Newsletter

ClinChoice
The Standard of Excellence

REGULATORY NEWSLETTER

October - December 2023

Contents

MEDICINAL PRODUCTS/ DRUGS

News from the European Commission

First Electronic Product Information Published for Medicines

The Heads of Medicines Agencies (HMA), the European Commission (EC), and EMA have released electronic product information (ePI) for certain human medicines in the European Union (EU). This is the first time such information is available electronically and is part of a one-year pilot initiative. The ePI includes details like the summary of product characteristics, its labelling, and package leaflet.

The published ePIs are for medicines assessed by EMA or national authorities in Denmark, the Netherlands, Spain, and Sweden. Companies involved in the pilot create and submit the ePI as part of their regulatory application. The pilot, covering 25 medicines, will end in July 2024. The results will guide the integration of ePIs into regular practice and their expansion across the EU.

The ePIs can be viewed at the Product Lifecycle Management Portal in English for centrally approved medicines and in the local language for nationally approved ones. Ongoing testing aims to provide access to ePIs in all EU languages.

More information is available here.

News from the European Medicines Agency (EMA)

EMA Publishes Revised CTIS Transparency Rules

On 5 October 2023, the European Medicines Agency (EMA) has approved the Revised CTIS Transparency Rules, designed to speed up access to clinical trial information through the Clinical Trials Information System (CTIS). These changes eliminate the deferral mechanism, which previously allowed sponsors to delay publishing specific trial data and documents for up to seven years to protect personal data and commercially confidential information (CCI). The removal of the deferral function means that structured data fields and essential documents can be published earlier to meet the needs of patients and clinical researchers in the European Union/ European Economic Area (EU/EEA). Furthermore, the number of published documents will be reduced to simplify the process and lessen the workload for users involved in necessary redactions.

The implementation of these revised transparency rules within CTIS, including its public portal, is expected to be completed in the second quarter of 2024.

Until the new CTIS public website is launched, during interim period, sponsors can already adhere to the principles of the revised rules for initial applications. They should provide versions labelled ‘for publication’ and ‘not for publication’ only for documents covered by the revised transparency rules from 5 October 2023, and upload a page with suggested wording in Annex I to Q&A on the protection of CCI and Personal Data while using CTIS, for documents that will no longer be subject to publication.

Unredacted versions of the documents to be assessed must be provided in the 'not for publication' slot to allow proper evaluation by Member States.

For substantial modifications or additional applications in Member States, sponsors should consider the preferred approach for protecting personal data and CCI, aiming to decrease the burden depending on the trial status, i.e., whether deferrals are already in place.

For transition trial applications, sponsors should follow the principles of Q11 of the Guidance for the Transition of clinical trials from the CTD to the CTR and submit a redacted version 'for publication' only of the protocol, subject information sheet, and ICF.

For 'historical' trials (submitted to CTIS before the new transparency rules are implemented), the structured data will be published for all trial categories as per the revised rules, but documents will not be published. The publication of documents in scope of the revised rules will only occur when included in applications submitted after the rules are in place, regardless of previous deferrals or publication status.

For applications submitted in CTIS after the launch of the new CTIS Public Portal, the documents in scope of publication of revised rules will be published and should be redacted accordingly.

Additionally, the EMA updated the Q&A on the protection of CCI and Personal Data while using CTIS by introducing a new section 4 that addresses the revised transparency rules. This involved updating the text throughout the document to align with the principles outlined in section 4. To enhance comprehension of the revised rules, the EMA published a quick guide for users, summarizing the key principles and detailing which structured data and documents will be published and when.

Clinical Trials Information System (CTIS) - Sponsor Handbook Updated

In October 2023, the EMA released version 3.03 of the CTIS Sponsor Handbook. Numerous sections have been revised, incorporating pertinent links to guidance for transitional clinical trials, recently published guidance from the Clinical Trials Facilitation and Coordination Group (CTFG), cover letters for transitional trials, Q&A on the protection of commercially confidential information (CCI) and personal data in CTIS, and various other updates.

The references to the CTIS Sponsor Handbook are also included in the 'Sponsor quick guide: Getting started with CTIS.' This guide is designed to assist applicants in easily navigating the system and other tools linked to the CTIS.

Clinical Trials Regulation (EU) No 536/2014 (CTR) Questions & Answers (Q&A) Update

In December 2023, the European Commission released version 6.6 of the Q&A Document for Regulation (EU) 536/2014. In comparison to the previous version, the following Q&As have been revised or added:

- New Q&A 7.2 has been added (related to the definition of inpatient hospitalization in the context of serious adverse events), 7.41 (providing information on the format of the Annual Safety Report (ASR) for a non-commercial sponsor running a single clinical trial with an authorized Investigational Medicinal Product (IMP)), and a new point 370 (clarifying that the preferred language for the Annual Safety Report is English in all Member States, regardless of whether the submission is mono national or multinational).
- Points 289, 294, 404 (now numbered 290, 295, 405) have been revised.
- Annex II updated: for Portugal, the Protocol Synopsis and patient-facing documents must now be submitted in Portuguese and English. For Estonia, patient-facing documents are required in Estonian and English, with a note specifying submission of those documents in at least the official national language(s) of the region(s) where the trial is conducted; English is optional.
- Annex III updated: for Hungary, the email address for Part I-related enquiries has been updated. For Finland, the links to websites have been revised. For Sweden, an additional contact for Part II has been added.

EMA Recommends Consulting the Released Notes for CTIS

EMA continues to actively monitor user feedback, collaborating with stakeholders to implement ongoing system improvements and enhance the overall user experience. The latest updates are detailed in the published release notes and in the lists of known issues and proposed workarounds.

One noteworthy update advises applicants to refrain from creating draft applications for Substantial Modifications, Non-Substantial Modifications, or Additional Member State Concerned while the previous application is still under evaluation. Additionally, sponsors may encounter an error message when uploading new versions of documents. Prior to reaching out to the CTIS Service desk, sponsors are encouraged to refresh the webpage and verify if their changes are visible.

Among the recent CTIS improvements, Member States now have the capability to provide comments on the Request for Information (RFI) response even after the Reference Member State (RMS) has authorized the application. Moreover, users can now download documents with special characters in the title.

European Countries Public Holidays Saved in CTIS for 2024

The EMA has released a list of official public holidays in European countries for 2024, as documented in the Clinical Trials Information System (CTIS). These dates, recorded in the CTIS, can impact the timelines for applications. Public Holiday days or Winter clock stop days are not included in the calculation of timelines.

Moreover, for multinational trials, where each Member State (MS) may have a different holiday calendar, the process of selecting the Reporting MS will follow the calendar with the longest duration among the Member States Concerned.

Workplan to Guide Use of Artificial Intelligence in Medicines Regulation

EMA and the Heads of Medicines Agencies (HMAs) have jointly released an Artificial Intelligence (AI) workplan for the period 2023-2028. The plan, developed under the joint HMA-EMA Big Data Steering Group (BDSG), outlines a collaborative strategy to optimize the benefits of AI for stakeholders while effectively managing associated risks. Adopted by EMA's Management Board in December 2023, the workplan focuses on four key dimensions:

Guidance, Policy, and Product Support: Ongoing support for products in development and the development and evaluation of suitable guidance for AI's use in the lifecycle of medicines. The public consultation of the AI reflection paper (RP) concluded in December 2023, initiating the process. Work will commence in mid-2024 to prepare for the implementation of the AI Act.

Tools & Technologies: Implementation of Large Language Models (LLMs), particularly chatbots, as predominant tools in intellectual work, such as personal assistants. A survey of the Network's capability to analyse data, incorporating the use of AI.

Collaboration and Change Management: Starting to use tools that find important information. Using smart programs bit by bit and keeping an eye on how well they help. Asking the team about their ability to use these tools. Publication of the AI tools policy for the European Medicines Regulatory Network (EMRN).

Experimentation: Trying new things with AI every few months. Sharing important areas to study AI. Looking closely at specific tools and techniques, like digital twins, to learn more.

The ACT EU Multi-Stakeholder Workshop on Methodology Guidance

On 23 November 2023, the EMA organized an event where the Accelerating Clinical Trials in the EU (ACT EU) initiative hosted a multi-stakeholder workshop on clinical trial methodology guidance. Stakeholders, regulators, and the European Medicines Regulatory Network (EMRN) collaborated to gain insights into various stakeholder perspectives regarding the development of clinical trial methodology guidance.

They discussed the current status of guidance on priority clinical trial methodology topics and exchanged views on key methodology topics, emphasizing the needs of patients. The presentation slides covering various aspects of paediatric clinical trials from ethical, regulatory, and industry perspectives have been made available on the EMA website. Additionally, all slides presented during the workshop, covering topics such as randomized clinical trials, decentralized clinical trials, patient-centricity, and inclusion and representative-

ness in clinical trials, are accessible on the EMA website.

The outcomes of these discussions will be compiled into a workshop report on the event page, which will be used to guide the future work of the EMRN in the development of methodology guidance.

Other Initiatives

CTFG Best Practice Guide and Cover Letter Template Updated

The Clinical Trials Facilitation and Coordination Group (CTCG) has issued updated versions of the Best Practice Guide and cover letter template for sponsors transitioning multi-national clinical trials to the EU Clinical Trials Regulation (EU CTR) and Clinical Trials Information System (CTIS).

The revised guide now provides clarification on the concept of consolidated protocols, emphasizing the sponsor's responsibility to decide on the transition as a single clinical trial. It includes an annex with a graphical example of a consolidated protocol version. Additionally, there is clarification on the background treatment, specifying the status of non-Investigational Medicinal Products under the EU CTD considered as Investigational Medicinal Products (IMP) or Auxiliary Medicinal Products (AxMP) under the EU CTR.

Furthermore, the CTCG has approved an expedited and harmonized Member State evaluation procedure, open until 16 October 2024, focusing on validating minimum application dossiers restricted to documents already authorized under the EU CTD. Beyond this date and contingent on Member State workloads, this expedited procedure may not be available. The CRFG will be working on new guidance and updated documents, including a cover letter template, to assist stakeholders in simplifying the transition process from the EU CTD to the EU CTR and simultaneously supporting Member States.

ICH Adopts Guidelines on Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

The ICH Q5A Guideline, which is an important set of rules, completed a significant step in its development on 1 November 2023. This guideline focuses on giving guidance about dealing with viruses when making medicines. The main objectives of the guidance are:

1. Capture key scientific and regulatory considerations to promote harmonization in the evaluation of viral clearance, characterization, and testing.
2. Describe three main and complementary approaches to control potential viral contamination, which include:
    - Selecting and testing cell lines and other raw materials, including media components, to ensure the absence of undesirable infectious viruses.
    - Assessing the capacity of production processes to clear adventitious and endogenous viruses.
    - Testing the product at appropriate steps of production to ensure the absence of contaminating infectious viruses.

This guideline is meant to be used along with other existing guidelines, especially ones called ICH Q2, ICH Q5D, and ICH Q13.

Austria

BASG Fee Schedule for Clinical Trials Updated

Effective from 1 January 2024, a new fee regulation by the Austrian Federal Office for Safety in Health Care (BASG) has been implemented. This regulation applies to all applications received by the BASG from this date onward. You can find the current fees outlined in the BASG fee schedule.

Clarification on the Decision by BAGS on CTAs Submitted via CTIS

In December 2023, the BAGS provided clarification on the decision process for Clinical Trial Applications (CTAs) submitted through the Clinical Trials Information System (CTIS) where Austria is the Reference Member State (RMS) or the Member State Concerned (MSC). The decision on an application for approval, whether it's an initial application or a significant amendment, is made by the BAGS after completing the procedure. In the CTIS, this corresponds to finishing the "Authorize" task.

As per EU CTR, completing this task is enough to consider the decision on the application. If it's an authorization or an authorization with non-suspensive conditions, the clinical trial can start, or the requested modification can be implemented.

Furthermore, the following documents will be provided to the applicants:

- A confirmation letter of completing the "Authorize" task, sent via CTIS upon completion.
- A national decision sent by post to the sponsor or national applicant outside of CTIS within the next 14 days.

In the case of approval in CTIS, there's no need to wait for a positive decision, especially considering potential administrative or postal delays. If there's a rejection in CTIS, the negative decision is the basis of any appeal proceedings.

Document Templates for FORM and National Aspects for Part II

The BAGS provided clarification on document templates for Part II of dossier submitted under the EU CTR. They emphasize that the templates published by the Commission in Eudralex Vol. 10 ('Chapter I') are accepted or recommended by BAGS and the Austrian ethics committees. If sponsors choose to use their own templates, these must, at a minimum, contain the information found in the Commission's templates. It's crucial that Curriculum Vitae (CV) must be both dated and up to date (not older than 1 year), and no signature is required under CVs.

It's recommended to use national templates for Part II, particularly for the Patient Information Sheet and Site Suitability Form. For Insurance Policy and Terms and Conditions, a national contact point for questions about

Italy

List of National Ethics Committees and Territorial Ethics Committees

On 19 December 2023, the Italian Medicines Agency (AIFA) published an updated list of National Ethics Committees and Territorial Ethics Committees for the evaluation of applications for clinical trials. The list specifies which Ethics Committees are willing to work exclusively through the National Observatory on Clinical Trials (Osservatorio Nazionale sulla Sperimentazione Clinica – OsSC), both via the OsCC and Clinical Trials Information System (CTIS), or solely through CTIS. Contact emails for these committees are also provided.

Communication for Sponsors on the Migration of Clinical Trials to the CTIS system

The AIFA issued an announcement reminding applicants to prepare for the transition of Clinical Trials (CTs) from the EU CTD to the EU CTR. Particularly, for submissions without proper planning and those not staggered over time, it is advisable to consider the deadline of 16 October 2024, for submitting the transition application. This ensures that the procedural outcome is finalized by 30 January 2025.

Additionally, AIFA published slides outlining recommended timelines for migrating clinical trials to the Clinical Trials Information System (CTIS).

Summary of the Meeting with Local and National Ethics Committees and Presentations

On 21-22 November 2023, the Italian Medicines Agency (AIFA) and the National Coordination Centre of Ethics Committees (CCNCE), in collaboration with the Ministry of Health, organized an event titled “Meeting with Territorial and National Ethics Committees.” The event, conducted in a hybrid format (both in person and online), saw the participation of over 300 representatives from local (CET) and national (CEN) ethics committees, as well as regional representatives responsible for coordinating and governing the ethics committees. The meeting provided a significant platform to discuss relevant issues, identify challenges, and explore potential shared solutions. Participants shared their experiences and suggestions, contributing to the enhancement of dialogue and collaboration among the various stakeholders.

A summary of the event, including slides presented during the meeting for downloading, has been published by AIFA.

GCP Inspectorate Communication on Computerised Systems and Electronic Data in Clinical Trials

On 29 December 2023, the Italian Medicines Agency (AIFA) GCP Inspectorate published a guidance document on the Guideline on computerized systems and electronic data in clinical trials, following the EMA Guideline on this topic. The document emphasizes the crucial role of investigators in maintaining accurate and comprehensive records, including electronic data, during clinical trials. It highlights the need for regulations to responsibly adapt to technological advancements, giving priority to patient safety and data integrity.

Inspections at Italian clinical centres reveal a diverse use of electronic systems, ranging from paper-based to in-house software without validation. The recommended approach is to assess the impact of each electronic system on participant rights, safety, and data reliability. A validation process, documented by a diverse team and end-users, should be proportional to the system’s significance. Leaders of healthcare institutions are encouraged to ensure their computer systems comply with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - Good Clinical Practice (ICH-GCP) and the EMA Guideline, safeguarding trial participants and maintaining data integrity for regulatory submissions.

The AIFA emphasizes that the approach outlined in the guidance document aligns with the principles of GCP-ICH E6 (R2) § 4.9.0 and will be further elaborated in the upcoming version R3 of GCP, currently in the finalization process.

Spain

Instruction Document for Conducting Clinical Trials in Spain Updated

The Spanish Agency of Medicines and Medical Devices (AEMPS) has updated Instruction document of the Spanish Agency of Medicines and Medical Devices for conducting clinical trials in Spain.

This document provides instructions for the conduct of clinical trials in Spain, specifically focusing on practical aspects related to the application of Regulation (EU) No 536/2014 (EU CTR) and Royal Decree 1090/2015. The information is presented in a question and answer format and covers various elements, including the Ethics Committees for Research involving medicinal products (CEIm) and the Spanish Clinical Trials Register. This document is intended to complement the "collaboration memo" between the AEMPS and the CEIm, and it is designed to be dynamic, with plans for updates to address any issues needing clarification or rectification based on experience.

The English version of the document is available here and the Spanish here.

The United Kingdom

New Streamlined Notification Scheme for Lowest-Risk Clinical Trials

On 12 October 2023, the Medicines and Healthcare products Regulatory Agency (MHRA) introduced a new streamlined notification scheme. According to the new scheme, initial applications for Phase 4 and the lowest-risk Phase 3 trials will now be processed within 14 days, a reduction from the statutory 30 days. The scheme excludes CTA applications for first in human (FIH), Phase 1, or Phase 2, as well as amendments currently. CTA applications submitted under this scheme must meet specific inclusion criteria.

It is anticipated that around 20% of UK initial clinical trial applications will be eligible for this scheme.

For details on the steps to follow when applying for a CTA under the New Notification Scheme, please refer to the MHRA instructions.

The UK for Costing and Contracting Process Reached Second Stage

In October 2023, NCVR (National Contract Value Review) entered Stage 2, removing local negotiations with NHS organizations, expected to further improve commercial set-up timelines across the UK.

The NCVR process is a standardized, national approach in the UK for costing and contracting in commercial contract research. It is led by National Health Service (NHS) England in collaboration with Department of Health and Social Care (DHSC), National Institute for Health and Care Research (NIHR) Clinical Research Network, the Health Research Authority (HRA), and devolved administrations. The goal is to speed up activities for commercial sponsors setting up multi-site studies, benefiting patients and the public.

NCVR involves two tools: the UK interactive Costing Tool (iCT) for resource estimation and site-specific pricing, and model agreements for standard contractual terms.

For multisite commercial clinical studies, the NCVR process includes creating the iCT, which is reviewed by an NHS costing expert. Then the approved iCT is shared with NHS organizations, determining site-specific prices using a UK-wide methodology for full cost recovery. The iCT output is integrated into the standard financial appendix within model agreements, forming contractual terms.

Since October 2023, NCVR became mandatory for late-phase (phase IIb and above) commercial trials in NHS organizations, significantly reducing set-up times. While not mandatory for certain studies (phase I-II a, Advance Therapy Medicinal Product (ATMP) studies and studies running in Primary Care), many NHS organizations voluntarily accept NCVR outcomes. In the past 12 months, over 600 studies underwent national review, with more than 60 completing the set-up process. This analysis shows a notable reduction in set-up times compared to pre-pandemic data, leading to more efficient study initiation.

UK Government Responses to the Review into Commercial Clinical Trials

The government provided its reply to the Lord O'Shaughnessy review of UK commercial clinical trials in May 2023. They accepted all the suggestions from the review and committed to five main actions. The ambitious plan is set for a 10-year vision to come to life. Details on the next steps, a summary of recommendations and responses, along with implementation timelines specific to commercial clinical trials, are available in the MHRA report.

Updates to the Commercial and Non-Commercial Model Agreements

Recently, the Health Research Authority (HRA) provided two updates on contract agreements. In October 2023, guidance for commercial agreements was revised for all UK nations (England, Scotland, Wales, and Northern Ireland). Key changes include:

- Clarification on archiving fees, which will be a one-time charge by participating National Health Service (NHS) and Health and Social Care (HSC) organizations to sponsors, Contract Research Organizations (CROs), or their agents at the study's close-down. This fee covers retention, destruction, and reasonable access requests, and its calculation occurs at the close-down.
- Introduction of a new clause in the financial appendix, ensuring NHS organizations can defer fund use into future financial years to enhance research capacity.

In December 2023, additional updates were made. While it is recommended to use the December 2023 model agreements, the October 2023 version will be accepted until June 2024.

These updates apply to the following templates and guidance:

- Commercial Model Clinical Trial Agreements (mCTA and CRO-mCTA)
- Commercial Primary Care Model Clinical Trial Agreements (PC-mCTA)
- UK template Hub and Spoke Agreements

Moreover, studies initially contracted without the General Data Protection Regulation (GDPR)-compliant data processing clauses should have been re-contracted. For research activities solely involving data processing, commercial sponsors are expected to use the mNISA or CRO-mNISA for contracting with participating NHS organizations. Non-commercial sponsors involved in research activities solely related to data processing should use the organisation information document for contracting with participating NHS organizations.

North America

United States of America

FDA Issues Guidance for Industry on Rare Diseases: Considerations for the Development of Drugs and Biological Products

On 22 December 2023, the Food and Drug Administration (FDA) issued a guidance for industry titled, "Rare Diseases: Considerations for the Development of Drugs and Biological Products" This guidance clarifies the FDA's thinking on important considerations in rare disease drug development to ultimately assist rare disease drug and biologic product developers in conducting successful drug development programs.

The purpose of this guidance is to assist sponsors of drugs for the treatment of rare diseases in conducting efficient and successful drug development programs. The statutory requirements for marketing approval for drugs to treat rare and common diseases are the same and issues discussed in this guidance are encountered in other drug development programs. These issues are frequently more difficult to address in the context of a rare disease for which there is often limited medical and scientific knowledge, poorly understood natural history data, sample size constraints, and lack of drug development experience.

A rare disease or condition, in part, is a disease or condition that "affects less than 200,000 persons in the United States." Most rare diseases, however, affect far fewer people.

The sponsor of an orphan drug (a drug intended for use in a rare disease or condition) may be eligible for orphan drug designation and certain financial incentives intended to help make developing drugs for small numbers of patients financially viable; however, the Orphan Drug Act does not create a statutory standard for the approval of orphan drugs that is different from the standard for approval of drugs for common diseases or conditions.

FDA is committed to helping sponsors create successful drug development programs that address the particular challenges posed by each disease and encourages sponsors to engage early with the Agency to discuss their drug development program.

Health Canada Announces the Implementation of the ICH E19 Guideline

On 21 December 2023, Health Canada announced the implementation of Notice – Implementation of ICH E19: A selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials.

Selective Safety Data Collection refers to the recording of certain data by investigators in case report forms. It does not affect the monitoring and clinical care of individual trial participants or documentation of their adverse events in medical records. It also does not affect regulatory reporting requirements. Therefore, all safety reporting requirements outlined in the regulations must still be met.

Examples of appropriate use of ICH E19 include:

- Clinical trials to support a new indication of an authorized drug where the two populations are similar (e.g., with respect to demographic characteristics, comorbidities, concomitant therapies), or when the patient population in the new indication was well represented in the trials that supported the approved indication.
- Clinical trials intended to expand the label information of an authorized drug with additional end-points in the same patient population.
- Safety trials designed to further investigate potential safety concerns focussing on specific parameters.
- Clinical trials designed to provide additional evidence of efficacy.

The protocol should clearly describe:

- Which data will not be collected or be collected at a reduced frequency.
- How the selective safety data collection will be implemented (i.e., for all participants, for a subset of participants, after an initial period of the trial, etc.).
- The clinical trial application should provide sufficient evidence to support the conclusion that the safety profile of the drug has been sufficiently characterised to justify selective safety data collection.

MEDICAL DEVICES

News from the European Commission

In December 2023, updates were applied to the Q&As on clinical investigations, marking the first revision since their initial publication in April 2021.

The Medical Device Coordination Group (MDCG) introduced 19 new Q&As and revised 13, including Annex I and II. Annex III, specifically addressing combination products, was updated to provide clarity on whether a combination product study requires an MDR clinical investigation submission.

The new general Q&As in the guidance documents address whether all clinical investigations fall under MDR requirements. They also provide information for applicants regarding clinical studies involving combinations of medical devices and medicinal products, outlining the regulatory pathway for conducting clinical studies to collect data for both a medicinal product and a device, even if not a single integral product.

Additionally, Q&As were added to the 'Timelines section for Clinical Investigations', highlighting Q 39 on when sponsors should notify early termination of a clinical investigation and Q 41 explaining the duration for retaining study documentation.

New sections 48, 49, and 50, delves into the role and responsibility of the sponsor's legal representative, stating, "In situations where the legal representative also functions as a CRO, it is recommended that the agreement between the sponsor and the CRO clearly defines what responsibilities are assigned in terms of the legal representative capacity and what tasks are assigned to the CRO capacity."

Annex I, focusing on clinical investigations under the MDR regulatory pathway, has been updated to include additional descriptions to the legend. It clarifies that Post-Market Clinical Follow-up (PMCF) studies without additional burdensome and invasive procedures fall under Article 82 of the MDR, with relevant national provisions applying.

Medical Device Software (MDSW) and Hardware Combinations - New Guidance

The MDCG has released guidance on MDSW designed to function alongside hardware or hardware components. This guidance aims to clarify the regulatory considerations when the hardware or its components, incorporating elements like cameras or sensors, are deemed medical devices or accessories to medical devices. It also outlines scenarios where these hardware elements are not considered medical devices or accessories.

The guidance specifically discusses two cases:

- External hardware components (e.g., sensors embedded in a dermal patch) providing input data to an MDSW app.
- Hardware components incorporated within a smartphone or wearable connected to an MDSW app on the smartphone or wearable.

The Appointment of Five EU Reference Laboratories for High-Risk In Vitro Diagnostic Medical Devices

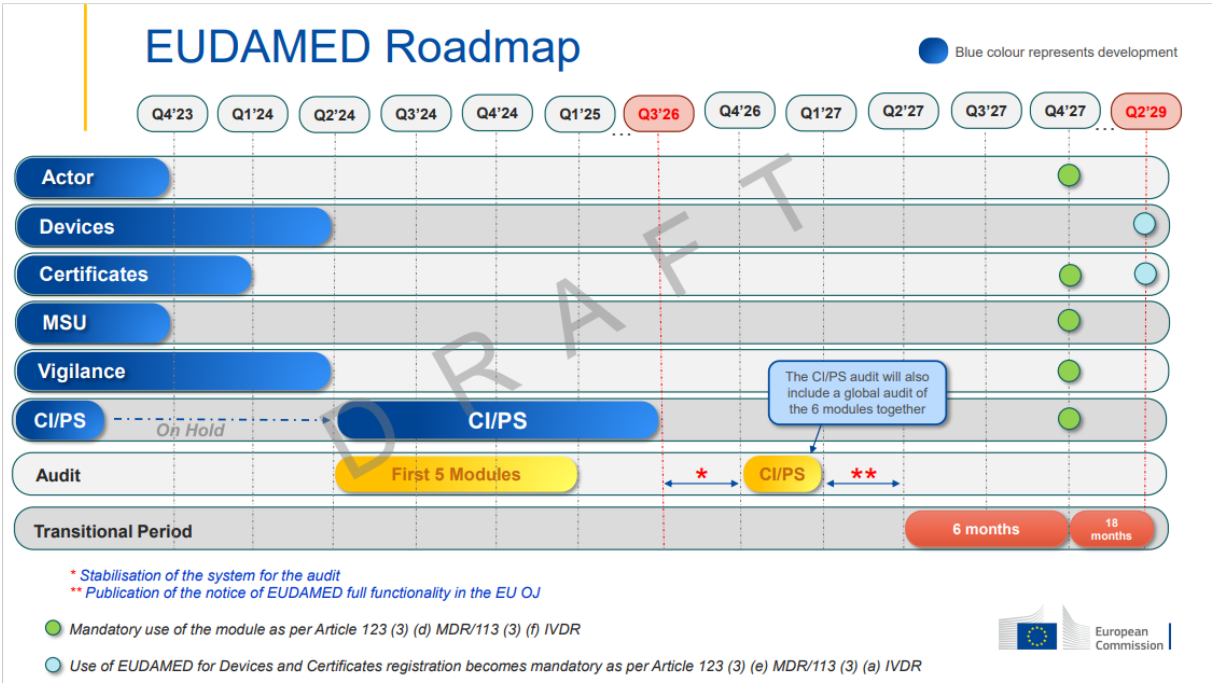
On 5 December 2023, the European Commission enacted an implementing act appointing five EU reference laboratories (EURLs) for in vitro diagnostic medical devices (IVDs). These EURLs were chosen from eight applications submitted by EU Member States. The selected EURLs will play a role in assessing the conformity of high-risk (class D) IVDs and will undertake certain advisory tasks. They specifically cover class D IVDs related to Hepatitis and retroviruses, Herpesviruses, Bacterial agents, and Respiratory viruses causing life-threatening diseases.

The designated EURLs are slated to commence their tasks in conformity assessment starting from 1 October 2024. In addition to their role in conformity assessment, EURLs have the capacity to offer scientific and technical assistance to the European Commission, the Medical Device Coordination Group (MDCG), Member States, and notified bodies in implementing Regulation (EU) 2017/746 (IVDR).

EUDAMED Roadmap

The European Commission has released the draft EUDAMED Roadmap, revealing that it will achieve full functionality until at least Q2 2027, followed by a transition period. The timeline highlights key milestones. All six modules are set to undergo an independent audit by Q4 2026, with the Clinical Investigation & Performance Studies module expected to be "audit-ready" by Q3 2026. The anticipated completion of the global audit for all six modules is scheduled for Q2 2027. Following a six-month period post-publication, EUDAMED will become mandatory, as outlined in the draft, in Q4 2027.

Additionally, a 24-month period for UDI/Device Registration and Notified Body & Certificates is stipulated, becoming mandatory in Q2 2029.



Guidance on Qualification and Classification of Annex XVI Products

In December 2023, the MDCG released guidance on the qualification and classification of products without an intended medical purpose listed in Annex XVI. This document provides explanations and examples for applying specific classification rules to such products. Due to the absence of specific definitions in Annex XVI, it is necessary to consult the provided product groups to determine coverage under the Medical Device Regulation (MDR).

The guidance emphasizes that to qualify a product as a device, we should "rely on information provided in the Annex XVI list and in the scope sections of the common specifications (CS). Specific characteristics, including product type, technology, functioning modalities, target body part, organ, or tissue, and intended purpose, should align with the provisions.

Tables within the guidance assist in interpreting terms for qualification. Additionally, a non-exhaustive list of Annex XVI examples, along with their classification and interpretation, is presented for reference.

Guidance on Demonstration of Equivalence for Annex XVI Products

The Medical Device Coordination Group (MDCG) has published a guide for manufacturers and notified bodies, addressing the demonstration of equivalence based on data related to an already existing device. This guide is intended for the purpose of CE-marking under the Medical Device Regulation (MDR) and is applicable to products without an intended medical purpose listed in Annex XVI of the MDR, which are covered by common specifications. For dual-purpose devices, those with both medical and non-medical intended purposes, this guidance specifically applies to the non-medical intended purpose.

Questions and Answers on Articles 13 & 14 of Regulation (EU) 2017/745 (MDR) and Regulation (EU) 2017/746 (IVDR)

In December 2023, the MDCG revised the Q&As guidance document on Articles 13 & 14 of the MDR and IVDR, marking its first update in two years. These articles pertain to importers and distributors. The document addresses questions to offer additional insights into the practical implementation of Articles 13 and 14. Noteworthy additions include new questions on 'fulfilment service providers,' the role of importers and distributors, system and procedure packs, and leasing companies. These updates aim to enhance understanding and compliance with the Regulations in a more operational and practical context.

MDCG Position Paper Notice to Manufacturers and Notified Bodies to Ensure Timely Compliance with MDR and IVDR Requirements

In November 2023, revisions were made to the notice addressed to manufacturers and notified bodies (NBs), emphasizing the importance of timely compliance with MDR and IVDR requirements.

The section titled "Call to manufacturers to transition to the Regulations and submit their applications for certification without further delay" has been updated. It stresses that, given the deadlines set by the Regulations, manufacturers are strongly encouraged to expedite their transition efforts and avoid further delays in submissions. Manufacturers are mandated to consistently provide data on the status of their devices.

Additionally, a new section has been added, titled "Call to notified bodies to streamline the certification process." In this section, the MDCG encourages notified bodies to simplify their procedures and exert necessary efforts to enhance transparency, timelines, predictability, and consistency in their conformity assessment activities. Notified bodies are urged to regularly share data on the status of device certifications.

Released an Overview of Conformity Assessment Bodies (CABs) and Notified Bodies (NBs)

The European Commission has released an overview of the CABs and NBs at various stages of the designation process. This overview also includes the number of notified bodies designated under the In Vitro Diagnostic Regulation (IVDR) and the Medical Device Regulation (MDR) as of December 2023.

Other Initiatives

Team-NB Press Release Call to Manufacturers Action

Team-NB, the European Association for Medical Devices of Notified Bodies, issued a 'TEAM-NB Notified Bodies call to action to manufacturers to apply' in October 2023.

Team-NB underlines that, due to increased IVDR requirements, delayed notified body designations, and the impact of the Covid-19 pandemic, the transition from IVDD to IVDR has been slower than expected. The amending Regulation (EU) 2022/112, effective 25 January 2022, provides extended transitional time for some medical devices (MDs) and in vitro diagnostic medical devices (IVDMDs), with the initial deadline for Class D devices set for 26 May 2025. The European Commission surveys indicate that the initial conformity assessment process for IVDMDs may range from 6-12 months for low to medium-risk devices (with quality annex certificates) and 13-18 months for high-risk devices (with product annex certificates). TEAM-NB urges manufacturers to promptly contact a notified body and submit their applications to ensure timely acceptance under IVDR and completion of the conformity assessment process.

News from Individual Countries

Belgium

Site Suitability Template Adapted for Clinical Investigations or Performance Studies in Belgium

The Federal Agency for Medicines and Health Products (FAMHP) has released a new template for site suitability, which is mandatory for use in clinical investigations or performance studies starting from October 2023. This template has received approval from the EU Clinical Trials Coordination and Advisory Group to align with EU CTR. Additionally, it has been endorsed by the Belgian National Contact Point and the Clinical Trial College Board to comply with Regulation (EU) No. 746/2017 on in vitro diagnostic medical devices (IVDR) and Regulation (EU) No. 745/2017 on medical devices (MDR).

United Kingdom

The Innovative Devices Access Pathway (IDAP) - Pilot Phase

The IDAP program aims to speed up the development of affordable medical devices and introduce them to the UK market. As of December 2023, the MHRA announced that the IDAP Pilot is closed for applications. Applicants can expect outcomes by the end of January 2024. To join this trial phase, a product had to meet specific requirements for eligibility and innovation. If anyone needs help with their application or wants to find out more, it is advised to write an email IDAPenquiries@mhra.gov.uk.

New Contract Templates for Sponsored Commercial Research Involving Medical Devices

The model Clinical Investigation Agreement (mCIA) and Clinical Research Organisation model Clinical Investigation Agreement (CRO-mCIA) were revised in October 2023 and December 2023. For all new Integrated Research Application System (IRAS) submissions (initial clinical investigations/ performance studies or addition of NHS site), it is recommended to use the December 2023 version of the relevant agreement. However, the October 2023 version will still be accepted until June 2024. These updated contract templates are intended for use without modification in company-sponsored commercial research involving medical devices in patients in hospitals across the UK Health Services by all UK nations.

Switzerland

New Requirements for Product Groups Without an Intended Medical Purpose and Alignment with the Amendments to EU MDR and EU IVDR

Switzerland has modified its Medical Devices Ordinance (MedDO) to comply with EU standards, particularly Implementing Regulation 2023/1194. This adjustment takes into account amendments to EU Medical Device Regulations (EU MDR) 2017/745, focusing on transitional periods for certificates, and to both EU-MDR and EU-In Vitro Diagnostic Regulations (EU IVDR) 2017/746, addressing the removal of deadlines for putting into service and placing on the market. The changes to the MedDO are effective from 1 November 2023.

Swissmedic has updated its website and released implementation guides accordingly.

Simultaneously, a common specification has been outlined in the Federal Gazette, extending the requirements of MedDO to product groups without an intended medical purpose.

The following guidance and form have been updated:

- Swissmedic information sheets:

  BW600_00_015e_MB Clinical investigations with medical devices (27Dec2023)

  BW600_00_016e_MB Performance studies with IVD (27Dec2023)

- Forms:

  BW610_10_021e_FO Authorisation clinical investigation MD (01Nov2023)

  BW610_10_023e_FO Application simplified review MD (01Oct2023)

  BW610_10_024e_FO Authorisation performance study IVD (01Nov2023)

  BW610_10_025e_FO Application simplified review IVD (01Oct2023)

  BW610_20_021e_FO Amendments, notifications, reports MD IVD (01Nov2023)

North America

United States of America

FDA Issues Updates to Final Guidance for eSTAR

On 2 October 2023, the FDA issued minor updates to the final guidance: Electronic Submissions Template for Medical Devices 510(k) Submissions. The updates are to support the use of the Electronic Submission Template and Resource (eSTAR) through the CDRH Portal. As of 1 October 2023, all 510(k) submissions, unless exempted, must be submitted as electronic submissions using eSTAR.

eSTAR is intended to enhance the incoming quality of submissions for a wide range of medical devices by helping to ensure submitters provide quality, comprehensive data for premarket review. With a standardized format, submitters can ensure their submissions are complete, and the FDA can conduct premarket reviews more efficiently to help promote timely access to safe, effective, and high-quality medical devices.

In addition, eSTAR is now available for voluntary use for the following Premarket Approval Applications (PMAs) submission types: Original PMAs; PMA Panel Track Supplements (PTS); PMA Real-Time (RT) Supplements; and PMA 180-Day Supplements.

FDA, Health Canada and MHRA Jointly Issued the Predetermined Change Control Plans for Machine Learning-Enabled Medical Devices: Guiding Principles

On 24 October 2023, the FDA, Health Canada, and the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) jointly issued the Predetermined Change Control Plans for Machine Learning-Enabled Medical Devices: Guiding Principles. The 5 guiding principles outline key characteristics of robust Predetermined Change Control Plans (PCCPs). PCCPs are one way to support the development of safe, effective, and high-quality devices enabled with AI/ML technologies.

In 2021, the FDA, Health Canada, and the MHRA jointly identified 10 guiding principles that can inform the development of Good Machine Learning Practice (GMLP). GMLP supports the development of safe, effective, and high-quality artificial intelligence/machine learning technologies that can learn from real-world use and, in some cases, improve device performance.

Health Canada Implements Revised Notice for Implementing the Regulatory Enrolment Process (REP) for Medical Devices Regulatory Activities

On 15 November 2023, Health Canada issued Implementing the regulatory enrolment process (REP) for medical devices regulatory activities: Revised notice - Canada.ca. The Health Products and Food Branch (HPFB) is implementing the regulatory enrolment process (REP) and use of the Common Electronic Submissions Gateway (CESG) for medical device regulatory activities. The decision is based on the results of a pilot project, which began in November 2019 and will end in June 2024. About 40 companies participated in the pilot. The pilot was positive. All medical device companies are now invited to begin to use this process beginning in July 2024. At the moment, the REP is voluntary.

The REP will be used to collect information from manufacturers on the company, dossiers, devices, regulatory activities, and transactions. It consists of a set of web-based templates that generate REP Extensible Markup Language (XML) files upon completion. Health Canada intends to make REP mandatory within 18 months from the implementation date.

OTHER "HOT" TOPICS FROM UNITED STATES

FDA Establishes New Advisory Committee on Digital Health Technologies

On 11 October 2023, the U.S. Food and Drug Administration announced the creation of a new Digital Health Advisory Committee to help the agency explore the complex, scientific and technical issues related to digital health technologies (DHTs), such as artificial intelligence/machine learning (AI/ML), augmented reality, virtual reality, digital therapeutics, wearables, remote patient monitoring and software.

The Digital Health Advisory Committee will advise the FDA on issues related to DHTs, providing relevant expertise and perspective to help improve the agency's understanding of the benefits, risks, and clinical outcomes associated with use of DHTs. The committee should be fully operational in 2024.

To support the development of safe and effective digital health technologies while also encouraging innovation, the FDA will solicit views from the committee, which will consist of individuals with technical and scientific expertise from diverse disciplines and backgrounds. This will help ensure digital health medical devices are designed and targeted to meet the needs of diverse populations.

Digital health is a rapidly evolving, cross-cutting space that spans a wide range of technologies. In addition to the technologies mentioned above, it also includes issues such as decentralized trials, patient-generated health data and cybersecurity.

FDA Publishes FDA Voices on Clinical Trial Transparency and FDA Oversight

On 4 December 2023, the FDA published the FDA Voices: "The Importance of Clinical Trial Transparency and FDA Oversight," by Robert M. Califf, M.D., Commissioner of Food and Drugs. The FDA takes its oversight of clinical trials seriously and encourages voluntary compliance with the ClinicalTrials.gov requirements.

The FDA communicates transparency expectations and obligations under the law and use a risk-based approach to prioritize compliance and enforcement actions for the violations that pose the greatest risk to public health. The FDA is committed to promoting clinical trial transparency and will continue to advance their compliance activities related to the ClinicalTrials.gov database.

Today, ClinicalTrials.gov provides a rich source of data regarding the state of clinical research, including information about research results. Almost half a million clinical trials are registered with ClinicalTrials.gov; however, only a small portion, less than 15%, appear to be applicable clinical trials (ACTs) subject to FDA oversight of registration and results information submission requirements.

FDA Publishes Final Rule on Increasing Options in Clinical Research to Facilitate Medical Product Development

On 20 December 2023, the FDA published "Catching Up with Califf: Increasing Options in Clinical Research to Facilitate Medical Product Development," by Robert M. Califf, M.D., Commissioner of Food and Drugs. In this "Catching Up with Califf," the Commissioner discusses another critical component of clinical research: "our work to harmonize clinical research regulations and to facilitate the development of medical products to benefit public health."

The FDA issued the final rule to help advance medical product development without compromising the rights, safety and welfare of people participating in clinical research. The rule provides an exception from the requirement to obtain informed consent when a clinical investigation poses no more than minimal risk to the people participating in the research, and the research includes appropriate safeguards to protect the rights, safety, and welfare of participants.

FDA anticipates this new rule will enable minimal risk research that would not be practicable to conduct otherwise. This could include studies comparing the effectiveness of approved products to determine which option works best for certain patients. Studies conducted with a waiver or alteration of informed consent under this final rule could result in more treatment and diagnostic options without compromising the rights, safety and welfare of people participating in those studies.

The final rule permits an institutional review board (IRB) to waive or alter certain elements of informed consent, or to waive the requirement to obtain informed consent entirely, under limited conditions, for certain FDA-regulated clinical investigations that pose no more than minimal risk to trial participants.

The rule continues to protect the rights, safety and welfare of research participants and enables minimal risk clinical investigations that may facilitate medical advances and promote public health.

FDA Issues Update on In-Person Face-to-Face Formal Meetings

On 18 December 2023, the FDA announced beginning 22 January 2024, CDER and CBER will expand in-person face-to-face (FTF) industry meetings (with a hybrid component), to include all Prescription Drug User Fee Act, Biosimilar User Fee Act, and Over-The-Counter Monograph Drug User Fee Program (OMUFA) meeting types. If an in-person meeting is being requested, the sponsor should specify this in their request.

A final determination on the format will be made by the review division and communicated to the sponsor should the format be different than requested. Existing meeting requests for the newly eligible meeting types received before 22 January 2024, or meetings already scheduled regardless of the scheduled meeting date, will not be converted to the in-person format, to permit fair implementation of the transition.

About ClinChoice

ClinChoice is a global full-service CRO specializing in clinical development and functional solutions for pharmaceutical, biotechnology, medical device, and consumer health companies. We have over 28 years of proven high-quality delivery and results across all our services. With over 4,000 professionals in more than 20 countries across the Americas, Europe, and Asia-Pacific, we are positioned to fulfill our clients' business requirements locally and globally. We offer high-quality, full-service clinical development and post-marketing solutions. For our clients, it means a reliable partner and quality results.

CONTACT US

HEADQUARTERS

ClinChoice Inc.
1300 Virginia Drive, Suite 408
Fort Washington, PA 19034 USA
Phone: +1 215 283 6035
Fax: +1 215 283 6382
Email: info@clinchoice.com

ClinChoice

www.clinchoice.com