CROM SOURCE
advise | agree | deliver

Regulatory Newsletter
July – September 2014

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 USA 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.

European Union

From European Medicines Agency (EMA)

- **Guideline on good pharmacovigilance practices (GVP) – Module VI – Management and reporting of adverse reactions to medicinal products, entering into force on 16 September 2014**

  On 8 September 2014, EMA published the first revision of the GVP-Module VI – Management and reporting of adverse reactions to medicinal products. The revised guideline entered into force on 16 September 2014.

  Compared to the previous version, the revised guideline introduced clarifications on what shall be regarded as a solicited report, on the collection and recording requirements for solicited reports, on the clock start for the reporting of valid individual case safety report (ICSR), on the handling of ICSRs reported in an official language of EU other than English and on the reports of suspected adverse reactions originating from organised data collection systems and other systems.

  In addition the revised guideline sets up updated requirements for the collection of adverse events and for the reporting of adverse reactions in non-interventional post-authorisation studies. In particular, in non-interventional post-authorisation studies with primary data collection, all collected adverse events are now required to be summarised as part of any interim safety analysis and in the final study report. It shall be noted that the new requirements for non-interventional post-authorisation studies will become mandatory for any new study started after 1 Jan 2015. For new or ongoing studies started before 1 Jan 2015, the implementation of the new requirements is optional.

  The new guideline can be downloaded from:

  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172402.pdf

- **Launch of the EudraCT result training environment on 1 August 2014**

  Since 21 July 2014, sponsors are obliged to post in the European Clinical Trials Database (EudraCT), the results of any of their clinical trials registered in EudraCT, in accordance with the following timeframe and specifications:

  - For any non-paediatric clinical trial ending on or after 21 July 2014, within 12 months following the end of the trial and providing the full data set as defined in EudraCT results module
  - For any paediatric clinical trial ending on or after 21 July 2014, within 6 months following the end of the trial (within 12 months if duly justified) and providing the full data set as defined in EudraCT results module

- For any trial ending prior to 21 July 2014, results must be submitted retrospectively in accordance with the modalities defined in EU guideline 2012/C302/03.

On 1 August 2014, in order to help sponsors representatives to familiarize and get further understanding of the EudraCT results application, the European Medicines Agency has launched a training environment for the result application of the European Clinical Trials Database (EudraCT).

To get access to the training environment, users have to register. Once registered, users can self-assign trials and can perform in the EudraCT training environment the following tasks:

- Create, update, validate and post result data sets as well as load summary attachments
- Save locally XML/pdf files of result data sets
- Manage users and delegate trial activities to other users

The EudraCT result training environment can be reached, with the following link:

https://eudract-training.ema.europa.eu/

From Individual Countries

France

- **Set up of a single contract for biomedical research with industrial sponsors in public health facilities on 18 June 2014.**

  The Ministry of Social Affairs and Health published on 17 June 2014, an instruction setting up the single contract for biomedical research with industrial sponsors in public health facilities.

  The measures laid down in this instruction entered into force on 18 June 2014.

  The aim of this instruction is to enhance the attractiveness of clinical research in France, by simplifying the contract process between industrial sponsors and public health facilities.

  Previously, industrial sponsors or contract research organisations (CRO's) needed to conduct separate contract negotiations with each involved public health facility. In some cases, additional negotiations for investigator contracts needed to be performed.

  The single contract instruction stipulate that now:

- Industrial sponsors or CRO's will sign a single contract for the same research facility, covering both facility costs and investigator fees
- Two templates for services agreement shall be used: one for the site where the national coordinator is located, one for the other participating sites
- A reference convention will be agreed and signed between the sponsor and the national coordinator public health site. This reference convention must be identically applied by all the other participating sites
- The deadline to sign the service agreement is fixed to 45 days for the national coordinator site and to 15 days for the participating sites

It shall however be noted that this instruction only covers research in public health institutions. For private centres, it is still needed to check which contract template(s) they agree to use.

The single contract instruction, with the contract templates and the tables for the calculation of additional costs to be used can be found at:

http://www.sante.gouv.fr/essais-cliniques-industriels-le-contrat-unique-simplifie-et-raccourcit-la-procedure.html

Germany

- **Ordinance on the delivery of medical devices and amending medical devices ordinances, published on 28 July 2014**

The ordinance "Verordnung über die Abgabe von Medizinprodukten und zurÄnderung medizinprodukterechltlicher Vorschriften), published on 28 July 2014 in the German Official Journal (Bundesgesetzblatt) has introduced several changes in the German regulatory framework for medical devices. This ordinance has established new requirements for the delivery and prescription of medical devices, now specified in a new ordinance (Medizinprodukte-Abgabeverordnung (MPAV)).

It also amended several ordinances related to clinical investigations:

- Medizinprodukte-Betreiberverordnung (MPBetreibV) , i.e." Professional user ordinance"
- Verordnung über klinische Prüfungen von Medizinprodukten (MPKPV), i.e " Ordinance on clinical investigations with medical devices"

- Medizinprodukte-Sicherheitsplanverordnung (MPSV), i.e. "Ordinance on the recording, evaluation and prevention of risks associated with medical devices"
- DIMDI-Verordnung (DIMDIV), i.e. "Ordinance on database information system for medical devices".

Except for some changes on the MPBetreibV, all the changes entered into force on 29 July 2014.

The new ordinance can be found on:

http://www.bfarm.de/DE/Medizinprodukte/mpAkt/mpsv_aenderung_07-2014.html?nn=3495216

With respect to the conduct of clinical investigations, the most important changes are those related to the amended MPKPV, DIMDIV and MPSV.

- ***Changes in MPKPV (Ordinance on clinical investigations with medical devices")***
  In the list of documents or information that need to be submitted to the Competent Authorities and Ethics Committees to obtain their approval for starting a clinical investigation, the point on preclinical evaluation has been updated. All scientific scientific evidence material that forms the basis for the preclinical evaluation are now required to be provided.

  The amended ordinance can be found on:

  http://www.gesetze-im-internet.de/mpkpv/

- ***Changes in DIMDIV (Ordinance on database information system for medical devices")***
  The annex 4, i.e. the application form to notify a clinical investigation to Competent Authorities and Ethics Committeees has been amended. It is reminded that this application form must be fulfilled on-line in the DIMDI database, by the applicant with a registered office in Germany.

  Compared to previous application form, the revised form requires more detailed information on sponsor, EU/EEA sponsor Authorised Representative, authorised applicant, study sites/investigators, the preliminary classification of the medical device and on the comparator product.

  The amended ordinance can be found on:

  http://www.gesetze-im-internet.de/dimdiv/index.html

- ***Changes in MPSV (Ordinance on the recording, evaluation and prevention of risks associated with medical devices)***

The following changes have been introduced for the safety reporting during clinical investigations:

- The investigator is no longer required to submit Serious Adverse Events (SAE) to the German Federal Competent Authorities. However, as previously, the investigator has to report each SAE immediately to the sponsor.
- Only the sponsor is now required to report SAE that occurred in Germany to the German Federal Competent Authorities (BfArM).
- Depending on the causal relationship, the SAE reporting timelines have been modified:
  a) In the case a causal relationship can not be excluded between the SAE and the investigational medical device, the comparator device or to any specific procedures used for the clinical investigation, the sponsor has to report the SAE immediately to BfArM.
     For these SAE, the BfArM published on 4 August 2014 a new safety electronic reporting form. This pdf-based reporting form is required to be fulfilled on-line in order to perform the mandatory electronic SAE reporting, according to the MPSV.
     A technical prerequisite to complete the form is to use Acrobat Reader version 9.1 or higher or its full versions.
     A guidance document named "Information regarding the electronic report" and explaining how to fill out and send the form was also issued by BfArM in July 2014.

  b) If a causal relationship can be excluded, the SAE must be collected, completely documented and reported by the sponsor to BfArM as quarterly listings. It shall be noted that the Competent Authorities may require other reporting conditions. So far, no specific template for the quarterly listings has been specified by BfArM. Hence it is recommended to regularly check BfArM webpage for up-to-date information.
- All SAE with causal relationship, that occurred in Germany, must be reported immediately by the sponsor to the other EU/EEA Competent Authorities, if the clinical investigation is also performed in those countries.
- If the clinical investigation is also performed in Germany, the sponsor must report to BfArM all SAE that occurred outside Germany. To fulfil this obligation, it is recommended to use the MEDDEV 2.7/.3 Summary Excel Table.

The amended ordinance can be found on:

http://www.gesetze-im-internet.de/mpsv/index.html

The new SAE electronic reporting form can be found on:
http://www.bfarm.de/SharedDocs/Formulare/EN/MedicalDevices/report_form_clinical_trials_SAE.pdf?__blob=publicationFile&v=9

The guidance document on SAE electronic reporting can be found on:

http://www.bfarm.de/SharedDocs/Downloads/EN/MedicalDevices/Hinweise-SAE_en.pdf?__blob=publicationFile&v=2

- ***Changes in MPBetreibV (Professional user regulation***)
  Since 29 July 2014, the amended MPBetreibV requires that patients with an active implantable device receives a written information as well as an implant passport from the professional user.

  The amended regulation foresees that in October 2015, these requirements will be extended to other implantable medical devices (heart valves, subsequent implantable products, non resorbable vascular prostheses and support systems, hip and knee implants, breast implants and vertebral body replacement systems and artificial discs).

  The amended ordinance can be found on:

  http://www.gesetze-im-internet.de/mpbetreibv/index.html

- **Update on electronic submission of applications to German Federal Competent Authorities for the authorisation of clinical trials with investigational medicinal products**

  According to Section 7(1) of GCP ordinance, the application for authorisation of clinical trials with investigational medicinal products to the German Federal Competent Authorities must be submitted in paper version and 1 copy on a electronic media carrier (CD-ROM/DVD).

  On 24 April 2013, both Federal German Competent Authorities (BfArM and PEI) announced on their web-page that they are gradually changing to a purely electronic processing of the documentation to be submitted for the authorisation of a clinical trial with an investigational medicinal product.

  For this purpose, BfArM and PEI developed a file format structure for electronic submission on an electronic data carrier (CD-ROM/DVD). All documents to be included must be submitted in pdf format, without password protection. The only exceptions to the pdf format concern the XML file of the EudraCT form and the SNIF form (Word Format) for studies with GMO's. To ensure a valid submission, all documents must be filed using the folder structure and naming convention as specified on the web-sites of both Federal German Competent Authorities.

  In the case the applicant completely adhere to the specifications for the electronic submission, only one paper version of the application dossier with original signature and one data carrier comprising all electronic documents are required. Additionally, the cover

letter shall mention that the application contained on the electronic data carrier and all related documents pertaining to it are submitted in accordance with the currently applicable specifications provided on the web-site of BfArM and PEI and that the electronic version is identical to the paper original version. In the case the folder structure and naming convention for the electronic submission are not strictly followed, 4 paper copies (with one with original signature) and one electronic submission are required.

Recent experience in the submission of clinical trial applications to German Federal Competent Authorities has shown that now, both BfArM and PEI have changed over to a purely electronic processing of the documents. In this regard, the compliance to the format on the electronic data carrier is becoming increasingly more important. Indeed, any non-formal compliance to the "electronic submission format" will lead to a rejection of the application dossier and a deficiency letter.

Detailed information on the required electronic submission structure can be found on Federal German Competent Authorities websites:

- BfArM:

  http://www.bfarm.de/EN/Drugs/licensing/clinicalTrials/news/ElectronicSubmission.html?nn=3497928

- PEI:

  http://www.pei.de/EN/information/license-applicants/clinical-trial-authorisation/electronic-submission-applications/electronic-submission-applications-node.html

United States of America

- **FDA draft guidance on Informed Consent Information Sheet, published on 25 July 2014**

  The draft guidance issued by FDA on 25 July 2014 is intended to assist the institutional review boards (IRB's), the clinical investigators and the sponsors involved in clinical studies with FDA regulated products, in order to fulfil their responsibilities related to subject informed consent.

  The draft guidance provides FDA recommendations and requirements for subject informed consent, in order to assure the protection of the rights and welfare of human subjects in clinical studies.

It describes the basic and additional elements that must be part of the informed consent and covers topics such as review of patient records, enrolment of non-English speaking subjects, children as subjects.

The draft guidance is open to public comments up to 27 October 2014.

When finally adopted, it will replace the current "Guide to Informed Consent", issued in September 1998.

The draft guidance can be found on:

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM405006.pdf

European Headquarters
Verona - Italy
Phone: **+39 045 8222811**

North American Headquarters
Cambridge - USA
Phone: **+1 617 871 1128**