CROM SOURCE
A ClinChoice Company

REGULATORY

NEWSLETTER N.43
July - September 2023

Including the latest updates on the EU CTR

CROMSOURCE, a ClinChoice company, 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

Launch of EMA-HMA Catalogues of Data Sources and Non-Interventional Studies in Early 2024

The European Commission informed that the European Medicines Regulatory Network (EMRN) is developing two new public catalogues to replace and improve upon existing databases: one for real-world data sources and another for non-interventional studies. These catalogues will replace and enhance the current ENCePP Resources Database, and the EU PAS Register at the beginning of next year, with the aim to:

- Facilitate the identification of suitable studies and data sources for regulators, researchers, and pharmaceutical companies based on the "FAIR" data principles (Findable, Accessible, Interoperable, and Reusable).
- Support the evaluation of study protocols and results by providing quick access to information regarding the suitability of proposed data sources in study protocols and references in study reports.
- Enhance transparency regarding studies and data sources used.

Key enhancements in the new catalogues include standardized metadata (data elements describing both data sources and studies) and establishing connections between data sources and conducted studies. Users will have access to modern technology with improved viewing, searching, exporting, and data submission features. To submit and manage content in the catalogues, users will be required to register.

Furthermore, activities to support the implementation of these catalogues, including the registration process, will be organized by the EMRN, and stakeholders will be contacted in the coming weeks.

Health Technology Assessment (HTA)/ EMA Big Data Steering Group Update Its Workplan

The European Commission has announced updates from the HMA/EMA Big Data Steering Group regarding its 2023-2025 workplan aimed at accelerating the transformation towards data-driven medicines regulation. The revised workplan of the Big Data Steering Group (BDSG) underscores the ongoing evolution and integration of big data and data analytics in medicines regulation. Collaboration with partners and stakeholders remains crucial for the successful transition to data-driven medicines regulation. Key additions to the updated workplan include:

- Real-world evidence (RWE): DARWIN EU® will address use cases from national regulators, and insights gained from RWE pilots will be collected and made publicly available.
- Real-World Data (RWD) quality considerations will be published following a public consultation.
- Engagement with patient organizations will intensify through various initiatives, including a public consultation on Patient Experience Data (PED), discussions on training needs, workshops on patient registries, a call to populate metadata and RWD source catalogues with PED, and exploration of use cases for analysing PED to determine their role in the regulatory decision-making process.
- Exploration of additional data types will be undertaken, including the development of use cases for genomics data, the launch of a 'proof of concept' for non-clinical raw data analysis, and discussions on Chemistry, Manufacturing, and Controls (CMC) data analysis.
- Ongoing experimentation with advanced analytics, including AI, will continue, and the first AI knowledge mining tool for core regulatory processes will be released to the EU regulatory network.
- Priority will be given to the development of the future European Medicines Regulatory Network data strategy, set for publication in 2025.

News from the European Medicines Agency (EMA)

Instructions on How to Navigate the Transition Process from the Clinical Trials Directive (CTD) to the Clinical Trials Regulation (CTR)

Sponsors are gearing up for the next phase of CTR implementation. By 30 January 2025, all ongoing trials that were previously approved under the CTD will transition to the CTR. This means these trials must be transferred to the Clinical Trials Information System (CTIS) and gain approval by the specified deadline. The EMA data informs that sponsors have already submitted approximately 320 transitional trials to CTIS in preparation for this change. It is important to note that there is an estimated total of 4,000 to 6,000 trials that need to undergo this transition process.

To help sponsors transitioning trials from the CTD to the CTR/CTIS the EMA in cooperation with the European Commission and Clinical Trials Coordination Group (CTCG) published following guidance:

- Guidance for the transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation published by the European Commission under EudraLex volume 10;
- the CTCG's best practice guide and cover letter template for sponsors of transitional trials;
- Module 23 of the CTIS online training programme updated by the EMA.

The transition process from the CTD to the CTR offers sponsors three different scenarios, depending on the level of harmonization among specific documents:

- **Scenario 1:** If key documents (e.g., Protocol Investigator's Brochure (IB), or Investigational Medicinal Product Dossier (IMPD)) are already approved in all Member States concerned under the CTD, sponsors can transition to the CTR by submitting a Clinical Trial (CT) application to CTIS without needing a substantial amendment. The cover letter should declare approval of these documents in all Member States under the CTD.
- **Scenario 2:** If there are minor substantial or non-substantial differences in these documents across Member States (e.g., related to subject population age groups or administrative details), a consolidated version may be transitioned as a single new version, without prior submission under the CTD. The cover letter should declare that no substantial content differences exist beyond these minor discrepancies.
- **Scenario 3:** In cases where there are significant substantial differences among Member States regarding the Protocol, IB, or IMPD, a substantial amendment (under the CTD) should be submitted to National Competent Authorities (NCAs) and ethics committees in the Member States where the trial is ongoing. This is necessary to harmonize these aspects of the documents across Member States before transitioning the trial to the CTR.

Launch of the Accelerating Clinical Trials in the EU (ACU EU) Website

A dedicated website has been launched for the ACT EU initiative, jointly led by the European Commission, HMA, and EMA. The website serves as a central hub for essential resources, recent developments, and upcoming events. It provides updates on various aspects, including the Multi-stakeholder platform, the implementation of the Clinical Trials Regulation (CTR), Multinational clinical trials by non-commercial sponsors and details on scientific advice procedures such as the Simultaneous National Scientific Advice (SNSA) pilot.

The Multi-stakeholder Platform (MSP) aims to facilitate dialogue and engagement with regulators by offering the following channels: MSP Advisory Group, Multi-stakeholder Events,

Consultations and Surveys, and Feedback Tools. The implementation of the Clinical Trials Regulation (CTR), among other includes Progress Reports on CTR Implementation (revised Key Performance Indicators (KPIs) on clinical trials (CTs)). The Multinational clinical trials by non-commercial sponsors aims to provide practical and standardized solutions to assist non-commercial sponsors in the setup and execution of multi-national clinical trials within the European Union (EU) and European Economic Area (EEA). Scientific advice procedures such as the Simultaneous National Scientific Advice (SNSA) pilot aims to better understand the scope of current scientific advice. To clarify the scope of scientific advice activities, ACT EU has undertaken a mapping exercise. This exercise involves gathering information about voluntary procedures that are available within the European medicines regulatory network. The aim is to provide a clear understanding of the landscape of scientific advice and related processes to stakeholders and participants.

Updated CTR Quick Guide for Sponsors

On 28 August 2023, the European Commission released an updated version of the Clinical Trials Regulation (EU) No 536/2014 in practice for sponsors. This revision provides additional clarity on the process of submitting the Investigational Medicinal Product Dossier (IMPD-Q) for investigational medicinal products manufactured at decentralized points of care, specifically at clinical trial sites in additional Member States, as detailed in Section 3.2.1 of the guidance.

EMA Reminder to Consult the List of Known Issues

The European Medicines Agency (EMA) periodically upgrades its website and the Clinical Trials Information System (CTIS) as part of its efforts to enhance the user experience and functionality. Users of the CTIS are encouraged to consult the most recent lists of known issues for sponsors or Member States on Website outages and system releases before submitting a ticket to the CTIS User Support Service. These documents provide information about potential problems that sponsors, and authority users may encounter when using the CTIS secure workspaces and offer possible solutions or workarounds. They also detail updates to the CTIS system, including enhancements to existing features, the introduction of new features, and technical improvements. Additionally, users should be aware of planned system interruptions for maintenance and updates.

Guidance and Question & Answers (Q&As)

The Clinical Trials Information System (CTIS) is designed to facilitate and support the business processes of clinical trial sponsors and national regulators at various stages of a clinical trial's lifecycle. The European Medicines Agency (EMA) provides access to the information needed for submissions or notifications in CTIS through a combined section under 'Support' via Q&As. This section includes the following categories: About CTIS, Clinical Trials, Guidance, Technical Support, Transparency, Transitional Trials, Support, and Training. This consolidated resource page offers easy access to up-to-date guidance to meet specific user needs.

ServiceNow for CTIS User Support Service (USS) Request Mandatory from 31 July 2023

The European Medicines Agency (EMA) implemented a new IT service management solution called ServiceNow to replace the current tool, JIRA, for CTIS USS requests. After 31 July 2023, JIRA will no longer be available for raising requests or incidents in CTIS and the CTIS Training Environment. However, existing data related to CTIS USS tickets opened before 31 July 2023, will continue to be accessible in JIRA until those tickets are resolved.

The goal of this change is to align CTIS processes with industry best practices and enhance the user experience by providing a more user-oriented service.

The new ServiceNow platform will be accessible through a link and a mobile app, with QR codes available for download in an annex. To log in, users will need to enter their EMA username followed by "@id.ema.europa.eu." For example, if a user's EMA username is "surname a," they should enter "surname_a@id.ema.europa.eu".

Users can find training materials and additional information on a dedicated site within the ServiceNow platform. If users encounter any issues or difficulties during the login process, they can seek assistance from the EMA Account Management website or contact ServiceNow@ema.europa.eu for support.

Draft Reflection Paper on the Use of Artificial Intelligence in the Lifecycle of Medicines

The European Medicines Agency (EMA) has issued a draft reflection paper for public consultation, outlining current considerations regarding the use of artificial intelligence (AI) in the development, regulation, and utilization of human and veterinary medicines. This paper discusses principles and factors related to AI and machine learning (ML) application across the entire medication lifecycle, spanning from drug discovery to post-approval phases.

This effort is part of a collaborative initiative involving the HMA-EMA Big Data Steering Group (BDSG), aimed at bolstering the capabilities of the European Medicines Regulatory Network in data-driven regulation. It also involves EMA's Committee for Medicinal Products for Human Use (CHMP) and its Committee for Veterinary Medicinal Products (CVMP).

The public consultation will remain open for input until 31 December 2023. Additionally, a joint HMA/EMA workshop is scheduled for 20-21 November 2023, to further discuss the subject. The feedback gathered from stakeholders during this consultation period will be carefully analysed and factored into the finalization of the reflection paper and the development of pertinent guidance for the future.

New GCP Q&As Regarding Direct Remote Access and the Requirements for Distribution of Updated IB and ICFs

The EMA's GCP Inspectors Working Group has added a new Question & Answer (Q&A) (No. 3) to the Good Clinical Practice (GCP) and Q&A No 19 to GCP Matters Q&As.

First Q&A specifically addressed the topic of direct remote access in the context of "Records of Study Subject Data Related to Clinical Trials."

Direct remote access refers to any access to data from a location or hardware that is not under the control and supervision of the investigator or institution conducting the clinical trial. Q&A refers to the Informed Consent Form process, requirements of Regulation (EU) No. 536/2014 (EU CTR) and technical considerations of different systems.

For informed consent it is underlined that the information of a direct remote access to participant's confidential health records should be clearly explained in the consent documentation, specifying that authorized individuals from the trial sponsor (e.g., monitors, auditors) and regulatory authorities (e.g., inspectors) may need such access.

The trial protocol must incorporate a description of how remote access arrangements align with data privacy regulations and outline measures to maintain the confidentiality of trial participants' records and personal data. Additionally, it should detail plans for addressing and mitigating the consequences of a data security breach if it occurs.

Before remotely accessing confidential health documents, it is strongly advisable for the sponsor's Data Protection Officer (DPO) and the Institution's DPO/Investigator to conduct a data protection impact assessment in order to identify and address risks related to remote access. This assessment should consider various aspects, including the location where access is granted, data transmission, and the location where the access occurs. It is essential to ensure that only data required by the trial protocol or legislation is documented off-site, minimizing unnecessary exposure of sensitive information.

Second Q&A No 19 is regarding the distribution of the updated Investigator's Brochure (IB) and Informed Consent Form (ICF) to investigators or clinical sites.

Investigator's Brochures (IB) with substantial changes should be promptly distributed to clinical sites and investigators upon approval by the competent authority. Waiting for approval in all EU Member States or globally is not necessary. However, sponsors should wait for approval in all Member States before using the updated Reference Safety Information (RSI).

Revised Informed Consent Forms (ICFs) should be distributed to clinical sites and investigators as soon as they receive a favourable opinion from the ethics committee and approval from the competent authority. Failure to do so, or using an outdated ICF missing essential new information, constitutes GCP non-compliance, as it means the trial participant was inadequately informed.

Summary of General Informed Consent Information for Paediatric Clinical Trials in Europe Updated by Enpr-EMA

The European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) has released an updated document titled "Informed Consent for Paediatric Clinical Trials in Europe" on 6 June 2023. This document outlines several key aspects, including the legal age for subject consent, mandatory or suggested age ranges for assent, the number of required signatures on consent forms, language requirements, and links to access data sources for European countries involved in paediatric clinical trials.

ICH Reflection Paper on Real-World Data (RWD) and Real-World Evidence (RWE)

The EMA has opened a public consultation on the International Council for Harmonisation (ICH) reflection paper on proposed international harmonisation of Real-World Evidence (RWE) terminology and convergence of general principles regarding planning and reporting of studies using Real-World Data (RWD). Stakeholders are invited to send their comments until 30 September 2023.

The objectives of this Reflection Paper are as follows:

- To initiate discussions within the ICH regarding the standardization of terminology related to RWD and RWE. This includes considering uniform formats for protocols and study result reports submitted to regulatory agencies at all stages of a medicinal product's lifecycle. Additionally, the paper aims to promote the registration of study protocols and reports.
- To provide valuable insights and information that can be used in the assessment of RWD and RWE for regulatory purposes.

Nonetheless, achieving a common international understanding of terminology and the role of RWD and RWE in reducing knowledge gaps for new and existing medicines is crucial for advancing access to innovative treatments.

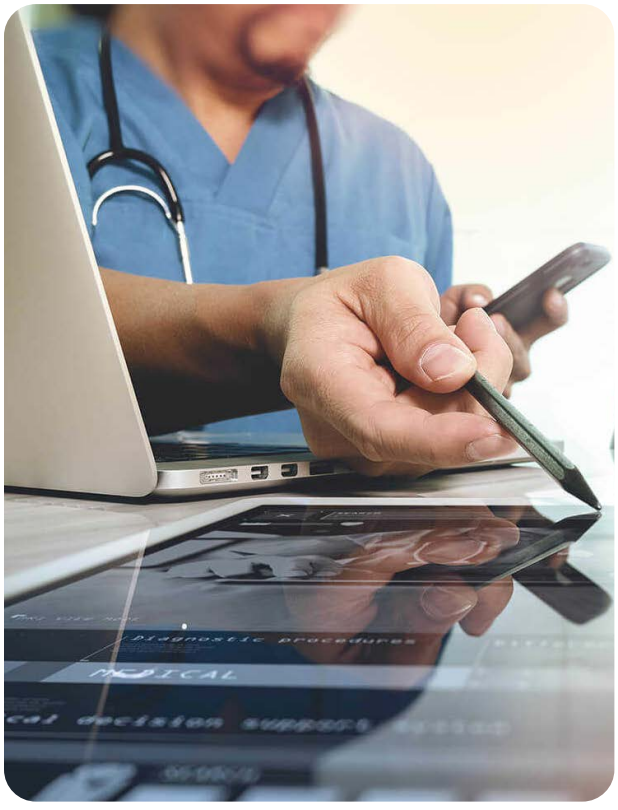
News from Individual Countries

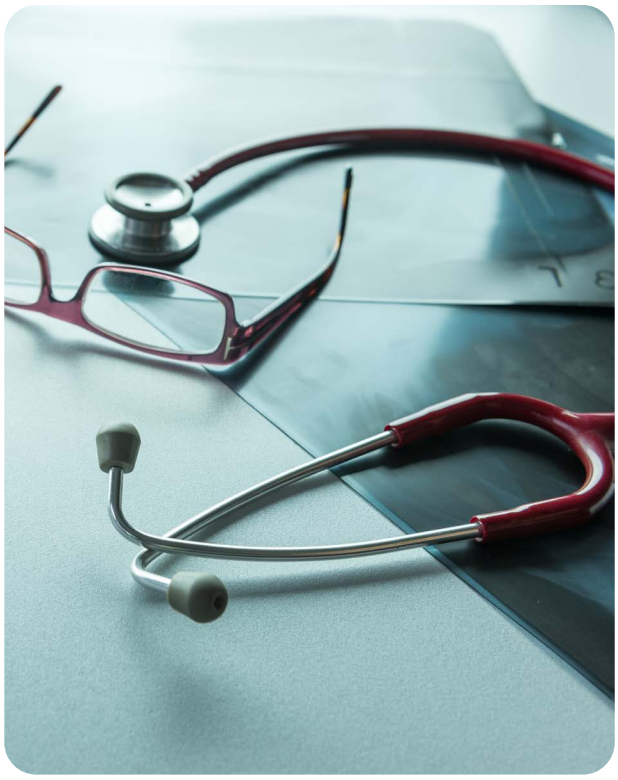
Italy

Questions & Answers (Q&As) on Authorisation and Registration Procedures for the Production and Import of Active Substances

An updated Q&As document has been released regarding the authorization and registration procedures for the production and import of active substances. This new version replaces the previous one from December 2021. Notable changes in this update include the introduction of Q&A numbers 76 and 77, as well as revisions to Q&A numbers 9 and 64.

The document is designed for use by producers, importers of active substances, Marketing Authorization (MA) holders, and manufacturers of medicinal products. Its purpose is to serve as a resource for companies, offering clarification on the authorization and registration procedures for the production and import of active substances, as established by the Good Manufacturing Practice (GMP) Raw Materials Inspection and Authorization Office.





The Netherlands

Updated CCMO Directive and Site Suitability Declaration

The CCMO (Central Committee on Research Involving Human Subjects) has released an updated version of its Directive on assessing the suitability of research centres (Toetsing geschiktheid onderzoeksinstelling, TGO). This directive is now available on the CCMO website and is in Dutch.

The primary reason for publishing this new directive is the revision of the Site Suitability Declaration (VGO) by the DCRF (Dutch Clinical Research Foundation), which is an integral part of the CCMO directive.

The goal behind revising the VGO was to align the document more closely with the everyday practices of participating research centres. A notable change in the revised VGO is the replacement of 'VGO Part A' and 'Part B' with 'Site Suitability Declaration (VGO)' and 'Appendices', respectively.

It is important to note that the use of this new Directive, along with the updated VGO, is mandatory and becomes effective from 1 June 2023. Researchers and organizations involved in research involving human subjects should be aware of and comply with these new guidelines.

Poland

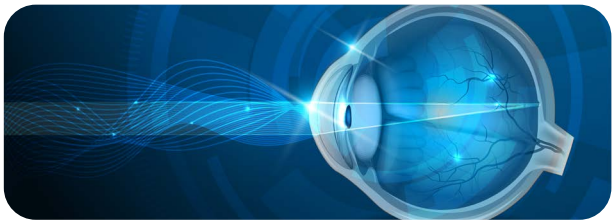
National Bioethics Committee, its Responsibilities and Fees Mandatory from 1 July 2023

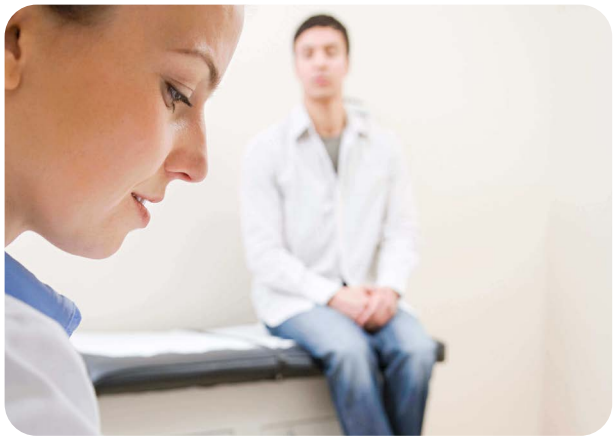
On 26 August 2023, the Ordinance of the Minister of Health, dated 18 August 2023, which outlines the regulations for the National Bioethics Committee (NBC) for Clinical Trials, came into effect (as published in the Journal of Laws 2023, item 1702). This regulation covers various aspects, including the functioning of the NBC in Poland, salary payments to its members, and training for bioethics committee members and service providers.

The key responsibilities of the NBC for Clinical Trials include:

- Collaborating with designated bioethics committees to perform ethical evaluations of clinical trials for medicinal products for human use.
- Cooperating with the President of the Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products concerning the ethical evaluation of clinical trials.
- Reviewing applications for the inclusion of bioethics committees authorized to perform ethical evaluations of clinical trials.
- Providing training to bioethics committee members on bioethics and the methodology of scientific research involving human subjects and human biological material, as well as for individuals offering services to bioethics committees.

Furthermore, fees for applications submitted to the Clinical Trials Information System (CTIS) have been established, effective from 1 July 2023. Sponsors are required to pay fees for the preparation of ethical evaluations for clinical trials of medicinal products for human use and significant amendments to such trials. These fees should be directed to the account of the Medical Research Agency, and the specific fee amounts are outlined in accompanying tables.





Switzerland

Instructions for Filling Out the eDok and Updated FO Submission Form

Swissmedic, the Swiss Regulatory Agency has introduced significant enhancements to the submission process for clinical trials involving medicinal products and advanced therapy medicinal products (ATMPs). As of 19 June 2023, a new portal has been made available for electronic submission of applications, marking a transition from traditional paper and CD/DVD submissions. This portal is accessible to sponsors, investigators, research institutions, and their contractual partners, facilitating fully electronic submissions for a range of purposes, including clinical trial approvals, modifications, and notifications related to clinical trials with medicinal products and ATMPs. It also supports electronic correspondence delivery from Swissmedic.

To assist applicants with this new electronic submission approach, Swissmedic issued instructions in September 2023 for filling out the eDok (KLV folder structure). These instructions provide clear guidance on how to organize submission documents in compliance with regulatory requirements.

Furthermore, Swissmedic has released the latest recommended version of the FO submission form, which serves as the Application Form in Switzerland for clinical trial applications. These measures collectively streamline and modernize the application process for clinical trials and are in alignment with contemporary practices in regulatory affairs.

The eDok folder and FO submission form can be downloaded from the Swissmedic website: Applications for clinical trials for medicinal products (swissmedic.ch).

New Requirements Regarding Individual Case Reports for Adverse Drug Reactions (ADRs)

Swissmedic has recently updated its pharmacovigilance FAQ page to provide guidance to companies that market products within its jurisdiction. Starting from 1 January 2024, Swissmedic will impose new requirements for manufacturers, especially regarding individual case reports for ADRs.

Manufacturers will need to provide more detailed information when submitting individual case reports. This will include assessing the likelihood of an ADR, identifying potential causes of these events, and determining whether any measures should be taken to reduce the risk to patients.

Swissmedic will adopt a risk-based approach to reporting requirements. Depending on the seriousness of the adverse event and whether it is already described on the product label, different reporting requirements will apply.

For low-risk ADRs that are not listed on the product label, Marketing Authorization Holders (MAHs) will only need to include information on the expected frequency of these events.

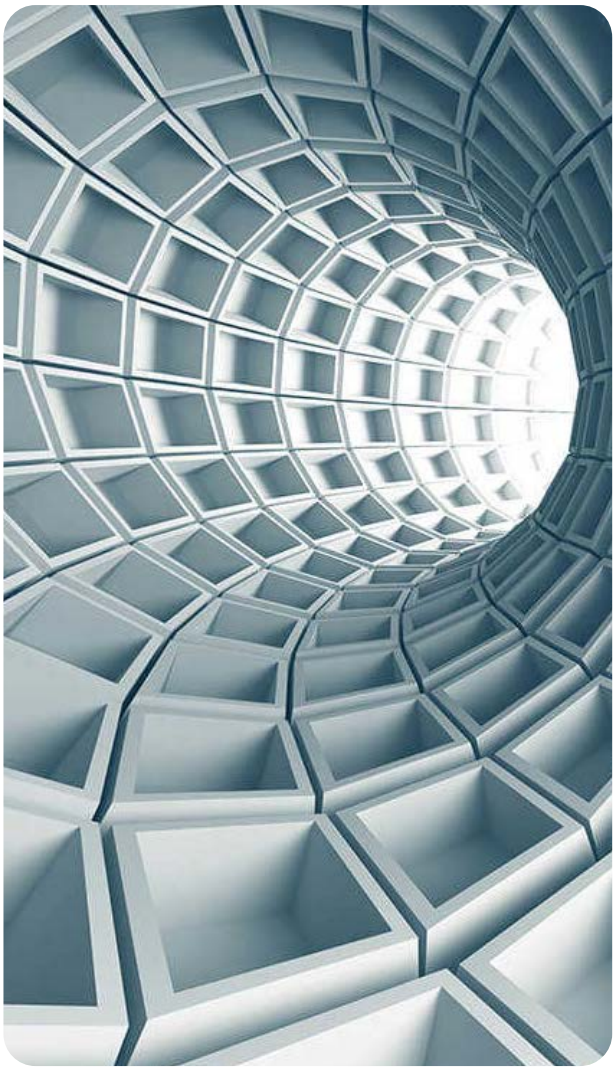
In the case of high-risk situations where a serious adverse event is reported, and it is not mentioned on the product label, Swissmedic will require MAHs to submit proposed risk-minimizing measures, in addition to the other required documentation.

Swissethics Updates to Their Templates, Documents and Links

Swissethics has made several updates to their templates, documents, and links related to clinical trials and data protection. These updates include:

- General Data Protection Regulation (GDPR) Application Template (Version in French);
- Annual Safety Report Template. A template for writing an 'Annual Safety Report' specifically designed for 'Investigator initiated trials' (IITs) according to Clinical Trial Ordinance (ClinO).
- Notification of Significant Changes Template (Version in French). This template applies to clinical trials under ClinO as well as research projects not involving clinical trials (HRO).
- Clinical Study Report Template for ClinO Chapter 4. Swissethics offers a template for writing a clinical study report for clinical trials conducted under Chapter 4, 'Other clinical trials,' as per the ClinO. This template should not be used for writing a clinical study report of a clinical trial with a medicinal product. For guidance on the latter, it is advised to refer to the ICH-E3 guideline, "Structure and Content of Clinical Study Reports."

Moreover, Swissethics has introduced a valuable tool in the form of a medical glossary for medical terms and abbreviations. This glossary is designed to improve the readability and comprehensibility of patient information. It accomplishes this by providing alternative word suggestions for medical terms, making it easier for both healthcare professionals and patients to understand medical information. It is available for German and French.



The United Kingdom

MHRA Performance Data for Assessment of Clinical Trials

On 15 September 2023, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) announced that, starting from 1 September 2023, there will be no delays in the regulatory assessment conducted by the MHRA. The MHRA is now completing regulatory assessments within statutory timeframes. The Agency has also enhanced communications and customer contact support. For information concerning the current status of any clinical trial application, applicants are encouraged to email ctdhelpline@mhra.gov.uk or call the helpline at 020 3080 6456.

New Improvement for Participant Information Sheets and Informed Consent Forms

The Health Research Authority (HRA) introduced new Participant Information Quality Standards and Participant Information Design and Review Principles to enhance the information provided to individuals invited to participate in research. These Quality Standards define the criteria for high-quality participant information, while the Design and Review Principles offer guidance to research organizations on how to meet these standards and how Research Ethics Committees (RECs) will assess compliance.

The Quality Standards and Design and Review Principles are being introduced gradually, commencing in September 2023, to enable sponsors and researchers to familiarize themselves with these documents. Any findings that exceed prior participant information expectations will be presented as recommendations in REC outcomes starting from September 2023.

From December 2023, the Quality Standards and Design and Review Principles will become mandatory and will apply to all research applications submitted for review. Applications not following these guidelines will receive a provisional opinion.

National Approach to Costing for Commercial Contract Research Enters Second Stage

The UK's National Contract Value Review (NCVR) is a crucial initiative aimed at improving the setup of commercial studies. Following the government's recognition of its value, changes are planned as NCVR enters stage two in October 2023. All commercial contract research within the National Health Service (NHS) will undergo a single study resource review using the interactive Costing Tool (iCT), regardless of their NCVR stage two inclusion.

The scope of NCVR remains unchanged, encompassing all commercial contract research within the NHS, except for phase I-IIa, Advanced Therapy Medicinal Product (ATMP) studies, and studies conducted in independent contractor primary care. These excluded studies are intended to be included in the full NCVR process soon. However, NHS organizations overseeing studies excluded from stage two of NCVR are strongly encouraged to accept the outcomes and iCT-generated prices.

The instructions stipulate that Sponsors and Contract Research Organizations (CROs) should seek a study resource review in iCT before submitting to the Integrated Research Application System (IRAS) and after technical assurance review for pharmacy and/or ionizing radiation, if applicable. NHS organizations must accept standardized prices and review outcomes for stage two NCVR studies. Local pricing is no longer permitted for most commercial contract research. A new finance appendix for UK commercial agreements is mandatory and cannot be modified starting October 2023. Study budgets will include site-specific multipliers for cost recovery. English NHS organizations will have non-negotiable multipliers based on NHS-wide data from October.

The instruction provided by the Health Research Authority (HRA). "From Sunday, 1 October 2023 you must:

- submit your iCT for study resource review at the same time as your IRAS submission;
- include the appropriate new UK template agreement, with the new financial appendix, in your IRAS submission. Do not use any previous agreements for any IRAS submission on or after 1 October;
- when available, copy the iCT finance schedule into the financial appendix of the agreement to share with sites;
- complete the site iCT process, before sharing the locked-down site-level iCT with the site inside Central Portfolio management System (CPMS). This should be done at the same time as sharing the completed contract template with the site, to support site invoicing and internal disbursement."

More information can be found here.

North America

United States of America

FDA Launches Pilot Program to Help Further Accelerate Development of Rare Disease Therapies

On 29 September 2023, the FDA is taking steps to help further accelerate the development of novel drug and biological products for rare diseases. The agency is announcing the opportunity for a limited number of sponsors to participate in a pilot program allowing for more frequent communication with the FDA staff to provide a mechanism for addressing clinical development issues.

Selected participants of the Support for Clinical Trials Advancing Rare Disease Therapeutics (START) Pilot Program will be able to obtain frequent advice and regular ad-hoc communication with the FDA staff to address product-specific development issues, including, but not limited to, clinical study design, choice of control group and fine-tuning the choice of patient population.

The program will be open to sponsors of products currently in clinical trials under an active Investigational New Drug application (IND), regulated by the Center for Biologics Evaluation and Research (CBER) and/or the Center for Drug Evaluation and Research (CDER). Eligibility criteria for the pilot differs between CBER and CDER-regulated products.

In addition to having an active IND, eligible CBER-regulated products must be a gene or cellular therapy intended to address an unmet medical need as a treatment for a rare disease or serious condition, which is likely to lead to significant disability or death within the first decade of life. Under CDER's eligibility criteria, the product must be intended to treat rare neurodegenerative conditions, including those of rare genetic metabolic type. More information on the program's eligibility requirements can be found in the Federal Register Notice.

Canada

Health Canada Proposing Amendments for the Regulation of Clinical Trials Conducted in Canada

On 10 July 2023, Health Canada is proposing amendments to the Food and Drug Regulations, Natural Health Products Regulations and Medical Devices Regulations to modernize the regulation of clinical trials conducted in Canada.

The proposed amendments would:

- Ensure that Canada remains an attractive place to conduct clinical trials while continuing to uphold high standards for protecting the health and safety of participants;
- Introduce a coherent risk-based approach to the regulation of clinical trials in Canada;
- Afford greater flexibility in the safe development of innovative therapies and products, and innovative clinical trial designs;
- Streamline regulatory processes toward greater efficiency and clarity; and
- Align with international best practices regarding clinical trial oversight and public access to information.

This regulatory initiative was identified by Health Canada in its Health and Biosciences Sector Regulatory Review Roadmap. This initiative is not part of a formal regulatory cooperation work plan. This regulatory proposal would better align Canada's requirements with those of other jurisdictions such as the United States and European Union.

MEDICAL DEVICES

EUROPE

News from the European Commission

Update of the Answers to the Questions to Provide Clarification on the Extension of the Transitional Period for the MDR and IVDR

In July 2023, the European Commission released an updated Q&A document regarding the practical implementation of Regulation (EU) 2023/607, which amends Regulations (EU) 2017/745 (CTR) and (EU) 2017/746 (IVDR) concerning transitional provisions for specific medical devices and in vitro diagnostic medical devices.

The purpose of these amendments through Regulation (EU) 2023/607 was to ensure a high level of public health protection and prevent shortages of essential medical devices. This is achieved by granting manufacturers and notified bodies more time to conduct conformity assessments in accordance with the MDR for devices covered by certificates or declarations of conformity issued under Directive 90/385/EEC or Directive 93/42/EEC. Additionally, the removal of the 'sell-off' date in the MDR and the IVDR is aimed at preventing the unnecessary disposal of safe devices.

The updated Q&A document provides further clarification on various aspects, such as whether a national derogation granted under Article 59 of the MDR or the application of Article 97 of the MDR after amending MDR and IVDR, triggers an extension of the transitional period. It also addresses the situation where the application to a Notified Body (NB) or a written agreement between the manufacturer and the NB is withdrawn.

The Q&A document in new question regarding legacy devices, states that such devices are not required to comply with Unique Device Identification (UDI) requirements during the extended transitional period. This approach remains unchanged, even with the condition that, from 26 May 2024, the manufacturer of a legacy device must establish a MDR-compliant Quality Management System (QMS). Article 10(9), point (h) of the MDR, which pertains to the verification of UDI assignments for relevant devices as part of the QMS, only applies when UDI assignment is necessary for those devices.

Q&A on Transitional Provisions for Products without an Intended Medical Purpose.

In September 2023, the European Commission released a new set of Q&As pertaining to the transitional provisions for products falling under Annex XVI of the Medical Device Regulation (MDR). This document has been developed to align with the requirements outlined in the amended MDR through Regulation (EU) 2023/607 and the amended Commission Implementing Regulation (EU) 2022/2346.

The Q&A document offers detailed information on the transitional provisions applicable to various categories of products falling under Annex XVI of the MDR. This includes medical devices, products incorporating a medicinal product, and dual-purpose devices with both medical and non-medical intended purposes. Manufacturers can refer to this document to understand how to demonstrate that their product benefits from the transitional period for these products.

Flowchart to Assist in Deciding Whether or Not a Device is Covered by the Extended MDR Transitional Period

The European Commission has released a flowchart designed to assist manufacturers and relevant stakeholders in determining whether a medical device falls under the extended transitional period outlined in Article 120 of Regulation (EU) 2017/745 on medical devices (MDR), as amended by Regulation 2023/607. This flowchart is divided into two parts:

Part 1: This section of the flowchart helps make decisions regarding two categories of devices:

'Legacy devices' mentioned in Article 120(3a) of the MDR, which includes devices that had certification issued by a notified body in accordance with Directive 90/385/EEC (AIMDD) or Directive 93/42/EEC (MDD) before 26 May 2021.

'Legacy devices' referenced in Article 120(3b) of the MDR, which covers devices for which the conformity assessment procedure under Directive 93/42/EEC (MDD) did not require notified body involvement, and the declaration of conformity was created before 26 May 2021. If these devices now require notified body involvement under the MDR, the flowchart helps determine their status.

Part 2: This part of the flowchart pertains to Class III custom-made implantable devices specified in Article 120(3f) of the MDR. It provides guidance on whether these devices are subject to the extended transitional period.

In essence, the flowchart serves as a tool for assessing whether specific medical devices are eligible for the extended transitional period defined in the regulations, based on their classification and certification history.

The Update of the Manual on Borderline and Classification for Medical Devices

In September 2023, the Medical Device Coordination Group (MDCG) released an updated version of the Manual on borderline and classification for medical devices under the Medical Device Regulation (MDR) and the In Vitro Diagnostic Medical Device Regulation (IVDR). This guidance document helps distinguish between medical devices (MDs) and various other types of products, including in vitro diagnostics (IVDs), medicinal products, substances of human origin, cosmetics, food, biocides, personal protective equipment, and general consumer products. It also outlines the classification rules for MDs and IVDs under both MDR and IVDR.

Additionally, the MDCG noted that the previous manuals issued under Directive 93/42/EC on medical devices, Directive 90/385/EEC on active implantable medical devices, and Directive 98/79/EC on in vitro diagnostic medical devices will no longer be updated. However, they will remain available for reference and use as long as devices with CE-marking issued under these directives continue to be available on the market.

Extension of EUDAMED Audit

The European Commission presented highlights of the delivery plan, outlined the scope of future releases, and discussed the steps towards achieving full functionality of EUDAMED. Development will continue for at least one more year, due to finalizing the Clinical Investigations/Performance Studies module. The audit of EUDAMED is now scheduled to begin in the second half of 2024 and expected to conclude by the end of 2024 year (Q4 2024). Afterward, a notice in the Official Journal of the European Union (OJEU) will declare EUDAMED as ready and functional. Six months after this publication, EUDAMED becomes mandatory, starting in Q2 2025. Based on the Medical Device Coordination Group (MDCG) - EUDAMED Subgroup Plenary meeting minutes, EUDAMED's mandatory status has shifted from Q2 2024 to Q2 2025.

For additional information about EUDAMED: Information Centre – EUDAMED.

News from Individual Countries

The Netherlands

The Investigational In Vitro Medical Device Dossier (IMDD-IVD) Template Released

The Central Committee on Research Involving Human Subjects (CCMO) has released the Investigational In Vitro Diagnostic Medical Device Dossier (IMDD-IVD) template, which is accessible as of 15 September 2023. This template is specifically designed for use on non-CE-marked in In Vitro Diagnostic (IVD) performance studies that fall within the purview of Article 58 of the EU In Vitro Diagnostics Regulation (IVDR).

Up until 1 January 2024, the use of IMDD-IVD for new submissions is optional. However, after this date, CCMO strongly encourages the adoption of IMDD-IVD for all new submissions. This recommendation is aimed at streamlining and improving the submission process for IVD performance studies and aligning it with regulatory standards.

The IMDD-IVD template outlines the required content for the technical documentation related to IVDs in performance studies. This documentation is to be submitted to the relevant review committee, which can be an accredited MREC or CCMO. To ensure consistency and standardization in the submission of documentation for IVDs in performance studies, the decision has been made to base the IMDD-IVD on the technical documentation requirements specified in Annex II of the IVDR.

Other Initiatives

Personalized Medical Devices – Regulatory Pathways and New IMDRF Guidance

On 14 September 2023, the International Medical Device Regulators Forum (IMDRF) published guidance Personalized Medical Devices – Regulatory Pathways. Personalized Medical Devices (PMDs) are MDs designed for specific individuals.

The guidance explains how regulatory bodies manage these devices, offering flexibility based on the regulatory agency's needs. This guidance categorizes PMDs into custom-made, patient-matched, and adaptable medical devices, establishing general requirements and manufacturing standards to ensure consistency and traceability.

According to the guidance custom-made medical devices typically involve authorized healthcare professionals providing design inputs and sharing responsibility for the product's safety and effectiveness within the regulatory pathway.

Patient-matched medical devices are customized for an individual's anatomy, often produced in batches, and solely manufactured by the producer, who bears full responsibility for their performance. According to the IMDRF, manufacturers must adhere to premarket and post-market regulatory requirements in their respective jurisdictions, encompassing clinical, safety, manufacturing, and other standards.

The IMDRF guidance states that adaptable medical devices are mass-produced MDs but can be adapted, adjusted, or shaped at the point of care. They must adhere to typical premarket and post market requirements based on regulatory jurisdiction.

The guidance allows manufacturers to add specific requirements for those adapting the device and may mandate user training before adaptation. It provides a decision tree for device categorization and appendices to address scenario-specific questions.

North America

United States of America

FDA Issues Final Guidance on Cybersecurity in Medical Devices for Premarket Submissions

On 26 September 2023, the FDA issued the final guidance Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions. This guidance provides recommendations on medical device cybersecurity considerations and what information to include in premarket submissions. The increased integration of wireless devices, electronic exchange of medical device-related information, and cybersecurity vulnerabilities and incidents, highlight the importance of having stronger cybersecurity measures.

Canada

Health Canada Seeking Comments on Draft Guidance for Determining Medical Device Application Type

On 11 September 2023, Health Canada is requesting feedback from industry, including medical device manufacturers and other medical device stakeholders on the draft Guidance for determining medical device application type. This guidance explains the different application types and will help manufacturers determine whether certain medical devices, including components and parts, should be combined, and submitted as one device license or authorization application.

OTHER "HOT" TOPICS FROM THE EUROPEAN UNION

Data Protection: The EU-U.S. Data Privacy Framework Adapted by the EU

On 10 July 2023, the European Commission has officially adopted its adequacy decision concerning the EU-U.S. Data Privacy Framework. This decision affirms that the United States (U.S.) offers a level of data protection equivalent to that of the European Union (EU), making it safe for personal data to be transferred from the EU to U.S. companies under this new framework. Importantly, this means that additional data protection measures are not required for such transfers.

The EU-U.S. Data Privacy Framework addresses the concerns previously raised by the European Court of Justice. It does so by implementing binding safeguards, including restrictions on access to EU data by U.S. intelligence agencies, ensuring that such access is necessary and proportionate. Additionally, it establishes a Data Protection Review Court (DPRC) that EU individuals can access.

This new framework represents a significant improvement over the previous Privacy Shield mechanism. For example, if the DPRC determines that data has been collected in violation of the new safeguards, it can order the data's deletion. These enhanced safeguards related to government access to data complement the obligations that U.S. companies importing data from the EU will have to adhere to, ensuring greater data protection and privacy for individuals in both regions.

Under the EU-U.S. Data Privacy Framework, European Union (EU) individuals will have access to multiple avenues for addressing mishandling of their data by U.S. companies. These avenues include:

- Independent Dispute Resolution: EU individuals can utilize independent dispute resolution mechanisms, which will be available at no cost to them. This provides a way for individuals to address data privacy concerns and seek remedies.
- Arbitration Panel: There will be an arbitration panel in place to manage disputes related to data privacy matters. This offers an additional layer of recourse for individuals if their data is mishandled.

Furthermore, the EU-U.S. Data Privacy Framework will undergo periodic reviews to ensure its effectiveness and adherence to data protection standards. These reviews will be conducted by the European Commission in collaboration with representatives from European data protection authorities and competent U.S. authorities.

The first of these reviews is scheduled to occur within a year after the adequacy decision comes into effect. This review aims to verify that all relevant elements of the framework have been fully implemented in the U.S. legal framework and are functioning effectively in practice. These reviews will help maintain and enhance data protection standards for EU individuals whose data is transferred to U.S. companies under this framework.

Background and more information can be found here.

OTHER "HOT" TOPICS FROM THE UNITED STATES

FDA Issues Final Guidance on Obtaining Informed Consent in Drug and Device Clinical Trials

The FDA on 15 August 2023, announced it has finalized Guidance to help institutional review boards (IRBs), clinical investigators, and sponsors comply with informed consent regulations for clinical investigations. The 61-page guidance revises a draft guidance issued in July 2014 and supersedes a guidance issued in September 1998.

The document provides general guidance for informed consent, covering exceptions to informed consent, avoiding coercion, and exerting undue influence on subjects, how to make language understandable to the subject or the legally authorized representative, and avoiding the use of exculpatory language on consent forms.

It also discusses the basic elements of informed consent, which addresses describing the clinical investigation, explaining the risk and discomforts as well as the benefits of the treatment to patients, and compensation and medical treatment in the event of an injury. The guidance also addresses the roles of IRBs, clinical investigators, sponsors, and the FDA in the informed consent process, followed by a series of frequently asked questions.

Changes from the draft guidance include new language on examples of coercion and undue influences. For example, the FDA "does not consider reimbursement for reasonable travel expenses to and from the clinical trial site (e.g., airfare, gas, tolls), and associated costs such as parking and lodging, to raise issues related to coercion and undue influence."

The final version also includes additional text under the section on "financial relationships and interests" which specifies additional responsibilities of the IRB with respect to financial arrangements.

FDA Issues Revised Draft Guidance for Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products

On 21 September 2023, the FDA issued the revised, draft guidance *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*. This draft guidance outlines the recommendations to industry on formal meetings between the FDA and sponsors or applicants relating to the development and review of drug or biological drug products. This draft guidance replaces the draft guidance *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* issued on December 29, 2017.

FDA Issues Final Guidance: Breakthrough Devices Program

On 14 September 2023, the FDA issued an update to the final guidance: Breakthrough Devices Program. The updates align with the actions outlined in the FDA's Center for Devices and Radiological Health Strategic Priorities to Advance Health Equity by supporting innovation of new and existing technologies that address health inequities. The FDA has also updated the Breakthrough Devices Program website to update the device designations data and the marketing authorizations list with information from 1 April to 30 June 2023.

The Breakthrough Devices Program is a voluntary program for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. The program is intended to provide patients and health care providers with timely access to medical devices by speeding up development, assessment, and review for pre-market approval, 510(k) clearance, and De Novo marketing authorization. Breakthrough Devices must meet the FDA's rigorous standards for device safety and effectiveness to be authorized for marketing.

FDA Issues Final Guidance for Institutional Review Board (IRB) Review of Individual Patient Expanded Access Submissions

On 11 September 2023, the FDA published final guidance providing recommendations to Institutional Review Boards (IRBs) and clinical investigators regarding the key factors and procedures IRBs should consider when reviewing individual patient expanded access submissions, including for reviews conducted by a single member of the IRB, to fulfil its obligations under 21 CFR part 56.

Expanded access refers to the use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition rather than to obtain the kind of information about the drug that is generally derived from clinical trials. This pathway, is sometimes called "compassionate use" for patients.

The FDA's latest guidance on the IRB review of individual patient expanded access submissions for investigational drugs and biological products represents a significant step toward ensuring efficient and consistent review processes.

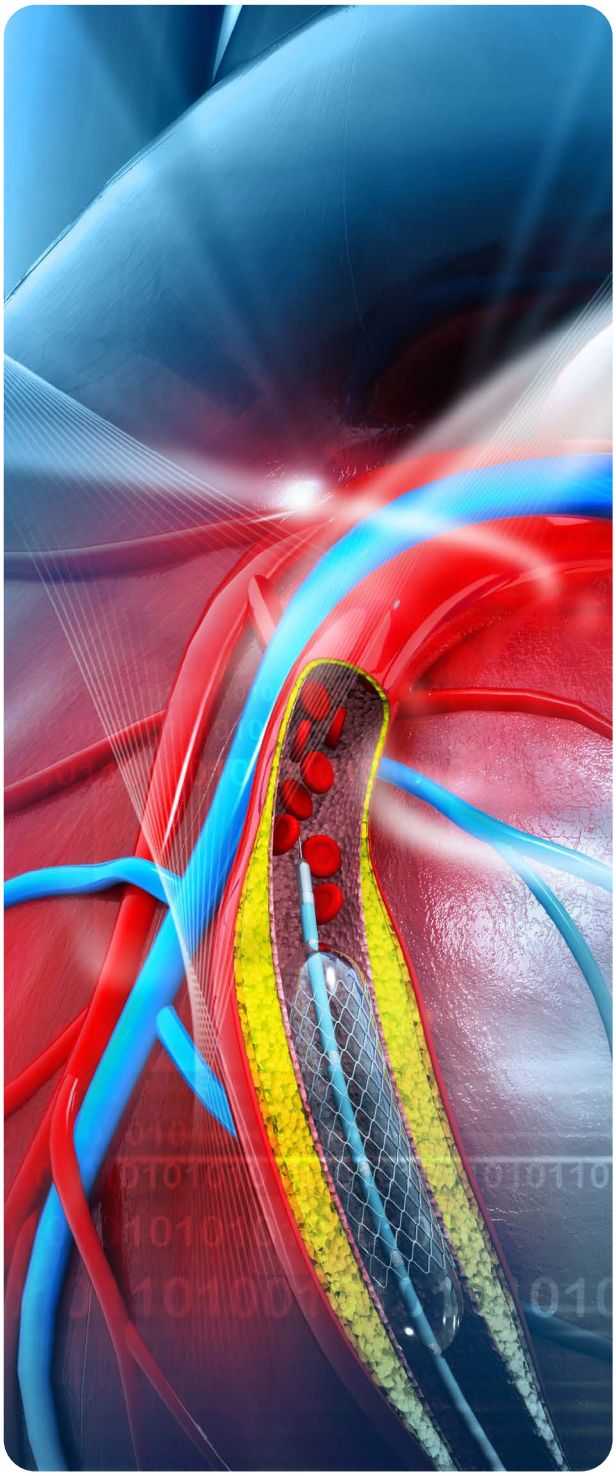
For additional information refer to Download FDA Guidance.

FDA Issues Draft Guidance Regarding Confirmatory Evidence of Clinical Trials

On 18 September 2023, the FDA issued the draft guidance, "Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence. The Confirmatory Evidence guidance supplements and expands the recommendations in the 2019 Substantial Evidence of Effectiveness draft guidance Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products by providing further detail on the use of data drawn from one or more sources to support the results of one adequate and well-controlled clinical investigation.

It also provides examples of types of data that could be considered confirmatory evidence. This guidance emphasizes the importance of early engagement with the agency for sponsors that intend to establish substantial evidence of effectiveness with one adequate and well-controlled clinical investigation and confirmatory evidence.

Sponsors should consider the clinical context for the proposed therapy when evaluating whether to approach establishing substantial evidence of effectiveness with one adequate and well-controlled clinical investigation and confirmatory evidence. Disease or condition-specific considerations may be relevant to whether such an approach is appropriate.



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