WEBINAR SUMMARY

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Pink Sheet
Informa Pharma Intelligence

EU Clinical Trial Regulation 2022 – Impact on Regulatory, Labeling & QP

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KEY TAKEAWAYS

- Current EU legislation is ill-conceived as it focuses on desired results without spelling out required steps and implementation timelines.
- The EU Clinical Trial Regulation introduces changes to terminology for medicinal products and import licenses.
- The most debated aspects of the Clinical Trial Regulation are its new labeling and import requirements and their impact on supply chains.
- Brexit will have differential impact on the adoption of the Clinical Trial Regulation in the UK and Northern Ireland.

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OVERVIEW

The conduct of clinical trials in the EU under existing legislation suffers from disharmonized interpretation and wide variation in execution across member states. This has led to excessive administrative and regulatory burden, costs and delays—and ultimately a significant drop in the number of trials conducted in the region.

To remedy this situation, in 2014 the European Commission approved a new EU Clinical Trial Regulation intended to simplify clinical trials administration and create a more welcoming climate for pharmaceutical companies that operate in Europe. The regulation, which is legally binding and unifies regulatory, labeling, and Qualified Person (QP) requirements, is set to come into force early next year. In order to make the most of it and successfully complete clinical trials in the EU market, it is essential for sponsors to understand the changes and requirements it introduces.

CONTEXT

A panel of Thermo Fisher Scientific experts discussed the implications of the new EU Clinical Trial Regulation for pharmaceutical companies and their research and commercial partners, things to watch out for, and the special case of Great Britain and Northern Ireland.

KEY TAKEAWAYS

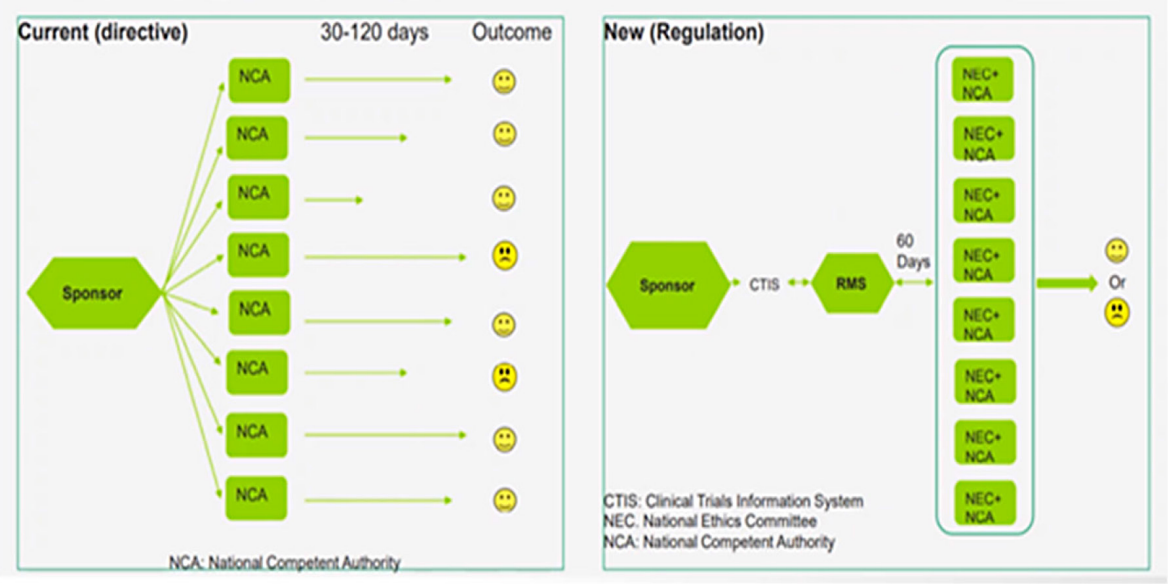
Current EU legislation is ill-conceived as it focuses on desired results without spelling out required steps and implementation timelines.

Currently, clinical trials within the EU are governed by a directive (Directive 2001/20/EC) that dates back 20 years and is considered by many pharmaceutical companies, researchers, and other stakeholders to be ineffective. By definition, EU directives indicate results that must be achieved, but allow member states to decide how to transpose them into national law; as a consequence, each member state has leeway to interpret the directive and enact its own laws independently. In the case of clinical trials, which often run concomitantly in several countries and can benefit from having the same criteria applied across sites, such diversity ends up being counterproductive.

A regulation, on the other hand, is a binding legislative act, which enters into force on a set date and is directly translated into national law, essentially formulating one set of rules for all countries to follow. By centralizing some of the most critical elements of clinical trials, such as application, approval, labeling, and import licenses, the EU Clinical Trial Regulation (EU No 536/2014) aims to achieve such unison. It is set to come into force on January 31, 2022.

> The Clinical Trial Regulation was passed for the express purpose of simplifying clinical trial administration in the EU. Back in its infancy, clinical trials were reducing in number in the EU partially due to the bureaucracy of the setup, which led to enormous variation in their execution and expectations across the different member states, and partially because of the decentralized nature of the application process. Under the new regulation, this process will be centrally authorized.
>
> *Harry Berlanga, Thermo Fisher Scientific*

Figure 1: Assessment procedure timelines under Directive 2001/20/EC and EU Clinical Trial Regulation 536/2014



To summarize, the upcoming regulation will streamline the application procedure for clinical trials via a single-entry point, make available an electronic database for all clinical trial controls, require a single authorization procedure, and simplify reporting requirements. It will have a transition period lasting 12 months for switching the clinical trial submissions format from the directive to the regulation and three years for clinical manufacturers to adapt their submissions and therefore packaging, labeling, and distribution processes.

The EU Clinical Trial Regulation introduces changes to terminology for medicinal products and import licenses.

Under the new regulation, investigational medicinal products (IMPs) and non-investigational medicinal products (nIMPS) used in clinical trials will acquire a new status. Instead of being referred to as *licensed* or *unlicensed*, as they have been to date in relation to their provenance (EU sourced and non-EU sourced, respectively), going forward they will be designated as either *authorized* or *unauthorized*. This change in terminology corresponds with the intent behind their use rather than with their origin: whether they are going to be running in a clinical trial.

Further, once the new legislation goes into effect, nIMPs will be termed *auxiliary medicinal products* (AMPs). Again, as with the previous shift in terminology, the new nomenclature captures more accurately the intent behind their use: to aid in resolving medical complications that may arise while testing an IMP in a clinical trial (rescue medication).

With respect to import licenses, they remain largely unchanged except for a UK-only scenario:

- **IMPs always require only a manufacturer's import authorization (MIA).** There are no special import requirements, regardless of whether the IMP is authorized or unauthorized.
- **AMPs require different licenses depending on their destination.** These are a wholesale dealer's authorization (WDA) if the AMP is authorized, a manufacturer's specials license (MS) if it is unauthorized for import in the UK only, and a MIA if unauthorized for import in EU member states.

The most debated aspects of the Clinical Trial Regulation are its new labeling and import requirements and their impact on supply chains.

Despite its aim to simplify the administrative burden surrounding clinical trials, the regulation has raised concerns about its new labeling requirements, which focus heavily on the 'period of use' indication. This indication, which refers to the expiry date of an IMP or AMP, must be placed on the product's immediate or primary packaging, as well as on its secondary packaging. The challenges this requirement creates for manufacturers include concerns about:

- **Rework costs.** Those include the costs of producing additional labels and associated project management and cabin fees, which are amplified in the case of kits with multiple primary containers.
- **The appearance of tampering.** Complying with the requirement in many cases will imply breaking the tamper seals of the secondary packaging (e.g., a box containing a vial of medication).
- **Site capabilities.** Since these labeling activities need to be done in a controlled GMP environment, there is the potential for some sites not being equipped to print, inspect, or even apply the labels.
- **Cold product labeling.** Medicinal products that must be maintained at deep cold temperatures at all times present additional challenges in terms of relabeling.
- **Waste and delays.** Because of the difficulties involved in labeling primary packaging, there is an increased risk of damaged and discarded products.

A poll among webinar attendees revealed that 83% were in favor of lobbying the European Commission for a more pragmatic approach to labeling due to these concerns. In the meantime, some potential solutions were identified.

Figure 2: Potential solutions to the 'period of use' labeling requirement

> Once the hurdle of the [updated] label requirements is overcome, sponsors may experience many of the benefits of the new regulation, including mandatory timelines on the review of applications and one final decision on the application's approval, which will represent the decision of all member states where the clinical trial is proposed to take place.
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> *Lindsey Zweig, Thermo Fisher Scientific*

Brexit will have differential impact on the adoption of the Clinical Trial Regulation in the UK and Northern Ireland.

Beyond expiry date labeling, the other big issue discussed in the context of the new EU regulation was Brexit. The political separation of United Kingdom from the EU has introduced complication in terms of strategy setting and managing supply chains between the UK and the EU.

Specifically, the EU Clinical Trial Regulation is not adopted by Great Britain, which as of January 2022 will regulate clinical trials under national Medicines for Human Use Regulations. However, because Northern Ireland is in regulatory alignment with the EU, the legislation will apply there. This divergence will likely give rise to different label and release strategies within the United Kingdom and clearly between Great Britain and the EU. Issues include:

- **Unidirectional import protocols between Great Britain and Northern Ireland.** A further complication is that importing IMPs or commercial medicines from Britain into Northern Ireland will require a manufacturing holding license or batch testing, respectively, and QP certification, but no such checks will be required in the opposite direction.
- **The QP Oversight rule, which aggravates the conduct of clinical trials in the UK once the EU Clinical Trial Regulation takes place.** Starting January 1, 2022, this rule will require British QPs to ensure that IMPs imported from the EU have been certified by a QP in the originating country.

> The UK QP oversight process is coming in the same month as the EU Clinical Trial Regulation. That's hitting us at the same time if you're running clinical trials across the UK and in the EU.
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> *Kevin Shea, Thermo Fisher Scientific*

ADDITIONAL INFO

Please click here to access the full webinar.

BIOGRAPHIES

Harry Berlanga BSc(Hons) MSc CBiol MSB

Senior Director, Quality, EMEA, Thermo Fisher Scientific

A chartered biologist, with a Masters in Pharmaceutical Sciences, Harry has over 20 years' industry experience in Steriles, Biologics & Solid Dose in both Commercial and Clinical Manufacturing and Packaging. Harry currently holds the position of Senior Director, Quality, EMEA, leading the EMEA Quality function across the Clinical Trials Division at Thermo Fisher Scientific. Based in Horsham, UK, Harry oversees 6 sites specializing in the Manufacture, Packaging, and Distribution of Investigational Medicinal Products (IMPs). Harry previously led Quality at the Thermo Fisher Scientific Horsham site for several years. Harry is an experienced Qualified Person (QP) for clinical and commercial products.

Kevin Shea

Senior Label Program Director, Thermo Fisher Scientific

Kevin currently serves as Senior Label Program Director and has been with Thermo Fisher Scientific since May 2004. His experience is in clinical supplies, with expertise in clinical labels, label translation, and regulatory services, that spans many years and includes roles in manufacturing and project management. With a bachelor's degree from Hobart College, Kevin likes to balance his work with quality family time with his wife and two children.

Lindsey Zweig

Senior Manager, Regulatory Affairs, Thermo Fisher Scientific

Ms. Lindsey Zweig is a senior-level Quality Assurance Manager with around 20 years of experience in the pharmaceutical and biotechnology industry. Her core skills include development and implementation of effective and robust quality management systems, hosting client and regulatory authority inspections, analysis, and reporting of quality metrics and trends. Lindsey works collaboratively with internal and external clients to ensure operational activities comply with company, client, and regulatory requirements. In her current role at Thermo Fisher Scientific as Senior Manager, Regulatory Affairs, Lindsey is responsible for ensuring compliance to emerging international regulations including the recently implemented medical device regulations as well as the upcoming EU Clinical Trial Regulation 2022.