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Regulatory Newsletter
January - March 2017

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

EU Council adopts new Medical Device Regulation (MDR) and In Vitro Diagnostic Regulation (IVDR)

On 5 April 2017, the European Parliament adopted two new Regulations – the Medical Device Regulation (MDR) and the In Vitro Diagnostic Regulation (IVDR) without amendment.

The two new EU regulations:

- "provide a stronger mandate to independent notified bodies in their assessment of medical devices before they can be placed on the market, and strengthen the oversight of these bodies by national authorities; the new rules also ensure that notified bodies meet the same high safety standards throughout the EU; these measures will **improve the safety of medical devices**
- improve the availability of clinical data on devices and clearly set out manufacturers' responsibilities for the follow-up of the quality, performance and safety of devices placed on the market; this will **allow** manufacturers **to react quickly in the event of concerns being raised and** help them **improve** their **devices continuously** on the basis of actual data
- improve the traceability of medical devices throughout the supply chain to the end-user or patient by using a unique identification number; this **will allow fast and effective measures to be taken in the event of safety problems**
- set up a central database to provide patients, healthcare professionals and the public with comprehensive information on products available in the EU; this will enable them to **make better informed decisions"**

Source: https://www.eu2017.mt/en/news/Pages/Safer-Medical-Devices-Council-adopts-new-EU-rules.aspx

The Regulations will be set to be formally published in *the Official Journal of the European Union* in May 2017. "The Commission heartily welcomes the final compromise which contains a series of crucial improvements to the current system," said European Commissioner of Health and Food Safety Vytenis Andriukaitis.

The Regulations in 24 languages are available here:

- Medical Device Regulation *final text on 08Mar2017 http://eur-lex.europa.eu/oj/direct-access.html?locale=en soon in the Official Journal of the European Union*
- In Vitro Diagnostic Regulation *final text on 08Mar2017 http://eur-lex.europa.eu/oj/direct-access.html?locale=en soon in the Official Journal of the European Union*

The regulations will apply three years after publication (in 2020) for medical devices and five years after publication (in 2022) for in vitro diagnostic medical devices.

Please find below "New EU rules to ensure safety of medical devices - factsheet" Ref. Ares (2017)1821704 - 05/04/2017 http://ec.europa.eu/DocsRoom/documents/22522 (copied on 06 April 2017)

EXISTING RULES	NEW RULES
Outdated rules – rules on medical devices date back to the 1990s and don't reflect the technological progress made since then	**Up-to-date rules** – new rules take into account technological progress and drive innovation
Control of high-risk devices such as implants relies **on national Notified Bodies** – separate bodies risk inconsistency	Control of high-risk devices such as implants involve also **panels of independent experts** at EU level
Clinical trials taking place in more than one Member State are subject to **multiple national assessments**	Clinical trials taking place in more than one Member State will be subject to **a single coordinated assessment**
Most aesthetic products, such as coloured contact lenses, are **regulated as general products**	Many aesthetic products are **regulated as medical devices and subject to stricter controls**
Only one in five *in vitro* diagnostic medical devices is checked by a Notified Body before they are placed on the market	**Four out of five** *in vitro* diagnostic medical devices are checked by a Notified Body before they are placed on the market
European database contains **limited** information on medical devices that is not publicly accessible	European database contains **extensive** information on medical devices, most of which is publicly available
Varying and often limited information on implanted devices available to patients	An **"implant card"** for implanted devices gives patients more information
In case of harm resulting from medical devices, compensation is **not guaranteed** if, for example, manufacturer goes bankrupt	A financial mechanism **ensures patients are compensated** in case defective medical devices harm them
Multiple registration procedures might be required for medical devices in different EU countries	**Simplified procedure** allows manufacturers to register their device only once at the EU level

Source: http://ec.europa.eu/growth/tools-databases/newsroom/cf/itemdetail.cfm?item_id=9119&lang=en

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=

Over 1,000 studies recorded in EU register of post-authorisation studies (PAS)

On 10 February 2017, the European Medicines Agency announced the uploading of the 1,000th study in the European Union (EU) electronic Register of Post-Authorisation Studies PAS).
The EUPAS Register provides a wealth of information on the safety and effectiveness of authorised medicines. It is an openly accessible platform with information on post authorisation research in medicines already marketed in Europe and includes study protocols, study results, related publications and other relevant information.

EU PAS Register has a focus on observational research, and its purpose is to:

- increase transparency,
- reduce publication bias,
- promote the exchange of information and facilitate collaboration among stakeholders, including academia, sponsors and regulatory bodies,
- ensure compliance with EU pharmacovigilance legislation requirements.

The EU PAS Register is available here: http://www.encepp.eu/encepp_studies/indexRegister.shtml

Source:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/02/news_detail_002692.jsp&mid=WC0b01ac058004d5c1

Mapping of multinational initiatives by the EMA

The EMA is a member of the International Coalition of Medicines Regulatory Authorities (ICMRA). ICMRA is a voluntary, executive level entity of medicines regulatory authorities worldwide providing strategic coordination, advocacy and leadership.

On 09 January 2017, the EMA published eight mapping documents of multinational initiatives made by relevant, world-wide organizations. The information for the mappings was compiled by the ICMRA.

ICMRA - Mapping of the bilateral arrangements between the ICMRA members
ICMRA - Mapping of supply chain/anticounterfeiting initiatives
ICMRA - Mapping of pharmacovigilance initiatives
ICMRA - Mapping of multinational project initiatives
ICMRA - Mapping of IT initiatives as a support to global medicines regulation
ICMRA - Mapping of GMP inspection initiatives
ICMRA - Mapping of generic initiatives
ICMRA - Mapping of crisis management initiatives

Source:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000626.jsp&mid=WC0b01ac058085284f

Common European Single Submission Portal (CESSP)

The European Medicines Agency (EMA) and Heads of Medicines Agencies (HMA) have published a statement of intent (EMA/666963/2016) on replacing electronic application forms (eAFs) for human and veterinary medicines applications with a Common European Single Submission Portal (CESSP). It will integrate the HMA's Common European Submission Platform (CESP) and EMA's eSubmission Gateway

into a single system. The first version will cover initial and extension applications, and will be available by Q1 2018. At a later stage, the CESSP will replace all other eAFs for variation and renewal applications. A visual representation of the milestones is available here and information on the main changes can be found in the release notes.

Further information about eSubmission is available on the EMA website:
http://esubmission.ema.europa.eu/index.htm

Source:
http://esubmission.ema.europa.eu/cessp/CESSP%20statement%20of%20intent.pdf

Adjusted fees for applications to EMA from 1 April 2017

Beginning of 1 April 2017, the fees collected by the European Medicines Agency (EMA) from applicants and market authorization holders, except for pharmacovigilance procedures, will increase by 1.2%, in line with the inflation rate in the EU for 2016.
All applications received by 31 March 2017 will be charged at the current fee and reduction rates. Applications received after that date will be charged the adjusted fees and be subject to the revised reduction rates, where applicable. For scientific advice and protocol assistance, the cut-off date will be the date of validation of the request for advice. For annual fees the anniversary date defines the applicable fee and consequently any anniversary on or after 1 April 2017 will attract the new fee.
Fees charged for pharmacovigilance procedures in accordance with Regulation (EU) 658/2014 are expected to be updated from 1 July 2017.

Source:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/02/news_detail_002701.jsp&mid=WC0b01ac058004d5c1

New fees:
http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/03/WC500224062.pdf

Guidelines/Recommendations

Guideline on clinical development of fixed combination medicinal products

On 23 March 2017, The EMA's Committee for Medicinal Products for Human Use (CHMP) released a revised Guideline on clinical development of fixed combination medicinal products. The revised guideline covers fixed combination medicinal products containing two or more active substances, which can be either well-known or not yet authorised in the European Union for the intended claim. The date of coming into effect is 1 October 2017.
The guidance applies primarily to small molecules irrespective of route of administration and dosage form (immediate versus modified release), but the general principles also apply to biological products. The scientific principles are also applicable to a substance designed to dissociate *in vivo* into two or more active substances that form its principal therapeutic moieties. The guideline does not apply to a single molecule active substance that affects multiple pharmacological targets (i.e. has affinity to multiple receptors involved in the desired therapeutic outcome).
It is expected that the same principles would generally apply to fixed combination medicinal products containing three or more active substances.

The guideline does not address the requirements for combination packs, i.e. where active substances are included in separate pharmaceutical forms marketed in the same package. The clinical development of herbal fixed combinations as well as those composed of vitamins, oligo-elements and minerals are also outside of the scope of this guideline.

Source:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001241.jsp&mid=WC0b01ac0580032ec4

Adopted guideline, currently under revision:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/03/WC500224836.pdf

Consultation documents on clinical trials

Concept paper on developing a guideline on quality requirements of medicinal products containing a device component for delivery or use of the medicinal product

On 16 February 2017, the European Medicinal Agency (EMA) published for consultation the "Concept paper on developing a guideline on quality requirements of medicinal products containing a device component for delivery or use of the medicinal product". The consultation end date is 16 May 2017. Comments should be submitted to qwp@ema.europa.eu.
This concept paper addresses the need for development of a guideline on dossier requirements for medical devices that are supplied along with medicinal products where a device is necessary for administration or localisation (site-specific delivery) of the medicinal product.

Source:
http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500221747&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

The concept paper for consultation:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/02/WC500221747.pdf

The ICH E11 Guideline on Clinical Investigation of Medicinal Products in the Pediatric Population- Addendum

On 17 February 2017, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) informed that the ICH E11 (R1) draft Addendum on Clinical Investigation of Medicinal Products in the Pediatric Population reached Step 2b of the ICH Process and is currently under public consultation (European Commission by 13 April 2017, FDA by 21 February 2017). Step 4 and final guideline is expected in November 2017.

Description provided by ICH: "Since the adoption of the ICH E11 Guideline on Clinical Investigation of Medicinal Products in the Pediatric Population in 2000, pediatric drug development has been enhanced by advancements in several areas of general adult drug development. Targeted scientific and technical issues relevant to pediatric populations, regulatory requirements for pediatric study plans, and infrastructures for undertaking complex trials in pediatric patient populations has been considerably

advanced in the last decade, without a parallel development of harmonised guidance in these areas. This Addendum is proposed to address new scientific and technical knowledge advances in pediatric drug development"

Source: http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html#11-2

The draft Addendum to ICH E11 guideline is here:
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/ICH_E11_R1_Step_2_25Aug2016_Final.pdf

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

On 13 February 2017, the European Medicinal Agency (EMA) published 'Overview of comments received by EMA on 'ICH guideline E17 on general principles for planning and design of multi-regional clinical trials - Step 2b' (EMA/CHMP/ICH/453276/2016). The comments will be sent to the ICH E17 Expert Working Group for consideration in the context of Step 3 of the ICH process. Step 5 would be the final one.
The purpose of this document is to outline general principles for the planning and design of multiregional clinical trials with the aim of increasing their acceptability in global regulatory submissions. The document addresses some strategic programme issues as well as aspects specific to the planning and design of confirmatory MRCTs and should be used together with other ICH efficacy guidelines, including E2, E3, E4, E5, E6, E8, E9, E10 and E18.

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

ICH guideline E17, Step 2b (current version) is available here:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500211312.pdf

Overview of comments receive by EMA on ICH guideline E17, Step 2b:
http://www.ema.europa.eu/docs/en_GB/document_library/Overview_of_comments/2017/02/WC500221551.pdf

Other Initiatives

ICH Reflection on "GCP Renovation": modernization of ICH E8 and subsequent renovation of ICH E6

In January 2017, the International Council for Harmonisation (ICH) invited public review and comment on a reflection paper on Good Clinical Practice (GCP) "Renovation", which contains the ICH proposal for further modernization of the ICH Guidelines related to clinical trial design, planning, management, and conduct. The scope of the proposed renovation includes the current E8 General Considerations for Clinical Trials and further revision to the E6 Guideline for Good Clinical Practice, which is already undergoing modernization with the recent production of ICH E6 (R2).

Addendum to ICH Good Clinical Practice (GCP) Guideline E6 (R2) was adopted by the European Medicines Agency (EMA) on 15 Dec2016 and will come into effect on 14 June2017.

The ICH invited stakeholders to submit comments by 11 March 2017 to gcprenovation@ich.org.

According to ICH: "The goal of the potential renovation is to provide updated guidance that is both appropriate and flexible enough to address the increasing diversity of study types and data sources that are being employed to support regulatory and other health policy decisions, as appropriate. The underlying principles of human subject protection and data quality would remain. ICH's decision to invite stakeholder comment on the proposed renovations at this early stage, ahead of guideline development efforts, recognises the considerable stake and relevant expertise in the research community beyond ICH. The seeking of stakeholder comment on the current reflection paper is seen as a first step in an enhancement of the ICH process with respect to public consultation for the revision of ICH E8 and E6. The GCP Renovation reflection paper outlines additional steps that are also being considered to enhance stakeholder engagement."

Source ICH website: http://www.ich.org/ichnews/press-releases/view/article/ich-reflection-on-gcp-renovation-modernization-of-ich-e8-and-subsequent-renovation-of-ich-e6-1.html

Q&A: Good clinical practice (GCP) on EMA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000016.jsp&mid=WC0b01ac05800296c5

Voluntary Harmonisation Procedure plus (VHP-plus)

In January 2017, the Clinical Trial Facilitation Group (CTFG) published a new list of Members States (MS) participating in Voluntary Harmonisation Procedure (VHP) and Voluntary Harmonisation Procedure-plus (VHP-plus) procedures. The CTFG was established in 2004 by the Head of Medicines Agencies (HMA) to coordinate the implementation of the EU Clinical Trials Directive 2001/20 EC across the Member States. The VHP for clinical trials was first established in March 2009. The target of the CTFG was to harmonize the situation of clinical trials after the implementation of the Clinical Trials Directive in 2004. "The main key features of the CTFG were:

- Only electronic documents sent to one address (one stop shop)
- Only general documents required, which are part of any clinical trial application (Protocol, Investigators brochure, Investigational Med. Product Dossier)
- Reliable timelines for Sponsor and Member States (MS)
- Harmonised scientific discussion resulting in harmonised applications in the Member States; no tracking of Member States specific modifications necessary
- consolidated lists of grounds for non-acceptance, if needed"

The VHP fulfilled all the listed features and has been developed for more initiatives. Since 2016 the VHP gave permission to the Member States to involve Ethics Committees in the clinical trial assessment on a voluntary basis. This process has been named as "VHP-plus". The participation of Ethics Committees is possible only for Member States included in the list published by CTFG here . Inclusion of Ethics Committees is only possible for initial applications (not for amendments) at the moment.

The European Union recorded over 1000 VHP applications for authorization of clinical trials in all concerned Member States. The Members States' Agencies encourage sponsors to continue VHP or VHP-plus procedures until new Clinical Trial Regulation (EU) No 536/2014 will be fully effective. It is foreseen that the Regulation (EU) No 536/2014 will be fully applicable in October 2018.

The main characteristics of the new Regulation are similar to those of VHP and VHP-plus:

- "A streamlined application procedure via a single entry point, the EU portal.
- A single set of documents to be prepared and submitted for the application defined in Annex I of the Regulation.
- A harmonised procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is jointly assessed by all Member States concerned. Part II is assessed by each Member State concerned separately.
- Strictly defined deadlines for the assessment of clinical trial application.
- The involvement of the ethics committees in the assessment procedure in accordance with the national law of the Member state concerned but within the overall timelines defined by the Regulation."

Professor Klaus Cichutek, Head of the HMA Management Group and President of the Paul-Ehrlich-Institut (PEI) said: "The HMA is proud that the Voluntary Harmonisation procedure has in the meantime been so well accepted by applicants world-wide, simplifying and reducing the period required for the authorisation of such multinational studies. Importantly, the VHP served as a model for the procedure to become applicable with the new regulation on clinical trials in future for the authorisation of multinational European clinical trials in Europe." (http://www.hma.eu/whatsnew.html)

References to the main key features of the CTFG:
http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2010/06/WC500093380.pdf)

References to the main characteristics of the Clinical Trials Regulation EU No 536/2014:
http://ec.europa.eu/health/human-use/clinical-trials/regulation_en

Voluntary Harmonisation Procedure (VHP) : http://www.pei.de/EN/information/license-applicants/clinical-trial-authorisation/vhp-voluntary-harmonisation-procedure/vhp-node.html

More details about VHP can be found in this EMA presentation:
http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2010/06/WC500093380.pdf

EMA's New Home

On 29 March 2017 the United Kingdom triggered article 50 starting the two-year Brexit negotiation with European Union. "The European Federation of Pharmaceutical Industries and Associations (EFPIA), EuropaBio and Medicines for Europe are intended to minimize the risk of disruption when EMA moves from its current home in London, United Kingdom to a new location as part of Brexit." The three trade groups submitted a letter to European Commission which highlighted six essential criteria for the selection process: "…easy access to an airport, transport links to the rest of the EU, adequate local hotel capacity and enough space for EMA meetings and events. Finally, the letter's authors request the commission minimize disruption for EMA staff by factoring in the availability of international schools, labor market access and social security."

The criteria presented by trade groups favor countries in Western Europe: Denmark or the Netherlands due to their necessary regulatory capacity and easier relocation for current EMA staff. However, other countries like Ireland, Croatia, Malta, Spain, Portugal, Italy, France, Sweden, Finland, Hungary and Bulgaria have made public their interest in housing the agency.

On 5 April 2017, the European Parliament called for an agreement to be reached "as quickly as possible" to relocate the headquarters of the European Medicines Agency (EMA).
But Sir Kent Woods, former EMA chairman of the board and former chief executive of the UK's Medicines and Healthcare products Regulatory Agency (MHRA) said: "It is in the interests of the global pharmaceutical and devices industries, and of the public health, that there is continuity during the transition. There is, for example, no reason in EU law why the EMA must be located in a Member State; any move will be disruptive if it results in losses of staff and expertise". (http://raps.org/Regulatory-Focus/News/2017/04/06/27294/European-Parliament-Calls-for-Rapid-Relocation-of-EMA-Headquarters/?utm_source=Email&utm_medium=Informz&utm_campaign=Informz%2DEmails)

References: European Regulatory Roundup: EU Trade Groups Propose Criteria for Deciding EMA's New Home (2 March 2017) | RAPS

News from Individual Countries

The United Kingdom

a. Common issues identified during clinical trial applications

On **22 March 2017**, the Medicines and Health Regulatory Agency (MHRA), the Competent Authority in the United Kingdom published several guidance documents on common issues that have been identified during the assessment of clinical trial applications and how to avoid them.

These documents are very detailed and refer to validation issues, non-clinical issues, clinical issues and pharmaceutical issues (IMP, labels, QP, GMP). Also provided is a guide containing useful resources for CTA applications.

The MHRA receives more than 1000 clinical trial authorisation (CTA) applications for investigational medicinal products (IMP) per year and more than half of these applications require further information before they are considered approvable. The purpose of these documents is to assist applicants in understanding the common reasons for MHRA requiring additional information and to provide direction to where further information and guidance can be found. MHRA does caution that these documents should not be seen as a 'tic-box' guide and that "every trial will have its own peculiarities and each is assessed on a case by case basis, which may lead to questions needing to be asked on specific areas".

Source and guidance: https://www.gov.uk/government/publications/common-issues-identified-during-clinical-trial-applications

b. Leadless cardiac pacemaker therapy: new guidance

On 13 March 2017, the MHRA Expert Advisory Group published initial recommendations on leadless cardiac pacemaker therapy.

"This guidance applies to new devices and all design changes or iterations and enhancements that might affect the clinical safety or performance of the leadless device. However, each device modification or iteration must be assessed individually to determine whether all aspects of the guidance fully apply (e.g.

appropriate follow-up duration for changes that impact only the ease of placement of the leadless device).
While this guidance applies principally to leadless pacing, it is envisaged that it may apply equally to other leadless CIEDs (cardiac implantable electronic devices) as the technology advances. This guidance will be revised periodically as the evidence base for these technologies grows."

Source: https://www.gov.uk/government/publications/leadless-cardiac-pacemaker-therapynew-guidance-from-an-mhra-expert-advisory-group

Guidance:
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/598730/Leadless_cardiac_pacemaker_therapy_-_EAG_initial_recommendations_.pdf

c. A new 'Pay on Invoice' process announced by the MHRA

The MHRA announced that on 1 April 2017 a new 'Pay on Invoice' process would be implemented. This new process replaces the current process of paying in advance for medicines licenses, clinical trials, clinical investigations and its amendments. Everyone submitting applications to the MHRA will no longer need to attach proof of payment. According to the MHRA: "The benefits of the new process include removing the need to work out complex fees and reducing the chance of applications being rejected for incorrect payment details"

For example, in case the applicant would like to carry out a clinical investigation to obtain a CE marking for the medical device, he/she does not need to attach proof of payment to application. The applicant will receive an invoice to allow him/her to make payment for the correct amount once the application has been validated.

In addition **starting 1 April 2017**, the MHRA has implemented new fees for Medical Devices amendments:

- The fee for notification of a clinical investigation amendment for Class I, IIa, or IIb other than implantable or long-term invasive devices has been changed from £225 to **£207**.
- The fee for notification of a clinical investigation amendment for Class IIb implantable or long-term invasive, Class III, and active implantable devices has been changed from £225 to **£331**.

Other fees for clinical trials and clinical investigations have not been changed.

Source: https://www.gov.uk/government/news/a-new-way-to-pay

Fees: https://www.gov.uk/government/publications/mhra-fees

How to make the payment to MHRA: https://www.gov.uk/guidance/make-a-payment-to-mhra

Greece: New Decree concerning the application of the Regulation No 536/2014

On **22 December 2016**, the Government Gazette No 4131/B/22.12.2016 published the Ministerial decisions "Provisions concerning the application of the Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20EC". The Greek Ministers of Economy and Development – Health have implemented Clinical Trials Regulation No 536/2014 into Greek Law.

The National Organization for Medicines (E.O.F.), the Greek Competent Authority has been designated as "national contact point", within the meaning of article 83 of Clinical Trial Regulation No 536/2014. In order to obtain an authorization, the applicant will need to submit the dossier via a single "EU portal" (not effective yet). The process of submission and validation should be done in accordance with Article 5 of the Regulation: within six days of presenting to the reporting Member State and within ten days of validation. "The application, the protocol, the informative material addressed to the patients, the informed consent form, the labeling, the patients' cards and the insurance policy (contract) shall be submitted in the Greek language. " The assessment should be done by the E.O.T. and National Ethics Committee (NEC) in accordance with Article 6 and 7 of the Regulation No 536/2014. The NEC should submit their assessment in five days prior the expiration of the deadlines set by the E.O.T.

Any substantial amendments should also be submitted thought "EU portal". The NEC shall draw up the assessment and communicates the opinion to E.O.T. The E.O.T. as a "national contact point" in Greece will issue one single approval for the clinical trial.

Greece implemented all points of the Clinical Trial Regulation No 536/2014 and started a "pilot phase". Greece wants to be ready when Clinical Trial Regulation No 536/2014 comes into effect, which is foreseen to be October 2018 and when "the EU portal" becomes effective.

Source: http://www.eof.gr/web/guest/clinical &
http://www.eof.gr/web/guest/clinical/neweuregulation in Greek

Italy

a. New fees and new on-line payment process to AIFA

Please be informed that starting **on 15 Feb 2017** the following new decree entered into force:

"DECRETO 6 dicembre 2016 - Aggiornamento delle tariffe vigenti e determinazione delle tariffe relative a prestazioni non ancora tariffate".

This new decree provides, in its Attachement 1, the new fees to be payed to Agenzia Italiana del Farmaco (AIFA), the Italian Regulatory Agency, forthe evaluation of CT applications, the evaluation of substantial amendments and the AIFA inspections of clinical trials.

The decree specifies that the new rates will apply to all applications submitted after the entry into force of the decree.

In case of an application submitted after the 15 Feb 2017 but for which the old fees have been paid prior to 15 February 2017, there must be an integrated matching of the difference between the amount paid and the new fee. In this case, the evaluation of the application will not be suspended but the applicant will be expected to supplement the already paid fee.

To better explain the decree, AIFA published the **Note 15Feb2017** to remind that, in accordance with the laws in force, AIFA proceeded to:

- update the old fees in force since 1 January 2015
- identify the fees for services not yet priced out,
- for small and medium-sized enterprises, reduce fees on Marketing Authorization variation (variazioni AIC) if related to administrative tasks and production site modification

Fees have been incremented as reported in the Annex to the Note mentioned above

There is a discrepancy between the fees reported in the attachment of the **decree** and the one reported in the attachment of the AIFA **Note 15Feb2017.**The correct ones are those reported in the attachment to AIFA **Note 15Feb2017** (the fees in **bold** are sum of the fees in the table):

Valutazione dell'ammissibilità alla sperimentazione clinica di fase II-III-IV "no profit"	ESENTE	ESENTE
Valutazione dell'ammissibilità alla sperimentazione clinica di fase II e di fase III	€ 7.083,33	€ 1.545,58
Valutazione dell'ammissibilità alla sperimentazione clinica di fase IV	€ 4.250,00	€ 927,35
Valutazione di emendamenti sostanziali alla sperimentazione clinica	€ 1.666,67	€ 363,67
Ispezione di sistema ai sensi dell'art. 31, comma 5, del D. Lgs. n. 200/2007, connessa con il riconoscimento di idoneità delle strutture sanitarie che eseguono sperimentazioni cliniche di fase I	€ 1.704,32	€ 362,17
Ispezione di sistema ai sensi dell'art. 1-bis, ultimo periodo, del D.M. 19 marzo 1998	€ 1.136,21	€ 241,44

- Validation of non-commercial clinical trials (phase II, III and IV) – free
- Validation of commercial clinical trials (phase II and III) – **8628,91 euro**
- Validation of commercial clinical trials (phase IV) – **5177,35 euro**
- Validation of substantial amendment in commercial clinical trials – **2030,34 euro**
- Inspection of clinical trial (phase I) – **2066,49 euro**
- Inspection of clinical trial – **1377,65 euro**

AIFA also released another new **Note 03Mar2017**, providing "Chiarimenti e modalità operative per la presentazione della domanda di autorizzazione alla sperimentazione clinica/emendamento sostanziale di fase II-III-IV a seguito dell'entrata in vigore del DM 6 Dicembre 2016" (Clarifications and operating procedures for the presentation of the request for authorization for clinical trial / substantial amendment of phase II-III-IV, following the entry into force of the DM December 6, 2016).

This note clarifies that Pharma Companies having a SIS code ("Sistema Informativo Sanitario" - Health Information System) and having a Reference person (Amministratore Utenze Aziendali (AUA)) shall provide the payment via "Sistema di Versamento Tariffe" – Fees Payment System (named "pagamenti on-line POL" - payment on line).

Acting as applicant, the Pharma companies shall attached to the CT application and substantial amendments application, the summary of the auto certification of payment (named POL): this document is released by the system "Sistema di Versamento Tariffe".

The CRO can perform the payment as follow:

• The pharmaceutical company must make the payment and provide its POL to the CRO. The POL must accompany the application for authorization for the trial and/or for the substantial amendment.
• Alternatively, since the CRO can't require the SIS code since they are not Pharma Companies, they can register on the Agency's institutional portal http://www.aifa.gov.it/it/content/accesso-ai-sistemi-informatici-di-aifa-21032013, generate a User account and request the SIS code of the Pharma company. The responsible person, Amministratore Utenze Aziendali (AUA), of the Pharma Company will provide the SIS code to the CRO.

The CRO will have to submit an application for authorization for clinical trials / substantial amendment and the POL. This POL will be generated using the SIS code of the Pharma company we are working on behalf of. The expected payments may be carried out both by the company and by the CRO. The payment must indicate the POL number. The Sistema di Versamento Tariffe (system for paying the fees) has an interface in English and that the details for the payment (IBAN, BIC / SWIFT code) are available within the same platform.
With regard to the CT applications submitted online via Osservatorio Nazionale per la Sperimentazione Clinical (OsSC), the POL must be attached to the document "CA / EC which expresses the favorable opinion" - section "General Information" - sub-section "of the fee payment receipt."
For applications submitted in paper format, the above summary should be part of the package of documents presented.

The applications without the POL will not be considered valid.

AIFA released another note, **Note 10Mar2017,** clarifying that the SIS code is required in order to be able to perform on-line payments**.**

All commercial sponsors, including any Public Institution wishing to conduct a commercial (profit) trial, require a SIS code. This SIS code is unique for each Sponsor (it's a numeric code that uniquely identifies the Company). The code is independent from the type of study and from the number of study conducted: it is only linked to the Sponsor.

Obtaining a SIS Code:

1. **A Commercial Sponsor, with a registered office (sede legale) in Italy, who wants to conduct profit trials in Italy can ask for the SIS code following the instructions at the following link.** http://www.agenziafarmaco.gov.it/sites/default/files/attribuzione_CodiciSIS_Comunicazione_AIFA.pdf

   After this, a physical person acting as AUA should be identified. The instructions to be followed are included in the User manual for the registration (Manuale utente per la registrazione) available at the following link: http://www.aifa.gov.it/content/accesso-ai-sistemi-informatici-di-aifa-21032013

   Once the AUA has been identified and registered, any other user (including a CRO) can ask for AUA authorization to access to the relevant AIFA electronic systems (including the one for the fee payment) by asking for authorization from the AUA via the following link: https://servizionline.aifa.gov.it using the web application "Gestione profili per utenti già censiti"

2. **A Commercial Sponsor, with a registered office abroad (sede legale all'estero) (both European and/or non-European countries), who wants to conduct profit trials in Italy can ask for the SIS code following the instructions at the following link:** http://www.aifa.gov.it/sites/default/files/aifa__sis_en_apr2011_0.pdf

   After this, a physical person acting as AUA should be identified. The instructions to be followed are included in the User manual for the registration (Manuale utente per la registrazione) available at the following link: http://www.aifa.gov.it/content/accesso-ai-sistemi-informatici-di-aifa-21032013

Once the AUA has been identified and registered, any other user (including a CRO) can ask for AUA authorization to access to the relevant AIFA electronic system (including the one for the fee payment) by asking for authorizationfrom the AUA via the following link: https://servizionline.aifa.gov.it using the web application "Gestione profili per utenti già censiti"

NOTE: For technical reasons only, the request to the AUA for being able to access the systems for the POL is only available at the following labelling "Rinnovi AIC" or "Variazioni I e II" at https://servizionline.aifa.gov.it/

References:

Ministry of Health Decree, 6 December 2016 *"Decreto Ministeriale 6 Dicembre 2016 - Aggiornamento delle tariffe vigenti e determinazione delle tariffe relative a prestazioni non ancora tariffate*" (Ministry of Health Decree, 6 December 2016,"Updating the current fees and determination of charges for services not yet priced out) available at http://www.gazzettaufficiale.it/atto/serie_generale/caricaDettaglioAtto/originario?atto.dataPubblicazioneGazzetta=2017-01-31&atto.codiceRedazionale=17A00625

AIFA **Note 15Feb2017** "*Aggiornamento delle tariffe vigenti e determinazione delle tariffe relative a prestazioni non ancora tariffate*" (Updating the current fees and determination of charges for services not yet priced out available at: http://www.aifa.gov.it/content/aggiornamento-delle-tariffe-vigenti-e-determinazione-delle-tariffe-relative-prestazioni-non-

AIFA **Note 03MAR2017** "*Chiarimenti e modalità operative per la presentazione della domanda di autorizzazione alla sperimentazione clinica/emendamento sostanziale di fase II-III-IV a seguito dell'entrata in vigore del DM 6 Dicembre 2016*" (Clarifications and operating procedures for the presentation of the request for authorization for clinical trial / substantial amendment of phase II-III-IV, following the entry into force of the DM December 6, 2016) available at: http://www.aifa.gov.it/content/tariffe-relative-alle-domande-di-autorizzazione-alla-sperimentazione-clinica-emendamento-sos

AIFA **Note 10MAR2017 "***Chiarimenti relativi al codice SIS per i Promotori di sperimentazioni cliniche a seguito dell'entrata in vigore del DM 6 Dicembre 2016*" (Clarifications relating to the SIS code for the Sponsor of clinical trials following the entry into force of the Ministerial Decree of December 6, 2016) available at: http://www.aifa.gov.it/content/chiarimenti-relativi-al-codice-sis-i-promotori-di-sperimentazioni-cliniche-seguito-dell%E2%80%99entr

b. New cover letter for CT and substantial amendments application

The AIFA **Note 03Jan2017** reported that starting from 16 Jan 2017 new templates for the cover letters for CT and substantial amendments application for phase II-III-IV trials are available at the following links:

- *cover letter for CT applications:* http://www.aifa.gov.it/sites/default/files/Allegato-1_03.01.2017.docx - *Modello di lettera di trasmissione per la richiesta di autorizzazione della sperimentazione clinica di fase II-III-IV*
- *cover letter for* substantial amendments *applications:* http://www.aifa.gov.it/sites/default/files/Allegato-2_03.01.2017.docx - *Modello di lettera di*

trasmissione per la richiesta di autorizzazione di un emendamento sostanziale alla sperimentazione clinica di fase II-III-IV

References:

AIFA Note 03Jan2017: Aggiornamento: modalità di esercizio delle funzioni in materia di sperimentazioni cliniche di medicinali (Update: exercising the functions in terms of clinical trials with medical devices) available at http://www.aifa.gov.it/content/aggiornamento-modalit%C3%A0-di-esercizio-delle-funzioni-materia-di-sperimentazioni-cliniche-di--1

Belgium: Clinical Trial Regulation project (CTR project) started

On 11 January 2017, the Federal Agency for Medicines and Health Products (FAMHP), the Belgian Competent Authority announced the "CTR project" was starting due to the new Clinical Trial Regulation (CTR) No 536/2014 which is expected to enter into force in October 2018.
"The CTR pilot is organized in collaboration with the ethics committees. The procedure to authorise the trial will follow the national legislation of 7th May 2004 but the dossier to be sent and its evaluation will follow the spirit of the new regulation and the draft Belgian law."
Sponsors of trials were invited to express their intent to become a candidate for the "CTR project" by sending an email to ct.rd@afmps.be prior to 24 January 2017**.**
The "CTR project" will help Belgium to be ready when the European Regulation comes in to effect. The main points of the "CTR project" are to reach one "single decision" in Belgium which have to be provided to the EU portal. "The assessment of the dossier will have to be performed independently and in parallel by the competent authority and by the Ethics committee and consolidated as the single decision will have to be reached in a short timeline. Close collaboration between the FAMHP and the future College and between the future College and the EC's will thus become crucial."

Detailed guidance for "CTR project" in Belgium can be found here: https://www.fagg-afmps.be/sites/default/files/procedure_ctr_pilot_project_-_famhp_-_rd_-_20170110_1.pdf

Source: https://www.fagg-afmps.be/en/human_use/medicines/medicines/research_development/clinical_trials

The new law on CTR will likely be published in the Belgisch Staatsblad/Moniteur Belge in Q2 of 2017.

A set of new Royal Decree's is also planned by the FAMHP.

France:

a. Practical information guide for applicants submitting study within the "pilot phase" issued by ANSM

In January 2017 , the Agence nationale de sécurité du médicament et des produits de santé (ANSM), the French Regulatory Agency published a practical information guide for applicants "Clinical Drug Trials submitted within the Pilot Phase to ANSM (French National Agency for Medicines and Health Products Safety) and the CPP (French Ethics Committee)" in English.

France was the first European Union country to launch a "pilot phase" of Clinical Trial Regulation No. 536/2014. The first phase of this experimental procedure started on 28 September 2015. The main issue in implementing the "pilot phase" for clinical trials involving medicinal products was to ensure that France will be ready when the European Regulation comes into force.

The entry into force of this regulation in the various Member States of the European Union, was originally scheduled for May 2016, but will now become effective only with the provision of the European portal "EU portal" and the " European database", which are expected in October 2018.

At the moment this pilot phase is optional and the sponsor can choose from two options:
1. In accordance with the current legislation
2. Or in accordance with the pilot phase proposed by ANSM, which is described in the applicable guide.
The pilot phase concerns only clinical trials involving medicinal products (including radiopharmaceutical), all phases in drug clinical trials in all therapeutic areas for all clinical trial sponsors academic or private. It does not include medical device trials.

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

b. New National Application Forms issued by the ANSM

The National Agency for the Safety of Medicine and Health Products (the ANSM) updated several new forms dated **16 December 2016** for Investigational Medicinal Products (IMP) and for Medical Devices (MD). The new templates are for initial submissions and substantial amendments for clinical trials and clinical investigations to the ANSM and the CPP (French Ethics Committee).

New application forms for IMP:

- Formulaire de demande d'autorisation auprès de l'ANSM et de demande d'avis à un Comité de protection des personnes d'une recherche mentionnée au 1° de l'article L. 1121-1 du code de la santé publique portant sur un médicament à usage humain
- Courrier de demande d'autorisation d'une recherche impliquant la personne humaine mentionnée au 1° de l'article L. 1121-1 du code de la santé publique portant sur le medicament
- Formulaire de demande de modification(s) substantielle(s) d'une recherche mentionnée au 1° de l'article L. 1121-1 du code de la santé publique portant sur un médicament

Are available here:
http://www.microsofttranslator.com/BV.aspx?ref=IE8Activity&a=http%3A%2F%2Fansm.sante.fr%2FActivites%2FMedicaments-et-produits-biologiques%2FAvis-aux-promoteurs-Formulaires%2F%28offset%29%2F2

New application forms for MD:

- Formulaire de demande de modification substantielle d'une recherche mentionnée au 1° ou au 2° de l'article L. 1121-1 du code de la santé publique portant sur un dispositif médical ou un dispositif médical de diagnostic in vitro
- Courrier de demande d'autorisation de modification substantielle d'une recherche interventionnelle mentionnée au 1° de l'article L. 1121-1 du code de la santé publique portant sur un dispositif médical (DM) ou un dispositif médical de diagnostic in vitro (DMDIV) auprès de l'Agence nationale de sécurité du médicament et des produits de santé (ANSM)
- Formulaire de demande d'autorisation auprès de l'ANSM et demande d'avis du comite de protection des personnes (CPP) pour une recherche mentionnée au 1° ou au 2° de l'article L.
- Courrier de demande d'autorisation d'essai clinique portant sur un dispositif médical (DM) ou dispositif médical de diagnostic in vitro (DMDIV) 1121-1 du code de la santé publique portant sur un dispositif médical (DM) ou un dispositif médical de diagnostic *in vitro* (DMDIV)

(Recherches interventionnelles mentionnées au 1° de l'article L. 1121-1 du code de la santé publique)

Are available here: http://ansm.sante.fr/Activites/Dispositifs-medicaux-et-dispositifs-medicaux-de-diagnostic-in-vitro/Formulaires-et-modeles-a-telecharger/(offset)/3

Portugal: Changes of advertising of medicines and medical devices

On 6 January 2017 the new Decree-Law 5/2017 was published in Portugal and entered into force on 5 February 2017.

The major changes brought by Decree-Law 5/2017 are the following:

- "Introduction of a broad legal definition of benefit, meaning any advantage or payment whatsoever, including non-monetary, irrespectively of the means whereby it is granted, and thus enhancing the robustness of public disclosure obligations triggered by the granting of any benefits to health institutions or professionals;
- Change to the applicable disclosure proceeding, being the granting of any benefits by pharma industry entities or medical devices players to healthcare organizations or professionals subject to mandatory registration in the transparency platform displayed in Infarmed's website (www.placotrans.infarmed.pt). Instead of a double registration of the benefits by the grantor and the receiver that was applicable formerly, the new legal transparency framework provides for the obligation of the grantor to report the granting of the benefit within 30 days as from the date it becomes effective, and the duty of the receiver to validate the receipt of the relevant benefit. This validation entails an electronic notification to the beneficiary by Infarmed.
- The newly enacted framework also clarifies which entities are considered as beneficiaries in cases where third parties are involved, notably service providers, when the benefit is granted in the interest of a certain health organization, or of benefits made to a healthcare provider that ultimately are granted in the interest of healthcare professionals. In these cases a successive registration is required, firstly identifying the institution as beneficiary, and then the healthcare professionals as ultimate beneficiaries."

This new legal act establishes principles that shall be accomplished by marketing authorization holders and distributors of medicines, as well as manufacturers and distributors of medical devices in their advertising and promotion activities.

Source: http://www.chcuk.co.uk/portugal-changes-in-the-legal-framework-of-advertising-of-medicines-and-medical-devices/

Germany: The amendment of the German Drug Act

The 4th law on the amendment of the German Drug Act came into force on **24 December 2016** (G. v. 20.12.2016 BGBl. I S. 3048 (Nr. 63)).

The new law specifically amends the existing clinical trial rules to establish compliance of German law with the Clinical Trial Regulation (EU) No 536/2014. Significant changes to the approval procedure (i.e. one approval for a study) and the competences of the ethics committees and regulatory authorities (i.e. a new federal ethics committee can be established by the regulatory authorities) for clinical trials with human drugs are expected to enter into force in October 2018.

The majority of changes to the 4th law do not have any impact on the conduct of non-interventional studies in Germany. Per Article 4 (23) AMG, non-interventional studies are not considered clinical trials.

Changes related to non-interventional studies were made in Articles 63 f and 67 (6) AMG. As a result of the amendment, the German health insurance head organizations: Kassenärztliche Bundesvereinigung (KBV), Verband der Privaten Krankenversicherung (PKV), Spitzenverband Bund der Krankenkassen (GKV) are charged with creating uniform conditions for the notification of such studies Art. 67 (6) Sentence 13.

Art. 63 f defines the principles for voluntary post-authorization safety studies (voluntary PASS). A post-authorisation safety study (PASS) is a study that is carried out after a medicine has been authorised to obtain further information on a medicine's safety, or to measure the effectiveness of risk-management measures. Voluntary PASSs are sponsored or conducted by Marketing-authorisation holders (MAHs) on their own initiative. They include non-imposed studies that are requested in risk-management plans. For the voluntary PASS including PASS, an approval should be obtained from Research Ethics committee of National Coordinator or Local Research Ethics Committee(s) and Hospital/Institution for contract execution. Notification should be done to Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)/ Paul-Ehrlich-Institut (PEI) the German Competent Authorities and separately to the three German health insurance head organizations: KBV, GKV, PKV (all notifications can be done online).

Source: https://www.bundesgesundheitsministerium.de/ministerium/meldungen/2016/4-amg-novelle-verabschiedet.html

Pilot project details: http://www.bfarm.de/DE/Arzneimittel/zul/klinPr/pilotprojekt/_node.html

The Netherlands:

a. New WMO- medical research with minors and incapacitated subjects

The Medical Research Involving Human Subjects Act (WMO) in the Netherland has been amend as of **1 March 2017**. The new legislation 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).

According to the new WMO research subjects under the age of 16 and incapacitated adults cannot give legal consent for participation in medical/scientific research. This prohibition does not apply to research which is of direct benefit to the research subject (therapeutic) and non-therapeutic research which can only be conducted with that group of people (group restricted) and for whom the risks are negligible and the objections minimal. Therapeutic research and observational (non-therapeutic) research with subjects under the age of 16 and must be submitted for review to an accredited MREC. Non-therapeutic observational research with incapacitated adults must also be submitted for review to an accredited Medical Ethical Reviewing Committee (MREC). Non-therapeutic intervention research with these subjects (under 16 and incapacitated adults) must be submitted for review to the Central Committee for Research Involving Human Subjects (CCMO). An accredited MREC can transfer the review of a proposal for non-therapeutic observational research with subjects under the age of 16 and incapacitated adults to the CCMO as long as it has reason to do so. If this occurs, the MREC will inform the submitting party."

The requirements for the Patient Information Sheet and the Informed Consent Form have also been changed, effective 1 March 2017. "In case of research with children under the age of 12, both parents/legal guardian must give consent for participation in the research. Adolescents aged 12 to 16 years give consent together with their parents/legal guardian, and adolescents aged 16 years and older give consent by themselves."

In case of incapacitated adults (18 years and older), a representative must provide consent for these subjects. "That person could be someone appointed by a judge, such as a curator or mentor. If there is no such person, an authorised person can give consent. And if such a person also does not exist, then the spouse, registered partner or other life partner can give consent on behalf of the participant. If these do also not exist, then adolescents who are deemed able to understand the context are allowed to give context. And lastly, if there is/are no such person(s), then brothers or sisters who are deemed able to understand the context may provide consent on behalf of the participant."

See more about differences between therapeutic vs non-therapeutic research at: CCMO-note therapeutic versus non-therapeutic research

Source: http://www.ccmo.nl/en/research-with-incapacitated-adults

http://www.ccmo.nl/en/research-with-subjects-under-the-age-of-16

More information about the WMO was presented in the Regulatory Newsletter October –December 2016: "the Netherlands: Broadening of the possibilities for medical research with minors and incapacitated subject"

b. New Template Subject Information has been changed

On 1 March 2017, the Template Subjects information, which is used to compile the research subject information leaflet, was changed due to the amendment of the WMO Act. The main changes:

- The age at which subjects can give legal consent for participation in medical research;(see article above)
- Information about sending data and/or bodily material outside the European Union;
- Collection of cause of death data from the Centraal Bureau voor de Statistiek (CBS)-Statistics Netherlands;
- The text about pregnancy;

Some textual changes and clarifications, also due to comments from the field.

See the Template Subjects Information in English

Source and the Template Subjects Information in Dutch see at:
http://www.ccmo.nl/nl/nieuwsarchief/model-proefpersoneninformatie-gewijzigd

News from the United States of America

FDA Details Combination Product Postmarket Safety Reporting Requirements

A final rule detailing the requirements for postmarket safety reporting for combination products was published in the Federal Register December 20, 2016. This rule became effective January 20, 2017.
As described in an FDA webinar, this rule creates 3 basic reporting obligations:

1. Postmarket safety events for combination products must be reported according to market application type.
2. Postmarket safety events for combination products will eventually need to be reported according to the regulatory guidelines for all constituent parts.
3. Constituent part applicants will eventually need to notify each (information sharing) other of certain safety-related events.

Compliance by January 20, 2017 is required for the first reporting obligation and compliance by June 20, 2018 for the remaining reporting obligations as the Agency is developing draft guidance for those obligations.

Webinar:
https://www.fda.gov/CombinationProducts/MeetingsConferencesWorkshops/ucm537047.htm

Final Rule:
https://s3.amazonaws.com/public-inspection.federalregister.gov/2016-30485.pdf

Guidance Document Update

Between January 1, 2017 and March 15, 2017, FDA published 28 guidance documents, both draft and final, for Industry. The list below contains links to 8 documents that may be of interest to CROMSOURCE and its customers.

Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions

Release Date: January 13, 2017

Implementation Period: 60 days

Summary: The purpose of this guidance document is to provide greater clarity "regarding the principal factors that FDA considers when assessing the benefits and risks of IDE applications for human clinical studies". "This guidance applies to both diagnostic and therapeutic devices."

https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm451440.pdf

Assessment of Abuse Potential of Drugs

Release Date: January 2017

Summary: The purpose of this guidance document is to "assist sponsors of investigational new drugs and applicants for approval of a new drug in evaluating whether their new drug product has abuse potential. This guidance also provides recommendations to applicants who intend to submit new drug applications (NDAs) for prescription drug products that may have abuse potential."

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf

Non-proprietary Naming of Biological Products Guidance for Industry

Release Date: January 2017

Summary: The purpose of this guidance document is to describe "FDA's approach to designating the proper name for originator and related biological products licensed under section 351(a) of the PHS Act and for biosimilar products licensed under section 351(k) of the PHS Act."

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm459987.pdf

180-Day Exclusivity: Questions and Answers

Release Date: January 2017 (draft)

Summary: The purpose of this guidance document is to "address questions that have been raised about the provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act) that relate to generic drug exclusivity, which commonly is known as 180-day exclusivity for generic drug products."

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536725.pdf

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

Release Date: January 2017 (draft)

Summary: The purpose of this guidance document is to "assist sponsors in obtaining a preliminary assessment from the U.S. Food and Drug Administration (FDA or Agency) through the Pre-Request for Designation (Pre-RFD) process." The Pre-RFD process provides "informal, non-binding feedback regarding the regulatory identity or classification of a human medical product as a drug, device, biological product, or combination product. In addition, this informal process provides information about a non-combination or combination product's assignment to the appropriate Agency Center (Center for Drug Evaluation and Research (CDER), Center for Devices and Radiological Health (CDRH), or Center for Biologics Evaluation and Research (CBER)) for premarket review and regulation."

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

Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA:

Release Date: January 2017 (draft)

Summary: The purpose of this guidance document is to assist applicants planning to develop and submit an abbreviated new drug application (ANDA) of a combination product that includes both a drug constituent part and a delivery device constituent part with the expected human factors testing.

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536959.pdf

Considerations in Demonstrating Interchangeability With a Reference Product

Release Date: January 2017 (draft)

Summary: The purpose of this guidance document is to "assist sponsors in demonstrating that a proposed therapeutic protein product is interchangeable with a reference product for the purposes of submitting a marketing application or supplement under section 351(k) of the Public Health Service Act (PHS Act) (42 19 U.S.C. 262(k))."

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm537135.pdf

Multiple Endpoints in Clinical Trials Guidance for Industry

Release Date: January 2017 (draft)

Summary: The purpose of this guidance document is to "describe various strategies for grouping and ordering endpoints for analysis and applying some well-recognized statistical methods for managing multiplicity within a study in order to control the chance of making erroneous conclusions about a drug's effects."

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf