

Client Alert

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Europe Adopts New Rules for Clinical Trials in Medicinal Products

A few days ago, the European Parliament voted on the new Clinical Trials Regulation (Regulation), an important piece of legislation that establishes new rules for the conduct of clinical trials in medicinal products. First and foremost, the Regulation replaces Clinical Trials Directive 2001/20/EC, which not only failed to reach its objective of harmonizing the clinical trial requirements throughout the European Union (EU), but worse, had hindered a swift handling of clinical trial applications and generated a very burdensome and costly administration that undermined competitiveness in clinical research. Second, the Regulation will model the future rules on clinical investigations for medical devices. The final text of the Regulation is slightly different from the version agreed on in December 2013 by the European Parliament and Council.

The Regulation revises the current rules, in particular the authorization procedures, and introduces new principles, such as public access to clinical trial information. Overall, the new regime should reduce administrative costs for industry and facilitate the authorization and conduct of clinical trials. Moreover, because the European Commission (Commission) chose a regulation as its legislative instrument, it ensures that identical rules will apply throughout EU. This will increase harmonization of the rules; however, certain issues, such as ethics, sponsor or insurance, will remain governed by national law.

The Regulation will enter into force shortly after its publication in the Official Journal, but it will become applicable only once the EU portal and the EU database are fully functional and such functionality has been formally confirmed by the Commission. The new rules therefore are not expected to be applicable before the second semester of 2016. Meanwhile, the Commission will develop guidelines or revise the current guidelines consistent with the Regulation.

Scope. — The Regulation has the same scope as Directive 2001/20/EC (i.e., interventional clinical trials and investigational medicinal products (IMPs)), but certain key definitions have been amended (e.g., clinical trial, non-interventional clinical trial) or introduced (e.g., “clinical study,” “low-intervention clinical trial” or “ethics committee”).

Risk Categorization. — The Commission proposal adopted a risk-based approach to clinical trials and distinguished between low-intervention clinical trials and other clinical trials. Low-intervention clinical trials benefit from less burdensome requirements (e.g., safety reporting, labelling and insurance) and shorter authorisation timelines. The Regulation kept the distinction but reduced its impact.

Streamlined Authorization Procedures. — Under Directive 2001/20/EC, a clinical trial is approved by a competent national authority and an ethics committee in each Member State where the sponsor intends to conduct the trial, and the authorization procedure is conducted in parallel in all the Member States. These parallel national procedures are replaced by a form of decentralized procedure, which also applies to purely national trials.

For the key features of the new authorization procedure, see our recent *Contract Pharma* article “[New Rules on Medicinal Product Clinical Trials in Europe.](#)”

The Regulation does not go as far as the Commission proposal with regard to the coordination of the national authorisations. Specifically, it extends the reasons a Member State may reject the conclusion of the assessment report prepared by the reporting Member State. The authorisation timelines have also been extended so that the national decisions on an application may now take from 60 to 106 days (plus 50 days if the product is an advanced therapy or biotech product). Hopefully, in practice, the Member States will use shorter timelines and thereby restore competitiveness in European clinical trials.

The content of the application dossier is listed in Annex I to the Regulation. The use of the English language is not mandatory, but Member States are encouraged to accept documents in English.

Protection of Subjects and Informed Consent. — The Regulation sets out new rules with specific and strict conditions for conducting clinical trials in pregnant or breastfeeding women, as well as on consent in emergency situations and cluster trials. With regard to data privacy, the Regulation expressly allows consent for secondary use of data and the use of collected data despite a subject's withdrawal from the clinical trial; however, it also refers to the data privacy rules, which are currently under revision and could strictly regulate both the secondary use of data and the effect of a withdrawal.

Streamlined and Simplified Safety Reporting. — The rules on safety reporting are streamlined and simplified. Reporting of certain adverse events by the investigator to the sponsor can be excluded in the protocol, and suspected unexpected serious adverse reactions (SUSARs) can be reported by the sponsor directly to EudraVigilance (i.e., the EU pharmacovigilance database) instead of each Member State. SUSARs must be reported for the underlying clinical trial, as well as any other clinical trial for the same active substance conducted in a third country. More detailed rules on safety reporting, which partly codify the current Commission guidance, are contained in an annex to the Commission's proposal.

Increased Reporting. — Sponsors must notify each Member State of certain clinical trial events within 15 days of their occurrence: start of the trial; first visit of first patient; end of recruitment; end of trial; end of trial in all Member States; end of trial in all third countries; temporary halt of trial; resuming trial after temporary halt; and early termination of trial. Sponsors will need to implement a system to ensure the timely notification of all such events.

Conduct of Clinical Trials Outside the EU. — Results of clinical trials conducted outside the EU to support marketing authorisation applications in the EU must comply with regulatory requirements at least equivalent to those in the EU. This obligation is already included in Annex I to Directive 2001/83/EC. Further, it is unclear how equivalence between foreign and EU clinical trial requirements will be assessed and, more importantly, how third countries will be convinced to adopt requirements that are similar to the EU rules.

Indemnity and Insurance. — Directive 2001/20/EC introduced an obligation for sponsors to compensate trial subjects for damages resulting from clinical trials (in accordance with national law) by way of an indemnity or insurance. The Regulation simply states that compensation systems must be in place in the form of insurance, guarantee or the like, and specifies that such system may not be required for low-intervention clinical trials if the damages are already covered by a compensation system already in place.

EU Database. — Under Directive 2001/20/EC, clinical trials are registered in a central database (EudraCT). That database is not publicly available except for pediatric trials, but protocol-related information and trial results are indirectly made public through another database (EudraPharm). The Regulation creates a new EU database that contains all information and data relating to the clinical trials, including those fed through the EU portal, separate summaries of results for regulators and laypersons (to be made available one year after the end of the trial in all Member States) the contents for these are defined in annexes to the Regulation, and the clinical study report (to be made available 30 days after the granting of the marketing authorization or the withdrawal of the marketing authorization application). Information in the EU database is fully accessible to the public, excluding personal data, confidential commercial information (unless there is an overriding public interest) the need for effective supervision of the conduct of the clinical trial by a Member State, and confidential communication among Member

States relating to the assessment reports. This increased clinical trial transparency is in line with the general European trend in the pharmaceutical sector and will be key in the still ongoing debate between the regulators and the industry on public disclosure of clinical data by the regulators.

Other Aspects. — The Regulation covers other aspects of clinical trials, such as:

- Co-sponsorships: The Commission expressly allows co-sponsorship of clinical trials. Each co-sponsor takes full regulatory responsibility for the entire clinical trial unless the co-sponsors agree by contract to “split” the regulatory responsibilities among themselves. The rules do not address civil or criminal liability of co-sponsors.
- Obligation for sponsors to report to the Member States (through the EU portal) “serious” breaches to the Regulation or the protocol within seven days of acquiring the knowledge.
- Revised rules on manufacturing and importation of IMPs.
- Revised rules on labelling of IMPs (detailed in an annex).
- Ban on gene therapy clinical trials that result in modifications to the subject’s germ line genetic identity.

What is missing? — The Regulation does not address specific topics, in particular the following:

- *No centralized authorization procedure* by the European Medicines Agency or another EU authority. The industry favored a centralized procedure, but the Commission anticipated a strong opposition by Member States and opted for a coordinated procedure instead.
- *No specific rules for non-commercial trials* except for reduced application fees and waivers of inspection fees.
- *No specific rules for personalized medicines.* The Regulation is a missed opportunity to address the issues raised by a parallel / common testing of a medicinal product and a companion diagnostic.

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