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WHITEPAPER

EU Clinical Trial Regulation 2022: Understanding the impact on clinical research in Europe

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Executive summary

Eight years after its adoption, the EU Clinical Trial Regulation (CTR) 2022 has come into full application, radically altering the regulatory landscape for conducting clinical trials in EU member states and European Economic Area (EEA) countries.

The regulation is intended to streamline clinical trial application, review, and supervision while also improving process transparency. The backbone of the regulation is the Clinical Trials Information System (CTIS). The CTIS is a centralised portal and database that will allow drug sponsors to apply for trials in up to 30 EU/EEA countries using one online application. It will also support interactive collaboration among regulators from all the countries included in a submission. These features are expected to make authorisation and patient recruitment for multinational trials much easier.

As is often the case with regulatory legislation, the CTR is complex. Its multiple layers and transitional provisions will likely have far-reaching implications for in-process and planned clinical trials. Therefore, sponsors will need to be strategic with planning and implementation to avoid delays in clinical trial initiation.

This whitepaper provides insight into the key changes introduced by the regulation and guidance for managing anticipated challenges, focusing specifically on the following considerations:

- The impact of the new regulation on existing clinical trials
- The implications for good manufacturing practice (GMP) guidance and the Clinical Trial Application (CTA) process
- New labelling requirements, the challenges they may pose, and potential solutions
- The UK's approach to clinical trial regulation and the impact of the EU CTR changes on Qualified Person (QP) requirements and other legislation

The rollout of the EU CTR will extend over three years, including an initial one-year grace period during which sponsors can choose to submit applications via CTIS or through established systems. The sooner sponsors get past the initial learning curve and become comfortable with the platform, the greater the progress will be toward true harmonisation and promotion of clinical trial execution in Europe.

Introduction

Since 2004, the (EU) Clinical Trial Directive 2001/20/EC (EU-CTD) has governed the conduct of clinical trials in the EU. Perhaps recognising that directives do not carry the same weight as regulations, and certainly acknowledging the challenges with the implementation of the EU-CTD and subsequent decline in the number of clinical trials in the region, the EU adopted the EU Clinical Trial Regulation (EU CTR) in 2014. In response to variation in the execution of clinical trials, inconsistent expectations across the different member states, and the decentralised nature of the application process, the CTR aimed to improve the application process and increase transparency in clinical trials.

Beginning 31 January 2022, the CTIS was released into full application, providing a streamlined way for sponsors to apply for clinical trials in up to 30 EU/EEA countries in a single application.

The regulation is a binding legislative act and overrules national law, providing a single set of rules by which all member states must abide. Following eight years of validation efforts, the key component of the CTR—the Clinical Trials Information System, or CTIS—is now completed. Beginning 31 January 2022, the CTIS was released into full application, providing a streamlined way for sponsors to apply for clinical trials in up to 30 EU/EEA countries in a single application. This streamlined approach supports not only the application, but also the review and supervision of trials.

The EU CTR is accompanied by non-legislative, legally binding acts to supplement legislation. These include Delegated Regulation (EU) 2017/1569, which specifies principles of and guidelines for good manufacturing practices (GMPs) for Investigational Medicinal Products (IMPs) for human use and arranges for inspections. An implementing act (Implementing Regulation 2017/556) specifies how highly technical aspects of the legislation should be executed. The EU Commission published stipulating arrangements for good clinical practice inspection procedures pursuant to the new CTR.

Implementation timeline

The EU Commission established a three-year rollout for CTR implementation, as illustrated in Figure 1. The timeline includes a 12-month period in which sponsors may choose whether to submit new applications via previous processes or under the regulation via the CTIS.

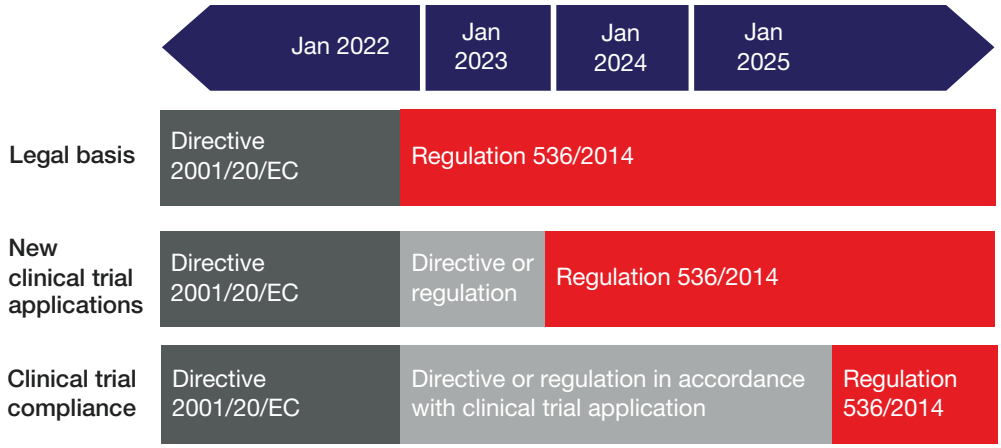

Figure 1. Timeline for the EU Clinical Trial Regulation

Impact on existing clinical trials

Existing trials have three years from the CTR effective date (1 Jan 2022) to achieve compliance with the new regulation. During this period of transition, clinical manufacturers, packaging facilities, and distributors can submit documents as per the directive or the regulation. Qualified Persons (QPs) must understand which studies are being run under the CTR to ensure compliance. This is especially important for clinical trial approvals and other considerations, such as labelling.

Key changes: What you need to know

The changes introduced by the CTR include several new requirements for documentation. Delegated Regulation (EU) 2017/1569 replaces the previous GMP, but there are minimal substantive changes outside of the terminology and definitions employed. One of the goals of the regulation was to more closely align principles for IMPs and commercial products, given that they are often produced at the same locations.[1] On its website, the EMA provides a Questions and Answers document to offer guidance on GMP. Sponsors with clinical trials in EU member states should consider regular review of this document to stay abreast of changes in industry thinking.

Changes in terminology

The CTR introduces several new terms and no longer uses some used in previous guidance documents. Under the new regulation, IMPs and non-IMPs (nIMPs) used in clinical trials will be designated as either authorised or unauthorised, rather than as licensed or unlicensed based, as they have been to date in relation to their origin (EU sourced and non-EU sourced, respectively). This change in terminology corresponds with the intent behind their use—specifically, whether they are going to be running in a clinical trial—versus their provenance.

Additionally, under the new legislation, nIMPs will be termed *Auxiliary Medicinal Products (AMPs)*—a change that is also intended to more accurately reflect the intent behind their use. For instance, some clinical trial protocols require the use of medicinal products such as concomitant or rescue/escape medication for preventive, diagnostic, or therapeutic reasons or to ensure that adequate medical care is provided for the patient.

Import license terminology remains unchanged but for the following UK-only exceptions:

- **IMPs always require only a Manufacturing and Importation Authorisation (MIA)**. There are no special import requirements, regardless of whether the IMP is authorised or unauthorised.
- **AMPs require different licenses depending on their destination**. These include a wholesale dealer's authorisation (WDA) if the AMP is authorised, a manufacturing specials (MS) license if it is unauthorised for import in the UK only, and an MIA if it is unauthorised for import in EU member states.

The Clinical Trial Application process

The CTA process has been streamlined under the new legislation. Previously, sponsors were required to complete separate applications to each member state in which they planned to conduct their study, with each member state providing rejections or questions within 30 to 120 days of application. The CTR provides a centrally authorised application process via the CTIS and a database for all clinical trials conducted in the EEA. The application requires a single set of documents to be prepared and submitted for Annex or application, and all questions are submitted at the same time with the goal of providing a single overarching approval or rejection at the end of the process. The CTR also provides defined deadlines, involvement of an ethics committee in the assessment of clinical trials, simplified reporting procedures, and enhanced transparency for the sharing of clinical trial data.

Rethinking labelling requirements

Perhaps the greatest challenge for sponsors with respect to the CTR stems from Annex VI and centers on labelling requirements for inner packaging. Previous EU GMPs allowed for the expiry date to be omitted on the immediate packaging. Under the CTR, inner packaging of IMPs supplied must include expiry dates. Commercial comparators require further labelling, as well. These requirements pose many potential challenges that were likely unintended and unforeseen during the development of the CTR.

- **The cost of rework** for labelling IMPs is likely to be significant, particularly in IMPs with multiple primary containers (e.g., kits), each requiring the addition of an expiry date. Sponsors should be aware of additional costs relating to purchasing labels, releasing supplies with the new expiry date, and associated project management fees.
- **Breaking the tamper seal** to add expiry dates could lead to damaged packaging or a perception that the product has, in fact, been tampered with, raising quality concerns.

- **Depot and site capabilities** may pose challenges to reaching compliance with labelling requirements. Capabilities should include printing, inspecting, and applying labels in a controlled GMP environment, and ultimately releasing the product. Individual sites may be unwilling to conduct these extra measures.
- **Conditions of release** should be considered. A QP must have some oversight of any relabelling activities, particularly those involving expiry dates.
- **Label space** must be sufficient for the new expiry dates to be added. This may be particularly challenging with smaller containers (e.g., vials, biosyringes) where much information must be conveyed in an already limited space. Legibility and font size may also pose challenges for patient safety.
- **Deep cold product labelling** could pose unique challenges. Some products have only a limited window wherein they may be taken out of the controlled environment. Additionally, there may be challenges with labels adhering in deep cold temperatures.
- **Throughout the entire labelling process**, there is the potential for waste and delays. The risk of damaged and discarded products will increase, and additional packaging time may extend timelines. Proper planning is critical to eliminate the risk of patients not receiving a drug on time.
- **Errors associated with relabelling** could lead to unintentional unblinding if labels are not consistently applied across all the packaged supplies. It has been suggested that the complications associated with the requirement for inner expiry dates far outweigh the risk of omitting the expiry from inner packaging.[2] [EFPIA 2021]

Minimising the labelling disruption

There is no single best solution to the challenges the labelling requirements pose. The best approaches will need to be determined after careful consideration by the study team (including quality colleagues), vendors, and ideally, a trusted and experienced pharma services partner. Some possible solutions include:

- **Labelling separate supplies based on country/region and requirements for expiry dates.** This introduces new complexities but could represent a better option than disrupting the entire supply chain.
- **Keeping the product at the central packaging site until the last possible moment prior to distribution, and printing just-in-time (JIT) labels.** Additional printing, packaging, and release situations should be factored in here. This solution is ideal for small volumes or quick turnaround situations but may not be sustainable for all studies.
- **Developing unique packaging designs**. For example, feeding primary labels out through the carton would create an opportunity to have the initial expiry date listed and leave space for multiple subsequent expiry dates if needed. This approach requires thoughtful (and forward-thinking) design of the label itself, as well as a method for keeping the labels in place to prevent them from being damaged during shipping. In addition to adding the new expiry dates, the old expiry dates must be crossed out and the lot number repeated. The protocol number must be repeated as well.
- **Exploring innovative primary-only packaging models based on unique components (e.g., a molded vial holder).** This could act as the primary and secondary packaging, avoiding the need to kit or carton the supply itself.
- **Over-labelling and relabelling at the site/depot**. This is becoming a solution of great interest among sponsors. The site/depot must have capabilities for printing, inspecting, and releasing the supplies and ensuring that they are processed in the controlled environment.
- **Pushing for better stability data up front.** This would involve communicating with the study team that packaging cannot be completed until better stability data are provided for the products. Alternatively, companies could package at-risk using the latest possible expiry dates.
- **Implementing eLabel solutions.** This has been discussed for many years, but regulatory pushback has prevented it from becoming a widely accepted model. Now may be the time for stakeholders to move these ideas forward within the industry and regulatory spaces.

Stringent compliance with the CTR is required to ensure that studies can be implemented safely for patients, sites, and sponsor companies.

In all cases, sponsors should consider any effects these approaches may have on how the study itself is executed, including the budget and timeline. Different studies may require different solutions. It is highly recommended that sponsors not look for workarounds to the regulation. Stringent compliance with the CTR is required to ensure that studies can be implemented safely for patients, sites, and sponsor companies. Any new approaches should be reviewed by multiple stakeholders to ensure that they are aligned with all requirements.

Industry response to labelling changes

The European Federation of Pharmaceutical Industries and Associations (EFPIA), which has called for a reversal of the requirement for expiry dates on primary packaging, published a whitepaper describing an interim, risk assessment–based approach for expiry date labelling of IMP immediate packaging.[3] The risk assessment variables include packaging configuration, label type, blinding factors, and labelling site. Though not approved at this time, one suggested interim solution involves labelling the inner packaging with the initial expiry date and including a statement referencing the outer packaging which will have the most current expiry date.

TransCelerate, a nonprofit organisation working across the research and development community to help improve the delivery of medicines, proposed an eLabel which would contain basic information and a barcode which could be scanned to obtain full information. At this time, the expiry date is required to be on the packaging, and an eLabel would not fulfill that requirement. TransCelerate provides an implementation toolkit on its website for facilitating the use of an eLabel approach and engaging with the Health Authority.[4]

The International Society of Pharmaceutical Engineering (ISPE) has published commentary on the concerns and potential solutions to the labelling requirements. The authors discuss eLabels, propose several operational solutions, and raise the issue of environmental impact associated with wastage.[5]

Notably, many large pharmaceutical companies have announced their support for the regulation and their commitment to the transparency of clinical trials promoted through adherence to its components.

In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) has issued a Consultation for Clinical Trials & Clinical Research which states that the presence of expiry on the primary pack will likely not be part of the UK approach to clinical trial labelling. Instead, the focus of labelling of medicines will be based on risk. For example, ultra-low–temperature medicines may not require an expiry date because doing so could expose the medicine to undue risk to quality.

The CTR and the UK regulatory landscape

The political separation of Great Britain from the EU has complicated the strategic planning of clinical trials and the management of supply chains between the UK and the EU, because Great Britain has not adopted the EU CTR. Clinical trials are rarely performed only in the UK, and as such, an understanding of the similarities, differences, and interactions of the UK's Medicines for Human Use Regulations and the EU's CTR requirements is crucial. Importantly, because the UK is not governed by the CTR, the UK will have separate submissions and labelling requirements. With regard to serialisation codes and new supply chains for comparator supply, all centralised finished products will need to be decommissioned upon export and entry into the clinical supply chain. Where this takes place, and its impact on CTR compliance labelling, are two of many factors that must be considered when planning supply chains involving the UK and EU. It is yet to be determined whether these complications will result in fewer clinical trials being conducted in the UK.

QP oversight is another area requiring consideration. UK QPs still exist and have the same duties as before. Thus all EU QP-certified material going into Great Britain requires UK QP oversight, adding more complexity to the supply chain. Incidentally, new legislation surrounding UK QP processes came into effect in January 2022, the same month as the CTR. The 'safety features' elements of the EU Falsified Medicines Directive (FMD, 2011/62/EU) and Delegated Regulation (2016/161) ceased to have effect in Great Britain from 31 December 2020, and end users in Great Britain are disconnected automatically from the UK National Medicines Verification System.

Progressing clinical trials across the regions requires a strong understanding of how to navigate the complexities of multiple governing documents and the changing environment.

Northern Ireland: Who can provide what to whom?

Further complicating the post-Brexit landscape are the regulatory differences between the UK and Northern Ireland (NI). Sponsors using investigator sites in NI should be aware that the region continues to be aligned with the EU for regulatory purposes. IMP supply to NI from Great Britain requires full importation via an MIA holding site and QP certification prior to supplying the product to the investigator site. Any commercial medicines from Great Britain will also require full batch testing. Conversely, supply from NI to Great Britain will not be required to be imported. The EU/EEA can continue to supply NI due to the NI protocol, which provides continued compliance to EU laws. Labelling in NI must follow the requirements of the CTR.

QPs in NI will still be recognised by the EU, and NI will continue to follow EU rules as part of the customs union. Under the terms of the Northern Ireland Protocol, part of the UK's Withdrawal Agreement with the EU, the EU Falsified Medicines Directive will still apply in NI. End users should ensure that they are registered with SecurMed UK.

Conclusion

The CTR introduces several changes to the clinical trial application and implementation process, and additional guidance is expected. Sponsors should take action now to review their clinical trial portfolios to determine the impact of the regulation on processes, budgets, and timelines. Particular consideration should be given to potential delays associated with initial rollout of the information system.[6]

One of the greatest challenges will be managing changes in labelling requirements, but many potential strategies exist to mitigate associated risks and costs. Once those challenges are addressed, sponsors should begin realising the benefits of the new regulation, which include a streamlined, single application portal; mandatory timelines for review; greater transparency; and a single decision on approval across all trial locations.

For pharmaceutical companies based both in Europe and elsewhere, it is critical to understand the EU GMP and legislative requirements and the roles and responsibilities companies will have as sponsors under the new legislation. It is also important to understand what options and routes to compliance exist, including leveraging the extensive labelling, regulatory, and QP expertise that industry leaders provide.

Key advice for managing the CTR transition

To reap the most benefits from the streamlined regulatory processes that the CTR and CTIS will bring, sponsors and other stakeholders should develop a robust transition strategy that suits their specific needs and meets the requirements of the transition period. Following is some key advice for moving forward.

- **Devise a system to differentiate the period of use** and whether the product is subject to the CTR or the previous directive.
- **Plan ahead**, particularly around labelling. Start talking about it now.
- **Check QP release strategies** to be sure they are able to adapt to changing supply chains.
- **Spread the word about words**. Make sure your teams, vendors, and partners understand the new terminology being used in the CTR. Include glossaries in your documentation (e.g., Standard Operating Procedures and Quality Technical Agreements).
- **Don't forget about Northern Ireland**. NI is aligned with the regulatory requirements of the EU and is expected to be compliant with the CTR.

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About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics, and commercial manufacturing to customers through our Patheon brand. With more than 65 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, cell therapy manufacturing, formulation, clinical trials solutions, logistics services, and commercial manufacturing and packaging. We give pharma and biotech companies of all sizes instant access to a global network of facilities and technical experts across the Americas, Europe, Asia, and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. Our Quick to Clinic™ solution is designed to accelerate the journey from DNA to INA/IMPD and may help biopharma companies reach Phase I/First-in-Human trials and file for Investigational New Drug (IND) review in as little as 13 months from transfection. As a leading pharma services provider, we deliver unrivaled quality, reliability, and compliance. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.

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A chartered biologist with a master's degree in pharmaceutical sciences, Harry has more than 20 years of industry experience in steriles, biologics, and solid dose in both commercial and clinical manufacturing and packaging. Harry leads the EMEA Quality function across clinical sites at Thermo Fisher Scientific. Based in Horsham, UK, Harry oversees six sites specialising in the manufacture, packaging, and distribution of Investigational Medicinal Products (IMPs). Harry previously led Quality at the Horsham site for several years. Harry is an experienced Qualified Person (QP) for clinical and commercial products.

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Kevin 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—and includes roles in manufacturing and project management. Kevin earned a bachelor's degree from Hobart College. He likes to balance his work with quality family time with his wife and two children.

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Lindsey has 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, and analysis and reporting of quality metrics and trends. Lindsey works collaboratively with internal and external clients to ensure that operational activities comply with company, client, and regulatory requirements. In her current role, 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.

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