CROM SOURCE
advise | agree | deliver

Regulatory Newsletter
October - December 2016

Introduction

CROMSOURCE is committed to sharing our expertise with our clients and future clients. This reflects the first part of our 'Advise Agree Deliver' motto! In this spirit we have pleasure in making available this issue of our Regulatory Newsletter.

This newsletter is put together by our expert regulatory team and tracks the changes occurring in European and US regulations relating to clinical research performed in both medicinal products and medical devices.

The Newsletter is a quarterly publication distributed via email and posted on the CROMSOURCE website. We hope you find this information useful, and welcome feedback, questions and suggestions. Contact us on cromsource@cromsource.com at any time.

Contents

News from the European Commission

Update of New Medical Device Regulation (MDR) and IVD Regulation legislation

The European Parliament and the Council of Ministers will soon pass the new Medical Device Regulation (MDR) and the *In Vitro* Diagnostic (IVD) Regulation. These regulations, once adopted, will replace the existing three medical devices directives [93/42/EEC on Medical Devices Directive (MDD) (1993), 90/385/EEC on Active Implantable Medical Devices Directive (AIMDD) (1990) and 98/79/EC on *In Vitro* Diagnostic Medical Devices (IVDMD) (1998)].

The next step will be the formal publication which, was expected to occur in late 2016 but, is now expected to occur in early 2017. After that publication, there will be a three-year transition period.

Council's Position on Medical Devices Regulation of 16 November 2016:
http://eurlex.europa.eu/procedure/EN/2012_266?qid=1483544792424&rid=1

Council's Position on IVD Regulation of 16 November 2016:
http://eurlex.europa.eu/procedure/EN/2012_267?qid=1483544507714&rid=1

The list of upcoming European Commission events and meetings related to medical devices in 2017:
http://ec.europa.eu/growth/tools-databases/newsroom/cf/itemdetail.cfm?item_id=9045&lang=en

Consultation on the Evaluation of the Aerosol Dispensers Directive

On 30 September 2016, the European Commission published a public consultation on the evaluation of the Aerosol Dispersers Directive (75/324/EEC). The Aerosol Dispersers Directive is one of the oldest EU legislations related to product safety. The Directive was adopted in 1975 harmonising the differing national legislations in force at that time in order to create a genuine European market based on common requirements concerning the safety of the dispensers and the hazards due to pressure.

The objective of the evaluation is to assess whether the Directive is meeting its objectives of guaranteeing free circulation of aerosol dispensers within the EU while ensuring a high degree of safety. The aim is to collect stakeholders' feedback about the Directive to assess the extent to which the Directive has been successful in effectiveness, efficiency, relevance (given the needs and its objectives), coherence and achieving EU added-value.

The consultation consists of an on-line questionnaire available in English, French, German, Spanish, Italian and Polish. Deadline for sending questionnaires surveys was until 15 January 2017.

Source: http://ec.europa.eu/growth/tools-databases/newsroom/cf/itemdetail.cfm?item_id=8941

The Aerosol Dispersers Directive (75/324/EEC): http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:31975L0324

News from the European Medicines Agency

The source of each news item below is the EMA website.
Source:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/landing/whats_new.jsp&month=1&year=2017&mid=WC0b01ac058004d5c4

Guideline for Good Clinical Practice E6 (R2)

On 15 December 2016, the European Medicines Agency (EMA) adopted the ICH Good Clinical Practice (GCP) Guideline E6 (R2) step 5, issued as EMA/CHMP/ICH/135/1995. Date of coming into effect is 14 June 2017.

The ICH Good Clinical Practice (GCP) Guideline dated 1996 has been amended to encourage 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. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated. In this "Integrated" Addendum, changes were integrated directly into several sections of the parental Guideline and they are highlighted by adding word 'Addendum' to each new section.

So far, ICH GCP E6 (R2) has been adopted only in Europe. Japan, USA, Canada and Switzerland are expected to adopt the Guideline in the first or second quarter of 2017.

Source ICH website: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/integrated-addendum-good-clinical-practice.html

The guidance is available here:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf

Clinical Data Publication

In October 2016, the European Medicines Agency (EMA) began publishing clinical data submitted by pharmaceutical companies to support their regulatory applications for human medicines under the centralised procedure. This is based on EMA's flagship policy on the publication of clinical data.

By proactively publishing clinical data, EMA intends to help:

- Avoid duplication of clinical trials, foster innovation and encourage development of new medicines;
- Build public trust and confidence in EMA's scientific and decision-making processes;
- Academics and researchers to re-assess clinical data.

The Agency has developed extensive guidance for industry facilitate compliance with this policy. Version 1.1 published 19 December 2016 and may be found here:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/12/WC500218567.pdf

Source:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&mid=WC0b01ac0580607bfa%23http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000555.jsp&mid=WC0b01ac0580607bfa

Online access to clinical data for medicinal products for human use is here:
https://clinicaldata.ema.europa.eu/web/cdp/home

Tailored Scientific Advice Pilot Project

The European Medicines Agency (EMA) will launch a scientific advice pilot project in February 2017 to test the added value and feasibility of tailored scientific advice for the development path of biosimilars.

The tailored procedure will advise developers on the studies they should conduct, based on a review of the quality, analytical and functional data they already have available.

The pilot project is open to all types of biosimilars and includes a pre-submission meeting to review the suitability of the data package. Applicants should note that the Scientific Advice Working Party (SAWP) will need an extra month in addition to normal scientific advice timelines to review applications.

EMA plans to run the pilot until it has completed six scientific advice requests, with a maximum of one scientific advice request accepted per month. The Agency will analyse the outcome after completing the pilot.

On 16 December 2016, the EMA published a list of questions that biosimilar developers may have on the scientific advice procedure:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/12/WC500218206.pdf

Source:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/12/news_detail_002668.jsp&mid=WC0b01ac058004d5c1

EU-USA Strategic Meeting on the Future of Paediatric Medicines

On 28 September 2016, EMA hosted an EU-US strategic bilateral meeting to discuss the future of paediatric medicines, intensify collaboration, increase convergence and identify future challenges.

Participants included representatives from the European Commission, the European Medicines Agency and the US Food and Drug Administration.

Processes were discussed to increase harmonisation and further streamline global paediatric product development. The envisioned goal in the next few years is:

Aim for a convergent and harmonised paediatric development programme for each medicine, through:

- Early and proactive collaboration to increase efficiency during paediatric product development
- Joint outreach programmes to identify high priority paediatric need areas and to facilitate related research and development
- Collaboration with all stakeholders to bring experts, researchers and industry together to address scientific issues in paediatric medicine development

Source:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/09/news_detail_002609.jsp&mid=WC0b01ac058004d5c1

Meeting Report:
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/12/WC500218004.pdf

Guideline on Preclinical Pharmacological and Toxicological Testing of Vaccines - WITHDRAWN

The CHMP guideline on preclinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465/95): http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004004.pdf has been withdrawn. Companies should now refer to the WHO guideline on non-clinical evaluation of vaccines: http://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/en/

A questions and answers document has been published to provide clarification on the grounds for this decision and its impact for companies (EMA/CHMP/SWP/242917/2016):
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/07/WC500210581.pdf

Scientific Recommendations on the Classifications of Advanced Therapy Medicinal Products

The European Medicines Agency's Committee for Advanced Therapies prepared scientific recommendations on whether a medicine can be classified as an advanced therapy medicinal product (ATMP) and published these recommendations in summary reports according to product description.

Summary reports:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000301.jsp&mid=WC0b01ac05800862c0

Post-Orphan Medicinal Product Designation Procedures

On 22 November 2016, the EMA issued guidance for sponsors on post-orphan medicinal product designation procedures

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

- Incentives
- Annual reports
- Transfer of sponsorship
- Change of sponsor’s name or address
- Amendment of designated condition
- Marketing authorisation application
- Review of the maintenance of orphan medicinal product designation at the time of marketing authorisation application

- Review of the maintenance of orphan medicinal product designation at the time of extending the therapeutic indication post-authorisation
- Withdrawal of orphan designation

A full guideline for sponsors:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196994.pdf

Guidelines/Recommendations

ICH Guideline Q3C (R6) on Impurities: Guideline for Residual Solvents

On 15 December 2016, the EMA adopted a new guideline on impurities for residual solvents. This guideline will come into effect 14 June 2017.

The objective of this guideline is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guideline recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.

The guideline can be found here:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/03/WC500104258.pdf

Source:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000742.jsp&mid=WC0b01ac0580028e8c

Guideline on the Clinical Development of Medicinal Products Intended for the Treatment of Pain

On 15 December 2016, the EMA adopted a guideline on the clinical development of medicinal products intended for the treatment of pain. This guideline will come into effect 01 July 2017.
This Guideline is intended to provide guidance on the clinical development of new medicinal products for the treatment of pain. It replaces and updates the separate guidelines on neuropathic (CPMP/EWP/252/03) and nociceptive pain (CPMP/EWP/612/00).
The new document should be considered as a general guidance. The main requirements for the development of medicinal products for the treatment of pain with regard to study design, patient populations and outcome measures are described. Specific issues, including patients with difficult to treat chronic pain and other specific patient groups (children and elderly) are addressed.

The guideline is available here:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/12/WC500219131.pdf
Source:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001161.jsp&mid=WC0b01ac0580034cf5

Clinical Investigation of Medicinal Products for Prevention of Venous Thromboembolism (VTE) in Non-Surgical Patients

On 10 November 2016, the European Medicines Agency (EMA) adopted a guideline on clinical investigation of medicinal products for prevention of venous thromboembolism (VTE) in non-surgical patients. This guideline will come into effect 01 June 2017.

This guideline replaces the 'Guideline on Clinical Investigation of Medicinal Products for the Prophylaxis of Venous Thromboembolic Risk in Non-Surgical Patients' (CPMP/EWP/6235/04).

Venous thromboembolic disease (VTE) is a common condition, including deep vein thrombosis (DVT) and/or pulmonary embolism (PE) with a reported annual incidence of two per 1,000 general population. The majority of patients developing VTE are non-surgical, accounting for three out of four fatal pulmonary emboli cases. VTE is associated with significant morbidity-mortality and long-term sequelae, such as post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension. The primary aim of prophylaxis and/or treatment of thromboembolism is the prevention of PE resulting from proximal DVT of the lower limb venous system. Distal DVTs are usually less serious unless propagating proximally.

Medical patients have a heterogeneous risk for VTE. Current clinical practice guidelines recommend routine thromboprophylaxis with low-molecular-weight heparin (LMWH), low-dose unfractionated heparin (UFH) or fondaparinux in acutely ill hospitalized medical (non-surgical) patients at high risk of thrombosis during the period of risk (usually no more than 10 days). Thromboprophylaxis (with LMWH or low-dose UFH) is also recommended in critically ill patients.

The aim of this guideline is to provide guidance regarding the development of medicinal products in the prevention of venous thromboembolism in non-surgical patients. The revised guideline does not deal with the development of medicinal products for prevention of long-term sequelae of VTE, such as post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension.

A guideline may be found here:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/11/WC500217355.pdf

Source:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001084.jsp&mid=WC0b01ac0580034cef

Guideline on Non-Clinical and Clinical Development of Similar Biological Medicinal Products Containing Low-Molecular-Weight-Heparins

This guideline was adopted on 10 November 2016 by the EMA and will come into effect on 01 June 2017.

This guideline lays down the non-clinical and clinical requirements for low molecular weight heparins (= low molecular mass heparins, LMWHs) containing medicinal products claimed to be biosimilar to another one already marketed. The quality section addresses some aspects specific to LMWH, the non-clinical section addresses the pharmaco-toxicological requirements and the clinical section the requirements for pharmacokinetic, pharmacodynamic and, where needed, safety/immunogenicity studies as well as pharmacovigilance aspects. Whereas the parent guideline required a comparative clinical trial by default, the revised guideline focusses on demonstration of biosimilarity based on a strong and convincing physicochemical and functional data package and comparable pharmacodynamic profiles. Pre-marketing

clinical immunogenicity data may not be necessary if the immunogenic potential can be adequately characterized in suitable and sensitive *in vitro* tests. In addition, the non-clinical section has been amended to follow a risk-based approach.

This guideline replaces 'Guideline on Non-Clinical and Clinical Development of Similar Biological Medicinal Products Containing Low-molecular-Weight-Heparins' (EMEA/CHMP/BMWP/118264/2007).

A full guideline:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/11/WC500217126.pdf

Scientific Guidance on Post-Authorisation Efficacy Studies (PAES)

On 12 October 2016, the EMA adopted new scientific guidance on post-authorisation efficacy studies. This guideline will come into effect on 01 June 2017.
The intention of this guideline is to provide scientific guidance for a Marketing Authorisation Holders (MAHs) and for competent authorities on PAES in the context of EU regulatory decision-making with regard to the general need for such studies and general methodological considerations. For specific scenarios where PAES may be considered, additional clarifications are given together with study designs which may be applied. Some principles of study conduct are also highlighted.

The full guidance may be found here:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/12/WC500219040.pdf

Guideline on the Clinical Investigation of Medicinal Products to Prevent Development/Slow Progression of Chronic Renal Insufficiency

A guideline on the clinical investigation of medicinal products to prevent the development and to slow the progression of chronic renal insufficiency will come into effect on 01 April 2017.

The main focus of the guideline is on the conduct of clinical studies with medicinal products intended to prevent or slow progression of chronic renal insufficiency, describing different potential claims in relation to the kidney disorder (i.e., primary and secondary prevention), description of study populations including prognostic factors for the evolution of the kidney disorder and study objectives and endpoints.

Recommendations are given regarding assessment methods to be used in relation to selected endpoints, strategy and design of clinical trials, criteria for the choice of comparator, study duration, factors confounding the interpretation of study results, specific aspects to be considered for paediatric and elderly patients, and for safety assessment, focusing on overlapping safety signals and encouraging broader exploration of more sensitive tools, namely biomarkers.

The link to a full guideline is here:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/10/WC500214980.pdf

Guideline on Influenza Vaccines

The non-clinical and clinical modules of the guideline on influenza vaccines will come into effect on 01 February 2017. The new guidance takes into account the current understanding of the predictive value of

non-clinical studies for clinical situations and knowledge that individual types of influenza vaccines may differ from each other in terms of their immunogenicity, efficacy and safety. It also reflects lessons learned from the influenza A (H1N1) pandemic and experience acquired from scientific advice and marketing authorisation applications. Two other separate modules of this guideline cover the quality and regulatory requirements for new influenza vaccines: (Guideline on Influenza Vaccines – Quality Module: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167817.pdf
and Guideline on influenza vaccines – submission and procedural requirements :
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/07/WC500189035.pdf

A full guideline on Influenza Vaccines is available here:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211324.pdf

Direct-Acting Antivirals for Hepatitis C: EMA Confirms Recommendation to Screen for Hepatitis B

On 16 December 2016, the European Medicines Agency (EMA) confirmed its recommendation to screen all patients for Hepatitis B before starting treatment with direct-acting antivirals for Hepatitis C; patients infected with both Hepatitis B and C viruses must be monitored and managed according to current clinical guidelines. These measures aim to minimise the risk of Hepatitis B reactivation with direct-acting antivirals.

Source:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/12/news_detail_002669.jsp&mid=WC0b01ac058004d5c1

The EMA recommendations may be found here:
http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2016/12/WC500218204.pdf

Consultation Documents on Clinical Trials

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/11/WC500216158.pdf

Treatment and prophylaxis of respiratory syncytial virus (RSV) infection
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/10/WC500215353.pdf

ICH E11 Clinical investigation of medicinal products in the paediatric population
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001256.jsp&mid=WC0b01ac0580032ec4

ICH guideline E17 on general principles for planning and design of multi-regional clinical trials
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211312.pdf

Addendum to the 'Guideline on the Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections' to address the clinical development of new agents to treat disease due to Mycobacterium Tuberculosis
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/08/WC500211447.pdf

Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211315.pdf

Guidance for individual laboratories for transfer of quality control methods validated in collaborative trials with a view to implementing 3Rs
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211432.pdf

Others Initiatives

New CIOMS International Ethical Guidelines Now Available

On 06 December 2016, the text of the new CIOMS International Ethical Guidelines for Health-Related Research involving Humans was posted on the website for the first time. This text was approved by the CIOMS Executive Committee during the XXII General Assembly of CIOMS on 29 November 2016. This text is still subject to additional formatting reviews and should not be considered as the final version.

Source: http://www.cioms.ch/

Final CIOMS guidelines: http://www.cioms.ch/ethical-guidelines-2016/

The reasons for the revisions and significant changes were published an article on 06 December 2016 by the Journal of American Medical Association (JAMA):
http://jamanetwork.com/journals/jama/fullarticle/2592245

WEB-RADR project

The WEB-RADR project was launched in September 2014. This ground-breaking three-year project investigates how to utilise social media and new technologies for pharmacovigilance purposes. The project is funded by the Innovative Medicines Initiative (IMI), Europe's largest public-private initiative supporting collaborative research projects.

WEB-RADR has two areas of focus: mobile applications (apps) to facilitate reporting of suspected adverse drug reaction (ADRs) by patients and healthcare professionals to medicines regulators, and the mining of social media data as a means of identifying potential issues related to the safe use of medicines. The project is also working on the development of recommendations for a future framework of regulatory guidance to support these activities.

The National Competent Authorities utilising these apps are:

- The Medicines and Healthcare products Regulatory Agency (MHRA)

The Yellow Card app is available for worldwide download:
https://itunes.apple.com/gb/app/yellow-card-mhra/id990237487?ls=1&mt=8 and
https://play.google.com/store/apps/details?id=uk.org.mhra.yellowcard&hl=en_GB

- The Netherlands Pharmacovigilance Centre LAREB

The LAREB app is available for worldwide download:
https://itunes.apple.com/ie/app/bijwerking/id1060529495?mt=8 and
https://play.google.com/store/apps/details?id=nl.lareb

- The Agency for Medicinal Products and Medical Devices of Croatia (HALMED)

The HALMED app is available for worldwide download:
https://itunes.apple.com/us/app/halmed/id1080314179 and
https://play.google.com/store/apps/details?id=hr.halmed

More information about improving pharmacovigilance through new technology: https://web-radr.eu/

Source:
http://www.ema.europa.eu/docs/en_GB/document_library/Agenda/2016/08/WC500211521.pdf

European Network of Paediatric Research at the EMA (Enpr-EMA)

The European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) is a network of research networks, investigators and centres with recognised expertise in performing clinical studies in children. The first European Medicines Agency workshop on the European network of paediatric research was in 2009.

The EnprEMA has its own Network Database: http://enprema.ema.europa.eu/enprema/index.php

On 10 December 2016, the EnprEMA issued a summary of general informed consent information for Paediatric Clinical Trials in Europe. This is a very useful guidance for everyone who plans clinical trials in the paediatric population.

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

News from Individual Countries

The Netherlands: Broadening of the Possibilities for Medical Research with Minors and Incapacitated Subjects

On 25 October 2016, the Upper House approved the proposal to amend the Medical Research Involving Human Subjects Act (WMO). The new legislation is expected to come into effect on the 01 March 2017. An important alteration concerns the broadening of the possibilities for carrying out medical research with minors and incapacitated subjects which is not of direct benefit to the individual subjects (so-called non-therapeutic research). The new legislation allows for this type of research to be carried out as long as the risks and burdens are minimal in comparison to the standard treatment. The amendment is expected to offer more room for development of new treatment methods, in particular with regards to paediatrics.

Previously, non-therapeutic medical research with minors and incapacitated subjects could only be carried out if it was not possible to carry out the same research with a group of legally-capable subjects. Furthermore, an extra requirement was stipulated stating that the risks of the research had to be negligible and the objections (such as pain and discomfort) had to be deemed minimal.

Under the new legislation the minimum age requirement for being deemed able to independently give consent for participation in research will be lowered from 18 to 16 years. In relation to this, the rules regarding compensation for 16 and 17-year-old subjects has also been altered. Another alteration concerns the make-up of the Medical Ethical Reviewing Committees (METC): METCs that review research with minor subjects must have an appointed paediatrician in the committee.

More information on: http://www.ccmo.nl/en/news-archive/broadening-of-the-possibilities-for-medical-research-with-minors-and-incapacitated-subjects

Details about transitional procedure to amend the Medical Research Involving Human Subjects Act: http://www.ccmo.nl/nl/verruiming-mogelijkheden-medisch-wetenschappelijk-onderzoek-met-minderjarige-en-wilsonbekwame-proefp?583306b7-6848-4dcb-b686-1bd0c35ff8ba

Austria: Pilot Project for Clinical Trials According to Regulation (EU) 536/2014

The National Competent Authority (BASG) and Ethics Committees (IEC) in Austria started a pilot project for clinical trials to develop and test practical scenarios to reach the 'single decision' for one clinical trial.

Currently applicable legislation will not be overruled by the pilot and the procedure will result in a valid legal decision. An application will not be delayed or have to be resubmitted due to the pilot project. The goal primarily for BASG and IEC is to adhere to the timelines of the regulation 536/2014. It is equally recommended for the applicant. If a timeline cannot be adhered to, the fallback positions are current legal timelines. The BASG will serve as the single point of contact during the procedure for responding to validation requests and considerations.

The first step of the pilot is limited to trials with one of the IECs acting as leading IEC. The initial submission needs to be timed with the meeting dates of this IEC. Parallel, but separate, submissions to BASG and IEC is currently necessary. It is planned to remove these limitations in later steps of the pilot.

Phase 0 with a single trial started in August 2016 for the IEC meeting in September 2016. The pilot project will be continued through the end of 2017 with involvement of further IECs.

Executive summary issued by BASG is available here: http://www.basg.gv.at/fileadmin/user_upload/BASG_EC_pilot_project_executive_summary_2016-07-15.pdf

Source: http://www.basg.gv.at/en/medicines/prior-to-authorisation/clinical-trials/pilot-project-for-clinical-trials-according-to-regulation-eu-5362014/

Czech Republic: New Guideline KLH-21 Version 6

The State Institute for Drug Control published a new guideline, KLH-21 version 6- Reporting Adverse Reactions to Medicinal Products for Human Use in a Clinical Trial and to Medicinal Products Without

Marketing Authorisation, with an effective date of 01 December 2016**.** This guideline supersedes the previous guideline KLH-21, version 5.

The guideline is intended for the sponsors, investigators and persons cooperating with them within the clinical trial, for holders of registration decisions, if they participate in implementation of clinical trials. The purpose of prompt reports of suspected serious unexpected adverse reactions in clinical trials is to feed new and important information into the pharmacovigilance system of clinical trials that ensures timely identification of signals, which can represent a health risk to the included subjects or possibly may result in a change of the safety profile of the investigational medicinal product (the risk outweighs the potential benefit).

The functional pharmacovigilance system also allows for evaluating identified serious signals and, if necessary, for taking measures to minimise the risk associated with the use of the investigational medicinal products for the subjects participating in the trial, including ensuring that all the parties involved (sponsors, investigators, participating subjects, regulatory bodies and members of ethics committees) are informed in a timely manner. The guideline defines the "reporting obligation" of all those who are involved in the system, the scope of such obligations and the manner of performing such obligations (see the overview table at the end of this guideline).

Source and full text for downloading is available on the SUKL website:
http://www.sukl.eu/medicines/klh-21-verze-6

Denmark: Interactive Adverse Drug Reaction Overviews

On 08 December 2016, the Danish Medicines Agency launched a new web-based database that researchers and other interested parties can use to search for reported suspected adverse reactions.

The new web-based database – the Interactive Adverse Drug Reaction (ADR) overviews – makes it easy to find reported suspected adverse reactions associated with specific medicinal products.

The interactive ADR overviews provide data about suspected adverse reactions reported in Denmark for a specific type of medicine. The information comes from the Danish Medicines Agency's pharmacovigilance database, which contains all reported suspected adverse reactions from 1968 when the database was established. The database contains reports from healthcare professionals, patients and relatives.

Up to now, reported adverse reactions have been available as PDF files, but the new database presents the reports in a far more user-friendly interface. With the interactive ADR overviews, users can select filter options when they want to search the database.

Before starting searching the interactive ADR overviews, it is important to read and accept the terms and conditions: http://laegemiddelstyrelsen.dk/en/sideeffects/side-effects-from-medicines/interactive-adverse-drug-reaction-overviews/terms-of-use-of-the-interactive-adr-overviews

Source: http://laegemiddelstyrelsen.dk/en/sideeffects/side-effects-from-medicines/interactive-adverse-drug-reaction-overviews

France: New Decree Introduces New Requirements for Clinical Research

On 17 November 2016, the Official Journal of the Republic of France published new Decree No. 2016-1537 dated 16 November 2016 relating to research involving the human person.

The Decree No. 2016-1537 dated 16 November 2016 relating to research involving the human person introduces many changes that will impact authorisation of clinical trials and pharmacovigilance, as well as new definitions.

The notion of “biomedical research” has been replaced by "research involving the human person" which includes interventional and non-interventional clinical trials. Previously, non-interventional research was excluded from the biomedical research framework.

The law Implemented by the decree of 16 November, 2016 distinguishes three types of research:

- Interventional research with risk above minimal risk. This includes research on drugs, medical devices, other health products, and non-health product research (e.g. research on foodstuffs). Interventional research was previously defined as “biomedical research”. (Type 1 research / Art. L1121-1 1° CSP)
  An authorisation of the National Agency for the Safety of Medicine and Health Products (ANSM) and the Committees for the Protection of Persons (CPP) is required.
- Interventional research that involves minimal risks and constraints. Such studies may involve the use of health products, but these are then used under the usual conditions of use. They may involve minimally invasive procedures (venous blood sampling, non-invasive imaging, etc.). Thus, part of this research corresponds to what was previously referred to as "research to evaluate routine care". (Type 2 research / Art. L1121-1 2° Code de la santé publique (CSP)
  These studies must be declared to the ANSM but not required authorization. The CPP favourable opinion required.
- Non-interventional or observational research. This is research that does not involve any risk or constraint added by the research, or any modification of the usual care. (Type 3 research / Art. L1121-1 3° CSP)
  In this context, distinguish two subtypes:
  - *Research with patients involved, even without risk* (may include taking a blood sample or by a questionnaires). It is the involvement of the patients that defines the research. Such research must have a sponsor, a favourable opinion of a CPP and requires notification to the ANSM including the CPP approval.
  - *Research concerns only data, already collected or to be obtained from collections or old samples*. This research does not fit into the ANSM-CPP circuit, but should be sent to the CEREES (Committee for Expertise in Research, Studies and Evaluations in the field of Health) for advice (to the Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé (CCTIRS) until April 2017).

It is the Sponsor who qualifies a research project in one of the categories above. But the CPP or the ANSM can refuse this classification and requalify a project. Before presenting a complete file unnecessarily, the sponsor can ask the CPP for a preliminary advice on the typology of the research.

Source: http://cpp.idf.5.free.fr/CaDefinitions.html

The conditions for authorisation of certain clinical research are reinforced, especially for First-in-Human (FIH) studies. In this case, the authorisations are issued for three years instead of seven years.

The Decree determines the mission and way of functioning of the National Commission for Research Involving the Human Person (NCR), including the coordination of the CPP ('*Comités de Protection des Personnes*'- the Committees for the Protection of Persons - the French Ethics Committees).

According to the new Decree, the Sponsor (or his authorised representative) will be obligated to send the request for authorisation and/or opinion on a research to the NCR. The secretariat of the NCR will delegate the competent CPP. To obtain the random designation of the CPP, the applicant first must obtain a registration number for the research on the National Agency for the Safety of Medicine and Health Products - the ANSM website ("ID-RCB number" https://ictaxercb.ansm.sante.fr/Public/index.php) . After receiving "ID-RCB number" the applicant will be able to apply to the secretariat of the NCR via the Volontaires Recherches BioMédicales (VRB) portal: https://vrb.sante.gouv.fr

The NCR will ask the applicant to provide the EudraCT number, ID-RCB number provided by the ANSM, a title of the research, type of the project with information if the research requires the inclusion of volunteers, and declare participating investigators. After submitting the information, the applicant will receive an email containing the link on which he/she will have to click to confirm receipt and get the name of the randomized CPP. The NCR will choose the CPP, not the Sponsor. Everything will be recorded in the system.

The appointed CPP will have 10 days to check if an application is complete and request any missing documents. The moment the application dossier is complete will be called T0 (Time 0) and then the CPP will have 45 days to give its opinion to the NCR. The 45 day procedure applies to interventional research that involves minimal risks and constraints, non-interventional studies or observational research when only the CPP favorable opinion will be required. The authorisation from the ANSM will be not required but registration of the studies will be still required on the ANSM website ("ID-RCB number).

In cases when the research is interventional, the application shall be transmitted to the competent authority (the ANSM) and to the NCR secretariat in parallel or on the same day. In such case, the deadline for giving opinion shall be 60 days for both the ANSM and the CPP. The ANSM authorisation and a CPP favorable opinion will be required to start the study. The most important requirement is that the files to the ANSM and the CPP must be sent without delay. If the applicant does not forward the file without delay, the CPP will cancel the application and the procedure of application will have to be repeated from the beginning. The CPP will be obligated to notify the NCR and the ANSM of their opinions.

Within one month (used to be 15 days) of notification of the CPP's adverse opinion, the sponsor may refer a request for reconsideration to the secretariat of the National Commission for Research Involving the Human Person (NCR).

All the provisions of this decree have been entered into force on 16 November 2016, however those relating to the information system when the investigators/applicants and the CPP will be managed by the secretariat of the NCR will be implemented as soon as this system is made fully-operational by decision of the Minister of Health and no later than 31 December 2017. By this time, the draw of the CPP is made at the initiative of the Investigators, or applicants and the exchanges between the bodies concerned are performed by post or electronically.

The Decree has also changed requirements for pharmacovigilance. The deadline for notification of serious adverse events, as well as expected (SARs) and unexpected serious adverse reactions (USARs) by the sponsor to the ANSM in research involving medicines, medical device and non-health product research (occurring in France and outside the national territory) and resulting in death or risk of death , has been changed from seven days into 'without delay'. For other unexpected serious adverse events the period is maximum 15 days. In both cases, additional information must be provided within eight days following the declaration.

The Decree No. 2016-1537 dated 16 November 2016 has changed the definitions for trials involving first administration or use of a health product in healthy volunteers. In case any serious adverse reaction constitutes a new finding in trials involving healthy volunteers, the sponsor must inform the ANSM, the CPP and the Director-General of the ARS (Regional Heath Agency) without delay.

Source and full Decree is available here in French:
https://www.legifrance.gouv.fr/eli/decret/2016/11/16/AFSP1621392D/jo/texte

The questions & answers regarding new Decree dated 25 November 2016 here:
http://social-sante.gouv.fr/systeme-de-sante-et-medico-social/recherche-et-innovation/article/recherches-impliquant-la-personne-humaine

News from the United States of America

Updated Requirements for Posting Studies and Results on Clinicaltrial.gov

On 21 September 2016, the Department of Health and Human Services released a 710-page final rule document expanding the requirements for registering applicable clinical trials and submitting results, including adverse event data, to ClinicalTrials.gov. These expanded regulations became effective on 18 January 2017. Sponsors will have until 18 April2017 to comply.

Key Elements Include:

1. Clarification of the definition of an applicable clinical trial (ACT). ACTs are now defined as:
    - Clinical trials of drug and biological products that are controlled, clinical investigations, of a product subject to FDA regulation.
    - Prospective clinical studies of health outcomes comparing an intervention with a device product against a control in humans.
    - Any pediatric post-market surveillance studies required by FDA under the FD&C Act.
    - NOTE: Phase I investigations and small feasibility studies are not considered ACTs.
2. All ACTs must be registered on ClinicalTrials.gov no later than 21 days after the first participant is enrolled.
3. Results for all ACTs, including adverse event data, must be submitted no later than one year after the primary completion date. It is possible to receive permission delaying this posting for up to an additional two years for trials of unapproved products or for products for which initial FDA marketing approval or clearance is being sought, or approval or clearance of a new use is being sought.
4. FDA has the ability to assess monetary penalties of up to $10,000 USD per day for non-compliance.

Link to the Final Rule

https://s3.amazonaws.com/public-inspection.federalregister.gov/2016-22129.pdf

The New England Journal of Medicine published a special report on this topic.

http://www.nejm.org/doi/full/10.1056/NEJMsr1611785#t=article

Clinicaltrials.gov has prepared several training presentations.

https://clinicaltrials.gov/ct2/home

Humanitarian Use Device Definition Change – Affected Individuals Increased

The US Food and Drug Administration (FDA) announced on 13 December 2016 that the definition of a humanitarian use device (HUD) was changing. A HUD is now defined as "a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year".

http://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/designatinghumanitarianusedeviceshuds/default.htm

Guidance Document Update

Between 01 October 2016 and 31 December 2016, the FDA published 55 guidance documents, both draft and final, for Industry. The list below contains links to 11 documents most applicable to CROMSOURCE.

Software as a Medical Device (SAMD): Clinical Evaluation

Release Date: 10/14/2016 (Draft)

Summary: The purpose of this draft document, which was written by the International Medical Device Regulators Forum (IMDRF), is to establish a method for demonstrating the safety, effectiveness and performance of software that is considered a medical device. Software as a Medical Device (SaMD) is defined, according to *SaMD N10*, "as software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device."

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm524904.pdf

Collection of Race and Ethnicity Data in Clinical Trials

Release Date: 10/26/2016 (Final)

Summary: The purpose of this guidance is "is to provide FDA expectations for and recommendations on use of a standardized approach for collecting and reporting race and ethnicity data in submissions for clinical trials for FDA regulated medical products conducted in the United States and abroad."

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm126396.pdf

Non-Inferiority Clinical Trials to Establish Effectiveness

Release Date: 11/7/2016 (Final)

Summary: "This document provides guidance to sponsors and applicants submitting investigational drug applications (INDs), new drug applications (NDAs), biologics licensing applications (BLAs), or supplemental applications on the appropriate use of non-inferiority (NI) study designs to provide evidence of the effectiveness of a drug or biologic, usually because a superiority study design (drug versus placebo, dose-response, or superiority to an active drug) cannot be used."

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm202140.pdf

Medical Device Reporting for Manufacturers (Post-market Adverse Event Reporting)

Release Date: 11/8/2016 (Final)

Summary: "This guidance document describes and explains the Food and Drug Administration's current regulation that addresses reporting and recordkeeping requirements applicable to manufacturers of medical devices for device-related adverse events and certain malfunctions."

Note: This guidance document applies to adverse event reporting for medical devices legally marketed in the US. It does not apply to adverse event reporting for investigational devices unless the investigational device is also a legally -marketed device.

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm359566.pdf

Providing Post-Marketing Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report)

Release Date: 11/28/2016 (Final)

Summary: "This guidance describes the conditions under which applicants can use an alternative reporting format, the International Council for Harmonisation (ICH) E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER), in place of the U.S. periodic adverse drug experience report (PADER), U.S. periodic adverse experience report (PAER), or ICH E2C Periodic Safety Update Report (PSUR), to satisfy the periodic post-marketing safety reporting requirements in §§ 314.80(c)(2) and 600.80(c)(2) (21 CFR 314.80(c)(2) and 600.80(c)(2)). This guidance also describes the procedures applicants should follow if they wish to submit a PBRER in place of a PADER, PAER, or PSUR."

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm346564.pdf

Use of Electronic Informed Consent – Questions and Answers

Release Date: 12/14/2016 (Final)

Summary: "This guidance provides recommendations on the use of electronic systems and processes that may employ multiple electronic media to obtain informed consent for both HHS-regulated human subject research and FDA-regulated clinical investigations of medical products, including human drug and biological products, medical devices, and combinations thereof. FDA's requirements for electronic records/electronic signatures, informed consent, and IRBs are set forth in 21 CFR parts 11, 50, and 56, respectively. HHS requirements regarding the protection of human subjects are set forth in 45 CFR part 46."

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm436811.pdf

Public Notification of Emerging Post-Market Medical Device Signals ("Emerging Signals")

Release Date: 12/14/2016 (Final)

Summary: "This guidance document explains the factors CDRH intends to consider in deciding whether to notify the public about emerging signals related to devices and the processes and timelines it intends to follow in issuing and updating the notification."

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm479248.pdf

Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions

Release Date: 12/27/2016 (Final)

Summary: "FDA has developed this guidance document to provide clarity for FDA staff and industry regarding the benefit and risk factors FDA may consider in prioritizing resources for compliance and enforcement efforts to maximize medical device quality and patient safety."

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm506679.pdf

Post-Market Management of Cybersecurity in Medical Devices

Release Date: 12/28/2016 (Final)

Summary: "This guidance clarifies FDA's post-market recommendations and emphasises that manufacturers should monitor, identify, and address cybersecurity vulnerabilities and exploits as part of their post-market management of medical devices. This guidance establishes a risk-based framework for assessing when changes to medical devices for cybersecurity vulnerabilities require reporting to the Agency and outlines circumstances in which FDA does not intend to enforce reporting requirements under 21 CFR part 806."

"This guidance applies to any marketed and distributed medical device including: 1) medical devices that contain software (including firmware) or programmable logic; and 2) software that is a medical device, including mobile medical applications. In addition, this guidance applies to medical devices that are considered part of an interoperable10 system and to "legacy devices," i.e., devices that are already on the market or in use."

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm482022.pdf

Providing Regulatory Submissions in Electronic Format—Submission of Manufacturing Establishment Information

Release Date: 12/28/2016 (Draft)

Summary: "This draft guidance discusses the requirements and implementation of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) regarding valid electronic submissions of manufacturing

establishment information (MEI). Twenty-four months after this draft has been finalized, MEI contained in new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologics license applications (BLAs), and amendments, supplements, or resubmissions of these application types must be submitted electronically in the format specified in this guidance. This draft guidance also applies to drug master files that are submitted for incorporation by reference into an NDA, ANDA, or BLA."

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm534709.pdf

Medical Device Accessories – Describing Accessories and Classification Pathway for New Accessory Types

Release Date: 12/30/2016 (Final)

Summary: "This guidance document describes what the FDA generally considers an "accessory" and how the FD&C Act's risk- and regulatory control-based framework for classification applies to accessories to other medical devices."

"In addition, this guidance describes use of the *de novo* classification process to classify accessories of a new type under Section 513(f) (2) of the FD&C Act."

http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm429672.pdf

For the complete list of guidance documents,

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