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.
Medical Devices

- Update on the recast process of the European Union Medical Device Regulatory Framework

With the aim to strengthen and update to technological process the current European Union Medical Device Regulatory framework, the European Commission published on 26 September 2012, two regulation proposals:

- Proposal for a Regulation on Medical Devices to replace Directive 93/42/EEC regarding medical devices and Directive 90/385/EEC regarding active implantable medical devices, also named MDR (Medical Device Regulation)

- Proposal for a Regulation on in-vitro diagnostic medical devices to replace Directive 98/79/EEC, also named IVDR (In-Vitro Diagnostic Regulation).

In accordance with European Union legislation procedure, both proposals were submitted end 2012, to the European Parliament and the Council for review and approval.

The responsible European Parliament Committee, ENVI (Environmental, Public Health and Food Safety) made several amendments to the proposals and voted on the proposed amendments reports during its meeting of 25 September 2013. It should be highlighted that in order to get a full picture of the current recast proposal, the ENVI reports need to be reviewed in conjunction with the European Commission regulation proposals.

The ENVI reports can be consulted on:


The main focus of the introduced changes is linked to medical devices transparency and traceability aspects: introduction of Unique Device Identifier (UDI), labelling requirements, publication of extended information in EUDAMED database on market approval status and clinical investigation data. Additionally, amendments include new approaches to enhance the control of the competence and performance of Notified Bodies, in the frame of the conformity assessment procedure for high risk medical
devices. Namely, for certain high risk medical devices, a special case-by-case assessment will be conducted by a proposed new expert body, the Assessment Committee for Medical Devices.

  The major changes are related to the reinforcement of patient safety for in-vitro diagnostic medical devices in special area such as diabetes, HIV and DNA testing.

The next step towards regulation for both MDR and IVRD is the plenary vote by the full European Parliament. This plenary vote is scheduled for the session of 22 October 2013. Should the European Parliament adopt the documents during this session, both the MDR and IVDR might enter into force by end 2013, with full application of all provisions, three years later, i.e. by end 2016. Finally, it shall be highlighted that both MDR and IVDR empower the European Commission to adopt delegated acts to ensure uniform application of the regulations.

Within the same context of recast of the EU medical devices regulatory framework, the European Commission adopted two additional measures on 24 September 2013:

- **Commission Implementing Regulation No 920/2013 on the designation and the supervision of notified bodies**

- **Commission Recommendation No 2013/473/EU on the audits and assessments performed by notified bodies in the field of medical devices**
  In particular, the Commission recommends unannounced audits of manufacturers by notified bodies.
From Head of Medicines Agencies (HMA)

- Revised guidance for the format and content of the final study report of non-interventional post-authorisation studies (PASS), published on 2 August 2013

From 10 January 2013, Marketing Authorisation Holders (MAH) have the obligation to submit the abstract and the final study report of a non-interventional post-authorisation study imposed by a national competent authority or the EMA, in a format complying with the provisions laid down in Annex III of EU Regulation No 520/2012. The use of the format is recommended for PASS initiated on a voluntary basis by the MAH.

The EMA document provides guidance for writing the abstract and the final study report of a PASS.

Compared to the previous version of January 2013, the updated EMA guidance document introduces changes in the sections 11 (Discussion) and 13 (Conclusion) to clearly highlight the need to discuss the impact of the study-results on the benefit-risk balance of the concerned medicinal product(s).


From Individual European Countries

Belgium

- Circular N°599 on pharmacovigilance on medicinal products for human use, published on 15 July 2013

Further to the transposition into Belgian law of the provisions laid down in Directive 2010/84/EU on pharmacovigilance for medicinal products for human use, the Belgian Competent Authorities have published the circular n°599, in order to explain the practical application of the new pharmacovigilance requirements in Belgium.

In particular, the circular describes the modalities applicable in Belgium with respect to non-interventional Post-Authorisation Studies (PASS)

Harmonized National Template for Informed Consent, published on 19 August 2013

As announced in previous newsletter, the harmonized national templates for “Patient Information and Informed Consent Form” have been published on the website from the Belgian Competent Authorities on 19 August 2013.

In total, 4 templates have been developed:

- for interventional clinical trials on adults
- for interventional clinical trials on adults temporarily unable to take an autonomous decision and hence with the involvement of a legal representative
- for interventional clinical trials on adults for participation in an emergency situation

The templates are available in French, Dutch and English.
With some adaptations, they can also be used for clinical studies on medical devices.
The use of these templates is strongly recommended by the Belgian Competent Authorities.

These templates can be downloaded using the following link:

Additionally, an explanatory circular from the Belgian Competent Authorities is under preparation and expected to be published in the course of Q4, 2013.

Finally, it should be highlighted that some Belgian Ethics Committees have already refused the validation of clinical submission packages not including the Patient Information Consent in accordance with the harmonized national template. Therefore, from now, the harmonized national template for informed consent shall be used for submission to the Belgian Ethics Committees.
**Additional requirements for the submission of clinical investigations applications by some Ethics Committees**

During these last months, it has been noted in the frame of submission of clinical investigation applications that some Ethics Committees (EC) are still requiring to provide, on top of the electronic application through DIMDI database, additional copies of submission package documents on paper or on an electronic media (CD-ROM, USB-stick). This request is unexpected as it is not foreseen in the German regulatory framework for medical devices. Indeed, the submission via the DIMDI database to both the Competent Authorities and EC’s is mandatory and should be the only way to submit clinical investigation applications and related documentation.

Currently, 47 EC’s are authorised in Germany to evaluate applications for medical device investigations and most of them are accepting submission through DIMDI only.

However, there are examples of EC’s requesting to different extent, additional copies either by paper or on electronic tools:

- EC Uniklinik Freiburg:  
- EC Fakultät für Medizin der Technischen Universität München:  
- EC Medizinische Fakultät der Ludwik Maximilian Universität München:  
  - [http://www.ethikkommission.med.uni-muenchen.de/hinw_antragssteller/mpg/index.html](http://www.ethikkommission.med.uni-muenchen.de/hinw_antragssteller/mpg/index.html)

Such situation results in additional work when preparing clinical investigations applications in Germany. Accordingly, it is recommended to carefully check EC requirements, when preparing clinical investigations applications.
**Netherlands**

- **Revised CCMO Template for insurance text for patient information leaflet, published on 8 August 2013**

CCMO published on 8 August a revised template for the insurance text for the Patient Information Leaflet ("CCMO-model verzekeringstekst proefpersoninformatie"). The use of this template is not mandatory but strongly recommended. In the case another document is used for insurance text, it shall be ensured that all topics required in the Netherlands are covered.

The template can be downloaded using the following link:

- **Revised CCMO guidance for Standard Research Dossier and for General Assessment and Registration Form (ABR-Form), published in August 2013**

CCMO published in August revised guidance documents for the Standard Research Dossier as well as revised explanatory notes for the ABR-Form.

The revised guidelines can be downloaded using the following link:

- **Tri-partite research contract template in English published in July 2013**

An uniform English template for 3-way (sponsor-trial institution- principal investigator) clinical trial agreement was developed in joint cooperation between the Dutch pharmaceutical industry association (Nefarma) and the Dutch association of teaching hospitals (STZ) and published in July 2013.

The template can be downloaded using the following link:
Spain

- **Law 10/2013 on medicinal products and medical devices, published on 24 July 2013**


The new law also modifies the law 26/2006 on the rational use of medicinal and health products.

With respect to clinical studies, the law introduces new fees requirements. From 26 July 2013, the following fees are applicable:

a) 4200 € for the first clinical trial with a medicinal product without a marketing authorisation in any ICH country
b) 111.19 € for clinical trial with a medicinal product with a marketing authorisation in Spain
c) 400 € for clinical trials with medicinal products, in situations other than a) or b)
d) 800 € for clinical investigations with medical devices.

Furthermore, it is now required to submit the application on the AEMPS website, within 10 days from the date of fees payment.

United States of America

- **Physician Payment Sunshine Act : requirements for data recording by manufacturers starting from 1 August 2013**

The Physician Payment Sunshine Act requires that manufacturers of drugs, biologics, medical devices, diagnostic and medical supplies publicly report payments they make to physicians and hospital/healthcare institutions.

To comply with the provisions of the Physician Payment Sunshine Act, the following timetable applies:

- From 1 August 2013 to 31 December 2013, manufacturers must start to track payments to physicians and healthcare institutions. Afterwards, they are required to submit reports to the Centers for Medicare &Medical Services (CMS), on an annual basis.
- From 1 January 2014, it is anticipated that CMS will launch the physician portal that allows physicians to sign-up for receiving notice when their individual consolidated report is available for review.
- From 31 March 2014, manufacturers will report to CMS the financial information for 2013 and physician/health institutions will start to check it.
- From 30 September 2014, CMS will release data on a public website.