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REGULATORY

NEWSLETTER N.26

April - June 2019

CROMSOURCE is committed to sharing our expertise with our clients and future clients. This reflects the first part of our 'Advise Agree Deliver' motto! In this spirit we have pleasure in making available this issue of our Regulatory Newsletter. This newsletter is put together by our expert regulatory team and tracks the changes occurring in European and US regulations relating to clinical research performed in both medicinal products and medical devices.

The Newsletter is a quarterly publication distributed via email and posted on the CROMSOURCE website. We hope you find this information useful, and welcome feedback, questions and suggestions.

Contact us on cromsource@cromsource.com at any time.

Contents

Abbreviations 3

NEWS FROM EUROPE: MEDICINAL PRODUCTS 5

News from the European Commission 5

European Commission Questions and Answers on the Interplay between the CTR and the GDPR .. 5

News from the European Medicines Agency 5

EMA Draft Guidance on Quality Requirements for Regulatory Submissions for Medicines that Include a Medical Device 5

European Union Clinical Trial Regulation - EMA Management Board Update 6

Other initiatives 7

ICH E8 (R1) on the General Considerations for Clinical Trials 7

News from Individual Countries 8

UK 8

Belgium 10

Italy 10

The Netherlands 11

NEWS FROM EUROPE: MEDICAL DEVICES 12

News from the European Commission 12

MDR- latest status 12

News from Individual Countries 15

Spain 15

UK 15

Switzerland 15

France 16

Other initiatives 16

IMDRF 16

OTHER "HOT" TOPICS IN THE EU 17

Key Brexit updates 17

NEWS FROM THE UNITED STATES OF AMERICA – "HOT" TOPICS 18

Ensuring Patient Safety and Drug Manufacturing Quality Through Partnership with European Union Regulators 18

FDA Urges Industry to Broaden Clinical Trial Diversity Efforts 20

Abbreviations

Acronym	Definition
AEMPS	Agency of Medicines and Sanitary Products (Spain)
ANSM	National Agency for the Safety of Medicine and Health Products (France)
ATMP	Advanced Therapy Medicinal Products
BBMRI	Biobanking and Biomolecular Resources Research Infrastructure
CA	Competent Authority
CCMO	Central Committee for Research Involving Human Subjects (The Netherlands)
CE	(Conformité Européenne) (European Conformity)
CGMP	Current Good Manufacturing Practices
COCIR	European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry
CRO	Clinical Research Organisation
CT	Clinical Trial
CTA	Clinical Trials Agreement
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation (EU): 536/2014
CWoW	Combined Ways of Working
DDC	Drug-Device Combination
DSUR	Development Safety Update Report
EC	European Commission
EDPB	European Data Protection Board
EMA	European Medicines Agency
EU	European Union
FAMHP	Federal Agency for Medicines and Health Products (Belgium)
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GSPR	General Safety and Performance Requirements
HCRW	Health and Care Research Wales
HRA	Health Research Authority
HSC	Health & Social Care (Northern Ireland)
ICH	International Council for Harmonisation
ICT	Interactive Costing Tool
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISO	International Standardisation Organisation
IVDR	In Vitro Diagnostics Regulation, EU 2017/746
LCRN	Local Clinical Research Network

Acronym	Definition
MAA	Marketing Authorisation Application
MD	Medical Device
MDCG	Medical Devices Coordination Group
MDR	Medical Device Regulation ,EU 2017/745
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MRA	Mutual Recognition Agreement
MS	Member State
MREC	Medical Research Ethics Committee (The Netherland)
NANDO	New Approach Notified and Designated Organisations
NB	Notified Body
NBOp	Notify Body Opinion
NCA	National Competent Authority
NHS	National Health Service
NIHR	National Institute of Health Research
NIHR CRN	National Institute of Health Research Clinical Research Network
OJ	Official Journal
Q&A	Questions and Answers
REC	Research Ethics Committee (The United Kingdom)
R&D	Research and Development (The United Kingdom)
SAE	Serious Adverse Events
UDI	Unique Device Identifier
UK	United Kingdom

NEWS FROM EUROPE: MEDICINAL PRODUCTS

News from the European Commission

European Commission Questions and Answers on the Interplay between the CTR and the GDPR

In April 2019, the European Commission published a document in the Questions and Answers format to explain the interplay between the Clinical Trials Regulation (EU) 536/2014 (CTR) and the General Data Protection Regulation (EU) 2016/679 (GDPR). The document is for information purposes only and has been consulted with the European Data Protection Board (EDPB).

The 11- page document includes questions which will be relevant only when CTR becomes applicable except for question 11 referring to the current legislative situation under Directive 2001/20/EC. In the first question are listed general obligations of the CTR with regards to personal data with references to appropriate articles in the Regulation. Next question explains that the data controller- sponsor or clinical institution of the investigator is responsible to determine the legal basis for processing of personal data in the context of clinical trials.

The document divides clinical trials data carried out in accordance with the CTR into two categories: "primary use" and "secondary use". All processing operations related to a specific to the clinical trial protocol, from the starting of the trial to the end including data in marketing authorisation, shall be understood as "primary use" of clinical trial data. The implications for use of personal data outside the protocol of the clinical trial (for example for future scientific purposes) shall be understood as "secondary use" of personal data by sponsor or institution. The processing operations related to reliability and safety purposes under CTR and processing operations purely related to research activities under GDPR, are explained in questions three, four and seven.

Additionally, the Q&A document informs that "The withdrawal of consent to participate in a clinical trial under CTR may not necessarily affect the processing of personal data gathered in the context of that trial. The personal data may continue to be processed where there is an appropriate legal basis for such processing under GDPR."

In addition to that the document explains how to process the personal data in the situation of emergency clinical trials, exceptionally without any prior informed consent. It is underline that the GDPR has not changed the rules regarding the transfer of personal data to an entity outside the EU, that are already exist under Directive 95/46," but expanded the possibilities to use existing transfer instruments and introduced new transfer tools."

News from the European Medicines Agency

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

EMA Draft Guidance on Quality Requirements for Regulatory Submissions for Medicines that Include a Medical Device

In June 2019, the EMA has published the second guideline addresses the new obligations in Medical Device Regulation (MDR), in particular the requirements under Article 117, Guideline on the quality requirements for drug-device combinations (DDCs). The guidance is in a draft version and will be under consultation until 31 August 2019.

The guideline explains that for "integral DDCs", defined as "drug-device combination products authorised under the medicines' framework", the marketing authorisation application (MAA) shall include evidence of the conformity of the device part with the relevant General Safety and Performance Requirements (GSPR). The evidence of the conformity, in accordance to article 117 of the MDR, should include an EU Declaration of Conformity issued by the device manufacturer or a Certificate of Conformity issued by a Notified Body (NB). If the above mentioned results of the conformity assessment are not available than for medical devices that, do not require the involvement of a NB and used separately, to be submitted the applicant's confirmation that the device part meets the relevant GSPRs. If the conformity assessment of the integral DDC, if used separately, would require the involvement of a NB, a Notified Body opinion (NBOp) will need to be issued by an appropriately-designated NB.

A "non-integral DDCs", for which the two or more separate components are not physically integrated during manufacturing but where the medicinal product and the specific device(s) are combined for administration, should be CE marked in accordance with the MDR.

The guideline covers DDCs where a medicinal products are chemical, biological or radiopharmaceutical. The guideline does not cover combined Advanced Therapy Medicinal Products (ATMPs) (where devices are part of the active substance and/or the formulation), electromechanical components of devices, veterinary DDCs , In-vitro diagnostic devices and medical devices incorporating, as an integral part, a medicinal substance or human blood derivative with a mode of action ancillary to that of the device.

Additionally the guidelines provides a template of proposal for Notified Body Opinion and template cover sheet for Notified Body Opinion.

The guideline, when adopted by EMA, should be read with recently published first EMA guideline offering general clarifications of Article 117 of MDR Questions & Answers document on implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations.

European Union Clinical Trial Regulation - EMA Management Board Update

In June 2019, the EMA Management Board had a meeting, where among others topics, an update on the status of the development of the Clinical Trials Information System (CTIS), formerly known as EU Clinical Trials Portal and Database and the safety reporting module were presented. The EMA Management Board was informed that Member States (MSs) and stakeholders are now directly engaged in the development of CTIS through nominated 'product owners' to ensure that their expectations are taken into account. In addition the CTIS has undergone testing, a key bugs where fixed and the safety reporting functionalities have also been developed.

It has been announced that in June 2019 the development of CTIS finally restarted. The CTIS has entered into a phase of agile, iterative delivery, initially to prepare the system for audit and then be further enhanced for 'go-live' version. Currently, it is still expected that after successful completion of the audit the 'go live' version of the EU Portal and Database and considering the six –month period required after publication of full functionality of CTIS in the Official Journal of the EU (OJ), CTR will be applicable in the middle of 2020.

During June's Management Board meeting EMA made no comment about the effect of the delay on the application of the CTR.

Other initiatives

ICH E8 (R1) on the General Considerations for Clinical Trials

In May 2019, the ICH E8(R1) draft Guideline on General Considerations For Clinical Studies reached Step 2b of the International Council for Harmonisation (ICH) process and at the same enters the public consultation until 30 October 2019. According to ICH working plan Step 4 and adoption of the guideline are anticipated in June 2020.

The ICH E8 has not been revised from 22 years. Due to that fact and also the changes in clinical trial design and more complex conduct of clinical trials, the ICH E8 version had undergone revision.

The main guideline objectives are:

- To describe internationally agreed upon principles and practices to facilitate regulatory acceptance.
- To provide guidance on the consideration of quality in the design and conduct of clinical studies, including: identification of factors critical to the quality of the study, management of risks to those factors during study conduct.
- To provide an overview of the types of clinical studies performed during the product lifecycle, including: study design aspects that support the determination of quality factors critical to ensuring the protection of study subjects and ability to meet the study objectives.
- To provide an updated cross-referencing of all other relevant ICH E (Efficacy) Guidelines.

This revised guideline “focuses on designing quality into clinical studies, considering the diversity of clinical study designs and data sources used to support regulatory and other health policy decisions”.

News from Individual Countries

- **UK**

The Combined Ways of Working pilot

In April 2018, the Health Research Authority (HRA) and Research Ethics Committee (REC) in close cooperation in the Medicines and Healthcare products Regulatory Agency (MHRA) launched a "pilot programme" to submit applications for review, processes and timelines of the CTR. In June 2019, the HRA published results of the pilot programme called the Combined Ways of Working pilot (CWoW), updated instructions for sponsors prepared based on recent experience, FAQs and others relevant guidance. The main aim of the pilot programme was also to develop the process for combined ways of working between the MHRA and the REC. The pilot phase showed a lot of benefits for all parties and moved to a further stage ahead to finally accept applications from all sponsors and CROs in the future.

At the moment the CWoW pilot is open to applications by prior agreement only by sending e-mail to cwow.admin@nhs.net or calling.

The process requires from applicant to pre-agreed date to a pre-agreed anticipated REC.
The CWoW pilot process involves a single submission via Integrated Research Application System (IRAS) to MHRA, REC and HRA, combined communications to request any further information required and a single communication to confirm the final decision. The final decision, a 'grounds for non-acceptance' letter from the MHRA and also a 'provisional opinion' letter from the REC, is provided to applicant in one e-mail.

The HRA provides a step by step instructions and guidance to be read before indicating the intention to take part in the CWOW pilot and preparing one submission package to the MHRA, REC. The guidance describes the process of validation and how to proceed when requested the clarification to assessment of part 1 (MHRA) and part 2 (REC).

The 'UK Local Information Pack' mandatory

The HRA and RECs in cooperation with NHS/ HSC (National Health Services/ Health & Social Care) organisations agreed to have UK-wide mechanism for setting up participating NHS/HSC organisations. From 5 June 2019, the UK Local Information Pack is fully implemented for all research projects involving NHS/HSC in the UK: commercial, non-commercial, CT with IMP, CT with MDs. The UK Local Information Pack should be sent after the Sponsor receives the Initial Assessment Letter or the Approval Letter from HRA/HCRW (Health and Care Research Wales) where participating NHS organisations are in England and Wales. For Scotland and Northern Ireland the submission must be done after the IRAS Form submission is validated by REC. The UK Local Information Pack should be send to the principal investigator or local collaborator (where and as applicable), the R&D office of the participating NHS organisation and, if a National Institute of Health Research (NIHR) portfolio study, the Local Clinical Research Network (LCRN) of participating NHS organisations in England. The R&D office of the participating NHS/ HSC organization after receiving 'the UK Local Information Pack' will begin the arranging of capacity and capability of the study site.

The content of the UK Local Information Pack for commercial studies is:

1. *Covering email using standard template format*.
   The Sponsor is expected to use the correct email template when sharing the UK Local Information Pack with participating NHS/HSC organisations (https://www.myresearchproject.org.uk/help/hlpsitespecific.aspx#UK-Local-Information-Pack)
2. *Localised Organisation Information Document.*

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2. *Localised Organisation Information Document.*

   The Organisation Information Document replaces:
   - The Statements of Activities that were used for non-commercial studies, in England and Wales; and
   - The NHS/HSC Site Specific Information (SSI) Form in Scotland and Northern Ireland.

   There are two types of the Organisation Information Document: outline Organisation Information Document(s) which must be electronically submitted as part of the IRAS Form application (with the checklist) and give only the information that will be common to all participating NHS/HSC organisation; localised Organisation Information Document is only the part of 'the UK Local Information Pack' and provides the participating NHS / HSC organisation with the basis for a conversation with the sponsor or authorised delegate, to allow arrangements to be made to undertake the study locally.

3. *HRA and HRCW Initial Assessment Letter (or HRA and HCRW Approval letter if application is already approved by the HRA and HCRW)*
4. *IRAS Form*
5. *Protocol and any amendments*
6. *Participant information and consent documents (without local logos/ headers)*
7. *Relevant model agreement*
8. *NIHR Industry Costing Template or confirmation that the NIHR Industry Costing Tool has been accepted*
9. *Delegation log.*

   This document is appropriate for studies that are clinical trials (defined as first four categories in IRAS Project Filter question 2). Sponsors may share the template of Delegation log in the UK Local Information Pack or they may indicate in the email template mentioned in point 1 that they will share the delegation log template at a later date (e.g. after a site initiation visit). The delegation log should include known research team names but not signatures.

10. *Any other documents that the sponsor wishes to provide to the site to support the set up and delivery of the study*

New European Commission Portal to Medical Devices Regulations

In England, where the study is intended to be on the NIHR CRN (National Institute of Health Research Clinical Research Network) portfolio the costing templates should be validated by the lead LCRN (Local Clinical Research Network) prior to submission for HRA / HCRW Approval. Where the study is not intended for the NIHR CRN portfolio, validation of the costing templates takes place within the HRA subsequent to submission. The costing templates provide a framework for transparent cost display and calculation to support swift local site budget negotiations when performing commercial trials in the NHS in England. The costing template is mandatory for REC & HRA submission. The NIHR launched new and improved, web-based interactive Costing Tool (iCT) to be used by sponsors from May 2019.

- **Belgium**

New Payment Method to FAMHP

From 11 April 2019 a new payment method via invoice has been implemented by the FAMHP, the Belgian Competent Authority. This new payment process replaced the process of paying in advance, among others, for clinical trial phase I accreditation, Unmet medical need, DSURs, clinical trials, clinical investigations of medical devices and its amendments. Everyone submitting applications to the FAMHP will no longer need to attach proof of payment with the submission. The FAMHP requests "that no advance payments be made for these services and contributions, but to wait for the invoice (or invitation to pay) with a structured message for payment."

- **Italy**

New Decree no. 52 on Reorganization and Reform of the Legislation on Clinical Trials of Medicinal Products for Human Use

In June 2019, the Italian Official Gazette published new Decree 52/2019 Implementation of the reorganization and reform of the legislation on the subject of clinical trials of medicinal products for human use, pursuant to article 1, paragraphs 1 and 2, of the law 11 January 2018, n.3. The no 52 came in force on 27 Jun 2019.

The Decree 52/2019 modifies some already applicable decrees like Decree 200/2007 implementing Directive 2005/28/ EC on GCP principles, Decree 211/2013 implementing Directive 2001/20/EC and introduces very important legislative concepts for clinical trials sector for 2019.

Main modifications covered by the Decree 52/2019:

- New principle of GCP: the methodological approach of gender medicine in clinical trials.
- Use of residual biological sample left at the study site for other clinical research.

The 'Istituto superiore di sanita', with the support of the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), after the opinion of the National Centre for the Coordination of Territorial Ethics Committees and the Italian Data Protection Authority, with appropriate guidelines, in compliance with the principle of informed consent, the GDPR and ensuring high quality standards, will identify homogeneous criteria for the use of biological samples from previous diagnostic or therapeutic activities in clinical trials.

- Facilitate and enhance no-profit clinical trials.

The decree anticipates a possible behaviour that can mask a pure profit trial into a no-profit trial that can

be reclassified. Even if clinical trial started as a no-profit, in case of re-classification, all the fees must be paid. The Sponsor or the transferee is required to pay and reimburse the direct and indirect expenses related to the trial, as well as to pay the relative tariffs, following the possible requalification of the trial itself as a profit-making activity, including the potential revenues deriving from the enhancement of intellectual property.

- Involvement of very well technically prepared personnel for IT systems supporting the trials. IT systems should be compliant with GDPR.
- Publication by the AIFA the list of the authorized, ongoing and concluded structures of the clinical trials.
- Update of a national template to be used for obtaining the EC opinion.

The new important decrees expected in 2019 and introduced by Decree 52/2019:

- Decree to establish the measures to facilitate and support the no- profit studies and the observational studies ; individuate the way for cooperation between public and private Sponsor, identify the type and requirements of the no-profit trial and the cooperation between profit and no profit Sponsors - expected by 31 October 2019,
- Decree related to new fees for GCP inspections on phase I studies - expected by 31 October 2019,
- Decree on requirements for study sites in compliance with CTR - expected by 26 August 2019,
- New requirements for study site in charge of clinical trial from phase I to phase IV - expected by 24 November 2019,
- Decree for the absence of conflict of interests in clinical trials - expected by 25 September 2019,
- Decree on new procedure for the trial authorization (involving also patients associations) - expected by 25 September 2019,
- Decree for the activation of Master on clinical research methodologies at Universities - expected by 25 Oct 2019

- **The Netherlands**

Adjustments for Clinical Trial Agreement (CTA) Submission

From 21 May 2019, the signed version of the clinical trial agreement (CTA) may be submitted to the review committee (accredited MREC or CCMO) after the primary positive decision has been issued.

In practice, this means that submitted CTA doesn't need to be signed by all parties but must be in a draft version with a reference and version number only. Reference and version number of the approved CTA will be mentioned in the decision letter issued by accredited MREC or CCMO. A signed copy of the approved version of the CTA (fully executed) must be submitted to the review committee for notification before the start of the study. Upon receipt of the signed CTA, the accredited MREC or CCMO will check whether it is the same version as the one she has approved.

In the case of multicentre research, one version of CTA will be sufficient for the submission to the review committee. In such case the sponsor must declare that the CTAs from the other sites are similar to the CTA which has been submitted for review.

"Any change to the CTA that leads to a new version number must be submitted to the review committee. A change relating to the two aspects of the CTA, that the review committee assesses criteria for early termination and publication of study results, is considered a substantial amendment."

As a result of the changes regarding submission of CTA to accredited MREC or CCMO the sponsors and investigators will get sooner the positive decision of the clinical trial.

NEWS FROM EUROPE: MEDICAL DEVICES

News from the European Commission

MDR- latest status

The MDR and IVDR were published in the Official Journal of the European Union in May 2017. The requirements of the MDR will came into force on 26 May 2020 and for the IVDR on 26 May 2022. For the MDR there are less than one year left before application. The European Coordination Committee of the Radiological, Electromedical and Healthcare IT Industry (COCIR) published assessment of the progress of implementation of the Regulations and their recommendations. At the conclusion they said: "This is a critical period for the entire medical devices regulatory system. If the European Union's ambition for medical devices are to be realised, the full regulatory framework will have to be in place and functioning. At this moment, it appears that much effort is needed to complete the framework in time."

See below COCIR updated assessment of the MDR's implementation status on 6 June 2019:

Annex: COCIR updated assessment of the MDR's implementation status

1. GENERAL FRAMEWORK	UNIQUE DEVICE IDENTIFICATION (UDI)		• Eight guidance documents published to date • Striving for convergence with global efforts at IMDRF level as far as the Regulation permits • Decision on nomenclature has been taken
	EUROPEAN DATABASE FOR MEDICAL DEVICES		• Implementation plan published on time • Data dictionary for UDI & Devices module published • Several modules so far delayed that they will not be part of first release in March 2020 • Timing for validation of actor registration remains a concern
	HARMONISED STANDARDS		• Standardisation request not yet adopted • List of candidate standards unclear and insufficient • Worsening administrative processes for harmonisation of standards
	TRANSITIONAL PROVISIONS		• No clarity on interpretation of significant change according to Article 120.3 (expect development of NBOG guidance) • Guidance for legacy devices (UDI obligation, sufficient clinical evidence etc.) delayed or requires more clarity
2. PRE-MARKET OBLIGATIONS	CLINICAL EVALUATION AND INVESTIGATIONS		• Lack of stakeholder consultation • Guidance on sufficient clinical evidence and equivalence for higher-risk legacy devices severely delayed • No plans as yet for guidance for lower-risk devices
	MEDICAL SOFTWARE		• Guidance on qualification and classification delayed (publication of classification guidance expected in June 2019) • Guidance on clinical evaluation of software progressing well
3. PMS	POST MARKET SURVEILLANCE AND VIGILANCE		• Field Safety Notice and MIR form published4 • Development of several guidance documents and templates (e.g. PSUR) delayed • No clarity on possible delegation of activities between Economic Operators (e.g. pre-evaluation of incidents by distributors)
4. RELEVANT ACTORS	ECONOMIC OPERATORS		• Uncertainty on sub-contracting of verification activities between different economic operators • No clarity on use of sampling methods by importers • Original Equipment Manufacturer/Own Brand Labeller obligations under discussion
	NOTIFIED BODIES		• Only 2 Notified Bodies designated by May 2019 • Significant increase in demand expected for Notified Bodies, particularly for software and apps, due to changes to classification rules • Uncertainty on MDR interpretation among Notified Bodies

Recent developments concerning the transition periods (up to 3 years for MDR, up to 5 years for IVDR) with the guidance published by European Commission for the last three mounts are summarised below.

European Commission Expert Panel on MDR and IVDR

In June 2019, the European Commission (EC) has called for applications to set up the expert panels for premarket product evaluation consultation procedures provide under the EU's Medical Device Regulation (MDR) and in Vitro Diagnostics Regulation (IVDR).

Guidance on Use of Symbols to Indicate Compliance with the MDR

To comply with new MDR requirements in an efficient manner before the relevant international standard is available, MedTech Europe published its guidance on graphical symbols to be used on medical devices' labels. The graphical symbols in this guidance have all been validated with users, including patients and healthcare professionals, according to international standards. These symbols have been submitted to ISO (International Standardisation Organisation) and are currently being considered in the revision of ISO 15223-1 Medical Devices - Symbols to be used with medical device labels, labelling and information to be supplied.

Impact of MDR on Healthcare Professional

The European Commission published Factsheet for healthcare professionals and health institutions. It provides a general overview of the impact of the new regulation under (2017/745/EU) (MDR) and the new (217/746/EU) (IVDR). Specifically, the requirements for clinical investigations (MDR Article 62 to 82) and Performance studies (IVDR Articles 57 to 77), Eudamed cooperation, device identity and traceability, implication of up-classifying certain medical devices on healthcare institution. The new rules describe clearly how these investigations shall be designed, notified and/or authorised, conducted, recorded and reported.

EUDAMED

Eudamed is the central European database which will allow all stakeholders to access basic information on MDs and IVDs, such as the identity of the device, its certificate, the manufacturer, the authorized representative and the importer.

Eudamed Data Exchange Guidelines was issued by the EC to help the competent authorities, notified bodies as well as all Economical Operators (Manufacturers, Authorised Representatives, Importers, and system/ Procedure Pack Procedures) in assessing the most Cost-Efficient Solution for their needs to comply with the Medical Devices Regulation. The guideline recommend the type of the software application suitable for the medical device manufacturers based on their business size (small manufacturer or large manufacturer). This solution is for the manufacturers who decide to in-house the desired software.

Furthermore, Eudamed.eu defines:

1. The most cost effective software solution for each manufacturer based on the number of devices manufactured.
2. For manufactures decide to in-house the UDI Software, The skills and resources necessary.
3. For those manufacturers who decide to outsource all or part of the in-house UDI project requirements, Eudamed offers a full software service, training, support, and consultancy and access point.

Timeline Registration of legacy devices in EUDAMED document was published by Medical Devices Coordination Group (MDCG). The Guidance deals with registration of Legacy Devices, which can continue to be placed on the market under current Directive certificates after the application date of MDR. The main key points of the legacy devices guidance are:

1. Manufacturers must enter data in Eudamed 18 month after date of Application, or after 24 months if Eudamed is delayed.
2. Legacy devices will be assigned a basic UDI-DI and UDI-DI by Eudamed at the moment they are registered in Eudamed.
3. Manufacturer can also assign a UDI;
4. Once they become certified according to the new Regulations they need to have a Basic UDI-DI and UDI-DI issued by a UDI issuing agency;
5. This"new" UDI does not have to impact device labelling.

NOTIFIED BODIES

The European Commission defined the UDI-DI set of data in relation to UDI database for both MDR and IVDR. According to Annex VI, Part C, the UDI-DI is "… a unique numeric or alphanumeric code specific to a model of device that is also used as the 'access key' to information stored in a UDI database." Obviously, a UDI-DI must be associated with exactly one Basic UDI-DI. The UDI-DI is needed to identify a specific device within the supply chain. If a change in the design could lead to misidentification of the device, a new UDI-DI should be created.

The data elements for the basic UDI-DI are: Basic UDI-DI value; Single Registration Number of the manufacturer; Name and address of the manufacturer; Name and address and Single Registration Number of the authorized representative; Risk class and additional characteristics necessary to identify specific conformity assessment features (implantable, measuring function, etc.); Medical device nomenclature code; Name or model identifying the Basic UDI-DI group in the technical documentation and/or certificate and declaration of conformity.

More information is available here:

MDR - UDI and device data sets to provide in EUDAMED

IVDR - UDI and device data sets to provide in EUDAMED

EUDAMED UDI Device Data Dictionary to give an understanding over the data that is to be provided to Eudamed and that can be communicated through Data Exchange process for the UDI/Device module.

The document presents the different attributes related to UDI/Device that may be communicated through XML, their correspondence to the fields from EUDAMED User Interface, the description of each field apart and the Rules applying at the level of the Entity of for each specific field apart.

UDI

In May 2019, TÜV Süd becomes the second Notified Body designated to issue CE Mark certifications under the upcoming European Medical Devices Regulation (MDR).

In June two NBs: British NB Lloyd's Register Quality Assurance and Swiss NB QS ZÜRICH AG announced that they decided to not apply for MDR/ INDR designation.

Questions and answers: Requirements relating to notified bodies

News from Individual Countries

- **Spain**

The AEMPS, acting as Spanish Notified Body Ceases to Process New Certificate Applications

The Spanish Agency of Medicines and Medical Products (AEMPS), acting as Spanish notified body (NB) informed that from 1 June 2019 will no longer accept new medical device applications for CE marking under Directive 92/42/EEC. In addition to that the AEMPS will also desist to process new certificate applications from existing clients from 31 July 2019. The explanation of AEMPS' decision is that there is a need to ensure the completion of all conformity assessments of medical devices certified according to Directive 93/42 / EEC will be approved before 26 May 2020, when MDR will become fully applicable in the EU. The AEMPS explains this in the published Q&A brochure "Information and conditions of CE marking", 2019 and provides clarifications on next steps for example how the Spanish NB will process the application and how long MD will be certified or what should be taken into account by manufacturer at the time of requesting extension of the certification.

- **UK**

Submission for Clinical Investigations to the MHRA via IRAS online system

From 19 February 2019 all applications to the MHRA for clinical investigations of medical devices must be submitted electronically using the Integrated Research Application System (IRAS). Previously, submissions of clinical trials with medical devices were available only for CD-ROMs. The electronic submission includes the 'MHRA Devices application form' and the associated supporting documents. To proceed the electronic submission, the application must obtain electronic authorisations signatures by Legal Manufacturer/ Authorised Representative/CRO, pass the verification tool step within IRAS and finally make submission by clicking 'E-submission' button.

- **Switzerland**

New Forms for Clinical Trials with Medical Devices

Swissmedic, the Swiss competent authority published new online forms for reporting domestic serious adverse events (SAE), including possible serious device deficiencies and an annual safety report comprising an updated written report and the list of SAEs including device deficiencies for Category C clinical trials.

Clinical trials Category C are those with medical devices not yet CE-marked or CE-marked MDs used out of its instructions for use. Such clinical trials must be authorised by Swissmedic and the competent ethics committee, and are monitored by Swissmedic until completion.

The following new forms has been published:

- BW510_00_004e_FO Clinical Trials with medical devices: Submission for approved trial (PDF, 1 MB, 30.04.2019) (to be used for annual safety report submission)
- BW510_00_006e_FO Clinical trials of medical devices: Serious adverse events and deficiencies in Switzerland (PDF, 1 MB, 30.04.2019) (to be used for reporting domestic Swiss cases)

In addition to this, the Swissmedic published new Application form for authorising Category C clinical trials with medical devices:

- BW510_00_005e_FO Clinical Trials with medical devices Application for authorisation (PDF, 1 MB, 20.06.2019)

- **France**

ANSM sets up a "pilot phase" for Clinical Investigations of Medical Devices in the Context of the Application of the New MDR

From 26 May 2020 the new MDR will implement new procedures for the authorisation of clinical trials with medical devices to the national competent authorities and the ethics committees in each member states in EU.

The National Agency for the Safety of Medicine and Health Products (ANSM), the French competent authority wants to go ahead as a first NCA in EU and set up a "pilot phase" that will simulate the new requirements under MDR while respecting current French Law on research involving the human person (known as the Jardé Law). The ANSM announced that "pilot phase" will begin on 16 September 2019. Before starting the programme, the ANSM encourages sponsors, manufacturers and CROs to join the information meeting on 4 July 2019, where main principles of the MDR and context, scope and practical guidelines of "pilot phase" will be presented.

Other initiatives

IMDRF

Personalized Medical Devices – Regulatory Pathways

The International Medical Device Regulators Forum (IMDRF) opened for consultation new proposal to harmonize regulatory pathways for personalized medical devices.

The document harmonises "the application of existing regulatory pathways to medical devices that are intended for a particular individual, and to identify special considerations for the regulation of each category of personalized medical device." The adoption of harmonised requirements for such medical devices will "offer significant benefits to the manufacturer, user, patient, and to Regulatory Authorities." The document includes decision tree for "custom-made medical device", "patient-matched medical device" and "adaptable medical device".

OTHER "HOT" TOPICS IN THE EU

Key Brexit updates

The European Council agreed to a further extension of the date for the UK's withdrawal from the EU. The first Brexit deadline of 29 March 2019 should be understood now as 31 October 2019.

European Commission report on the preparedness of the drug and medical device sectors after postponed Brexit to facilitate the community of medical supplies in the market in both EU 27 countries and UK. This includes the necessary actions to be taken by both the economic operators and the manufacturers.

Exporting Active Substance Manufactured in the UK in a No deal Scenario - update

In the event of no deal EU Exit, the UK will be recognized as a third country for the export of Active Substances for human used to the EEA. A Written Confirmation will then be required for each shipment of Active Substances manufactured in the UK that is exported to the EEA. The written confirmation will be generated for the UK Active Substance manufacturer whether they intend to export Active Substances or not, and will be published on the MHRA's website with availability for downloading.

For the Manufacturer of biological active substance and hold Manufacturing Authorisation (MIA) that includes manufacture of biological active substance, no separate registration as an active substance manufacturer is required.

EMA Reinstates Some Activities after Relocation to Amsterdam

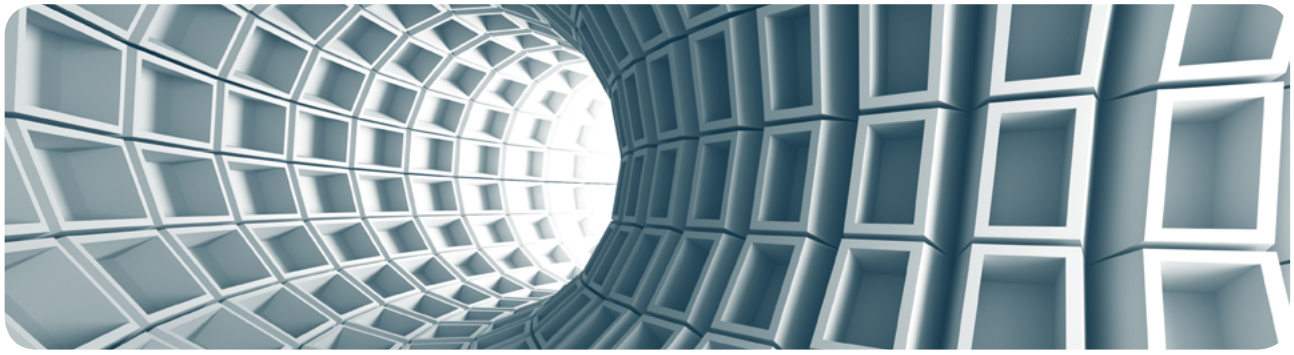
EMA has developed a business continuity plan to ensure operational continuity during its physical relocation and readiness for the UK's withdrawal from the EU. It enables EMA to deliver its highest priority activities and to temporarily scale back or suspend lower priority activities if required.

EMA will continue to operate under business continuity conditions until at least the end of 2019, to safeguard the Agency's core activities related to the evaluation and supervision of medicines. This is necessary as EMA will need several months to rebuild its workforce.

Three Marketing Authorisations Only Left to be Transferred from the UK to an EU27 Member State

The European Medicines Agency (EMA) and the European Commission are providing guidance to help pharmaceutical companies responsible for both human and veterinary medicines prepare for the United Kingdom's (UK) withdrawal from the European Union (EU), a process known as 'Brexit'.

This aims to ensure that companies are ready to take the necessary steps to enable undisrupted supply of their medicines in the EU for the benefit of patients, based on the assumption that the UK will become a third country. The EMA informed that in June 2019, only three marketing authorisations (for human medicines) needed to be transferred from the UK to the EU27 Member State.



NEWS FROM THE UNITED STATES OF AMERICA – "HOT" TOPICS

Ensuring Patient Safety and Drug Manufacturing Quality Through Partnership with European Union Regulators

As drug manufacturing has globalized, ensuring that companies meet the U.S. Food and Drug Administration's (FDA) strict standards for producing safe, effective and high-quality medicines has become increasingly challenging. One way the FDA has addressed this challenge is through the Mutual Recognition Agreement (MRA) with the European Union (EU), which allows FDA to more effectively deploy their inspectional resources across the globe.

Pharmaceutical establishments that make active pharmaceutical ingredients and finished drug products used by U.S. patients are subject to routine inspections by the FDA to determine if they are in compliance with Current Good Manufacturing Practices (CGMP). The FDA prioritizes and schedules these inspections, which we call surveillance inspections, based on a risk-based site selection model. During an inspection, FDA investigators focus on whether the facility is adequately controlling its manufacturing operations. This includes establishing strong quality managements systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations and maintaining reliable testing laboratories. With 4,600-plus registered establishments subject to surveillance inspections, three-fifths on foreign soil, routine surveillance is a large-scale endeavour for the FDA.

The MRA is designed to ease part of this burden and minimize resource-intensive duplicative inspectional efforts by the U.S. and the EU. The EU conducts similar inspections of establishments that manufacture medicines to be used in the EU, so under the MRA, the FDA may rely on the inspectional findings of EU member states in a European facility that will export to the U.S., and an EU nation may accept the FDA's inspectional findings at a U.S. facility that exports to a nation in the EU.

The MRA has been two decades in the making. In 1998, the United States and the European Community, which in 2009 was absorbed into the wider framework of the European Union, signed a broad Mutual Recognition Agreement. This Agreement included, among other things, a Pharmaceutical Annex (Annex) providing for anticipated and limited reliance on each other's CGMP inspections. However, this Agreement was never fully implemented.

After five years of close FDA-EU cooperation, as of July 11, 2019, FDA is pleased to announce that the FDA has completed capability assessments of 28 EU member states. The 28 regulatory authorities found to be capable are those located in: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom. Meanwhile, the EU made the same determination about the FDA in June 2017.

FDA's sees evidence that the MRA is creating important efficiencies. Before the MRA was implemented, the EU and the FDA sometimes would inspect the same facilities in the same year, even if the facility had a strong record of compliance. We expect the MRA will reduce this duplication, allowing the FDA and the EU to reallocate their resources towards inspection of drug manufacturing facilities that have potentially higher public health risks. In addition, information from EU inspection reports will help to inform their risk-based site selection model for inspections, ensuring that FDA resources are allocated in the most efficient

and appropriate manner, while considering risks in the product and manufacturing process that could cause potential harm to patients.

Currently, the MRA is being applied to surveillance inspections conducted only within FDA's respective borders. However, the U.S. and the EU have the option of relying on inspection reports for manufacturing facilities located outside each other's territories. And while the MRA is now limited to inspections of facilities manufacturing human drug products, FDA is evaluating the possibility of including other regulated products, such as veterinary products, human vaccines, and plasma-derived drugs, in the future.

At a time when medical product manufacturing is a global enterprise, there is much to be gained by partnering with regulatory counterparts to reduce duplicative efforts and maximize global resources in order to better fulfil FDA's public health mission.

More information can be accessed at https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/ensuring-patient-safety-and-drug-manufacturing-quality-through-partnership-european-union-regulators.

FDA Urges Industry to Broaden Clinical Trial Diversity Efforts

Despite concerted policy efforts in recent years, a new U.S. Food and Drug Administration (FDA) draft guidance FDA says "challenges to participation in clinical trials remain, and certain groups continue to be underrepresented in many clinical trials." It is aimed at increasing diversity in clinical trial populations as part of its efforts to encourage drug makers to enrol populations that more closely reflect the populations that will take the drugs in the real world.

The draft guidance issued on June 6, 2019, "Enhancing the Diversity of Clinical Trial Populations–Eligibility Criteria, Enrolment Practices, and Trial Designs," recommends new approaches for sponsors to consider to safely broaden eligibility criteria. At the same time, the guidance acknowledges there are often clear reasons for the existence of specific eligibility criteria.

For example, patients with decreased renal function or certain concomitant illnesses are often excluded because of concerns they may be more susceptible to adverse effects from investigational drugs that are metabolized by the kidney or that interact with other medications the patient takes, the agency notes in the guidance.

"Sponsors should adopt practices for determining eligibility criteria that will allow the clinical trial population to reflect the diversity of the patients who will be using the drug if the drug is approved," FDA also says in the guidance.

Although there are many approaches a sponsor can take to broaden eligibility criteria in clinical trials, the FDA guidance provides several specific recommendations, including:

- Examine each exclusion criterion to determine if it is needed to help assure the safety of trial participants or to achieve the study objectives when developing clinical trial protocols. If not, consider eliminating or modifying the criteria to expand the study population as well as tailoring the exclusion criteria as narrowly as possible to avoid unnecessary limits to the study population.

- Consider whether criteria from Phase II studies—which may be more restrictive and are often transferred to Phase III protocols—can be eliminated or modified to avoid unnecessary limits on the study population. Although excluding certain participants may be scientifically or clinically justified under specific circumstances (e.g., certain drug-drug or drug-disease interactions or concerns regarding a population's vulnerability to a particular toxicity), such criteria may be removed or modified during study conduct based upon data available from the completion of other relevant studies (e.g., drug-drug or drug-disease interaction studies).

- Base exclusions on an appropriate measure of organ dysfunction that does not lead to the unnecessary exclusion of certain populations when such exclusions are necessary because participants with impaired organ function would be placed at unreasonable risk.

While inclusion and exclusion criteria play an important role in protecting patients and ensuring trial results are interpretable, FDA says that many patients are "excluded from trials without strong clinical or scientific justification."

However, by excluding patients, such as the elderly, pregnant women, children, patients with comorbidities or patients who are taking other drugs, without clinical or scientific justification, FDA says drug makers may miss important safety signals and end up with less generalizable results. For rare disease clinical trials, the guidance provides a separate set of recommendations for broadening eligibility criteria and enhancing recruitment.

"Because rare diseases often affect small, geographically dispersed patient populations with disease-related travel limitations, special efforts may be necessary to enrol and retain these participants to ensure that a broad spectrum of the patient population is represented," FDA writes.

As such, FDA recommends drug makers engage with patient advocacy groups early on to gather input on their trial designs and protocols.

In limited circumstances, FDA also suggests that drug makers should consider plans to re-enrol patients from early studies in later phases. "Traditionally, participants are often ineligible for a phase 3 trial if they had been previously exposed to the drug in an earlier-phase trial; however, with so few participants in rare disease trials, re-enrolling participants may facilitate the analysis of safety and efficacy in the broadest possible population," FDA writes.

Lastly, FDA says drug makers should consider offering an open-label extension study following early-phase studies "to encourage participation by ensuring that all study participants, including those who received placebo, will ultimately have access to the investigational treatment."

About CROMSOURCE

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

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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, France, Germany, Poland, Russia, Spain, Switzerland, the UK, the Netherlands, and the US.

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