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Regulatory Newsletter
July - September 2015

Introduction

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

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

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

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News from the European Commission

Public consultations on GMP for Investigational Medicinal Products

Article 63(1) of Regulation (EU) No 536/2014 requires the European Commission to:

A. Adopt delegated acts to specify the principles and guidelines on good manufacturing practice and detailed arrangement for inspection for ensuring the quality of investigational medicinal products, and
B. Adopt and publish detailed guidelines in line with those principles of good manufacturing practice for investigational medicinal products.

Currently the principles and guidelines of good manufacturing practice (GMP) for investigational medicinal products for human use are laid down in Commission Directive 2003/94/EC. However, once Regulation (EU) No 536/2014 becomes applicable, manufacture and import of investigational medicinal products (IMPs) used in clinical trials carried out under that Regulation cannot follow the GMP for IMPs set out in Directive 2003/94/EC. Instead those IMPs will have to be manufactured or imported under GMP for investigational medicinal products for human use laid down by the Delegated Act provided for in Article 63(1) of Regulation (EU) No 536/2014.

Therefore, on 28 August 2015, the European Commission released for open consultation two documents:

A. Commission Delegated Act on principles and guidelines on good manufacturing practice for investigational medicinal products and on inspection procedures, pursuant to the first subparagraph of Article 63(1) of Regulation (EU) No 536/2014
B. Detailed Commission guidelines on good manufacturing practice for investigational medicinal products, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014

Both documents are open to public comments from 28 August 2015 up to 24 November 2015. They can be downloaded from: http://ec.europa.eu/health/human-use/clinical-trials/developments/index_en.htm

Harmonised standards for demonstrating conformity of medical devices

In order to demonstrate the conformity of a medical device with the essential requirements laid down in Annex I of Directives 90/385/EEC, 93/42/EEC and 98/79/EEC, the medical device manufacturer must use harmonised standards as adopted by the European Union.

The updated list of the harmonised standards to be used was published in the Official Journal of the European Union on 10 July 2015.

It can be found on:

http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:C:2015:226:FULL&from=EN

With respect to clinical investigation, the harmonised standard remains ISO EN 14155:2011.

News from the European Medicines Agency (EMA)

Revisions to class waivers allowable under paediatric legislation

With the entry into force of the Paediatric Regulation (EC N° 1901/2006) in January 2007, pharmaceutical companies applying for a marketing authorisation for a new medicinal product must submit early in the product development, a plan (called Paediatric Investigation Plan[PIP]) describing how the medicinal product will be studied in children.
The EMA's Paediatric Committee (PDCO) assesses and agrees the content of the PIP, to ensure necessary data are generated through studies in paediatric population when it is safe to perform them, with the aim to support the authorisation of medicinal products for children.

The requirement to develop the new medicine for children and to submit a PIP can be waived by the PDCO for a specific medicinal product (product-specific waiver) or classes of medicinal products (class waivers):

- when the medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population
- when the medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients
- when the medicinal product is intended to treat a condition that only occurs in adults.

Class waivers are regularly reviewed and updated by the PDCO.

Taking into consideration its experience and the scientific developments since the Paediatric Regulation came into force, the PDCO decided in 2011 to conduct an extensive review of its class waivers list. The purpose of this extensive review was to assess how well the current list maintains an appropriate balance between supporting the development of medicines with a potential therapeutic benefit for children while avoiding unnecessary studies in paediatric population.

Further to its assessment of available information, the PDCO decided:

- to revoke 8 class waivers as new information available since the class waivers were granted showed that the disease can occur in children. The concerned diseases are : liver and intrahepatic bile duct carcinoma, kidney and renal pelvis carcinoma, non-juvenile Parkinson disease, Huntington chorea, amyotrophic lateral sclerosis, coronary atherosclerosis/peripheral atherosclerosis/vascular dementia and vascular cognitive disorder/impairment.
- to update 15 class waivers on the ground the medicinal products classes are likely to be ineffective in all of the paediatric population or do not represent a significant therapeutic benefit over existing treatment for paediatric patients in the concerned condition.
- to confirm 9 class waivers from the current list.

The PDCO decision on class waivers was published on EMA website on 23 July 2015 and will supersede all previous class waiver decisions. The revised class waiver list will come into effect in July 2018. This means that from July 2018, all regulatory submissions for marketing authorisation will be validated against the revised class waiver decision. Furthermore, companies developing medicinal products not covered by the revised class waiver list will need to submit a request for a PIP or a product-specific waiver for scientific review and agreement by the PDCO. PDCO's decision can be found on:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/07/WC500190385.pdf

Consultation on draft revised GVP guidelines

With the implementation of the new EU pharmacovigilance legislation, post-authorisation safety study (PASS) may be imposed to marketing authorisation holders by competent authorities or may be initiated by a marketing authorisation holder to investigate a safety concern as described in the risk management plan. To provide support to pharmaceutical companies in fulfilling their obligations related to non-interventional PASS, EMA issued in July 2012 a guideline, named "*Guideline on good pharmacovigilance practices – Module VIII- Post-authorisation safety studies*".

On 11 August 2015, EMA released for public consultation the draft of a revised version of this guideline. Compared to the current version, the draft revised guideline clarifies the link between the legislation requirements and the different categories of non-interventional PASS, provides recommendations on adverse events that will not be reported and collected during the study and specifies the requirements on protocol core elements for joint studies. The public consultation will be open up to 9 October 2015 and the final guideline is expected to come into effect in QI, 2016 The document can be viewed here:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/08/WC500191780.pdf

Consultation on draft revised ICH Guideline for GCP (E6)

Since the adoption of ICH GCP guideline in 1996, the complexity of clinical trials has increased and new technology capabilities for the monitoring, trial management, data handling and record keeping have appeared. Recently, several regulatory authorities (EMA, FDA, MHLW/PMDA) have issued guidances related to clinical trial quality but the scope of the documents is different.

Such lack of harmonisation may lead to inconsistency in approaches taken by sponsors among the different regions. Therefore, it was decided in June 2014 that ICH develop an addendum to ICH E6 providing recommendations on quality risk management and quality-by-design process with upfront assessment of risks specific to a study protocol, on use of electronic trial data systems, and on risk based monitoring.

The draft addendum was released for public consultation on 4th August 2015. It contains the following changes:

- 3 new definitions (certified copy, monitoring plan, validation of computerized system)
- new sections on investigator responsibilities (team supervision at trial site, source data recording)
- a completely new sponsor section on quality management including risk assessment
- addition of a sponsor section on computer validation and electronic recordings
- introduction of risk-based monitoring
- addition of a sponsor section for development and implementation of monitoring plan
- root-cause analysis of significant non-compliance to protocol, SOP's, GCP and regulatory requirements to be performed by sponsor
- clarification that the TMF may contain additional documents not specifically mentioned in the essential document list
- warnings about sponsor exclusive control of CRF data reported by the investigator to the sponsor.

The addendum to ICH E6 is now open to public consultation until 3 February 2016 in both EU and USA and was open to public consultation up to 30 September 2015 in Japan.

The changes introduced by the addendum have been directly integrated into the several sections of the parent guideline. It is expected that the final revised guideline will be issued in November 2016.

The draft integrated guideline can be found on:

http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500191488&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

Scientific advice pilot for post-authorisation safety studies

With the aim to improve the design of safety studies for medicinal products, EMA launched a 12-month pilot for scientific advice on post-authorisation safety studies (PASS). This voluntary optional procedure focuses on protocols for non-imposed PASS and started on 10 August 2015.

The new scientific advice procedure systematically involves the PRAC (Pharmacovigilance Risk Assessment Committee) at all the stages of the procedure. All submitted documents in the frame of the scientific advice are available to the PRAC who endorses the PASS protocol.

With this pilot, EMA hopes to further develop an integrated lifecycle approach for scientific advice on medicinal products and to support Marketing Authorisation Holders in proactive pharmacovigilance planning.

Detailed information on the PASS scientific advice pilot can be found on EMA website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9

Temporary unavailability of the results module of EudraCT

An error has been detected in the software used to load clinical trial results summaries into the EU Clinical Trial Register (the portal for public access to clinical trials information in EU).

As a consequence, since 31 July 2015 all the clinical trials summary results entered into EudraCT are currently reviewed. During this review, the summary results will be temporarily unavailable to public. In addition, sponsors access to enter or edit existing results has been blocked. A solution to the software error leading to the problem is currently searched.

In the meantime, in order for sponsors to comply with regulatory requirements within EU for publication of clinical trial results, the sponsors and the PIP addressees should maintain verifiable records of when they had the results available to post. When the system will become available again, sponsors will be required to post the results into EudraCT within 20 business days.

For more information, please consult: https://eudract.ema.europa.eu/

News from Individual Countries

Belgium

Compassionate use and medical need programs updated questions/answers document and guideline, published on 27 July 2015

The new Royal Decree of 25th April 2014 for compassionate use and medical need programs came into force on 1st July 2014. From that date, all compassionate use and medical need programs to be conducted in Belgium must be submitted and performed in accordance with the requirements laid down in the new Royal Decree.

In order to perform a compassionate use or medical need program, an application needs to be submitted for approval to the Belgian Competent Authorities (FAMHP). Only a single indication can be approved per program. Approval or rejection of the program is delivered in a 60 days timeframe.

Upon approval of the program both the "summarized information for publication" and the informed consent form are published on the FAMHP's website.

In order to provide guidance for the conduct of these programs according to the new legislation, FAMHP has published both a guideline and questions/answers documents.

The updated versions of these guidances issued on 27 July 2015 provide additional clarifications on the following points:

- Archiving requirements
- Pharmacovigilance duties
- Requirements for the central register
- Requirements for the safety register

The guideline and the questions and answers documents can be accessed on:

http://www.fagg-afmps.be/fr/binaries/CUP-UMN%20Guidance-2015-07-27-OK_tcm291-264696.pdf
http://www.fagg-afmps.be/fr/binaries/UMN%20FAQ%20V1.1-EN-2015-07-17-OK_tcm291-262978.pdf

France

Pilot phase for the application of the Clinical Trials Regulation, launched by ANSM on 28th Sept 2015.

With the view to the start the preparation of the application of the Clinical Trials Regulation, the French Competent Authorities (ANSM) announced on 14 April 2015 the implementation of a pilot phase to be launched on 28 September 2015. This pilot phase will proceed in cooperation with all clinical trial stakeholder representatives (Competent Authorities, Ethics Committees and sponsors).

Indeed the application of the Clinical Trials Regulation (EU n°536/2014) requires the Competent Authorities and Ethics Committees to adopt new work measures, in order to respect dossier assessment deadlines and strengthening the relationships between Competent Authorities and Ethics Committees. To prepare for the implementation of the Regulation, French Competent Authorities decided to launch a pilot phase. This should enable French concerned bodies to simulate the new organisation required by the Regulation. In particular, the pilot phase shall help to define the various organisational phases in the assessment process and to identify solutions for ensuring cooperation between ANSM and the Ethics Committees.

Currently 18 out of the 39 CPP ('*Comités de Protection des Personnes*' i.e. the French Ethics Committees) have volunteered to participate in this pilot phase. Sponsor participation in the pilot phase is also on voluntary basis, the current system still being able to be used. For sponsors, taking part in the pilot phase shall help in preparing for the new procedures related to the application of the Regulation and in receiving a single authorisation from ANSM at the end of the assessment of the clinical trial request. The official ANSM announcement can be found on:

http://ansm.sante.fr/var/ansm_site/storage/original/application/e99721b13073303e3b922903ebc1e404.pdf

In order to provide practical information to sponsors wishing to use the pilot phase, ANSM issued on 14 September 2015 a guidance document. This document specifies how a clinical trial authorisation request must be submitted by the sponsor to both ANSM and the CPP under the pilot phase. The pilot phase applies to any interventional clinical trial with a medicinal product, excluding those with advanced therapy medicinal products or with a medicinal product containing genetically modified organism and those subject to a Voluntary Harmonisation Procedure. The pilot phase only concerns the initial authorisation request. It shall be noted that to really simulate the conditions of the Clinical Trials Regulation, sponsors using the pilot phase are required to answer questions raised by ANSM and CPP, within a maximum of 12 calendar days. ANSM guideline can be found on the same web page as the ANSM announcement.

With the aim to provide sponsors with practical information on the clinical trial dossier process, format and content, the French Competent Authorities (ANSM) released on 1st September 2015 a revised notice for sponsors.

The new notice replaces previous version issued in June 2015 and shall be used since 1st September 2015.

The revised guidance is related to the decree §2015-692 bringing modification to clinical trials with medicinal products containing genetically modified organisms (GMO's). It is now required that the authorisation clinical trial dossier with medicinal products containing GMO's includes the advice from the HCB Scientific Committee to specify whether or not the research involves a deliberate release of GMO's.

If the HCB Scientific Committee has decided that the research involves a deliberate release of GMO's, the clinical trial authorisation request dossier must contain the following additional documents:

- Summary Notification Information Format (SNIF) in compliance with Directive 2001/18/EC,
- Technical dossier in compliance with Directive 2001/18/EC and a public information sheet.

Germany

New approach for the approval of clinical trials with Genetically Modified Organisms (GMO), announced by Paul-Ehrlich-Institute (PEI) on 6th August 2015

In accordance with §9 (4) of the GCP Verordnung, the authorisation of a clinical trial involving an investigation medicinal product (IMP) consisting of, or containing genetically modified organisms (GMO) includes the authorisation of the deliberate release of the GMO. Until recently, the scope of this deliberate release authorisation was however limited to the administration of the GMO to the study subjects.

Now additional activities such as short-term IMP storage, in-house IMP transportation, IMP reconstitution may be covered by the release authorisation of the GMO. As a consequence the PEI does no longer request the applicant to provide proof of notification/approval in accordance with the Genetic Engineering Act (§ 8 (1) or (2) GenTG) for these activities".

To allow evaluation whether the above mentioned activities may be integrated into the release authorisation, the PEI is requesting to include the following information in the Environmental Risk Assessment (ERA) documentation of a clinical trial application:

- Specific information on the duration and location of storage and any safety measures applied to ensure proper storage of the IMP and any materials that may contain the GMO (contaminated materials and waste, subject samples) at the study site
- Information on safety measures for in-house transportation of the IMP and any materials that may contain the GMO (contaminated materials and waste, subject samples).

PEI announcement can be found on:

http://www.pei.de/EN/information/license-applicants/clinical-trial-authorisation/gmo/clinical-trial-gmo-content.html

Netherlands

Amendment to Dutch Law for medical research with human subjects, entering into force on 1st Oct 2015

The investigation on the Propatria study by the Dutch Health Inspectorate, the CCMO and the Food and Consumer Product Safety Authority led to the conclusion that the requirements for SAE reporting in clinical studies other than clinical trials with an investigational medicinal product were not clearly enshrined in the law for medical research with human subjects (Wet Medisch-Wetenschappelijk Onderzoek met mensen, WMO). In order to extend the reporting obligation of serious adverse events to any type of clinical study, the WMO was amended in June 2015. This amendment will enter into force on 1 October 2015.

The main changes introduced by this amendment are:

- Investigator obligation to report immediately all SAEs, except those that the protocol identifies as not requiring immediate reporting, to the study sponsor
- Sponsor obligation to report all SAEs to the reviewing medical research ethics committee (MREC or CCMO). The procedure for SAE reporting and notification shall be described in the research protocol and will be assessed by the reviewing MREC.
- Digital submission of SAE reports through webportal ToetsingOnline.

In order to ensure uniformity in the assessment of the SAE notification procedure, the CCMO together with the Dutch Association of Ethics Committees has developed a guidance document for MRECs. This document also provides information relevant for sponsors and investigators.

The amendment to the WMO can be accessed, via the following link:

https://zoek.officielebekendmakingen.nl/stb-2015-240.html

The guidance document can be found, via the following link:

http://www.ccmo.nl/attachments/files/leidraad-voor-erkende-metc-procedure-sae-meldingen-versie-14-september-2015.pdf

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