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REGULATORY NEWSLETTER

January - March 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 and US regulations relating to clinical research performed in both medicinal products and medical devices.

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

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

Contents

Abbreviations

Acronym	Definition
ABPI	Association of British Pharmaceutical Industry
AEMPS	Agency of Medicines and Sanitary Products (Spain)
AESGP	Association of the European Self Medication Industry
AIFA	Italian Medicines Agency (Italy)
ANDA	Abbreviated New Drug Application
ANSM	National Agency for the Safety of Medicine and Health Products (France)
ATMP	Advanced Therapy Medicinal Product
BIA	Bio Industry Association
BGMA	British Generic Manufacturers Association
CAMD	Competent Authorities for Medical Devices
CBER	Center for Biologics Evaluation and Research
CCMO	Central Committee for Research Involving Human Subjects (The Netherlands)
CDER	Centre for Drug Evaluation and Research
CDRH	Centre for Devices and Radiological Health
CE	Commission Européen
CENELEC	European Committee for Electrotechnical Standardization
CER	Clinical Evaluation Report
CfQ	Case for Quality
COMP	Committee for Orphan Medicinal Products
CPP	French Ethics Committee
CSR	Clinical Study Report
mCTAA	model Clinical Trial Agreement
CTFG	Clinical Trials Facilitation Group
CTR	Clinical Trials Regulation
DCRF	Dutch Clinical research Foundation (The Netherlands)
DMA	Danish Medicine Agency (Denmark)
DMARDs	Disease Modifying Anti Rheumatic Drugs
DNA	Deoxyribonucleic Acid
EDPB	European Data Protection Board
EEA	European Economic Area
EEC	European Economic Community
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency

Acronym	Definition
EOP	End of Phase
EPAR	European Public Assessment Report
EU	European Union
EUCOPE	European Confederation of Pharmaceutical Entrepreneurs
EVCTM	Eudravigilance Clinical Trials Module
FAERS	FDA Adverse Events Reporting System
FDA	(United States) Food And Drug Administration
FOPH	Federal Office of Public Health (Switzerland)
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPvP	Good pharmacovigilance Practice
GUDID	Global Unique Device Identification Database
HRA	Health Research Authority
HPRA	Health Products Regulatory Authority (Ireland)
HSC	Health & social Care (Northern Ireland)
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IDE	Investgational Devic Exemption
IMDRF	International Medical Device Regulators Forum
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug (US)
IRAS	Integrated Research Application System
IRB	Independent Review Board
ISO	International Standard Organisation
IVD	*In Vitro* Diagnostic
IVDR	*In Vitro* Diagnostic Regulation
MAH	Marketing Authorisation Holder
MD	Medical Device
MDCG	Medical Device Coordination Group

Acronym	Definition
MDDT	Medical Device Development Tool
MEP	Member of the European Parliament
MedDo	Medical Device Ordinance
MDR	Medical Device Regulation
MEDDEV	Medical Devices: Guidance Document from the European Commission
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NB	Notified Body
NCA	National Competent Authority
NDA	New Drug Application
NEST	National Evaluation System for health Technology
NHS	National Health Service (UK)
OJEU	Official Journal of the European Union
OUS	Outside of United States
PAGB	Proprietary Association of Great Britain
PGx	Pharmacogenomics
PRO	Patient Reported Outcome
PUP	Previously Untreated Patients
REC	Research Ethics Committee
R&D	Research and Development
RSV	Respiratory Syncytial Virus
SAR	Serious Adverse Reactions
RFC	Regional Pharmacovigilance Centres (France)
PMA	Premarket Approval
Pre-RTD	Pre-Request for Designation
RSI	Reference Safety Information
RTA	Refuse to Accept
SMEs	Small and Medium-sized Enterprises
SmPC	Summary of Product Characteristics
SR	Significant Risk
UDI	Unique Drug Identifier
UK	United Kingdom

Acronym	Definition
US	United States
WRO	Written Responses Only

NEWS FROM EUROPE:

The General Data Protection Regulation applicable across the EU in May 2018

On 25 May 2018, the 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), will be finally applicable across the European Union (EU). This regulation replaces Directive 95/46/EC (the Data Protection Directive), that, together with local national laws implementing it, had been the reference for data protection since 1995.

General changes, modernisations and updates under the GDPR compared with the Data Protection Directive are:

- "Reinforcing individuals rights;
- Strengthening the EU internal market;
- Ensuring stronger enforcement of the rules;
- Streamlining international transfers of personal data and;
- Setting global data protection standards."

Source: http://europa.eu/rapid/press-release_MEMO-18-387_en.htm

The changes in the GDPR will give people more control over their personal data and enable easier access to these data. Personal information will be have greater protection, no matter where the data is sent or how it is used (e.g. outside the EU, processed or stored). Individuals will have the right to lodge a complaint with a supervisory authority, in particular in the Member State (MS) of his or her habitual residence, place of work or place of the alleged infringement if they consider that the processing of personal data relating to him or her infringes this Regulation.

Companies should be well aware of their accountability under the Regulation in this regard. Given the imminent timescale, appropriate technical and organisational measures need to be in place to ensure that they are "protecting natural persons (people) with regard to the processing of personal data".

What does "appropriate" mean? Well, companies will no longer have a list of "minimum" requirements to be implemented: they must put the effort into determining how to protect data in the best way they can. This means a strong analysis of the data they have, how it is processed and the foreseen risks and then developing a plan of action for the technical and organisational measures deemed to be appropriate to ensure that processing is performed in accordance with this Regulation.

Each company, taking into account the nature, scope, context and purposes of processing as well as the likelihood and severity of the risk for the rights and freedoms of natural persons, should not only implement those planned measures but be able to provide evidence that they have done this.

It's not a question of just creating documents or revising procedures, the Regulation represents a cultural revolution in which all in the company, starting from upper management to the most junior employee must feel the importance of protecting personal data when working with clients, vendors, patients, and all other personnel the company interacts with.

A key feature of the GDPR is that companies are asked to implement the above mentioned appropriate technical and organisational measures to ensure that, by default, only personal data which are necessary for each specific purpose of the processing are processed. That obligation applies to the amount of personal data collected, the extent of processing, the period of data storage and accessibility.

The process is not established once and then fixed: measures should be reviewed and updated where necessary and, when appropriate, this should include the implementation of appropriate data protection policies.

Naturally, any "failure" of this process must be handled carefully: high attention is indeed given to the management of the privacy breach within the Regulation. Privacy breach is defined as a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed.

In the case of a personal data breach, the controller, not later than 72 hours after having become aware of it, shall notify the personal data breach to the supervisory competent authority.

When the personal data breach is likely to result in a high risk to the rights and freedoms of natural persons, the controller shall communicate the personal data breach also to the personnel to which the breach occurred.

Companies based outside of Europe will have to apply to the same rules when they offer services on the EU market.

The GDPR will be a single, pan-European law for data protection, replacing the current, inconsistent national laws of MSs and as the Regulation does not need to be transported and adopted into national laws by each MS, it will be directly enforceable.

The European Commission has published Questions and Answers – General Data Protection Regulation. This explains the perceived benefits of the regulation for the EU citizens and for businesses.

http://europa.eu/rapid/press-release_MEMO-18-387_en.htm

The body in charge of ensuring the consistent application of this Regulation is the European Data Protection Board (EDPB), formerly known as Working Party on the Protection of Individuals set up under Article 29 of Directive 95/46/EC. It is composed of the head data protection supervisory authority of each MS and of the European Data Protection Supervisor. To that end, the EDPB will be a body of the Union with legal personality and shall, among others, monitor and ensure the correct application of this GDPR, advise the Commission on any issue related to the protection of personal data in the EU and issue guidelines, recommendations, and best practices on procedures.

The EDPB has already published guidelines which provide advice of the processing of personal data in IT governance and IT management by EU institutions, bodies, offices and agencies.

https://edps.europa.eu/sites/edp/files/publication/it_governance_management_en.pdf

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

https://edps.europa.eu/data-protection/our-work/subjects/general-data-protection-regulation_en

The GDPR is available in 26 languages:
http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2016.119.01.0001.01.ENG&toc=OJ:L:2016:119:TOC

NEWS FROM EUROPE: MEDICINAL PRODUCTS

News from the European Commission

Excipients in the labelling and package leaflet of medicinal products for human use

In March 2018, the European Commission published guidelines for Competent Authorities and MAH: Excipients in the labelling and package leaflet of medicinal products for human use. The guideline explains that all excipients of medicinal product must appear on the labels (outer package or immediate package, if outer is not available). The guideline does not apply to excipients which are an active substance. In addition, the European Commission published an Annex to the guideline. The Annex presents the list of excipients that should be included on a medicine's label and the information for those excipients that must appear on the package leaflet.

The EMA published Annex in 25 languages:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001646.jsp

MAHs who received a marketing authorisation before the publication of the revised Annex must update labels, package leaflets and the SmPC at the first upcoming regulatory procedure affecting Product Information.

Source:https://ec.europa.eu/health/documents/eudralex/vol-2_en

Guidelines: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/c/guidelines_excipients_march2018_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 the EMA and European Commission

In March 2018, the EMA Management Board had a meeting where the EU portal and database update was presented. During the meeting the developer of both IT systems submitted a revised project plan with improved project management, development and testing processes and resources. The project plan showed that release version 0.7 should be available for an audit in early 2019. Currently, it is expected that the EU CTR will enter into application by the end of 2019, but the EMA Management Board said that more precise information on timelines will be provided after the audit.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/03/news_detail_002923.jsp&mid=WC0b01ac058004d5c1

Parallel to the development of the EU portal and database the European Commission has refined the EudraLex - Volume 10 - Clinical trials guidelines and made the distinction between the current applicable EU guidance documents relevant to clinical trials authorised under Directive 2001/20/EC, and guidance documents authorised under EU Clinical Trial Regulation. Sponsors and applicants can browse the theme by clicking "Set of documents applicable to clinical trials use under Directive 2001/20/EC" or "Set of documents applicable to clinical trials that will be authorised under Regulation EU No 536/2014, once it becomes applicable", whichever is applicable. During the three-year of transition period the sponsors of clinical trials submitted to NCAs and Ethics Committees before entry into application of the CTR and within one year after the entry into application of the CTR, will be able to choose to set of documents under the Directive.

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

Introduction of Orphan maintenance assessment reports

Orphan medicines are medicines use to treat rare conditions that have been referred to as an orphan disease. The orphan designation is given by the EMA's COMP and confirmed by the European Commission. Orphan designation also gives access to a number of incentives to foster research and innovation, including fee reductions for scientific advice and ten years market exclusivity (similar medicines for the same indication cannot be placed on the market through ten years). In January 2018, the EMA decided to start publishing "orphan maintenance assessment reports" for every orphan designated medicine which has been recommended for marketing authorisation. It will be assessed whether a medicine still fulfils the designation criteria reviewed at the time of its authorisation. The report will be published as part of a medicine's EPAR.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/01/news_detail_002885.jsp&mid=WC0b01ac058004d5c1

General and Marketing Authorisation Holders fee to EMA rise from 1 April 2018

On 28 March 2018, the EMA announced a 1.7% increase in fees for general EMA tasks like administration, scientific advice, annual fee and for MAH activities like application for marketing authorisation via centralised procedure, extension or renewal of procedure. The increases and also some reductions of fees have are for medicinal products for human use and veterinary products. The fees reflect the current inflation rate and will be applicable on 1 April 2018.

- An initial request for scientific advice will be €43,000 and this can increase to €86,100 depending on level of advice.
- A full dossier application for a medicinal product having one pharmaceutical form with one strength and presentations will be €286,000.
- Applications for which a full dossier does not need to be presented will be €185,500.

EMA stated, "[a]ll applications received by 31 March will be charged the current fee and reduction rates. Applications received after that date will be charged the adjusted fees. For scientific advice and protocol assistance, the cut-off point will be the date of validation of the request for advice. For annual fees, the anniversary date of the decision granting the marketing authorisation defines the applicable fee and consequently a new fee will be applicable at the time of any anniversary on or after 1 April 2018."

The fee increase does not apply to pharmacovigilance activities by the EMA.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/03/news_detail_002935.jsp&mid=WC0b01ac058004d5c1

Explanatory note on general fees payable to the EMA: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2018/03/WC500246428.pdf

Guidelines coming into effect

Reflection paper on physical frailty: instruments for baseline characterisation of older populations in clinical trials

This guideline was adopted on **24 January 2018**, effective immediately.

The reflection paper describes how to characterise the baseline frailty status of older patients (i.e. aged ≥ 65 years) enrolled in clinical trials or clinical investigations other than by their age. The aim is to ensure that clinical trial populations are representative of the users of the medicine, as the benefit-risk balance in older patients may depend on their physical frailty status. The reflection paper supplements also the requirements of ICH E7: Studies in Support of Special Populations: Geriatrics Questions & Answers
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E7/Q_As/E7_Q_As_step4.pdf

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/clinical_general/general_content_001232.jsp&mid=WC0b01ac0580032ec4

The guideline: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/02/WC500244285.pdf

ICH guideline E17 on general principles for planning and design of multi-regional clinical trials

This guideline will come into effect on **14 June 2018.**

The purpose of this document is to outline general principles for the planning and design of multi-regional clinical trials with the aim of increasing their acceptability in global regulatory submissions. It presents, among others, a strategy for managing a scientific advice, subject selection, choice of end points, selection of comparators, handling concomitant medications, collecting and handling of efficacy and safety information and statistical analysis planning for multi-regional clinical trials.

The guidelines recommend pooling of regions (geographical, countries or regulatory regions) or subpopulations (the subjects from a particular region with similarly defined subsets from other regions) to help provide flexibility in sample size allocation to regions, facilitate the assessment of consistency in treatment effects across regions, and support regulatory decision-making. For example, the guideline suggests pooling Canada and the US into a North American region is often justified due to similar medical practices and similar use of concomitant medications.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/ich_efficacy/general_content_001728.jsp&mid=WC0b01ac0580029590

The guideline: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/12/WC500240543.pdf

Guidelines Published

Procedural advice on the evaluation of advanced therapy medicinal product in accordance with Article 8 of Regulation (EC) No 1394/2007

This guideline was published on **25 January 2018** as a part of the joint action plan published by the EMA and European Commission to streamline procedures and better address the specific requirements of ATMP developers which are often small and medium-sized enterprises or academic.

The guideline has been addressed to support sponsors and MAHs by giving procedural advice on how to navigate the regulatory process in the EU for these innovative medicines.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/01/news_detail_002895.jsp&mid=WC0b01ac058004d5c1

Procedural advice: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2018/02/WC500242957.pdf

Guideline on clinical investigation of medicinal products for the treatment of rheumatoid arthritis

This guideline was published on 10 January 2018 and will enter into effect on **1 July 2018.**

This document gives guidance on the clinical evaluation of medicinal products (synthetic and biological DMARDs in the treatment of rheumatoid arthritis. Intra-articular products (i.e. administered by entry into a joint) are excluded from this guideline.

The guideline provides criteria and standards for patient selection, possible indications or treatments goals of rheumatoid arthritis, what primary and secondary endpoints should be selected, the strategy and design of clinical trials, clinical safety evaluations and studies in elderly and paediatric populations.

Source:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001136.jsp&mid=WC0b01ac0580034cf4

The guideline:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/01/WC500241042.pdf

Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease

This guideline was published on 28 February 2018 and will enter into effect on **1 September 2018.**

The aim of document is to provide guidance for the development of medicines across all stages of Alzheimer's disease. Before finalising the guideline, the EMA organised workshops for patients, academia staff, regulators and independent experts to ensure that it was aligned with current understanding regarding Alzheimer's disease and its treatment. The EMA also discussed the Alzheimer's disease approach in clinical trials with stakeholders and to translate their experiences into scientific advice.

The guideline for the treatment of Alzheimer's disease covers:

- Impact of new diagnostic criteria including early and even asymptomatic disease stages on clinical trial design;
- Factors to be considered when selecting parameters to measure trial outcomes at the different disease stages in Alzheimer's;
- Potential use of biomarkers in the various stages of medicine development;
- Design and analysis of efficacy and safety studies.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/02/news_detail_002913.jsp&mid=WC0b01ac058004d5c1

Published guideline: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/02/WC500244609.pdf

Guideline on good pharmacogenomic practice

This guideline was published on 19 March 2018 and will enter into effect on **1 September 2018.**

The document provides guidance on methods of evaluation of genetic variations related to pharmacokinetics and response where this could affect efficacy and/or safety. Quality aspects of pharmacogenomics (PGx) analyses (pre- analytical or for retrospective PGx related studies) are presented and recommendations made concerning study design for genetic variations evaluation. The guideline focuses only on germline DNA (constitutional DNA) - the DNA in germ cells (egg and sperm cells that join to form an embryo). Germline DNA is the source of DNA for all other cells in the body.

Annex I of the guideline presents an examples of pitfalls in genomic studies.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/md_pharmacogenomics/general_content_001395.jsp&mid=WC0b01ac058002958e

Published guideline: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/03/WC500245944.pdf

Guidelines under public consultation

Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products

This was published for consultation by the EMA on 1 February 2018. The consultation end date is **30 April 2018.** Comments should be submitted to: atmpguideline@ema.europa.eu

Summary: This guideline replaces the guideline on safety and efficacy follow-up - risk management of advanced therapy medicinal products (EMEA/149995/2008). The guideline describes specific aspects of pharmacovigilance, risk management planning, safety and efficacy follow-up of authorised advanced therapy medicinal products (ATMPs), as well as some aspects of clinical follow-up of patients treated with such products.

The guideline is a part of a joint action plan published by the European Commission on ATMPs, which aims to streamline procedures and better address the specific requirements of ATMP developers.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000294.jsp&mid=WC0b01ac05800241e0

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/md_gene_therapy/general_content_001909.jsp&mid=WC0b01ac058002958d

Draft guideline: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/02/WC500242959.pdf

Public consultation concerning the European Union template for good manufacturing practice non-compliance statement

This was published for consultation by the EMA on 3 April 2018. The consultation end date is **15 May 2018**. Comments should be submitted to: adm-gmdp@ema.europa.eu

Summary: The aim of this public consultation is to collect relevant information from stakeholders to help the Good manufacturing practice (GMP)/Good distribution practice (GDP) Inspectors Working Group to develop an effective and harmonised risk-based approach for dealing with the supply of critical medicines in case of serious GMP non-compliance. This will amend the compilation of community procedures and exchange of information.

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/manufacturing/general_content_001921.jsp&mid=WC0b01ac0580028e8b

Other Initiatives

The clinical trials facilitation group reference safety information Q&A cover note

In November 2017, the clinical trials facilitation group (CTFG) updated a Q&A document on Reference Safety Information (RSI) and recommended that sponsors make a broader description of the safety profile to the RSI sections in the Investigator's Brochure (IB) "to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial".

Some of the EU NCAs recommended full compliance with the Q&A document updated by CTFG e.g. the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the Danish Medicines Agency (DMA).

Following publication of the Q&A document, further discussions between NCAs and sponsors led to the publication of rectification CTFG RSI Q&A cover note on 8th March 2018. The cover note advises that the RSI section of the IB to comply with the procedures set out in the Q&A shall be submitted to NCAs as an amendment at the earliest opportunity or at the next routine IB update.

"CTFG acknowledges that a number of important changes to sponsor procedures may be necessary in order to comply with the new guideline for RSI". In such case, the CTFG advises that a one-year transition period will apply for the duration of 2018 "before the recommendations outlined in the Q&A are strictly enforced by NCAs". The NCAs represented at CTFG are advised to implement the guidance more strictly from 1 January 2019.

Source: http://www.hma.eu/ctfg.html

CTFG RSI Q&A cover note: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2018_03_CTFG_RSI_Q_A_Covernote.pdf

News from Individual Countries

Denmark

New concept for national scientific advice

In March 2018, the DMA announced a new concept of national scientific advice for marketing authorisations or clinical trials. The concept is a part of new government plan: "New growth plan to pave the way for world-class Danish life science" to make Denmark more attractive in performing clinical trials, improving opportunities for innovators, company start-ups, digitalisation and to give better access to skilled labour. The new concept has just started and the DMA will inform of its development and new fees on their website.

Source: https://laegemiddelstyrelsen.dk/en/news/2018/new-concept-for-national-scientific-advice/

Danish government plan: https://em.dk/english/news/2018/03-06-life-science

France

Good pharmacovigilance practice updated

On 5 February 2018, the National Agency for the Safety of Medicines and Health Products (ANSM), the French Competent Authority published their updated guideline on Good pharmacovigilance practice (GPvP).

The update has been launched to adapt the EMA guideline and requirements to national French specificities.

The aim of the update was to guide all engaged parties in France in the pharmacovigilance system by detailing the role of everyone in the system, the methods of reporting adverse effects, their management and treatment.

The document features chapters that describe the roles of the ANSM in pharmacovigilance, the health professionals, patients, stakeholders and regional pharmacovigilance centres (RFCs) in France. It advises how to fill in the declaration form and the content of the declaration to report adverse effects by patients or health professionals. Explanation on the role of RFCs is provided: The RFCs are responsible for collecting, recording and evaluating reports of adverse reactions from health professional and patients. In France there are 31 RFCs and they constantly exchange information with the ANSM to analyse risk.

The guide describes also principles of good communication of safety information.

Source and the guideline (available only in French): http://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Actualisation-des-Bonnes-pratiques-de-pharmacovigilance-Point-d-Information

The Netherlands

New CTA template

In February 2018, the DCRF (Dutch Clinical Research Foundation) presented a new Clinical Trial Agreement (CTA) template for the Netherlands. The DCRF is a foundation created through collaboration between various organisations of university medical centers, contract research organizations (CROs), drug development companies, ethics committees, patients, patient organisations, the government, and others. The initiative to update the Clinical Trial Agreement template was initiated and financed by the pharmaceutical industry and has been adapted based on the feedback from users of the previous version and due to new requirements of the GDPR, which will be become applicable on 25 May 2018.

The version 2018 template is not mandatory to use by commercial sponsors, academic or non-academic hospitals, and others but is recommended by the DCRF.

Source of information (in Dutch) and template (in English): https://dcrfonline.nl/werkgroepen/clinical-trial-agreement/

Switzerland

Swissmedic changes biosimilar guidance

In January 2018, the Swiss Agency for Therapeutic Products (Swissmedic) has changed its rules on the comparators used in biosimilar clinical trials. Before 1 January 2018 Swissmedic accepted only comparator products for main studies from the EU and for complementary studies from Japan. New changes give the sponsors allowance to use comparators for main studies from EU and USA and for complementary studies, from Japan and Canada.

Due to this decision, Swissmedic updated its guidance: Authorisation Biosimilar. The document provides information about general requirements, pharmacovigilance in case of comparators from USA or Canada and explains requirements for the documents to be submitted.

Source: and access to the guidance: https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/information/aktualisierung_wegleitung_und_faq-Dokument_zulassung_biosimilar.html

Italy

New Law no 3 on clinical trials of medicines on human use

On 15 February 2018 entered into force the new Italian Law no 3 of 11 January 2018 **Delegation to the Government on clinical trials of medicines as well as provisions for the reorganization of the health professions and for the management of the Ministry of Health.** The Law no 3 foresees different implementing decrees will be adopted within 12 months as of 15 February 2018.

The Law no 3 has been established, among others, to make the revision and adaptation of clinical trials provisions of EU Clinical Trials Regulation No 536/2014 into Italian Law, to identify requirements of clinical trial sites and to determine qualifications and the absence of conflict of interest for clinical trial applications evaluators. The new law refers also to independence and impartiality of investigators, new technical tools for clinical trial application (such as the Osservaotrio OssC), a new sanctioning system, and a new training path on clinical research methodology.

Source: http://www.salute.gov.it/portale/news/p3_2_1_1_1.jsp?lingua=italiano&menu=notizie&p=dalministero&id=3237

The Law no 3 (only in Italian):http://www.gazzettaufficiale.it/eli/gu/2018/01/31/25/sg/pdf

Detailed instructions from AIFA regarding amendments to the clinical trials

In March 2018, the Italian Medicines Agency (AIFA) published very detailed instructions for sponsors and CROs how to properly submit the application for authorisation of the substantial amendment to the clinical trial in Italy. The AIFA has not presented new requirements but refreshed the guidance for applicants. The initiative has been raised by the AIFA due to the number of requests for integration of information regarding validation and evaluation phases of substantial amendments to clinical trials.

The AIFA explains, among others, how substantial or non-substantial amendments should be presented, general aspects and what is a substantial amendment or non- substantial amendment for Competent Authority/ Ethics Committee in Italy.

In addition, quality aspects of the IMP in amendments are also the subject of focus within the instruction document. Within the Frequently Asked Question (FAQ) section, the AIFA provides explanation to the following: “What information should be reported in the letter of transmission of the application for authorization of a clinical trial, if the same IMPD has been presented in the context of other clinical trial applications?” and “In the case of changes to the sections of the quality part of the IMPD, is it always necessary to submit a request for a substantial amendment to the AIFA or is it possible, in some cases, to simply notify it?”

The AIFA reminds that for each substantial amendment, it is necessary to report in a summary table

- the “present” text and the “modified” text,
- the reason for making the change,
- the reason to consider it substantial.

Source (available only in Italian): http://www.agenziafarmaco.gov.it/content/richiamo-sulle-modalit%C3%A0-di-presentazione-della-domanda-di-autorizzazione-degli-emendamenti-s

Spain

The AEMPS revision of clinical trials guidance

The following revised guidelines and annexes have been updated by the Spanish Agency of Medicines and Sanitary products (AEMPS) between January and March 2018:

- **"Documento de instrucciones de la Agencia Española de Medicamentos y Productos Sanitarios para la realización de ensayos clínicos en España"**

The guide, presented in the Q&A format, provides instructions and clarifications on how to conduct clinical trials in Spain in accordance with Royal Decree 1090/2015. This guide version is nine and is updated periodically by the Spanish Agency. The AEMPS marked new questions and answers by adding new dates and using red colour. The document consists of 37 pages and is available only in Spanish.

The guide can be found here:
https://www.aemps.gob.es/en/investigacionClinica/medicamentos/docs/Instrucciones-realizacion-ensayos-clinicos.pdf

- **Annex I. Trial documentation and identification of documents when loaded into the ECM Portal** (Slight corrections applied)

Spanish version: https://www.aemps.gob.es/investigacionClinica/medicamentos/docs/anexo1-Ins-AEMPS-EC.pdf
English version: https://www.aemps.gob.es/en/investigacionClinica/medicamentos/docs/annex1-Ins-AEMPS-EC.pdf

- **Annex II. Safety related documentation that the sponsor should submit to the health authorities of the Autonomous Communities (AC).**

This is an update of safety related documentation that the sponsor should submit to the health authorities of the Autonomous Communities. A detailed description has been presented also in the Regulatory Newsletter October – December 2017.

Spanish version: https://www.aemps.gob.es/investigacionClinica/medicamentos/docs/anexo2-Ins-AEMPS-EC.pdf
English version: https://www.aemps.gob.es/en/investigacionClinica/medicamentos/docs/annex2-Ins-AEMPS-EC.pdf

- Annex VIIIA. Guideline for correct preparation of a model patient information sheet and informed consent form (PIS/ICF).

Spanish version: https://www.aemps.gob.es/investigacionClinica/medicamentos/docs/anexo8a-Ins-AEMPS-EC.pdf
English version: https://www.aemps.gob.es/en/investigacionClinica/medicamentos/docs/annex8a-Ins-AEMPS-EC.pdf

- **Annex VIIIB. Paragraphs to be included in the Informed Consent for the collection and use of biological samples in clinical trials**

Spanish version only: https://www.aemps.gob.es/investigacionClinica/medicamentos/docs/anexo8b-Ins-AEMPS-EC.pdf

- **Annex X. Contact persons for managing a contract with a research site**. (Slight corrections applied)

Spanish version: https://www.aemps.gob.es/investigacionClinica/medicamentos/docs/anexo10-Ins-AEMPS-EC.pdf
English version: https://www.aemps.gob.es/en/investigacionClinica/medicamentos/docs/annex10-Ins-AEMPS-EC.pdf

- **Contactos EPA-CCAA: Lista do de puntos de contacto en materia de estudios posautorización en las Comunidades Autónomas y en la AEMPS**

This is an updated list of contact points for post-authorisation studies in the Autonomous Communities (local CAs) and the AEMPS.
Spanish version only: https://www.aemps.gob.es/investigacionClinica/medicamentos/docs/estudios-PA/contactos_EPA-CCAA.pdf

In addition, the AEMPS published an English version of some Annexes as instructional documents of the Spanish Agency of Medicines and Medical Devices for conducting clinical trials in Spain: https://www.aemps.gob.es/en/investigacionClinica/medicamentos/anexos-instrucciones-AEMPS-realiza-EC.htm

The United Kingdom

The HRA guidance for handling information relating to research participants with regard to the new EU General Data Protection Regulation (GDPR)

In January 2018, the Health Research Authority (HRA) in the UK, published **Guidance for researchers and study coordinators on implications of the General Data Protection Regulation for the delivery of research in the UK.** The guidance has been issued with regard to the GDPR. It is version 1.0 and has been published as a living document that will be updated by the HRA.

The guidance has been addressed to researchers, sites and sponsors managing individual research projects to help them to make the necessary changes for Patient Information Sheets (PISs) and Informed Consent Forms (ICFs) as non-notifiable, non-substantial or substantial amendment.

The guidance advises that in most cases it will be not required to update existing PISs and ICFs. However, from 25 May 2018, sponsors will need to provide transparency information about the legal basis and other details of processing personal data. The guidance includes Appendix 1, which indicates what transparency information needs to be provided depending on whether personal data are collected directly or indirectly from participants. It is advised 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 approvals. The HRA will publish recommended wording for these documents. The HRA presents the following scenarios and advice on how to proceed when the change applies to collection of personal data before and after enforcement of the GDPR:

a. New study not submitted for approvals before 25 May 2018
b. Study approved and recruiting new participants after 25 May 2018
c. Study approved and participants are still in the study after 25 May 2018
d. Study approved and participants will have completed the study by 25 May 2018

Additionally, the HRA informs that “any changes to study documents to update references from previous legislation (i.e. Data Protection Act 1998) to new legislation are classified as non-substantial, non-notifiable amendments.”

Source with access to the guidance: https://www.hra.nhs.uk/about-us/news-updates/gdpr-guidance-researchers/

HRA single, new model of CTA for England, Scotland, Wales and Northern Ireland

In February 2018, the HRA published the revised templates of model Clinical Trial Agreement (mCTA) and Clinical Research Organisation model Clinical Trial Agreement (CRO-mCTA). The new models of contracts are designed to be used without modification for industry-sponsored trials in National Health Service (NHS)/ Health and Social Care (HSC) patients in hospitals throughout the UK Health Service. These model CTAs replace the 2011 versions.

The HRA has stated that from February 2018 the revised templates can be used as a single contract for the four nations in the UK (England, Scotland, Wales and Northern Ireland) for the same study. Sponsors are expected to use the new mCTAs. In cases where negotiations commenced using the previous, 2011 version, these negotiations should be continued and the NHS/HSC organisations will accept this CTA. If negotiations have commenced but sites have not received yet the proposed template of contract, the new model should be recommended to them.

Additionally, the HRA published guidance which provides an overview of how the mCTAs should be used and an overview of some of the provisions within the mCTAs.

Source: https://www.hra.nhs.uk/about-us/news-updates/new-templates-published-streamline-commercially-sponsored-trials-set-/

The templates and guidance:
https://www.myresearchproject.org.uk/help/hlptemplatesfor.aspx#Contracts-Agreements

Sponsors to take responsibility for passing on capacity and capability decision

In March 2018, the HRA made a change to its approval and amendment process. It has been decided that sponsors, not the HRA, will be responsible for informing NHS organisations when the HRA has made the decision that no formal confirmation of capacity and capability is required. The HRA also published the following guidance: **Collaborative working between sponsors and NHS organisations in England for HRA Approval studies, where no formal confirmation of capacity and capability is required** explaining what it means for sponsors and applicants in practice.

Some key points are presented below:

- "The term Formal Confirmation of Capacity and Capability refers to the type of confirmation given by an NHS organisation in England to state that it is ready to commence and deliver a particular study."
  Where formal confirmation of capacity and capability from all or some of the participating NHS organisations is not required, the Initial Assessment Letter will specify the timeline for these organisations to be informed ofthis by the sponsor. The HRA will also remind the sponsor of its responsibility to notify organisations and instruct to provide them a local information pack.

Previously, the HRA has contacted NHS organisations in England directly to inform them of that decision.

- In situations where the Initial Assessment Letter is not provided to the sponsor, the HRA Approval Letter will provide the necessary information to the sponsor with regards to their responsibilities in this regard.
- The sponsor will be required to use the (Research and Development) R&D Forum website: http://www.rdforum.nhs.uk/content/contact-details/ and will also will be provided with a link to a spread sheet containing contact details and the password to access this file.
- The study should only be commenced when an NHS organisation confirms it is ready to participate in the study and the HRA Approval letter is in place (including MHRA approval).
- In cases where the sponsor decides to add new site or NHS organisation in England, the sponsor will be required to notify the new organisation that formal confirmation of capacity and capability is not required, as evidenced by the HRA Approval Letter. "The 35 day deadline will start from the date that the sponsor provides the full local information pack."

Source and access to the guidance under the link "this document" are available here: https://www.hra.nhs.uk/about-us/news-updates/sponsors-take-responsibility-passing-capacity-and-capability-decision/

MHRA offers new guidance of data integrity

On 9 March 2018, the MHRA published the 'GXP' Data Integrity Guidance and Definitions, where 'X' is used as a collective term for GDP – Good Distribution Practice, GCP – Good Clinical Practice, GLP – Good Laboratory Practice, GMP – Good Manufacturing Practice and GPvP – Good Pharmacovigilance Practice.

MHRA stated, "[t]his document provides guidance on the data integrity expectations that should be considered by organisations involved in any aspect of the pharmaceutical lifecycle or GLP studies regulated by MHRA."

The guidance presents ten principles of data integrity. The first principle states, "[t]he organisation needs to take responsibility for the systems used and the data they generate. The organisational culture should ensure data is complete, consistent and accurate in all its forms, i.e. paper and electronic." The guidance refers to the acronym ALCOA (Attributable, Legible, Contemporaneous, Original, and Accurate) to define the attributes of data quality that are suitable for regulatory purposes.

The GXP guidance also explains that, "data has varying importance to quality, safety and efficacy decisions". What is important is how the data, especially critical data, is used to influence the decisions made. Data can be generated on paper, electronically, by hybrid system (both paper-based and electronic records constitute the original record) and in other formats such as photography or imagery.

Additionally, the MHRA provides information on how to design systems and processes to assure data integrity and create the "right environment" to enable data integrity controls to be effective.

Section six of the guidance focuses on definition of terms and interpretation of requirements. Among others, there is information on understanding of metadata, data integrity, data lifecycle, data processing, original record, true copy, computerised system transaction, electronic signatures and audit trail. Each term includes information on MHRA's interpretation and examples are also provided for some terms.

For example, the term **true copy**, "[a] true copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original…True copies of original records may be retained in place of the original record (e.g. scan of a paper record)…Accurate and complete copies for certification of the copy should include the meaning of the data (e.g. date formats, context, layout, electronic signatures and authorisations)."

The document refers also to IT Suppliers and Service Providers of 'cloud' or 'virtual' services where data is held. The MHRA states that, "attention should be paid to understanding the service provided, ownership, retrieval, retention and security of data."

Source: https://www.gov.uk/government/publications/guidance-on-gxp-data-integrity

The guidance: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf

NEWS FROM EUROPE: MEDICAL DEVICES

News from Individual Countries

Switzerland

Revision of the Swiss Medical Device Law

Switzerland has decided to align Swiss Medical Device Law with the new EU's MDR and IVDR. The revision of the Medical Device Ordinance (MedDO) in October 2017 gave the Swiss conformity assessment bodies the ability to register as designated bodies according to the new regulations as of 26 November 2017. The revision also allowed Swissmedic to participate in the EU expert group.

The Federal Office of Public Health (FOPH) has proposed adjustments to Acts such as the Therapeutic Products Act and the Human Research Act. These are intended to provide a solid statutory basis for a complete overhaul of the MedDO as well as a new Ordinance for IVDs. The consultation period on the proposed amendments started on 2 March and will finish on 11 June 2018. Entry into force of the legislative changes is scheduled for the first half of 2020.

Source and documents for consultation (only available in French, German and Italian): https://www.bag.admin.ch/bag/en/home/themen/mensch-gesundheit/biomedizin-forschung/heilmittel/aktuelle-rechtsetzungsprojekte/revision-med-prod-verord-mepv.html

The United Kingdom

New online service to support customers of the Devices Division

In January 2018, the MHRA launched a new online service for Device Registrations and Certificates of Free Sale to support customers of the Devices Division. The new online system passed the pilot phase and achieved its aim to get all customers on the new system by the end of February 2018.

The online system:

- Offers customers a better way to do business with MHRA
- Provides a single online account with the MHRA
- Provides access to the full range of services via an online portal
- Allows MHRA staff to access and provide information to customers more quickly and in a more joined-up way
- Enhances MHRA customer service.

Customers did not have to re-register and each customer was informed as to what action had to be taken to update their new account.

Source: https://www.gov.uk/government/news/mhra-streamlines-services-for-devices-customers

New application form for clinical investigations

The MHRA has changed the Integrated Research Application System (IRAS) application form for clinical investigations from the 18 April 2018. If a final form has not been completed before the 18 April, a new application form will need to be filed to ensure that the data fields have been transferred from the old form into the new form.

"The main changes can be summarised as:

- Significantly more detail about the investigational devices
- Incorporation of sterilisation questions and software questions within one form
- Significantly more detail about the study bringing MHRA and IRAS forms closer into alignment
- Electronic sign off – no longer need to print and sign the form."

Source: https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device#history

Other initiatives

IMDRF Guidance on the essential principles of safety and performance of MD and IVDs

In January 2018, the International Medical Device Regulators Forum (IMDRF) published the guidance 'Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices' for consultation. The end of the consultation period was 18 April 2018.

"The purpose of this IMDRF guidance is to harmonize the documentation and procedures that are used to assess whether a medical device conforms to the regulations that apply in each jurisdiction." IMDRF said. The formal worldwide adoption of the requirements harmonised in the guidance will offer benefits to manufacturers by reducing the amount of their time and costs, to users, consumers or patients by allowing them earlier access to new technologies and treatments, and to Regulatory Authorities.

Source: http://www.imdrf.org/consultations/consultations.asp

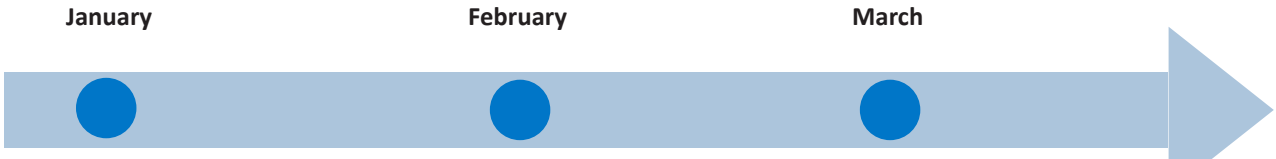
The IMDRF guidance: http://www.imdrf.org/docs/imdrf/final/consultations/imdrf-cons-epsp-n47.pdf

Other 'hot' topics in the EU

Key Brexit Updates

3rd: HPRA Ireland publish Brexit guidance
16th: MHRA update to pharma
23rd: EMA survey of pharma announced
29th: EU ministers adopt new set of negotiating directives on transition period
29th: EMA updates Q&A guidance document and provides procedural guidance

15th and 19th: Draft Withdrawal Agreement updated following latest round of negotiations
21st: UK Health and Social Care Select Committee publishes Brexit report
23rd: European Council publish (Art. 50) Guidelines



28th: Revised Dutch offer regarding permanent EMA headquarters endorsed
29th: Draft Withdrawal Agreement published by EU

2nd phase of negotiations

On 29 January 2018, EU27 ministers adopted a new set of negotiating directives giving details on the EU27 position on the transition period. The main points were:

- The proposed end date for the transition period in the negotiating directives is 31 December 2020
- During the transition period the whole of the EU acquis will continue to apply to the UK as if it were a member state, and any changes to it would also apply in the UK
- The UK will remain bound by the obligations stemming from the agreements concluded by the EU, while it will no longer participate in any bodies set up by those agreements
- The UK, as already a third country, will no longer participate in the institutions and the decision-making of the EU
- All existing EU regulatory, budgetary, supervisory, judiciary and enforcement instruments and structures will also apply, including the competence of the Court of Justice of the European Union.

Source: https://europa.eu/newsroom/highlights/special-coverage/brexit_en

MHRA update to pharmaceutical companies on exit preparations

On 16 January, the MHRA issued an update to pharmaceutical companies on preparations for exiting the EU. The statement notes that the MHRA is aware that companies who market pharmaceuticals in the EU and UK will need to plan and make decisions in advance of the UK's departure from the EU in March 2019. Guidance is provided on the MHRA's intended approach should no transition agreement be agreed but notes that that this is not a desirable outcome for either party. Emphasis is also placed on the fact that the current regulatory relationships between the UK and EU remains unchanged.

Source: https://www.gov.uk/government/news/mhra-update-to-pharmaceutical-companies-on-exit-preparations

In response, the Association of the British Pharmaceutical Industry (ABPI) published a statement welcoming the update and agreed that the UK and EU should have a close working relationship. However, there needs to be a realistic transition period and ABPI urged negotiators to prioritise medicines regulation and supply chain during the 2nd phase of negotiations.

Full statement: http://www.abpi.org.uk/media-centre/news/2018/january/preparing-for-brexit-abpi-s-reaction-to-mhra-update-for-pharma/

HPRA Ireland publish Brexit guidance

HPRA Ireland published Brexit guidance regarding the key issues they and their stakeholders are facing on 3 January. This guidance is based on the expectation of a 'hard Brexit' whereby the UK becomes a third country on 30 March 2019. The guidance contains information on medicines availability, joint labelling, post-UK withdrawal licensing scenarios for marketing authorisation holders, clinical trials, pharmacovigilance operations, GMP compliance, QC testing and batch release.

The guidance is likely to be updated in light of the outcome of future negotiations between the UK and EU.

Source: https://www.hpra.ie/homepage/about-us/publications-forms/guidance-documents/item?id=9b4c0a26-9782-6eee-9b55-ff00008c97d0&t=/docs/default-source/publications-forms/guidance-documents/hpra-brexit-guidance---human-and-veterinary-medicines

Link to guidance document: https://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/hpra-brexit-guidance---human-and-veterinary-medicines.pdf?Status=Master&sfvrsn=8

Draft Withdrawal Agreement

On 29 February the ***Draft Agreement on the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community*** was published by the European Commission.

The draft Withdrawal Agreement translates into legal terms the Joint Report from the negotiators of the European Union and the United Kingdom Government on the progress achieved during phase 1 of the negotiations, published on 8 December 2017, and proposes text for outstanding withdrawal issues. It also integrates the text on the transition period, based on the supplementary negotiating directives adopted by the Council (Article 50) on 29 January 2018.

Source: http://europa.eu/rapid/press-release_IP-18-1243_en.htm

This draft was subsequently updated on 15 March and 19 March, following the latest negotiation round with the UK from the 16 – 19 March.

The latest draft of the agreement is a marked-up version showing the progress made between EU and UK negotiators. Text highlighted in green (which now comprises a large portion of the document) indicates negotiators have reached an agreement on its content and only technical legal revisions are needed. Portions of the document highlighted yellow indicate that the policy is agreed but drafting changes or clarifications are still needed. Those sections not highlighted comprise proposed wording by the EU that continues to be discussed. For the not highlighted sections, no agreement has been made to date.

Marked-up version of the draft agreement: https://ec.europa.eu/commission/publications/draft-agreement-withdrawal-united-kingdom-great-britain-and-northern-ireland-european-union-and-european-atomic-energy-community-0_en

A summary of the key points within the current draft withdrawal agreement are outlined below:

Transition Period Extension

According to the draft withdrawal agreement, the transition period will be 21 months from the date the UK exits the EU and therefore end on 31 December 2020.

In response, the associations representing the European and British life science industry (AESGP, ABPI, BIA, BGMA, EBE, EFPIA, EUCOPE, EuropaBio, Medicines for Europe, PAGB, Vaccines Europe) welcomed the news but noted that they continue to advise their members to prepare for every scenario. Further clarity over the UK and Europe's future relationship with regards to the regulation, supply and trade of medicines is needed as soon as possible. Source: http://www.medicinesforeurope.com/news/statement-in-response-to-the-eu-council-ratifying-the-brexit-transition-deal/

Failure to reach agreement on Notified Bodies during transition

Negotiators have failed to reach an early agreement on Article 42 of the draft withdrawal agreement which describes making available of information held by notified bodies established in the United Kingdom or in a MS. This articles covers the requirements imposed on both notified bodies in the UK and MS during the transition period. It is currently not highlighted in the marked-up draft agreement, meaning that discussions are ongoing.

Medical Device Regulation looks set to apply in the UK

According to the EU Withdrawal Bill, article 3 (1), "Direct EU legislation, so far as operative immediately before exit day, forms part of domestic law on and after exit day". Article 122 (1) of the Draft Withdrawal Agreement, which covers the scope of the transition and has been agreed by negotiators, states that 'Union law shall be applicable to and in the United Kingdom during the transition period.' With the transition period now agreed (but still subject to final approval) as 31 December 2020 and the Date of Application of the Medical Devices Regulation (MDR), 26th May 2020, it appears that this legislation will become UK law. Although the In Vitro Diagnostics Regulation (IVDR) will not apply until 2022, it is appears likely that negotiations will ensure that this also becomes applicable in UK law. What this could mean for the medical device industry remains unclear.

Agreement regarding information on past authorisation procedures for medicinal products

Article 41 of the European Commission's draft withdrawal agreement with the UK says that the UK should be ready to make available information on past authorisation procedures for medicinal products has been discussed and agreed at negotiator's level.

No agreement on pending applications for supplementary protection certificates in the UK

Discussions are ongoing regarding the terms of articles Article 56 which covers the applications for supplementary protection certifications including medicine products and applications for the extension of the duration of such certifications that have been submitted to a UK authority before the end of the transition period.

European Council (Art. 50) Guidelines published

On 23 March the European Council published guidelines with a view to the opening of negotiations on the overall understanding of the framework for the future relationship EU-UK.

Link to guidelines: http://www.consilium.europa.eu/media/33458/23-euco-art50-guidelines.pdf

On 23 March 2018, the European Council (Art. 50) welcomed the agreement reached on parts of the legal text and called for intensified efforts to make progress on the remaining withdrawal issues. The European Council (Art. 50) further stated that nothing was agreed until everything is agreed. This means that a transition period between 30 March 2019 and 31 December 2020 may be agreed, but this is not certain at this stage.

Source: https://ec.europa.eu/info/brexit/brexit-preparedness_en

EMA relocation update

The EMA's Management Board met on 28 February in an extraordinary session, voting to endorse the revised offer of the Dutch government regarding the agency's new permanent headquarters in the Zuidas business district of Amsterdam. The bespoke premises will be ready by 15 November 2019 according to the Dutch authorities.

Source: https://www.raps.org/news-and-articles/news-articles/2018/2/ema%E2%80%99s-new-amsterdam-hq-to-be-ready-by-november-201

In March, the law enacting the EMA's relocation from London to Amsterdam, due to Brexit, was approved by MEPs. MEPs also set the timeline for the EMA headquarters move to ensure that the move from London to the temporary location in Amsterdam is completed by no later than 1 January 2019 and to the new permanent headquarters no later than 16 November 2019.

Source: http://www.europarl.europa.eu/news/en/press-room/20180309IPR99434/european-medicines-agency-move-to-amsterdam-meps-back-plans-but-set-conditions

The report can be found here: http://www.europarl.europa.eu/sides/getDoc.do?type=REPORT&reference=A8-2018-0063&format=XML&language=EN

EMA has also published a tracking tool on the main milestones and deliverables for the move and a more detailed breakdown for each work stream (except external communication which is an ad hoc activity).

Source: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_001893.jsp&mid=WC0b01ac0580cb2e5c

An interactive PDF version of the tool can be found here:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2018/03/WC500244941.pdf

EMA Updates Q&A Guidance on Brexit

Version "Rev 02" of the Q&A guidance on Brexit was published on 29 January 2018. It does not amend the Q&A, but consists of a technical revision of the introductory text on page 1 to introduce standardised wording across all sectorial guidance documents.

Q&A guidance "Rev 02": http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500228739.pdf

EMA procedural guidance: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/11/WC500239369.pdf

EMA surveys pharma companies on their preparedness for Brexit

On 23 January, EMA launched a survey to gather information from marketing authorisation holders of centrally authorised medicines on their plans to submit transfers, notifications or variations to their marketing authorisations in preparation for Brexit.

The aim is to:

- Identify companies where there is a need for concerted action to address medicines supply concerns due to Brexit in order to protect human and animal health and,
- Help EMA and the Commission plan resources in the areas where these submissions will be processed.

EMA also hopes that the survey will provoke action in those companies who have not yet started planning for Brexit. Findings and recommendations from the survey will be shared with the European Commission and presented to the EMA's management board.

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

UK Health and Social Care Select Committee publishes Brexit report

On 21 March, the UK Commons Select Committee for Health and Social Care published a report into Brexit: medicines, medical devices and substances of human origin. The report urges negotiators on both sides to "heed the call of industry and patient groups in securing the closest possible regulatory alignment in the next round of Brexit talks". In particular, the Committee welcomes the Government's intention to maintain regulatory alignment with the EMA (as stated by Prime Minister, Theresa May, in the Mansion House speech of 2nd March).

> "The overriding message from almost all of the evidence received in this inquiry is that the UK should continue to align with the EU regulatory regimes for medicines, medical devices and substances of human origin both during any transition period and afterwards."

The committee is now awaiting the UK government's response.

Source: https://www.parliament.uk/business/committees/committees-a-z/commons-select/health-committee/inquiries/parliament-2017/brexit-medicines-substances-human-origin-17-19/

Link to the report: https://publications.parliament.uk/pa/cm201719/cmselect/cmhealth/392/392.pdf

MDR/ IVDR - latest status

The MDR and IVDR were published in the Official Journal of the European Union in May 2017. At the same time, the countdown to the implementation of both began. 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. Recent developments concerning the transition periods (up to 3 years for MDR, up to 5 years for IVDR) are summarised below.

Guidance documents to assist stakeholders in implementing the Medical Devices Regulations

In March 2018, the European Commission published four guidance documents to assist stakeholders in implementing the Medical Devices Regulations.

The Medical Device Coordination Group (MDCG), which was established by Article 103 of Regulation (EU) 2017/745 and composed of representatives of all MS with a representative of the European Commission as chair has published two guidance documents:

- **MDCG 2018-1: Draft guidance on BASIC UDI-DI and changes to UDI-DI**

"This guidance is intended to provide a clarification on the notion of Basic UDI-DI, its use in relevant documentation and the factors triggering UDI-DI changes. Main provisions related to the establishment of the UDI system are contained in Chapter III and Annex VI of the two medical device Regulations."

- **MDCG 2018-2: Future EU medical device nomenclature Description of requirements**

"This document intends to provide a detailed description of requirements and criteria that the future nomenclature is expected to fulfil. According to Article 26 of the MDR and Article 23 of IVDR, the European Commission is required to make available a medical device nomenclature to support the functioning of the future EUDAMED."

The EU Unique Device Identification Work Group with acceptance by MDCG launched the following guidance:

- **UDIWG 2018-1: UDI Database, Definitions/Descriptions and formats of the UDI core elements**

This guidance provides a list of data to be provided to the UDI database and a table of definitions/descriptions and formats of the core data elements to be provided to the UDI database.

- **UDIWG 2018-2: The architecture of the UDI database - Basic UDI-DI and UDI-DI attributes for Medical devices and In-vitro diagnostic medical devices**

This document presents two slides of the architecture of the UDI database.

The documents are not a European Commission documents and it cannot be regarded as reflecting the official position of the European Commission. However, according to Article 34 paragraph 1 of the MDR "The Commission shall, in collaboration with the MDCG, draw up the functional specifications for EUDAMED. The Commission shall draw up a plan for the implementation of those specifications by 26th

May 2018" and Article 28 "The Commission, after consulting the MDCG shall set up and manage a UDI database to validate, collate, process and make available to the public the information…". https://www.emergogroup.com/sites/default/files/europe-medical-devices-regulation.pdf

The fourth published guidance provides further steps to meet MDR/ IVMD requirements.

Source and access to guidance: Guidance - European Commission

MDR and IVDR transitional FAQs

In January 2018, the EU Competent Authorities for Medical Devices (CAMD), the group under which the national competent authorities in the EU work to enhance the level of collaborative work in what is a single market for medical devices, published a FAQ document covering the transition-related provisions of the MDR and IVDR. It was prepared by the Transition Sub Group (TSG) of the CAMD following internal discussion. These FAQs do not represent legal advice but rather TSG recommendations which will be updated continuously.

Topics currently covered by the TSG:

- "Transition in general
- Placing on the market of MDR/IVDR compliant devices until 26 May 2020/2022
- Placing on the market of AIMDD/MDD/IVDD compliant devices after 26 May 2020/2022
- The so called "sell off" provision of Art. 120 para 4 MDR / Art. 110 para 4 IVDR
- EUDAMED and its relevance for the application of certain provisions of the MDR/IVDR."

Source and FAQs: https://www.camd-europe.eu/regulatory/available-now-mdr-ivdr-transitional-faqs/

Survey on NBs applications against new regulations

After publication of Commission Implementing Regulation (EU) 2017/20185 in November 2017, notified bodies were given the green light to apply for designation under the MDR and the IVDR. Subsequently, the European Association for Medical Devices of Notified Bodies, known as "Team–NB" published a survey on notified body applications against new both regulations. The survey was taken from 26 November 2017 (the first day of application) to 17 February 2018.

Results showed that 80% of Team-NB members had submitted their application to be designated against the MDR. Of those Team-NB members who intend to be designated against the IVDR (55% of members), 73% had submitted their application to be designated against the IVDR before 12 February 2018.

Source: http://www.team-nb.org/survey-on-applications-by-the-team-nb-member-notified-bodies-under-the-mdrivdr-and-how-this-compares-with-their-current-scope-under-the-three-current-directives-aimddmddivdd/

NEWS FROM THE UNITED STATES OF AMERICA: Clinical Trials / Good Clinical Practice

New pilot program to increased transparency of clinical trial information announced

On January 16, 2018, FDA announced it was launching a new pilot program to evaluate if disclosing certain information contained within clinical study reports (CSR) following the approval of a New Drug Application (NDA) will improve public access to approval information. Up to nine volunteer sponsors will be selected.

Specific portions from pivotal clinical trial-related summaries such as the protocol and amendments and the statistical analysis plan will be posted on a new FDA webpage.

Press announcement

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm592566.htm

Updated information sheet on payments to clinical trial subjects

On January 29, 2018, the Food and Drug Administration (FDA) published an update to the Payment for Research Subjects - Information Sheet. This update clarified that reimbursement for travel expenses such as travel to and from the clinical trial site and any associated expenses such as airfare, parking and lodging is acceptable.

Source:https://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm

Webpage for Clinical Data Summary Pilot Program https://www.fda.gov/drugs/developmentapprovalprocess/ucm589210.htm

FDA adopts ICH E6(R2)

The ICH E6 (R2) guideline, which has been in effect in the EU since November 2016, was officially adopted by FDA in March 2018. The E6 (R2) guideline has been updated with new information that reflects the evolution in technology and complexity of clinical trials and encourages the "implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results". Specific areas updated include:

- Introduction
- Section 1 - Glossary
- Section 2 - The Principles of ICH GCP
- Section 4 - Investigator
- Section 5 - Sponsor
- Section 8 – Essential Documents for the Conduct of a Clinical Trial

NOTE: Training was conducted on the updates to this guideline. The presentation can be found in the eLearning system. Newcomers will be trained as soon as they join CROMSOURCE.

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm464506.pdf

ACRP releases CRC competency guidelines

On January 30, 2018 the Association of Clinical Research Professionals (ACRP) announced it was publishing competency guidelines for Clinical Research Coordinators (CRCs). The guidelines are published in excel format. There are three levels: entry, intermediate and senior and eight domains, which are further broken down into specific tasks. The domains are:

1. "Scientific Concepts: Encompasses Knowledge Of Scientific Concepts Related To The Design And Analysis Of Clinical Trials.
2. Ethical and Participant Safety Concerns: Encompasses Care of Patients, Aspects of Human Subject Protection, And Safety in the Conduct of a Clinical Trial.
3. Investigational Products Development and Regulation: Encompasses Knowledge of How Investigational Products are Developed and Regulated.
4. Clinical Study Operations (Good Clinical Practice): Encompasses Study Management and GCP Compliance; Safety Management (Adverse Event Identification and Reporting, Post-Market Surveillance, and Pharmacovigilance), and Handling of Investigational Product.
5. Study and Site Management: Encompasses Content Required at the Site Level to Run a Study (Financial And Personnel Aspects). Includes Site and Study Operations. (Does Not Include Regulatory /GCP).
6. Data Management and Informatics: Encompasses How Data are Acquired and Managed During A Clinical Trial Including Source Data, Data Entry, Queries, Quality Control and Correction and the Concept Of A Locked Database.
7. Leadership and Professionalism: Encompasses The Principles and Practices of Leadership and Professionalism in Clinical Research.
8. Communication and Teamwork: Encompasses All Elements Of Communication Within The Site And Between the Site and Sponsor, CRO And Regulation. Understanding of Teamwork Skills Necessary for Conducting a Clinical Trial."

ACRP notes that these guidelines can also support CROs in the site selection process.

Source: https://www.acrpnet.org/core-competency-guidelines-clinical-research-coordinators-crcs/?utm_campaign=News&utm_medium=email&utm_source=internal&utm_content=CRCCompetency-PR-01302018&utm_term=btn-downloadguidelines

Guidance Document Update

Between December 16, 2017 and March 30, 2018, FDA published over 60 guidance documents on a variety of subjects. Brief summaries of the clinical trial 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.

Chronic Obstructive Pulmonary Disease: Use of the St. George's Respiratory Questionnaire as a PRO assessment tool

Final: March 2018

Summary: The purpose of this guidance is to provide information to sponsors on the use of the St. George's Respiratory Questionnaire (SGRQ) in interventional clinical trials evaluating drugs for the treatment of chronic obstructive pulmonary disease (COPD).

SGRQ is a patient-reported outcome (PRO) tool designed to measure the impact on overall health, daily life and perceived well-being and may be used to assess efficacy. It may be used as a co-primary endpoint or as a secondary endpoint in a clinical trial.

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071575.pdf

Pregnant women: scientific and ethical considerations for inclusion in clinical trials

Draft: April 2018

Summary: Some pregnant women need to use drugs to manage chronic conditions or treat acute medical problems. Unfortunately, there is often a lack of information on how the drug behaves in a pregnant woman, which can make the health care provider reluctant to treat the underlying condition. In some cases, the lack of treatment may result in more harm to the woman and the fetus than if she had received the medication. This guidance discusses the rationale for including pregnant women in clinical trials for drug and biologic products and provides guidelines and recommendations for doing so.

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm603873.pdf

E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population

Final: April 2018

Summary: In 2000, the International Council for Harmonisation (ICH) published the E11 guideline, Clinical Investigation of Medicinal Products in the Pediatric Population. Pediatric drug development has evolved since 2000. "The purpose of the addendum is to complement and provide clarification and current regulatory perspective on topics in pediatric drug development."

Source: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm530012.pdf

Link to all FDA guidance documents

https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

NEWS FROM THE UNITED STATES OF AMERICA: DRUGS

Oncology Center of Excellence

The Oncology Center of Excellence celebrated its one-year anniversary on January 19, 2018. This is the first FDA center to focus on a specific disease rather than a specific product. The goal of the Center is to expedite the development of oncology and hematology products for the treatment of cancer. Noteworthy accomplishments include the approval of 16 new drug and biologic applications, including the first two cell-based gene therapies, two biosimilar applications in oncology and several in vitro diagnostics.

Website: https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/oce/default.htm

FDA Voice: https://blogs.fda.gov/fdavoice/index.php/author/fda_voice/

Guidance Document Update

CDER guidance agenda for 2018

On January 19, 2018, the Center for Drug Evaluation and Research (CDER) released a list of 98 new and revised guidance documents that are planned for publication during 2018. These are organized into the following 18 categories:

1. Advertising
2. Clinical/Antimicrobial
3. Clinical/Medical
4. Clinical Pharmacology
5. Clinical/Statistical
6. Drug Development Tools
7. Drug Safety
8. Electronic Submissions
9. Generics
10. Labeling
11. Over-The-Counter
12. Pharmaceutical Quality/Microbiology
13. Pharmaceutical Quality/CMC
14. Pharmaceutical Quality/Manufacturing Standards (CGMP)
15. Pharmacology/Toxicology
16. Procedural
17. Rare Diseases
18. User Fees

Titles of some of the planned guidance documents include:

- Assessing the Effects of Food on Drugs in INDs or NDAs – General Considerations
- Pregnant Women in Clinical Trials – Scientific and Ethical Considerations
- Pregnancy, Prevention and Planning: Recommendations for Pregnancy Testing and Contraception for Drugs with Teratogenic Potential

- Assessing the Effects of Food on Drugs in INDs or NDAs – General Considerations
- Adaptive Design Clinical Trials for Drugs and Biologics; Revised Draft
- Adjusting for Covariates in Randomized Experiments
- Meta-Analysis of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biologic Products.

Source: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm417290.pdf

FDA published guidance

Between December 16, 2017 and March 30, 2018, FDA published over 60 guidance documents 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.

Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases

Draft: December 2017

Summary: This guidance explains the rationale behind FDA's decision to no longer grant orphan drug designation to drugs for pediatric subpopulations of common diseases. The exception to this decision is if the use of the drug in the pediatric subpopulation meets the regulatory criteria for an orphan subset, or the disease in the pediatric subpopulation is considered a different disease from the disease in the adult population.

Link to guidance: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm589710.pdf

Formal Meetings Between the FDA and Sponsors of Applicants

Draft: December 2017

Summary: FDA offers several types of meetings to sponsors on the development and review of drug or biological drug products. This new draft guidance is an update to the previous guidance "Formal Meetings Between the FDA and Sponsors of Applicants," which has been in use since May 2009. The new guidance makes several modifications to the meeting process. Timelines for Written Responses Only (WRO) feedback is provided. A new category of meetings has been added, Type B End-of-Phase (EOP). The most noteworthy change is that the briefing package must be submitted at the time of the request for all Type A meetings and for all Type C meetings concerning the use of a biomarker as a new surrogate endpoint that has never been previously used as the primary basis for product approval in the proposed context of use. Additional important changes concern the timing of the submission of briefing package for Type B End-of-Phase (EOP) meetings and Type C meetings. Briefing packages must be submitted no later than 50 days before the scheduled date of the meeting or WRO for Type B EOP meetings and 47 days for Type C meetings.

Link to guidance:
https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm590547.pdf

Best Practices for Communication Between IND Sponsors and FDA During Drug Information
Final: December 2017

Summary: This comprehensive guidance describes the best practices to be followed by sponsors of investigational new drug application (IND) including the best use of emails, telephone calls and faxes. This guidance also provides several sources of resources for sponsor including contact information for 19 specialized programs and offices (i.e. Biomarker Qualification Program, Emerging Technology Team, Office of Pediatric Therapeutics).

Link to guidance: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm475586.pdf

Good ANDA Submission Practices

Draft: January 2018
Summary: The purpose of this guidance is to assist applicants of abbreviated new drug applications (ANDAs). This guidance discusses several common deficiencies that may lead to a delay in the approval of an ANDA and provides recommendations on how to avoid these deficiencies. Deficiency areas discussed include (1) patents and exclusivities, (2) labeling, (3) product quality, and (4) bioequivalence (BE).

Link to guidance: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm591134.pdf

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

NEWS FROM THE UNITED STATES OF AMERICA: MEDICAL DEVICES

Goals and Accomplishments for the Center for Devices and Radiological Health (CDRH)

On January 17, 2018, CDRH update the public on its progress on its 2016-2017 Strategic Priorities and, at the same time, published its 2018-2020 Strategic Priorities.

The 2016-2017 Strategic Priorities and results are

1. ESTABLISH A NATIONAL EVALUATION SYSTEM FOR MEDICAL DEVICES

Goal: Increase Access to Real-World Evidence to Support Regulatory Decision Making.

Target: Gain access to 100 million electronic patient records with device identification.

Result: Accessed to 103 million.

Goal: Increase the Use of Real-World Evidence to Support Regulatory Decision Making.

Target: Increase by 100% the number of premarket and postmarket regulatory decisions using real-world evidence.

Result: Increased by 193%.

2. PARTNER WITH PATIENTS

Goal: Promote a Culture of Meaningful Patient Engagement by Facilitating CDRH Interaction with Patients.

Target: Establish 20 patient groups and have 90% of CDRH staff interact with patients as part of their job duties.

Results: 48 patient groups established. 96% of CDRH staff have interacted with patients.

Goal: Increase Use and Transparency of Patient Input as Evidence in Our Decision Making.

Target: Include a public summary of relevant patient perspective data in 100% of PMA, de novo and HDE decisions.

Results: All (100%) of PMA, de novo, and HDE pre-market decisions made by CDRH now include a public summary of available and relevant patient perspective data.

Target: Increase the number of patient perspective studies used in support of premarket and post-market decisions.

Results: The number of patient perspective studies conducted by sponsors in support of pre- and post-market regulatory decisions increased from none to six.

Target: Increase the use of patient reported outcomes (PRO)* used in support of premarket and post-market decisions.

Results: The number of approved IDEs (pivotal studies only) with patient reported outcomes increased by 75%.

3. PROMOTE A CULTURE OF QUALITY AND ORGANIZATIONAL EXCELLENCE

Goal: Strengthen FDA's Culture of Quality within CDRH

Target: Be eligible for ISO 9001 certification.

Results: Implementing recommendations made by a 3rd party internal assessment.

Target: Submit a formal application to assess progress towards adopting the Baldrige Performance Excellence Criteria.

Results: Application submitted. Feedback report received. Recommendations being addressed.

Target: 25% increase in CDRH staff with quality and process improvement credentials.

Results: 670% increase.

Goal: Strengthen Product and Manufacturing Quality within the Medical Device Ecosystem

Target: Propose a voluntary program to recognize independent evaluation of product and manufacturing quality.

Result: Case for Quality (CfQ) Pilot Program was announced.

Impact on Industry

The medical device industry has seen CDRH's initiatives come to life in the following ways:

1. The creation of new policies and procedures to facilitate the development and approval of clinical research protocols and the initiation and conduct of clinical trials in the US;
2. Increased use of post-market data;
3. Increased use of real-world evidence;
4. Increased qualification of patient reported outcomes (PRO);
5. Increased use of patient input into regulatory decisions.
6. The creation of the Parallel Review Program with the Centers for Medicare and Medicaid Services, which streamlines the pathway from FDA market authorization to payer coverage and reimbursement.

The Strategic Priorities for 2018-2020 are:

1. EMPLOYEE ENGAGEMENT, OPPORTUNITY, AND SUCCESS

This priority "aims to improve our work life and work environment by reducing unnecessary burdens, promoting an environment of trust and mutual respect, facilitating open dialogue, fostering creativity and teamwork, providing a reasonable work life balance, and creating opportunities for professional growth and personal development".
As CDRH notes, "an organization cannot be optimally successful unless its employees are fully engaged, the organization is fully invested in their professional and personal development and committed to their retention, they have the resources they need, and work in an environment that helps them succeed".
Success Metric
By December 31, 2020, achieve at least an 80 percent employee engagement level.

Impact on Industry

Possibly more support and fewer decision delays due to fully engaged employees.

2. SIMPLICITY

This priority addresses CDRH's polices, processes and programs. CDRH interprets this to mean "we stop doing or streamline what we determine is not sufficiently "value added" to the regulatory process and free our CDRH team to spend more time on what matters most to patients and staff." In addition, "it means removing unnecessary burdens we impose on ourselves, such as through cumbersome processes, vague policies, and out of date information technology systems".
Success Metric
By December 31, 2020, lean at least 80 percent CDRH core processes.

Impact on Industry
This focus on simplicity has resulted in the reclassification of several Class III device types to Class II, it has increased the number of 510(k)-exempt Class II devices and has supported the release of the Early Feasibility Clinical Study Guidance.

3. COLLABORATIVE COMMUNITIES
The aim of this priority is the creation of Collaborative Communities with "broad and fair representation to solve problems and proactively build for the future".
Success Metric
By December 31, 2020, establish at least 10 new Collaborative Communities.

Impact on Industry
Industry could see continued investment in the National Evaluation System for health Technology (NEST) and the use of real-world data in regulatory decision-making. In addition, industry could see more revolutionary advances in healthcare. In the past, CDRH has collaborated with diabetes patient groups, physician and medical device manufactures. This collaboration resulted in the approval of the world's first automated insulin delivery system.

2016 – 2017 Strategic Priorities – accomplishments
https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhvisionandmission/ucm592694.pdf

FDA Voice – Charting Our Course for 2018 – 2020
https://blogs.fda.gov/fdavoice/index.php/2018/01/charting-our-course-for-2018-2020/

Strategic Priorities for 2018 – 2020
https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM592693.pdf

*Value and Use of Patient-Reported Outcomes (PROs)
https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM588576.pdf

*CDRH PRO Compendium
https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhvisionandmission/ucm588577.xlsx.

Guidance Document Update

Between December 16, 2017 and March 30, 2018, FDA published over 60 guidance documents on a variety of subjects. Brief summaries of the medical device 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.

Investigational IVDs Used in Clinical Investigations of Therapeutic Products - Draft Guidance for Industry, Food and Drug Administration Staff, Sponsors, and Institutional Review Boards

Draft: December 2017

Summary: This guidance describes the situations in which the IDE regulations may apply to an investigational IVD and the situations in which an investigational IVD may be considered a significant risk device.

Investigational IVDs are often exempt from most of the IDE regulation. However, when an investigational IVD is used to "guide the therapeutic management of subjects in a therapeutic product trial, and trial results provide information on the safety and effectiveness of the investigational IVD in addition to the safety and effectiveness of the investigational therapeutic product", IDE regulations may apply.

There are three categories of device studies: significant risk (SR) studies, non-significant risk (NSR) studies, and exempt studies. An IVD may be considered an SR device if:

(1) It is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject or,

(2) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

The evaluation of risk and the determination of exemption under the IDE regulation, for investigational IVDs in therapeutic product trials is independent of the determination of whether an IND is required for that same trial. IVDs that are considered SR devices must have an approved IDE with FDA.

If a therapeutic product trial is permitted under the IND regulations, or is exempt from the requirements of the IND regulations, the sponsor must still have an IDE that is approved or approved with conditions by the FDA if the trial includes a SR investigational IVD.

IRB approval for SR investigations, NSR investigations and Exempt investigations.

The guidance includes a discussion section in the format of questions and answers related to the following topics, which will help sponsors, and IRBs make risk determinations.

1) Factors to Consider in Making a Risk Determination
2) Investigational IVD Risk and the Design of Clinical Investigations for Therapeutic Products
3) How Investigational IVD Risk May Change During the Course of a Clinical Investigation
4) Recommendations for IRBs and Sponsors in Evaluating Investigational IVDs in the Context of Clinical Investigations for Therapeutic Products
5) Common Questions about Investigational IVD Use in Clinical Investigations of Therapeutic Products and Compliance with the IDE Regulation
6) Inclusion of Investigational IVD Information in an IND
7) Managing IDEs and INDs for the Same Study
8) Q-Submission Meetings

This guidance concludes with two appendices:

Appendix A - Contents of an IDE Application

Appendix B - FDA Review of IDE Applications

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm589083.pdf

Medical Device Accessories – Describing Accessories and Classification Pathways

Final: December 2017

Summary: FDA defines an accessory as a "finished device that is intended to support, supplement, and/or augment the performance of one or more parent devices". This guidance describes the accessory classification process FDA will follow in determining the risk and regulatory oversight required for accessories. This guidance concludes with an appendix describing how to request classification for new accessory through the de novo process.

Link to guidance: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm429672.pdf

Unique Device Identification: Policy Regarding Compliance Dates for Class I and Unclassified Devices

Final: January 2018

Summary: The Unique Device Identifier (UDI) Rule requires a device to bear a UDI on its label and packages unless an exception or alternative applies. The UDI Rule also requires that data pertaining to the key characteristics of each device required to bear a UDI be submitted to FDA's Global Unique Device Identification Database (GUDID). This guidance lists the compliance dates for Class I and Unclassified Devices.

Note: Investigational devices are exempt from the UDI rule.

Link to guidance: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm592340.pdf

Acceptance and Filing Reviews for Premarket Approval Applications (PMAs)

Final: January 2018

Summary: A Premarket Approval (PMA) is an application made to FDA for a Class III medical device. The application must be approved by FDA prior to marketing the device. The PMA regulations (21 CFR 814) identify the required contents of an application and the criteria for refusing to accept or file an application. Once a PMA is submitted to FDA, it will undergo two reviews. The first review is an acceptance review. This review is conducted to ensure the PMA is administratively complete. The applicant will receive a written response within the first 15 calendar days of receipt if the PMA is administratively complete and has been "Accepted". FDA will then proceed to the filing review. This review is conducted to determine the basic adequacy of the technical elements of the PMA. The applicant will be notified in writing within 45 calendar days of receipt whether the PMA has been "Filed" or "Not Filed. This guidance contains checklists and decision trees which may be used by medical device companies to ensure their application is complete and that it will be accepted and filed by FDA.

Link to guidance: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm313368.pdf

Refuse to Accept Policy for 510(k)s

Final: January 2018

Summary: A Premarket Notification 510(k) is a premarket submission made to FDA for a Class II device. This submission must be cleared by FDA before the device can be placed on the market. There are three types of 510(k) submissions: traditional, special, and abbreviated. After any type of 510(k) is submitted to FDA, it undergoes an acceptance review. The purpose of this review is to determine if the 510(k) submission is complete and ready for a substantial review. The submitter will be notified electronically within the first 15 calendar days after receipt of the submission of the results of the acceptance review. If the submission is accepted, the substantive review will begin. If the submission is not complete, it will not be accepted, [Refuse to Accept (RTA)]. This guidance includes checklists for each of the types of 510(k) submissions that outline the necessary items that must be included in a 510(k).

Link to guidance: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm315014.pdf

How to Prepare a Pre-Request for Designation (Pre-RFD)

Final: February 2018

Summary: This guidance describes how to prepare a Pre-Request for Designation (Pre-RFD). A Pre-RFD is a process available to sponsors when the classification of a product (drug, device, biological product, or combination product), regulatory pathway or the Center assignment (Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), or Center for Biologics Evaluation and Research (CBER)) is unclear. Informal and non-binding feedback will be provided to the sponsor within 60 calendar days of receipt. This guidance includes a discussion, in a Question and Answer format, regarding the information that should be included in a Pre-RFD and how a Pre-RFD should be submitted to FDA. The guidance concludes with a Pre-RFD Screening Checklist.

Link to guidance: https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM534898.pdf

Acceptance of Clinical Data to Support Medical Device Applications and Submissions - Frequently Asked Questions

Final: February 2018

Summary: FDA published a final rule on the acceptance of data from clinical investigations conducted outside the United States that will be used to support investigational and market applications for medical devices in the Federal Register on February 21, 2018. This rule will become effective one year after publication. This guidance describes the new information FDA expects to receive in order to determine if the investigations were conducted in accordance with good clinical practice (GCP). FDA is requiring several statements be included in the applications or submissions to FDA. For example,

US statement: For investigations conducted in the US, the rule requires applicants and sponsors to state whether the investigation complied with 21 CFR parts 50, 56, and 812.

EU statement: Likewise, for investigations conducted OUS, the rule requires a statement regarding conformance with GCP and the submission of supporting information to demonstrate that conformance.

Multi-center statement: When a multi-center investigation includes sites both inside and outside the US, in addition to the required statements discussed above, **the sponsor or applicant should provide a statement regarding the international nature of the investigation, and the compliance of sites with their applicable local requirements.**

Link to guidance: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm597273.pdf

Link to all FDA guidance documents

https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

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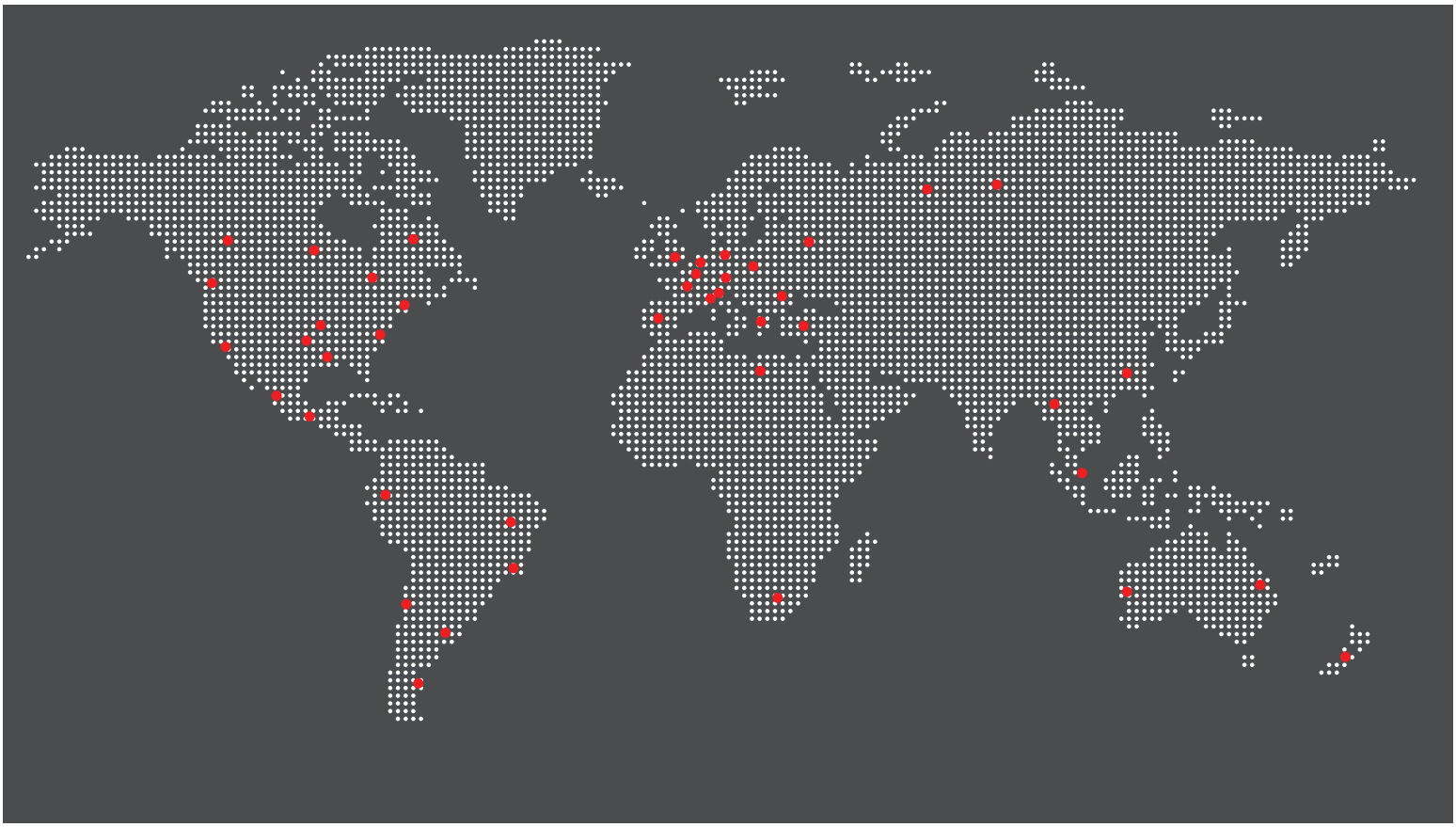

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CROMSOURCE Quality

ISO 9001:2015 multi-site certified quality management system.

ISO 14155:2011 conformity confirmed.

European Headquarters

Via Giorgio De Sandre, 3

37135 Verona - Italy

Direct: +39 045 8222811

Fax: +39 045 8222812

North American Headquarters

309 Waverley Oaks Road, Suite 101

Waltham, MA 02452 - USA

Direct: +1 617.871.1128

Fax: +1 617.871.1129

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