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REGULATORY NEWSLETTER

July - September 2017

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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 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

News from the European Commission

The European Commission adopted two legal acts on Good Manufacturing Practices for medicines

On 16 September 2017, the European Commission (EC) adopted and published in the Official Journal of the European Union two legal acts aimed at improving patient safety in the European Union (EU) through good manufacturing practices (GMPs) that ensure the highest quality of medicines for human use.

The first act is the **Commission Directive (EU) 2017/1572** of 15 September 2017 supplementing Directive 2001/83/EC of the European Parliament and of the Council concerning the principles and guidelines of good manufacturing practice for medicinal products for human use. ''This Directive lays down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use whose manufacture or import requires the authorisation referred to in Article 40 of Directive 2001/83/EC". Article 40 refers to medicinal products which are manufactured within the Member States (MS) territory or exported to or import from a third country into a MS. This process applies to "both total and partial manufacture, and for the various processes of dividing up, packaging or presentation" of medicinal products for human use. This Directive shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union.*

The second act is the **Commission Delegated Regulation (EU) 2017/1569** of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections. ''This Regulation specifies the principles and guidelines of good manufacturing practice for investigational medicinal products for human use the manufacture or import of which requires an authorisation as referred to in Article 61(1) of Regulation (EU) No 536/2014 and lays down arrangements for inspections of manufacturers in relation to compliance with good manufacturing practice in accordance with Article 63(4) of that Regulation. This Regulation shall enter into force on the twentieth day following that of its publication in the Official Journal of the European Union. It shall apply from six months after the date of publication in the Official Journal of the European Union of the notice referred to in Article 82(3) of Regulation (EU) No 536/2014 or 1 April 2018, whichever is the later.''

"The principles and guidelines for GMP set out in these acts take into account recent updates to the well-established EU rules on the safety of medicines", stated the European Commission.

Source: http://ec.europa.eu/newsroom/sante/newsletter-specific-archive-issue.cfm?newsletter_service_id=327&newsletter_issue_id=5153&page=1&fullDate=Mon%2018%20Sep%202017&lang=default

The Commission Directive (EU) 2017/1572 in 24 languages is available here: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2017.238.01.0044.01.ENG&toc=OJ:L:2017:238:TOC

The Commission Delegated Regulation (EU) 2017/1569 in 24 languages is available here: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2017.238.01.0012.01.ENG&toc=OJ:L:2017:238:TOC

The European Union and the United States cooperation in medicine inspections

The European Union (EU) and the United States (US) regulators have signed a mutual recognition agreement (MRA) on good manufacturing practice (GMP) inspections. The MRA will enter into force on 1 November 2017 and will be in transition phase until July 2019.

"The aim of the MRA is to encourage greater international harmonisation, make better use of inspection capacity and reduce duplication" the European Medicines Agency (EMA) stated.

During the transition phase the authorities will assess each other's pharmaceutical legislation, guidance documents and regulatory systems as part of the agreement. The Food and Drug Administration (FDA) must sign a confidentiality agreement with each Member State in the EU, before inspection reports may be shared. Imported products still need to be batch tested until the FDA recognises all EU Member States' authorities for human pharmaceuticals.

In addition, to facilitate the implementation of the MRA, the EMA, the European Commission (EC) and the FDA signed a confidentiality commitment in August 2017, which allows the FDA to share full inspection reports of medicine manufacturers, including trade secret information with EU regulators.

"This allows the two agencies to make decisions based on findings in each other's inspection reports and to make better use of their inspection resources to focus on manufacturing sites of higher risk."

Source: https://ec.europa.eu/health/human-use/quality_en#euus

EMA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000651.jsp&mid=WC0b01ac0580a51ff3

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001843.jsp&mid=WC0b01ac058005f8ac

News from the European Medicines Agency

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

Systems and guidelines coming into effect

New EudraVigilance system in the EEA

After an independent audit and a subsequent favourable recommendation from the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) in May 2017, the EMA announced that the final EudraVigilance (EV) system would be set to go live on 22 November 2017.

EudraVigilance is the European information system where marketing authorisation holders (MAHs) and sponsors of clinical trials must report and evaluate suspected adverse drug reactions during the development and following the marketing authorisation of medicinal products in the European Economic Area (EEA).

On 10 August, the EMA published version 1.1 of the Questions and Answers (Q&A) from stakeholders: The launch of the new EudraVigilance System.

The questions cover a wide variety of topics such as how to log into the reporting system, what kind of IT requirements are needed and how to grant access to Clinical Research Organizations (CROs). The questions were received through the EMA's service desk and as part of the technical and pharmacovigilance/EudraVigilance support webinars organised by the EMA since June 2017. The Q&A has been updated to version 1.2 dated 05 October 2017. The EMA will publish updated versions of the Q&A on its website. Companies are advised to check on a regular basis:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000153.jsp&mid=

In addition, on 3 October 2017 the EMA published EudraVigilance go-live plan and Technical Note on the planned EudraVigilance downtime from 8 to 21 November 2017.

The new version of EudraVigilance requires the transfer of more than 11 million Individual Case Safety Reports (ICSRs) from the post-authorisation phase and clinical trials. Due to the transfer of such a large amount of data, some functionalities of the system will be entirely or partially unavailable for a period of ten working days, **from 8 to 21 November 2017**.

The EudraVigilance go-live plan provides steps to be followed by MAHs, national competent authorities (NCAs), and sponsors of clinical trials in the EEA during the cutover time (8-21 November 2017). The NCAs and MAHs have 3 options for submitting Individual Case Safety Report (ICSRs) (in adverse drug reaction reporting; ADR) and suspected unexpected serious adverse reactions (SUSARs).

Option 1: MAHs and NCAs stop submitting ICSRs during the cutover and report them electronically AND the sponsors of clinical trials stop the electronic submission of SUSARs from clinical trials.

Option 2: MAHs and NCAs stop submitting ICSRs during the cutover and report them electronically AND the sponsors of clinical trials stop the electronic submission of SUSARs. But, in addition, the MAH/ sponsor has to follow one of the three alternative arrangements during the cutover period presented in the EudraVigilance go-live plan.

Option 3: MAHs continue to submit ICSRs electronically to national authorities where this is technically feasible and NCA continue providing ICSRs to the World Health Organization Uppsala Monitoring Centre (WHO-UMC). When electronic reporting is not feasible, MAHs must submit the reports electronically after the cutover period and continue to follow dedicated national reporting arrangements.

The sponsors of clinical trials continue with the electronic submission of ICSRs to the Member State where this is technically feasible or continues with the current established reporting method for SUSARs to the Member State.

Where electronic reporting is not feasible, the sponsor has to follow alternative arrangements for reporting to the Member State during the cutover period based on one of the provisions presented in the EudraVigilance go-live plan: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/09/WC500235774.pdf

Options for the cutover time (8-21 November 2017)	Countries where options must be followed by NCA, MAHs and sponsors
Option 1	
ICSRs (ADR reporting)	Austria, Belgium, Bulgaria, Cyprus, Estonia, Spain, Finland, France, Croatia, Ireland, Liechtenstein, Luxembourg, Lithuania, Latvia, Malta, The Netherlands, Norway, Poland, Portugal, Sweden, Slovenia, Slovakia.
SUSARs reporting	Belgium, Bulgaria, Cyprus, Estonia, Finland, Ireland, Liechtenstein, Lithuania, Latvia, Malta, The Netherlands, Norway, Sweden.
Option 2	
ICSRs (ADR reporting)	Hungary, Czech Republic, Denmark, Greece, Iceland, Romania, Italy.
SUSARs reporting	Austria , Hungary, Czech Republic, Denmark, Spain, Greece, Italy, Croatia, Poland, Portugal, Romania, Slovenia, Slovakia
Option 3	
ICSRs (ADR reporting)	The United Kingdom, Germany.
SUSARs reporting	Germany, France, Luxembourg, Iceland, The United Kingdom

In addition, all Sponsors should notify Member States within 3 days of any action needed to protect the health and safety of clinical trial subjects.

Sponsors should continue to report any safety issues not falling within the definition of SUSAR in accordance with the detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')(2011/C 172/01). With EudraVigilance Clinical Trial Module (EVCTM) not being available as of 8 November 2017, sponsors need to be aware that acknowledgement messages (ACKs) for safety messages sent on 6 and 7 November, may not be returned.

Safety messages must NOT be submitted to EVCTM during the cutover period!

The safety messages will NOT be queued and will be discarded!

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

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/10/news_detail_002820.jsp&mid=WC0b01ac058004d5c1

Questions and Answers (Q&A) from stakeholders version 1.2: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/07/WC500230934.pdf

EudraVigilance go-live plan: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/09/WC500235774.pdf

Technical Note on the planned EudraVigilance downtime from 8 to 21 November 2017: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/09/WC500235775.pdf

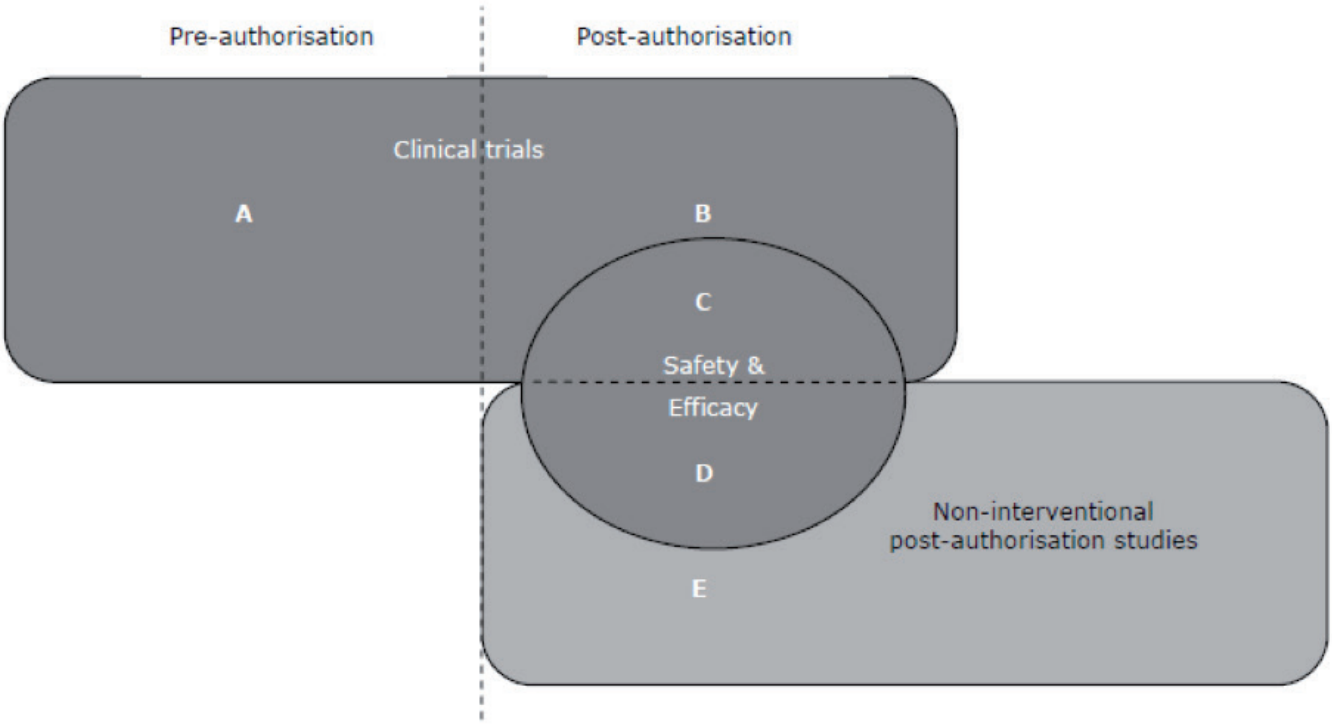
Revision 2 of good pharmacovigilance practices Module VI

The European Medicines Agency (EMA) has revised its good pharmacovigilance practice (GVP) guideline and published final Revision 2 of Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products. Revision 2 comes into effect on the 22 November 2017 at the same day when the final new EudraVigilance (EV) system will be set to live in the European Economic Area (EEA).

This Module of GVP addresses the legal requirements detailed in Directive 2001/83/EC and Regulation (EC) No 726/2004, which are applicable to competent authorities (CAs) in Member States, marketing authorisation holders (MAHs) and the EMA as regards the collection, data management and submission of individual reports of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorised in the European Union (EU).

On the first page of the guideline is a note listing 10 new updates made in Revision 2. The guideline also includes a figure describing the different types of clinical trials and studies conducted in the EU and the safety requirements applicable to each type of study.

Figure VI.1. Different types of clinical trials and studies conducted in the EU



The management of individual safety reports for clinical trials designated by sections A, B, and C follows the requirements of Directive 2001/20/EC, whereas individual safety reports for non-interventional post-authorisation studies corresponding to section D and E follows the requirements of Directive 2001/83/EC and Regulation (EC) No 726/2004."

If clinical trials, conducted under the scope of Directive 2001/20/EC (section A), yield safety concerns which impact on the risk-benefit balance of an authorised medicinal product, the competent authorities in the Member States where the medicinal product is authorised and the EMA, should be notified immediately.

Where an untoward and unintended response from a clinical trial conducted in accordance with Directive 2001/20/EC is suspected to be related only to a medicinal product other than the Investigational Medicinal Product (IMP) and does not result from a possible interaction with the IMP, it should be managed in line with the requirements provided in Art 107(3) and 107a (4) of Directive 2001/83/EC. The same applies when the adverse reaction is suspected to be related only to an authorised non-investigational medicinal product (NIMP). In this context, the investigator or the sponsor is encouraged to report the case to the competent authority in the Member State where the reaction occurred or to the MAH of the suspected medicinal product, but not to both to avoid duplicate Individual Case Safety Reports (ICSRs) submission.

Table VI.1 of Revision 2 provides more detailed guidance for all collected adverse events (AEs) and those not collected AEs, as specified in the study protocol for non- interventional post-authorisation studies (section D and E).

Table VI.1. Management of adverse events for non-interventional post-authorisation studies with a design based on primary data collection

For collected adverse events, including all adverse events with fatal outcome	
Requirements for adverse events	• Collect and record comprehensive and high quality information. • Perform causality assessment. • Summarise all collected adverse events in the interim safety analysis and in the final study report.
Requirements for suspected adverse reactions	• Cases of adverse reactions which are suspected to be related to the studied medicinal product by the primary source or the notified organisation should be recorded in the pharmacovigilance database. • Valid ICSRs should be managed classified and submitted as solicited in line with the appropriate time frames. • In certain circumstances, suspected adverse reactions with fatal outcome may not be subject to submission as ICSRs. A justification should always be provided in the protocol.
For adverse events not collected, as specified in the study protocol	
Requirements for suspected adverse reactions	• Inform healthcare professionals and consumers of the possibility to report suspected adverse reactions to the marketing authorisation holder or to the concerned competent authority via the national spontaneous reporting system. • Valid ICSRs should be managed, classified and submitted as spontaneous in line with the appropriate time frames. • When made aware of them, these ICSRs should also be summarised in the relevant study reports by the marketing authorisation holder sponsoring the study.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c

Final guidance: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/08/WC500232767.pdf

Module VI Addendum I – Duplicate management of suspected adverse reaction reports

On 28 July 2017, the European Medicinal Agency (EMA) adopted the Addendum I of Module VI: Duplicate management of suspected adverse reaction reports.

The guideline proposes methods for detecting, confirming and managing duplicate cases suitable for organisations receiving pharmacovigilance data in various different formats and describes methods for stakeholders to collaborate with the EMA in the detection and management of duplicate cases.

The simplified reporting rules described in the guideline will come into effect on 22 November 2017 and are expected to significantly reduce the number of duplicate cases. The guideline states "In large databases like EudraVigilance (EV), there is a strong need to eliminate duplicates".

This guideline is part of the good pharmacovigilance practices (GVP) and an Addendum to GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products, Revision 2.

Examples from the guideline of common causes of duplicate reports:

- A consumer and a healthcare professional reporting the same reaction occurrence;
- Multiple health care professionals treating the same patient reporting the same reaction occurrence;
- A reaction occurrence being reported to EV by the original reporter to both the marketing authorisation holder and a competent authority in a Member State;
- Literature reporting of the same reaction occurrence for generics.

GVP Module VI of the Guideline states that when one party is made aware that the primary source(s) may also have reported the suspected adverse reaction to another concerned party, the report should still be considered as a valid individual case safety report (ICSR). All the relevant information necessary for the detection of the duplicate case should be included in the ICSR.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c

Guideline: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/08/WC500232765.pdf

Updated guidelines to be released as final in 2018

Guideline on first-in-human clinical trials

On 20 July 2017, the European Medicines Agency (EMA) published Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products Revision 1. The guideline will come into effect on 01 February 2018.

First-in-human (FIH) trials, also called First-in-man/Phase-1 studies, are studies where investigational medicinal product (IMP) is administered to people for the first time. FIH studies are a key step in the development of medicines. Participants in these trials are often healthy volunteers but can also include patients.

This guideline covers FIH/early clinical trials (CTs) including those studies which generate initial knowledge in humans on tolerability, safety, pharmacokinetics (PKs) and pharmacodynamics (PDs). The guideline applies to all new chemical and biological IMPs. While advanced therapy medicinal products (ATMPs) are not within this scope, some principles of this guideline are relevant on a case-by-case basis.

Revision 1 is intended to assist stakeholders in the transition from non-clinical to early clinical development and in identifying factors influencing risk for new IMPs. The guideline gives strategies for mitigating and managing risks, including principles on the calculation of the starting dose to be used in humans, the subsequent dose escalations, the criteria for maximum dose and the conduct of the trial inclusive of multiple parts.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/07/news_detail_002783.jsp&mid=WC0b01ac058004d5c1

Guideline: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/07/WC500232186.pdf

Clinical investigation of medicinal products for the treatment of chronic heart failure

On 20 September 2017, the European Medicinal Agency (EMA) published Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure. This Revision 2 will enter into effect on 01 March 2018.

The scope of this guideline is restricted to the development of medicinal products for the treatment of patients with chronic heart failure (CHF) including those in the post-acute phase of heart failure.

This guideline is intended to assist applicants during the development phase and is for guidance only.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/clinical_cardiovascular_system/general_content_001089.jsp&mid=WC0b01ac0580034cef

Adopted guideline: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/09/WC500235089.pdf

Other guidelines published by the EMA

Post-authorisation safety studies: questions and answers - updates

On 14 July 2017, the European Medicine Agency (EMA) updated its three guidances for post-authorisation activities:

- Pre-submission checklist for type II variation applications
- Questions and answers for post-authorisation safety studies (PASS)
- Classification of post-authorisation changes - Quality aspects

The main aim of these updates was to improve the quality of post-authorisation applications by better assisting applicants in complying with the legal and regulatory requirements and avoiding frequent mistakes.

For the guidance Questions and answers for post-authorisation safety studies (PASS), the EMA has added 15 new questions and answers to provide marketing authorisation holders (MAHs) with detailed information on the submission requirements, assessment and implementation of outcomes for protocols, protocol amendments and final study reports of non-interventional imposed PASS.

A PASS is any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk management measures (Directive 2001/83/EC Article 1(15)). A PASS may cover clinical trials and non-interventional studies. A PASS is a non-interventional study (NIS) if the medicine:

EMA action plan for small and medium-sized enterprises (SMEs)

- is prescribed in the usual way in accordance with the terms of the marketing authorisation;
- decision how to treat a patient is based on current practice and not a trial protocol;
- prescription of the medicine is clearly separated from the decision to include the patient in the study;
- patients do not undergo additional diagnostic or monitoring procedures;
- data analysis uses epidemiological methods (systematic reviews and meta-analyses of safety data should be considered NIS PASS).

A European Union competent authority (CA) may impose a NIS PASS, either as a condition of marketing authorisation (category 1) at the moment of granting the marketing authorisation or in the post-authorisation phase; or as a specific obligation in a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (category 2).

The EMA has posted on their website questions and answers for PASS. Topics covered include: how the submission process should be performed; where to submit the protocol, amendments, and final study report; and where to register the NIS PASS. Topics that are new or revised are marked 'New' or 'Rev.' upon publication.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/07/news_detail_002777.jsp&mid=WC0b01ac058004d5c1

Questions-and-answers for post-authorisation safety studies (PASS):

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000134.jsp&mid=WC0b01ac0580796d88

Post-orphan medicinal product designation procedures

On 12July 2017, the European Medicines Agency (EMA) published Revision 7 of Post-orphan medicinal product designation procedures as the Guidance for Sponsors.

The "orphan medicines" are medicines for rare diseases. The opinions on orphan designation are adopted by the Committee for Orphan Medicinal Products (COMP) at their monthly meetings at the EMA. The final COMP opinion (negative or positive) is forwarded to the European Commission (EC) and the sponsor. The decision on the designation is adopted by the EC within 30 days of receipt of the COMP opinion and forwarded to the sponsor. The designated medicinal product is entered in the Community Register here:
http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm

This guideline covers the following information and procedures applicable to orphan designated products:

- Incentives
- Annual reports
- Transfer of sponsorship
- Change of sponsor's name or address
- Amendment of designated condition
- Marketing authorisation application

- Review of the maintenance of orphan medicinal product designation at the time of marketing authorisation application
- Review of the maintenance of orphan medicinal product designation at the time of extending the therapeutic indication post-authorisation
- Withdrawal of orphan designation.
- Information for sponsors with reference to the United Kingdom's withdrawal from the EU ('Brexit')
- General advice

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500196994&mid=WC0b01ac058009a3dc

Published guidance: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196994.pdf

Common EMA/FDA Application for Orphan Medicinal Product Designation

In September 2017, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) published Common EMA/FDA Application for Orphan Medicinal Product Designation.

The agreement between Agencies and created common application allow the sponsors to apply for orphan designation of the same medicinal product for the same use in both jurisdictions to EMA and FDA.

The sponsor must submit one original copy in paper (signed and dated) and two electronic copies to EMA. FDA requires either two paper copies of the application or it may be submitted via electronic format through the use of physical media.

EMA: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000519.jsp&mid=WC0b01ac05804ece5e

FDA: https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm124795.htm

Application Form: http://www.ema.europa.eu/docs/en_GB/document_library/Template_or_form/2013/09/WC500148543.pdf

EMA Scientific recommendation on classification of ATMPs

On 18 August 2017, the European Medicinal Agency (EMA) published 15 reports of the EMA scientific recommendations on classification of advanced therapy medicinal products (ATMPs). Each report is a summary for public release of a scientific recommendation on classification of ATMPs. Each report contains a brief description of the active substance, a brief description of the finished product, the proposed indication and the EMA/Committee for Advanced Therapies (CAT) conclusion stating whether the product falls within the definition of a gene therapy medicinal product as provided in Article 2(5) of Regulation (EC) 1394/2007.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/landing/whats_new.jsp&month=8&year=2017&mid=WC0b01ac058004d5c4

Guidelines under public consultation

Concept paper on the revision of the guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells - Superseeding document

On 24 July 2017, the European Medicinal Agency (EMA) published for consultation the Concept paper on the revision of the guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells - Superseeding document. The consultation end date is 31 October 2017. Comments should be submitted to: catsecretariat@ema.europa.eu.

The revised guideline referred to in this concept paper will replace the guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (EMA/CAT/GTWP/671639/2008). The guideline covers all cases of genetically modified cells intended for use in humans, independent of whether the genetic modification has been carried out for clinical indication (i.e. gene therapy medicinal products), for manufacturing purposes or any other reason. The genetically modified cells can be of human origin (autologous or allogeneic) or animal origin (xenogeneic cells), either primary or established cell lines. Genetically modified cells of bacterial origin are excluded from the scope of this guideline.

Source: http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500231995&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

Concept paper: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/07/WC500231995.pdf

Concept paper on the development of guidance on the non-clinical evaluation of radiopharmaceuticals - First version

On 01 August 2017, the European Medicinal Agency (EMA) released for consultation the Concept paper on the development of guidance on the non-clinical evaluation of radiopharmaceuticals - first version. The consultation end date is 31 October 2017. Comments should be submitted to swp-h@ema.europa.eu.

The concept paper is intended to seek external stakeholder views on potential guidance development related to overarching considerations for non-clinical data in support of clinical development and approval of radiopharmaceuticals. This guidance is intended to complement currently available guidelines (such as ICH M3(R2), ICH S6(R1), ICH S9 or the EMA Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products) and includes the different intended uses of radiopharmaceuticals including radiodiagnostics as well as radiotherapeutics. The paper will focus on opportunities to targeted non-clinical programs according to specific development settings and product types and is not intended to duplicate guidance related to dosimetry.

Source: http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500232667&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

Concept paper: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/07/WC500232667.pdf

- Non-interventional or observational research (refers to Art. L1121-1 3° CSP). These researches do not involve any risk or constraint added by the research or any modification of the usual care. Such studies include post-CE marked MD and IVDMD using according to its indications. These clinical interventions must be notified to the ANSM including the CPP approval and submitted for a favourable opinion to CPP. Clinical Investigations concerns only data, already collected or to be obtained from collections or old samples do not fit into the ANSM-CPP circuit, but should be sent to the CEREES (Committee for Expertise in Research, Studies and Evaluations in the field of Health) for advice (to the Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé (CCTIRS).

The Tom I guidance consists of 70 pages with 10 Annexes. There are step by step instructions on how to proceed with submissions to the ANSM, list of required documents, references, recommendations, answers to frequently asked questions. The document could be considered as a work instruction for sponsors and applicants on how to go through the whole authorization process of Clinical Investigation or evaluation with MD and IVDMD in France.

The guidance is available only in French.

Resource and guidance: http://ansm.sante.fr/Activites/Dispositifs-medicaux-et-dispositifs-medicaux-de-diagnostic-in-vitro/Essais-cliniques-portant-sur-les-dispositifs-medicaux-et-dispositifs-medicaux-de-diagnostic-in-vitro/(offset)/0

Draft ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, step 2b - Revision 1

On 31 August 2017, the European Medicinal Agency (EMA) published draft addendum for public consultation Draft ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, step 2b - Revision 1. The consultation end date is 28 February 2018. Comments should be submitted to ich@ema.europa.eu

The addendum provides guidance on the design, conduct, analysis and evaluation of clinical trials of an investigational product in the context of its overall clinical development. It also assists with preparing application summaries or assessing evidence of efficacy and safety, principally from clinical trials in later phases of development.

Source: http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500233916&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

Draft addendum: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/08/WC500233916.pdf

Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle

On 28 July 2017, the European Medicinal Agency (EMA) published concept paper for consultation by 15 November 2017 on predictive biomarker-based assay development in the context of drug development and lifecycle. Comments should be submitted to: pgwpsecretariat@ema.europa.eu

The proposed concept paper is intended to be developed into a guideline which will replace the reflection paper on co-development of pharmacogenomic biomarkers and assays in the context of drug development. The guideline will provide recommendations on the interface between predictive biomarker-based assays including Companion diagnostic (CDx), and the development and lifecycle of a medicine.

The concept paper is the first step in the preparation of a guideline that will address the development challenges of personalised medicines with companion diagnostics.

The term personalised medicine in the context of this guidance refers to the targeted use of a treatment in a patient on the basis of the individual's characteristics and genetic makeup and the understanding of how the treatment works.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/07/news_detail_002788.jsp&mid=WC0b01ac058004d5c1

Concept paper: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/07/WC500232420.pdf

ICH guidelines entered into the implementation period

ICH Q11 Q&A

In August 2017, the ICH Q11 Q&A reached Step 4 of the ICH (International Council for Harmonisation) process. The document is now entering Step 5 – the implementation period.

These Q&As are intended to provide additional clarification and to promote convergence on the considerations for the selection and justification of starting materials and on the information that should be provided in marketing authorisation applications and/or Master Files. The focus of the Q&A document is on chemical entity drug substances.

Source: http://www.ich.org/ichnews/newsroom/read/article/the-ich-q11-qa-reaches-step-4-of-the-ich-process.html

ICH Q11 Q&A: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Q11IWG_Step4_QA_2017_0823.pdf

The ICH E11 (R1) Addendum on Clinical Investigation of Medicinal Products in the Pediatric Population

On 12 September 2017, the International Conference for Harmonization (ICH) posted on its website that ICH E11 (R1) Addendum on Clinical Investigation of Medicinal Products in the Pediatric Population reached Step 4 in August 2017 and has now entered into the implementation period (Step 5).

The ICH description: "Since the adoption of the ICH E11 Guideline on Clinical Investigation of Medicinal Products in the Pediatric Population in 2000, pediatric drug development has been enhanced by advancements in several areas of general adult drug development. Targeted scientific and technical issues relevant to pediatric populations, regulatory requirements for pediatric study plans, and infrastructures for undertaking complex trials in pediatric patient populations has been considerably advanced in the last decade, without a parallel development of harmonised guidance in these areas. This Addendum is proposed to address new scientific and technical knowledge advances in pediatric drug development."

Source: http://www.ich.org/ichnews/newsroom/read/article/the-ich-e11r1-addendum-reaches-step-4-of-the-ich-process-copy-1.html

Final addendum: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/E11-R1EWG_Step4_Addendum_2017_0818.pdf

Other Initiatives

ICH Releases Concept Paper for Planned Guideline on Collecting Safety Data

On 26 July2017, the International Conference for Harmonization (ICH) released the final concept paper and business plan for new guidance E19: Optimisation of Safety Data Collection.

This new guideline is proposed to provide internationally harmonised guidance on when it would be appropriate to use a targeted approach to safety data collection in some late-stage pre-marketing or post-marketing studies, and how such an approach would be implemented.

The ICH presented main milestones: Step 1-May 2018, Step 2-November 2018, Step 3-November 2019 and Step 4-June 2020

Source: http://www.ich.org/ichnews/newsroom/read/article/ich-m7r1-addendum-reaches-step-4-of-the-ich-process-copy-1.html

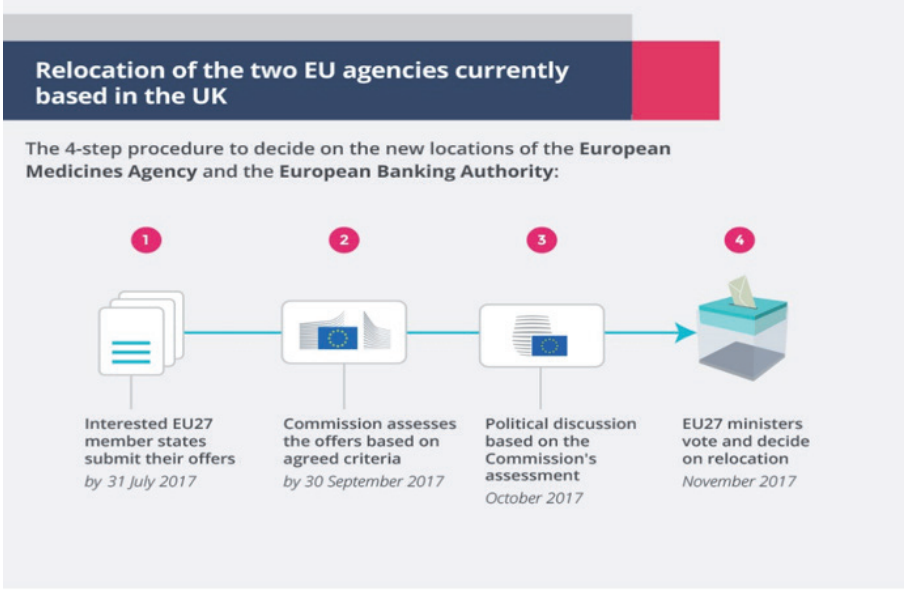
Final concept paper: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E19/E19_EWG_Concept_Paper_27Jun2017.pdf

Final business plan: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E19/E19_EWG_Business_Plan_27Jun2017.pdf

EMA new home - continuation

a. General Assessment Summary

At the beginning of July, the European Council published a timetable for the relocation of the European Medicines Agency (EMA) after the UK leaves the EU on 30 March 2019. The graphics below illustrate the procedure for the relocation of the EMA and the European Banking Authority (EBA).



Council of the European Union
General Secretariat

The European Commission (EC) has subsequently assessed the 27 offers provided by the Member States. There have been nineteen offers to host the EMA and eight for the EBA. On 30 September 2017, the EC submitted its assessment of the offers to the Secretary-General of the Council. The assessment consisted of the following documents:

- Commission note
- General assessment summary, one for each Agency
- Individual assessment summaries, one for each offer
- Individual assessment grids, one for each offer

The assessments are available for download here: https://ec.europa.eu/info/about-european-union/relocation-uk-based-eu-agencies_en

The General assessment summary includes a summary of each MS offer in relation to availability of buildings for the Agencies, accessibility, education facilities for children of the EMA and EBA employees, languages availabilities, labour market, social security, medical care, business continuity and geographical spread.

The individual assessment summaries discussed specific issues taken by the EC and presented proposals by each country for the issue and the EC assessment.

In addition, the EC published on 30 September the Question and Answers regarding assessment of MS offers to host EMA and EBA after Brexit. The EC explains why the assessment must be done, what the EMA and EBA are and that some information presented by the MSs have not been published on the assessments due to some MSs request for keeping particular data confidential. (http://europa.eu/rapid/press-release_MEMO-17-3584_en.htm).

On 3 October EMA published comments on Member States' hosting bids. See:

http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2017/10/WC500236021.pdf

Further to the June 2017 meeting of EMA Management Board and initial plan, on 16th October EMA's business continuity plan for Brexit was published. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/10/news_detail_002828.jsp&mid=WC0b01ac058004d5c1

In October, the European Council will have a political discussion based on the assessment.

On 20 November, the decision on where the EMA and the EBA will reside will be taken by vote of the 27 EU ministers at the General Affairs Council meeting.

b. MHRA Response to EU Referendum

In August, the Medicines & Healthcare Products Regulatory Agency (MHRA), the British Competent Authority, updated its response to the outcome of the EU referendum regarding medicine regulation, device regulation, vigilance and market surveillance, and future regulatory partnership.

The Secretary of State for Health and the Secretary of State for Business, Energy and Industrial Strategy laid out the three principles which will underpin the development of a post-Brexit regulatory system for medicines and devices:

- "Patients should not be disadvantaged;
- Innovators should be able to access the UK market as quickly and simply as possible;
- And we will continue to play a leading role in both Europe and the world in promoting public health."

The MHRA will be continuing implementation of EU Clinical Trial Regulation 536/2014, the new Medical Device Regulation and the In-Vitro Diagnostic Regulation.

MHRA website: https://www.gov.uk/government/news/medicines-and-healthcare-products-regulatory-agency-statement-on-the-outcome-of-the-eu-referendum

c. A Perspective from MedTech Europe

In September, the leaders from three medical devices and in vitro diagnostics industries in

Europe and the United Kingdom: MedTech Europe, the Association of British Healthcare

Industries (ABHI) and the British In Vitro Diagnostics Association (BIVDA) submitted a letter to European Commission and the United Kingdom negotiators calling for the UK to retain close ties to the EU after Brexit.

The leaders highlighted the need for the UK to "remain an active part" of the CE-mark system "under a full implementation of the new Medical Devices and In Vitro Diagnostic Medical Devices Regulations".

(http://www.medtecheurope.org/sites/default/files/resource_items/files/Joint%20Medical%20Technology%20Associations%20Brexit%20Letter.pdf)

Source: https://www.theyworkforyou.com/wrans/?id=2017-09-04.7565.h&s=pharmaceutical#g7565.q0

In addition, on 20 September BioIndustry Association (BIA) and the Medicines & Healthcare Products Regulatory Agency (MHRA) published a report 'Innovation in life sciences in a changing and dynamic environment' https://www.gov.uk/government/news/bia-mhra-publish-report-innovation-in-life-sciences-in-a-changing-and-dynamic-environment

EMA is preparing a series of further guidance documents which will be published on its website. Companies are advised to regularly check EMA's dedicated webpage on the consequences of Brexit.

Question and Answer guidance published by the EMA: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500228739.pdf

Source: http://www.consilium.europa.eu/en/meetings/european-council/2017/06/22/

NOTE: CROMSOURCE will continue to track the EMA and the EC decisions about EMA new home due to the United Kingdom's withdrawal from the EU. Updates will be published in the Regulatory Newsletter.

News from Individual Countries

Austria

Guide to Compassionate Use

On 29 August 2017, the Austrian Federal Office for Safety in Health Care (BASG), the Austrian Competent Authority, published an updated Guidance Compassionate Use Programmes in Austria. The guide is available in German and English.

The scope of this guidance is to detail the definition of the term "Compassionate Use"(CU), and to outline the procedural details for compassionate use programme (CUP) applications in Austria.

The document provides information about the submission process, where the CUP applications should be submitted, the fees, recommendations for protocol, lists of documents which should be submitted in application, describes assessment process by authorities, reporting obligations, and pharmacovigilance requirements for CU in Austria. In addition, advice is provided how to proceed in case of a CUP with a medicinal product that fulfils the definition of a gene therapy or with a medicinal product that constitutes a genetically modified organism.

The BASG also compares requirements for CU versus Named Patient Use (NPU), Clinical Trials and Non-Interventional Studies.

Source: http://www.basg.gv.at/en/medicines/prior-to-authorisation/compassionate-use/

France

Updated Guide: Clinical Drug Trials submitted within the Pilot Phase to ANSM and the CPP (v 6.0)

In August 2017, the Agence nationale de sécurité du médicament et des produits de santé (ANSM), the French National Agency for Medicines and Health Products Safety, published updated Practical information guide for applicants planning submission for clinical trials authorisation within the Pilot Phase to ANSM and the CPP (French Ethics Committee). The document is available in English and French.

The guidance emphasizes that participating in the Pilot Phase at the moment is still optional and the sponsor can choose from two options:

1. In accordance with the current legislation

2. Or in accordance with the pilot phase proposed by ANSM, which is described in the applicable guide.

The document describes the very detailed submission process to both the ANSM and the CPP. The deadlines, timelines and contact emails depend on the applicant's situation. The Guide includes the list of documents mandatory for submission and the summary of the dialog between Sponsor, the ANSM and the CPP in case the sponsor decides to take part in the Pilot Phase in France.

Source and Guide: http://ansm.sante.fr/Activites/Medicaments-et-produits-biologiques/Phase-pilote-application-du-Reglement-UE-N-536-2014-du-Parlement-europeen/(offset)/6

Czech Republic

Updated the Text of Patient Information Leaflet Trial Subject Information Sheet /Informed Consent

The State Institute of Drug Control (SUKL), the Czech Republic Regulatory Agency, published updated Requirements Governing the Text of Patient Information Leaflet Trial Subject Information Sheet /Informed Consent Form KLH-22 version 3 with an effective date of 14 September 2017.

The Guideline is for recommendation, however the requirements presented in the KLH-22 v. 3 for Patient Information Sheet (PIS) and Informed Consent Forms (ICFs) are preferred by the Czech Authority and Ethics Committees. Apart from the general requirements that should be specified in each section of the PIS and ICF, the guidance includes suggested translations of parts of the text into Czech.

In addition, there are instructions for Information Sheets for paediatric patients, guardians, caregivers, in case patients unable to provide consent are being enrolled or in case patients unable to write and/or read are being enrolled.

Source and Guidelines in English http://www.sukl.eu/medicines/klh-22-verze-3

The United Kingdom

a. Combined IRAS form to be used across the UK

The Health Research Authority (HRA), the Central Ethics Committee for the National Health Service (NHS) in England and in the United Kingdom announced that as of 28 June 2017, one combined Integrated Research Application System (IRAS) form is to be used for projects where the lead NHS R&D (Research & Development) office is based in England as well as for projects where the lead NHS/Health and Social Care (HSC) R&D office is based in Northern Ireland, Scotland or Wales.

IRAS is a single system for applying for permissions and approvals to research ethics committees (RECs) in the UK and helps to meet regulatory and governance requirements.

Previously, if the project had been led from Northern Ireland, Scotland, or Wales, the IRAS form was not applicable. Since 28 June 2017, the combined IRAS form replaced the separate REC and R&D forms that had been used in Northern Ireland, Scotland, or Wales. The separate submission for ethical review and review against NHS/HSC standards will be continued as per current process in those three nations of the UK (not HRA approval process).

In England, the single electronic submission of the IRAS form and accompanying documents for both ethical review and for review against NHS/HSC standards will remain (HRA approval process).

“Adoption of the single IRAS form UK-wide will save time and effort for applicants and sponsors and help build UK-wide consistency” HRA stated.

Source: http://www.hra.nhs.uk/news/2017/06/21/combined-iras-form-replaces-separate-ethics-rd-application-forms-uk-wide-basis/

b. Electronic vs ink signatures in research approval documents

On 12 July 2017, the Health Research Authority (HRA), published clarification regarding the use of electronic vs ink signatures in research approval documents.

The published statement was also agreed to by the Health Research Authority (HRA) in England, Health and Social Care (HSC) in Northern Ireland, NHS Research in Scotland and Health and Care Research in Wales:

"The HRA welcomes efficient methods of document transfer in the research approvals and study set-up process. Applications to RECs and HRA Approval are made electronically from IRAS, and applications to CAG should be made by email. Applications in IRAS have electronic authorisation. Other documents may include electronic signatures. HRA does not require ink signatures on any research approval documents. Some sponsors continue to prefer ink signatures where other arrangements would be disproportionate or impractical. In relation to NHS site set up, HRA encourages use of time efficient methods of exchange of contracts and agreements, including exchange of confirmation by email. HRA does not stipulate use of ink signatures."

The HRA is also planning to issue a joint statement with the MHRA.

Source: http://www.hra.nhs.uk/news/2017/07/12/electronic-vs-ink-signatures-research-approval-documents-clarification/

c. MHRA offers Interactive Guide on new EU Medical Device, IVD Regulations

On 29 August 2017, the Medicines & Healthcare Products Regulatory Agency (MHRA), the British Competent Authority, published guidance Medical devices: EU regulations for MDR and IVDR.

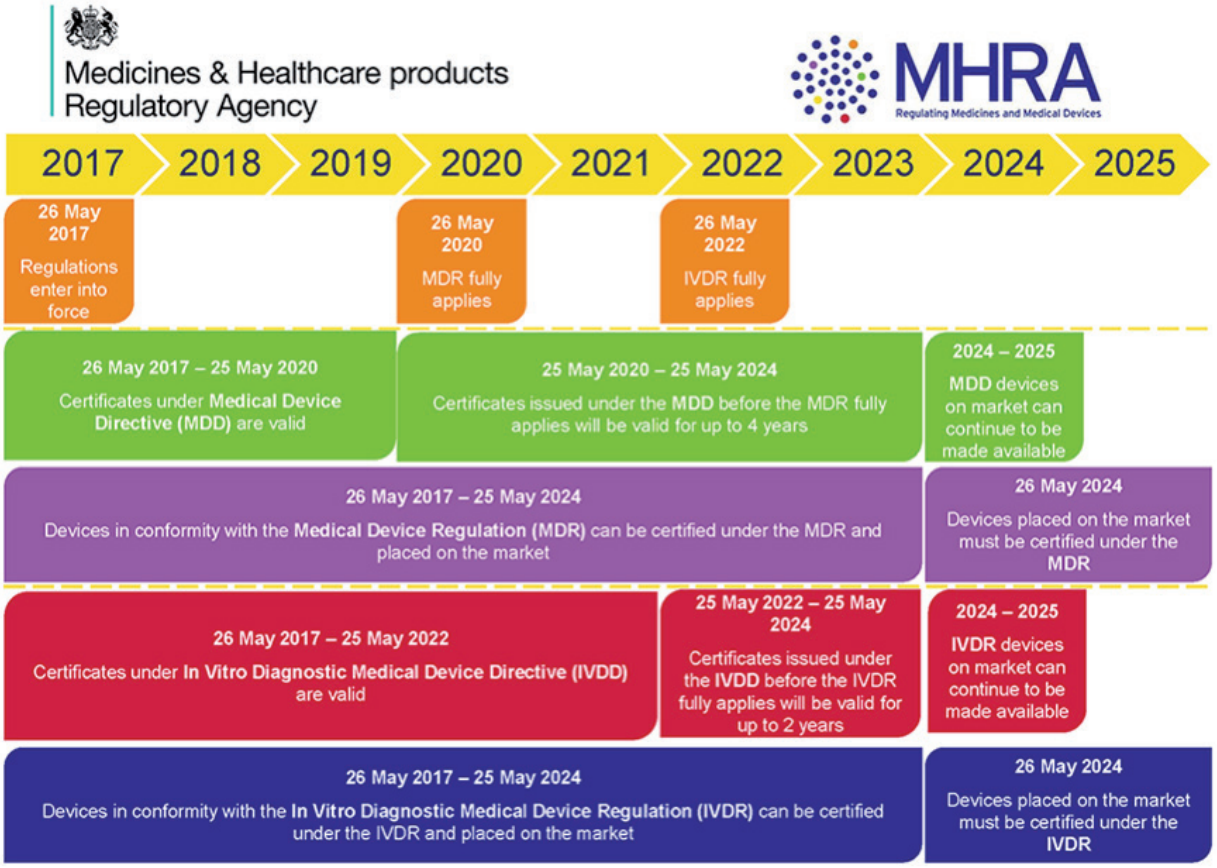
In addition, the MHRA created an interactive guidance: Introductory guide to MDR IVDR, which covers:

- Transition and implementation timeframes
- MDR (Medical Device Regulation) and IVDR (In-Vitro Diagnostic Regulation) definitions for medical devices and IVD products
- New European classification schemes
- MDR and IVDR conformity assessment requirements
- Unique Device Identifier (UDI) and EUDAMED requirements under the MDR and IVDR
- Post-market surveillance and vigilance obligations

The requirements of the MDR will come into force between May 2017 and 2020. In the case of the IVDR, the requirements should be implemented between May 2017 and 2022.

The MHRA said "During the transition period, devices can be placed on the market under the current EU Directives, or the new Regulations (if they fully comply with the new Regulations)."

The MHRA published very detailed chart timelines that could be helpful for manufacturers and CROs to understand the transition process and for Notified Bodies to plan how to issue CE certificates under the current Directives, within the transition period of new Regulations and after the dates of their full application when MD and IVD products will be placed in the market.



In addition, the MHRA provided some recommendations on what must be ensured by manufacturer to meet new obligations set out in the Regulations:

- "the device has been correctly classified against the new risk classification criteria (Annex VIII of the MDR and IVDR)
- general safety and performance requirements are met, including for labelling and technical documentation and quality management systems (Annex I of the MDR and IVDR)
- increased requirements for clinical evidence are met (Annex XIV of the MDR and IVDR)
- manufacturers have a person responsible for regulatory compliance in place (Article 15 of the MDR and IVDR)
- economic operators in the supply chain are compliant
- sufficient financial coverage is in place, in respect of a manufacturer's potential liability (Article 10 of the MDR and IVDR)
- the new vigilance reporting timescales are met and that an annual periodic safety update report is created (Chapter VII, Section 1 and 2 of the MDR and IVDR)"

Source: https://www.gov.uk/guidance/medical-devices-eu-regulations-for-mdr-and-ivdr

Interactive guidance: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/640404/MDR_IVDR_guidance_Print_13.pdf

d. Guidance on applying human factors to medical devices

On 19 September 2017, the Medicines & Healthcare Products Regulatory Agency (MHRA) published Guidance on applying human factors to medical devices. The guidance discusses the importance of applying human factors to medical devices.

"Human factors" refers to how a person uses or interacts with a device taking into consideration the environment in which the device is used, the technology involved, the education and training of the user and whether the device is intended for use in a hospital or at home.

The guidance explains safety considerations and principles that make a device "more pleasing to use and are therefore likely to lead to better adherence to correct use, at the required frequency".

"Users should not have to read, understand and remember complex instructions for use and adapt to the requirements of the device, or use it in an uncomfortable, incorrect and possibly dangerous way: a well-designed product will be easy to use, and will have a user interface that is consistent with user experiences and expectations," the guidance says.

The guidance is applicable to manufacturers of all device classes, drug-device combination products and notified bodies and should be treated as advisory recognising the importance of human factors in managing patient safety. The document applies to the design of future products and changes in user interfaces of existing products, rather than medical devices and others already approved for the UK and European Union (EU) market.

The guidance refers to the essential requirements under the three existing EU Medical Device Directives that currently regulate devices. In addition, the MHRA confirms that it will also be relevant for compliance with new EU MD Regulations stating that "This guidance should be equally useful in supporting the demonstration of compliance with the new regulations, recognising that specific details will be updated."

The guidance is intended to be consistent with existing US FDA guidance on human factors related to medical devices.

Source: https://www.gov.uk/government/publications/guidance-on-applying-human-factors-to-medical-devices

The guidance: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/645862/HumanFactors_Medical-Devices_v1.0.pdf

News from the United States of America

Failure to Address Observations Cited in a FDA Form 483 Results in an FDA Warning Letter

The United States Food and Drug Administration (FDA) routinely conducts inspections of manufacturers of FDA-regulated products such as drugs, biologics and medical devices in order to verify the products comply with FDA regulations and are not adulterated or misbranded. FDA also conducts inspections of companies involved in conducting clinical trials of FDA-regulated products such as Clinical Research Organizations (CROs).

FDA inspections can be routine inspections such as a pre-approval inspection, a directed inspection such as one conducted to investigate reported complaints or a for-cause inspection such as an inspection to investigate not following the protocol. At the conclusion of the inspection, the FDA inspector will summarize any significant findings on Form FDA 483 Inspectional Observations, and discuss the findings with corporate management.

A company that receives Form FDA 483 at the conclusion of an inspection should provide a thorough response to FDA along with measurable follow-up actions and adhere to any timelines stated in their response. Failure to perform any follow-up measures may escalate the situation to a warning letter should FDA conduct another inspection. All warning letters are readily accessible on FDA's website and are often reported as news stories by many industry news groups.

A recently posted warning letter notes that similar violations were cited in previous inspections and that since similar violations are still being observed, FDA has concluded that the oversight and control at the facility is inadequate.

"Repeat violations at facility

In a previous inspection of your facility from October 12 to November 25, 2014, FDA cited similar CGMP violations. You proposed specific remediation for these violations in your December 17, 2015, response. These repeated failures demonstrate that your facility's oversight and control over the manufacture of these products is inadequate."

https://www.fda.gov/iceci/enforcementactions/warningletters/2017/ucm574981.htm

CONCLUSION: Any firm that receives a 483 at the conclusion of an FDA inspection should address the observations and take steps to prevent future occurrences.

User Fees

The FDA user fee program began in 1992 with the passage of the Prescription Drug User Fee Act (PDUFA). This law authorized FDA to collect fees from drug manufacturers submitting either a New Drug Application (NDA) or a Biologics License Application (BLA). The purpose of these funds was to supplement FDA's drug approval budget. In return, FDA was required to meet performance goals. PDUFA must be reauthorized by Congress every 5 years.

Due to the success of PDUFA and the continued desire to provide the American public with access to the latest medical innovations, Congress expanded the user fee program by passing the Medical Device User Fee Act (MDUFA), the Generic Drug User Fee Act (GDUFA) and the Biosimilars User Fee Act (BsUFA). These fees provide FDA with funding to hire additional staff allowing for a reduction in review timelines and quicker market access for drugs and medical devices.

Like PDUFA, these additional Acts require reauthorization every five years. The reauthorization process begins approximately 2 years prior to the expiration of these Acts and involves meetings and negotiations with pharmaceutical and medical device stakeholders.

User Fees for FY 2018

Prescription Drug User Fees	Standard Fee
New Drug Application (With Clinical Data)	$2,421,495
New Drug Application (Without Clinical Data)	$1,210,748
New Drug Application Supplement (With Clinical Data)	No Fee for FY 2018
Program Fee	$304,162
NDA Establishment	No Fee for FY 2018
Annual Product Registration	No Fee for FY 2018

Generic Drug User Fees	Standard Fee
Abbreviated New Drug Application	$171,823
Prior Approval Supplement	No Fee for FY 2018
Drug Master File	$47,829
Finished Dosage Form Facility (Domestic)	$211,087
Finished Dosage Form Facility (Foreign)	$226,087
Active Pharmaceutical Ingredient Facility (Domestic)	$45,367
Active Pharmaceutical Ingredient Facility (Foreign)	$60,367
Program Fee	No Fee for FY 2018

Biosimilar User Fees	Standard Fee
Biological Product Development (Initial)	$227,213
Biological Product Development (Annual)	$227,213
Biosimilar Application (With Clinical Data)	$1,746,745
Biosimilar Application (Without Clinical Data)	$873,373
Biosimilar Supplement (With Clinical Data)	No Fee for FY 2018
Product Fee	$304,162
Establishment Fee	No Fee for FY 2018
Biological Product Development (Reactivation)	$454,426

Medical Device User Fees	Standard Fee	Small Business Fee1
510(k) Premarket Notification	$10,566	$2,642
513(g) - Request for Classification	$4,195	$2,098
De Novo Classification	$93,229	$23,307
PMA, PDP, PMR, BLA	$310,764	$77,691
panel-track supplement	$233,073	$58,268
180-day supplement	$46,615	$11,654
real-time supplement	$21,753	$5,438
BLA efficacy supplement	$310,764	$77,691
PMA annual report	$10,877	$2,719
30-day notice	$4,972	$2,486
Annual Establishment Registration	$4,624	$4,624

[1]FDA defines a small business as "a business with $100 million or less in gross receipts or sales, including receipts or sales from all affiliates". A small business must apply to FDA for designation as a small business.
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM573375.pdf

FDARA

https://blogs.fda.gov/fdavoice/index.php/2017/08/fdara-making-a-difference-for-industry-and-patients/

User Fees

Prescription Drugs

https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

Biosimilars

https://www.fda.gov/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/default.htm

Generic Drugs

https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm

Medical Devices

https://www.fda.gov/ForIndustry/UserFees/MedicalDeviceUserFee/ucm573383.htm

Early Feasibility Program

FDA has updated its website with information about its Early Feasibility Studies (EFS) Program, the types of devices best suited for the program and how to submit an application.

FDA defines an EFS as "a limited clinical investigation of a device early in development" and explains that an "EFS may be applicable when clinical experience is necessary because non-clinical testing is unavailable or inadequate to provide the information needed to advance device development."

The EFS program is available to devices subject to Premarket Approval (PMA), Premarket Notification (510[k]), De Novo classification, or Humanitarian Device Exemption (HDE)." EFS may be conducted on new devices without prior clinical experience and in some cases, may also be conducted on devices with limited prior clinical experience. For example devices previously used under a Compassionate Use approval, devices used outside of the United States, or marketed devices being proposed for a new indication are suitable for investigation in an EFS."

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm572934.htm

Medical Device Development Tools (MDDT) Program

> "The FDA's Medical Device Development Tools (MDDT) program is a way for the FDA to qualify tools that medical device sponsors can use in the development and evaluation of medical devices."
>
> "Qualification means that the FDA has evaluated the tool and concurs with available supporting evidence that the tool produces scientifically-plausible measurements and works as intended within the specified context of use."
>
> There are three categories of MDDT: (1) a clinical outcome assessment such as a patient-reported outcome scale, (2) a biomarker test such as an assay for an analyte, and (3) a nonclinical assessment model such as a computational model.
>
> Once a tool has been qualified, it can be used by any medical device manufacturer for that context without having to reconfirm suitability. Although there is no requirement to use a qualified tool, FDA believes using a qualified tool will streamline the process of making new devices available. FDA states, in the final guidance on this topic, "CDRH reviewers should accept the MDDT for the qualified context of use without the need to reconfirm the suitability and utility of the MDDT when used in a CDRH regulatory submission."

https://www.fda.gov/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/ucm20041609.htm

Digital Health Innovation Action Plan

FDA has long recognized that its traditional approach to regulating medical devices is not well suited for digital health technology. The 21st Century Cures Act clarified the regulation of medical software by amending the definition of a medical device to exclude certain software functions. As stated in FDA's Digital Health Innovation Action Plan, "software that supports administrative functions, encourages a healthy lifestyle, serves as electronic patient records, assists in displaying or storing data, or provides limited clinical decision support, is no longer considered to be and regulated as a medical device."

The Digital Health Innovation Action Plan calls on FDA to issue new guidance concerning implementation of the 21st Century Cures Act and to develop a new process for regulating digital health products. The guidances planned for 2017 include mobile medical applications, medical device data systems, medical image storage systems, and medical image communication devices. A guidance on clinical decision support software is planned for 2018.

https://www.fda.gov/MedicalDevices/DigitalHealth/default.htm

https://blogs.fda.gov/fdavoice/index.php/2017/07/fda-announces-new-steps-to-empower-consumers-and-advance-digital-healthcare/

Action Plan: https://www.fda.gov/downloads/MedicalDevices/DigitalHealth/UCM568735.pdf

Guidance Document Update

Between June 16, 2017 and September 15, 2017, FDA published 59 guidances on a variety of subjects. Brief summaries of the guidance documents most applicable to CROMSOURCE and its customers are presented below. A link to all FDA guidance documents is included at the end of this section.

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices - Guidance for Industry and Food and Drug Administration Staff

Final August 31, 2017

Summary: This guidance document clarifies how FDA plans to evaluate Real World Data (RWD) and Real World Evidence (RWE) and their application in regulatory decisions for medical devices. RWD is defined as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources" and RWE is defined as "clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD."

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm513027.pdf

IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects

Final July 13, 2017

Summary: This guidance document was issued in response to the 21st Century Cures Act (Cures Act). The Cures Act amended a section of the Federal Food, Drug and Cosmetic Act by granting FDA the authority to permit an exception from informed consent for minimal risk clinical investigations. Although the regulations governing the protection of human subjects (21 CFR parts 50 and 56) only allow for exceptions to informed consent in certain situations, the purpose of this guidance is to inform sponsors and investigators that FDA now has the authority to grant exceptions to informed consent for minimal risk clinical investigations and will not object to any IRB that grants an exception.

FDA plans to promulgate regulations reflecting this change.

https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM566948.pdf

Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies - Guidance for Industry and Food and Drug Administration Staff

Final September 12, 2017

Summary: This guidance document outlines FDA's expectations and provides "recommendations for the evaluation and reporting of age-, race-, and ethnicity-specific data in medical device clinical studies". This guidance document applies to medical devices that include clinical information in support of a marketing submission. The recommendations included in this guidance document apply to post-approval study submissions and postmarket surveillance studies. Section IV of this document provides recommendations for enrollment. Section V provides recommendations for study design and data analysis and interpretation.

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm507278.pdf

Link to all FDA guidance documents: https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

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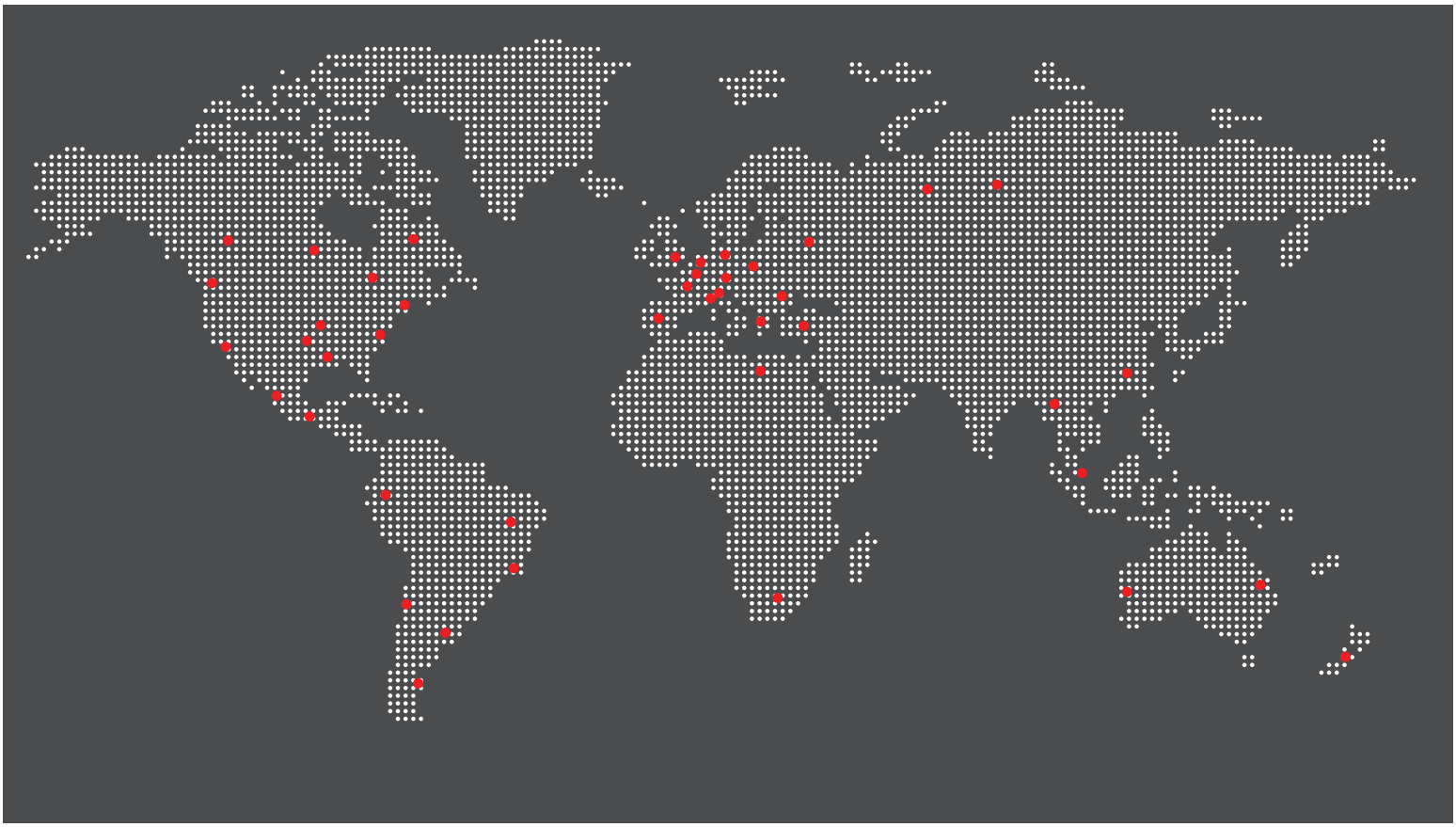

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CROMSOURCE is an international provider of outsourced services to the Pharmaceutical, Biotechnology and Medical Device industries, specialized in clinical development and staffing solutions

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