REGULATORY

NEWSLETTER N.39
July - September 2022

Including the latest updates on the EU CTR

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

Contents

MEDICINAL PRODUCTS/DRUGS

Europe

News from the European Commission

Proposal for a New Regulation for Substances of Human Origin - New Legislation on Blood, Tissues, and Cells (BTC)

On 14 July 2022, the European Commission has issued Proposal for a Regulation on standards of quality and safety for substances of human origin intended for human application and published Questions and answers on the proposal for a new legislation on blood, tissues, and cells. In the Q&As document the Commission highlights that the current legislation on blood and on tissues and cells is now outdated and does not reflect the health and societal evolutions. The Regulation will repeal the Blood Directive (2002/98/EC) and the Tissues and cells Directive (2004/23/EC).

This new proposal of Regulation:

- Supports the continued provision of substances of human origin (SoHO) therapies, now and in the future, based on high safety and quality standards and up-to-date technical rules
- Extends protective measures to new groups of patients, to donors and to offspring born from medically assisted reproduction
- Improves harmonisation across Member States, facilitating cross-border exchange of SoHO and improving patient access to the therapies they need
- Creates conditions for safe, effective, and accessible innovation in a unique sector driven by public health services and voluntary and unpaid donations
- Improves crisis preparedness and resilience to safeguard access to therapies
- Implements digital-ready policies
- Contributes to the European Health Union by pooling of technical expertise and achieving economies of scale.

The proposed Regulation puts forward the creation of an EU SoHO Platform, a central digital tool for authorities and stakeholders to facilitate data exchange and administration in the sector.

The proposal of the Regulation will now be discussed by the Council and the European Parliament. Once the final text is agreed and adopted, it will come into force with a two-year transition period before most provisions apply and a three-year period for some provisions.

Manufacture of Sterile Medicinal Products - the European Commission Revision

In August 2022, the European Commission has published guidelines for The Principles On Medicinal Products in the European Union Volume 4 EU Guidelines on Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. This document consists of an annex, which is a revision of the 2007 version of Annex 1 prompted by the recommendation of the GMP/GDP Inspectors Working Group and the PIC/S Committee to revise the current version of Annex 1, on the manufacture of sterile medicinal products, to reflect changes in the regulatory and manufacturing environment.

The aim of the revised guidelines is to remove ambiguities and inconsistencies and to take account of technological advances, thereby making it easier for manufacturers to take advantage of new opportunities through the use of innovative tools resulting from the application of increased process understanding.

The main objective of the document is to provide guidelines for the manufacture of sterile products, therefore presented are basic guidelines which should be applied to the design and control of facilities, equipment, systems, and procedures used to manufacture all sterile products by applying the principles of Quality Risk Management (QRM), so that no microbiological, particulate or endotoxin/pyrogen contamination occurs in the final product.

The deadline for manufacturers of implementing the changes into operation is 25 August 2023: one year from the date of publication in Eudralex Volume 4.

News from the European Medicines Agency (EMA)

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

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

In September 2022, the European Commission published version 6.2 of Questions and Answers Document - Regulation (EU) 536/2014. New question 1.24 has been added explaining how patient facing documents (i.e., questionnaires, patient diary, patient card or patient reported outcomes) are expected to be submitted through the Clinical Trials Information System (CTIS). It is underlined that patient facing documents should not be submitted in Part II dossiers for recruitment materials or subject information sheets. Patient facing documents that are linked to the endpoints of the clinical trial shall be provided together with the protocol in Part I of the clinical trial application. The explanation of such decision is provided in number 81 of the Q&As informing that "There is currently no legal basis in the CTR to request the submission of all patient facing documents in the part II documentation package and/or to require their translation".

Moreover, Chapter 11 of arrangements for transitional period, Q&A 2.6 No. 94 regarding labels and Q&A 3.8. No. 171 regarding references to the Investigational Medicinal Product Dossier (IMPD) submitted under Clinical Trials Directive (CTD) in "mother CT" to the IMPD dossier submitted under CTR were updated.

At the end, Annex II of Q&As has been completed for language requirements for part I documents in Denmark, Greece, Latvia, Hungary, and Sweden.

CTIS Evaluation Timelines Document Publication

The EMA published new guidance for sponsors, Contract Research Organisations (CROs) and authorities providing an overview of timelines and deadlines for tasks and actions across the Clinical Trial Application process. The guidance covers initial submission of the clinical trials application, substantial modifications, and addition of the Member State (MS). The processes are presented on several flowcharts with a detailed description from sponsors and members states perspective.

CTIS Latest Updates in the Clinical Trials Highlights

In July 2022, the EMA issued the 10th edition of the Clinical Trials Highlights. In this edition, the EMA is focusing mostly on the CTIS updates for events updates, training materials, provides brief information about upcoming changes of the new look of the EMA Account Management platform and shares sponsor's first experiences with CTIS.

Moreover, the July edition refers to a new article published in Pharmaceutical Statistics exploring statistical approaches for handling disturbances to ongoing clinical trials caused by the COVID-19 pandemic which affect the interpretability of the measured endpoints.

EMA Reports of Clinical Trial Applications Submitted via CTIS Portal

The European Commission, European Medicines Agency and Heads of Medicines Agencies have published Key Performance Indicators (KPIs) to monitor the European clinical trials environment - Metrics on the Clinical Trials Regulation (CTR) and Clinical Trials Directive (CTD). This document is a report providing an overview of the Key Performance Indicators (KPIs) related to the CTR, in force since 31 January 2022, according to which the European Commission assesses the impact of the CTR on scientific and technological progress.

The content of this report presents KPIs generated from two databases containing information on clinical trials in the EU/European Economic Area (EEA): Clinical Trials Information System (CTIS) and EudraCT.

Through descriptions and graphs, different data are compared. For example, the report presents the number of clinical trial applications (CTAs) submitted under the CTR in CTIS since the launch on 31 January 2022 and shows that the number of CTAs under CTR progressively increases. See Figure 1.

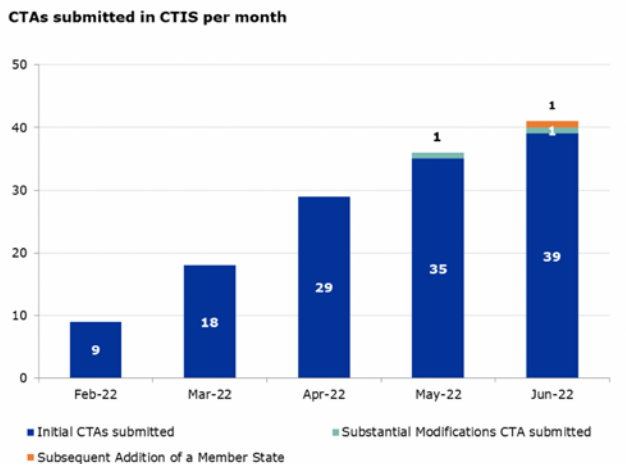


Figure 1

And for the same period of time for CTAs under the CTD sent by Member States to EudraCT, counted as an individual clinical trial protocol the data shows a dropping number of CTAs submitted under CTD. This could be explained by the fact that from 31 January 2023 submission of the CTA under CTR will be mandatory and all CT under the CTD must be completed or ended before 31 January 2025.

Furthermore, presented are data on the number of mono-national-multinational studies and data on the number of studies for which issued were decisions adopted by phase, National Competent Authority (NCA) decisions and Ethics Committee opinions under CTR or under CTD, Advanced Therapy Medicinal Products (ATMP) decisions under CTR.

In addition, the KPI on another graph (Figure 2) shows the distribution of appointment of Reporting Member State (RMS), amongst the applicable Member States Concerned, for clinical trial applications on which a decision has been issued. The data shows that such countries as Denmark, Belgium, Germany, and Spain more frequently have been proposed and/or accepted to be the RMS than other EU Member States.

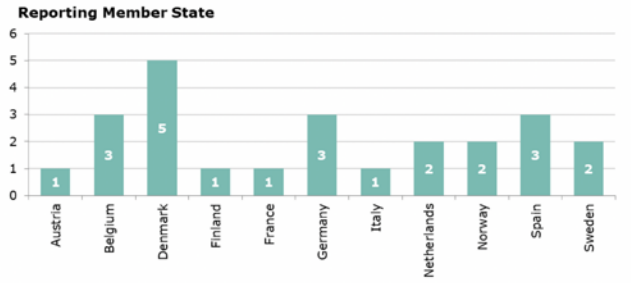


Figure 2

At the end of the report, an Annex I shows an average time from submission to decision for initial CTAs.

Protection of Personal Data and Commercially Confidential Information (CCI) for Documents Uploaded and Published in CTIS

The draft guidance on protection of personal data and CCI for documents uploaded and published in the Clinical Trial Information System (CTIS) was under consultation until 8 September 2022 with the final version expected in January 2023 before the CTIS use for the Clinical Trials Authorization under CTR is mandatory. In July 2022, the EMA organised a workshop on draft guidance to provide an opportunity for invited stakeholders to present their views. The summary of the meeting and the presentations have been published by EMA. They are the source of the information about deferrals, redacted and not redacted documents to be submitted via CTIS.

EC-HMA-EMA Workplan 2022-2026

Heads of Medicined Agencies (HMA) and European Medicines Agency (EMA) have published ACT EU multi-annual Workplan 2022-2026. The ACT EU 2022 - 2026 multi-annual Workplan operates on the basis of the EC-HMA-EMA Accelerating Clinical Trials in the EU initiative adopted on 13 January 2022 and presents ten priority actions to transform clinical trials in Europe which can be found in Annex 1 of the Workplan.

The purpose of the ACT EU 2022 - 2026 multi-annual Workplan is to present and outline the main objectives of each priority action, while emphasising key areas of focus to further facilitate innovation in clinical research, stakeholder engagement and regulatory network collaboration. In the first part of the document given is a detailed description of priority actions covering mapping and governance, the effectiveness of Clinical Trials Regulation (CTR) implementation, Good Clinical Practice modernisation, targeting of the communication campaign, clinical trial data analytics, scientific advice, clinical trial safety, the training programme, and also described are new and innovative clinical trial designs and methodologies and the design of a multi-stakeholder platform.

The document uses a flowchart to show the implementation of individual actions from 2022 to 2026 within the ACT EU priority actions described earlier, highlighting activities such as the development of a regulatory network responsibility assignment matrix for extended network groups, the development of a dashboard for clinical trials in the EU, the development of a consolidated scientific advisory process, the launch of modules on clinical trials, data science, pharmacoepidemiology and biostatistics, and the compilation of modules for different target groups.

Big Data Workplan 2022-2025 of Real-World Data (RWD) and Real-World Evidence (RWE)

Heads of Medicine Agencies (HMA) and European Medicines Agency (EMA) has a published Big Data Workplan 2022-2025. Big Data aims to improve decision-making by effectively integrating data analytics into its evaluation processes, which will benefit public health by accelerating drug development, improving patient outcomes, and facilitating earlier access to new treatments for patients.

Big Data Workplan 2022-2025 includes the Data Analysis and Real-World Interrogation Network (DARWIN EU). EU DARWIN is a federated network to enable access and analysis of RWD.

The activities undertaken by the work plan of the Big Data HMA-EMA Joint Steering Group covers: data quality and representativeness, data discoverability, EU network capability, EU network process, network capacity for analysis, EU DARWIN network, governance framework, international initiatives including the international collaboration on RWE, stakeholder engagement, veterinary recommendations, and provision of expert advice. Annex I of the document presents the priority recommendations of the HMA-EMA joint Big Data task force.

News from Individual Countries

The United Kingdom

Decommission of electronic Suspected Unexpected Serious Adverse Reaction (eSUSAR) Website

The Medicines and Healthcare products Regulatory Agency (MHRA) informed that as of 30 September 2022 the eSUSAR website will be decommissioned. Submissions after this date will not be received by the MHRA. From 1 October 2022 SUSARs will only be accepted via Individual Case Safety Report (ICSR) Submissions.

The MHRA provides a grace period for the eSUSAR website to remain open to enable users to continue downloading and collecting historical reports for example for planned inspections or for reference when submitting follow up reports, until 31October 2022.

Recommendations of the Request Approval of Trials with Complex Innovative Designs

The MHRA published the instructions on Requesting approval of trials with complex innovative designs. It is recommended that the sponsors who are planning to start the complex innovative clinical trial in the UK should choose the best design to address the trial objectives, to ensure that the benefit-risk balance of the trial is positive and to ensure the reliability of results. The MHRA presents different kinds of major adaptations for the trials which should be taken by the sponsors if not provided in initial submission and to be provided via substantial amendment.

Before submitting a Clinical Trial Authorisation application for a complex trial or Substantial amendment sponsors are recommended to establish a dialogue with the MHRA and seek advice.

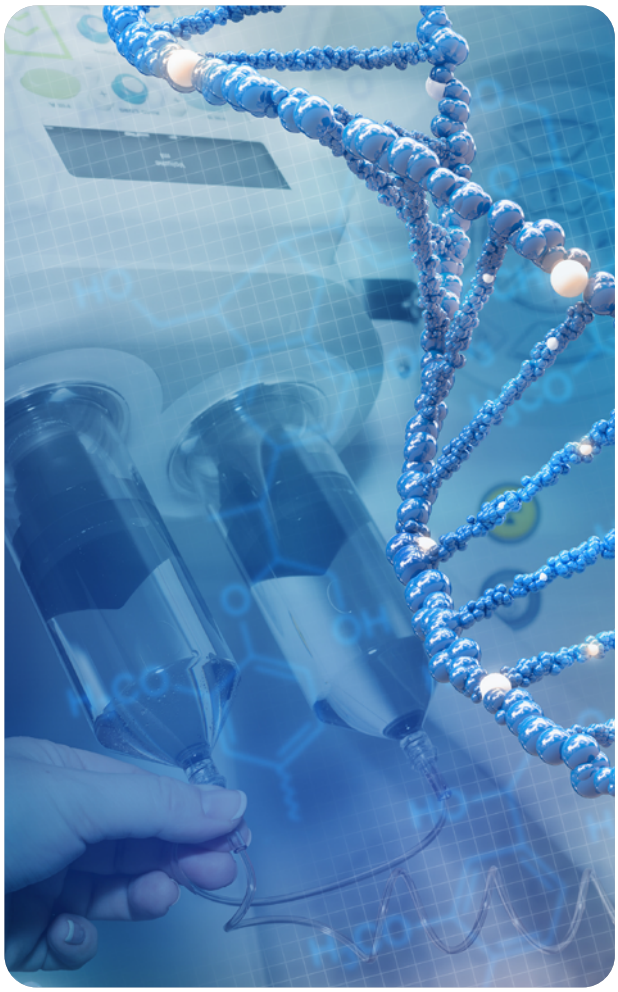
National Contract Value Review (NCVR) Process

From 1 October 2022, all eligible commercial study interactive costing tools (iCTs) submitted for a study resource review are included in the National Contract Value Review Process.

Eligible studies are all those commercial studies which will be conducted in acute, specialist and mental health trusts in England and counterparts in the devolved administrations, with the exception of phase I – IIa and advanced therapy medicinal product (ATMP) studies.

The NCVR will replace the current process whereby each National Health Service (NHS) organisation negotiated with each commercial sponsor for every study in order to agree bespoke contract value. From 1 October 2022, NHS organisation specific prices will be available to commercial companies prior to site selection and costs will be transparent. A single national negotiation of study costs will take place with no local negotiation. The UK NCVR will be shorter and in practice should take up to one month.

Once the iCT is submitted for eligible study, NCVR coordinator will be assigned and a single, national negotiation will be set up. The assessment will include checking the consistency of the research study protocol activities and the completed interactive costing tool, together with the negotiation of the resource required to deliver the protocol at any UK-based NHS location. NCVR contract value review coordinators will carry out the review.



The Netherlands

Guidance and Templates for CTR Studies

The Central Committee for Research Involving Human Subjects (CCMO) published the guidance from start to finish on Clinical Trials Applications (CTAs) under CTR. The instructions are detailed and provide relevant information for applicants starting from preparation of the initial submission dossier to archiving requirements.

Moreover, the CCMO issued a new model of Subject Information (PIF) for subjects aged 16 and older (adults). The changes were made to keep adjustment to the CTR, the Medical Research Involving Human Subjects Act (WMO) and the Insurance Decree. New model of PIF should be used immediately for CTR studies, starting from the date of publication on 15 July 2022.

On 21 July 2022, the CCMO published the template of clinical study protocol for studies covered by the CTR. The model was developed for non-commercial sponsors but can also be used by commercial sponsors for all clinical trials with investigational medicinal products. The template is not mandatory but recommended by the CCMO.

Germany

New Electronic Tool for the Compilation of Informed Consent Documents

The Office of the Ethics Committee (EC) of the Technical University of Munich launched an electronic Tool for the compilation of Informed Consent documents (eTIC). The eTIC tool helps an applicant to create correct Patient Information Sheet and Informed Consent Form for studies with medicinal products or medical devices, children 7-11 years old, non-interventional studies, led-investigators studies, patient information surveys, questionnaires, or interviews.

Based on the study specific information entered into the tool in German, the software identifies the mandatory text components for the patient Informed Consent documents. The applicant gets a suitable sample of texts. The software analyses the readability of the freely formulated texts. Moreover, the sentences and words that are difficult to understand are displayed and can be specifically optimized. The eTIC is free to use and strongly recommended by the ethics committees in Germany.

North America

United States of America

New FDA Draft Guidance Aims to Protect Children who Participate in Clinical Trials

On 23 September 2022, the U.S. Food and Drug Administration issued a draft guidance that, when finalized, will provide the agency's perspective on the ethical considerations for including and protecting children in clinical trials. The draft guidance is intended to assist industry, sponsors, CROs and institutional review boards (IRBs) when considering the enrollment of children in clinical investigations of drugs, biological products and medical devices.

Historically, children were not included in clinical trials because of a misperception that excluding them from research was in fact protecting them. This resulted in many FDA-approved, licensed, cleared, or authorized drugs, biological products, and medical devices lacking pediatric-specific labeling information. If the medical product was the best available treatment option for the child, doctors were left with no choice but to use a product that had not been reviewed by the FDA for safety and effectiveness in children. It became clear that children can be better protected by including them in clinical research. The draft guidance describes the ethical framework for protecting children in clinical research, which includes risk and benefit considerations.

It outlines and explains fundamental concepts for the ethical framework that IRBs, sponsors and industry should consider when reviewing or conducting clinical trials involving children, including: scientific necessity of conducting a clinical investigation; risk categories for interventions or procedures that do not offer a prospect of direct benefit to the child; how to evaluate whether an intervention or procedure offers a prospect of direct benefit to the child; assessment of risk for interventions or procedures with a prospect of direct benefit; component analysis of the risks of interventions or procedures; potential for review, under a regulatory provision, of research that is not otherwise approvable by an IRB; and parental or guardian permission and child assent.

Additional design considerations for clinical investigations of drugs and medical devices are provided.

Canada

Health Canada: Guidance Document for Biosimilar Biologic Drugs

Health Canada (HC) announced the release of the Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs in September 2022 for the addition of an indication where there is no/minimal data required to accompany the submission.

Comments received from the consultation on the draft version of the guidance document were reviewed and considered in the finalization of this document. This came into force 30 days from the date of the notice.

HC is applying the labelling-only fee and related timelines to the biosimilar submissions for the extension of indication(s) where there is no additional data requested and it is to align with indications of the innovator. Sponsors will be required to submit a Sponsor Attestation form in Module 1.2.3 Certification and Attestation Forms at the time of filing.

MEDICAL DEVICES

EUROPE

News from the European Commission

Guidance on Harmonised Administrative Practices and Alternative Technical Solutions until EUDAMED is Fully Functional for In Vitro Diagnostics Regulation (IVDR)

In July 2022, the European Commission's Medical Device Coordination Group (MDCG) published guidance on alternative solutions to submit and/or exchange information as required under the IVDR in the absence of a fully functional EUDAMED system.

The guidance refers to many provisions of IVDR where the EUDAMED use is mandatory or linked. In the absence of the EUDAMED in case of application for performance studies, performance studies regarding devices bearing the CE marking, its substantial modifications and reporting the end of a performance study or in the event of a temporary halt or early termination, the MDCG advice is to proceed in accordance with the respective national procedures applicable to performance studies.

Regarding recording and reporting of adverse events that occur during performance studies, sponsors are required to report them via the respective national procedures applicable to performance studies.

For manufacturers reporting of serious incidents and field safety corrective actions (FSCAs) is required via relevant national vigilance systems. Moreover, the current FSCA form should be used, and the new Manufacturer Incident Reporting (MIR) form has already been adapted to IVDR requirements and should be used accordingly by manufacturers.

EUDAMED Timeline Updated

In June 2022, the European Commission's updated the European Database on Medical Devices (EUDAMED) time line of audit and mandatory use of the EUDAMED. Audit results presented to the Medical Devices Coordination Group (MDCG) have been postponed until quarter 2 (Q2) 2024. End of six months transitional period after publication of the notice in the Official Journal of the European Union (OJEU) of the full functionality of the system has been postponed from Q4 2023 to Q4 2024.

EUDAMED - European Database on Medical Devices

EUDAMED Time line

The European Commission planning – June 2022

Q4 2023	Q1-Q2 2024	Q2 2024	Q2 2024	Q4 2024	Q2 2026
End of the EUDAMED MVP[1] development for all six modules	Independent **Audit**	Audit results presented to the Medical Devices Coordination Group (MDCG)	EUDAMED has achieved full functionality following the outcome of the Audit. **Publication of a Commission notice** in the *Official Journal of the European Union* **(OJEU)** The full EUDAMED system (all 6 modules) is released.	End of 6 months transitional period after publication of the notice in the OJEU The use of **EUDAMED** becomes **mandatory** as regards obligations and requirements related to **Actors, Vigilance, Clinical Investigation & Performance Studies and Market Surveillance modules**	End of 24 months transitional period after publication of the notice in the OJEU The use of **EUDAMED** becomes **mandatory** as regards obligations and requirements related to **UDI/Device and NB & Certificate modules**

[1] EUDAMED Minimum Viable Product (MVP) means that the system developed implements at least the minimum Medical Devices Regulations requirements and allows competent authorities and all stakeholders to comply with their legal obligations.

Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices

In September 2022, the European Commission published a manual for stakeholders concerning the aspects on the borderline between medical devices and other types of products and classification rules of medical devices. The manual includes records agreed by the Member State members of the Borderline and Classification Working Group (BCWG) following the exchanges under the Helsinki Procedure under the MDR and the IVDR.

The document is split up into two parts. First part is dedicated to the qualification on medical devices and classification. It covers the borderline between products that may fall under the MDR or under the IVDR; between medical devices and medicinal products; between medical devices and biocides and others. The second part covers the demarcation between products that may fall under the IVDR or under the MDR, where the conclusion is that the product should be qualified as an IVD. The manual provides examples of products qualified and classified properly.

The Manual should be read in conjunction with other documents published by the Medical Device Coordination Group (MDCG) on borderline medical devices and its classification.

Expert Decision and Opinion in the Context of the Clinical Evaluation Consultation Procedure (CECP)

The European Commission has published an Expert decision and opinion in the context of the Clinical Evaluation Consultation Procedure (CECP). This expert opinion presents the experts' views on the clinical evaluation assessment report (CEAR) of the notified body, which is presented in the context of the clinical evaluation consultation procedure (CECP).

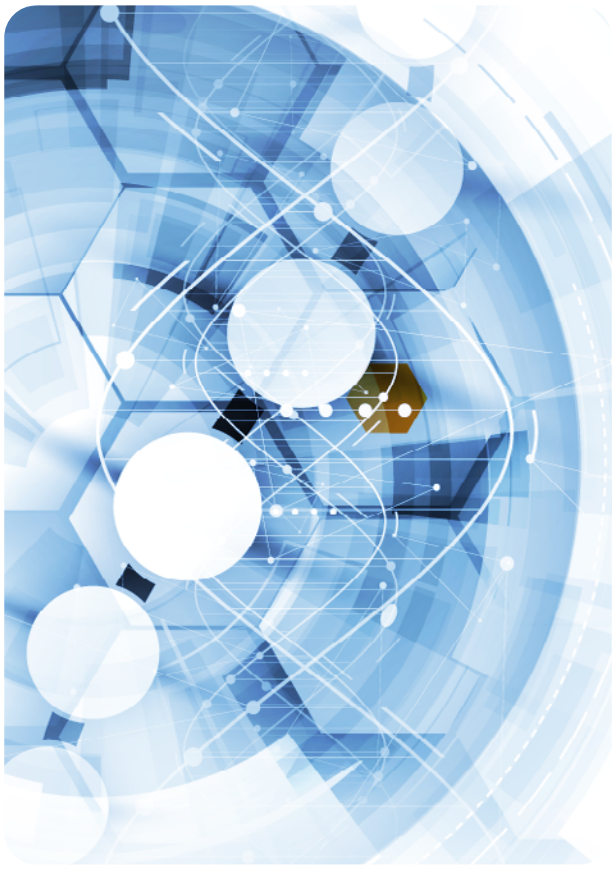
It is the responsibility of the Notified Body to take into account the scientific opinion of the expert panel when, in the opinion of the experts, the level of clinical evidence is insufficient. With the help of ready-made templates, it is shown how the different parts of the CEAR of the Notified Body should look like.

The first part is the decision of the verification experts, where they inform the NB and the committee of their intention to issue an opinion. This part presents, inter alia, the assessment of the three qualification criteria, which are the novelty of the product being assessed, the health concerns in the event of a product failure and the issue of serious incidents relevant to the product. The second part of the report is the scientific opinion of the thematic expert panel/subgroup, which includes, a summary of the opinion, detailed elements of the opinion and conclusions and recommendations.

Implementation Rolling Plan Regulation (EU) 2017/745 and Regulation (EU) 2017/746 - Latest Update

In July 2022, Implementation Rolling Plan with reference to Regulation (EU) 2017/745 (MDR) and Regulation (EU) 2017/746 (IVDR) was updated. The scope of this plan covers all relevant implementing acts and any initiatives that the Commission has adopted or intends to adopt in the future.

This plan consists of two parts: implementing acts and other initiatives and for each position a column is included with the legal basis, description, expected date of implementation and proposed next steps. An important piece of information worth highlighting is that this plan should be read in conjunction with the 'MDR/IVDR roadmap'.



Regulation (EU) 2022/1107 of 4 July 2022 Laying Down Common Specifications for Certain Class D In Vitro Diagnostic Medical Devices

The Official Journal of the European Union has published the Commission Implementing Regulation (EU) 2022/1107 of 4 July 2022 laying down common specifications for certain class D in vitro diagnostic medical devices in accordance with Regulation (EU) 2017/746 (IVDR) of the European Parliament and of the Council.

The European Commission by this Regulation establishes common specifications for certain Class D in vitro diagnostic medical devices in relation to the performance requirements set out in Section 9.1, points (a) and (b), Section 9.3 and Section 9.4, point (a), of Annex I to Regulation (EU) 2017/746. Thus, the European Commission takes into account that for certain Class D in vitro diagnostic medical devices no harmonised standards exist for certain requirements of Annex I to this Regulation, although for certain devices covered by Directive 98/79/EC they remain valid.

Furthermore, it has been made possible for manufacturers, economic operators and notified bodies to comply voluntarily with the common specifications laid down in this Regulation before its entry into force and, as a transitional measure, it is appropriate to provide that products complying with Decision 2002/364/EC shall be presumed to be in compliance.

This Regulation consists of 13 annexes laying down common specifications for specific products. Transitional provisions are also set out and it is announced that this Regulation shall enter into force on the twentieth day following that of its publication in the Official Journal of the European Union.

Notified Body Approach for the Technical Documentation Assessment Approach of Multiplex In-Vitro Diagnostic Devices

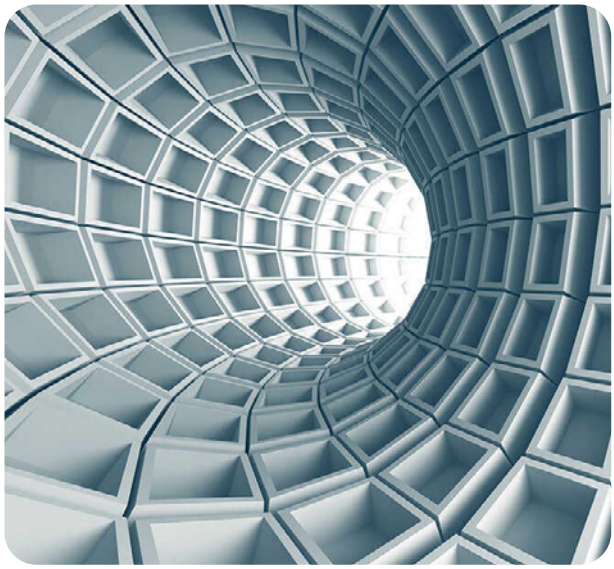
The European Association of Medical devices Notified Bodies and Notified Bodies Coordination Group has published a Notified body approach for the Technical Documentation assessment approach of multiplex in-vitro diagnostic devices. The goal of this document is to establish a standardised procedure for a notified body to use when evaluating the technical dossier of multiplex IVD devices. For the purpose of this document, multiple in vitro diagnostic devices (IVD) are defined as devices in which two or more targets/markers are simultaneously detected by a common procedure and which are sold as a single device Basic UDI-DI, with a single intended purpose statement that can cover a potentially large number of targets/markers making the evaluation of the technical documentation of these devices and the review of clinical data problematic.

In the document, the considerations for Basic UDI-DI sampling are presented and described, as they are not presented in the MDCG 2019-13 guidance for MDR Class IIa / Class IIb and IVDR Class B / Class C device sampling. Proposed and explained is risk-based sampling approach for deciding which specific data of which marker should be reviewed, but only for markers/targets that would be classified as Class C and B, as for Class D markers the technical documentation for all will be reviewed. In the final section of the document, examples are used to explain the approaches to be taken in assessing the technical documentation.

Guidance on Designation, Re-assessment and Notification of Conformity Assessment Bodies and Notified Bodies

Medical Device Coordination Group (MDCG) has published a Designation, re-assessment and notification of conformity assessment bodies and notified bodies document. This document provides guidance for evaluations of conformity assessment bodies (CABs) seeking designation as a notified body (NB) and for re-evaluations of NBs carried out by joint assessment teams (JATs) and notified body authorities. The document is a kind of guidance to ensure consistency and alignment of the working practices of the different designating authorities in the Member States for the assessment, designation, notification and reassessment of CABs and NBs.

The document outlines the various steps starting with the assessment of designations. Clarified are the issues of pre-assessment and off-site activities, on-site assessment activities, post-assessment on-site activities and the matter of the designation decision. The process of filing and publication in New Approach Notified and Designated Organisations (NANDO) is also described, detailing issues relating to the content of the filing, supporting documents, the objection period and publication in NANDO and the validity of the designation. Also addressed in the document is the reassessment of notified bodies and the updating of NANDO notifications. The final section of the document includes two annexes in the form of flowcharts of the activities and timing of designation assessment and reassessment.



MDCG Position Paper Transition to the MDR and IVDR Notified Body Capacity and Availability of Medical Devices and IVDs

Medical Device Coordination Group (MDCG) has published a position paper on Transition to the MDR and IVDR and Notified body capacity and availability of medical devices and IVDs. This document sets out proposed actions to improve the effectiveness of the application of the regulatory requirements in particular with regard to safety, as, as the MDCG notes, significant and urgent challenges remain in ensuring sufficient notified body capacity and manufacturer readiness to enable medical devices and in vitro diagnostic medical devices to be certified in compliance with the MDR and IVDR during the transitional periods provided in the Regulations.

Firstly, measures were proposed to increase the capacity of notified bodies. Among the proposals mentioned are the use of hybrid audits, the use of evidence or elements of evidence from previous assessments, proper supervision" of existing products, the elimination of the administrative burden of notified bodies, streamlining of internal administrative procedures, changes to the frequency of full re-evaluations of notified bodies and speeding up the process of evaluation, designation, and notification of conformity assessment bodies. Further proposals concerned access to notified bodies with the MDCG suggesting, among other things, taking into account the interests of Small and medium-sized enterprises (SMEs), allocating capacity to SME manufacturers and first-time applicants, organising structured dialogues, and increasing the willingness of manufacturers. The MDCG's final proposals in the final section of the document relate to other actions to facilitate the transition to MDR/IVDR and/or to avoid device shortages.

News from Individual Countries

Austria

Guidance Documents and Forms for Regulation (EU) 2017/746 (IVDR)

As of 15 August 2022, a new fee regulation of the Austrian Federal Office for Safety in Health Care (BASG) was put into force. From this date new fees apply for:

- Clinical investigations of medical devices according to Regulation (EU) 2017/745
- Performance studies of in-vitro diagnostics according to Regulation (EU) 2017/746
- Amendments of ongoing studies according to Directives 90/385/EEC and 93/42/EEC

For academic clinical investigations of medical devices and performance evaluation studies of in-vitro diagnostics the same fees for initial and amendment applications apply as for commercial studies.

The United Kingdom

Notification of Medical Devices Study Deviations

The Medicines and Healthcare products Regulatory Agency (MHRA) updated Medical device stand-alone software including apps guidance by providing changes of In vitro diagnostics software and intended purpose. The guidance is interactive and easy to navigate. The MHRA reminds that CE marked medical devices will be recognised on the Great Britain market until 30 June 2023. Instead of CE mark it will be mandatory to use UKCA mark (UK Conformity Assessed). Moreover, four appendices have been added: Appendix 1- symptoms checkers; Appendix 2- clinical calculators; Appendix 3 – 'drives or influences the use of a device' and Appendix 4 – Field Safety Warnings and End-of-Life notification.

North America

United States of America

Send and Track Medical Device Premarket Submissions Online: CDRH Portal

FDA announces that medical device companies may now send electronic copy (eCopy) or electronic Submission Template and Resource (eSTAR) premarket submissions online through the CDRH Customer Collaboration Portal ("CDRH Portal"). Building on the progress tracker for 510(k) submissions launched in 2021 and the trial process of electronic uploads launched in July 2022, the CDRH Portal now allows anyone to register for a CDRH Portal account to send CDRH eCopy or eSTAR premarket submissions online.

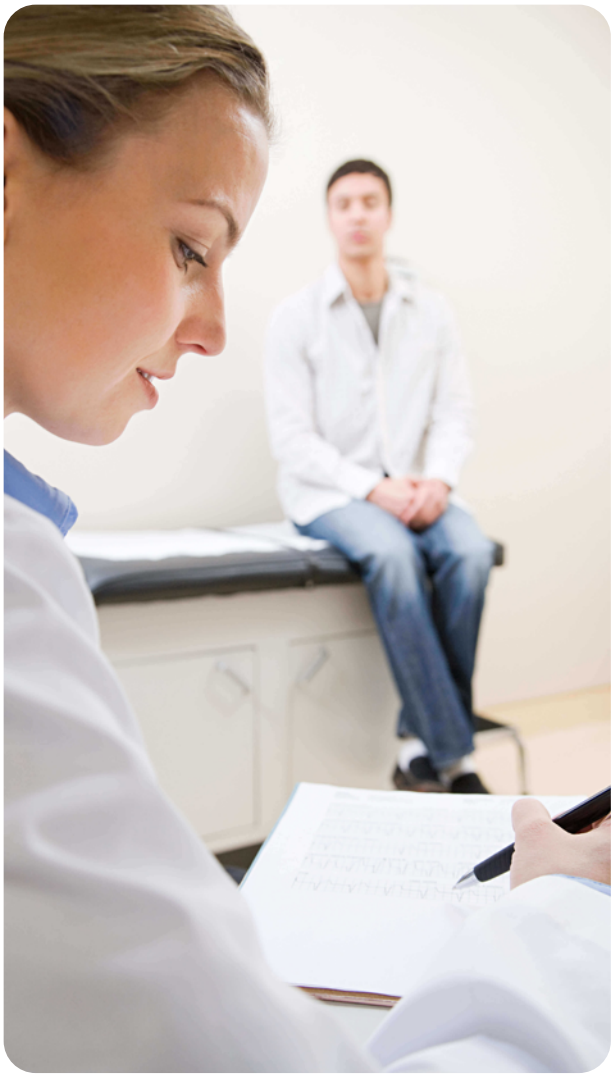
As noted in the final guidance, Electronic Submission Template for Medical Device 510(k) Submissions: Guidance for Industry and FDA Staff, all 510(k) submissions including original submissions for Traditional, Special, and Abbreviated 510(k)s, and subsequent Supplements and Amendments and any other subsequent submissions to an original submission, unless exempted in Section *VI.A Waivers and Exemptions From Electronic Submission Requirements* of the guidance, are required to be submitted as electronic submissions. The electronic submission template, eSTAR, is the only currently available electronic submission template to facilitate the preparation of 510(k) electronic submissions.

Starting 1 October 2023, all 510(k) submissions, unless exempted, must be submitted as electronic submissions using eSTAR.

Canada

Regulatory Initiative: Adaptive Machine Learning-enabled Medical Devices

Health Canada is proposing to add a description of Adaptive Machine Learning-enabled Medical Devices to Schedule G, Advanced Therapeutic Products Pathway for Adaptive Machine Learning-enabled Medical Devices allowing these devices to be regulated as Advanced Therapeutic Products. These devices would be the first Advanced Therapeutic Products to be listed in Schedule G, a schedule added when new authorities were added to the Food and Drugs Act in 2019. These new authorities are intended to enable the use of customized regulatory requirements to allow for the agility and flexibility necessary to determine the appropriate oversight of innovative health products.



OTHER "HOT" TOPICS FROM THE UNITED STATES

Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices

On 5 October 2022, the FDA added 178 devices to the list of artificial intelligence and machine learning (AI/ML)-enabled devices legally marketed in the U.S. by 510(k) clearance, granted De Novo request, or approved PMA. The Center for Devices and Radiological Health's (CDRH) Digital Health Center of Excellence first posted this list in 2021. With this update, the FDA has also added the ability to download the list as an Excel file. This list is not meant to be an exhaustive or comprehensive resource of AI/ML-enabled medical devices. Rather, it is a list of AI/ML-enabled devices across medical disciplines, based on publicly available information.

As technology continues to advance every aspect of health care, software incorporating artificial intelligence (AI), and specifically the subset of AI known as machine learning (ML), has become an important part of an increasing number of medical devices. One of the greatest potential benefits of ML resides in its ability to create new and important insights from the vast amount of data generated during the delivery of health care every day.

Digital Health Software Precertification (Pre-Cert) Pilot Program

On 26 September 2022, the FDA issued The Software Precertification (Pre-Cert) Pilot Program: Tailored Total Product Lifecycle Approaches and Key Findings, a report authored by the Center for Devices and Radiological Health's (CDRH) Digital Health Center of Excellence. With this report, the FDA is marking the completion of the Pre-Cert Pilot Program. Based on the observations from the pilot discussed in this report, the FDA has found that rapidly evolving technologies in the modern medical device landscape could benefit from a new regulatory paradigm, which would require a legislative change.

The digital health sector continues to grow as interoperable computing platforms, sensors, and software improve. In particular, software is increasingly being used in the treatment and diagnosis of diseases and conditions, including aiding clinical decision-making, and managing patient care. From fitness trackers to mobile applications, to drug delivery devices that track medication adherence, software-based tools can provide a wealth of valuable health information and insights.

OTHER NEWS IN DATA PRIVACY

European Data Law Is Impacting FDA

On 9 August 2022, the FDA's Office of Global Policy and Strategy published "How a European Data Law is Impacting FDA," which looks at how the European Union's General Data Protection Regulation (GDPR) may be impacting the FDA's public health activities. So far, the FDA's bioresearch monitoring program, which oversees the conduct and reporting of FDA-regulated research, has been most affected by the law. FDA's Europe Office has been closely following the potential impact of the GDPR on the agency's public health activities.

Under bioresearch monitoring program (BIMO), FDA investigators conduct inspections and remote regulatory assessments (RRAs), a tool often used when onsite inspection is not possible, in countries where patients have been enrolled in clinical trials supporting marketing applications. Some of those countries involved in FDA-regulated research include the nations of the EEA. The purpose of this inspectional oversight is to help ensure the quality and integrity of the study data and to protect the rights and welfare of the human subjects.

The GDPR poses other potential concerns for the FDA in different areas, including clinical trial data. FDA's regulatory process requires companies to submit participant level data from clinical trials to support the safety and effectiveness of investigational medical products. The data often come from multi-national clinical trial sites, and any sites in the EU would include clinical trial participants who are EU citizens. Inability to transfer such data from the EU could negatively impact the robustness of data submitted to the FDA and impact investigational product reviews and approvals.

Another area is the New Drug Application/ Biologic License Application (NDA/BLA). As part of its review of NDAs and BLAs, the FDA requires certain information (e.g., demographic information) from industry which may be protected under the GDPR. Inability to receive, or delays in receiving, this information may impact FDA's ability to complete reviews. Another area is adverse event reporting because of multiple adverse event and safety reporting systems for different FDA regulated products.

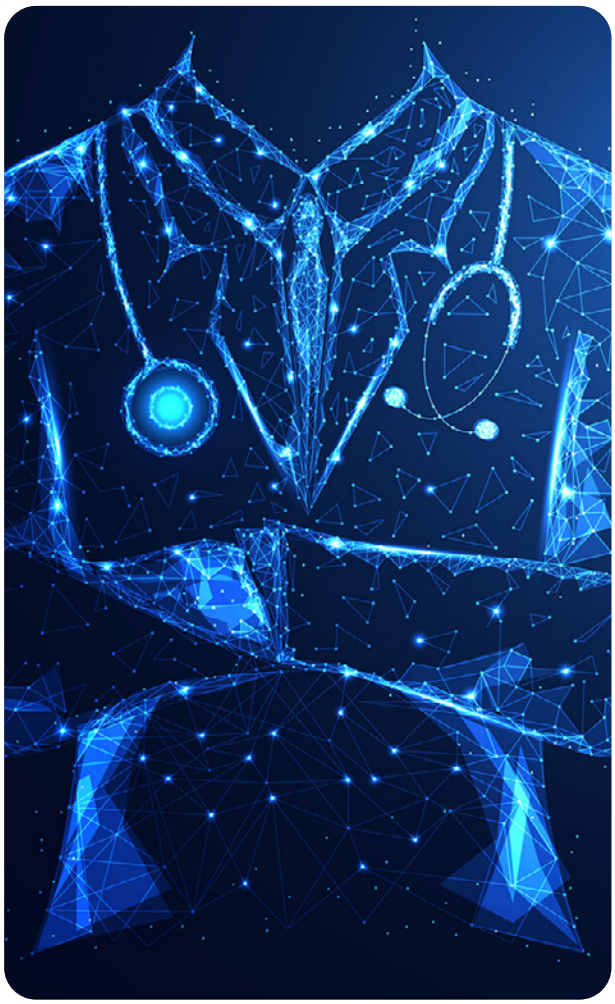
The National Institutes of Health has been working directly with its counterparts in the EU member states to address any GDPR impediments to specific research collaborations. There is also strong interest in this topic across other U.S. agencies. The Europe Office will be closely tracking developments in the months and years ahead.

EU-U.S. Data Privacy Agreement signed by U.S. President

On 7 October 2022, the U.S. President Joe Biden signed an executive order on EU-U.S. data privacy agreement. The Decree will be sent to Brussels where the European Commission will transpose the text into the EU rules.

It is expected that the process of transposing the text will take around six months and will lead to a final pact being published in March 2023.

More information is available here.



About CROMSOURCE

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

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CROMSOURCE supports the full spectrum of clinical development via our Pharmaceutical, Medical Device and Staffing Solutions divisions. We seamlessly move biopharmaceutical products from first-in-human through all subsequent phases of pre- and post- approval research internationally.

We also support medical device projects through regulatory planning and execution, to pre- and post-market clinical investigations in Europe and North America.

Global Reach

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

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