

**CROM**  
**SOURCE**  
advise | agree | deliver

Regulatory Newsletter  
January - March 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](mailto:cromsource@cromsource.com) at any time.



**Passionate about  
your projects.  
High quality, on time, on budget.  
Guaranteed.**

**It's a simple concept, really.  
Quality data. On time. On Budget. Guaranteed.**

At CROMSOURCE we believe experts should keep their word. After 18 years of success we provide the industry's only End-to-End Guarantee™. Starting at the RFP stage with our uniquely detailed Feasibility Plus™ process we guarantee:

1. Your study will start on time
2. We will enroll 100% of the contracted patients
3. We will finish on time with a set date for database lock
4. The price you contracted is the price you pay. No CRO-initiated changes-in-scope.

We know that budgets must be competitive, and you can rest assured that our End-to-End Guarantee™ does not come with a premium price. As an ISO-certified organization, you can also rest easy about quality. **Don't you owe it to your project to learn more?**  
Contact us to request more information.

**END-TO-END GUARANTEE™**  
TIME, COST & QUALITY GUARANTEED

**1 ONE TRIAL ONE PRICE™**  
GUARANTEED FIXED PRICE BUDGET

**FEASIBILITY PLUS™**  
GUARANTEED ENROLLMENT & TIMELINES

**CROM  
SOURCE**  
advise | agree | deliver

European Headquarters: Via Giorgio De Sandre, 3, 37135 Verona, Italy Phone +39 045 8222811  
North American Headquarters: One Alewife Center, Suite 120, Cambridge, MA 02140, USA  
Phone +1 617 871 1128

e-mail us at: [cromsource@cromsource.com](mailto:cromsource@cromsource.com)

[www.cromsource.com](http://www.cromsource.com)

---

## European Union

---

### From the European Commission



#### Medical Devices

- **Updated References of Harmonised Standards under Directives 90/385/EEC, 93/42/EEC and 98/79/EEC, published on 16 Jan 2015**

In order to demonstrate the conformity of a medical device with the essential requirements laid down in Annex I of Directives 90/385/EEC, 93/42/EEC and 98/79/EEC, the medical device manufacturer must use harmonised standards as adopted by the European Union.

The updated list of the harmonised standards to be used was published in the Official Journal of the European Union on 16 Jan 2015.

It can be found on:

<http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:C:2015:014:FULL&from=EN>.

With respect to clinical investigation, the harmonised standard remains ISO EN 14155:2011.

### From European Medicines Agency (EMA)

- **Policy on publication of clinical data for medicinal products for human use, entering into force on 1 January 2015**

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.

The policy enters 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.

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

- **Draft proposal for an addendum, on transparency, to the functional specifications for the EU portal and EU database to be audited, released on 21 January 2015**

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.

It also aims to increase the transparency and availability of information on clinical trials and their results for the general public. All these processes need to be supported by a EU Portal and a EU Database to be developed and maintained under EMA responsibility.

The new EU Database will serve as the source of public information on clinical trials conducted in the EU, from the time of decision to authorise a trial up to the finalisation of the trial and results inclusion in the database.

In accordance with the Regulation, the EU database shall be publicly available unless one or more exceptions apply. These exceptions are:

- to protect personal data
- to protect commercially confidential information, in particular taking into account the marketing authorisation status of the medicinal product, unless there is an overriding public interest
- to protect confidential communication between Member States in preparing their assessment
- to protect the supervision of clinical trials by Member States.

The draft addendum published on 21 January 2015 proposed options for the application of these exceptions. The document was open to public consultation up to 18 February 2015.

The aim of the consultation was to get the stakeholders views on the applications of these exceptions, in particular for the timing of when certain information should be made public.

The rules and criteria on what data and documents are to be made public and on the publication timing, will be included in an addendum to the functional specifications for the EU portal and EU database. Further to the review of the responses to the public consultation, the final text of this addendum will need to be submitted for endorsement to the EMA Management Board.

It is expected that the final addendum will be published in October 2015.

The draft proposal for this addendum can be downloaded from:

[http://www.ema.europa.eu/ema/doc\\_index.jsp?curl=pages/includes/document/document\\_detail.jsp?webContentId=WC500180618&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=WC500180618&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc)

- **Guideline on adjustment for baseline covariates in clinical trials, published on 27 March 2015**

ICH E9 “Note for guidance on statistical principles for clinical trials” is briefly addressing the issue of adjustment for covariates. The purpose of the new EMA guideline is to clarify when and why baseline covariates should be included in the primary analysis that will need to be specified in the protocol and how the results should be presented and interpreted in the study report.

The EMA guidance also addresses the issue whether the adjusted or unadjusted analysis should be declared as primary in the protocol.

The new EMA guidance replaces previous European guideline (Points to consider on adjustment for baseline covariates (CPMP/EWP/2863/99) and will come into effect on 1 September 2015. Compared to previous guideline, the major change of the new guideline related to the use of dynamic allocation methods.

The EMA guideline can be downloaded from:

[http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2015/03/WC500184923.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500184923.pdf)

- **Draft concept paper on the need for revision of the guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials, published on 30 March 2015**

Currently the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials are provided in guideline CHMP/QWP/185401/2004. This guideline entered into operation on 1 October 2006.

With the upcoming implementation of the Clinical Trials Regulation, it is considered that an update of this guideline is needed, in order to fully reflect the recent development and changes both in the legislation and in the scientific knowledge. In particular, the revised guideline will update the section covering amendments(substantial/non-substantial) based on the experience gained so far.

The concept paper addresses this revision need and is open to public consultation up to 30 June 2015.

The concept paper can be downloaded from:

[http://www.ema.europa.eu/ema/doc\\_index.jsp?curl=pages/includes/document/document\\_detail.jsp?webContentId=WC500184944&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=WC500184944&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc)

---

## From Individual Countries

### Belgium

---

- **Compassionate use and medical need programs questions/answers document and guideline, published respectively on 9 February 2015 and 2 March 2015**

The new Royal Decree of 25 April 2014 for compassionate use and medical need programs came into effect on 1 July 2014. From that date, all compassionate use and medical need programs to be conducted in Belgium must be submitted and performed in accordance with the requirements laid down in the new Royal Decree.

In order to conduct a compassionate use or medical need program, an application needs to be submitted for approval to the Belgian Competent Authorities (FAMHP). Only a single indication can be approved per program. Approval or rejection of the program is delivered in a 60 days timeframe.

Upon approval of the program both the “summarized information for publication” and the informed consent form are published on the FAMHP’s website.

During the program, the treating physician shall communicate every adverse drug reaction to the responsible physician of the program. The program responsible physician shall anonymize the information and send it to the responsible of the program, i.e. usually a sponsor.

During the program, the responsible of the program must keep a central register of all patients included as well as records of suspected serious adverse events.

The purpose of the questions/answers document and the guideline is to provide guidance on the following points related to a compassionate use or medical need program:

- Content and format of the application
- Process to include patients in a program
- Template for summarized information for publication
- Template for Informed Consent Form
- Template for Protocol
- Information on Responsible of the program
- Information on Responsible physician
- Information on Central Register

The guideline and the questions and answers document can be accessed on:

---

[http://www.fagg-afmps.be/en/binaries/CUP-UMN%20Guidance%202015-03-20-OK\\_tcm292-264696.pdf](http://www.fagg-afmps.be/en/binaries/CUP-UMN%20Guidance%202015-03-20-OK_tcm292-264696.pdf)

[http://www.fagg-afmps.be/en/binaries/UMN%20FAQ%20V1.0-EN-2015-02-17-OK\\_tcm292-262978.pdf](http://www.fagg-afmps.be/en/binaries/UMN%20FAQ%20V1.0-EN-2015-02-17-OK_tcm292-262978.pdf)

or on Regulatory Library Sharepoint (RC Library\Medicinal Products\European Union\Belgium).

## France

- 
- **New form to submit an authorisation request for clinical investigation with a medical device, published on 22 January 2015**

The French Competent Authorities (ANSM) have published a new version of the formular to request an approval for a clinical investigation with a medical device. The new formular version (Formular 1, Version 3) must be used, since 22 January 2015 in any approval request submitted to ANSM and the French Ethics Committee.

Compared to the previous formular version, additional information are required for the description and marketing authorisation status of the device as well as in the section general information on the research.

The new application form can be downloaded from:

[http://ansm.sante.fr/Activites/Dispositifs-medicaux-et-dispositifs-medicaux-de-diagnostic-in-vitro/Formulaires-et-modeles-a-telecharger/\(offset\)/3](http://ansm.sante.fr/Activites/Dispositifs-medicaux-et-dispositifs-medicaux-de-diagnostic-in-vitro/Formulaires-et-modeles-a-telecharger/(offset)/3)

---

[www.cromsource.com](http://www.cromsource.com)



---

**European Headquarters**

Verona - Italy  
Phone: +39 045 8222811

**North American Headquarters**

Cambridge - USA  
Phone: +1 617 871 1128