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REGULATORY NEWSLETTER N.22

April - June 2018

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Introduction

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 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.

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Contents

Abbreviations

Acronym	Definition
AEMPS	Agency of Medicines and Sanitary Products (Spain)
AIFA	Italian Medicines Agency (Italy)
ANSM	National Agency for the Safety of Medicine and Health Products (France)
ATMPs	Advanced Therapy Medicinal Product
BASEC	Business Administration System for Ethics Committees
CA	Competent Authority
CAR-T	Chimeric antigen T cell receptor
CCMO	Center for Biologics Evaluation and Research
CE	Conformité Européene (European Conformity)
CESP	Common European Submission Portal
CHMP	Committee for Medicinal Products for Human use
COMP	Committee for Orphan Medicinal Products
CPMP	Committee for Proprietary Medicinal Products
CTA	Clinical Trial Application
CTR	Clinical Trials Regulation
DSUR	Development Safety Update Report
EBMT	European Society for Blood & Marrow Transplantation
EC	Ethics Committee
EDPB	European Data Protection Board
EMA	European Medicines Agency
EU	European Union
FAMHP	Federal Agency for Medicines and Health Products (Belgium)
GDPR	General Data Protection Regulation
HCRW	Health and Care Research Wales (UK)
HPRA	Health Products Regulatory Authority (Ireland)
HRA	Health Research Authority (UK)
ICF	Informed Consent Form
ICH	International Conference for Harmonization
IMDRF	International Medical Device Regulators Forum
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
IRIS	EMA online portal for orphan designation process
IVDR	In Vitro Diagnostics Regulation, EU 2017/746

Acronym	Definition
MAH	Marketing Authorisation Holder
MD	Medical Device
MDR	Medical Device Regulation, EU 2017/745
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
NCA	National Competent Authority
NHS	National Health Service (UK)
PIS	Patient Information Sheet
PRAC	Pharmacovigilance Risk Assessment Committee
REC	Research Ethics Committee
SoA/SoE	Statement of Activities/Schedule of Events
SPC	Supplementary Protection Certificate
SSI	Site Specific Information
SUSAR	Serious Unexpected Suspected Adverse Reaction
UDI	Unique Drug Identifier
UK	United Kingdom
VHP	Voluntary Harmonisation Procedure

NEWS FROM EUROPE:

General Data Protection Regulation comes into force

Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, better known as the **General Data Protection Regulation** (**GDPR**), became applicable across the European Union (EU) on 25 May 2018. This regulation replaced Directive 95/46/EC (the Data Protection Directive). Under the GDPR, privacy rights are strengthened and extended, organizations are given more responsibilities, need to be lawful, fair and transparent when processing or controlling the processing of personal data, and all European Union privacy supervisors are given the same powers.

Source: https://ec.europa.eu/info/law/law-topic/data-protection_en

Source: https://ec.europa.eu/info/law/law-topic/data-protection/data-protection-eu_en

Guidelines on Consent under Regulation 2016/679 (wp259rev.01) were published on April 2018 by the European Commission at Article 29 Working Party [1]. These guidelines provide a thorough analysis of the notion of consent in GDPR. The guidelines lists elements of valid consent and provides an examples for each section. The examples are taken from everyday life where people could be asked to sign the consent. There is information with examples how to provide minimum content requirements for consent to be 'informed', how information must be provided in order to fulfil the requirement of informed consent, how to obtain explicit consent, what are children's consent and parental responsibilities and how to withdrawal of consent (data subjects must, in practice, be able to withdraw the consent equally as easily as sign). At the end of guidelines there are described sections referring to scientific research and Data subject's rights. The Guidelines are also available in 22 languages.

Source: http://ec.europa.eu/newsroom/article29/item-detail.cfm?item_id=623051

Although, the term 'scientific research' is not defined in the GDPR, the new Regulation has consequences for the collection and processing of personal data in clinical research. Some individual European countries published official instructions or guidance explaining the GDPR impact on Informed consent process in clinical trials.

Some examples are presented below:

- **The Netherlands**

The GDPR is known in Dutch as Algemene Verordening Gegevensbescherming (AVG). The Centrale Commissie Mensgebonden Onder (CCMO), the Dutch Competent Authority provides the information guidance in the format of Q&A. The CCMO informs that is not mandatory to ask subjects again for their permission to participate in the clinical trials with new Informed Consent Form (ICF). If the sponsor wants to provide current participants with information regarding AVG, they can do this by notifying the Ethics Committee (EC), but it is not mandatory. The CCMO emphasises that the national media campaign explaining the new Regulation requirements should be enough for patients to understand its impact on their current life. The CCMO also presents new model of Patient Information Sheet (PIS) and ICF and explains that new model should contains information, clarifications about how personal data are processed in the research, contact details of the "controller" of data, " data protection officer" and references to location for information on the "rights of data subjects", if necessary.
Source with access to the adapted PIS & ICF new model:
http://www.ccmo.nl/en/algemene-verordening-gegevensbescherming

[1] The Article 29 Working Party ceased to exist on 25 May 2018 and was replaced by the European Data Protection Board (EDPB). The EDPB monitors and ensures the correct application of the GDPR, advises the Commission on any issue related to the protection of personal data in the EU and issues guidelines, recommendations, and best practices on procedures. EDPB website: https://edpb.europa.eu/

- **Spain**

On 21 May 2018, the Spanish Agency of Medicines and Sanitary Products (AEMPS) published guidance: **Anexo VIIIC Instrucciones para la actualización del apartado Protección de datos personales en la hoja de información al sujeto (HIP/CI) en lo relativo al Reglamento (UE) nº 2016/679 General de Protección de Datos**. The Annex VIIIC provides instructions for the update of the data protection section of the PIS and ICF according to GDPR, called in Spain: Reglamento General de Protección de Datos (RGPD), and presents the information subjects should be informed of in the PIS & ICF. For subjects already involved in a study (informed consent already obtained) the information from Annex VIIIC can be delivered without re-consenting. For subjects to be enrolled in an ongoing study, they should sign the already approved ICF and receive the information included in Annex VIIIC. For subjects that have finalised their participation in a study there is no need to notify the information to them.

In addition, the sponsors are obligated to inform sites about the Annex VIIIC, and before 25 July 2018 inform the EC how the information has been delivered to the subjects attaching delivered documentation via the Spanish web portal. After 25 July it will be no longer needed to inform the EC. A Substantial amendment is required only when the reason of modification of PIS &ICF differs from the implementation of GDPR and modifications to the data protection section are not already included in the Annex VIIIC. Spanish CA and EC are working on a new guide for the creation of the new PIS &ICF template.

Source: https://www.aemps.gob.es/investigacionClinica/medicamentos/ensayosClinicos.htm

- **Italy**

On 1 June 2018, the Italian Medicines Agency (AIFA) announced how to handle amendments to the ICF regarding GDPR. The announcement highlights that “any amendment to the informed consent form, only needed to make it in compliance with the GDPR, falls in the category of non-substantial amendment”. Where changes to the ICF also concern the contents of the form itself a request for substantial amendment must be submitted to the relevant EC.

Source: http://www.agenziafarmaco.gov.it/content/emendamenti-al-modulo-di-consenso-informato-inerenti-informativa-e-manifestazione-del-consen

- **United Kingdom**

The Health Research Authority (HRA) published various guidance on GDPR, including recommended transparency wording templates for NHS sites, sponsors and others. It is advised by the HRA that transparency information will need to be submitted in a separate document from the PIS and to be classed as a non-substantial, non-notifiable amendment that does not need to be submitted for approval.

Source: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/

- **Germany**

At the end of March 2018, Working Group of Medical Ethics Commissions in the Federal Republic of Germany eV published guidelines for EC how to implement GDPR in current and already completed clinical trials in Germany. For already included subjects in ongoing studies it is required to submit a supplementary information on the points mentioned in the guidelines, which are not already addressed in the existing ICF. The supplementary information does not have to be signed by the subjects. The points which should be taken in particular into consideration are:

a. The person responsible for the data processing in the project is to be named.

b. The name and contact details of the responsible Data Protection Officer (local and sponsor/study management) shall be indicated.

c. It should be advised that there is a right of appeal to a data protection supervisory authority (data protection representative of the federal state or federal data protection commissioner of the site, data protection representative of the federal state or federal data protection commissioner of the sponsor/study management). The responsible data protection supervisory authorities must be mentioned. The information should be adapted for each site.

d. The persons concerned are to be informed of their right to obtain information (including the free provision of a copy) of the personal data concerned and to ask for their correction or deletion, if necessary.

If the supplementary information relates exclusively to the points a) to d) above, it does not have to be submitted to the responsible EC for evaluation in advance.

Source: http://ak-med-ethik-komm.de/index.php?lang=de

NEWS FROM EUROPE: MEDICINAL PRODUCTS

News from the European Commission

European Union Clinical Trials Regulation – Q&A document published

In April 2018, the European Commission published a draft Questions & Answers (Q&A) document referring to the Clinical Trials Regulation (CTR) EU: 536/2014. This is a living document that will be updated and published progressively to help prepare for upcoming changes. The questions refer to the scope of CTR, initial authorization, substantial amendments, documents to be submitted in Part I and Part II to Members States and any other requirements of CTR. In addition, some questions are dedicated for arrangement of transition period. The document explains how sponsors to be prepared in case the study does not comply with CTR criteria or what will happen with the clinical trials included in the Voluntary Harmonisation Procedure (VHP).

Source: European Commission > DG Health and Food Safety > Public health > Vol 10: Clinical Trials

Q&A document: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

News from the European Medicines Agency

The source of each news item below is the EMA website.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/Home_Page.jsp&mid=

European Union Clinical Trials Regulation – update from EMA

In June 2018, EMA Management Board presented the EU portal and database update. The auditable version of the EU portal and database is nearing completion and is in an intensive phase of testing. The EMA's relocation to Amsterdam could impact overall timing for the project but it will not be a major and will be under control. The EMA Management Board said that due to Brexit:
"Some further planning adjustments may be required. These include timing of:

- user acceptance testing of the auditable version, which is planned for November 2018, to allow for completion of the relocation of the development data centre beforehand;
- the audit, due to start in early 2019, will need to accommodate relocation of staff in early March 2019."

It has been highlighted that EU portal and database- the new clinical trials system "to be a priority in EMA's Brexit preparedness business continuity plan".

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp&mid=WC0b01ac05808768df

EudraVigilance operational plan from 2018 to 2020

On 8 June 2018, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) adopted the EudraVigilance operational plan from 2018 to 2020. This follows the launch, on 22 November 2017, of the new EudraVigilance (human) system providing enhanced functionality for effective reporting and monitoring to national Competent Authorities (NCAs), EMA and marketing authorisation holders (MAHs) for effective reporting and monitoring of suspected adverse reactions and detection of risks related to the safety of medicines. The system also facilitates the reporting of investigational medicinal products (IMP) suspected unexpected serious adverse reactions (SUSAR) during clinical trials.

Milestones related to the EudraVigilance operational plan for the next three years are also presented.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp&mid=WC0b01ac05800250b5

EudraVigilance operational plan: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2018/06/WC500250477.pdf

New EudraVigilance system Questions and Answers (Q&A) - updated

On 18 June 2018, the EMA published a Q&A document regarding new EudraVigilance system launched on 22 November 2017. The Q&A document is intended to be updated monthly by EMA and should be consulted as a first reference before contacting the EMA's service desk.

The EMA highlights that clinical trials SUSAR reporting has not been changed. The changes will be applicable after full application of the CTR.

Extended EudraVigilance medicinal product dictionary (XEVMPD) training should be provided to at least one user from each MAH or sponsor of clinical trials.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp&mid=WC0b01ac05800250b5

EudraVigilance training and support

Extended EudraVigilance medicinal product dictionary (XEVMPD) training

Q&A document: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/07/WC500230934.pdf

New EMA online portal for the orphan designation process

On 19 June 2018, EMA launched a new secure online portal "IRIS" for sponsors to submit applications for orphan designation (a status assigned to a medicine intended for use against a rare condition) and to manage post-designation activities.

Starting 19 June 2018 onwards, organisations seeking to apply to the EMA for a product to be considered for orphan designation will be able to follow a new process or current process of submission. The new process of application for orphan designation will become mandatory from 19 September 2018.

[2] Orphan medicinal products are regulated by Regulation (EC) No 141/2000 which lays down a procedure for the designation of medicinal products as orphan medicinal products and provides incentives for the development and placing on the market of designated orphan medicinal products. The Regulation also established the Committee for Orphan Medicinal Products (COMP) which within EMA gives the orphan designation confirmed by the European Commission.

The IRIS portal can be used for:

- Applying for an orphan designation
- Requesting a pre-submission meeting
- Tracking the process of submitted application
- Responding to requests from EMA for supplementary information
- Viewing submitted historic application
- Changing the name or address of a sponsor
- Requesting an Appeal
- Removing or transferring an orphan designation to a new sponsor

In order to help applicants with the transition, EMA has developed guidelines documents: **Procedure for orphan medicinal product designation** (the current existing submission process until 19 Sept 2018 or via IRIS secure online portal) and **IRIS Quick guide to registration**.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/06/news_detail_002976.jsp&mid=WC0b01ac058004d5c1

Access to IRIS the online web portal: https://iris.ema.europa.eu/

Summary of general informed consent information for Paediatric Clinical Trials in Europe updated by Enpr-EMA

On 26 June 2018, the European Network of Paediatric Research at the EMA (Enpr-EMA) published updated **Informed Consent for Paediatric Clinical Trials in Europe**.

Document updated by Enpr-EMA presents a legal age of consent to be signed by subjects, mandatory or suggested age of ranges defined for assent, number of required signatures, language requirements and links with access to source of these data for European countries.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp&mid=WC0b01ac05801df74a

The documents is available here: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/12/WC500199234.pdf

ICH Guidelines coming into effect

ICH S9 guideline on nonclinical evaluation for anticancer pharmaceuticals - questions and answers

On 16 May 2018, the EMA adapted the **ICH S9 guideline on nonclinical evaluation for anticancer pharmaceuticals - questions and answers**.

[3] The Enpr-EMA is a network of research networks, investigators and centres with recognized expertise in performing clinical studies in children. The first EMA workshop on the European network of paediatric research was in 2009. One of main objectives of Enpr-EMA are fostering high-quality, ethical research on the quality, safety and efficacy of medicines for use in children; helping with the recruitment of patients for clinical trials; enabling collaboration between networks and stakeholders.

The Q&A guideline provides clarity on the guideline scope, studies to support nonclinical evaluation such as toxicological studies, nonclinical data to support clinical trial design and marketing and other considerations referring for example to liposomal products or evaluation of drug metabolites.

This ICH Q&A guideline comes in to effect on 16 November 2018.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000957.jsp&mid=WC0b01ac0580029570

Q&A guideline: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/05/WC500248965.pdf

Guidelines under public consultation

Draft guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with good clinical practice and good manufacturing practice.

This draft guideline was published for consultation by the EMA on 23 May 2018. The consultation end date is **30 August 2018**. The guideline lays down the principles for the two-step release and shipping of the investigational medicinal products by the qualified person and the sponsor. The guideline also describes the areas of interface between the manufacturer and the sponsor and the required contractual agreements.

Source: http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500249275&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

Concept paper on preparation of a revised guideline on the evaluation of medicinal products indicated for treatment of bacterial infections.

This was published for consultation by the EMA on 13 June 2018. The consultation end date is **13 September 2018**. This concept paper proposes the development of a single guideline on the clinical evaluation of medicinal products indicated for treatment of bacterial infections. The development of this single guideline is intended to merge, revise and add to the guidance that is currently included in two separate documents as follows: guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev. 2), adopted in 2011 and in force since 2012 and the addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013), adopted in 2013 and in force since 2014.

Source: http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500250568&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

Guideline on clinical evaluation of vaccines

This was published for consultation by the EMA on 24 April 2018. The consultation end date is **30 October 2018**. This guideline addresses the clinical evaluation of vaccines intended for the prevention of infectious diseases. It includes considerations for trials intended to document the safety, immunogenicity and efficacy of new candidate vaccines and to support changes in the prescribing information of licensed vaccines. It also considers the need for and use of vaccine effectiveness studies. The draft guideline includes specific considerations for clinical trials with vaccines in special populations, such as pregnant women or the elderly. It also adds considerations to priming and boosting strategies, including the option of heterologous prime-boost, which entails administration of one type of vaccine first followed by a different type of vaccine for the same pathogen later.

Source: http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500248095&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

Draft addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address paediatric-specific clinical data requirements - First version

This was published for consultation by the EMA on 06 April 2018. The consultation end date is **30 October 2018**. This document proposes the development of an addendum to the Guideline on the evaluation of medicines indicated for treatment of bacterial infections (CPMP/EWP/558/95 rev 2), to provide specific guidance on paediatric clinical development programmes to support the authorisation of antibacterial agents for treating infectious diseases in children.

Source: http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500247102&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

Draft qualification opinion on Cellular therapy module of the European Society for Blood & Marrow Transplantation (EBMT) Registry

This was published for consultation by the EMA on 29 June 2018. The consultation end date is **21 August October 2018**. The European Society for Blood & Marrow Transplantation (EBMT) Registry holds data on patients given a haematopoietic stem cell transplantation (HSCT) procedure. Draft qualification opinion describes where the cellular therapy module of the EBMT registry is deemed by CHMP as an appropriate data source for post-authorisation studies to support regulatory decision making concerning CAR-T cell therapy for haematological malignancies, together with CHMP's response to the questions posed by EBMT.

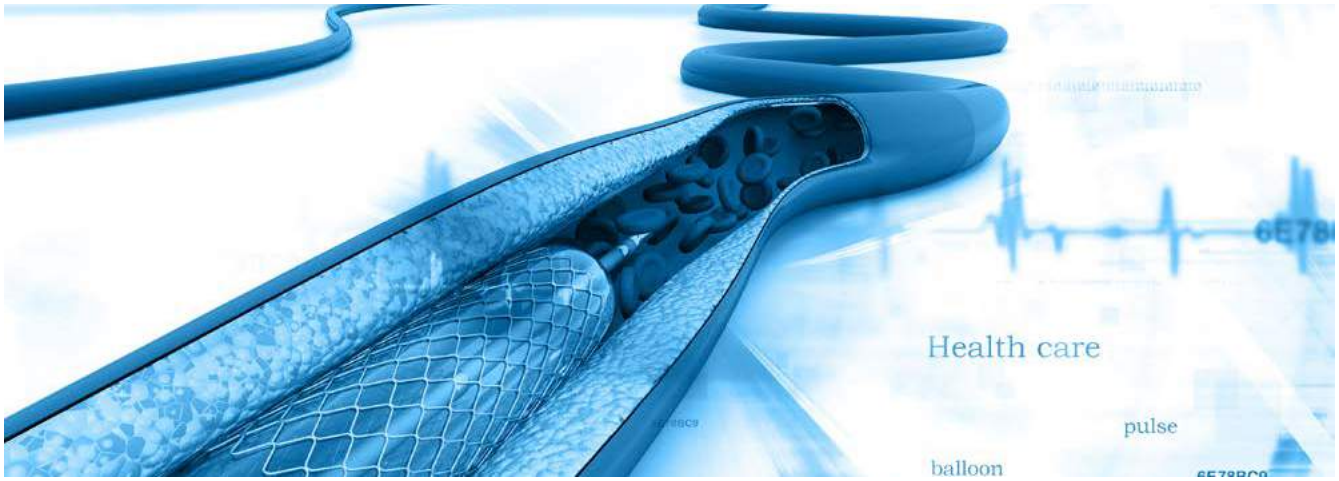
Source: http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500251193&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

Other Initiatives

EMA Info day: regulatory toolbox for medicines and combined devices developers

On 26 October 2018 at the EMA office, London, UK there will be an information day for micro, small and medium-sized enterprises (SMEs). The event will provide an update on regulatory affairs topics for developers of human medicines and combined devices. It covers subjects such as data exclusivity and market protection, orphan and paediatric rewards, legal basis for submission of a marketing authorisation application, conditional marketing authorisations and approvals under exceptional circumstances, classification of advanced therapies and EMA activities in relation to the new medical device legislation. An update on Brexit-related activities will also be provided at the end of the event.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2018/05/event_detail_001633.jsp&mid=WC0b01ac058004d5c3



News from Individual Countries

- ### Belgium

New guidance for submission of clinical trial applications (CTA), substantial amendment notifications and end of trial declarations to the R&D (human) Division of the FAMHP.

On 30 May 2018, the Federal Agency for Medicines and Health Products, the Belgian Competent Authority published Guidance for submission of dossiers to the Research & Development division at FAMHP. This guidance updates and supersedes the circular letter 575.

From 15 May 2018 the submission dossier of CTA and substantial amendments may be entirely electronically submitted via CESP (Common European Submission Portal). During transition period from 15 May to 30 September 2018 it will be still possible to do the submissions using one of options by post (CD-ROM + signed cover letter) or via CESP. From 1 October 2018, all submissions of applications/documents for clinical trials, performance studies and Unmet Medical Need (UMNs) program will be mandatory via CESP to the R&D (human) Division and CD-ROM submissions will not be accepted any more. For 'deliberate release' clinical trial applications with a genetically modified organism the FAMHP will still request to perform the submission by post (CD-ROM/USB + signed cover letter).

Source: https://www.famhp.be/en/news/new_guidance_for_submission_of_clinical_trial_applications_substantial_amendment_notifications

Guidance: https://www.famhp.be/sites/default/files/content/guidance_for_submission_of_cta_initial_dossiers_substantial_amendments_and_end_of_trial_notifications_to_the_rd_division_v1.1_30-05-2018_4.pdf

New database for clinical trials in Belgium

On 7 May 2018, the Belgian Competent Authority, the FAMHP informed about creation an online database to hold the information on all clinical trials that have been approved by the FAMHP and which have not yet been closed. Everyone, including healthcare professionals, will be able to search for a clinical trial. The database is available in English, French and Dutch.

Source: https://www.famhp.be/en/news/new_database_for_clinical_trials_in_belgium

Database: https://clinicaltrialsdatabase.be/en

- ### Denmark

Phase I clinical trials – free of charge

On 3 May 2018, the Danish Medical Agency informed that starting 1 July 2018 commercial and non-commercial sponsors will not be charged (no payment) for authorisation to start a Phase I clinical trial or to make a substantial amendment and they no longer have to pay an annual fee for such trials. The fee changes will improve the framework conditions for clinical trials in Denmark.

Source: https://laegemiddelstyrelsen.dk/en/news/2018/better-conditions-for-clinical-trials-in-denmark/

- ### France

The ANSM revision of clinical trials guidance

The following revised guidelines, annexes and forms have been updated by National Agency for the Safety of Medicine and Health Products (ANSM) between April and June 2018:

- **Avis aux promoteurs d'essais cliniques de médicaments, y compris les essais cliniques portant sur les médicaments de thérapie innovante (MTI) - Tome 1 (31 May 2018)**

The guide, provides instructions and clarifications for sponsors and their representatives on how to conduct clinical trials with medicinal products and Advance Therapy Medicinal Products (ATMPs) in France.

The ANSM also updated the following annexes and appendixes for initial application of clinical trials, substantial amendments and the end of trial declaration:

- Annex 1- Reference texts on clinical trials with medicines (01 June 2018)
- Annex 2- Definitions (01 June 2018)
- Annex 3 - Methods of sending by e-mail the files for clinical trials with medicines (01 June 2018)
- Appendix 4 – Authorization application file summary list of the documents for clinical trial with medicines submitted to the ANSM (01 June 2018)
- Annex 5 - General recommendations on the conditions of use and management of psychoactive substances, in particular narcotics during clinical trials with medicines. (01 June 2018)
- Appendix 6 - Information to be specified in the application file for a clinical trial authorization for early-phase trials (01 June 2018)
- Annex 8 - Contents of the Clinical Trial Application File Without Administration of that medicine for that Trial (01 June 2018)
- Appendix 9 - Contents of the Auxiliary Drug File (01 June 2018)
- Annex 10 - Content of the technical file relating to a medical device or in vitro diagnostic medical device used for research purposes (01 June 2018)
- Appendix 11 - Recommendations on the Admissibility of Clinical Trial Application Files (01 June 2018)
- Appendix 12 - Procedure for resubmission to ANSM of a clinical trial application file (01 June 2018)
- Annex 13 - Contents of the clinical trial application file for a trial that has been the subject of a European coordinated assessment under the VHP procedure (01 June 2018)
- Appendix 14 - Procedures for pre-submission to ANSM for clinical drug trials (01 June 2018)
- Annex 15 - Examples of substantial and non-substantial amendments for the ANSM (01 June 2018)
- Appendix 16 - Examples of presentation of the substantial amendments made to the documents previously submitted to the ANSM (11 June 2018)
- RIPH- Courier application for clinical trial authorization (AEC) - Research 1 on a medicinal product for human use (11 June 2018)
- Form IAA - Application for Attestation to Import Drugs Required to Conduct the Research (01 June 2018)

The guide (Tome 1, is version four repealing version three from 2015). Annexes, appendixes and forms are available only in French.

Source with access to all above mentioned updated guidance: http://ansm.sante.fr/Activites/Medicaments-et-produits-biologiques/Avis-aux-promoteurs-Formulaires/(offset)/2

• Switzerland

Swissethics- new Safety Form

On 6 June 2018, swissethics, the Swiss EC on research involving humans, informed about the new Safety Form to be used for notification of safety events like Serious Adverse Events, Suspected Unexpected Serious Adverse Reactions, Development Safety Update Reports or Annual Safety Reports, urgent safety notifications and other safety notifications) to ECs via the BASEC online system. The Safety Form is mandatory **from 11 June 2018** and the submission of safety reports by email or through the main application form will no longer be accepted.

Source: https://submissions.swissethics.ch/en/

https://swissethics.ch/basec_frontend_faq/knowledgebase.php?article=26

• Italy

AIFA closing the Clinical Research Portal

On 26 June 2018, the Italian Medicines Agency (AIFA) informed sponsors and other organizations like CROs, sponsors' local subsidiaries, EC and Regions/Autonomous Provinces about closing of the Clinical Research Portal. The Clinical Research Portal has been closed due to pending the activation of the new AIFA portal. In case of submission to a new EC, which has not yet been registered in the Clinical Research Portal, the applicant can wait with the submission until the entry into service of the new AIFA platform or submitted in paper format. Dismissal of the Clinical Research Portal will not have impact on so far registered ECs, applicants and sponsors.

The AIFA informs that new platform will be soon implemented but exact date is not mentioned.

Source: http://www.aifa.gov.it/en/content/closing-clinical-research-portal-portale-ricerca-clinica-prc

• The United Kingdom

Consistency across England and Wales for researchers

On 16 April 2018, the Health and Care Research Wales implemented an interim step to align its processes and paperwork so that there is consistency across England and Wales for researchers. From 16 April 2018 all researchers starting new applications in IRAS with sites in Wales will need to complete a Statement of Activities/schedule of events (SoA/SoE). Completion of Site Specific Information (SSI) applications will be not required. From 10 June 2018, SSI applications will be not accepted in Wales, but after this date using SoA/SoE will be mandatory.

In addition, all applications received in Wales after 16 April 2018 will follow a process that is aligned across England and Wales and HRA Approval became HRA and Health and Care Research Wales (HCRW) Approval.

Source: https://www.healthandcareresearch.gov.wales/news/interim-step-in-wales-to-support-4-nations-implementation-of-the-local-information-pack/

The Governance Arrangements for Research Ethics Committees (REC)

On 17 Jun2018, the HRA informed about new the Governance Arrangements for REC. The document is a policy document of the Devolved Administrations, the Health Research Authority and the UK Ethics Committee Authority. It describes what is expected from the research ethics committees that review research proposals and explains when review by these committees is required. This policy covers the principles, requirements and standards for research ethics committees. The HRA informs that the current version remains in place until 16 September 2018 and the new version applies from 17 September 2018.

Source: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/governance-arrangement-research-ethics-committees/

NEWS FROM EUROPE: MEDICAL DEVICES

News from the European Commission.

Update of borderline device classification manual

In April 2018, the European Commission released an update of **Manual on Borderline and Classification in the Community regulatory framework for medical devices** version 1. 19 following the release of Version 1.18 in December 2017.

"Borderline cases are considered to be those cases where it is not clear from the outset whether a given product is a medical device, an in vitro diagnostic medical device, an active implantable medical device or not. Or alternatively, borderline cases are those cases where the product falls within the definition of a medical device but is excluded from the Directives by their scope. Where a given product does not fall within the definition of medical device or is excluded by the scope of the Directives, other Community and/or national legislation may be applicable."

The European Commission added one classification of new type of product, provided six product statuses and presented their outcome:

- A rugby helmet - classified as not a medical device
- An autopsy saw- classified as not a medical device
- UV flow germicidal lamp intended to decrease the level of microbiological load in hospitals - classified as not a medical device
- A water filter- classified as not a medical device, it should also not be considered an accessory.
- Bone void fillers containing animal growth factors to be used to stimulate bone growth and enhance the resorption of the matrix (osteoinduction) – classified as Class III device
- Weight management products (A product that mimics starch in food) - classified as not a medical device
- Whole body and partial body cryotherapy chambers (around –110°C) to the body for short periods of time (around 3 minutes) to be used for pain relief, limitation of oedema post-surgery, treatment of rheumatologic pathologies and muscular injuries, and/or for reduction of inflammation – classified as class II b medical devices

Source: https://ec.europa.eu/docsroom/documents/29021

News from Individual Countries

- **Ireland**

HPRA practical information pack of new EU Devices Regulations

The HPRA, the Irish Competent Authority have just launched a **New EU Device Legislation Information Pack presenting** practical information of New EU Devices Regulations: MDR (Medical Device Regulation, EU 2017/745) and IVDR (In Vitro Diagnostics Regulation, EU 2017/746). The HPRA presents tables with examples of products that will now be considered as a medical device and figures illustrate key obligations outlined in the Regulation. In addition there is information of timeframes for certificate validity according to MDR and IVDR and timelines for the notified body designation process. There is described the scrutiny process defined in the MDR, Chapter V; time frames for reporting serious incidents and listed key changes in the Clinical Investigation process in the MDR. The document provides a summary of the responsibilities of Authorised Representatives, Distributors and Importers under the new EU Device Regulations. There is presented classification of MD and IVDR with examples. The HPRA also describes about innovations in the MedTech sector.

Source: http://www.hpra.ie/homepage/medical-devices/regulatory-information/new-eu-device-regulations

New EU Device Legislation Information Pack: http://www.hpra.ie/docs/default-source/default-document-library/hpra-eu-device-legislation-info-pack.pdf?sfvrsn=0

- **The United Kingdom**

Medical devices: software applications (apps) - new version

On 20 June 2018, The MHRA, the British Competent Authority uploaded a new version of the guidance **Medical device stand-alone software including apps (including IVDMDs)**. The guidance is presented as a step-by-step interactive document and helps software and app customers to identify if their product is a medical device, an in vitro diagnostic device or active implantable medical device and needs to get a CE mark, and how to comply with the legal requirements. The guidance uses examples within flowcharts. The new version includes a new appendix on symptom checkers, and edits to the introduction, diagnosis and new links related to GDPR.

Source: https://www.gov.uk/government/publications/medical-devices-software-applications-apps

Other Initiatives

IMDRF - Unique Device Identification (UDI) Application Guide

The International Medical Device Regulators Forum (IMDRF) established working group to globally harmonised approach to the application of a UDI system and to publish in the future **Harmonized Unique Device Identification (UDI) Application Guide**. "The Work Item is, therefore, intended to contribute to the achievement of the perceived benefits of UDI for regulators and stakeholders implementing UDI around the globe". The working group will start to develop an IMDRF **Technical Document** for UDI providing guidance (definition, instruction, context, etc.) and then the document will be sent for consultation. The IMDRF does not inform on website about timelines to be considered.

Source: http://www.imdrf.org/workitems/wi-udi-application-guide.asp

OTHER "HOT" TOPICS IN THE EU

Brexit updates

Brexit: new guidelines on the framework for future EU-UK relations

On 19 April 2018, the House of Commons Library published **Brexit: new guidelines on the framework for future EU-UK relations**. The Brexit negotiation entered to 3rd phase of negotiation and published guidelines provide information how the EU and the UK envisage their relationship after Brexit. The guidelines affect plenty of aspects of relationships and future cooperation from economical, free movement, transport, regulatory and others point of view.

Source: https://researchbriefings.parliament.uk/ResearchBriefing/Summary/CBP-8289

Brexit: new guidelines: http://researchbriefings.files.parliament.uk/documents/CBP-8289/CBP-8289.pdf

EMA relocation update

On 24 April 2018, the EMA and the Netherlands have finalised the text of a Seat Agreement. The agreement describes how the EMA, its bodies and its employees will be treated by the Dutch Government once they start operating in the Netherlands. The Dutch government and EMA signed the agreement on 1 July 2018.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/04/news_detail_002945.jsp&mid=WC0b01ac058004d5c1

On 28May 2018, a new building in the Zuidas business district of Amsterdam was marked with a ceremony. EMA's new building has been commissioned by the Dutch government. Construction is expected to be finished by November 2019.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002963.jsp&mid=WC0b01ac058004d5c1

Supplementary protection certificates after Brexit

On 27 April 2018, The European Commission published **Brexit – guidance to stakeholders on impact in the field of supplementary protection certificates for medicinal products and plant protection products**. "Supplementary protection certificates (SPCs) are an intellectual property right that serve as an extension to a patent right. They apply to specific pharmaceutical and plant protection products that have been authorised by regulatory authorities." https://ec.europa.eu/growth/industry/intellectual-property/patents/supplementary-protection-certificates_en

The guidance analyses the legal consequences of the United Kingdom's withdrawal on SPCs.

The documents informs that an authorisation to place the product on the market granted by British competent authority as of the withdrawal date will not be considered a first authorisation to place the product on the market in the European Union.

Source: https://ec.europa.eu/growth/content/brexit-—-guidance-stakeholders-impact-field-supplementary-protection-certificates-medicinal_en

The impact of Brexit on the pharmaceutical sector

On 17May 2018, the Business, Energy and Industrial Strategy (BEIS) Committee published 9th report - **The impact of Brexit on the pharmaceutical sector**. The Committee presents regulatory alignment for approval process of medicines, manufacturing and testing requirements and the view of future relationship with the EU and the future of EMA.

"The success of EU-wide regulation of manufacturing and regulation of testing and release of medicines, with the Medicines and Healthcare products Regulatory Agency an integral and influential part, means the Government should prioritise a form of membership with the European Medicines Agency that maintains cooperation and does not require replication of manufacturing sites, testing or roles."

Source: https://www.parliament.uk/business/committees/committees-a-z/commons-select/business-energy-industrial-strategy/publications/

The Report: https://publications.parliament.uk/pa/cm201719/cmselect/cmbeis/382/38202.htm

The European Commission project "Horizon Europe"

On 23 May 2018, the MHRA published presentation explains the UK Government's vision for the future UK-EU Partnership: **Framework for the UK -EU partnership Science, research and innovation**.The presentation is related to the European Commission project "Horizon Europe" which allows third countries "a fair balance as regards the contributions and benefits " in accordance to the European Commission proposal establishing "Horizon Europe": https://ec.europa.eu/commission/sites/beta-political/files/budget-may2018-horizon-europe-regulation_en.pdf.

Horizon Europe would run from 2021 to 2027. The presentation prepared by the UK negotiating team presents the UK own plans for the future and seeking "full association" with "Horizon Europe".

Source: https://www.gov.uk/government/publications/framework-for-the-uk-eu-partnership-science-research-and-innovation

Q&A update for marketing authorisation holders

On 19 June 2018, the European Commission and the EMA have updated and published **Questions and Answers related to the United Kingdom's withdrawal from the European Union**. The Q&A contains information on:

- "location of entities, including:
  - marketing authorisation holders and applicants;
  - orphan designation holders;
  - qualified persons for pharmacovigilance (QPPVs);
  - minor use/minor species (MUMS)/limited markets classification holders;
  - companies' manufacturing and batch release sites.
- effects of Brexit on marketing authorisation applications, batch release processes and inspection outcomes by the UK national competent authority
- authorisation of different types of products, such as generic, hybrid and biosimilar medicines and ancillary medicinal substances in medical devices
- multi-country packs of medicines, where one of the countries in which the packs are to be sold is the UK"

In addition, the EMA also published an updated **Practical guidance for procedures related to Brexit for medicinal products for human and veterinary use within the framework of the centralised procedure** Revision 2. It covers necessary changes to marketing authorisations after Brexit.

Source with access to Q&A and practical guidance: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/06/news_detail_002975.jsp&mid=WC0b01ac058004d5c1

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_001891.jsp&mid=WC0b01ac0580cb2e5b

EMA tracking tool- update

On 25June 2018, the EMA has updated a tracking tool: relocation to Amsterdam. The document is prepared in pdf format and illustrates main milestones for relocation to the new building and availability of temporary building, and then permanent building. The tracking tool shows when is expected a relocation of EMA staff and what process is in progress or on risk.

EMA tracking tool: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2018/03/WC500244941.pdf

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