



Regulatory Newsletter
October - December 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.



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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 November 2014, discussions on both draft regulations restarted at European Parliament and it was decided to forward the draft proposals to the European Council.

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 are 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.

The final Medical Devices Regulation and In-Vitro Diagnostic Medical Devices Regulations are hence to be awaited as the draft proposals need further discussion and probably will need to be reviewed, further to European Council position.

More details on the European Council current opinion can be found on:

<http://www.europarl.europa.eu/oeil/popups/summary.do?id=1369346&t=e&l=en>

From European Medicines Agency (EMA)

- **Policy on publication of clinical data for medicinal products for human use, published on 2 October 2014**

In the frame of a growing demand for additional transparency about clinical data on which regulatory decisions are based, the EMA took the initiative to develop a policy for the proactive publication of clinical data for medicinal products for human use.

The process started with a workshop on clinical trial data and transparency organised by the Agency on 22 November 2012 in order to discuss the views, interests and concerns of a broad range of institutions, pharmaceutical companies, patient and health care professional organisations, academia and individuals having an interest in this issue. This was followed at the beginning of 2013 by the formation of advisory groups to inform the Agency on the following topics: protection of patient confidentiality, clinical trial data formats, rules of engagement, good analysis practice and legal aspects. In June 2013, taking into account all the advices received, the Agency released for public consultation its draft policy on the publication and access to clinical trial data. Following extensive consultations with all stakeholders, the Agency published on 2 October 2014 its policy.

With the issue of the policy, the EMA expects:

- to increase EU citizens awareness and trust on regulatory decisions
- to foster the development of new medicines as it allows medicines developers to learn from past successes and failures
- to further promote public health as it enables the scientific community to use clinical data to develop new knowledge.

The policy will enter into force on 1 January 2015. It will apply 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.

The policy will be implemented in phases and in a stepwise approach:

- From 1 January 2015, the policy will apply 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.

In the first phase, only clinical reports will be published. In a second phase, the Agency also intends to make available Individual Patient Data. Given the various legal and

technical issues related to patient data access, the Agency will first consult with the different stakeholders, in order to ensure that patient privacy is adequately protected before their data are released.

The policy can be downloaded from:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf

- **Functional specification for the EU portal and EU database to be audited, released on 19 December 2014**

The new Clinical Trial Regulation (Regulation EU N°536/2014) establishes a harmonised approach for the submission, assessment and reporting of clinical trials throughout the Member States. All these processes need to be supported by a EU Portal and a EU Database. Furthermore, the Regulation will only apply after an audit has shown that the EU portal and EU database are fully functional. This audit will be based on agreed functional specifications.

In accordance with the Regulation,

- EMA shall in collaboration with the Commission and the Member States set up and maintain a portal at Union level as a single entry point for the submission of data and information relating to clinical trial. This portal shall be technically advanced and user-friendly so as to avoid unnecessary work. (Article 80)
- the Agency shall in collaboration with the Member States and the Commission set up and maintain at Union level a EU Database containing all data and information submitted in accordance with the Regulation and the Agency shall be the controller of the EU database. (Article 81)
- EMA shall in collaboration with the Member States and the Commission draw up the functional specifications, together with the timeframe for their implementation. (Article 82)

Therefore, in order to ensure its obligations as laid down in the Regulation, EMA released on 10 October 2014, the draft functional specifications for the EU portal and EU database to be audited.

The document was open to public consultation up to 31 October 2014.

EMA Management Board adopted the final specifications in its December 2014 meeting. The final specifications document was released on EMA website on 19 December 2014.

The EMA functional specifications document can be downloaded from:

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

The next step in the development of the EU portal and EU database by EMA will be the presentation to March 2015 EMA Management Board of the timelines for the development and deployment of the system.

- **Report on classification and analysis of the GCP inspection findings of GCP inspections conducted at the request of the CHMP, published on 8 Dec 2014**

In accordance with Directive 2001/83/EC, all clinical trials included in marketing authorisation applications for the European Union must be conducted in compliance with GCP and ethical principles equivalent to those of the Clinical Trials Directive (Dir 2001/20/EC), whatever the geographical location the clinical trials were performed. When the Committee for Medicinal Products for Human Use (CHMP) finds it necessary, it can request that the compliance with GCP is assessed by EU/EEA inspectorates of the national Competent Authorities. Inspection may be required in EU/EEA but also in third countries (i.e. countries outside EU/EEA).

The information included in the report published by EMA on 8 December 2014 refers to GCP inspections carried out from January 2000 to December 2012. It presents an analysis of the GCP inspection findings from a statistical point of a view.

By publishing data on inspection results, the EMA GCP inspector's working group (GCP IWG) intends to communicate to the public details on its inspection activity and hence provides more transparency on the inspection process and findings.

Another purpose of the report is to identify area that require more attention. This should provide support to sponsors in applying a risk based quality management to their clinical trials.

The report can be found on:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500178525.pdf

From Head of Medicines Agency (HMA)

- **CTFG – Guideline to confirm OECD GLP(Good Laboratory Practice) status of non-clinical studies in clinical trial applications, published in October 2014**

Several EU Directives (e.g. Directive 2001/83/EC, Directive 2004/10/EC, Directive 2010/63/EU) state that all non-clinical pivotal (i.e. pharmacological safety and-toxicological) studies conducted to support clinical trial applications must be carried out in conformance with the principles of OECD-GLP and in a country that is part of the OECD Mutual Acceptance of Data (MAD) system.

As clinical trial applications do not include individual study reports, the CTFG guideline specifies that sponsors shall include a statement confirming the OECD-GLP status, either within the Investigator's Brochure or with the cover letter.

The guideline can be downloaded from:

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_06_HMA_CTFG_GLP_in_clinical_trials.pdf

- **CTFG – Recommendations related to contraception and pregnancy testing in clinical trials, published in October 2014**

When clinical trial applications are submitted, limited data concerning reproductive toxicity are usually available. Therefore great care shall be taken to absolutely avoid any damage to the unborn child.

The purpose of the CTFG recommendations document is to supplement existing guidelines related to embryofetal risk mitigation and to provide practical guidance on contraception use and pregnancy testing in clinical trials. The guideline applies to all clinical trials with investigational medicinal products, except those with advanced therapy medicinal products.

Sponsors are required to follow the recommendations laid down in the guideline. Any deviation must be duly justified by the sponsor. In all cases, sponsors must justify and detail their strategy for contraceptive measures and pregnancy testing in the study protocol.

The guideline can be downloaded from:

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

- **CTFG – Updated Guidance Document for Sponsors for a Voluntary Harmonised Procedure (VHP) for the Assessment of Multinational Clinical Trial Applications, published in December 2014**

The updated VHP guidance document introduces the concept of a mandatory Reference National Competent Authority (REF-NCA) who is responsible for the principal scientific assessment, the consolidation of the grounds for non-acceptance and the assessment of sponsor's response.

In the request for VHP, the applicant is asked to propose one of the participating National Competent Authorities (P-NCAs) as REF-NCA. It shall be noted that this proposal is not binding for the P-NCAs and might be overruled by P-NCAs decision. Hence the updated guideline also specifies what will happen if the proposed REF-NCA declines to act as REF-NCA. As the VHP is a voluntary process, in case no other P-NCAs accepts to be REF-NCA, the VHP application will be rejected. The final decision on the REF-NCA will be communicated to the applicant, within 5 working days after receipt of the VHP-request.

The concept of a mandatory REF-NCA in the updated VHP guideline shall be seen as a preparatory step for the future implementation of the EU Clinical Trials Regulation that will make compulsory the coordinated assessment of the clinical trial application by a Reference Member State.

The updated VHP guidance document can be consulted on:

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_12_HMA_CTFG_VHP_sponsors.pdf

From Individual Countries

Belgium

- **Circular N°613, published on 7 November 2014**

Further to the recent changes introduced on the law concerning experiments on the human person, the Belgian Competent Authorities have issued the Circular n°613 in order to provide guidance to sponsors.

In particular, the circular provides explanations and recommendations on the following points:

- the concomitant submission (i.e. same day submission by registered mail) of the initial clinical trial application to the Belgian Competent Authorities and all involved Ethic Committees (Lead Ethic Committees and local Ethic Committees, in case of multicentric studies).

In the case of a substantial amendment request, the concomitant submission is not mandatory but is highly recommended taking into perspective the future implementation of the EU Clinical Trials Regulation.

- the motivated single opinion from the Lead Ethic Committee (LEC)

It is reminded that this opinion shall be provided by the LEC, using a specific template provided in annex I of the Royal Decree of 4 April 2014

- the addition of new investigational site(s) after the initial approval

Addition of new investigational site(s) can only be done after 3 months further to the initial approval. For subsequent additions, there is no waiting period.

The new circular can be accessed on:

http://www.fagg-afmps.be/fr/binaries/Circulaire%20613_tcm291-258804.pdf

- **Circular N°616, published on 18 December 2014**

In accordance with article 30 of the Law on experiments on the human person, the amounts of fees to be paid to the Competent Authorities (CA) and Ethics Committees (EC), in the frame of the assessment for clinical trials and clinical investigations have been amended.

From 1 January 2015, the following fees are required to be paid:

- *Clinical Trials*

Initial Submission: 3672.23 € (CA); 1243.58 € (Lead EC); 373.08 € (Local EC)
Substantial Amendment : 604.63 € (CA); 310.89 € (Lead EC)
DSUR : 655.02 € (CA).

- *Clinical Investigations*

Initial Submission: 2373.65 € (CA- Active Implantable Medical Devices); 2267.02 € (CA- Medical Device); 1243.58 € (Lead EC); 373.08 € (Local EC)
Substantial Amendment : 310.89 € (Lead EC)

Full details on fees payment for clinical trials to CA are specified in circular n° 616, published on 18 December 2014.

The new circular can be consulted using the following link:

http://www.fagg-afmps.be/en/binaries/Circulaire%20616%20FR%20paiements%20pour%20les%20demandes%20d%27essais%20cliniques%202015_tcm292-260628.pdf

Germany

- **Draft joint BfArM and PEI guideline for the mandatory notification of non-interventional studies to Competent Authorities, published on 27 October 2014**

After the third amendment of the Medicinal Products Act and related legislations (Arzneimittelgesetz –AMG) of 7 August 2013 entered into force, extensive changes for the mandatory notification to German Competent Authorities of observational studies (Anwendungsbeobachtungen – AWB) came into effect.

Accordingly the BfArM and PEI joint recommendations guideline of 7 July 2010 for the implementation, planning and analysis of observational studies needed to be revised.

Furthermore, with the entry into force of the second amendment of the Medicinal Products Act and related legislations (Arzneimittelgesetz – AMG) on 19 October 2012, new notification requirements for PASS (non-interventional Post Authorisation Safety Studies, *“nichtinterventionelle Unbedenklichkeitsprüfungen”*) by the holder of the marketing authorization came into effect.

Therefore, the draft updated joint recommendations guideline from BfArM and PEI, published on 27 October 2014 is intended to provide guidance for notification requirements of both AWB and PASS.

A public consultation of this draft document was initiated on 27 October 2014 and ended on 31 December 2014.

Until the publication of the final new recommendations guideline, it is advised to consult the FAQ, section AWB on BfArM or PEI websites, for detailed information on AWB notification requirements.

Full information on the draft joint recommendations guideline can be found on both BfArM and PEI website, under the following link:

- BfArM: http://www.bfarm.de/DE/Arzneimittel/zul/klinPr/nichtInterventPruef/_node.html
- PEI: http://www.pei.de/DE/infos/pu/genehmigung-klinische-pruefung/anwendungsbeobachtungen/awb-empfehlungen-konsultation-2014-inhalt.html;jsessionid=A1BA4477B725AA3216086271AF94E47A.1_cid319

- **New fees for medical devices investigations, in force since 11 November 2014**

A new fees Ordinance relating to the Medical Devices Act (Gebührenverordnung zum Medizinproduktegesetz) was published on 3 November 2014.

With respect to clinical investigations with medical devices, the following new fees are required to be paid, since 11 November 2014:

- Initial submission to Competent Authorities (CA) : 3000 to 9900 €
- Substantial amendment submission to CA : 600 to 1700 €
- Non-substantial amendments to CA : 100 to 400 €
- Exemption applications to CA : 500 to 2000 €
- SAE reporting to CA : 25 to 250 €

The new fees ordinance can be consulted using the following link:

<http://www.gesetze-im-internet.de/bundesrecht/bkostv-mpg/gesamt.pdf>

Italy

- **New version of National Monitoring Centre on Clinical Trials (OsSC), in force on 1 October 2014**

Starting from 1 October 2014, the submission of application requests for clinical trials with medicinal products as well as the related supporting documents must be done through the New OsSC (Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali) database. The electronic submission through OsSC shall be performed for submission to Competent Authorities, Coordinating Ethics Committees (CEC) and involved Ethic Committees.

The information required for these requests are compliant with the Ministerial Decree of 21 December 2007.

The submission through the new OsSC database is applicable:

- for any new initial application if the ethics committees involved in the trial have been validated to work through the new portal.
- for any substantial amendment submission related to the trials mentioned above.

Further information are available at the following links:

- [Ripristino dell'Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali \(OsSC\)](#)
- [Nuova piattaforma "Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali" \(OsSC\)](#)
- [Circular "New AIFA Information Systems"](#)

Netherlands

- **Revised Decree for mandatory insurance for medical research with human subjects, published on 9 December 2014**

On 9 December 2014, a revised Decree for the mandatory insurance for medical research with human subjects has been published in the Official Dutch Journal (Staatsblad). It will be implemented on 1 July 2015.

The major changes introduced in the revised 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
- Removal of exclusions which unduly restrict the coverage of the damage
- Burden of proof in case of damage.

In preparation for the implementation, it is expected that a number of insurance companies will revise their research subject insurance policies, as of 1 January 2015 and contact the institutions.

It shall be noted that the revised Insurance Decree is not applicable for clinical studies started before 1 July 2015.

The revised Insurance Decree can be accessed, via the following link:

<https://zoek.officielebekendmakingen.nl/stb-2014-477.html>

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