Pharmaceuticals

This section updates readers on the latest developments in pharmaceutical law, giving information on legislation and case law on various matters (such as clinical and pre-clinical trials, drug approval and marketing authorisation, the role of regulatory agencies) and providing analysis on how and to what extent they might affect health and security of the individual as well as in industry.

Clinical Trials Regulation: A Further Step towards Increased Medical Innovation in the EU

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On 27 May 2014, after two years of debates and extensive amendments by the EU's law-making institutions, the EU Clinical Trial Regulation[1] was published. The Regulation repeals and replaces the Clinical Trials Directive,[2] an instrument described by the European Commission as "arguably the most heavily criticised piece of EU-legislation in the area of pharmaceuticals".[3] The Clinical Trials Regulation is intended to improve the existing framework, and will become applicable at the earliest on 28 May 2016. This report reviews the most significant changes to the existing system brought about by the Clinical Trials Regulation, and how this Regulation purports to strike a balance between its objective of increasing clinical trial activity in the EU and the need to protect clinical trial subjects' rights, safety and well-being.

I. Streamlined, Centralised Procedures

The Clinical Trials Directive had often been criticised for its failure to establish a streamlined procedure for conducting clinical trials in more than one Member State.[4] Under the Directive, sponsors were indeed required to submit an application for a clinical trial authorisation in each Member State where they intend the clinical trial to be conducted.[5]

Perhaps the most significant novel aspect of the Clinical Trials Regulation is the establishment of the EU Portal, a "one-stop shop" through which sponsors can apply for an authorisation to conduct a clinical trial in any number of Member States.[6] The application is reviewed primarily by a reporting Member State, with the input of all Member States on whose territory the clinical trial will be conducted. In particular, Member States will be required to review arrangements for the protection of subjects on their territory, such as recruitment arrangements and the informed consent form, the suitability of facilities, and proof of insurance.[7]

The Regulation will, moreover, introduce shorter timelines into the system of applications for clinical

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1 Regulation (EU) 536/2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, p. 1 (the "Clinical Trials Regulation" or the "Regulation").

2 Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L 121, 1.5.2001, p. 34, as amended (the "Clinical Trials Directive" or the "Directive").

3 European Commission, Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, COM (2012) 369 final, section 1.

4 See e.g. statement released as part of the CLINT Project (Establishment of infrastructure to support International Prospective Clinical Trials in Stem Cell Transplantation) at http://www.ebmt.org/sites/clint2/clint/Lists/News/DispForm.aspx?ID=5&ContentTypeId=0x010400DBE31DC8D6E8F84BB37B4D1B0382F985 (accessed on 19 June 2015).

5 Clinical Trials Directive, Article 9(2).

6 Clinical Trials Regulation, Article 5.

7 Clinical Trials Regulation, Article 6(5).

trials. Under the current system, Member State authorities have 60 days in principle to approve or reject an application to conduct a clinical trial on their territory.[8] Under the new rules, the default timeline for the assessment of clinical trial dossiers (both by the reporting Member State and the concerned one(s)) will be 45 days.[9]

Another area where the Regulation will simplify and streamline sponsors' operations is with respect to the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) arising during the clinical trial. Under the current system, sponsors can report SUSARs to Member States either centrally via Eudravigilance or directly to the Member States concerned.[10] Under the Regulation, the latter option will no longer be available. Also, sponsors will no longer be required to report SUSARs separately to ethics committees, as is currently the case.[11]

All of the above developments are intended to streamline procedures, reduce timelines, and ultimately generate cost savings for companies planning to sponsor clinical trials in the EU.

II. Codifying Existing Standards

The Regulation also codifies and gives legal force to various obligations that featured up to now only in written guidance and standards from the European Commission and/or the International Conference on Harmonisation (ICH).[12]

For instance, the contents of the clinical trial application dossier are now listed in Annex I of the Regulation; these are currently contained in guidance from the European Commission.[13] Likewise, sponsors will now be expressly required by the Regulation to monitor the clinical trials under their responsibility (to ensure, *inter alia*, that the rights, safety and well-being of subjects are protected); currently, this express requirement is set out in the ICH's Good Clinical Practice guideline.[14] Finally, the requirements as to the contents of the informed consent form are more detailed than under the Directive, and are also in line with the requirements described in the ICH GCP.[15]

That being said, and despite some clarifications compared to existing requirements (for instance, with respect to safety reporting) the Regulation does not significantly amend or expand the scope of existing rules and standards for clinical trials. In particular, the role and structure of ethics committees will remain largely determined by national law.[16] The Regulation will continue (like its predecessor Directive) not to apply to non-interventional studies.[17] Various aspects of the clinical trial relating to the protection of subjects will continue to be ultimately determined by national law, provided that the baseline standard in the Regulation is complied with.[18] These aspects will be assessed by the Member State(s) on whose territory the clinical trial will be conducted.[19]

III. A Greater Focus on Transparency

A very widely-publicised innovation introduced by the Regulation is its increased transparency requirements. Under the Regulation, sponsors will be legally required to submit various materials to the public EU clinical trials database, such as a summary of the results (including a summary understandable to laypersons) and the clinical study report, where the clinical trial is conducted in support of a marketing authorisation.[20] Member States are required to establish penalties for failure to provide this information.[21]

Some critics have pointed out that the transparency requirements apply only to clinical trials that are approved from the date of application of the Regulation (not earlier than 28 May 2016), and that patients

8 Clinical Trials Directive, Article 9(4).

9 Clinical Trials Regulation, Articles 6-7.

10 European Commission, "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')", OJ C 172, 11.6.2011, p. 1.

11 Clinical Trials Directive, Article 17.

12 ICH, Guideline for Good Clinical Practice (E6 – the "ICH GCP").

13 European Commission, "Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial (CT-1)", OJ C 82, 30.3.2010, p. 1.

14 Clinical Trials Regulation, Article 48; ICH, Guideline for Good Clinical Practice (E6), Section 5.18.

15 Clinical Trials Regulation, Article 29; Clinical Trials Directive, Articles 2(j) and 3; ICH GCP, Section 4.8.10.

16 Clinical Trials Regulation, Article 4 and Preamble, Recital 18.

17 Clinical Trials Directive, Article 1(1) ; Clinical Trials Regulation, Article 1.

18 See e.g. Articles 29(7), 29(8) and Article 34.

19 Clinical Trials Regulation, Annex I, sections K-Q.

20 Clinical Trials Regulation, Article 37(4).

21 Clinical Trials Regulation, Article 94(2).

and the medical community will not obtain further clinical data for products that are on the market as of that date.[22] Also, the results of the first trials approved under the Regulation may not be published until 2019/2020.[23]

While the above is true, it should also be pointed out that in practice, an increasing number of companies have been (of their own initiative) establishing formal processes to provide access to anonymised patient-level data upon request, for scientifically relevant research projects.[24] Also, the European Medicines Agency has recently begun implementing its policy to publish clinical trial data supporting new EU marketing authorisations, after the decision on the marketing authorisation has been made.[25] The results of the first trials covered by this policy are expected to be published in the course of 2015. Therefore, patients and the medical community will begin to have access to a limited amount of clinical data for marketed drugs before clinical data begins to be released under the Clinical Trial Regulation in 2019/2020.

Although regulatory procedures are only one of many factors determining the level of medical innovation in the EU, the measures and new functionalities of the Regulation will hopefully contribute to increasing clinical trial activity in the EU. While the Regulation does not significantly change the standards under which trials must be conducted in the EU (notably in terms of subject safety and well-being), its new transparency measures are expected to benefit patients in the long run, through better information about products and less duplication of research.

Even though there is at least a year left before the Regulation comes into force, companies should consider preparing for it, for instance by reviewing their informed consent forms and the EMA guidance on the specifications of the EU portal and EU database for any future clinical trial applications.[26]

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22 See e.g. http://www.alltrials.net/news/europe-votes-for-clinical-trial-transparency/ (accessed on 18 June 2015).

23 See European Medicines Agency, "Questions and answers on the European Medicines Agency Policy on Publication of Clinical Data for Medicinal Products for Human Use", EMA/357536/2014 Rev. 1, p. 7.

24 See e.g. the sponsors listed on https://www.clinicalstudydatarequest.com/ (accessed on 18 June 2015).

25 European Medicines Agency, "Policy on Publication of Clinical Data for Medicinal Products for Human Use", EMA/240810/2013.

26 European Medicines Agency, "Functional specifications for the EU portal and EU database to be audited", EMA/42176/2014 Rev. 1.