REGULATORY

NEWSLETTER N.40
October - December 2022

Including the latest updates on the EU CTR

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

Amendment to the CTR on Investigational Medicinal Product (IMP) Labelling

The European Commission (EC) published an amendment to the Clinical Trials Regulation (CTR) with the Delegated Regulation 2022/2239. The amendment entered into force 20 days after its publication in the Official Journal of the EU (published on 15 November 2022).

The current CTR requires mention of an expiry date on both the immediate and outer packaging labels. The amendment changes labelling requirements for immediate packaging for unauthorised investigational and unauthorised auxiliary medicinal products for human use. In the case where the immediate and outer packaging are intended to remain together, for the immediate packaging, the expiry date is to be omitted. If the immediate packaging takes the form of blister packs or small units such as ampoules, the expiry date for them can be also omitted.

The EC underlines that this amendment will avoid potential risks affecting the quality and safety of those products if it is required for them, frequent updates of the expiry date on the immediate packaging due to the changes in stability data and shelf-life. "One such potential risk may be damages stemming from the need to open the packaging by breaking tamper evident seals and disassembling the multilayer kit. Another potential risk may stem from the prolonged exposure to light or higher temperatures for medicinal products with specific sensitivities."

Recommendations on Decentralised Clinical Trials with Investigational Medicinal Product (IMP)

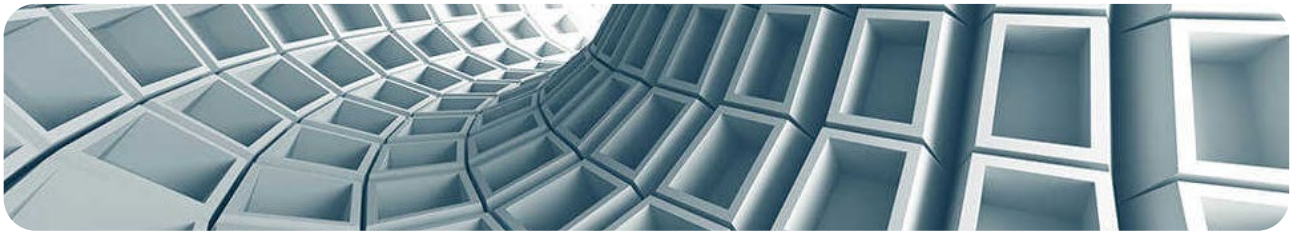
The European Commission, European Medicines Agency and Heads of Medicines Agencies have published Recommendation paper on decentralised elements in clinical trials.

Decentralised clinical trials are those where procedures are used conducted outside the traditional 'clinical trial site'. The recommendation paper provides instructions on decentralised elements in the conduct of clinical trials in the EU/EEA, regardless of any health crisis, and in consideration of the currently limited national guidance on decentralisation in clinical trials.

The document focuses on clinical trials oversight and roles and responsibilities for the Investigator and sponsor in case of conducting the off-site clinical trial. It is explained how to implement decentralised elements into the trial remote monitoring, contact with patients, and at the same time, comply with the General Data Protection Regulation (GDPR).

Another important section is related to the Informed Consent Process where the recommendations for digital ICF are provided. The document also instructs how to deliver IMP to a patient's home and guarantee it is properly administered by the patient. Moreover, the recommendation paper provides what kind of clinical trial related procedures may take place outside of the clinical trial site; how to manage data collection from the investigator/investigator site to the trial participants and/or their caregiver and/or service providers.

Appendix of the document: National provisions overview includes answers from the individual Member States to the questions related to the context of the recommendation paper. Each Member State answered whether elements of decentralised clinical trials are acceptable from their national regulatory point of view.



News from the European Medicines Agency (EMA)

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

Clinical Trials Information System (CTIS) Events and Trainings Updates by the EMA

From 31 January 2023, all new applications for clinical trials with medicinal product (MP) and combination products (MP/ medical devices (MD)) within the EU/EEA must be submitted through CTIS. Submission throughout EudraCT under Clinical Trials Directive (CTD) will be no longer possible from this date. All clinical trials that were approved under the CTD and have not been completed by 31 January 2025 will also be subject to the Clinical Trials Regulation and must be entered in CTIS.

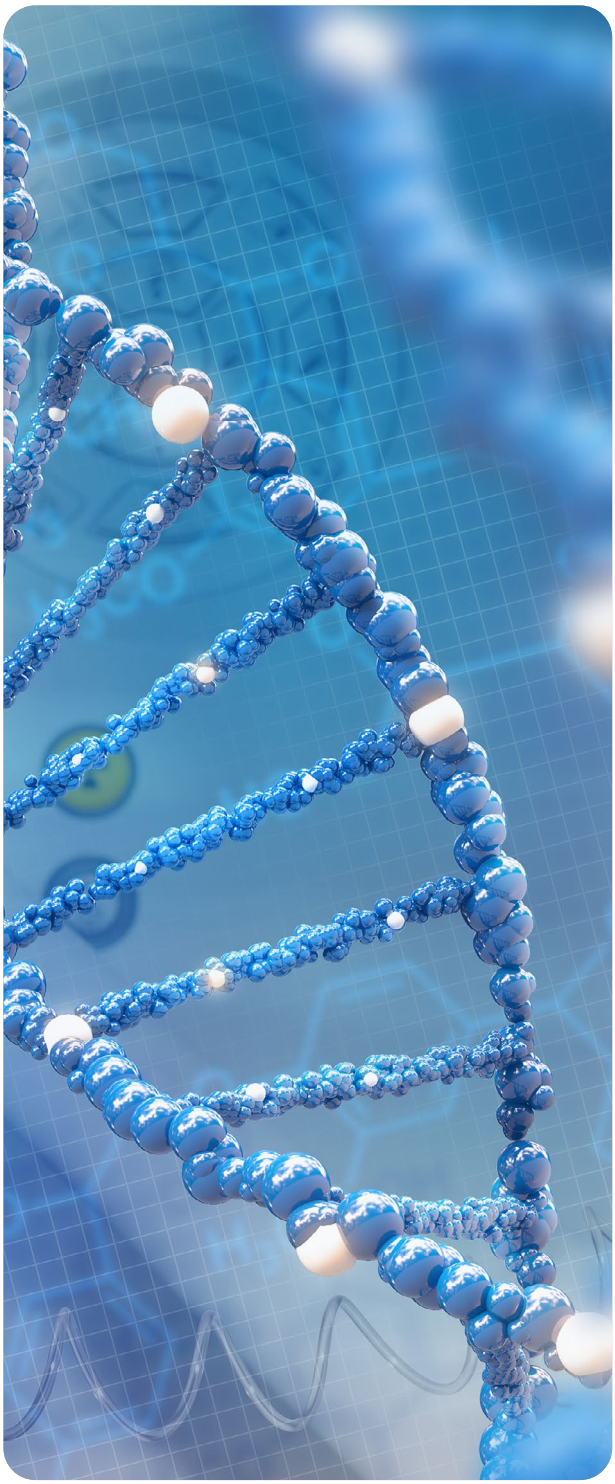
The EMA and the European Medicines Regulatory Network (EMRN) provided trainings, events, and information sessions to support CTIS users throughout 2022.

The video recordings of CTIS walk-in clinics, which provide sponsor users the opportunity to raise questions about any CTIS functionality and receive advice from CTIS experts are available on their respective event pages: 28 March, 22 April, 5 May, 19 May, 2 June, and 15 June and 31 August. Processing and publication of the video recording of the CTIS walk-in clinics from 15 November will be available up to 60 days of the event.

The monthly CTIS bitesize talks where sponsor users can learn from CTIS experts about a specific system functionality and ask questions are recorded on the EMA website. There are: User access and role management, Initial clinical trial application, Requests for information, Modifications, Transitional trials and additional Member State concerned (MSC) application, Deferral rules and Public website, Notifications - Part 1, Notifications – Part 2 and Annual Safety Report.

CTIS Latest Updates in the Clinical Trials Highlights

In October 2022, the EMA issued the 11th edition of the Clinical Trials Highlights. In this edition, the EMA is focusing mostly on the CTIS updates for events updates, training materials, provides updates on new process of requesting roles in EMA Account Management, instructs how to change a username to emails username in EMA Account Management, and informs about multi-factor authentication for all user logins to EMA-managed systems. The edition also presents EMA's Service Desk and new EMA Service Now portal which is activated on 12 September 2022.



CTIS Improvement to Prepare for Compulsory Use on 31 January 2023

A new CTIS release went live on 23 November 2022 and 12 December 2022, implementing functional improvements, including:

- Increased maximum upload size to 50 MB per document;
- Added active substance name field in the summary tab for unauthorised products;
- Improved subtasks assignment from the CT Coordinator to other users;
- Optimised search results for organisation names with special characters;
- Defined permissions for trial creation by the CT Admin user role;
- Resolving the issues with reporting member state (RMS)/concerned member state (MSC) raising Requests for Information (RFIs) on due dates of tasks and the extension of response due dates for sponsors, thus alleviating the need to use workarounds;
- Allowing trial sites which cannot be registered in OMS (i.e., not registered in a national business registry) to be recorded directly into CTIS;
- Enhancing the lock mechanism feature allowing multiple users to work on a clinical trial application;
- Ensuring visibility of documents "Agreement from another Sponsor" and "PIP Opinion" in the MS workspace following upload by Sponsor;
- Improving the MS API to display conditions provided in Part II conclusion

The EMA published guidance CTIS Release Notes – Release v1.0.9.0 describing in the details what was recently improved and corrected in the system.

Clinical Trials Information System (CTIS) - Sponsor Handbook Updated

On 29 November 2022, the EMA has published version 3.0 CTIS Sponsor handbook. Many sections have been updated and four new have been added such as Marketing Authorisation Holder (MAH) group of users (section 3.5); how to get a clinical trial application started in CTIS (section 4); how to create a transitional trial in CTIS (section 5.3); and how to manage trials transitioned to the CTR in CTIS (section 5.4). CTIS Sponsor handbook is recommended to be used by sponsors as a starting point when reviewing the available training material ahead of any clinical trial application submission.

Document Codes and Titles in the Clinical Trials Information System (CTIS)

The Clinical Trials Coordination Group (CTCG) have published a Best Practice Guide for Sponsors of document naming in CTIS (version 1.4, dd 7 September 2022). The document provides the naming convention for the documents to be submitted under CTR via CTIS in Part I and Part II.

The guide recommends using proposed codes and titles but underlines that the applicant cannot include special characters ()/,.;|[] for any filename. Version number and date should not be in the document title, instead indicate the correct version number and date in the corresponding fields in the upload window in the CTIS.

News from Individual Countries

The United Kingdom

UK Research Ethics Committee (REC) Standard Operating Procedures Updated

The Health Research Authority (HRA) published an updated version of the Standard Operating Procedures for Research Ethics Committee (RECs)-version 7.6. It has also been published the Summary of Changes document highlighting all the updates from the previous version 7.5.1 to the new version 7.6.

Decision Tool to Check What Type of Research Ethics Committee (REC) Review Will the Research Need

The HRA published a decision tool to help researchers and applicants to find out more, before submitting the study, whether it requires a full REC review or is suitable for Proportionate Review Service (PRS).

The PRS provides an accelerated, proportionate review of research studies which raise no material ethical issues.

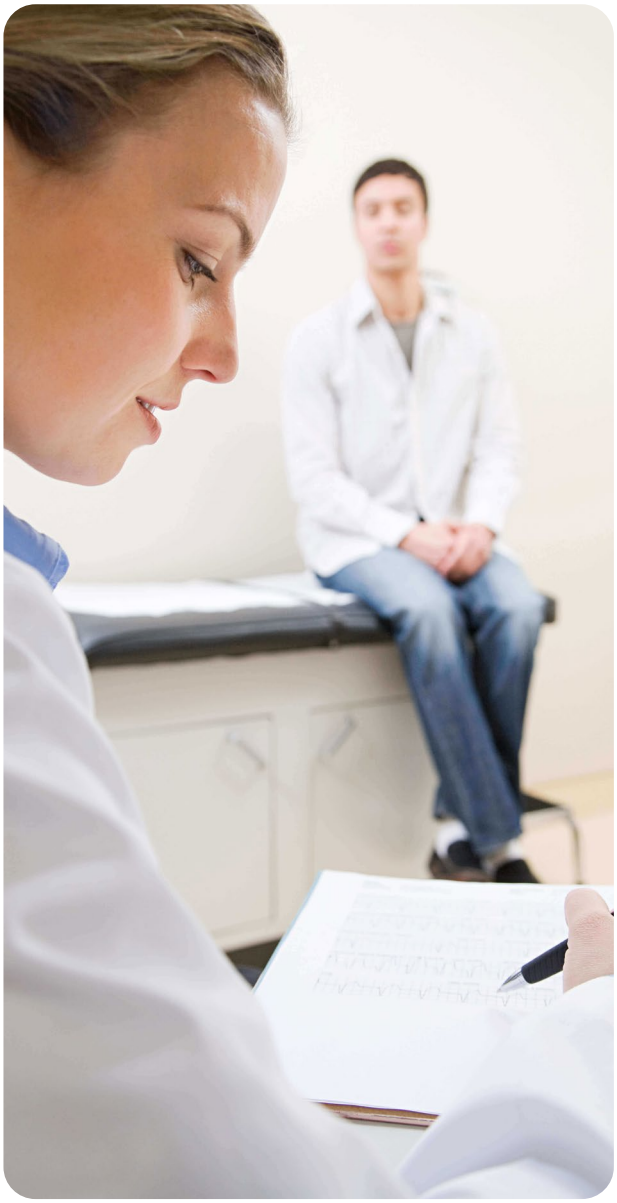
The toolkit is prepared in the MS PowerPoint and to be used by answering the questions by selecting the appropriate box. The HRA also published a text version of the toolkit.

A New Aligned Process for Regulation 5 Application

New way of submission of Regulation 5 was launched by the Health Research Authority (HRA) to allow both Confidentiality Advisory Group (CAG) and Research Ethics Committee (REC) applications to be submitted jointly via a single electronic submission. If approval is given by the HRA under Regulation 5 (statutory provision under Section 251 of the NHS Act 2006), it allows disclosure of confidential patient or service user information for medical research purposes without consent and without the data provider being in breach of the Common Law.

New Commercial Hub and Spoke Agreement Between the Sponsor (and CRO) and Lead Trial Site (Participating NHS Organisation)

The HRA informed about releasing the UK template Hub and Spoke Agreements which are for use between Lead Trial Sites (Trial Sites where a Principal Investigator is based) and Other Trial Sites (Trial Sites whose research activity is overseen by a Principal Investigator based at a Lead Trial Site). It is expected that the hub and spoke templates are used without modification. The intention to use a hub and spoke study delivery model should be proposed in the IRAS submission application for initial Clinical Trial Application (CTA) and in the cover letter, or by subsequent amendment.



Spain

Update of the Instructions for Conducting Clinical Trials in Spain

In November 2022, the Spanish Agency of Medicines and Sanitary Products (AEMPS) updated the document on instructions for conducting clinical trials in Spain: Instrucciones-realizacion-ensayos-clinicos.

Here are the most significant changes:

- When cells and tissues of human origin are used for the manufacture of investigational medicinal products in accordance with Regulation 1394/2007 on Advanced Therapy Medicinal Product (ATMP) (in which the cells or tissues undergo substantial manipulation and/or are used with a function different from that in origin), the donation, procurement and testing of these tissues or cells shall be carried out in accordance with Directive 2004/23/EC, transposed into the Spanish RD 9/2014.

  Therefore, the Spanish sites in which human cells or tissues are going to be obtained for the manufacture of ATMP under clinical research must be authorized for the donation of the specific cell type or tissue to be donated in accordance with the requirements established by RD 9/2014.

  Doubts regarding the administrative procedure to follow to obtain the donation authorization, should be addressed to the mail ont@sanidad.gob.es.

- When the clinical research involves cells and/or tissues that are not considered medicinal products but are considered transplants, Article 29 of the Spanish RD 9/2014 should be considered in this case.

  In such cases the study must be evaluated by an Ethics Committee and authorized by the local Competent Authority (usually the Autonomous Transplant Coordination). The experts of the Commission of Transplants and Regenerative Medicine of the Interterritorial Council of the National Health System must authorise the study.

  If any doubts whether human cells and/or tissues are considered ATMP, the online form should be sent through to the AEMPS.

- Update to the exceptional measures applicable to clinical trials to manage problems arising from the COVID-19 emergency.

  During COVID-19 emergency it was mandatory to prepare, for each trial, a report about all the exceptional measures adopted, together with the risk assessment conducted and its justification which will be sent to the Competent Authority and the Ethics Committee in the four months following 21 June 2020.

  If it was necessary to take new exceptional measures, or there were updates on the exceptional measures taken after 21 June 2020, these shall be notified to the Competent Authority and Ethics Committee in a complementary report on a 4-month basis (i.e., reports covering 4-month periods). After 18 November 2022, the period is extended to **ANNUAL** reports if needed.

- When submitting Clinical Trial Application (CTA) through the CTIS Portal it is important to take into account the following:
  - Either Spain is going to be proposed as a Reporting Member State (RMS) or not, the selected Ethics Committee must be contacted to be involved in the evaluation of the application on the proposed dates;
  - It is not necessary to contact the Competent Authority prior to sending the request to assess whether or not Spain could act as a RMS. The assessment of whether or not Spain can function as RMS, will be made within 5 working days after receipt of the request.

Compliance with Spain Applicable Rules for the Collection, Storage and Future Use of Human Biological Samples Template Released

The AEMPS released the form (Annex XIII) to be used by Sponsors of clinical trials in the Part II application dossier to provide information about "compliance with the applicable rules for the collection, storage and future use of biological samples from clinical trial subjects" (Regulation (EU) No 536/2014, Article 7.1 (h)). This is not a mandatory form and different national arrangements may be in place, which should be confirmed prior to submission.

Other Initiatives

Draft Adequacy Decision for the EU-US Data Privacy Framework Transmitted to the European Data Protection Board (EDPB)

On 13 December 2022, the European Commission (EC) transmitted a draft implementing decision on the adequate protection for personal data transferred under the EU-U.S. Data Privacy Framework to the EDPB requesting for their opinion. The EDPB and the EC assessment in the draft implementing decision seeks to determine whether the United States guarantees a level of protection for personal data transferred under the EU-U.S. Data Privacy Framework that is "essentially equivalent" to the level of protection ensured within the European Union.

The deadline for the EDPB opinion is 15 February 2023.

Thereafter, the EC will need to obtain acceptance from representatives of the EU Member States and the opinion of the European Parliament. The adoption of the Adequacy decision for the EU-US Data Privacy Framework is expected in 2Q 2023 or even later.

Letter to the EDPD Chair.

ICH Releases M11 Step 2 Guideline Proposing Harmonized Template for Trial Protocols

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use has published a draft version for public consultation of ICH Harmonised Guideline of Clinical Electronic Structured Harmonised Protocol (CESHARP). This document is primarily intended to provide a protocol template that will provide value to all parties involved in a clinical trial and eliminate any ambiguity and difficulty in searching, reviewing, and evaluating clinical trial protocols, and currently no internationally accepted and harmonised standard for the format and content of a clinical protocol has been established. This template presents the format and structure of the protocol including the table of contents, headings and content and describes precise guidelines for the design of protocols and any supporting documents so that they are acceptable to all ICH regulators. Moreover, the guidance supports to keep the clinical trials consistency across sponsors and for the electronic exchange of protocol information.

North America

United States of America

High Concordance in Breakthrough Therapy and PRIME Decisions with FDA and EMA

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) agreed on nearly two-thirds of decisions to grant or deny requests for drugs and biologics seeking Breakthrough Therapy or Priority Medicines designation, according to a new analysis published on 28 October 2022.

The findings highlight the need for agencies and sponsors to take advantage of collaborative opportunities, including the Parallel Scientific Advice program, to support global drug development that addresses unmet medical needs, wrote Zahra Hanaizi, of the EMA, along with colleagues at EMA and FDA, wrote in Therapeutic Innovation & Regulatory Science.

FDA's Breakthrough therapy (BT) designation, launched in 2012, and EMA's Priority Medicines (PRIME) designation, launched in 2016, are designed to provide support and scientific advice during the development of products that have the potential to address unmet medical needs.

After the launch of PRIME, FDA and EMA began monitoring similarities and differences in what was submitted and designated under the two programs to find ways to better support global development. The researchers added designations made through the FDA's Regenerative Medicines Advanced Therapies (RMAT) program at the time of its launch in 2018.

From 4 April 2016 to 31 December 2020, 151 requests were made to both programs, with the agencies reaching the same conclusion – to approve or deny an application - in 93 cases (62%). Of the 93 cases in which the agencies agreed, 42 applications were granted and 51 were denied. The researchers noted that just one of the 42 applications approved by both agencies was the subject of formal Parallel Scientific Advice, a program that allows EMA and FDA to advise a sponsor collaboratively. Divergence of opinion by the agencies occurred with 58 applications, or 38.4%. In most cases, the reason for diverging conclusions was a difference in interpreting the same data or differences in program implementation policy. Less often there were different data submitted or differences with currently available treatment across regions.

Canada

Health Canada Provides Guidance for Clinical Trials on Psychedelics

Health Canada has issued Notice to stakeholders: Health Canada's expectations regarding risk-management measures for clinical trials involving psychedelic-assisted psychotherapy on 6 December 2022 to stakeholders in the psychedelics industry, physicians, therapists and others regarding its future expectations for clinical trials and regulations for psychedelic-assisted therapy going forward. The government department provided the guidance information due to a growing interest in the use of psychedelic-assisted psychotherapy and the inherent need to mitigate physical and psychological risks for participants involved in the studies.

In order for a clinical trial to proceed in the country, Health Canada must complete an assessment of risk management measures to determine whether it would be in the best interest of participants. Due to the increased risk of psychological harm to participants and the sensitive nature of these treatments, Health Canada has outlined risk-management measures that it will require for all clinical trial applications (CTAs). It says companies/entities/sponsors must present a sufficient plan in adherence with those measures or a viable alternative risk-management strategy prior to commencing in-human studies with psychedelics.

Health Canada says it expects that all therapists involved with clinical trials will be adequately trained on evidence-based protocols for psychedelic-assisted psychotherapy and that they should be certified to provide psychotherapy by a regulatory body in their jurisdiction (if applicable).

A qualified investigator looking to perform a clinical trial with a psychedelic restricted drug must apply for an authorization under the *Controlled Drugs and Substances Act* (i.e., Part J of the FDR) from the Office of Controlled Substances. Health Canada's webpage provides information regarding this process, including the application form for an exemption to use a controlled substance for clinical studies, which should be completed by a qualified investigator.

MEDICAL DEVICES

EUROPE

News from the European Commission

Commission Implementing Regulations

On 1 December 2022, the European Commission published two Implementing Regulations:

- Regulation (EU) 2022/2346 establishes common specifications for product groups that do not have an intended medical use listed in Annex XVI of Regulation (EU) 2017/745 on medical devices
- Regulation (EU) 2022/2347 laying down the methods of application of Regulation (EU) 2017/745 as regards the reclassification of groups of certain active products that do not have a medical intended use

Regulation (EU) 2017/745 (MDR) will apply to the product groups listed in Annex XVI from 22 June 2023. However, the Implementing Regulation (EU) 2022/2346 provides for derogations if:

- The involvement of a notified body in the conformity assessment procedure in accordance with Regulation (EU) 2017/745 is envisaged;
- A clinical investigation is planned;
- The product in question has been certified in accordance with Directive 93/42/EEC.

The Commission Implementing Regulation (EU) 2022/2347 defines the risk classes for some active products. In particular:

- Equipment emitting high intensity electromagnetic radiation intended to be used on the human body for dermal treatment is reclassified in class IIb , unless it is intended solely for hair removal, in which case it is reclassified in class IIa;
- Equipment intended to be used to reduce, remove, or destroy fatty tissue is reclassified to class IIb;
- Equipment intended for brain stimulation which applies electric currents or magnetic or electromagnetic fields passing through the skull to modify the neuronal activity of the brain is reclassified to class III.

Guidance on Authorised Representatives

Guidance on Authorised Representatives Regulation (EU) 2017/745 on medical devices (MDR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR) has been published in October 2022 by Medical Device Coordination Group. The main focus of this document is to provide guidance to authorised representatives, manufacturers, and other entities on the relevant requirements, since if the manufacturer is not located in a Member State, an authorised representative must be appointed. The document describes the minimum tasks and responsibilities of an authorised representative and addresses registration and verification obligations.

Furthermore, the situations of termination of the mandate and change of the authorised representative are described. Market surveillance responsibilities are also presented and the role of the person responsible for compliance (PRRC) are explained.

Questions and Answers: Requirements Relating to Notified Bodies

Medical Device Coordination Group has published the fourth revision of Questions and answers: Requirements relating to notified bodies. This document is a compilation of questions and answers on the requirements relating to notified bodies under Regulation (EU) 2017/745 on medical devices (MDR) and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR).

This guidance contains answers to questions on organisational and general requirements, quality management system, resource and process requirements and other requirements relating to notified bodies. The document expounds on the activities of the conformity assessment body (CAB) and the clarification of specific phrases and definitions in the above regulations.

Data Generated from 'Off-Label' Use of a Device under the EU Medical Device Regulation 2017/745

The European Association of Medical devices Notified Bodies has published a Position Paper concerning data generated from 'Off-Label' Use of a device under the EU Medical Device Regulation 2017/745. The MDR guidance requires the manufacturer's post-market clinical (PMCF) plan to identify systematic misuse and off-label use of a medical device, that is, when a device is used outside the approved instructions for use, and the manufacturer is obliged to include data of such evaluation as part of the overall clinical evaluation.

This document defines when off-label use of a device may include use of the device outside the approved indications. The document also provides answers to whether off-label data can be applied to extend the intended purpose or indications and presented are also proceedings in the case of a deviation from the conformity assessment procedures for a medical device for an unsatisfied medical need.

Best Practice Guidance for the Submission of Technical Documentation under Annex II and III of Medical Device Regulation (EU) 2017/745 (MDR)

The European Association of Medical devices Notified Bodies has published a Position Paper concerning Best Practice Guidance for the Submission of Technical Documentation under Annex II and III of Medical Device Regulation (EU) 2017/745. This document is a collection of best practices developed by members of the NB Team with the aim of developing a standardised approach in terms of expectations for the technical documentation submission by manufacturers. The reasons for delays in technical documentation reviews are outlined and practical solutions are proposed. Above this, there is also a presentation of what the device description and specification should contain, as well as information on design and manufacturing, facility, subcontractors, and safety requirements.

Furthermore, this document presents and explains all the information concerning the risk analysis, validation, verification, biocompatibility, software, performance, usability, sterilisation and clinical evaluation of the medical device and post-market surveillance.

News from Individual Countries

The United Kingdom

New Section Added 'Risk Classification of Medical Devices' to Borderline Products Guidance

The Medicines and Healthcare Products Regulatory Agency (MHRA) has updated on 16 November 2022 a Guidance on borderline products to answer on how to tell if the product is a medical device and which risk class should be applied to a medical device. This guidance outlines how the MHRA determines whether a product falls within the definition of a medical device as some products such as medicines, cosmetics, food supplements, biocides or personal protective equipment are difficult to distinguish from a medical device. The types of borderline devices, which are those without a defined status yet, and the process for resolving whether a product is a medical device are presented and described. Furthermore, the risk classification process for medical devices is presented and guidance documents are provided in order to receive advice on a product.

Changes to Submitting Adverse Incidents to Medical Devices to the MHRA

The Medicines and Healthcare Products Regulatory Agency (MHRA) informed that from November 2022, reports relating to adverse incidents for devices, such as Manufacturer Incident Report (MIR), Field Safety Corrective Actions (FSCAs), Trend Reports, and Period Summary Reports (PSRs) and also Serious Adverse Events (SAEs) must be submitted via new MORE portal. During the transition period, the reports can be submitted via email AICxml@mhra.gov.uk until 30 April 2023. Reports submitted via email from November 2022 until 30 April 2023 will not be visible on the applicant's account. They will need to be downloaded again once the account in the new MORE portal that is created.

The new MORE portal requires registration which is available from September 2022. The roles in the system are as follows: Manufacturer, UK Responsible Person, EU Authorised Representative for Northern Ireland and Other (e.g., Sponsor of Clinical Investigation). For users who are registered under 'Other' role, there are two levels of access: standard user (submits reports, verifies whether the submitted reports are validated, views and updates them, receives notifications about submitted reports, accesses guidance and help for the system) and the organisation lead (person responsible of the account and able to manage the standard users on the account). The Organisation lead must be approved by the MHRA.

The Netherlands

New Rates for the Assessment of Clinical Studies with Medicinal Products and/or Medical Devices

The Central Committee for Research Involving Human Subjects (CCMO) published new rates for the medical-ethical assessment of research in the Netherlands that falls under the Clinical Trials Regulation (CTR), Medical Device Regulation (MDR) and In-Vitro diagnostics Regulation (IVDR). The new rates will apply from 1 January 2023.

North America

United States of America

FDA Updates Breakthrough Devices Guidance Focused on Health Equity

On 21 October 2022, the FDA issued a draft guidance, "Select Updates for the Breakthrough Devices Program Guidance: Reducing Disparities in Health and Health Care."

The Breakthrough Devices Program is a voluntary program for certain medical devices that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases. The draft guidance proposes updates to clarify how the Breakthrough Devices Program may be applicable to certain medical devices that promote health equity.

It also proposes updates to clarify considerations in designating devices, including eligible devices that may benefit populations impacted by disparities in health and health care, as well as how the FDA discloses the Breakthrough status of designated devices once they receive marketing authorization.

The Breakthrough Devices Program is comprised of two phases. The first is the Designation Request phase, in which an interested sponsor of a device requests that the FDA grant that device Breakthrough Device designation. The second phase encompasses actions to expedite development of the device and the prioritized review of subsequent regulatory submissions.

Learn more about the Breakthrough Devices Program principles and features in the Breakthrough Devices Program final guidance.

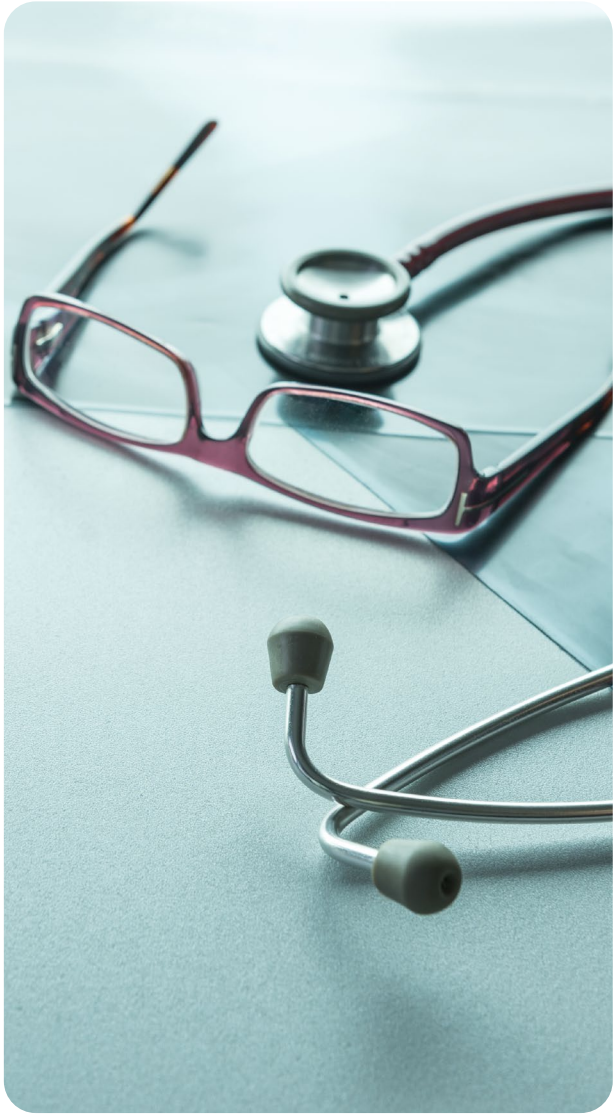
Canada

Health Canada Issues Guidance on Clinical Evidence Requirements

Health Canada has finalized on 5 December 2022 the Guidance on Clinical Evidence Requirements for Medical Devices. This guidance outlines the general principles and criteria for clinical evidence that may be required for Class III and IV license applications or requested for certain Class II license applications and other obligations throughout a medical device's life cycle.

The guidance provides discussions on when clinical data/evidence is required, what common methods to use in generating clinical data, and how to compare devices appropriately. A companion document that provides specific examples of clinical evidence requirements to help manufacturers determine if clinical evidence will be required or requested is also included in the guidance.

The guidance describes in detail the approach to be applied when determining the scope of clinical evidence to be submitted to substantiate the claims made by the medical device manufacturers, and also when determining whether clinical evidence should be submitted in a specific case.



OTHER "HOT" TOPICS FROM THE UNITED STATES

FDA Updates Statistical Approaches for Assessing Bioequivalence

On 2 December 2022, U.S. Food and Drug Administration's Center for Drug Evaluation and Research (CDER) released a revised draft guidance, "*Statistical Approaches to Establishing Bioequivalence*." The guidance provides recommendations to sponsors and applicants planning to analyze in vitro or in vivo Bioequivalence (BE) studies for investigational new drugs (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs) and supplements to these applications.

There are several statistical approaches that can be used for BE comparisons, and this guide explains how to utilize them both generally and in specific situations. The update replaces a previous version in February 2001 and adds new topics such as assessing the bioequivalence for narrow therapeutic index (NTI) drugs and highly variable drugs, using adaptive trial designs, and statistical approaches for filling in missing patient data.

The guidance incorporates the principles of the adaptive design approach, which "allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial." The guidance intends to "help applicants plan and analyze their BE studies with the goal of minimizing the number of assessment cycles necessary for approval."

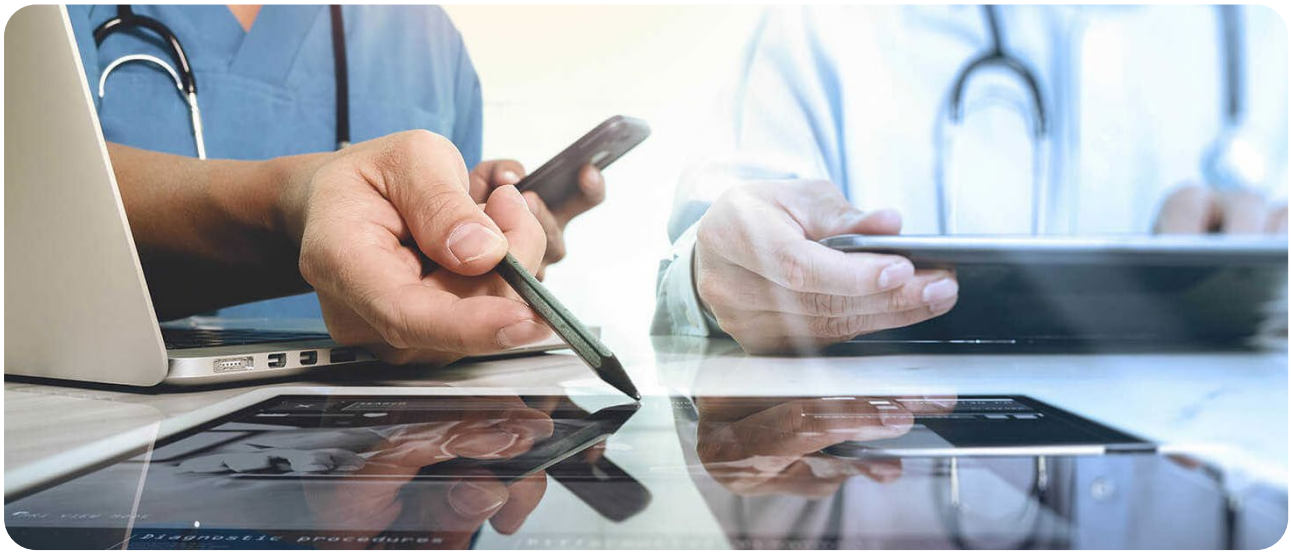
It also addresses dealing with missing data caused by events such as a subject's refusal to continue in the study, the emergence of adverse events, or the subject's failure to meet scheduled appointees for evaluation. "Missing data and intercurrent events can introduce problems such as bias, misleading inference, loss of precision and loss of power, which make it hard to interpret the trial outcome," said FDA.

FDA Finalizes Umbrella Clinical Trial Guidance for Cell and Gene Therapies

The FDA laid out its recommendations for sponsors to study multiple versions of a cellular or gene therapy in a clinical trial for a single disease. The agency said its final guidance on 4 November 2022 should help sponsors conduct umbrella trials of similar products for the same disease more efficiently to bring cell and gene therapies to market sooner.

While clinical trials typically evaluate a single product, umbrella trials use a single-trial infrastructure, design, and master protocol to simultaneously evaluate multiple products for a disease or condition, which can be more efficient.

"Sponsors have expressed interest in gathering preliminary evidence of safety and activity using multiple versions of a cellular or gene therapy product in a single clinical trial," FDA said. "Although multiple versions of a product can be studied together in a single clinical trial, each version of the product is distinct and is generally submitted to FDA in a separate investigational new drug application (IND). The objective of these early-phase clinical studies is to guide which version(s) of the product to pursue for further development in later-phase studies."



FDA stressed that the guidance only applies to early-phase studies of multiple versions of a cellular or gene therapy product being studied in a single disease. If sponsors want to apply the same type of umbrella trials to other types of products, they should speak with the Center for Drug Evaluation and Research (CBER) first.

FDA also emphasized that the guidance does not apply to trials conducted outside the narrow scope of umbrella trials discussed in the document by the agency and noted that the guidance does not apply to basket trials, in which a single therapy is tested in different populations. If a sponsor is interested in conducting such studies, the agency says they should talk to CBER and request a pre-IND meeting to discuss potential clinical trial designs.

FDA Updates Guidance on Expanded Access for Investigational Drugs under IND

On 2 November 2022, FDA has updated its Guidance for industry on expanded access to investigational drugs under an investigational new drug (IND) application. The guidance now includes new frequently asked questions about how expanded access should be implemented given new regulatory access and statutory requirements through the 21st Century Cures Act (Cures Act) and FDA Reauthorization Act of 2017 (FDARA).

While the guidance remains largely the same from 2017, FDA added new recommendations for Institutional Review Board (IRB) review, informed consent, and new requirements in Cures Act and FDARA to publicly share sponsor policies on evaluating and responding to expanded access requests, the agency said.

The manufacturer or distributor is required to include their contact information, procedures for submission of expanded access requests, general criteria for evaluation and response, the anticipated time frame for acknowledgement of such requests, and a hyperlink or other reference to the record in ClinicalTrials.gov that contains information about availability of the drug under expanded access.

About CROMSOURCE

CROMSOURCE is an ISO-certified international provider of outsourced services to the pharmaceutical, biotechnology and medical device industries, specialising in clinical development and staffing solutions. CROMSOURCE was founded in 1997, more than 25 years ago. Its successful growth has been built on stability, integrity, and high levels of customer satisfaction, all of which contribute to a high rate of repeat and referral business. We have grown steadily, but responsibly, to become an organisation of over 350 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-in-human through all subsequent phases of pre- and post- approval research internationally.

We also support medical device projects through regulatory planning and execution, to pre- and post-market 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, 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 around the globe to provide expert capabilities in regions including the Middle East, Africa, APAC, and South America.