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REGULATORY NEWSLETTER

April - June 2017

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Introduction

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

News from the European Commission

EU Medical Device Regulations come into force and starting transition period

The Regulation (EU) 745/2017 called the Medical Device Regulation (MDR) and the Regulation (EU) 746/2017 called the In Vitro Diagnostic Regulation (IVDR) were published in the Official Journal of the European Union in May 2017. At the same time the countdown to the implementation of both of them begins. The requirements of the MDR will come into force between May 2017 and 2020. In the case of the IVDR, the requirements should be implemented between May 2017 and 2022.

The next steps for the European Commission will be for certain articles of the regulations to start to come into force. For example, they must "draw up a list of codes and corresponding types of devices" to specify the scope of notified bodies and cover the establishment of expert committees such as Medical Device Coordination Group (MDCG). The MDCG must be composed of persons designated by Members States "to provide advice to the Commission and to assist the Commission and the Member States in ensuring a harmonised implementation of the regulations. The MDCG should be able to establish subgroups in order to have access to necessary in-depth technical expertise in the field of medical devices including in vitro diagnostic medical devices. When establishing subgroups, appropriate consideration should be given to the possibility of involving existing groups at Union level in the field of medical devices." (Position (EU) No 2/2017 of the Council at first reading with a view to the adoption of a Regulation of the European Parliament and of the Council on medical devices, 7 March 2017).

The first deadline for coming into force above-mentioned articles from the regulations is 26 November 2017. Subsequently, other articles from the regulations discussing cooperation between member states and the European Commission should be implemented during three-year period for MDR and five-years for IVDR.

Source: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52017AG0002(01)

The Regulations in 24 languages are available here:

- the Medical Device Regulation (MDR) http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32017R0745
- the In Vitro Diagnostic Regulation (IVDR) http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32017R0746

The Implementing Regulation (EU) 2017/556 on the detailed arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536/2014

The Implementing Regulation (EU) 2017/556 on the detailed arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536/2014 of the European Parliament and of the Council was published on 25 March 2017 in the Official Journal of the European Union.

Regulation (EU) No 536/2017 called Clinical Trial Regulation (EU) No 536/2014 sets the legal framework for the conduct of clinical trials on medicinal products for human use in European Union. Article 63 of the CT Regulation empowering the European Commission to adopt delegated acts specifying the detailed arrangements for good manufacturing practice inspections as regards investigational medicinal products.

The Implementing Regulation (EU) 2017/556 establishes the detailed arrangements for the inspection procedures with regard to good clinical practice as well as for the requirements on qualification, training and experience of the inspectors. Inspectors among of their completed education, appropriate trainings, knowledge are require to be independent. "Member States shall keep records of the qualifications, training and experience of each inspector and maintain those records up-to-date for as long as inspector is in active duty".(Article 4 "Qualifications, training and experience" of Chapter II "INSPECTORS")

If necessary, the inspections may be carried out unannounced. The inspection results shall be recognized by all Member States. "Member States shall collaborate with each other, with the Commission and with the European Medicines Agency." "In case of divergences between Member States in relation to the verification of compliance with the applicable legislation, the Member States, or the European Medicines Agency within the framework of its powers shall inform the Commission. The Commission, after consulting those Member States and the European Medicines Agency, may request a new inspection." (Article 11 "Recognition of inspection conclusions" of Chapter III "INSPECTION PROCEDURES")

The Implementing Regulation came into force on the twentieth day following that of its publication in the Official Journal of the European Union and will apply from 6 months after the date of publication in the Official Journal of the European Union of the notice regarding the functionality of the EU portal and the EU database referred to in Article 82 Paragraph 3 of the Clinical Trial Regulation (EU) No 536/2014.

Source: http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0556&from=DE

"Questions and Answers" document regarding the implementation of the rules on the safety features for medicinal products for human use (version 7.0)

The European Commission has prepared a "Question and Answers" document to facilitate the implementation of Regulation (EU) 2016/161 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use. Date of publication for "Questions and Answers " is June 2017.

The safety features Regulation (EU) 2016/161 will apply on 9 February 2019. Belgium, Greece and Italy have the option of deferring the application of the rules by an additional period of up to 6 years. The Commission has prepared the document to help implementing the Regulation (EU) 2016/161.

"The safety features consist of two elements placed on the packaging of a medicinal product:

(1) A unique identifier, a unique sequence carried by a two-dimensional barcode allowing the identification and authentication of the individual pack on which it is printed; and

(2) A device allowing the verification of whether the packaging of the medicinal product has been tampered with (anti-tampering device)." (Question 1.1.)

Also included is information about technical specifications of the Unique identifier (UI) which verifies the authenticity of the medicinal product, where the UI should be placed during labelling and packaging and if the rules on the safety features apply to medicinal products intended for research and development trials.

Source: https://ec.europa.eu/health/human-use/falsified_medicines_en

"Question and Answers" https://ec.europa.eu/health/sites/health/files/files/falsified_medicines/qa_safetyfeature_v7_0.pdf

News from the European Medicines Agency

The source of each news item below is the EMA website. http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/Home_Page.jsp&mid=

Clinical Trial Regulation EU No. 536/2014 postponed to October 2019

In June 2017, the Management Board of the European Medicines Agency (EMA) discussed the progress made regarding the development of the EU clinical trial portal and database, which are mentioned in Article 82 Paragraph 3 of the Clinical Trial Regulation EU No 536/2014. They have decided to postpone activation of the EU clinical trial portal and database and consequently rescheduled when the Clinical Trial Regulation (EU) 536/2014 will apply.

The EU clinical trial portal and database supports the ambitious modernisation of the processes for authorisation and oversight of clinical trials in the EU laid down in the EU Clinical Trial Regulation. The system will provide a single portal for submission and maintenance of clinical trial applications and authorisations, and support coordinated assessment and supervision. The portal and database will also serve as the source of public information on the full lifecycle of all clinical trials conducted in the EU, from their initial review up to the publication of their results.

Due to technical difficulties with the development of the IT systems, the portal's go-live date has to be postponed.

The EU Clinical Trial Regulation will now become applicable in October 2019 instead of October 2018.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/06/news_detail_002764.jsp&mid=WC0b01ac058004d5c1

EMA to launch new EudraVigilance System

On 23 June 2017, the European Medicinal Agency (EMA) published an updated "EudraVigilance stakeholder change management plan". According to plan, a new EudraVigilance TEST environment (XCOMP) was released on 26 Jun2017. The final EudraVigilance system will be launched on 22 November 2017. The EMA invited National Competent Authorities (NCAs) in the European Economic Area (EEA), Marketing Authorisation Holder (MAHs) and sponsors of clinical trials to use this document as a starting point to develop their own internal implementation plans to prepare for the launch of new EudraVigilance system in November 2017.

The new EudraVigilance system will have significant benefits, including:

- MAHs will no longer have to provide the Individual Case Safety Reports (ICSRs) to national authorities, but will provide them directly to EudraVigilance, which will likely reduce duplicative efforts;
- Increased transparency and more access, including enhanced search options, to suspected adverse events by health professionals and the public;
- More efficient collaboration with the World Health Organization (WHO) as EMA will make ICSRs available to the WHO Uppsala Monitoring Centre directly from EudraVigilance, meaning member states will no longer need to carry out this task.

The NCAs and MAHs must start the testing of the ICSRs in the new ISO/ICH E2B (R3) format as well as the message exchange (NCA re-routing and MAH ISCR download functionalities).

All stakeholders are invited to ask their users to check the validity of their user-IDs and passwords and to contact the EudraVigilance Registration team if user credentials need to be updated or if new users need to be registered.

The EMA published also an instruction "EudraVigilance checklist and technical support plan for Marketing Authorisation Holders and Sponsors of Clinical Trials in the EEA". The Agency notes that there will be no changes to the reporting of suspected unexpected serious adverse reactions during clinical trials until the application of the new Clinical Trial Regulation No 536/2014 and not all steps outlined in the EudraVigilance checklist apply to sponsors of clinical trials but will only apply to MAHs in accordance with the new simplified reporting rules set out in the pharmacovigilance legislation.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000165.jsp&mid=WC0b01ac0580a69263

EudraVigilance checklist: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/06/WC500229797.pdf

The EMA is organizing the courses to support NCAs and MAHs in the European Economic Area (EEA). Training includes targeted e-learning and face-to-face trainings, webinars and information days. More information about training is here: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000162.jsp&mid=WC0b01ac0580a1a1fb

External guidance on the implementation of the European Medicines Agency policy on the publication of clinical data for medicinal products for human use Revision 2

On 12 April 2017, the European Medicines Agency (EMA) published a new version of "External guidance on the implementation of the European Medicines Agency policy on the publication of clinical data for medicinal products for human use" Revision 2. The EMA policy is called Policy 0070 and was adopted on 02 October 2014. Policy 0070 requires the EMA to publish clinical reports (the clinical overviews, clinical summaries and the clinical study reports (phase 1) and individual patient data (IPD) (the individual data separately recorded for each participant in a clinical study) (phase 2).

The scope of "External guidance" relates to phase 1 of Policy 0070 and clarifies the type of clinical data for medicinal products for human use to be published under Policy 0070 and especially includes the following precisions:

"All clinical study reports cross-referred to within a paediatric extension or modification of indication application submitted in the context of regulatory procedures not falling within the scope of Policy 0070 will be subject to publication."

"Where clinical study reports are cross-referred to within extension or modification of indication and line extension applications other than paediatric, only the pivotal clinical study reports submitted in the context of regulatory procedures not falling within the scope of Policy 0070 and considered the basis for that application will be subject to publication."

In addition, in chapter 2, Clinical report document types, the EMA clarifies that it is acceptable to remove individual patient data from the section on "Abnormal Laboratory Value Listing" from clinical studies reports before publication. However, individual patient data in other sections of the clinical study reports should be anonymized and included.

The EMA has added a validation checklist for sponsors in order to assist applicants/ Marketing Authorisation Holders (MAHs) when submitting clinical data and a template for abbreviated anonymization reports that can be used for applications that do not contain patient identifiers.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001799.jsp&mid=WC0b01ac0580b2f6ba

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001743.jsp&mid=WC0b01ac0580ae88cc

Guidance: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/04/WC500225880.pdf

Parallel Scientific Advice (PSA) - EMA & FDA

"The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services have a program to provide parallel scientific advice (PSA) to sponsors. The goal of the PSA program is to provide a mechanism for EMA assessors and FDA reviewers to concurrently exchange with sponsors their views on scientific issues during the development phase of new medicinal products (i.e., new human drugs and biologics)."

On 19 May 2017, the European Medicines Agency (EMA) published a chart comparing timelines and requirements expected by both Agencies.

Overview of Scientific advice and protocol assistance: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp

General Principles of PSA PDF: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/11/WC500014868.pdf

Parallel Scientific Advice (FDA-EMA) chart: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500228108.pdf

Consultation guidelines on clinical trials

Draft guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol

On 23 May 2017, the European Medicines Agency (EMA) released for consultation a draft guideline on serious breaches of Clinical Trial Regulation EU No 536/2014 or clinical trial protocol. The consultation end date is 22 August 2017. Comments should be submitted to gcp@ema.europa.eu.

The guideline outlines the practical arrangements for notification of serious breaches of clinical trials authorised in the Europe Union (EU) / European Economic Area (EEA). It aims to provide advice on what should and what should not be classified as a serious breach and what must be reported. It does not include guidance related to urgent safety measures or other reporting obligations related to subject safety.

A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

The most important points of the guidance are:

- The sponsor or anyone that has contractual agreement with the sponsor (CROs, contractors, co-development partners, etc.) and has become aware of the breach must report it within 7 days through the EU CT system (EU CT portal and database) or to the Member States concerned (MSC) when breaches are occurring exclusively outside the EU/EEA and might have an impact on data integrity of a CT already authorised or being conducted in the EU/EEA territory.
- Technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial should be documented (in the case report form (CRF) or the trial master file (TMF)) in order for appropriate corrective and preventative actions to be taken. This division should be considered when a clinical study report (CSR) is produced.
- Lack of an adequate system in place for Sponsor, CROs, contractors and/or failure to report serious breaches may result in findings during GCP Inspections.

The guidance provides examples of serious breaches: a breach of the Regulation or of the protocol which results in Serious Adverse Event (SAE) or Suspected Unexpected Serious Adverse Reaction (SUSAR) can constitute a serious breach. If failure to manage safety events, for example lack of SUSAR reporting, results in trial subjects being put at a significant degree of risk, then this will constitute a serious breach. In this case a serious breach notification will need to be submitted in addition to the submission of those SUSARs to the EudraVigilance database.

Source: http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500228199&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

Draft Guidance: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/05/WC500228199.pdf

Draft guideline on good-clinical-practice compliance in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials

On 12 April 2017, the European Medicines Agency (EMA) released for consultation a new draft guideline on good-clinical-practice compliance (GCP) in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials. The consultation end date is 11 July 2017. Comments should be submitted to gcp@ema.europa.eu.

The guideline on Trial Master File (TMF) aims to describe the requirements for TMF as covered in the new Clinical Trials Regulation (EU) No 536/2014 and ICH-GCP E6 and to assist sponsors, CROs and investigators in maintaining a TMF that facilitates trial management, GCP compliance and inspection.

The guideline explains Sponsor and Investigator responsibilities for generating or holding a TMF, TMF structure and contents and explains that there is no difference between paper and electronic TMFs and that all the basic requirements are the same.

In addition, the guideline:

- Provides examples of documents that are essential, but not listed in section 8 of ICH GCP R2 E6 and reminds that duplication of any documentation in the TMF should be avoided,
- Describes the relevance of electronic correspondence (emails) for the TMF and emphasizes that it is important to keep the TMF up to date and to ensure that it is complete at the end of a trial,
- Provides instructions for Sponsors on how to clearly define expectations regarding creation, management, exchange or remote access and retention of documentation if multiple vendors are involved (CROs and other sub-contractors) and,
- Addresses archiving of the TMF, clarifying retention times, in particular expectations in case of digitization and consecutive destruction of paper documentation.

Source: http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500225871&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

A draft guideline for consultation: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/04/WC500225871.pdf

Draft guideline on multiplicity issues in clinical trials

On 31 March 2017, the European Medicines Agency (EMA) published for consultation, "Guideline on multiplicity issues in clinical trials".

The consultation end date was 30 June 2017.

The guideline is intended to provide guidance on how to deal with multiple comparison and control of type I error in the planning and statistical analysis of clinical trials. From the points to consider document published in 2002, aspects related with multiplicity issues in safety, drug-response studies, secondary endpoints, subgroup analysis and estimation were added or updated, and statistical terms were clarified.

Source: http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500224998&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

Concept paper on a guideline on the evaluation of medicinal products indicated for treatment of influenza

On 04 May 2017, the European Medicinal Agency (EMA) published for consultation the "Concept paper on a guideline on the evaluation of medicinal products indicated for treatment of influenza". The consultation end date is 31 July 2017. Comments should be submitted to: IDWPSecretariat@ema.europa.eu.

This concept paper proposes the development of a guideline on the clinical evaluation of medicinal products indicated for the treatment of influenza for which there is no regulatory guidance currently available within the European Union (EU).

Source: http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500226734&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

Other Initiatives

Adoption of the addendum the European Medicines Agency's (EMA) E6(R2) guideline by one more county - Canada

The Integrated Addendum to ICH Good Clinical Practice (GCP) Guideline E6 (R2) was adopted by the European Medicines Agency (EMA) on 15 Dec2016 and came into effect on 14 June2017 in the European Union.

The ICH GCP Guideline Integrated Addendum provides a unified standard for the European Union, Japan, the United States, Canada, and Switzerland to facilitate the mutual acceptance of data from clinical trials.

On 29May 2017, Health Canada (the Canadian Agency) announced that it plans to fully implement the addendum to the ICH E6 (R2) in April 2018. The guideline went into effect in May 2017 and now the Agency wants to consult it with stakeholders over the next year as it prepares to fully implement the guidelines. In addition, Health Canada plans to develop training programs for stakeholders and internal staff prior to implementation of ICH E6 (R2).

The addendum to ICH E6 (R2) is still waiting for a notification from US, Japanese and Swiss regulators.

Source: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/announce-annonce/e6r2-step4-notice-avis-eng.php

New Guideline on Adverse Event Reporting offered by IMDRF

In April 2017, the International Medical Device Regulators Forum (IMDRF), a voluntary and global group of device regulators published new final guideline" IMDRF terminologies for categorized Adverse Event Reporting (AER): terms, terminology structure and codes" with Annex A.

"Widespread use of a single, appropriate adverse event terminology and coding system is expected to improve signal detection by adverse event management systems enabling a faster response by both industry and regulatory agencies." (INTRODUCTION of Guideline)

The guideline offers IMDRF definitions, codes and harmonized terminology to be used for pre- CE marked and post-CE market adverse event reporting for medical devices including in-vitro diagnostics.

IMDRF started to work on new IMDRF terminologies for categorized Adverse Event Reporting (AER): terms, terminology structure and codes –Annex B. The document is under consultation.

Source: http://www.imdrf.org/consultations/consultations.asp

Guidelines: http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-170316-aer-n43.pdf

MA new home - continuation

On 29 March 2017, the United Kingdom (UK) notified the European Council of its intention to withdraw from the European Union (EU), a process known as 'Brexit'. The EMA is making preparations to ensure that they can continue to deliver on its mission and protect public and animal health even if the UK becomes a third country as of 30 March 2019.

In May 2017, the EMA and the EC published guidance to help pharmaceutical companies to prepare for the United Kingdom's withdrawal from the European Union. The guidance relates to both human and veterinary medicines. The document : "Questions and Answers related to the United Kingdom's withdrawal from the European Union with regard to the medicinal products for human and veterinary use within the framework of the Centralised Procedure "concerns information related to the location of establishment of a company in the context of centralised procedures and certain activities, including the location of orphan designation holders, qualified persons for pharmacovigilance (QPPVs) and companies' manufacturing and batch release sites.

EMA is preparing a series of further guidance documents which will be published on its website. Companies are advised to regularly check EMA's dedicated webpage on the consequences of Brexit.

Question and Answer guidance: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500228739.pdf

In addition, in June 2017, the European Council started the procedure to determine where the European Medicines Agency (EMA) will be relocated following the UK's withdrawal from the EU.

According to the procedure Agencies from 27 EU countries can offer to host the European Medicines Agency and the European Banking Authority (EBA) by 31 July 2017 at the latest. By 30 September 2017 at the latest, the Commission will submit its assessment of the offers and will also make it publicly available. In October, a "political discussion" of the Commission's assessment is planned and in November 2017, the decision on where EMA will reside will be taken by vote of the EU27 ministers at the General Affairs Council meeting.

Source: http://www.consilium.europa.eu/en/meetings/european-council/2017/06/22/

NOTE: CROMSOURCE will continue to track the European Medicinal Agency (EMA) and European Commission (EC) decisions about EMA new home due to the United Kingdom's withdrawal from the European Union. Updates will be published in the Regulatory Newsletter.

EMA action plan for small and medium-sized enterprises (SMEs)

On 30 May 2017, the EMA published “an action plan for small and medium-sized enterprises”.

In accordance with the EU Medicines Agencies Network Strategy to 2020, the EMA is reviewing whether it provides adequate support and an appropriate regulatory environment for those that drive innovation including SMEs and academia.

The plan aims to address the challenges identified by SMEs and their stakeholders through actions focusing on communication and cooperation.

The actions address the following challenges identified through SMEs stakeholders’ consultations:

1. Awareness of the EMA SME initiative

2. Training and education

3. Support to innovative medicines’ developments

4. Engagement with SMEs, EU partners and stakeholders

More information can be found: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/05/news_detail_002758.jsp&mid=WC0b01ac058004d5c1

New action plan document: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500228736.pdf

News from Individual Countries

Austria

The new fees since 1 June 2017

On 01 June 2017, the Austrian Federal Office for Safety in Health Care (BASG), the Austrian Agency , published updated the fee guidelines "Verordnung des Bundesamtes für Sicherheit im Gesundheitswesen über den Gebührentarif gemäß GESG". The new fees apply from 01 June 2017 and have been changed to the following:

- 3039€ Clinical Trials phase I-III
- 1528€ Clinical Trials Phase IV
- 510 € Notification of a compassionate use program pursuant to § 8a AMG on the basis of an opinion from the Committee on Human medicines
- 1528 € Notification of a compassionate use program pursuant to § 8a AMG without submission of an opinion from the Committee on Human medicines
- 3039 € Clinical Investigations
- 507 € Substantial Amendment

Source: http://www.basg.gv.at/en/about-us/fees/

The fee guidelines in German: http://www.basg.gv.at/index.php?eID=tx_nawsecuredl&u=0&g=0&t=0&hash=8996d4b1a9f33c68d9ef6da646880222721475d2&file=fileadmin/user_upload/190517_Gebuehrentarif.pdf

Belgium

Clinical Trial Regulation project (CTR project) guidance

OAs reported in the last Regulatory Newsletter January - March 2017, the Federal Agency for Medicines and Health Products (FAMHP), the Belgian Competent Authority announced in January about starting the "CTR project" due to the new Clinical Trial Regulation (EU) No 536/2014.

In May, the FAMHP experts have written a guidance document: "Voluntary Joint Pilot between FAMHP, the future College, accredited Ethics committees and sponsors for processing of applications for the authorisation of clinical trials and substantial modifications on medicinal products for human use in accordance with the spirit of the Regulation (EU) No 536/2014 and of the draft text of the law on CTR." Version 2.0.

The guidance has been written to assist everyone involved in the process of pilot phase to find relevant information. The guidance can be updated during a pilot phase. The Sponsor still has a choice to make for initial submission with medicinal product in accordance with circular letter 575, normal process or via pilot CTR procedure following the published guidance.

The FAMHP issued an email contact point, (CTRpilot@afmps-fagg.be), and the sponsor can stay in close contact in order to refine the submission date if necessary.

The submission dossier (structure and contents) must comply with the requirements of Annex I of the CT Regulation (EU) No 536/2014. The Regulation provides the option of separately submitting the documentations for Part I and Part II. The FAMHP informs that on that stage of pilot phase Part I and part II packages have to be submitted together at the same moment to the national contact point.

At the time of the submission, the cover letter must point out that participation in the pilot project has been confirmed and must contain the pilot project number.

The cover letter must be provided hand signed and scanned in the Eudralink submission.

For the sake of a quick treatment of the dossier, it is asked to the sponsor to submit the CTA package by Eudralink. The expiry date of each Eudralink package in this pilot will be set to its maximum of 90 days.

All communications (additional information, responses to questions, etc.) from the sponsor during the pilot procedure are to be sent by email and/or Eudralink to the Belgian contact point.

Source: https://www.fagg-afmps.be/en/news/update_on_the_new_clinical_trial_regulation_pilot

Guidance Version 2.0: https://www.fagg-afmps.be/sites/default/files/procedure_ctr_pilot_project_for_sponsors_-_rd_08-05-2017.pdf

France

a. Guidance regarding authorization, substantial amendment and end of the clinical investigation

On 14 June 2017, the National Agency for the Safety of Medicine and Health Products (ANSM) published new guidance regarding authorization, substantial amendment and end of the clinical Investigation involving the human person involving medical device (MD) or in vitro diagnostic medical device (IVDMD) "Tome I Application for research authorization, start, modifications, end and research results"

The ANSM provided very detailed instructions how to make a submission to receive authorization of a clinical investigation with MD or IVDMD. There is a list of relevant contacts points in any cases we have: submission of Clinical Investigation, substantial amendment, resubmission and any enquires to Direction des dispositifs médicaux thérapeutiques et des cosmétiques Essais cliniques department.

The guidance explains how medical devices will be categorized after new decree no. 2016-1537 dated16 November 2016 comes into force

The MDs and IVDMDs for the purpose of diagnosing, treating or preventing pathological conditions, are divided into three categories:

- Interventional research with risk above minimal risk (interventional research refers to Art. L1121-1 1° Code de la santé publique (CSP)). Such studies are research that involves intervention on people. For clinical investigations it will be pre-CE marked studies with MD and IVDMD or CE-marked devices for a new purpose other than the original.
- Interventional research was previously defined as "biomedical research".
- These studies must receive the ANSM authorization from ANSM and (Comité de Protection des Personne (CPP), the French Ethics Committee.
- Interventional research that involves minimal risks and constraints interventions (refers to Art. L1121-1 2° CSP). Such studies include post-CE marked MD and IVDMD using according to its indications. Thus, part of this research corresponds to what was previously referred to as "research to evaluate routine care". These studies must be notified only to the ANSM and submitted for a favourable opinion to CPP.

- Non-interventional or observational research (refers to Art. L1121-1 3° CSP). These researches do not involve any risk or constraint added by the research or any modification of the usual care. Such studies include post-CE marked MD and IVDMD using according to its indications. These clinical interventions must be notified to the ANSM including the CPP approval and submitted for a favourable opinion to CPP. Clinical Investigations concerns only data, already collected or to be obtained from collections or old samples do not fit into the ANSM-CPP circuit, but should be sent to the CEREES (Committee for Expertise in Research, Studies and Evaluations in the field of Health) for advice (to the Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé (CCTIRS).

The Tom I guidance consists of 70 pages with 10 Annexes. There are step by step instructions on how to proceed with submissions to the ANSM, list of required documents, references, recommendations, answers to frequently asked questions. The document could be considered as a work instruction for sponsors and applicants on how to go through the whole authorization process of Clinical Investigation or evaluation with MD and IVDMD in France.

The guidance is available only in French.

Resource and guidance: http://ansm.sante.fr/Activites/Dispositifs-medicaux-et-dispositifs-medicaux-de-diagnostic-in-vitro/Essais-cliniques-portant-sur-les-dispositifs-medicaux-et-dispositifs-medicaux-de-diagnostic-in-vitro/(offset)/0

b. New National Application Forms for medical device issued by the ANSM

The National Agency for the Safety of Medicine and Health Products (the ANSM) has published on their websites new forms dated 15 June 2017 for medical device (MD) and in vitro diagnostic medical device (IVDMD). The new templates are for initial submissions, substantial amendments and the end of clinical investigations to the ANSM and the Comité de Protection des Personne (CPP), the French Ethics Committee.

New application forms for MD and IVDMD:

- Courrier de demande d'autorisation d'essai clinique (AEC) portant sur un dispositif médical (DM) ou dispositif médical de diagnostic in vitro (DMDIV)(Recherches interventionnelles mentionnées au 1° de l'article L. 1121-1 du code de la santé publique)
- Courrier de demande d'autorisation de modification substantielle (MSA) d'essai clinique portant sur un dispositif médical (DM) ou dispositif médical de diagnostic in vitro (DMDIV) (Recherches interventionnelles mentionnées au 1° de l'article L. 1121-1 du code de la santé publique)
- Formulaire de demande de modification substantielle d'une recherche mentionnée au 1° ou au 2° de l'article L. 1121-1 du code de la santé publique portant sur un dispositif médical ou un dispositif médical de diagnostic in vitro
- Formulaire de déclaration de la fin d'une recherche mentionnée au 1° de l'article L. 1121-1 d code de la santé publique portant sur un dispositif médical ou sur un dispositif médical de diagnostic in vitro auprès de l'ANSM et du comité de protection des personnes

References: http://ansm.sante.fr/Activites/Dispositifs-medicaux-et-dispositifs-medicaux-de-diagnostic-in-vitro/Avis-aux-promoteurs-Formulaires/(offset)/1

Spain

a. New updated guidance for conducting clinical trials in Spain

On 29 Jun 2017, the Spanish Agency of Medicines and Sanitary Products (AEMPS) published a new guidance: "The Instruction document of the Spanish Agency of Medicines and Sanitary Products for conducting clinical trials in Spain". The guidance refers only to medicinal products, is in a question-and-answer format and provides practical aspects for sponsors and applicants. It is not a change of the legislation in Spain but a periodic update of the instructions on the interpretation of the Royal Decree 1090/2015, of 4 December 2015, regulating clinical trials with medicinal products, Ethics Committees for Investigation with medicinal products and the Spanish Clinical Studies Registry." entered into force on 13 January 2016.

References: https://www.aemps.gob.es/investigacionClinica/medicamentos/ensayosClinicos.htm#noticias

Updated guidance in Spanish: https://www.aemps.gob.es/investigacionClinica/medicamentos/docs/Instrucciones-realizacion-ensayos-clinicos.pdf

b. New forms and additional guidance issued by AEMPS

The Spanish Agency of Medicines and Sanitary Products (AEMPS) has published new forms and guidance for sponsors and applicants:

- Anexo II. Documentación de seguridad que el promotor debe remitir a las autoridades sanitarias de las Comunidades Autónomas dated 8 May 2017 (The guidance of instructions how sponsor should proceed with submission of SUSARs, DSURs and ad hoc urgent measures to the regional Competent Authorities (Autonomous Communities)
- Anexo III. Idoneidad del investigador dated 18 April 2017 (The template of Principal Investigator suitability. There should be mentioned centers participating in the clinical trial and number of subjects. The CV of PIs and their GCP training Certificate should be attached to the Annex III.
- Anexo IV. Idoneidad de las instalaciones dated 23 June 2017 (The Annex is a declaration by the Principal Investigator or Director of center that the site has the human resources, equipment and facilities to carry out the research.)
- Anexo V. Modelo de certificado de seguro dated 18April 2017 (This is an template for Insurance Agencies to be used for the clinical trial with medicinal products. The template can be used by default for clinical Investigations with medical device).
- Anexo VI. Modelo de compromiso del promotor para ensayos clínicos sin ánimo commercial dated 18April 2017_It is a template for clinical trials when the entity managing the clinical study is the hospital or any foundation. For such Institutions the legislation allows to go ahead with the clinical trials without contracting an insurance.
- Anexo VII. Modelo de certificado del representante del centro organización para ensayos clínicos de bajo nivel de intervención dated 18 April 2017 (It is a template to be signed by the sponsor confirming that there is an insurance in place and that the clinical trial is a "low-intervention CT".
- "Low-intervention clinical trial": A clinical trial which fulfils all of the following conditions:

  1. The investigational medicinal products, excluding placebos, are authorised.
  2. According to the protocol of the clinical trial:
     a. The investigational medicinal products are used in accordance with the terms of the marketing authorisation; or
     b. The use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned.

3. The additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned.

- Anexo VIII. Guía para la correcta elaboración de un modelo de hoja de información al paciente y consentimiento informado (HIPCI) dated 18April 2017(It is guide for the correct elaboration of a model of patient information sheet and informed consent form (PISICF))
- Anexo IX Documentación mínima necesaria para solicitar la gestión del contrato para la realización de ensayos clínicos entre el promotor (003) dated 18 April 2017 (It is a guide about a minimum documentation required to request the management of the contract for conducting clinical trials between the Sponsor and the centres.)
- Anexo X Contactos para la gestión del contrato con un centro de investigación dated 8 May 2017(It is a list of contact point for contracting management in the centres to start contract negotiation.
- Anexo XI Informe anual de seguimiento del ensayo clínico dated 23 June 2017 (It is a template of Annual Study Report.
- Anexo-notificacion-incumplimientos-graves-(This is a template of notification to the the Spanish Agency of Medicines and Health Products (AEMPS) of serious breaches to the protocol of an authorized clinical trial).

Resources: https://www.aemps.gob.es/investigacionClinica/medicamentos/anexos-instrucciones-AEMPS-realiza-EC.htm

Sweden

The MPA and ethical review boards initiated a pilot phase for the new Clinical Trial Regulation (EU)536/2014

In May 2017, the Medical Product Agency (MPA), the Swedish Agency published a report adapted to Clinical Trial Regulation (EU)536/2014: "Assignment for a new authorization procedure for clinical trials". At the same time the six regional committees ' offices located at the universities of Gothenburg, Linköping, Lund, Umeå, Uppsala and at the Karolinska Institute in Stockholm and the MPA have initiated a pilot phase for CT Regulation (EU) 536/2014.

The published report explains the basic requirements of CT Regulation 536/2014, how a cooperation between the MPA and Regional Ethics Committees (RECs) should look and provides detailed information how to proceed with submission in the pilot phase in Sweden.

In the spring, the MPA and REC initiated two trials in pilot phase and they are planning to widen the initiative for more applications by the end of year to ensure the process of cooperation will be well functioning.

Source: https://lakemedelsverket.se/Alla-nyheter/NYHETER-2017/Ny-EU-forordning-ger-effektivare-beslutsvag-for-kliniska-provningar/

A report in Swedish: https://lakemedelsverket.se/upload/nyheter/2017/Rapport%20Uppdrag%20om%20nytt%20tillst%c3%a5ndsf%c3%b6rfarande%20f%c3%b6r%20kliniska%20l%c3%a4kemedelspr%c3%b6vningar.pdf

Switzerland

A new eSubmissions platform for the electronic document launched

From 30 March 2017, Swissmedic, the Swiss Agency for Therapeutic Products has informed about setting up a new eSubmissions platform for the electronic document exchange or the electronic application processing.

This new service is available in two versions:

1 OPTION "Fully electronic", including receipt of legally signed signatures

2 OPTION "Semi-electronic": Swissmedic dispatches relevant documents by post.

An applicant can register either directly as a user or as a company administrator and open an eSubmission platform as a company.

Swissmedic informed all firms that are already working on an existing portal about eSubmission platform. All new companies can register directly via the Swissmedic website. The Swissmedic has prepared videos trainings.

With the introduction of the new platform, the existing portal will be shut down as of 30 September 2017.

The video training for submission of new application: https://vimeo.com/222179270

Log in eSubmission plantform Swissmedic portal: https://www.gate.swissmedic.ch/portal/secure/?login&login?lang=en

Source: https://www.swissmedic.ch/aktuell/00673/03835/index.html?lang=en

The United Kingdom

a. Medical devices: software applications (apps)

On 21 April 2017, the Medicines & Healthcare Products Regulatory Agency (MHRA), the British Competent Authority updated their guidance "Medical device stand-alone software including apps (including IVDMDs)". The guidance is presented as a step-by-step interactive PDF and helps software and app customers to identify if their product is a medical device and needs to get a CE mark, and how to comply with the legal requirements.

The guidance is intended to be viewed on screen rather than printed.

John Wilkinson, MHRA's Director of Medical Devices said: "Where apps or stand-alone software make a diagnosis or recommend a treatment, people should check for CE-marking before using their apps and developers should make sure they are complying with the appropriate medical device regulations."

Source: https://www.gov.uk/government/publications/medical-devices-software-applications-apps#history

https://www.gov.uk/government/news/is-your-app-a-medical-device-its-healthy-to-know-regulator-issues-updated-guidance

Interactive guidance: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/610189/Software_flow_chart_Ed_1-03.pdf

b. New email address to the MHRA

Starting from 10 April 2017, the MHRA has removed ".gsi" from their email addresses: info@mhra.gsi.gov.uk will now be info@mhra.gov.uk. The new email addresses will be more secure.

Source: https://www.gov.uk/government/news/losing-gsi-mhra-emails-are-changing

c. Make a payment to MHRA - update

In the last Regulatory Newsletter (January - March 2017), CROMSOURCE informed that the MHRA had announced a new 'Pay on Invoice' process would be implemented. On 28 June the MHRA updated the information adding that iRIS (an online account management facility for customers and applicants to check their account details) is scheduled to be decommissioned after summer 2017 and applicants with only receive a Monthly Statement showing details of their account. The applicant will not need to attach proof of payment to applications but the applicant will receive an invoice to allow him/her to make payment for the correct amount once the application has been validated.

Source: https://www.gov.uk/guidance/make-a-payment-to-mhra

News from the United States of America

FDA Amends Humanitarian Device Exemption (HDE) Regulations (Technical Amendment)

A final rule amending Humanitarian Use Devices was published in the Federal Register on 7 June 2017. This rule became effective immediately.

The technical amendment removes the term "local" from the description of IRB review in the HDE regulation. In addition, the definition of a humanitarian use device (HUD) was changed. An HUD can be used to treat or diagnose a condition manifesting in up to 8,000 individuals per year. Previously, it was 4,000 individuals per year.

Final Rule:
https://s3.amazonaws.com/public-inspection.federalregister.gov/2017-11816.pdf?source=govdelivery&utm_medium=email&utm_source=govdelivery

Medical Devices; Exception From General Requirements for Informed Consent--21 CFR 50.23

In the Federal Register of June 7, 2006 (71 FR 32827), FDA issued an interim final rule to amend its regulations to establish a new exception from the general requirements for informed consent, to permit the use of investigational in vitro diagnostic devices to identify chemical, biological, radiological, or nuclear agents without informed consent in certain circumstances.

The Agency took this action because it was concerned that, during a potential terrorism event or other potential public health emergency, delaying the testing of specimens to obtain informed consent may threaten the life of the subject. In many instances, there may also be others who have been exposed to, or who may be at risk of exposure to, a dangerous chemical, biological, radiological, or nuclear agent, thus necessitating identification of the agent as soon as possible. FDA created this exception to help ensure that individuals who may have been exposed to a chemical, biological, radiological, or nuclear agent are able to benefit from the timely use of the most appropriate diagnostic devices, including those that are investigational.

Source: https://www.gpo.gov/fdsys/pkg/FR-2017-04-18/html/2017-07768.htm

Guidance Document Update

Between 16 March 2017 and 15 June 2017, FDA published 4 guidance documents, both draft and final, for Industry. The list below contains links to the 2 documents that may be of interest to CROMSOURCE and its customers.

Form FDA 3674 - Certifications To Accompany Drug, Biological Product, and Device Applications/ Submissions

Revised June 2017

Summary: FDA released a revised version of the guidance "Form FDA 3674 - Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions". This guidance document recommends that a certification using Form FDA 3674 accompany the following types of applications and submissions:

- IND
- New Clinical Protocol Submitted to an IND
- NDA
- Efficacy Supplement to an Approved NDA
- BLA
- Efficacy Supplement to an Approved BLA
- ANDA
- PMA
- PMA Panel Track Supplement
- HDE
- 510(k) that refers to, relates to, or includes information on a clinical trial

https://www.fda.gov/RegulatoryInformation/Guidances/ucm125335.htm

Use of electronic records and electronic signatures in Clinical Investigations Under 21 CR Part 11 – Questions and Answers (DRAFT)

Published June 20, 2017

Summary: This draft guidance "clarifies, updates, and expands upon recommendations in the guidance Part 11, Electronic Records; Electronic Signatures – Scope and Application that pertain to clinical investigations conducted under 21 CFR 312 and 812." In particular, this guidance discusses the procedures that may be followed to help ensure that electronic records and electronic signatures meet FDA requirement and the use of a risk-based approach when deciding to validate electronic systems, implement audit trails for electronic records, and archive records that are pertinent to clinical investigations conducted under parts 312 and 812.

In particular, this guidance clarifies:

- The part 11 controls that must be implemented in the current technological environment and,
- The risk-based approaches to validation of electronic systems, implementation of electronic audit trails and the archiving of electronic records to continue to ensure the quality, authenticity, and reliability of electronic records form their point of creation to their modification, maintenance, archiving, retrieval, or transmission.

This guidance applies to the following electronic records and electronic signatures:

- Records required for clinical investigations of medical products that are maintained in electronic format in place of paper format, including all records that are necessary for to reconstruct a study,
- Records required for clinical investigations of medical products that are maintained in electronic format and where the electronic record is relied on to perform regulated activities and,

- Records for clinical investigations submitted to FDA in electronic format under predicate rules, even if such records are not specifically identified in FDA regulations (see 122 § 11.1(b)).

This guidance addresses applicability to the following electronic systems:

- Electronic systems, including commercial off-the-shelf (COTS) and customized electronic systems owned or managed by sponsors and other regulated entities,
- Electronic services, outsourced by the sponsor or other regulated entities,
- Electronic systems primarily used in the provision of medical care,
- Mobile technology and,
- Telecommunication systems.

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm563785.pdf

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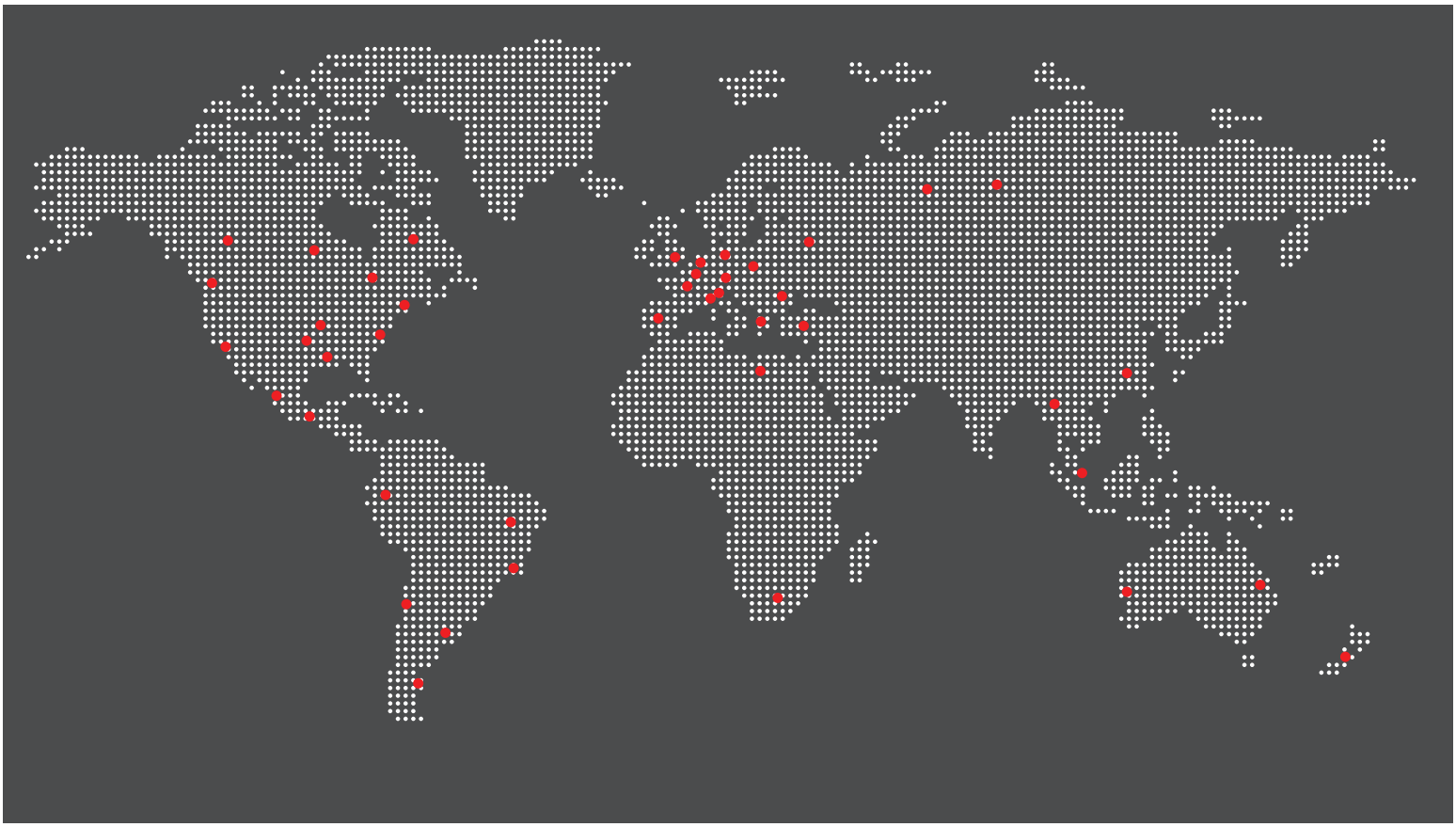

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