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European Regulatory Newsletter
April - June 2013



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 the first 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.

In future the Newsletter will be 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



Medicinal Products

- **Template for the Qualified Person's Declaration Equivalence to EU GMP for Investigational Medicinal Products manufactured in Third Countries, published on 3 May 2013**

Article 13 (3)(b) of Directive 2001/20/EC requires that for an investigational medicinal product (IMP) imported from a third country, each production batch is manufactured and checked for compliance with standards of Good Manufacturing Practice (GMP) at least equivalent to those laid down in EU Directives. Furthermore the CT-1 guidance specifies that when the IMP does not have a marketing authorisation in the EU or an ICH country and is not manufactured in the EU, the documentation for the request of the Clinical Trial Authorisation (CTA) shall include a copy of the importation authorisation and a declaration by the Qualified Person (QP) in the EU that the manufacturing complies with GMP at least equivalent to the EU GMP.

The document issued by the European Commission provides a harmonised template for the required QP's declaration and shall be used by at latest, November 2013.

It can be found on http://ec.europa.eu/health/files/eudralex/vol-10/2013_04-template-imp.pdf

Medical Devices

- **Recommendation on a Common Framework for a Unique Device Identification System of Medical Devices in the Union, published on 5 April 2013**

In order to enhance the traceability of CE-marked medical devices throughout the whole supply chain, the European Commission has issued a recommendation on a common framework for a Unique Device Identification System (UDI) of medical devices, within the European Union.

It should be noted that traceability is currently not regulated by the medical device directives. However the proposals from the European Commission for a regulation on medical devices and for a regulation on in-vitro diagnostic medical devices, published in September 2012 include traceability provisions. It is currently anticipated that both proposed regulations will enter into force throughout the European Union in 2016.

In the meantime, the purpose of the recommendation is to pave the way to the mandatory implementation of an internationally compatible UDI system of the Union.

The primary objectives of a UDI system are patient safety enhancement and patient care optimisation, by improving incident reporting, facilitating efficient recalls and field safety corrective actions, facilitating efficient post market actions by national competent authorities, enabling queries in data systems and reducing the likelihood of medical errors linked to the misuse of the device.

The Recommendation can be found on:

<http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:099:0017:0024:EN:PDF>

From Head of Medicines Agencies (HMA)

- **CTFG – Updated Guidance Document for Sponsors for a Voluntary Harmonised Procedure (VHP) for the Assessment of Multinational Clinical Trial Applications , published in June 2013**

The updated VHP guidance document includes the following main changes:

- Introduction of a 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
- Introduction of procedural steps to address the fulfilment of conditions, at the end of a positive VHP outcome
- Introduction of a second round procedure to include one or more additional Member State(s), after the initial VHP
- Introduction of the possibility for limited additional information request during the assessment of a substantial amendment
- Introduction of fees compensation by Participating National Competent Authorities, in case of VHP rejection, withdrawal by applicant or sponsor's decision of not conducting the trial in a Member State.

The updated guidance document can be consulted on:

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01About_HMA/Working_Groups/CTFG/2013_06_CTFG_VHP.pdf

International

From World Medical Association (WMA)

- **Draft Revised Declaration of Helsinki, published on 15 April 2013**

The World Medical Association published a proposal for a revised version of the Declaration of Helsinki on 15 April 2013. The proposal was open for public comments up to 15 June 2013. The proposed revised Declaration is the result of an intense analysis by an international working group, started in 2010.

Compared to the current version, the following main changes are included in proposed revised Declaration of Helsinki:

- More requirements for the protection for vulnerable groups
- More precise and specific requirements for post-study arrangements for study participants
- For the first time, addition of a statement for adequate compensation of patients, harmed as a result of participation in a research
- Introduction of a more systematic approach for the use of placebos
- Introduction of the requirement to submit at the end of the study, a final report to the Ethics Committees

The proposed revised declaration can be consulted on:

<http://www.wma.net/en/20activities/10ethics/10helsinki/15publicconsult/>

From Individual European Countries

Belgium

- **Loi portant des dispositions diverses en matière de santé , published on 29 March 2013**

The law published on 29 March 2013 is amending the Law of 7 May 2004, concerning experiments on the human persons and entered into force on 8 April 2013.

The law clearly distinguishes two types of Ethics Committees (EC):

- EC with partial agreement
- EC with full agreement.

Only an EC with a full agreement can provide the single opinion on a clinical trial request. Competences of EC with partial agreement are restricted to make a judgement for the institution to which the EC is attached, on the competences of the investigator and collaborators, the quality of site facilities and the patient informed consent.

The law sets up new conditions for the accreditation of the EC by the Competent Authorities (CA). To be eligible for a full agreement, the EC with partial agreement must satisfy the following conditions:

- have a quality system for GCP application
- have a system of registration and management of the interest conflicts of its members
- have a system to control members expertise
- have analysed on an annual basis average, in the frame of multicentre studies, at least 25 new study protocols as Single Opinion EC or at least 40 new study protocols.

The law is also requiring the EC to motivate their opinion (favourable or not) to the sponsor.

Furthermore, the law sets the Belgian CA (the Federal Agency for Medicines and Health Products) in a new role, i.e. a coordination role of the Ethics Committees.

Finally the law lays provisions for a closer collaboration between the EC and the Federal Agency, for the assessment of a protocol. It also establishes that communication between EC and the Agency will occur through an interactive secure website from the Federal Agency.

According to information received from the Belgian Pharmaceutical Industry Organisation, this website should become available by end 2013.

The new law can be consulted on:

[http://www.ejustice.just.fgov.be/cgi_loi/loi_a.pl?=&sql=\(text+contains+\(''\)\)&rech=1&language=fr&tri=dd+AS+RANK&numero=1&table_name=loi&F=&cn=2004050732&caller=image_a1&fromtab=loi&la=F&pdf_page=2&pdf_file=http://www.ejustice.just.fgov.be/mopdf/2013/03/29_2.pdf](http://www.ejustice.just.fgov.be/cgi_loi/loi_a.pl?=&sql=(text+contains+(''))&rech=1&language=fr&tri=dd+AS+RANK&numero=1&table_name=loi&F=&cn=2004050732&caller=image_a1&fromtab=loi&la=F&pdf_page=2&pdf_file=http://www.ejustice.just.fgov.be/mopdf/2013/03/29_2.pdf)

- **Circular n°598 on fees payment for clinical trial request, published on 13 May 2013**
Given the new role of the Federal Agency, the fees to be paid to the Belgian CA for a clinical trial have been increased as follows:

- Initial submission : 3644, 07 Euros
- Amendment : 600 Euros

The new fees amounts are effective from 13 May 2013.

- **Harmonized National Template for Informed Consent, agreed on 26 June 2013**

Further to a project launched at the initiative of the Ethics Committees with the support of the Belgian Competent Authorities, harmonized national templates for “Patient Information and Informed Consent Form” were agreed upon on 26 June 2013.

By the end of 2013, the use of these templates for any clinical study will be strongly recommended.

An explanatory circular from the Belgian Competent Authorities is foreseen for end 2013.

The harmonized national templates will be posted on the Ethics Committees and Belgian Competent Authorities websites.

The Ethics Committees have opted for a format for the informed consent form in 3 parts and limited to around fifteen pages:

1. The **information** essential to the decision to take part :
This part must contain **all the information essential to the decision-making process** of the participant, such as
 - a. A brief, clear presentation of the rights of the participant (voluntary participation; confidentiality; insurance, etc.)
 - b. a clear description of the research project (context, objectives, inclusion/exclusion criteria, methodology & course) highlighting the constraints in addition to the standard treatment (outside the study),
 - c. descriptions of the risks & benefits and presentation of the measures taken to minimise the risks ;
2. **Consent;**
3. **Supplementary information** (appendices) that gathers together information that does not fall directly within the decision-making process but which includes
 - a. useful information such as the number, frequency and content of each of the visits scheduled in the methodology,
 - b. additional information to that presented in the first part, such as the details of the risks associated with the study procedures;
 - c. more detailed information on participants’ rights.

France

- **Decree regarding the application of transparency of benefits provided by health and cosmetic products companies to health professionals , published on 22 May 2013**

France is the first European country who has voted a text clarifying the relations between the physicians and the pharmaceutical/medical devices/cosmetic industry. Published in the "Journal Officiel" on 22 May 2013, the decree is a kind of "Sunshine Act", the US law aiming to guarantee the independency of the experts and the declaration of conflict of interests. The decree is issued in order to apply the article 2 of the law n°2011-2012 of 29 December 2011 (the so-named "Loi Bertrand"), that reinforces the health security of health products.

From 1 October 2013, it will become mandatory to publish the links between the health and cosmetic industry and the health professionals, health professional associations, students and scientific associations.

The information to be made public will cover:

- Every advantage ≥ 10 €
- The nature of this advantage (diner, invitation, book...) as well as the existence of the conventions signed (for example, research conventions), starting from any advantage granted/conventions concluded in 2012

This publication will be done on a unique centralised public website.

This website must still be created. In the meantime, the information will be published on the website of the concerned professional orders and on the website of the companies.

The decree can be consulted on:

<http://www.legifrance.gouv.fr/affichTexte.do;jsessionid=?cidTexte=JORFTEXT000027434029&dateTexte=&oldAction=rechJO&categorieLien=id>

Comments of the French Ministry of Social Affairs and Health can be seen on:

<http://www.social-sante.gouv.fr/actualite-presse,42/communiqués,2322/sunshine-act-transparence-entre,15851.html>

The circular from the Ministry of Health providing additional interpretation was published on 29 May 2013.

It can be consulted on the link for comments of the French Ministry.

Germany

- **Requirements for Electronic Submission of Applications to German Federal Competent Authorities for the Authorisation of Clinical Trials for Investigational Medicinal Products, published on 23 April 2013**

According to Section 7(1) of GCP Ordinance, the application for authorisation of clinical trials with investigational medicinal products to German Federal Competent Authorities must be submitted in 4 hard copies and 1 copy on an electronic media carrier (CD-ROM/DVD).

On 23 April 2013, both Federal German Competent Authorities (BfArM and PEI) have announced on their web-page that they are gradually changing to a purely electronic processing of the documentation. Therefore, BfArM and PEI have developed a file format structure for electronic submission. All documents to be included must be submitted in pdf format, except the XML file of the EudraCT form and the SNIF Form (Word Format) for studies with GMO's.

Provided the required electronic submission file format is strictly adhered to, only one CD-ROM/DVD and one paper copy will now be required for any application related to clinical trials to German Federal Competent Authorities. Additionally, the cover letter shall mention that the application contained on the electronic media carrier and all related documents are submitted in accordance with currently applicable electronic submission specifications and that the electronic version is identical to the paper original version.

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

- BfArM:
http://www.bfarm.de/DE/Arzneimittel/1_vorDerZul/klinPr/news/ElektronischesEinreichungsFormat.html
- PEI : <http://www.pei.de/EN/information/license-applicants/clinical-trial-authorisation/electronic-submission-applications/electronic-submission-applications-node.html>

Spain

- **Registro Español de Estudios Clínicos (REec) - Spanish Clinical Trials Register, launched on 20 May 2013**

Since 20 May 2013, the Registro Español de Estudios Clínicos (REec) is open to the general public. It has been created with the purpose of promoting transparency of clinical drug studies approved in Spain and easing the availability of complete and accurate information about them.

The REec is accessible through the following link: <https://reec.aemps.es>

Currently, it only contains information on interventional clinical trials authorised by the AEMPS from 1 Jan 2013. However in the coming future, it is planned to include information on all clinical studies with medicines for human use, authorised in Spain (i.e. interventional clinical trials, except non-paediatric Phase- I trials and observational studies). Furthermore, AEMPS intends to open the Register on a voluntary basis to other studies e.g. Medical Devices Investigations. All studies with a favourable opinion of an Ethics Committee will hence be eligible for registration in the REec.

The information currently available in the REec is presented in both English and Spanish and is taken directly by the AEMPS from the EUDRACT database.

- **Draft of new Royal Decree on clinical studies with medicinal products, published on 17 May 2013**

In order to implement the latest European guidance (i.e. CT-1 and CT-3), Spain published a Draft Royal Decree regulating clinical studies with medicinal products for human use. This draft also includes changes in the requirements for the Ethics Committees involved clinical research as well as some aspects reflected in the current EU Clinical Trials http://www.cromsource.com/wp-admin/admin.php?page=wpseo_dashboard Regulation proposal. It is foreseen that the new Royal Decree will be published in Q4 2013 and it will repeal the actual one.

The proposed text is available in Spanish only and can be consulted at the following link: <http://www.msssi.gob.es/normativa/docs/Rdensayosclinicasm.pdf>

If this draft of Royal Decree is accepted, the main changes in Spain will be:

1) Ethic Committees

There will be a re-definition of functions, requirements for accreditation, infrastructure and composition of the ECs. Only the ECs which are accredited to evaluate clinical studies with medicinal products or medical devices will be allowed to do so. These ECs will be renamed CEIm - *Comités de Ética de la Investigación con*

medicamentos. The CEIm will come together at least once every 15 days (it used to be once a month).

2) Authorization of clinical trials (IMP)

Submissions will only be admitted **electronically** and will be required to be performed **simultaneously** to both AEMPS and CEIm.

The submission dossier will contain two parts: part I (core documents, e.g. protocol, IB) and part II (patient related documents, insurance and site specific). While AEMPS will only evaluate part I, the CEIm will evaluate both part I (except IMPD) and part II.

The timelines for approval of Clinical Trials, both initial and amendments, will be shorter than the current ones (60/35 days).

For initial application

After the receipt of a valid application, the CEIm will have 20 days (or 35 in case of ATMP study) to transmit its opinion on part I to AEMPS and 30 days to transmit its opinion on the part II directly to the sponsor. After the reception of a valid submission, the AEMPS will give the joined opinion on part I to the sponsor within 45 days (60 days for ATMP's).

For substantial amendment

Part I - the CEIm will have 20 days to transmit its opinion on part I to AEMPS. For the AEMPS, the 35 days for tacit approval will not change (e.g. IMPD).

Part II - the CEIm has 20 days to transmit its opinion directly to the sponsor.

3) Contracts

Agreements with any Spanish site/investigator will have to follow a unique national contract template and negotiation will be independent from EC/CA evaluation. After sponsor request, the contract should be finalized and signed within 60 days. The signature of the contract by the sponsor and the site will mean the agreement of the site's direction (*conformidad de la dirección del centro*).

4) End of Trial (EoT)

Contrary to CT1, the sponsor will have to notify EoT in Spain 90 days after that the study ends in this country as well as the Global study ending.

5) Low risk clinical trial

The concept of low risk clinical trial will be introduced. These trials are defined as studies where the medicinal products are used in accordance with the terms of marketing authorization and the additional diagnostic or monitoring procedures foreseen in the protocol will only pose a minimal risk or burden to the patients compared to normal clinical practice.

For these trials, the damage and prejudice to the subjects will be covered by collective or individual insurance covering the activities of the healthcare practice of the investigators. The approval of trials in this category will be shortened to 20 days. After AEMPS acceptance of the classification of the trial as low risk trial within 10 days, the evaluation of these trials will be totally done by the CEIm and they will be considered authorized on the day the CEIm gives its favourable opinion.

6) Regional Competent Authorities - RCAs

As soon as the AEMPS has established the platform for sharing information on clinical trials with the Regional Competent Authorities (*Comunidades Autónomas*), sponsor will no longer be requested to notify the RCAs about: start of the study, domestic SUSARs, DSURs, EoT in Spain and the study results.

7) Protocol deviations

Serious or very serious protocol deviations that occur in Spain will be required to be notified to AEMPS within 7 days by the sponsor.

8) Paediatric clinical trials

For studies which include paediatric populations, the ICF of the parent will be considered valid if signed by one of the parents with the consent of the other.

Foreign sponsors will be required to notify the clinical trial authorization to the Minors Coordination Unit of the State General Prosecution.

With these changes, Spain wants to make the authorization process of clinical trials quicker and smoother, in order to attract more sponsors and studies in their country. Since the changes in IT facilities, organization and infrastructure are quite demanding, a transition period of 1-2 years should be expected.

United Kingdom

- **MHRA – New fees for clinical trials, published on 1 April 2013**

The MHRA published on its website on 1 April 2013 the revised fees for clinical trials applications.

From 1 April 2013, the following fees are required to be paid to the UK Competent Authorities (MHRA):

- Initial submission : £3400
- Substantial Amendment : £250

- **MHRA Updated Guidance for Manufacturers on Clinical Investigations to be carried out in the UK, published in May 2013**

The MHRA published on its website in May 2013 a revised guidance to perform clinical studies with medical devices in UK.

The main changes are:

- Removal of paper copies for submission. Notifications are required to be sent via 8 rewritable CD-ROMs, each containing a full set of the supporting documentation
- Revised definition for Serious Adverse Event and revised timelines and template form for reporting that should be in accordance with MEDDEV 2.7/3
- Revised fees (Group A (low risk devices): £3820 ; Group B (High risk devices) : £5040)

The updated guidance can be consulted at the following link:

<http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007504.pdf>

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