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REGULATORY

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July - September 2020

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EU-U.S. Privacy Shield No Longer Valid Since 16 July 2020

On 16 July 2020, the Court of Justice of the European Union (CJEU) issued a judgment invalidates the European Commission's Decision (EU) 2016/1250 of 12 July 2016 on the adequacy of the protection provided by the EU-U.S. Privacy Shield. The EU-U.S. Privacy Shield should guarantee that the level of protection granted to personal data in the U.S. is essentially equivalent to that guaranteed within the EU. Due to the CJEU decision from 16 July 2020, the EU-U.S. Privacy Shield Framework is no longer a valid mechanism to comply with EU data protection requirements when transferring personal data from the European Union to the United States.

On 10 August 2020, the U.S. Secretary of Commerce, Wilbur Ross and European Commissioner for Justice, Didier Reynders issued a Joint Press Statement noting that "The U.S. Department of Commerce and the European Commission have initiated discussions to evaluate the potential for an enhanced EU-U.S. Privacy Shield framework to comply with the July 16 judgment of the Court of Justice of the European Union in the Schrems II case."

Regulation on Clinical Trials with and Supply of Medicinal Products Containing or Consisting of Genetically Modified Organisms (GMOs) Intended to Treat or Prevent COVID-19 Infection

On 15 July 2020, the European Commission has adopted the Regulation (EU) 2020/1043 on the conduct of clinical trials with and supply of medicinal products for human use containing or consisting of genetically modified organisms (GMOs) intended to treat or prevent coronavirus disease (COVID-19). This Regulation is to ensure that clinical trials with investigational medicinal products (IMPs) containing or consisting of GMOs intended to treat or prevent COVID-19 infection can start without delay to support the rapid availability of COVID-19 vaccines and treatments in case of emergency is ensured.

The Regulation shall apply as long as the World Health Organisation (WHO) has declared COVID-19 to be a pandemic or as long as an implementing act by which the Commission recognises a situation of public health emergency due to COVID-19.

EU Strategy for COVID-19 Vaccines

In June 2020, the European Commission has issued a communication on the EU Strategy for COVID-19 vaccines.

The strategy has the following objectives:

- Ensuring the quality, safety and efficacy of vaccines.
- Securing timely access to vaccines for Member States and their population while leading the global solidarity effort.
- Ensuring equitable access for all in the EU to an affordable vaccine as early as possible.

News from the European Medicines Agency (EMA)

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

First Rolling Review of a COVID-19 Vaccine in the EU by EMA

On 01 October 2020, the EMA announced that its Committee for Medicinal Products for Human Use (CHMP) has started the first 'rolling review' of a COVID-19 vaccine, which is being developed by the company AstraZeneca in collaboration with the University of Oxford. A rolling review is one of the regulatory tools that EMA uses to speed up the assessment of a promising medicine or vaccine during a public health emergency. The CHMP has started evaluating the first batch of data on the vaccine, non-clinical data which comes from laboratory studies. The CHMP's rolling review will continue until enough evidence of the vaccine's safety and effectiveness is available to support a formal marketing authorisation application.

The AstraZeneca/University of Oxford vaccine candidate is based on an engineered chimpanzee adenovirus vector platform that has previously been studied for several other infectious diseases.

European Union Clinical Trials Regulation-Update

The EMA announced on its website, that the audit of the Clinical Trials Information System (CTIS) will commence in November 2020.

The application of Regulation (EU) No. 536/2014 (EU Clinical Trial Regulation) (EU CTR) is conditional on the conduct of an independent audit to verify that the EU portal and EU database, that form the major parts of CTIS, have achieved full functionality and meet the functional specifications. During the last EMA Management Board in June, the Board proposed to fix the go-live date of CTIS to December 2021.

The CTIS go-live date is the end of the six months after the European Commission publishes its notice in the Official Journal. It means that EU CTR will be fully applicable in December 2021, if no unexpected delays occur.

Following the progress of CTIS, the EMA has released its first CTIS newsletter CTIS Highlights, dated June 2020, which will be published twice a year. The newsletter gives updates on the development of the CTIS and insight into its functionalities.

In addition, the European Commission has released version 2.4 of the Clinical Trials Regulation (EU) No 536/2014 Questions & Answers, dated July 2020.

Preparedness of Medicines' Clinical Trials in Paediatrics

The European Network of Paediatric Research at the EMA (Enpr-EMA) has set out recommendations about clinical trial preparedness in paediatrics by releasing a document Preparedness of medicines' clinical trials in paediatrics. To identify potential gaps and presenting a more comprehensive view of the situation of clinical trials for children, the document was previously publicly consulted. The document lists the principles of good preparation of paediatrics clinical trials and instructs how to collect relevant information, how best to collaborate with Health Authorities and how to interact with pharmaceutical companies to facilitate studies that increase the availability of medicines for children.

Guideline on Registry-Based Studies

The European Medicines Agency (EMA) has published its draft Guideline on registry-based studies for a public consultation. The deadline for comments is 31 December 2020.

Registry-based study is an investigation of a research question or hypothesis using data from new or existing registry(ies) for patient recruitment and data collection. A registry-based study may be a clinical trial or a non-interventional trial/study. In addition, the studies derived from patient registries can also provide information that is critical to understanding the benefits and risks of medicines in everyday use, by patients and healthcare professionals. The guideline addresses methodological, legal and operational aspects in the use of registry-based studies to support regulatory decision-making.

Remote GCP Inspection by the EMA

The EMA, has published guidance for inspectors on how to initiate and conduct remote inspections to verify compliance with Good Clinical Practice (GCP) standards during the COVID-19 pandemic.

The guidance covers all phases of remote GCP inspections, with a particular focus on the more challenging aspects, such as inspection initiation, feasibility assessment and preparation.

News from Individual Countries

Switzerland

Update for the Swiss National Clinical Trials Portal (SNCTP)

The Swiss portal for clinical trials (SNCTP) including all approved clinical trials in Switzerland has been further enhanced and supplemented with new functions. The update covers, among others, new filter options for children, adolescents and healthy persons, references to additional study information in the national language and displays the ethics committee that has approved the clinical trial, as well as the date of approval. Observational studies are excluded from the SNCTP.

The Netherlands

New Model of Subject Information for Adults

The Central Committee for Research Involving Human Subjects (CCMO) published new model of subject information for subjects 16 years and older (adults). The model has been rewritten to make the information easier to read and understand for patients. The CCMO strongly advises to use the model as soon as possible but they are requested to do so, in any case, when submitting new research files from 01 November 2020.

Statement on Subject Insurance Abolished Immediately

The CCMO has informed that from 03 September 2020, the statement on subject insurance, so far submitted with a clinical trial file to the review committee, will no longer be required. The CCMO confirmed that the certificates of insurance usually provide sufficient information for reviewers and will be enough for submission and issuing approval. This decision takes effect on 3 September 2020 and applies to newly submitted clinical trials applications.

The CCMO Changes of the Research Meetings

The CCMO informed that starting from October 2020, the research committee meetings for clinical trials with drugs, will be organised twice a month instead of once. In addition, an applicant will no longer receive deadlines for submitting documents. The documents may be submitted any time and an applicant will be notified by the research committee when the submission file will be discussed. Meeting dates.

Italy

Guidelines of the Informed Consent and New Models of Patient Information

The Italian Medicines Agency (AIFA) released the guidelines for the collection of the informed consent necessary for participation in clinical trials. The guidelines provide the instructions how to give a potential participant adequate information about the study and procedures. The document underlines that informed consent must be a process that begins with the first contact with the potential participant and continues throughout the study, until its end. The guidelines present a detailed description of the informed consent process, giving the Investigators, the ethics committees and stakeholders the principles and norms to be followed. The guidelines also address the instructions for conducting clinical trials in specific areas and within vulnerable populations.

In addition, the AIFA published new models of Patient Information Sheet and Informed Consent for adults (18 years old and above), adolescents patients (12-17 years old), minor patients (6-11 year old) and for parental/legal guardians.

National Contract Template Modification

The National Coordination Centre of the Territorial Ethical Committees for clinical trials on medicinal products for human use and on medical devices established by AIFA, the Italian Medicines Agency, modified the previous national contract template from 30 October 2019. The new contract template is highly recommended for contract negotiation with Italian sites in clinical trials with investigation medicinal products (IMPs).

France

Release of Decision No. 2020-077

The CNIL (Commission Nationale de l'Informatique et des Libertés), the French Agency for protecting personal data has informed about the release of Decision n ° 2020-077 of June 18, 2020 adopting a framework relating to the retention periods of personal data processed for the purposes of research, study or evaluation in the field of health. with investigation medicinal products (IMPs).

North America

United States of America

Prescription Drug User Fee Rates for Fiscal Year 2021

The Prescription Drug User Fee Act (PDUFA) was created by Congress in 1992 and authorizes FDA to collect fees from companies that produce certain human drug and biological products. Since the passage of PDUFA, user fees have played an important role in expediting the drug approval process.

The FDA has unveiled its user fees for prescription drug applications for fiscal year 2021 – slightly trimming some fees that increased by double digits for fiscal 2020. FDA has published the user fee amounts it will collect in FY2021 from manufacturers of pharmaceuticals, generic drugs, biosimilars, medical devices and outsourcing facilities.

ANDA (Abbreviated New Drug) submission rate increases, while the NDA (New Drug Application) and BLA (Biologics License Application) fee drops and the biosimilar fee is unchanged. A drug designated under section 360bb of this title for a rare disease or condition and approved under section 355 of this title or under section 262 of title 42 shall be exempt from prescription drug program fees under this section, if the drug meets all of the necessary conditions however.

For more information regarding the FY 2021 fee rates, access the FR notice available at: Prescription Drug User Fee Rates for Fiscal Year 2021.

FDA Finalizes Guidance on Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank

On 14 August 2020, the Food and Drug Administration issued final guidance, "Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank,"which outlines how the FDA intends to identify whether responsible parties have failed to submit required clinical trial registration and/or results information to the ClinicalTrials.gov data bank for applicable clinical trials involving FDA-regulated drug, biological, and device products; if they have submitted false or misleading information to the data bank; or if they have failed to submit or knowingly submitted a false certification to the FDA.

The guidance also describes the circumstances under which the FDA may decide to seek civil money penalties for noncompliance, the applicable procedures for assessing civil money penalties, and the civil money penalty amounts that may be assessed for violations related to the ClinicalTrials.gov requirements.

Canada

COVID-19 Guidance

On 13 August 2020, Health Canada issued a Ministerial Order that temporarily extended the default period to review non-COVID-19 clinical trial applications and amendments by from 30 days to 45 days. More information is available in a Notice issued on 14 August 2020.

On 5 August 2020, Health Canada updated Management of clinical trials during the COVID-19 pandemic: Notice to clinical trial sponsors, which provides guidance related to protocol deviation, participant safety, site monitoring, participant eligibility, pausing a study, and shipment of investigational products directly to patients. The guidance now notes the following:

- Until further notice, sponsors do not need to file clinical trial site forms for non-COVID trials
- Until further notice, sponsors do not need to submit notifications for non-safety-related changes for non-COVID trials

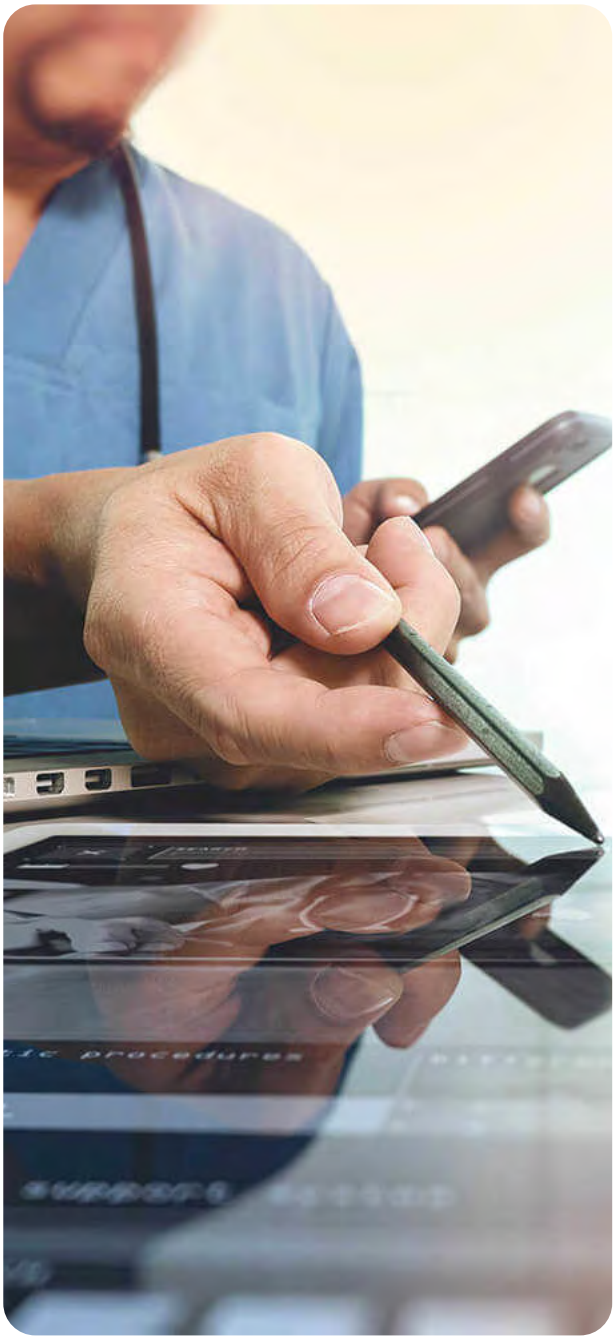
Canada Profile Update

The Canada profile was updated on 20 August 20 2020 to include the following information:

- Updates to Health Canada contact information (See Regulatory Authority)
- New information on the Research Ethics Board Attestation (See Scope of Review)
- Revised versions of the Clinical Trial Site Information (CTSI) form, CTSI Instructions, and the Clinical Trial Application/Attestation (See Submission Process and Submission Content)

The Canada profile in ClinRegs now includes the following updates:

- Updates to Health Canada contact information (See Regulatory Authority)
- New information on the Research Ethics Board Attestation (See Scope of Review)
- Revised versions of the Clinical Trial Site Information (CTSI) form, CTSI Instructions, and the Clinical Trial Application/Attestation (See Submission Process and Submission Content)
- New guidance on implementation of eCTD for clinical trial regulatory activities (See Submission Process)
- Updated informed consent guidance (See Documentation Requirements, Required Elements, and Consent for Specimen)



MEDICAL DEVICES

EUROPE

News from the European Commission

Commission Guidance Document on Conformity Assessment Procedures for Protective Equipment

On 10 July 2020, the European Commission provided a guidance document addressed to prospective manufacturers of protective equipment such as: face masks, gloves, coveralls, etc. The document is written in a Questions and Answers format and will be updated on a regular basis in order to address any additional questions or concerns expressed by the economic operators in the context of COVID-19. The document informs on mandatory standards the manufacturer should follow to produce protective equipment and provides recommendations referring also to World Health Organisation (WHO) guidelines.

News from Individual Countries

United Kingdom

Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol

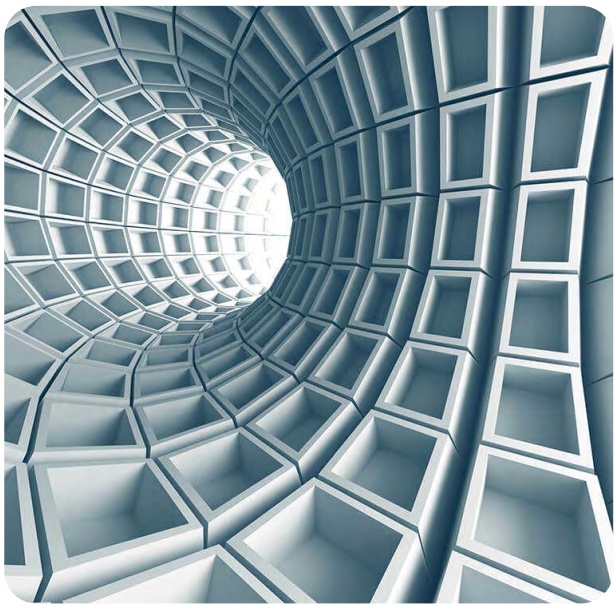
On 08 July 2020, the UK Medicines and Health products Regulatory Agency (MHRA) released version 6 of Guidance for the Notification of Serious Breaches of GCP or the Trial Protocol.

The guidance provides the practical arrangements for notification. It is underline that Sponsor, CRO or other parties delegated by the Sponsor, should notify of any "serious breach" to the MHRA first and within seven days of becoming aware of the breach. The guidance clearly states that sponsor does not have to wait to submit the notification until they have all the information, because a follow-up report is acceptable for the MHRA Inspectorate and can be provided simultaneously. The Sponsor may also initially contact the MHRA Inspectorate by telephone to discuss the "serious breach" and follow up with a written notification within seven days. The guidance provides an email contact to whom "serious breach" should be sent and links to the required forms to be completed. In addition, the guidance provides advice on what should and what should not be classified as a "serious breach" and what must be reported. The document also outlines possible actions that may be taken by the MHRA in response to notifications of serious breaches.

The Netherlands

CCMO as the Competent Authority for Clinical Investigations with Medical Devices

Starting from 01 October 2020, the Central Committee for Research Involving Human Subjects (CCMO) has become the competent authority for clinical investigations with medical devices. This means that a separate notification to the Health and Youth Care Inspectorate (IGJ) will be no longer required. All remaining notification procedures stay the same for the IGJ notification. The only change of notification process is that the CCMO has created new email address devices@ccmo.nl and all notifications of clinical investigation, reporting serious adverse events (SAEs), report suspension, (premature) end of study and questions on clinical investigations with medical devices, should be sent to this email. In addition, clinical investigations notified to the IGJ before 01 October 2020 should also report serious adverse events (SAEs) and (premature) end of investigation to the CCMO.



Other Initiatives

New ISO 14155:2020-GCP

In July 2020, a new ISO 14155:2020 Clinical investigation of medical devices for human subjects-Good Clinical Practice (GCP) has been published replacing the second edition (ISO 14155:2011). The ISO 14155:2020 IS the third edition of standards addresses good clinical practice for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the clinical performance or effectiveness and safety of medical devices. It provides guidance to manufacturers and clinical research professionals for how to implement GCP for early feasibility studies, pre-market clinical investigations, post-market studies and registries. ISO 14155:2020 does not apply to in vitro diagnostic medical devices, however, dependent on the device and national or regional requirements, it might be considered.

The main changes to the previous edition are as follows:

- Inclusion of a summary section of GCP principles (Clause 4)
- Reference to registration of the clinical investigation in a publicly accessible database (Clause 5.4)
- Inclusion of clinical quality management (Clause 9.1)
- Inclusion of risk-based monitoring (Clause 6.7)
- Inclusion of statistical considerations in Annex A
- Inclusion of guidance for ethics committees in Annex G
- Reinforcement of risk management throughout the process of a clinical investigation (planning to consideration of results) including Annex H
- Clarification of applicability of the requirements of this document to the different clinical development stages (Annex I)
- Inclusion of guidance on clinical investigation audits (Annex J).

"ISO 14155 has also been aligned with changes to other standards in the sector as well as regulations such as the European Medical Devices Regulation, the European Commission Guidelines on Good Clinical Practice and other similar guidance from the US Food and Drug Administration." said Danielle Giroud, Convenor of the ISO working group of experts.

The ISO 14155:2020 standard is valid from the moment of publication, 30 July 2020.

North America

United States of America

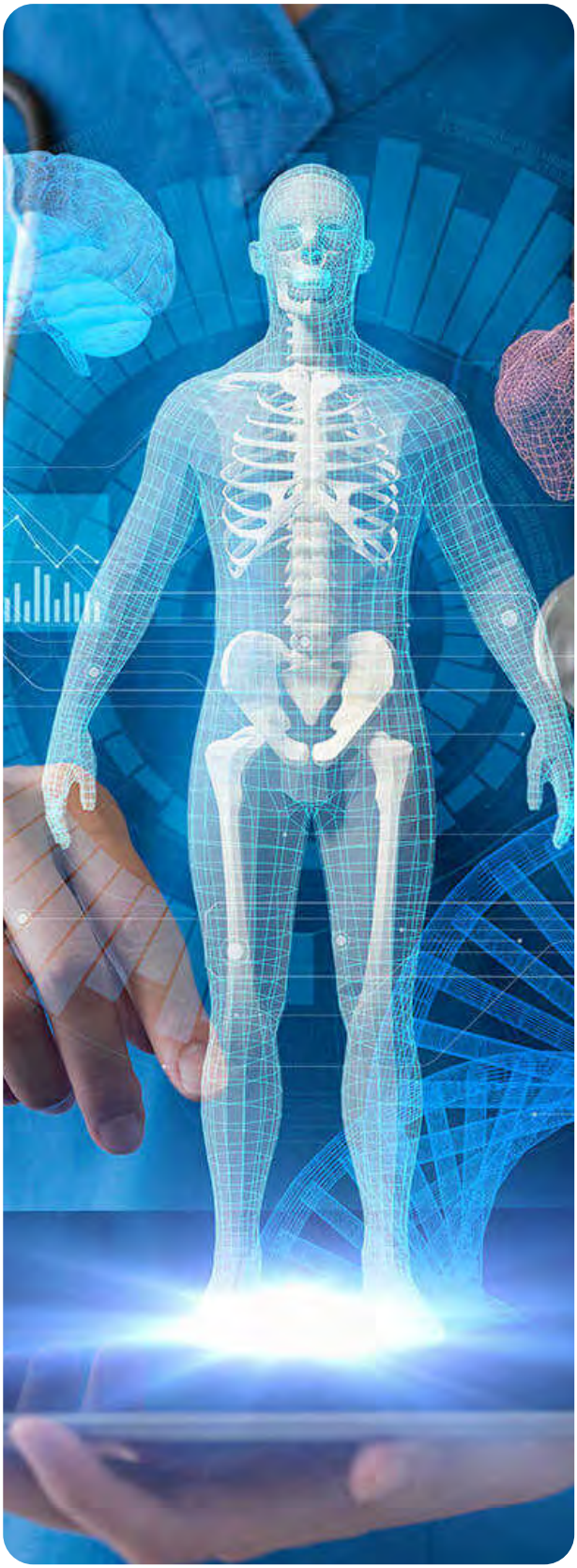
Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency

On 19 August 2020, FDA announced the availability of a temporary guidance for industry entitled, "Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers."

FDA issued the guidance to address frequently asked questions from industry regarding the impacts of the COVID-19 public health emergency on drug development programs, ongoing manufacturing operations and FDA's ability to conduct inspections. The guidance provides information related to inspections for facilities manufacturing pharmaceutical products and sites involved in the conduct of clinical, analytical and nonclinical studies.

This guidance confirms that FDA has resumed prioritized domestic inspections, which generally include pre-approval and surveillance inspections, and that it is conducting certain other "mission-critical" domestic inspections on a case-by-case basis. FDA also states that foreign pre-approval and for-cause inspection assignments that are not deemed mission-critical remain temporarily postponed, although those deemed mission-critical will still be evaluated on a case-by-case basis.

Both for-cause and pre-approval inspections may be deemed mission-critical, and FDA also considers issues such as the safety of investigators, site personnel, and trial participants and other patients at clinical study sites.



OTHER "HOT" TOPICS IN EUROPE

Medical Device Regulation (MDR): Latest Status

The application of the Medical Device Regulation (MDR) has been postponed until 26 May 2021. In July 2020, the European Commission published its Joint implementation plan on actions considered necessary to ensure the sound functioning of the new framework for medical devices under the MDR.

Fact Sheet on MDR Requirements for Transparency and Public Information

In July 2020, the European Commission published a Fact Sheet on MDR requirements that will be available to the public once the European database on medical devices (Eudamed) is fully functional in May 2022. The information accessible to the public in Eudamed will cover:

- The registration of all manufacturers, their authorised representatives and importers
- Registration of devices, the core elements of the UDI database
- Registration of certificates of conformity, their scope and validity period
- List of notified bodies designated under the MDR
- Scientific opinions of the expert panels and the written justification of the notified body where it has not followed the scientific opinion of the expert panel
- Clinical investigation reports and their summary
- The summary of safety and clinical performance reports for implantable devices and class III devices, manufacturer incident reports (partial access) and the field safety notices for Vigilance activities
- Summary of the results of market surveillance activities on their national territory by each EU Member State

Medical Device Coordination Group (MDCG) New Guidance or Revisions of Guidance and Templates Documents to Medical Device Manufacturers Assess in Implementing the MDR

- MDCG 2020-2 rev. 1 Class I Transitional provisions under Article 120 (3 and 4) – (MDR): July 2020
- MDCG 2019-15 rev.1 Guidance Notes for Manufacturers of Class I Medical Devices: July 2020
- MDCG 2019-10 rev. 1_Application of transitional provisions concerning validity of certificates issued in accordance to Directives 90/385/EEC and 93/42/EEC: July 2020
- MDCG 2019-16 rev.1 - Guidance on Cybersecurity for medical devices: July 2020
- MDCG 2020-13 Clinical evaluation assessment report template: July 2020
- Declaration of interest (DOI) form - Call for expression of interest for expert panels on medical devices and in vitro diagnostic medical devices (2019/C 323/05)

Eudamed Actor Registration Module and Single Registration Number Issue

On 30 October 2019, the European Commission published a notice by which it concluded that the full functionally of EUDAMED is foreseen for May 2022. However, in March 2020 the European Commission agreed to make available to Member States each EUDAMED module: actor registration module. The actor registration module shall allow the competent authority of a Member State to obtain a unique single registration number (SRN) and approve the issuing of it to the requesting manufacturer, authorised representative or importer. The Commission has confirmed its readiness to deploy the actor registration module as of 01 December 2020 and published Position Paper on the use of the EUDAMED actor registration module and of the Single Registration Number (SRN) in the Member States.

Guidance to Notified Bodies on How to Manage the MDR Audit Reports

The Medical Device Coordination Group (MDCG) published guidance to notified bodies on how to take into account the Medical Device Regulatory Audit Reports (MDSAP) issued by MDSAP auditing organisations e.g. an independent organisation or a Regulatory Authority which perform regulatory audits, when performing surveillance audits under EU Medical Devices Regulation (MDR) and EU In Vitro Diagnostic medical devices Regulation (IVDR). The guidance instructs notified bodies when and how to take MDSAP audit reports into account, explains of relevant information in each section of report and provides examples on how correlations between MDR requirements to sections of MDSAP audit reports may be established related to clinical evaluation, supplier controls and post-market surveillance.

Notified Body Group Team-NB Position Statement

The European notified body group Team-NB has published a position statement on the requirements for the EU MDR/IVDR Notified Body Partners under the Technical Cooperation Program (TCP) on exchange of Medical Device Quality Management System Regulation and ISO 13485 Audit Reports. Technical Cooperation Program is called TCP III and allows for the exchange of medical device QMS regulatory audit reports between EU notified bodies designated according MDR and/or IVDR and the Taiwan Food and Drug Administration (TFDA) authorised medical device QMS auditing organisations. The exchange of reports is through manufacturers only.

Key Brexit Updates

The UK has left the EU and the transition period after Brexit finishes at the end of 2020. The ninth round of EU-UK trade talks were taking place from 29 September to 02 October 2020 in Brussels. The fifth round of negotiations will take place in mid to late October 2020 between the UK and US.

Following the negotiations between EU and UK, the European Commission's (EC) website published documents, guidance and other press releases, informing on what has already been agreed and what is currently being negotiated and prepared.

MHRA Post Transition Period Guidance

The Medicines and Healthcare products Regulatory Agency (MHRA) has published post-transition period guidance for industry and organisations to follow from 01 January 2021.

CLINICAL TRIALS

Registration of clinical trials for investigational medicinal products (IMPs) and publication of summary results

The MHRA informs that from 01 January 2021, sponsors should continue using established international registers such as ISRCTN registry (UK), ClinicalTrials.gov (USA). For trials involving both UK and EU sites record in the EU Clinical Trials Register will also exist (other than adult Phase 1 studies). Sponsors are also instructed to publish summaries of trial results within six months for paediatric studies and within one year for adult trials, where they have registered clinical trials. There is no need to submit the clinical trial summary report to the MHRA, however, the sponsor or delegate, must send a short confirmatory email to CT.Submission@mhra.gov.uk once the result and related information has been uploaded to the public register and provide a link. In addition, it will be required to submit a final report to the Health Research Authority (HRA) within the same timeframe for reporting the summary of results.

Guidance on substantial amendments to a clinical trial

Sponsor/ Legal Representative (LR)			
European Union/European Economic Area (EU/ EEA)		**The United Kingdom (UK) [MHRA- UK Medicines and Health products Regulatory Agency]**	
LR required to be established in the EU/ EEA if the sponsor is from UK or from the rest of the world.	Substantial Amendment (SA) required to the relevant EU/EEA competent authorities	Established LR in the EU/EEA for an ongoing trial still accepted by MHRA.	No amendment submission to MHRA
		Established LR in the EU/EEA for an ongoing trial still accepted by MHRA.	No amendment submission to MHRA
		If a sponsor remains in the UK and a LR is added to cover EU/ EEA sites.	No amendment submission to MHRA

The guidance also explains when there are changes related to the certification and importation of IMP:

- If the sponsor would like to add or replace any IMP manufacturing, importation or certification site relevant for supply of IMP to an ongoing UK trial, the substantial amendment will need to be submitted to the MHRA.
- If the sponsor chooses to retain an existing UK IMP release site for the ongoing UK trial but includes an additional EU/EEA release site for trials in the EU/EEA only, then no substantial amendment to MHRA will be required.

For up to one year after 01 January 2021, IMP may be supplied direct from the EU/EEA Manufacturing and Import Authorisation MIA(IMP) holder to the ongoing UK trial site without the UK MIA (IMP) oversight process.

IMPORTING AND EXPORTING

Importing investigational medicinal products into Great Britain from approved countries from 01 January 2021

Sponsors of UK clinical trials that import investigational medicinal products (IMPs) into Great Britain from outside the UK will need to review their existing supply chains.

Where the product is sourced from a country on the 'approved country for import list', this will include a UK Manufacturing and Import Authorisation (MIA(IMP)) holder putting in place an assurance system to check these IMPs have been certified by a Qualified Person (QP) in a listed country, before release to trial sites.

IMPs imported into Great Britain from outside the UK that have been QP certified in a listed country (initially include all EU and EEA countries) will not require recertification in Great Britain.

There will be a one-year transition period from 01 January 2021 to implement UK MIA (IMP) oversight process.

NEW IT SYSTEMS FOR SUBMISSIONS

Registering to make submissions to the MHRA from 01 January 2021

From 01 January 2021 all pharmaceutical companies involved in making medicines regulatory submissions and vigilance activities, all medicines clinical trial sponsors wishing to make clinical trial submissions (Initial Applications, Substantial Amendments, End of Trial Notifications and Developmental Safety Update Reports (DSURs) to the Agency, e-cigarette producers and brokers of medicinal products will need to gain access to MHRA Submissions portal.

All current Eudravigilance Gateway users who wish to gain access to the new MHRA Gateway will need to firstly gain access to MHRA Submissions. The steps for gaining MHRA Gateway access are contained within MHRA Submissions.

As of 01 January 2021, all above submissions will be not possible via CESP (Common European Submission Portal).

PHARMACOVIGILANCE

Guidance on pharmacovigilance procedures from 01 January 2021

From 01 January 2021, for medicines authorised in Great Britain, the Marketing Authorisation Holder (MAH) will be required to submit pharmacovigilance data to the MHRA, according to GB requirements, including:

- UK and non-UK Individual Case Safety Reports (ICSRs)
- Periodic Safety Update Reports (PSURs)
- Risk Management Plans (RMPs)
- Post-Authorisation Safety Studies (PASS) protocols and final study reports

The MHRA will require submission of all UK ICSRs (serious and non-serious) and serious ICSRs from other countries via the new MHRA Gateway or/ICSR Submissions portal which have been developed.

MEDICAL DEVICES

Regulating medical devices from 01 January 2021

From 01 January 2021, there will be a number of changes on how medical devices are placed on the market in Great Britain. The summary:

- CE marking will continue to be used and recognised until 30 June 2023
- Certificates issued by European Economic Area (EEA)-based Notified Bodies will continue to be valid for the Great Britain market until 30 June 2023
- A new route to market and product marking will be available for manufacturers wishing to place a device on the market in Great Britain from 01 January 2021
- From 01 January 2021, all medical devices and in vitro diagnostic medical devices (IVDs) placed on the UK market will need to be registered with the MHRA. There will be a grace period for registering:

  - Four months for Class IIIs and Class IIb implantable and all active implantable medical devices

  - Eight months for other Class IIb and all Class IIa devices

  - 12 months for Class I devices
- The above 12-month grace period will not apply to manufacturers of Class I devices and general IVDs that are currently required to register with the MHRA
- A manufacturer based outside the UK who wishes to place a device on the UK market, will need to establish a UK Responsible Person who will take responsibility for the product in the UK.

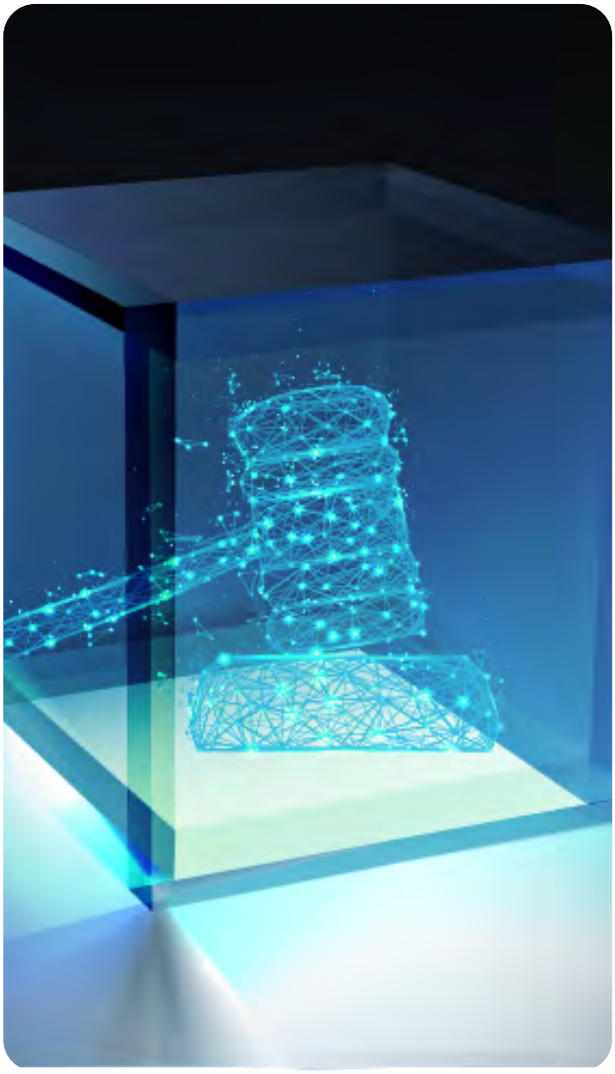
The MHRA informed that the EU Medical Devices Regulation (MDR) and In Vitro Diagnostic Medical Devices Regulation (IVDR) will "not automatically apply in Great Britain", as they will not take effect in the EU until after the transition period expires. The MHRA says that the UK has "the opportunity to develop a robust, world-leading regulatory regime for medical devices that prioritises patient safety" and it "will take into consideration international standards and global harmonisation in the development of our future system."

OTHER GUIDANCE DOCUMENTS

https://www.gov.uk/government/collections/mhra-post-transition-period-information?utm_source=Gov%20Delivery&utm_medium=E-mail&utm_campaign=MHRA_&utm_content=N-TA1#devices

National Institute for Biological Standards and Control (NIBSC) Guidance

One of the three centres of the MHRA, that plays a leading national and international role in assuring the quality of biological medicines and diagnostics, the NIBCS, has published Guidance for manufacturers of biological medicines - independent batch release in the United Kingdom from 1 January 2021



OTHER "HOT" TOPICS FROM UNITED STATES

FDA Orphan Drug Updates at NORD Summit

Officials from the US Food and Drug Administration (FDA) provided updates on the agency's efforts to support the development of medical products for rare diseases at the National Organization for Rare Disorders (NORD) Virtual Summit from 8th-9th October 2020.

In his keynote address on Thursday, FDA Commissioner Dr. Stephen Hahn said that FDA had already approved 51 orphan indications through July of this year and acknowledged that the agency's Office of Orphan Products Development (OOPD) has seen, "Large increases in the number of requests for orphan drug designation and rare pediatric disease designation."

Hahn also touched on recent developments related to the agency's Orphan Products Grants Program, which issued six grants worth $16 million over four years to support clinical trials of products for the treatment of prevention of rare diseases. In addition to the new trials being supported, FDA is providing additional funding to existing grantees to cover unexpected costs incurred due to the COVID-19 pandemic.

Speaking on a separate panel on regulatory science, OOPD Director Janet Maynard also announced two new programs stemming from FDA's Orphan Drug Modernization Plan. What is new, according to Maynard, is that the agency, "Will move from a paper-based process to a new cloud-based online submission portal. The new online portal will be available this year and will allow sponsors to submit orphan drug designations electronically."

Peter Marks, director of the Center for Biologics Evaluation and Research, discussed how COVID-19 has impacted the conduct of clinical trials. "We're observing patients, some of whom had biopsies as endpoints or other invasive procedures and some of those didn't happen," Marks said. "Our concern is that ultimately, after the pandemic … almost like after a hurricane passes, you don't see all the damage till the weather is clear."

"Some of the things we've learned is that complex clinical trials during the time of COVID-19 where there are complex assessments – frequent assessments – those have been challenging. On the other hand, trials that have been more streamlined, trials that relied on remote assessments have been able to continue, and so I think that some of what will happen coming out of COVID-19 is that we may be able to transition into trials that may be more patient friendly."

FDA Clarifies Types of Evidence Relevant to Determining the "Intended Use" of FDA-Regulated Products

On 22 September 2020, FDA proposed updates to their regulations to clarify the types of evidence the FDA considers when determining the "intended use" of a product. A product's intended use determines whether it is a medical product within the scope of FDA's jurisdiction.

This proposed rule, Amendments to Regulations Regarding "Intended Uses," is an important step forward in fulfilling FDA's public health mission and their promise to provide better clarity to regulated industry and other stakeholders.

The proposed revisions to the intended use regulations do not reflect a change in the FDA's policies and practices, but rather seek to clarify the regulatory language describing the types of evidence FDA considers relevant to determining a product's intended uses.

FDA's longstanding position is that, in evaluating a product's intended use, any relevant source of evidence may be considered. This longstanding position remains unchanged in the regulations being proposed today. However, the proposed revisions clarify an important point: that a firm's knowledge that a health care provider has prescribed or used an approved or cleared medical product for an unapproved use, standing alone, is not sufficient to establish the product's intended use.

FDA is issuing this proposed rule to clarify the types of evidence relevant to determining a product's intended uses, including determining whether a product meets the definitions of drug or device and whether an approved or cleared medical product is intended for a new use.

Clinical Holds on Investigational New Drug Clinical Trials: Holds have Risen

You have a patient with cancer who is participating in a clinical trial. The patient has just been told that the trial has been placed on a clinical hold. What does that mean? What should you say to your patient?

A clinical hold is an order issued by the U.S. Food and Drug Administration (FDA) is an order issued by the U.S. Food and Drug Administration (FDA) to the sponsor of an investigational new drug (IND) application to delay a proposed clinical investigation or to suspend an ongoing clinical trial. The reason for a clinical hold is concern for the safety of clinical trial participants. However, there are other reasons to consider including quality, clinical and toxicology issues.

The five most common reasons for clinical holds during Phase I are:

- Unreasonable risk of human harm that can lead to illness or injury
- Unqualified investigators due to lack of training or experience
- Misleading or incomplete investigator's brochure
- Insufficient information to perform a risk assessment for study subjects
- Gender bias in a study of patients with a life-threatening disease that affects both genders

A complete clinical hold is the delay or suspension of all clinical work requested under the IND, whereas a partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND (i.e., a specific protocol is not allowed to proceed but other protocols under the IND are allowed). A hold could also mean that no new participants may be recruited to the study. Complete and partial clinical holds can be placed on any IND, including expanded access INDs.

When a sponsor is far along in the IND, such as Phase II and III clinical studies, the sponsor should have a good working relationship with their IND consulting firm/CRO who can help them avoid clinical holds during these phases.

In addition to the Phase I reasons for clinical holds, if the protocol for the investigation is deficient in meeting its objectives due to a design flaw, the FDA will issue a hold. The FDA issues clinical holds for any study inadequately designed or lacking control. However, prior to ordering any clinical hold, the FDA will attempt to resolve the matter with the sponsor.

The sponsor will initially be notified of the hold by telephone or another means of rapid communication. The clinical hold order, with an explanation of the basis for the hold, will be provided to the sponsor no more than 30 days after imposition of the hold.

FDA Issues New Vaccine Guidance That Pushes Approval Past U.S. Election

The Food and Drug Administration has just released its long-awaited guidance in early October of 2020 on how it will issue Emergency Use Authorizations (EUAs) for COVID-19 vaccines. The FDA says safety data on any vaccine will need to be monitored for at least two months after Phase 3 clinical trials are completed, likely closing the door on the possibility of approving a vaccine before Election Day in the United States.

The FDA's Center for Biologics Evaluation and Research oversees the vaccine approval process and often consults with an outside advisory committee. The expert committee, set to meet on October 22, 2020 is made up of scientists, physicians, biostatisticians, and a consumer representative who are tasked with advising the FDA on the safety and efficacy of the vaccine. According to the FDA, the purpose of the meeting is not to "discuss any particular vaccine candidate."

By providing the committee with two months of data on risks and benefits after the Phase 3 trial is completed, the panel of experts will have more time to screen for severe COVID-19 disease and adverse events among study participants, according to the guidance.

FDA Commissioner Stephen Hahn said in a statement that he hoped the guidelines would help "the public understand our science-based decision-making process that assures vaccine quality, safety and efficacy."

"Data from Phase 3 studies should include a median follow-up duration of at least two months after completion of the full vaccination regimen to help provide adequate information to assess a vaccine's benefit-risk profile," the agency wrote in a briefing document for an upcoming vaccine advisory committee meeting.

An EUA does not require as much proof as the more exhaustive, standard FDA approval process, but can expedite treatments deemed beneficial in an emergency.

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, almost 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 500 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-into-human conducted in our exceptional early phase unit, through all subsequent phases of pre- and post- approval research internationally.

We also support medical device projects through regulatory planning and execution, to pilot and pivotal 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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