clinical trials and generic bioequivalence trial safety reports.

"The aim is to make the entire process more structured and predictable," Gottlieb said.

FDA Issues Draft Guidance on Bioavailability Trials

Sponsors may want to think about pilot trials to establish bioavailability or bioequivalence of a proposed treatment to help sponsors gauge appropriate time intervals to collect samples, and to determine the "washout periods" for a proposed treatment, among other things, says a new draft guidance from the FDA.

The agency also recommends that bioavailability trial sponsors only recruit healthy subjects. If there are safety concerns, patients may be enrolled, but only when their "disease is expected to be stable for the duration of the study."

When finalized, the guidance will replace the FDA's March 2014 draft guidance on bioavailability and bioequivalence studies submitted in NDAs or INDs.

Read the draft guidance here:
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM631943.pdf

Updated FDA Form 1572 Statement of Investigator

Statement of Investigator (Title 21, CFR Part 312) was updated on 03/2019 and new expiration date is March 31, 2022. No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

Copy of the Form is located at:
https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf

FDA Drafts Guidance on Inspections of Medical Device Establishments

The US Food and Drug Administration (FDA) issued draft guidance on March 2019 to implement uniform processes and standards for FDA inspections of domestic and foreign medical device establishments.

FDA has updated processes and standards for uniformity within and across inspections other than for-cause and to establish a standard timeframe for such inspections of device establishments. The uniformity in FDA investigators' approaches to these inspections "may inform firms' preparation for the inspection and set baseline communication and timing expectations for each party," the agency said.

The three-page draft guidance, which satisfies a requirement established by the FDA Reauthorization Act of 2017 (FDARA), provides for standardized communication methods during the inspection process. Practices for both FDA investigators and device establishments to facilitate the continuity of inspections are identified in the draft guidance as well.

The updates provide exceptions to such processes and standards, as deemed appropriate, an estimated timeframe for an inspection process and advanced notices, as feasible, of some records that will be requested from the establishment at the time of the site inspection. The uniform processes and standards are meant to help an inspection be conducted in a timely manner.

The agency's inspections can range from three to six continuous business days, though factors such as the nature of FDA-observed deficiencies can impact inspection duration and extensions may be needed under certain situations.

FDA's Center for Devices and Radiological Health (CDRH) issued draft guidance last month to identify a new standardized mechanism for device establishments to request nonbinding feedback on actions proposed to address FDA Form 483 observations. This draft guidance was also issued for FDA to comply with section 702 of FDARA. CDRH reported a 243% increase in the annual number of foreign device inspections and a 46% increase in that of domestic inspections between 2007 and 2017, underscoring the need for the new draft guidance to facilitate coordination before and after the inspection process.

The agency recently began compiling several data points on inspections for drug and device approvals in annual reports in line with provisions of FDARA. Its March 2018 annual report noted the median time between an FDA inspection request to the start of an inspection of a device establishment is 35 days.

Copy of the Form is located at:
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM631397.pdf

FDA Releases New Guidance on Principles of Premarket Pathways for Combination Products

FDA released new draft guidance in February 2019 and the current thinking of FDA on principles for premarket review of combination products, including how to determine which type of premarket submission is appropriate.

Combination products are medical products that combine a drug, device and/or biological product. The lead center in the regulation of a combination product is determined based on which part of the product contributes most to its intended effects – in other words, provides the "primary mode of action."

The guidance presents the current thinking of the FDA on principles for premarket review of combination products, including how to determine which type of premarket submission is appropriate, including new drug applications or abbreviated new drug applications for drug-led combination products; stand-alone or biosimilar biologics license applications for biologic-led combination products, and 510(k), De Novo or premarket approval applications for device-led combination products.

In order to ensure efficient review, a single application is generally appropriate for combination products. As these innovative products combine a drug, device and/or biologic, cross-center collaboration is key. The FDA will apply a consistent, risk-based approach to address regulatory questions, including scientific questions, utilizing relevant expertise from the lead and consulted centers. The framework outlines this collaborative model that the FDA will pursue.

Read the Draft Guidance at:
https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM630458.pdf

FDA Modernizes Clinical Trials with Master Protocols in 2019

The innovative regulatory approaches resulting from the 21st Century Cures Act are modernizing new drug development. The use of clinical trials with Master Protocol design is one example of a modern approach to expedite the development of oncology drugs and biologics. Because of the complexity of these trials and the potential regulatory impact, it is important that such trials are well designed and well conducted to ensure patient safety and to obtain quality data that may support drug approval.

Traditionally, oncology drug development involves a series of clinical trials studying one or two drugs in a single disease. Other clinical trials are intended to simultaneously evaluate more than one investigational drug and/or more than one cancer type within the same overall trial structure in adult and paediatric cancers.

FDA released the Draft Guidance for Industry back in late 2018 and currently a Draft as of April 2019 on – Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Cancer Drugs and Biologics provides recommendations on the design and conduct of the latter type of clinical trials. Master protocols may incorporate specific design features that require special considerations. Examples of types of master protocol design include trials commonly referred to as basket trials and umbrella trials.

The guidance document also describes additional aspects of master protocol designs; trial conduct; and related considerations, such as biomarker co-development, statistical analysis, safety considerations, and master protocol content. It provides advice on how sponsors can interact with FDA to facilitate efficient review. It also discusses challenges with the conduct and analysis of master protocols, such as concerns with assessing the rapidly emerging safety profile of investigational drugs.

FDA strongly encourages sponsors to discuss their plans to develop drugs under a master protocol with the clinical review division early in the development program to obtain feedback on the design of such a protocol before submission.

Read the Draft Guidance at:
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621817.pdf

About CROMSOURCE

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

CROMSOURCE was founded in 1997. Its successful growth over the last 20 years has been built on stability, integrity, and high levels of customer satisfaction, all of which contribute to a high rate of repeat business. We have grown steadily, but responsibly, to become an organisation of over 550 organised and well-trained experts.

A well established full service CRO, **CROMSOURCE** is unique in offering an end-to-end guarantee covering trial timelines, enrolment and contract price. This guarantees our clients that their trials are delivered on time and within the contract price with no CRO-initiated change orders. **CROMSOURCE** operates through offices across all regions of Europe and North America and delivers a comprehensive breadth of services.

CROMSOURCE supports the full spectrum of clinical development via our Pharmaceutical, Medical Device and Staffing Solutions divisions. We seamlessly move biopharmaceutical products from first-into-human conducted in our exceptional early phase unit, through all subsequent phases of pre- and post- approval research internationally. We also support medical device projects through regulatory planning and execution, to pilot and pivotal clinical investigations in Europe and North America.

Global Reach

CROMSOURCE, with world headquarters in Verona, Italy, is a leading CRO in Europe and the US with a solid infrastructure and operational subsidiaries in Belgium, France, Germany, Poland, Russia, Spain, Switzerland, the UK, the Netherlands, and the US.

From our office locations across Europe and North America, **CROMSOURCE** employs experienced field-based teams in locations across the globe to provide expert capabilities in regions including the Middle East, Africa, APAC, and South America.

It's a simple concept, really. Quality data. On time. On Budget. Guaranteed.

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