Central and Eastern European (CEE) Countries Prepare for the Clinical Trial Regulation

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Just like their counterparts in Western Europe, industry, regulatory, and other stakeholders in Central and Eastern European (CEE) Countries are preparing for implementation of the new EU Clinical Trials Regulation (536/2014) that will replace the current Directive 2001/20/EC (the legal framework for clinical trials in the EU since 2001) as soon as the EU clinical trials portal and database are functionally validated by an independent audit.

In October 2019, DIA EMEA presented in Bucharest (Romania) the first in a planned series of *Clinical Trials Information Day* conferences to help these CEE Countries prepare to implement the new Clinical Trials Regulation (CTR). This conference brought together representatives of regulatory authorities and ethics committees from Austria, Bulgaria, Italy, Poland, Romania, and Slovakia, and also featured Massimiliano Sara, Scientific Secretary of the Clinical Trial Facilitation Group (CTFG) and Camelia Mihaescu from the EMA.

European Developments: We've Come So Far, But Still Far To Go

Although progress made to date is a great achievement, providing sponsors and authorities with simultaneous access to clinical trial documentation remains the greatest challenge. In response, the EMA is currently developing a Clinical Trials Information System (CTIS) for the entire EU. All stakeholders—pharmaceutical companies, CROs, investigators, academia, patients and their advocates, and national/local authorities—eagerly await and anticipate this new "user-friendly" working tool that will help to electronically establish the multiple layers of users required to perform centralized submissions and coordinated reviews between EU Member States.

As soon as the EMA electronic portal goes live (most probably in early 2021, per current assumptions), implementing the new CTR will begin with an opening three-year transition period. Submitting a clinical trial application will be possible under either the Directive or the Regulation in the first year of this transition period; during the last phase of this transition period, sponsors will be urged to submit (transfer) all ongoing studies under the new requirements.

The new CTR also introduces a more formal collaboration between Competent Authorities and the Ethics Committees toward the aim of reaching a single decision, as well as a simplified authorization procedure for low-risk clinical trials (e.g., for previously authorized medicinal products) to hasten the commencement of such trials in Europe, among other important changes.

CTFG representative Sara, who serves in the Italian Medicines Agency (AIFA), illustrated the key changes and challenges associated with moving from the Directive to the Regulation, including the differences in required documentation and review timelines between different parts of this process. Representing the EMA Committees and Inspections Department, Mihaescu dwelled on two major topics: An overview of risk-based approaches in clinical trials per the latest concepts of the ICH E6 (R2) GCP guideline, and recommendations by the

clinical trials expert group for implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use.

But the most anticipated topic of the day was the current state of CTIS development, which seems to have entered a more agile stage this year due to the involvement of a new IT vendor and rethinking of the system preparedness approach for the audit, go-live, and post-go-live steps.

Member State Implementation Status: Two Sides, One Coin

Among the countries participating in this conference, Austria, Bulgaria, and the Czech Republic have taken the most significant steps forward in terms of dedicated task forces, defining the main scientific and administrative roles between parties, and reorganization of the Ethics Committees according to the Regulation.

Italy, Poland, Romania, and Slovakia are currently in an incipient stage of implementation because the Member States' relevant decision makers have not yet agreed upon new local guidelines and organizations. This conference was therefore the perfect opportunity for these local parties to collaboratively discuss the main guidelines for future development in a neutral and professional environment.

Patient-Centered Future Approach

There are many tasks that a Member State must undertake in preparing for implementation of the CTR, including development of their local legislation, reorganization of Ethics Committees if appropriate, clear agreement on CTIS roles and permissions, resource allocation and training, and appropriately transparent communication at all levels.

But the most critical activities for an EU Member State to conduct in preparation for the implementation of the CTR are those that will define the most competitive countries in terms of the number of clinical trials designed to provide patient access to innovative treatments under the new CTR in the near future. Therefore, it is widely expected that that the relevant decision makers in each Member State (Ministry of Health, Ministry of Research, Competent Authorities, Ethics Committees, etc.) will understand the importance of aligning regulatory frameworks and defining the most effective ways of working together at both the local and European levels.

Increasing the attractiveness of Europe among the main players in global clinical trials, the overall purpose of the new CTR, will only be achieved by regulators, sponsors, academia, and investigators engaging in prompt and correct application of its new changes. Its new requirement to **release study results to the public in layperson language** will also help create a more transparent research environment to the benefit of patients in the EU.