

# Client Alert

FDA &amp; Life Sciences Practice Group

January 7, 2014

For more information, contact:

**Beverly H. Lorell, MD**  
+1 202 383 8937  
blorell@kslaw.com

**Christina Markus**  
+1 202 626 2926  
cmarkus@kslaw.com

**Michael Petty**  
+1 202 626 5619  
mpetty@kslaw.com

**Nikki Reeves**  
+1 202 661 7850  
nreeves@kslaw.com

**Gillian Russell**  
+1 202 661 7978  
grussell@kslaw.com

**Pulina Whitaker**  
+44 20 7551 7586  
pwhitaker@kslaw.com

## King & Spalding

### London

125 Old Broad Street  
London EC2N 1AR  
Tel: +44 20 7551 7500  
Fax: +44 20 7551 7575

### Washington, D.C.

1700 Pennsylvania Avenue, NW  
Washington, D.C. 20006-4707  
Tel: +1 202 737 0500  
Fax: +1 202 626 3737

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

## Council of the European Union and European Parliament Agree on Proposal for New Clinical Trials Regulation

### *When Approved by the European Parliament, the Regulation Will Have the Force of Law in All EU Member States and Repeal the Current Clinical Trial Directive*

On December 20, 2013, the General Secretariat released the revised proposal for a regulation of the European Parliament and of the Council of the European Union (EU) entitled, “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.”<sup>1,2</sup> The path to the new clinical trials regulation was initiated on July 17, 2012 when the European Commission adopted a draft proposal for a clinical trials regulation. The provisional agreement reached by the EU Committee of Permanent Representatives (COREPER) marks the conclusion of three-way (trilogue) negotiations regarding the draft regulation among the European Parliament, the Council of the EU, and the European Commission in Belgium. If approved by the European Parliament in 2014, the regulation would repeal Directive 2001/20/EC (the Clinical Trial Directive). Unlike an EU directive, which sets out requirements that must be interpreted and enacted by separate legislation in each EU Member State, the clinical trials regulation, if approved by the European Parliament, would automatically be deemed to be incorporated in each EU Member State’s law under EC Treaty (Article 249). Thus, for the first time, clinical trials of investigational medicinal products<sup>3</sup> would be subject to identical regulation across the EU with the force of law. In addition, if enacted, the regulation would usher in substantial changes and harmonization in the processes for submission and approval of clinical trial dossiers. It would also provide new and expansive requirements for public transparency of clinical trial results.

### Background

In its introduction, the proposed regulation affirms two hierarchical precepts: “the rights, safety, dignity and well-being of subjects should be protected and the data generated should be reliable and robust,” and the “interests of the subjects should always take priority over all other interests.” To ensure that these principles are adhered to, the proposed regulation also affirms that a

clinical trial shall be subject to prior authorization. These precepts are unchanged from the Clinical Trial Directive.

As justification for the transition from a directive to regulation, the introduction to the proposed regulation states that, even though the Clinical Trial Directive aimed to simplify and harmonize provisions governing clinical trials in the EU, “experience shows that a harmonized approach to the regulation of clinical trials has only been partly achieved.” The rationale for the proposed regulation was also addressed in the Executive Summary of the Impact Assessment Report<sup>4</sup> that asserted that the Clinical Trial Directive contributed to a decline in the conduct of clinical trials in the EU, resulting in a negative impact on Europe’s competitiveness in clinical research and the development of new medicinal treatments. The Impact Assessment Report and the proposed regulation identify the following major problems with the Directive that are addressed by the proposed regulation:

- **Implementation of risk-based regulation of clinical trials.** Under the current system, the Clinical Trial Directive does not adequately address differences in safety risks of clinical trials nor is the definition of a clinical trial aligned with other EU legislation. The proposed regulation clarifies the definition of a clinical trial to better align with EU legislation governing medicinal products, which relies on the distinction between a “clinical trial,” in which a subject is prospectively assigned to an intervention, and a “non-interventional study.” The proposed regulation would apply to all clinical trials conducted in the EU, but it would not apply to non-interventional clinical studies. Among interventional trials, the proposed regulation identifies two separate risk categories:
  - “Clinical trials,” in which (a) the assignment of the subject to a particular therapeutic strategy (*e.g.*, to the investigational product or a placebo) is determined in advance and does not fall within normal clinical practice, (b) the decision to prescribe the investigational product occurs together with the decision to include the subject in the study, and (c) diagnostic or monitoring practices in addition to normal clinical practice are applied;
  - “Low-intervention clinical trials,” in which (a) the investigational product is already authorized, (b) its use in the trial is in accordance with the terms of the marketing authorization (*i.e.*, “on label”) or its use is based on published scientific evidence of safety and efficacy, and (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden compared to normal clinical practice in a Member State. Examples of such trials include comparative effectiveness clinical trials where different medicinal products might be compared regarding the same approved indications for use.
- **Simplification of the submission, assessment, and regulatory follow-up processes.** In the context of the globalization of clinical trials and the conduct of many trials in multiple Member States, a major rationale for the proposed regulation is simplification of the submission and assessment processes. The current process requires the submission, assessment, and regulatory follow-up of the same clinical trial in different Member States completely separate from each other, leading to inconsistent practices across the EU, administrative burdens, and delays in patient access to innovative treatments. The proposed regulation would simplify submission procedures via use of a single web-based portal, ensure that the content of the application dossier is the same for all Member States concerned with the clinical trial, and potentially accelerate the assessment process.
- **Eliminating need to navigate separate legislation in multiple Member States.** In the context of clinical trials taking place in more than one Member State, stakeholders will be able to directly rely on the provisions of the regulation in the design and conduct of the trial, including safety reporting and labeling of investigational products, rather than navigating separate legislation of multiple Member States.

## Highlights of the Proposed Submission and Authorization Process

**The EU Portal.** A major change in the proposed regulation is the requirement that a sponsor of a clinical trial shall submit one application dossier to the intended Member States through a single web-based portal (EU Portal). This portal shall be used whether or not the trial is to be conducted in a single or more than one Member State. The EU Portal is to be developed and hosted by the European Medicines Agency (EMA).

**Public Registration of the Clinical Trial.** The proposed regulation provides detailed specifications of the content and organization of the application dossier.

- Among these requirements, clinical data, which is submitted in an application dossier six months or more after the publication date of the final rule, shall be based on clinical trials that have been registered prior to their start in a public registry. The public registry must be a primary or partnered registry of the international clinical trials registry platform of the World Health Organization. Clinical trial data based on trials conducted before this date must also be registered or published in an “independent peer-reviewed scientific publication.”
- Clinical data in the dossier which does not comply with the requirements for clinical trial registration would not be considered in either the assessment for authorization of a clinical trial or a substantial modification of the authorization.

**The Reporting Member State.** To initiate the review and oversee the authorization process, the proposed regulation provides that a single Member State among those where the trial is to be conducted shall be proposed by the sponsor as the “reporting Member State.” If there is not agreement among the concerned Member States as to which state shall assume this function, the state proposed by the sponsor shall be the reporting Member State. The reporting Member State shall *validate* that the application dossier is complete and compliant with the requirements of the regulation and communicate the validation, or indicate that additional information is needed to accept the application, to the concerned Member States and the sponsor via the EU Portal.

**Assessment Process.** Following validation of the application, the reporting Member State shall draw up the assessment report in accordance with specifications in the regulation, including issuing a conclusion that the conduct of the clinical trial is (a) acceptable, (b) acceptable but subject to explicitly listed conditions, or (c) not acceptable. The final assessment report shall then be submitted to the sponsor and the other Member States via the EU Portal.

- If more than one Member State is to be involved in the trial, the assessment process shall consist of a 3-stage process: (a) an initial assessment phase and draft assessment report conducted by the reporting Member State and circulated to other concerned Member States, (b) a coordinated review involving all concerned Member States, and (c) a consolidation phase performed by the reporting Member State prior to issuing the final assessment report.
- Each of the sequential components in the assessment process following submission of the application has a maximum allowed timeframe that is specified in the proposed regulation. Prior to the submission of the final assessment report, additional information may be requested from the sponsor with an adjustment of timelines according to rules in the proposed regulation.
- Each Member State concerned with the application must ensure that these overarching timelines in the regulation are met while complying with review of the specified aspects that each Member State shall assess for its own territory. The aspects that are specified as subject to review by each Member State in accordance with the legal requirements of its own territory are the following:

- compliance with the requirements as set out in the proposed regulation for Informed Consent, arrangements for rewarding or compensating investigators and subjects, and arrangements for recruitment of subjects;
- compliance with applicable local requirements regarding collection, storage, and future use of biological samples of the subject;
- compliance with Directive 95/46/EC of the European Union (or the proposed data protection regulation if enacted by the time the clinical trial regulation is enacted), which sets forth requirements regarding the protection of individuals with regard to the processing of human data and on the free movement of such data;
- compliance with Article 46 in the regulation, “*Suitability of individuals involved in conducting the clinical trial*”;
- compliance with Article 47 in the regulation, “*Suitability of trial sites*”;
- compliance with Article 72 in the regulation, “*Damage compensation*,” referring to compensation for any damage suffered by a subject resulting from participation in a clinical trial conducted in the territory of a Member State.

***Decision on the clinical trial.*** Notification to the sponsor shall occur through the EU Portal in a single decision that incorporates whether the trial is authorized, authorized subject to conditions, or authorization is refused in each of the concerned Member States. The regulation provides explicit and limited grounds whereby an individual Member State may refuse authorization as well as an appeals process.

## **Highlights of the Proposed Rules for Protection of Human Subjects**

The proposed rules for the protection of human subjects and provision of informed consent are designed to be consistent with the Clinical Trial Directive. The proposed rules strengthen existing human subject protections by the inclusion of specific and clarified requirements of conducting clinical trials on vulnerable populations, including incapacitated subjects, minors, and pregnant and breastfeeding women. The proposed regulation also specifies the requirements for conducting clinical trials in emergency situations. A simplified method for obtaining informed consent is proposed for those trials that meet the criteria for a “low-intervention clinical trial.”

***Future uses of a subject’s clinical trial data.*** Notable new aspects in the proposed regulation are those that intersect with Directive 95/46/EC, which is the EU directive issued on October 25, 1995 on the protection of individuals with regard to the processing of human data and on the free movement of such data. The proposed regulation sets forth that “without prejudice to Directive 95/46/EC”:

- the sponsor may ask the subject at the time when he or she consents to participate in the clinical trial “to consent to use his or her data outside the protocol of the trial exclusively for scientific purposes. That consent may be withdrawn at any time by the subject.”;
- the withdrawal of consent by the subject “shall not affect the activities carried out and the use of data obtained based on consent before its withdrawal.”

Notably, these components of the proposed regulation step explicitly allow for greater uses of clinical trial data than are currently in place through United States law and regulations. As examples, FDA regulations in 21 C.F.R. Part 50, which define the required and discretionary elements of informed consent, do not specify whether or how the subject is permitted to be asked to consent to future uses of the data outside the protocol for scientific purposes. The FDA

regulations also do not specify that withdrawal of consent will not affect the use of data obtained based on consent before its withdrawal.

## New Requirements for Public Transparency of Clinical Trial Results

The proposed regulation requires the establishment of a single publicly accessible and searchable database for the results of EU clinical trials of medicinal products, which is to be expeditiously developed and hosted by the EMA. The proposed regulation sets forth new requirements that irrespective of the outcome of the clinical trial, within one year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the publicly accessible EU database a summary of the results of the clinical trial that is accompanied by a summary of results written in a manner understandable to lay persons. The only exception is (a) where, for scientific reasons detailed in the protocol, it is not possible to submit the results within one year and (b) the protocol specifies when the results are going to be submitted. The proposed regulation sets forth that the subject shall be informed that the summary of the results of the trial and a summary presented in terms understandable to a lay person will be made available, as a consequence of this regulation, in the EU database “irrespective of the trial outcome.” Additional major transparency provisions include:

- **Public accessibility of the Clinical Study Report.** The proposed regulation would require that the applicant for marketing authorization for the investigational medicinal product shall submit the full Clinical Study Report (CSR) to the publicly accessible EU database 30 days after (a) marketing authorization has been granted, (b) the decision-making process on a marketing application has been completed (*e.g.*, the application has been disapproved), or (c) the applicant has withdrawn the application.

These provisions go much farther regarding public disclosure of clinical trial results than current United States federal law and regulations. Title VIII of the FDA Amendments Act of 2007 (FDAAA) requires that certain applicable clinical trials be registered on ClinicalTrials.gov and that results be submitted for a subset of these trials. However, in contrast with the proposed EU regulation, FDAAA does not currently require public release of a summary of the clinical trial results if the investigational drug is not approved nor does it require the provision of public access to the Clinical Study Report.<sup>5</sup>

- **Sharing of raw per-person data.** The proposed regulation explicitly envisions the disclosure and sharing of raw per-person clinical trial data by the sponsor. The document states, “For cases where the sponsor decides to share raw data on a voluntary basis, the Commission shall provide guidelines for the formatting and sharing of those data.”

This provision is notable in the context of the ongoing endeavor by the EMA to develop a policy that would expand access to and sharing of both summaries of results and per-person clinical trial data. The EMA draft policy was published in June 2013<sup>6</sup> but has not yet been finalized, due in part to concerns of some stakeholders regarding the protection of patient confidentiality and uses of personal information as well as whether current informed consent processes encompass and allow for uses of the data for purposes other than those specified in the protocol.

- The inclusion in the proposed regulation of the specific option to obtain informed consent for other unspecified future uses of the clinical trial data at the time of the initial informed consent to participate in the clinical trial paves a way forward for addressing the concern about the relationship of the informed consent process and sharing of per-person data by the sponsor with other parties for purposes of scientific research.
- In addition, the inclusion of the paragraph regarding sharing of raw per-person data suggests that EU legislators who drafted this proposed regulation envision that guidelines for formatting and sharing of those data can potentially be developed by the Commission without violating the provisions of Directive 95/46/EC, the EU “data privacy” directive (or, if applicable, the data protection regulation).

## Considerations for Pharmaceutical Manufacturers

If enacted by the European Parliament, the new clinical trial regulation will streamline and harmonize the processes for submission of application dossiers and the conduct of clinical trials across the EU. It is not yet clear if the timeline between submission of the application dossier and authorization to conduct the clinical trial in multiple Member States will be materially shortened. The regulation has the potential to markedly increase public access to clinical trial protocols and results, including the provision of public access to the Clinical Study Report. Further, the regulation also has the potential to formally modify the informed consent process and reset expectations of human subjects and the public for future uses of clinical trial data outside of those specified in the protocol.

It is also noteworthy that the United States Department of Health and Human Services (DHHS) is currently engaged in the formal process of revising the DHHS regulations (including FDA regulations) that govern the protection of human subjects – including informed consent regarding future uses of clinical trial data – and has previously issued a related advance notice of proposed rulemaking (ANPRM).<sup>7</sup> DHHS also is in the process of determining whether and how to expand the requirements for registration and provision of clinical trial results on ClinicalTrials.gov. In the context of the globalization of clinical trials and focus on harmonization, the proposed new EU clinical trials regulation has the potential to influence the structure and content of the pending rulemakings and revision of United States regulations that govern the protection of human subjects and the sharing of clinical study information.

\* \* \*

*Celebrating more than 125 years of service, King & Spalding is an international law firm that represents a broad array of clients, including half of the Fortune Global 100, with 800 lawyers in 17 offices in the United States, Europe, the Middle East and Asia. The firm has handled matters in over 160 countries on six continents and is consistently recognized for the results it obtains, uncompromising commitment to quality and dedication to understanding the business and culture of its clients. More information is available at [www.kslaw.com](http://www.kslaw.com).*

*This alert provides a general summary of recent legal developments. It is not intended to be and should not be relied upon as legal advice.*

<sup>1</sup> “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. Council of the European Union.” Brussels, 20 December 2013. The provisional proposed regulation is accessible in the following attachment:

[http://www.kslaw.com/imageserver/KSPublic/library/publication/ca010814a\\_1.pdf](http://www.kslaw.com/imageserver/KSPublic/library/publication/ca010814a_1.pdf)

<sup>2</sup> Press release of the European Parliament. “Clinical trials: clearer rules, better protection for patients.” 20 December 2013. Accessible at

<http://www.europarl.europa.eu/news/en/news-room/content/20131220IPR31630/html/Clinical-trials-clearer-rules-better-protection-for-patients>

<sup>3</sup> An “investigational medicinal product” is an active ingredient in a pharmaceutical or placebo form tested or used as a reference in a clinical trial, including a medicinal product which is covered by a marketing authorisation but which is used off-label or in accordance with current clinical practice.

<sup>4</sup> “Executive Summary of the Impact Assessment Report on the Revision of the ‘Clinical Trials Directive.’ 2001/20/EC.” Brussels, 17 July 2012. Accessible at [http://ec.europa.eu/health/files/clinicaltrials/2012\\_07/summary/2012\\_07\\_summary\\_en.pdf](http://ec.europa.eu/health/files/clinicaltrials/2012_07/summary/2012_07_summary_en.pdf)

<sup>5</sup> FDAAA requires the U.S. Secretary of Health and Human Services to consider and potentially establish, by regulation, requirements for results disclosure concerning trials for drugs or devices that are not authorized for marketing in the U.S. See 42 U.S.C. § 282(j)(3)(D).

<sup>6</sup> The EMA “Draft policy 70. Publication and access to clinical-trial data” and the history of this initiative is accessible at

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/special\\_topics/general/general\\_content\\_000556.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000556.jsp)

<sup>7</sup> 76 Federal Register 44,512 (July 26, 2011).