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REGULATORY

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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

EU Clinical Trials Regulation and Clinical Trials Information System (CTIS) Finally Applicable in the EU/EEA

As of 31 January 2022 the Clinical Trials Regulation (EU) No 536/2014 (EU CTR) and CTIS are applicable and active for new initial clinical trial applications (CTAs) and for ongoing trials which must be either - ended in the EU/EEA or have been transitioned to CTIS by 31 January 2025.

On 27 March, the EMA reported that 20 CTAs have been submitted via CTIS under EU CTR and 278 CTAs have a status of "draft." Most of the applications were submitted by academic sponsors and a significant number were also submitted by pharmaceutical companies. The CTIS recorded 9,164 logins by 27 March 2022.

Moreover, the European Commission provides templates for Part II clinical trial application documents, including for the Investigator Curriculum Vitae (CV), site suitability form, and informed consent document. The document templates can be found in Chapter I of Eudralex Volume 10.

In January 2022, the European Commission published Questions and Answers Document - Regulation (EU) 536/2014 – Version 6.0. Several new questions have been added, for example, how to proceed in case of discrepancies between the CTR and ICH Good Clinical Practice guidance or how to proceed with informed consent in a clinical trial in an emergency situation. The Commission also added some Q&A to section 11 related to the transition period.

The Q&A guidance is accompanied by four Annexes. However, Annex III - acceptability of Part II templates in the Member States was under development by the Commission.

Furthermore, the European Medicines Agency (EMA) supports an applicant of CTIS by:

- Launching a new public Clinical Trials website
- Providing online modular training programme and other supporting materials
- Offering CTIS walk-in clinics to provide an opportunity for sponsors to receive practical advice about any CTIS functionality by asking questions to CTIS experts
- Organising CTIS bitesize functionality talks once a month, focusing on a specific CTIS functionality, including a live demonstration by CTIS experts, and an opportunity for users to ask questions

On 23 March 2022, it was presented on how to create an initial clinical trial application in CTIS. Next session will be organised on 28 April 2022, and the submission of a substantial modification in CTIS will be demonstrated.

Accelerating Clinical Trials in the EU (ACT EU) Initiative

On 13 January 2022, the European Commission (EC), the Heads of Medicines Agencies (HMA) and the European Medicines Agency (EMA) launched an initiative to transform how clinical trials are initiated, designed, and ran, and referred to as Accelerating Clinical Trials in the EU (ACT EU). The ACT EU has its Steering Group which has a decision-making role and reports to the EMA Management Board and HMA.

The aim of the ACT EU Steering Group is to:

- Coordinate the governance of clinical trials at the EU level;
- Monitor the activities and deliverables from the different ACT EU workstreams against the ACT EU objectives;
- Identify and make recommendations on critical issues related to the broad environment of clinical research; and
- Oversee the CTIS project.

The Clinical Trials Advisory Group (CTAG) Establishment

The CTAG is established by Article 85 of the Clinical Trials Regulation (CTR). The Group is chaired by the European Commission (EC) and its members are the CTR National Contact Points. The Clinical Trials Coordination Group (CTCG) and EMA are observers in CTAG. The CTAG conducts ad-hoc and regular meetings.

The purpose of CTAG is to:

- Support the exchange of information on the experience acquired regarding the implementation of the CTR;
- Assist the EC in the preparation of delegated acts;
- Assist the EC in providing support on coordinated safety assessment; and
- Prepare recommendations on criteria regarding the selection of a reporting Member State (RMS).

Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic

The European Commission, in cooperation with European Medicines Agency (EMA), and Heads of Medicines Agency (HMA) have published Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic, Version 5. The guidance has been mainly revised in the context of new the Clinical Trials Regulation (EU) No 536/2014 (EU CTR) applicable from 31 January 2022. In terms of changes to ongoing trials and various actions, the changes that should be considered by sponsors have been proposed and detailed. The priorities and principles for implementing the proposed changes were also mentioned.

The importance of communicating with the authorities on the implementation of major changes is emphasised and the process of such communication is described, including the application of various mitigation measures.

Procedures for changes in informed consent are presented, taking into account planned investigations to test new treatments for COVID-19 and trials involving patients with COVID-19 where several aspects are to be considered by the sponsors.

Also described are alternative actions when re-consent is needed to make new urgent changes to the conduct of the trial. The guidance also focuses on changes to the distribution of investigational medicinal products (IMPs), primarily outlining what such changes might include to prevent avoidable site visits and to ensure that trial participants receive the treatment they need.

Changes to the distribution of in vitro diagnostics and medical devices are also covered, while the issue of changes to monitoring describes a combination of elements such as on-site monitoring, centralised monitoring, and central review of collected data, off-site monitoring, and remote verification of source data.

The final section of the guide describes the issue of reimbursement of extraordinary costs and the process for initiating new research to test new treatment methods for COVID-19 disease including the application process. The guidance is accompanied by an annex outlining the protection of the rights of research participants during remote verification of source data, where appropriate controls are proposed to be implemented.

News from the European Medicines Agency (EMA)

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

New Regulation Reinforcing EMA's Role in Crisis Preparedness and Management of Medicinal Products and Medical Devices

As of 1 March 2022, the Regulation (EU) 2022/123 on a reinforced role for the European Medicines Agency (EMA) in crisis preparedness and management for medicinal products and medical devices became applicable. The Regulation establishes permanent structures and processes for the EMA during the COVID-19 pandemic and entrusting several new tasks to the EMA.

For the current EMA tasks, such as monitoring medicine shortages as well as reporting shortages of critical medicines during a crisis, the EMA will be engaged in coordinating responses of EU/EEA countries to shortages of critical medical devices and in-vitro diagnostics in crisis situations. On 1 March 2022, the EMA handed over from the Commission's Joint Research Centre (JRC) the coordination Secretariat of the Commission's exp ert panels on medical devices and in vitro diagnostic medical devices.

Moreover, the EMA will be significantly engaged in updating the role of the EU Single Point of Contact (SPOC) network, a system that EMA and national competent authorities use to exchange information on shortages.

The list of new the EMA tasks is available here.

Guideline on Good Pharmacovigilance Practices (GVP)

The European Medicine Agency and Heads of Medicine Agencies have published draft Guideline on good pharmacovigilance practices (GVP) Module XVI Addendum III - Pregnancy prevention programme and other pregnancy risk minimisation measures. End of consultation is on 31 May 2022.

To avoid adverse pregnancy outcomes due to the use of medicines and to preserve the health of both mother and baby, new guidelines have been introduced which set out the elements of a pregnancy prevention programme and provide for deciding when such a programme is required or when other risk reduction measures are considered appropriate.

The PPP (Pregnancy Prevention Programme) aims to protect the unborn child by ensuring that female patients (adolescents and adults) are not pregnant at the beginning of treatment, that they do not become pregnant during treatment, and that they do not become pregnant for a specified period after treatment has ended. Furthermore, although it is uncommon, the PPP may contain a referral to male patients. Criteria for requiring PPP or selecting pregnancy-specific risk minimisation measures are established further in the guidance.

The most common scenarios and requirements such as proven or strongly suspected teratogenicity, are possible, but unproven teratogenicity or unlikely teratogenicity are also outlined and described in detail. Regarding RMM (routine and additional risk minimisation measures), a pregnancy prevention programme should include all pregnancy specific RMMs, which must meet the criteria described in Module XVI of the GVP.

In the subsequent sections of the guidance detailed are RMMs such as the summary of product characteristics (SmPC) and package leaflet (EN), required prescribing conditions, required dispensing conditions, educational material aimed at healthcare professionals and those direct to patients, and outer packaging labelling.

ICH Guideline E8 (R1) on General Considerations for Clinical Studies

The ICH guideline E8 (R1) on general considerations for clinical studies adapted by the EMA finally will become applicable on 14 April 2022. This document provides guidance on the clinical development lifecycle, including quality design in clinical trials while taking into account the extensive range of clinical trial, designs, and data sources used.

Its main objectives are to describe the principles and practices of clinical trial design and conduct, provide guidance in planning and conducting clinical trials, an overview of the types of clinical trials, and a guide to ICH documents.

The first to be presented are the general principles, which include: protection of clinical trial participants; a scientific approach to the design, planning; conduct of analysis and reporting, and patient involvement in drug development. In the guidance, this is described as the process of quality planning in clinical trials, where the focus is on the concept of quality by design including critical factors and risk management. A specific framework is established to help identify these factors during the design and planning of the trial and during the conduct, analysis, and reporting of the trial.

Subsequently, the general principles to be considered in drug development planning are explained. Such planning must be in accorda nce with the principles of scientific research and proper study design, therefore the elements that must be taken into consideration to ensure the reliability of the results, such as the quality of the investigational product are presented and described. The studies are divided into clinical and non-clinical and listed are what these studies cover and what they involve. Because there is a wide range of study designs and data sources to meet the objectives of drug development research, the issue of design elements and data source for clinical trials is covered.

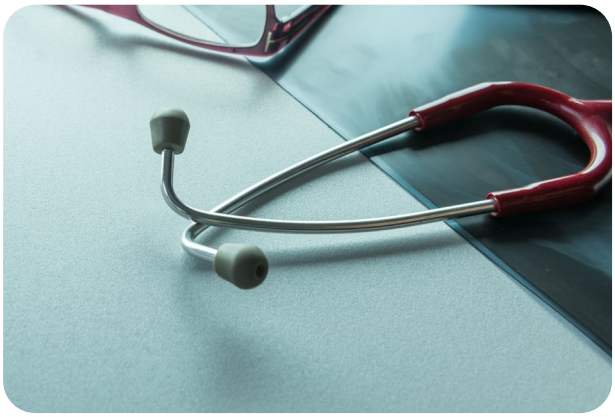
Key elements that can be used to define a study design are discussed, and various data sources that can be used in a study are provided. The topic of conduct, safety monitoring and reporting is also addressed. In terms of the conduct of the study information on protocol adherence, the training, the data management, and the access to periodic data, are also included. Monitoring participant safety during the conduct of the study and reporting of the study is also explained. In the final chapter, emphasis is placed on comments regarding the identification of critical factors for quality. An appendix to this guide is a table showing clinical trials categorized by purpose.

Reflection Paper on the Use of Interactive Response Technologies (Interactive Voice/ Web Response Systems) in Clinical Trials, with Particular Emphasis on the Handling of Expiry Dates

The EMA updated Reflection paper which was initially published on 10 December 2013, under reference EMA/INS/GCP/600788/2011, and reviewed in the context of the Clinical Trials Regulation (CTR) No. 536/2014. The main update refers only to clarify that the removal of expiry dates from the labels is not allowed for clinical trials conducted under the CTR, and the circumstances where the removal of expiry dates could be justified explained in the reflection paper applies only to the clinical trials under the Clinical Trial Directive (2001/20/EC).

The EMA states that: "The rest of the reflection paper was not reviewed and reflects the state of thinking at the time of initial publication."

In addition, the EMA is working on Guideline on computerised systems and electronic data in clinical trials which may be consulted for additional information on the expected requirements for interactive response technologies.



News from Individual Countries

The United Kingdom

Risk-Adapted Approach to Clinical Trials and Risk Assessments

The Guidance about Risk-Adapted Approach to clinical trials and Risk Assessments was published on 28 January 2022. In the beginning of the guidance, the focus is on the risk assessment process. The purposes of conducting a risk assessment are described, as well as the case for conducting a risk assessment when multiple studies are undertaken by a sponsor.

The MHRA scheme using the marketing authorisation status of the investigational medicinal product (IMP) is also explained. Outlined is when and how a risk assessment should be conducted, as well as the benefits of conducting a risk assessment at an early stage.

The people who are expected to be part of the personnel carrying out the risk assessment are listed, and how their presence in the process should be documented is described. The most efficient ways of compiling risk assessment documentation are presented, and the question of where to locate it is discussed. In addition, attention is given to what the GCP Inspectorate will consider when analysing a risk assessment. On the issue of storage and distribution, all recommendations are given, and it is proposed that the responsibility for the implementation and undertaking of the mitigation measures planned in the risk assessment should be assigned to a specific person so that all aspects identified in the risk assessment are then taken into account in the specific examination procedure.

It is outlined when the sponsor should review the risk assessment and when re-verification is needed. The importance of implementing systems to identify new or unexpected risks is also emphasised. A key aspect of the risk assessment process that must be taken into account is the experience and training of the trial site staff in clinical trials/GCP.

Recommendations are provided and ways to carry out training and check the competence of staff are suggested. The process of submitting risk assessments to the MHRA and REC is also detailed, as well as the importance of making such assessments and the benefits that follow. The final part of the guidance is devoted to providing examples of risk assessment documentation that have been reviewed by the Inspectorate and Clinical Trial Unit (CTU).

Oversight and Monitoring Activities

The Guidance of Oversight and monitoring activities was published on 28 January 2022, by Medicines & Healthcare products Regulatory Agency (MHRA). The guidance explains the relevance of monitoring where the sponsor has delegated its functions to others, either within the same organisation or to an external Contract Research Organisation (CRO). The detailed processes established in the monitoring strategy, which is implemented by the delegated parties is outlined. Methods such as monitoring and auditing, and their benefits are also described. Focusing on the monitoring method and described are the key objectives and recommendations, and detailed is what the strategy included in the risk assessment will depend on. On the issue of documentation of the supervision and monitoring strategy, where the necessary supervision/monitoring activities are introduced to mitigate the risks should be documented, and several documents used in many organisations are listed.

The development of templates is also suggested, and elements of documentation worth considering are presented for ease of reference. Furthermore, how documentation is compiled for multi-country studies is also included. The guidance also focuses on the adaptation aspect of the surveillance and monitoring strategy, which affects all areas of the investigation.

It is recommended that the documents comprising the monitoring strategy should be based on the vulnerabilities identified in the risk assessment and at the same time retain additional risk-based flexibility, which is supported by examples.

Examples of the intensity and focus of supervisory and monitoring activities are also illustrated by distinguishing and describing: Type A (where IMPs are used in accordance with normal clinical practice) involving vulnerable subjects or studies in emergency situations; a study in which pharmacokinetic analysis of samples is the main or important objective of the study, and an unlicensed IMP in a study classified as Type C.

The role of oversight committees in monitoring a clinical trial is also described, and these may be set up at national, regional, or global level, depending on the process and remit of the committee. The focus then shifted to site visits, detailing, and describing the investigator site assessment visit, initiating the investigator site visit, and the investigator site closing visit. The process of central monitoring of a clinical trial is described, with examples of documents, additional activities resulting from the process, and the impact of monitoring on site resources.

Explained is the role and purpose of statistical monitoring and examples of such monitoring are provided. The final part of the guidance focuses on actions in case of non-compliance and recommended in verifying source data to increase the reliability of the study results.

Italy

New Decree for Clinical Trials under CTR

On 19 February 2022, the Italian Official Gazette published a new Decree dated 30/11/2021 for clinical trials under Clinical Trials Regulation 536/2014 (CTR). The purpose of the Decree is:

- To facilitate and support the conduct of not-for-profit clinical trials of medicinal products and observational studies; and
- To regulate the transfer of data and results of non-profit trials for registration purposes pursuant to Article 1(1)(c) of the legislative decree 14 May 2019, no. 52.

The Decree also refers to the list of the Ethics Committees which assess clinical trials during the pilot phase according to the CTR, and which are reordered during the full implementation of the CTR.

Czech Republic

Instructions and Forms for Applicants Submitting Clinical Trial under EU CTR

The State Institute of Drug Control (SUKL), the Czech Competent Authority updated the Clinical Trails (CTs) Safety reporting information underlining that SUKL's guidelines KLH-21, "Reporting Adverse Reactions to Medicinal Products for Human Use in a Clinical Trial and to Medicinal Products without Marketing Authorisation," is still valid for clinical trials that goes under the Clinical Trials Directive 2001/20/EC (CTD). The notice confirms that all Suspected Unexpected Serious Adverse Reactions (SUSARs) for CT should be reported directly to Eudravigilance database EVCT-module either under CTD or the CTR. However, for CT under CTD, SUSAR still need to be reported in the form of line listening to the multicentre ethic committee. Moreover, Development Safety Update Reports (DSURs) or report of a domestic fatal case, that is not SUSARs under CTD, should be emailed to SUKL or sent via Common European Submission Portal (CESP). For CT assessed under CTR, the DSUR should be submitted directly to the Clinical Trials Information System (CTIS).

North America

United States of America

FDA Clinical Trial Guidances Share Administration's Goals for Advancing Development of Cancer Treatments

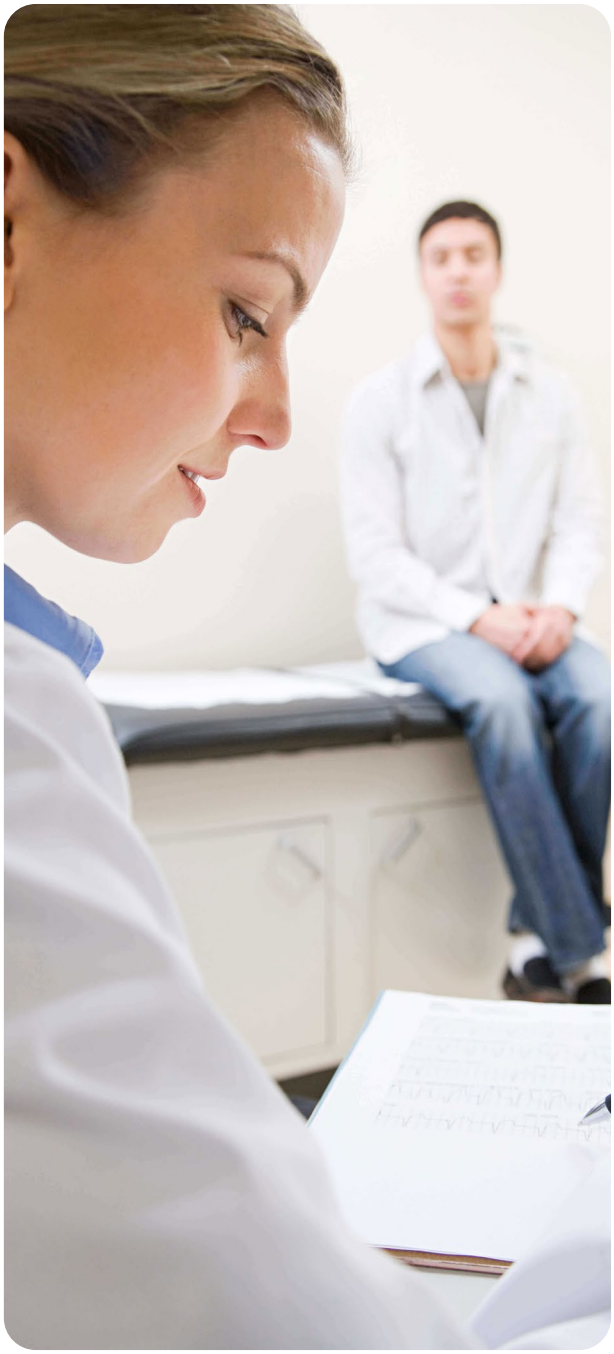
The U.S. Food and Drug Administration issued three final guidances on 1 March 2022 to industry regarding cancer clinical trials that parallel the goals of the current administration's recently announced effort to renew and build upon his 2016 Cancer Moonshot initiative to facilitate continued advancement in cancer prevention, detection, research, and patient care.

"With today's actions the FDA is recommending important principles that involve addressing inequities, targeting the right treatments to the right patients, speeding progress against the most deadly and rare cancers, and learning from the experience of all patients," said Richard Pazdur, M.D., Director for the FDA's Oncology Centre for Excellence.

The first guidance, "Inclusion of Older Adults in Cancer Clinical Trials," provides recommendations to sponsors and institutional review boards for including older adult patients, aged 65 years and older, in the clinical trials of drugs for the treatment of cancer. It recommends enrolling older adults in early phase studies of cancer clinical trials, if appropriate, to obtain information that better informs later phase studies. It also includes recommendations for trial design, recruitment strategies, information collection, and developing and reporting more discrete age groups to encourage enrolment of this historically excluded population.

The second guidance for industry "Expansion Cohorts: Use in First-in-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics," provides advice on designing and conducting trials with multiple expansion cohorts that allow for concurrent accrual of patients into different cohorts to assess safety, pharmacokinetics, and anti-tumour activity of first-in-human cancer drugs. Pharmaceutical companies and researchers can use trials with expansion cohort design to assess many different aspects of a drug in a single clinical trial to efficiently expedite the clinical development of the drug.

Finally, the "Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics" guidance addresses master protocol design including information on what sponsors should submit to the FDA as part of these trial design approaches. It also directs how sponsors should interact with the FDA to facilitate efficient review and mitigate risks to patients. These clinical trials can help expedite the clinical development of a drug to treat cancer because they allow more than one investigational drug or biologic, more than one disease type, or more than one patient population, to be evaluated under a single clinical trial structure.



Canada

Guidance Document: Preparation of Regulatory Activities in non-eCTD Format

On 28 February 2022, Health Canada issued Guidance document: preparation of regulatory activities in non-eCTD format - Canada.ca defining the filing requirements and provides guidance on the structure, content and transmission of regulatory transactions filed in the non-eCTD format.

Health Canada has published requirements for the mandatory filing of specified regulatory activities in eCTD format. Refer to the Filing Submissions Electronically information page for more comprehensive requirements.

Health Canada Changes Time for Keeping Clinical trial Records for Drugs and Natural Health Products

Health Canada announced on 11 February 2022, the release of Notice: Period reduced for keeping clinical trial records for drugs and natural health products - Canada.ca to reduce the period for keeping clinical trial records for drugs and natural health products from **25 years to 15 years**. This change reflects amendments to the *Food and Drug Regulations and Natural Health Products Regulations*. These amendments came into force on 11 February 2022, as part of *the Regulations Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19*.

Previously, clinical trial sponsors had to keep clinical trial records for 25 years. The new shorter period reflects their concerns about the cost and administrative burden the 25-year requirement placed on them. The period for keeping records starts on the date the record is created. To simplify the process, sponsors may choose to "start the clock" for keeping all study records when the trial is completed or terminated.

Health Canada is consulting stakeholders on the start date through consultations for the plan to modernize the regulation of clinical trials. The requirement to keep records for 15 years would apply to sponsors of: 1) clinical trials of all drugs and natural health products with ongoing record retention obligations prior to 11 February 2022; 2) and any new clinical trials authorized on or after 11 February 2022.

Health Canada will be updating the policies, guidance documents and other documents accordingly.

MEDICAL DEVICES

EUROPE

News from the European Commission

Guidance on Appropriate Surveillance Regarding the Transitional Provisions Under Article 120 of the MDR with Regard to Devices Covered by Certificates According to the MDD or the AIMDD

The Medical Device Coordination Group (MDCG) has published "Guidance on appropriate surveillance regarding the transitional provisions under Article 120 of the MDR with regard to devices covered by certificates according to the MDD or the AIMDD."

This document is intended to discuss the application of the transitional provisions with respect to devices covered by certification according to the MDD or the AIMDD. The transitional provisions apply to placing on the market or into service after the MDD start date and no later than 26 May 2024 which derives from Article 120(2) and (3) of the Medical Devices Regulation (EU) 2017/745 (MDR).

The document also aims to provide guidance to be followed by Notified Bodies in their respective surveillance. It describes requirements for certain manufacturers' obligations, in particular relating to their quality management system. This document is mainly intended for Notified Bodies that have legally issued certificates under the MDD or AIMDD, regardless of whether these Notified Bodies have applied for designation or are designated under the MDR.

The requirements for a manufacturer's quality management system and related responsibilities are described in detail and the provisions to be applied until the European Database on Medical Devices (EUDAMED) is fully functional are clarified. General comments on surveillance under Article 120(3) of the MDR are provided, which among other items, obliges Notified Bodies to ascertain their rights and obligations and then ensure that these apply, which should be done on a contractual basis. The contractual relationship has been described in detail.

It is also outlined what elements that should be verified by the Notified Body when reviewing the quality management system documentation. Attention is given to a detailed description of the audit activities, and when the Notified Body should refine the audit plan, and focusing on the elements that have been described in detail. It is also specified how to handle information provided to competent authorities whereby audit activities have revealed significant non-compliances. Possible scenarios for the Notified Body to select when establishing its surveillance procedures are also suggested.

The issue of evaluating the technical documentation based on sampling is not omitted either, outlining the cases whereby Notified Bodies are asked to continue to apply the sampling plan established within the MDD. An appendix to this document is a Comparative Table showing the quality management system requirements for MDD and MD.

Verification of Manufactured Class D IVDs by Notified Bodies

The Medical Devices Coordination Group (MDCG) has published the establishment of requirements for notified bodies involved in the conformity assessment of relevant classes of in vitro diagnostic (IVD) medical devices in accordance with Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR).

Conformity assessment procedures require Notified Bodies to verify batches of Class D IVD devices and manufacturers to provide Notified Bodies with reports of tests carried out on each batch produced and to make samples available to the Notified Body. The Notified Body in turn must contact one of the EU reference laboratories. The purpose of this document is to provide Notified Bodies with guidance clarifying their role and responsibilities regarding samples of manufactured Class D devices or batches of devices in accordance with Annexes IX and XI of the IVDR. Practices for carrying out compliance assessment procedures related to the verification of manufactured Class D IVD devices are presented.

Guidelines on the information to be included in the Notified Body procedures, the content of the required pre-agreed conditions and detailed arrangements, and the frequency of sending samples

of batches of products to the EURL are also described. The document details the guidelines for documenting the Notified Body's procedures, including the verification process, provisions for reaching agreement with the manufacturer and the development of a test plan. It also details the initial and specific arrangements between the notified body and the manufacturer.

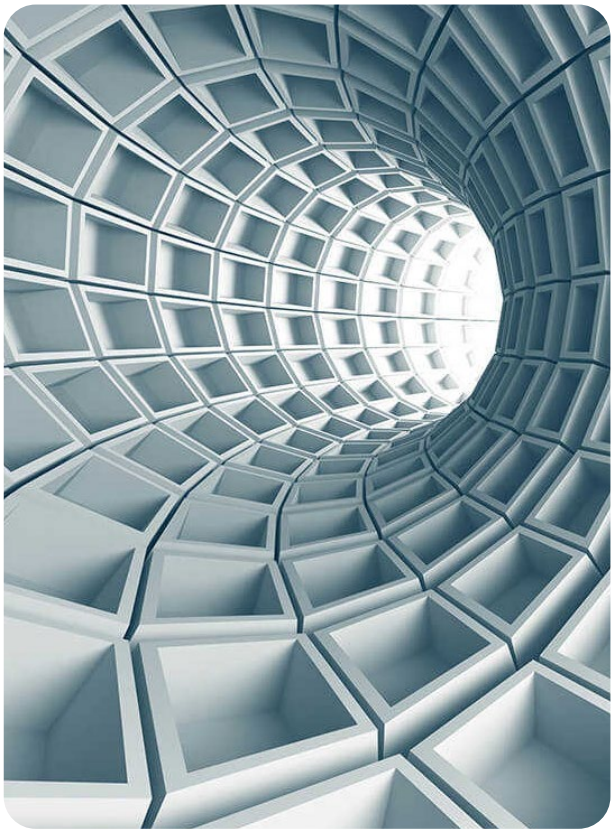
The elements to be included in the written agreement between the Notified Body and the EU reference laboratory are also specified. The procedures for sending samples to the EU Reference Laboratory are described in detail. Defined are the criteria for which products are to be available to the EU Reference Laboratory and at what frequency. A table describing infectious agents and blood groups in descending order of risk was used to determine the risk of product impact depending on the type of intended use.

Also described is how to determine the initial number of samples of Class D manufactured products or batches of products to be sent to the EURL laboratories. The process for re-evaluation of testing frequencies is also outlined, along with a list of items that should be included in the documentation. The possible options for determining the test frequency for each IVD Class D product group are also detailed. The final issue of the guide focuses on the verification of batches of Class D IVD devices by a Notified Body and outlines the minimum aspects that a Notified Body should review.

Guidance on Performance Evaluation of SARS-Cov-2 In Vitro Diagnostic Medical Devices

On 15 February 2022, the Medical Device Coordination Group has published Guidance on performance evaluation of SARS-CoV-2 in vitro diagnostic medical devices, Revision 1. The content of this document is expected to serve as the foundation for the common specifications that will be adopted in the coming months in accordance with Article 9 of Regulation (EU) 2017/746.

In the context of conformity assessment under Directive 98/79/EC or Regulation (EU) 2017/746, this guideline addresses the performance assessment of SARS-CoV-2 in vitro diagnostic (IVD) medical devices. It includes devices for detecting or quantifying SARS-CoV-2 nucleic acid, antigens, and detecting or quantifying SARS-CoV-2 antibodies. According to the document, the performance of the IVD SARS-CoV-2 should be evaluated in direct comparison with the most recent generation device. Devices for comparing and determining sample status are classified and described. Also described is the process for assessing performance and actions in case of discrepant results. In terms of sensitivity and specificity, the method for selecting the positive samples used to assess performance and how to negative samples should be defined is described.



The document also explains how to calculate the specificity. The interference and cross-reactivity are mentioned instructing the manufacturer to select potentially interfering substances to be evaluated, considering the composition of the reagents and the configuration of the device. Attention is also drawn to the importance of batch testing to ensure that any batch that consistently identifies the relevant antigens, epitopes, and antibodies is suitable for the declared sample types, and in terms of self-testing, ensuring that IVD equipment for SARS-CoV-2 self-testing meets the same sensitivity and specificity requirements as relevant equipment for professional use.

As an appendix to this document, there are tables that provide specific considerations for different types of IVD SARS-CoV-2 medical devices.

News from Individual Countries

Austria

Guidance Documents and Forms for Regulation (EU) 2017/745

The Federal Office for Safety in Healthcare has published guideline for the submission of clinical investigations and classification of amendments according to Regulation (EU) 2017/745 (MDR), as well as new notification forms which are mandatory for application.

Guidance documents are only available in German. English version is expected soon. Forms are bilingual.

Belgium

Guideline Submission Processes of Clinical Investigations According to MDR update

The Federal Agency for Medicines and Health Products (FAMHP), has updated its Guideline Submission Processes of Clinical Investigations according to MDR in Belgium. Updated version 7 includes new section number three entitled 'Clinical Investigations under MDR' and clarifies when the clinical investigation falls within the scope of the MDR and when it falls out of scope with the MDR. Moreover, section number seven, regarding clarification concerning safety reporting rules and materiovigilance has been updated. Referring to safety, a new Annex IV has been added, including a decision table for safety reporting.

The United Kingdom

UK to Pilot World-Leading Approach to Improve Ethical Adoption of Artificial Intelligence (AI) in Healthcare

The Department of Health and Social Care has published an article reporting that the United Kingdom will pilot a world-leading approach to improving the ethical adoption of artificial intelligence in healthcare. In response to the article, the NHS in England will launch a world-leading pilot of Algorithmic Impact Assessments (AIAs) in the healthcare system. The Ada Lovelace Institute's AIAs will be piloted to assist researchers and developers in assessing the potential risks and biases of AI systems. AI can help health services and its workforce, but it can also exacerbate existing health inequalities if issues like algorithm bias are not addressed. For the first time, it seeks to eliminate bias in artificial intelligence to eliminate health inequalities.

The NHS AI Lab's ethics team is working to ensure diversity and integration of datasets for training and testing of artificial intelligence systems in order to help create a healthcare system that works for everyone, demonstrating once again that the UK is at the forefront of implementing new technologies. By evaluating the impact of the algorithms, it is hoped that AI systems will be implemented not only in the health sector, but also in the public and private sectors.

The Health Research Authority (HRA) are developing new guidance that will support applicants doing data and AI-driven research.

North America

United States of America

FDA Statement on Medical Device User Fee Amendments (MDUFA)

The FDA and representatives from the medical device industry have reached an agreement as of 22 March 2022 on proposed recommendations for the fifth reauthorization of the medical device user fee program. Under the new agreement, the FDA would be authorized to collect at least $1.78 billion in user fees over five years, plus additional funding, for a total of up to $1.9 billion to further improve performance if specified goals are met. This funding would provide critical resources to the FDA ***medical device review program***. The proposed recommendations have been posted on FDA's website.

FDA would receive new authorities under proposals in legislation introduced alongside the *Medical Device User Fee Amendments* (MDFUA V) reauthorization bill and in its FY2023 budget request. Those authorities include requiring medical device manufacturers to address cybersecurity, fixing a loophole with generic drug patent challenge exclusivity and clarification of the term medical device remanufacturing.

FDA submitted its $8.4 billion budget request to congress which also includes a number of legislative changes that the agency says will help it do its job better. Over the past few years, the agency has developed pre- and post-market device cybersecurity guidances, published papers on cybersecurity best practices, and coordinated with the Department of Homeland Security and industry to address a growing number of threats and vulnerabilities.

This proposal would advance medical device safety by explicitly requiring that medical device manufacturers design cybersecurity into their devices and by ensuring that FDA and the public have certain information about device cybersecurity.

Specifically, "FDA seeks to have express authority to require: that premarket submissions to FDA include evidence demonstrating reasonable assurance of the device's safety and effectiveness for purposes of cybersecurity; that marketed devices demonstrate a reasonable assurance of the device's safety and effectiveness for purposes of cybersecurity; that devices have the capability to be updated and patched in a timely manner; that manufacturers provide a device Software Bill of Materials (SBOM) with their devices so users know which components of their devices are or may be subject to cyber threats; and that device manufacturers publicly disclose when they learn of a cybersecurity vulnerability so users know when a device may be vulnerable, and to provide direction to users to reduce their risk."

Another issue is the need for FDA to have regulatory flexibility especially when it comes to digital health products and artificial intelligence/ machine learning software on medical devices which require constant updating. Ironically, AI/ ML, FDA has already allowed 300 such products on the market including 50 in the past year alone.

Canada

Clinical Trials for Medical Devices and Drugs Relating to COVID-19 Regulations

The Clinical Trials for Medical Devices and Drugs Relating to COVID-19 Regulations (Regulations) were published on 2 March 2022. They came into effect on 27 February 2022, following the repeal of Interim Order No. 2 respecting clinical trials for medical devices and drugs relating to COVID-19 (IO No. 2). IO No. 2 was made on 3 May 2021.

The flexibilities under IO No. 2 will continue under the Regulations. This will ensure two things: 1) sponsors may continue conducting clinical trials authorized under the interim order; and 2) all authorizations, suspensions, and exemptions for clinical trials issued under the interim order will remain in effect.

The provisions of IO No. 2 are set to expire on 3 May 2022. They will be replaced by the Regulations, which came into force on 27 February 2022. The Regulations maintain the flexibilities set out by the interim order until the framework established through the Clinical Trials Modernization Initiative is in place.

Under the Regulations, all clinical trials applications (and amendments) for COVID-19-related drugs and medical devices will continue to be reviewed within 14 days. Research ethics boards are also prioritizing reviews and approvals for COVID-19 clinical trials.

OTHER "HOT" TOPICS IN EUROPE

Guidance on Data Subject Rights Adapted for Public Consultation

The European Data Protection Board (EDPB), established by the European Commission, among others, is responsible for issuing guidelines, recommendations, and best practices according to the rules of the General Data Protection Regulation (GDPR). The EDPB issued "Guidelines 01/2022 on data subject rights - Right of access", version 1.0 dated 18 January 2022 for public consultation. Such comments should have been sent by 11 March 2022 at the latest.

The EDPB says: "The right of access of data subjects is enshrined in Arti. 8 of the EU Charter of Fundamental Rights. It has been a part of the European data protection legal framework since its beginning and is now further developed by more specified and precise rules in Art. 15."

The guidance aims to provide an overall structure of the right of access for subjects, general considerations on the assessment of the data subject's request and scope of the right of access. Also, it is described how to provide access to the data subject and the controller role, what are the limits and restrictions allowed by the GDPR. The guidance is accompanied by an Annex presenting a flowchart explaining how to interpret and assess the request concerning personal data.

Guidelines on the Interplay Between the Application of Article 3 and the Provisions on International Transfers as per Chapter V of the GDPR Adapted for Public Consultation

The EDPB set up a deadline for public comments until 31 January 2022 for the guidance on transfer of personal data which are undergoing processing or are intended for processing after transfer to a third country or to an international organisation. The purpose of this guidance is to clarify interplay between Article 3(2) of GDPR and Chapter V whose aim is to ensure the continued protection of personal data after they have been transferred to a third country or to an international organisation. The guidance defines who is a controller or processor ("exporter"), joint controller or processor ("importer"). Furthermore, the guidance provides many examples when the European Union (EU)/ European Economic Area (EEA) information is shared with third countries. Also, are there different types of transfer tools which may be used in transferring data to third countries, and what are the consequences of not following Chapter V of the GDPR.

Guidelines on Codes of Conduct as Tools for Transfers of Personal Data to Third Countries or International Organisations Adapted

After public consultations, on 22 February 2022, the EDPB finalised the guidance providing clarification as to the role of the different actors involved for the setting of a code to be used as a tool for transfers of personal data to third countries or international organisations. The guidance also includes annexes presenting flow charts of adoption of a transnational code intended for transfers and amendments to a transnational code to be used as a code intended for transfers.

OTHER "HOT" TOPICS FROM THE UNITED STATES

FDA Releases Draft Guidances on Human Gene Therapy Products

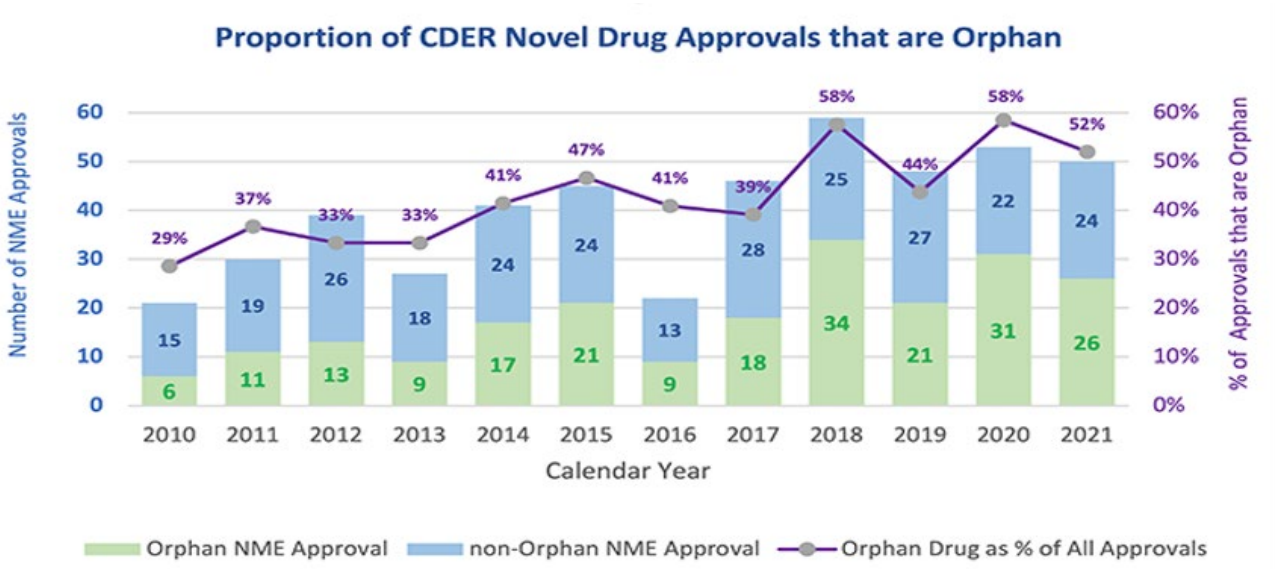
FDA announced on 15 March 2022, the availability of two draft guidance documents: "Human Gene Therapy Products Incorporating Human Genome Editing," and "Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products." The draft guidance, "Human Gene Therapy Products Incorporating Human Genome Editing," is intended to provide recommendations to sponsors developing human gene therapy products incorporating genome editing (GE) of human somatic cells. The draft guidance provides recommendations regarding information that should be provided in Investigational New Drug (IND) applications for GE products, including information on product design, product manufacturing, product testing, preclinical safety assessment, and clinical trial design. Human GE is a rapidly evolving field, and this guidance encompasses FDA's current thinking regarding the development of human GE products for clinical studies and licensure.

The draft guidance, "Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products," is intended to assist sponsors developing human gene therapy products in which the T cell specificity is genetically modified to enable recognition of a desired target antigen for therapeutic purposes. The guidance provides CAR T cell-specific recommendations regarding chemistry, manufacturing, and control (CMC), pharmacology and toxicology, and clinical study design.

FDA Publishes FDA Voices on Rare Diseases

On 4 March 2022, the FDA published the FDA Voices: "CDER Continues to Make Rare Diseases a Priority with Drug Approvals and Programming to Speed Therapeutic Development," by-lined by Patrizia Cavazzoni, M.D., director of the FDA's Centre for Drug Evaluation and Research (CDER). Over the past decade or so, FDA has seen an upward trajectory in the percentage of drugs approved to treat rare or "orphan" diseases.

In the first two months of 2022, CDER approved four new drugs for people with rare diseases in the areas of oncology and haematology. Last year, 26 of CDER's 50 novel drug approvals, more than half, were for orphan diseases.



A rare disease is any disease that affects less than 200,000 people in the U.S. Drug development for the approximately 7,000 rare diseases can be complex for many reasons. Challenges exist with using well-established trial designs. Selecting endpoints (outcome measures) can be difficult if there is a limited understanding of the natural history of the disease.

Because of the small patient populations, there may not be enough people available to participate in rare disease clinical trials. For these and other reasons, many of these diseases have few or no available treatments.

About CROMSOURCE

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

A well-established full service CRO, **CROMSOURCE** is unique in offering an end-to-end guarantee covering trial timelines, enrolment and contract price. This guarantees our clients that their trials are delivered on time and within the contract price with no CRO-initiated change orders. **CROMSOURCE** operates through offices across all regions of Europe and North America and delivers a comprehensive breadth of services.

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

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

Global Reach

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

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3. We will finish on time with a set date for database lock
4. The price you contracted is the price you pay. There will be no CRO-initiated changes-in-scope.

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