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Regulatory Newsletter
April - June 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 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 the European Commission

Medical Devices

- **Update on the proposed Medical Devices and In-Vitro Diagnostic Medical Devices Regulations**

On 2 April 2014, the European Parliament voted on its first reading on the draft Medical Device and In-Vitro Diagnostic Regulations. Some aspects were particularly addressed by the European Parliament e.g. a stricter monitoring and certification procedures to ensure traceability for medical devices, patient implant card and stricter safety rules for In-Vitro Diagnostic Medical Devices. Furthermore for these types of devices, the Parliament called for an ethics committee to be set up and to introduce provisions requiring the informed consent of patients to testing protocols and genetic counselling.

On 5 November2014, discussions on both draft regulations restarted at European Parliament and it was decided to forward the draft proposals to the European Council, in order to reach an agreement.

During its meeting of 1 December 2014, the Council debated on both proposals and decided that both draft regulations need further discussion before the Council can agree on its position. In particular, the following points were outstanding: reprocessing of single-use devices, unique device identification system, mechanisms for surveillance and appointment of the Notified Bodies responsible for conformity assessment of medical devices and In vitro diagnostic medical devices or clinical investigations.

Under the Latvian Presidency, the two regulation proposals were re-examined with the view to establish compromise texts covering, for both proposals, all articles and annexes but excluding the recitals.

During its meeting on 19 June 2015, the Council reached a “Partial General Approach”, i.e. it agreed on both proposed texts (excluding the recitals).

In particular, the Council’s agreement:

- tightens the rules for the designation of notifies bodies and their activities monitoring by national authorities
- set ups additional provisions for manufacturers’s responsibilities for the follow-up of the quality, performance and safety of medical devices placed on the market
- strengthens the rules on clinical investigations
- set ups requirements for a better traceability of medical devices

- set-ups an EU Portal where manufacturers will be required to report serious incidents and corrective actions taken.

The next step for the two draft regulations will be the preparation by the Council of the recitals and the check for technical inconsistencies, with a view to prepare complete General Approaches. These activities are expected to be completed by October 2015. Further to the finalisation of the recitals, negotiations between the Council and the European Parliament will be able to start, with the aim to finalise both regulations.

Current proposed texts for respectively the Medical Devices Regulation and the In-Vitro Devices regulations can be found on:
http://www.consilium.europa.eu/en/press/press-releases/2015/06/19-medical-devices-council-ready-talk-with-ep/

From European Medicines Agency (EMA)

- **Revised functional specifications for the EU portal and EU database to be audited, published on 16 April 2015**

  On 21 January 2015; a draft addendum was released for public consultation with proposed options to apply the exceptions provided in the Clinical Trials Regulation on its transparency requirements.

  Further to the draft addendum release, the section 6 of the "Functional specifications for the EU portal and the EU database to be audited" was amended to clearly indicate that this addendum will complement the functional specifications of the EU portal and EU database.

  It is expected that the final addendum will be published in October 2015, after endorsement by the EMA Management Board.

  The revised EMA functional specifications document can be downloaded from:

  http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500179339.pdf

- **Draft Good Practice Guides on medication errors, published on 14 April 2015**

  Under the new EU pharmacovigilance legislation that entered into force in July 2012, the reporting of all suspected adverse reactions resulting from medication errors through EudraVigilance has become mandatory.

  Medication errors are defined as any unintended error in the prescribing, dispensing or administration of a medicinal product that could cause harm to a patient. EU authorities

are particularly concerned about medication errors as they represent a major public health burden. Indeed, it is estimated that at least 19% of all adverse drug events among hospitalised patients result from medication errors. Furthermore, most of medication errors would be preventable by appropriate risk minimisation measures.

With the aim to support pharmaceutical industry, EMA published on 14 April 2015 two draft guidelines on medication errors. Both guidelines were open for public consultations up to 14 June 2015.

One guideline provides guidance on how suspected adverse reactions caused by medication errors should be recorded, coded, reported and assessed.
The other guideline describes the main sources and categories of medication errors and gives clarification for the prevention of medication errors.
Both draft guidelines can be found on EMA website as follows:

http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500185536&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

http://www.ema.europa.eu/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500185538&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc

- **Revised reflection paper on classification of advanced therapy medicinal products, published on 8 June 2015**

  In accordance with the "Advanced Therapy Medicinal Products (ATMPs) Regulation"(EC Regulation N°1394/2007), depending on their mode of action, ATMPs may be classified as gene therapy medicinal product, somatic cell therapy medicinal product or tissue engineered product.

  Given the complex nature of these medicinal products, questions of borderline may arise. To help the developers of these high technology medicinal products, the European Commission setted up a dedicated expert committee, the CAT (Committee for Advanced Therapies). One of CAT responsibilities is to provide scientific recommendation for the classification of ATMPs.

  The ATMP classification by CAT is conducted on the request of and on the basis of the information provided by a developer. It is free of charge. Although the issued classification is not binding, it shall help the developer to clarify the applicable regulatory framework and the scientific guidelines to be followed.

  In the frame of a clinical trial application, the ATMP classification provided by CAT shall help in preparing the submission application package.

The purpose of the revised reflection paper on the classification of advanced therapy medicinal products is to provide guidance on the key concepts used by CAT for the classification, based on the experience gained so far by CAT.

The revised reflection paper can be found on:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500187744.pdf

- **Questions and Answers on EMA policy on publication of clinical data for human use medicinal products, published on 8 June 2015**

On 1 January 2015, EMA policy on the publication of clinical data for medicinal products for human use (Policy 0070) entered into force. It applies to clinical reports contained in all applications for centralised marketing authorisations submitted after 1 January 2015. The reports will be released by EMA once the final decision on the marketing authorisation applications has been taken.

As previously communicated, EMA policy will be implemented in phases and in a stepwise approach:

- From 1 January 2015, the policy applies to any new marketing authorisation application submitted after that date
- From 1 July 2015, the policy will apply for already approved medicinal products to line extensions or extension of indications applications submitted as of that date.

The purpose of the Questions and Answers document is to provide a response to the main concerns raised in relation with the EMA policy.

The document can be downloaded from:

http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/10/WC500174378.pdf

To help the pharmaceutical industry in preparing for the publication of clinical reports , EMA organised on 24 June 2015 a webinar on the implementation ot its policy where the foreseen work processes (submission of redacted clinical reports, consultation process, publication of redacted clinical reports) were explained.

EMA is also preparing 3 guidance documents:

- Guidance to pharmaceutical industry on the submission of clinical reports intended for publication in accordance with EMA policy 0070
- Guidance to pharmaceutical industry on redacting Commercial Confidential Information (CCI) in clinical reports
- Guidance to pharmaceutical industry on the anonymisation of clinical reports for the purpose of publication in accordance with EMA policy 0070.

A face-to face meeting will be organised on 6 July 2015 at EMA to discuss in more details the draft guidance documents. It is expected that the final guidances will be published in October 2015.

- **EMA communication on reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials, issued on 17 June 2015**

  On 1 February 2013, EMA released for open consultation a reflection paper on GCP compliance of the Trial Master File. The consultation process ended on 30 April 2013.

  In view of the future implementation of the Clinical Trials Regulation, it has been decided that the issue of a revised version of the TMF guideline will be postponed and incorporated into a TMF guidance as part of the work needed for the implementation of the Clinical Trials Regulation.

  The EMA communication can be downloaded from:

  http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/02/WC500138893.pdf

From Individual Countries

Belgium

- **Circular N°619, published on 8 April 2015**

  Belgian Competent Authorities (FAMHP) have published on 8 April 2015, the circular n°619, with the new list of accredited Ethics Committees (EC's), with full agreement.

  In Belgium, only Ethics Committes with full agreement are allowed to provide the Ethics Committes approval, in order to perform either a clinical study with a medicinal product or with a medical device.

  Compared to previous list, 24 EC's are now authorised to provide the Ethics Committee approval, in the frame of either a monocentric study or a multicentric study.
  The EC full agreement is valid for a period of 4 years.

  The circular n°619 also provides additional explanations on how the selection of the Ethics Committee allowed to give EC approval must be performed, for any new study to be initiated in Begium.

  The circular n°619 can be accessed, via the following link:

http://www.fagg-afmps.be/en/binaries/circulaire%20619_tcm292-265755.pdf

France

- **New method of reporting adverse reactions in clinical trials with medicinal products, from 13 April 2015**

  Since 13 April 2015, new methods of reporting adverse reactions in clinical trials with medicinal products (SUSAR's) to French Competent Authorities (ANSM) apply.
  Previously the declaration to ANSM of Suspected Unexpected Serious Adverse Reactions (SUSAR) occurring during a clinical trial with a medicinal product was requiring to submit an accompanying SUSAR formular available on ANSM website and that must be fulfilled and submitted on-line.
  In order to simplify the procedure to transmit SUSAR's to ANSM, it is no longer required to submit the accompanying formular, from 13 April 2015.

  As previously, each SUSAR must be reported electronically to ANSM at **declarationsusars@ansm.sante.fr** in an individual e-mail, with the CIOMS form in pdf format.

  Additionally, the subject of the e-mail and the name of the CIOMS report must be made according to specific rules as defined on ANSM website.

  Detailed information for the reporting of SUSAR's to ANSM can be found under the following link:

  http://ansm.sante.fr/Activites/Medicaments-et-produits-biologiques/Declaration-des-effets-indesirables-SUSARs/(offset)/4

- **Implementation of a pilot phase for the application of the Clinical Trials Regulation announced by ANSM, on 14 April 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 strenghtening 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 13 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 autorisation 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/Activites/Medicaments-et-produits-biologiques/Phase-pilote-application-du-Reglement-UE-N-536-2014-du-Parlement-europeen/(offset)/6

In order to provide practical information to sponsors wishing to use the pilot phase, ANSM issued on 30 June 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. 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 annoucement.

- **ANSM new notice for sponsors for clinical trials with medicinal products, published on 1 June 2015**

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 1 June 2015 a revised notice for sponsors.

The new notice replaces previous version, issued in January 2009 and shall be used since 1 June 2015.
Compared to previous version, the revised guidance brings simplication in the transmission of information to ANSM as it is now highly recommended to submit any information to ANSM by e-mail.

Several simplifications have also been introduced for the initial authorisation request dossier.

Indeed the insurance certificate, the EudraCT number confirmation e-mail, the applicant authorisation letter from the sponsor are no longer required to be included in the dossier.

In addition, the revised guidance clarifies the requirements for:

- the investigator brochure update
- the chart for independent monitoring committee
- the request for extension of the clinical trial authorisation
- the substantial amendment.

Coupled with the publication of the revised notice, ANSM has issued a revised template for the " Courrier de demande d'autorisation", aimed to facilitate the assessment of the validity of the dossier.

The revised 'notice for sponsor' and template can be found:

http://ansm.sante.fr/var/ansm_site/storage/original/application/e555b29ab27c1b7d4ab901512ac8a686.pdf

http://ansm.sante.fr/Activites/Medicaments-et-produits-biologiques/Avis-aux-promoteurs-Formulaires/(offset)/2

Germany

- **Online public database for post-athorisation observational studies, open end March 2015**

The third amendment to the German Medicines Law (Arzneimittelgesetz – AMG) of 07 Aug 2013 entered into force on 13 August 2013. This amendment brought extensive changes for the mandatory notification to the German Competent Authorities of a post authorisation observational study with medicinal products (Anwendungsbeobachtung or AWB). This new law is mandatory for all AWBs with start dates later than 12 Aug 2013 and with an end date later than 31 Dec 2013.

Furthermore, according to the new Art. 67 Par. 6 (§ 67 Absatz 6 AMG), *"..the competent higher federal authority has to make the notifications received and the final reports available to the public through an internet portal."* As a consequence of this amendment,

the Federal Institute for Drugs and Medical Devices (BfArM) has implemented the new requirements on transparency by providing an online public database. In this public database, information on the AWB like study title, study objective, patient number, drugs used, start and end dates of the study as well as the treatment plans and final report submitted to BfArM, is accessible since 26 Mar 2015.

Before an AWB will be published in the open database, it has to be notifed to the German Competent Authorities, by fulfilling an on-line formular ("Anzeige einer Anwendungsbeobachtung (AWB)"). It shall be reminded that apart from the initial notification, notification of amendments and of the end of the study must also be performed, using this formular.

Full information on AWB notification requirements and AWB public dabase can be found on BfArM website, under the following link:

http://www.bfarm.de/DE/Arzneimittel/zul/klinPr/nichtInterventPruef/_node.html

Netherlands

- **Revised Decree for mandatory insurance for medical research with human subjects, entering into force on 1 July 2015**

  On 9 December 2014, a revised Decree for the mandatory insurance for medical research with human subjects has been published in the Dutch Official Journal (Staatsblad). This decrees enters into force on 1 July 2015 and applies to any new medical research file submitted after 1 July 2015. Research issued with a positive decision before 1 July 2015, irrespective of any study amendment to be assessed after 1 July 2015 will continue to be governed by previous insurance decree.

  The major changes introduced in the revised Insurance Decree relate to:

  - Increase in the insured amounts, in conformity with the market. The new insured amounts will be at least 650.000 € per subject and at least 5.000.000 € per clinical trial
  - Requirement that all research subjects in the Netherlands participating in a multicentre study are covered by a single research subject insurance
  - Removal of exclusions which unduly restrict the coverage of the damage
  - Burden of proof in case of damage.

  As a result of the new insurance decree, the CCMO guidance for multicentre study (CCMO Directive External Review 2012), the research declaration and the template for insurance text patient information were amended. All these updated documents must be used for any new research file submitted after 1 July 2015. In addition, for any new research file, the sponsor has to provide a "Research Subject Insurance Declaration (G1)"

where it must be declared whether all research subjects who participate in a given study in the Netherlands are insured, who the policy holder is and which insurance company was used.

All updated documents further to the new insurance decree can be accessed, via the following link:

http://www.ccmo.nl/en/news-archive/consequences-of-the-new-insurance-decree-and-ccmo-directive-external-review-as-of-1st-july-2015

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