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Water Cooler Chat

Navigating the New EU Clinical Trial Regulation

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PCI Clinical Trial Services hosts a bi-weekly "Virtual Water Cooler Chat" series, where our subject matter experts host informal discussions around a number of clinical supply "hot topics."

Navigating the New EU Clinical Trial Regulation

A panel of PCI's industry experts recently discussed the changes, benefits and potential challenges that the new EU Clinical Trial Regulation No 536/2014 will bring when it is made effective; the team also reviewed how the CTR will differ from the current EU Clinical Trials Directive 2001/20/EC which has been the principal legal directive in place since 2004, governing how clinical trials are conducted in the EU.

The European Union Clinical Trial Regulation 536/2014 (CTR) will be coming into full effect in 2022, and will significantly change how companies conduct their trials. The CTR will replace the Clinical Trial Directive (2001/20/EC), which has been in effect since 2004.

The directive was created to encourage trial sponsors to conduct their studies in the European Union (EU); however, it was left to EU member states to implement it. This created a fragmented system, in which each state had its own clinical trial application process.

By definition, a directive is a legislative act that sets goals all EU countries must achieve, however, it is up to member states to write the laws that achieve these goals. By contrast, a regulation is a binding legislative act, which is applied across the EU.

In other words, the CTR is a more forceful application of the concepts initially outlined in the directive and should streamline the EU's regulatory apparatus.

The CTR was first published in June 2014, but was held back pending development and validation of the Clinical Trial Information System (CTIS), the central portal and database, which is critical to CTR operation and implementation. The application of the CTR should begin in July 2021, with the CTIS going live on January 31, 2022.

The introduction of the new regulation brings a number of key changes that will affect how trial sponsors manage clinical trials in the EU. Here's a quick summary and additional resources to help organizations and sponsors get up to speed.

THE BEAUTY OF CENTRALIZATION

One of the CTR's most obvious advantages is that it centralizes the application process, removing national variations and creating a single EU-wide portal.

This is no small benefit. Consider running a trial under the current directive in Belgium, France, Poland, Hungary and Spain. A company would have to file five separate clinical trial applications – an administrative nightmare. The cost of conducting translations for each separate country alone can be quite onerous.

Currently process timing by country can also vary. One nation may have extensive questions, delaying patient recruitment and trial start dates. Some countries might request protocol or Investigational Medicinal Product Dossier (IMPD) changes, meaning different versions could be registered in each country. Aside from the administrative and cost burdens, this also adds compliance risks, as sponsors must fight to maintain correct submissions in each member nation.

By contrast, the NEW CTR's clinical trial portal will create one single application process. The application's evaluation will be coordinated by a national authority, the reporting member state (RMS), which will be designated in the sponsor's proposal or agreed upon by the EU states in the application.

The streamlined application process has been redesigned to eliminate duplication, ensure trials can be initiated at the same time in each member state and create a single set of clinical trial documents across all member states, eliminating regulatory variations.

TRANSPARENCY AND SAFETY

The CTIS is also intended to bring increased transparency to the process. Information in the CTIS will be in the public domain and sponsors must publish a final trial summary in lay language.

The final study report must be published within 12 months of trial completion. This could be challenging for sponsors, who will have to be extra diligent to finalize and post the report in time, particularly for complex phase 3 studies. On the safety side, the CTR allows protocols to note that not all adverse events and serious adverse events will be recorded and reported. For trials with more than one investigational medicinal product, a single safety report can be submitted in the EU Clinical Trial Portal and Database. Suspected unexpected serious adverse reactions will also be reported through the database rather than to each national authority.

The CTIS will have dedicated workspaces for sponsors and member states alongside the public domain. The EMA has published training notes to help sponsors prepare.

THE SUBMISSION PROCESS

Clinical trial applications are submitted through the CTIS portal to all relevant states. The sponsor nominates a RMS, which is confirmed within six days of submission. The application is then validated by the reporting state to determine if it is complete and valid. This process is normally completed within ten days of the initial submission, though a 15-day extension can be granted.

The application has two parts. Part one, assessed by the RMS, includes submission documents, such as cover letter, investigator brochure, GMP certificates, IMPD, scientific advice, examples of the labels and the application form. This process should take 45 days. If further information is required, the reporting state can issue an information request through the portal.

Part two is assessed by the ethics committees within each state in accordance with their national laws. This submission includes subject information, such as informed consent, Patient Information Leaflet (PIL), compensation arrangements, insurance and indemnities.

Each state submits an assessment report, with their conclusions, to the sponsor via the portal within 45 days of the validation day.

If the trial is for an advanced therapeutic medicinal product or biologic, the assessment period can be extended up to 50 days to consult with experts.

Ethics committees can request additional information, which can extend the assessment period by 31 days. Each state will notify the sponsor of its decision regarding part one and part two within five days of the part one reporting dates or within five days from the last day of the part two assessment, whichever comes later.

If a concerned state does not provide a decision within this timeframe, the part one assessment conclusion from the reporting state can be considered the decision – tacit approval.

The process is designed so that part one and part two can be assessed in parallel. However, in some situations, the sponsor company may choose to submit only part one. When this happens, part two must be submitted within two years of the part one reporting date. If this process is not completed, the part one application will lapse.

Sponsors can withdraw an application at any time up to the reporting date. However, if they do so, the entire application for all member states must be withdrawn.

AUXILIARY MEDICINAL PRODUCTS (AXMP & AMP)

The new CTR also clears up existing confusion around non-investigational medicinal products (NIMPs), which will now be called auxiliary medicinal products (AxMP). These are background treatments, such as rescue medications, challenge agents, etc.

AMPs are clearly defined in the CTR. Authorized AxMPs (aAxMPs) are licensed commercial medicinal products approved for use in the EU, while unauthorized AxMPs (uAxMPs) are not. If there are no authorized AxMPs available, sponsors can consider a non-EU product, which must be both specified and justified in the protocol. The CTR is quite specific that pricing (for example) cannot be a factor in choosing an uAxMP if there is an available EU-equivalent aAxMP.

EXPIRY DATE EXTENSION LABELING

One of the most contended changes within the new CTR is the Annex VI labeling requirements.

Previously, Interactive Response Technology (IRT) systems could control product expiry dates (thus allowing omission from the product labeling). However, Annex VI requires that expiry dates must be physically placed on both primary and secondary containers. Computerized systems, such as IRTs, can no longer be used to control these critical particulars.

Annex VI also brings a shelf life extension nuance in situations where new stability data is available and the expiry date needs amendment. Under the current directive, companies can apply a small label, which repeats the lot number and carries the new expiry date.
The new regulation instructs sponsors to include the protocol or trial reference number. This may prove challenging, especially for small ampoules/vials with limited space on clinical labels to apply an extension label. If there are multiple expiry date extensions, the new requirements could produce additional labeling challenges.

AUXILIARY MEDICINAL PRODUCTS (AXMP & AMP) LABELING

Companies that are centrally sourcing for a trial can apply for a reduced labeling strategy. However, even authorized AMPs must comply with local country regulations. For example, if a sponsor centrally procures a French approved pack and applies for a reduced labeling strategy, they may not be able to supply these packs to clinical sites in Italy.

As a result, there may be issues with authorities pushing back on reduced labeling. It is recommended that sponsors treat aAxMPs and uAxMPs similar to IMPs for labeling purposes.

Because this is a regulation rather than a directive, there is going to be little flexibility when it comes to labeling.

QP CONSIDERATIONS

One element that has not changed under the CTR is the often overlooked two-step release requirement: Batch certification by the qualified person (QP) and regulatory release by the clinical trial sponsor. Both steps should be recorded and retained in the clinical trial master file, which is held by, or on behalf of, the sponsor.

The compliance statement on QP certificates will, however, change. Companies may no longer need to QP-certify for individually-approved countries because, in the spirit of the CTR, it becomes one single approval.

QP requirements are noted in multiple documents: the CTR; the IMP GMP directive that spins out from the CTR; the GMP guidelines that add heft to the directive; and the EMA/202679/2018 guideline on sponsor responsibilities for the handling and shipping of IMPs for human use in accordance with GCP and GMP.

The GMP guidelines more fully outline QP responsibilities and partially align with existing Annex 13 and Annex 16 responsibilities. The guidelines discuss multiple QP involvement and the need for written agreements in these cases. In addition, should the quality agreement with the sponsor direct it, the QP can take responsibility for both the batch certification and regulatory release.

POST-BREXIT CONSIDERATIONS

It's likely the UK will eventually incorporate the CTR into its national law, though there may be some divergence as the Medicines and Healthcare products Regulatory Agency (MHRA) implements additional local regulations. However, as the UK is no longer an EU member state, any application to conduct a clinical trial within the UK has to be done through the MHRA portal.

FINAL THOUGHTS

As always, the most significant challenges come during implementation and more questions will crop up as the CTR is deployed. PCI will be monitoring this rollout closely and will continue to provide insights into how the regulation is impacting clinical trials within the EU.

Please let us know if we can help you answer any of these potentially complex regulatory questions. Here are some additional resources to help your organization navigate the CTR: *https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation#progress-updates-section*

ABOUT OUR SPEAKERS

Tristram Evans

VP Global Quality, Clinical Services.

Tris leads the Clinical Quality teams across PCI. In Tris' 6 years with PCI, he has been successful leading and building a well-recognized Global Clinical Quality team, ensuring harmonization of Clinical Quality standards globally. Tris has worked in the pharma industry within various Quality roles for 20 years with experience in commercial, investigational and unlicensed medicine manufacturing, release and supply. Tris is an EU Qualified Person (QP), qualifying in 2011 and is named on PCI commercial and clinical license in the UK and Ireland with experience in multiple product dosage forms.

Lisa Spence

Director, Clinical Supply Chain for the International Region at PCI Pharma Services.

Lisa joined PCI in March 2019 and has over 25 years clinical supply experience within in the pharmaceutical industry which was gained whilst working at GSK, Merck Sharp & Dohme, Pfizer and MedImmune. Lisa has industry expertise in clinical supply manufacturing, packaging, labeling/distribution, clinical supply chain project/programme management, regulatory and clinical operations. Lisa also has a BSc. Hons. degree in Pharmaceutical Science, which she gained at Greenwich University in 1995.

Since joining PCI Lisa has created a new team of clinical supply managers that provide clinical supply management support for PCI's EU/ ROW customers.

Uday Pathapati

Senior Manager, Clinical Project Management - Clinical Services, PCI Pharma Services

Uday currently leads one of the Clinical Project Management teams at PCI Bridgend, responsible for training and mentoring Project Managers and Associate project managers to ensure they are providing the industry leading customer experience. Since joining PCI in 2011 Uday has worked for 10 years on clinical projects from early Phase I to Phase III with a key focus on management of Compassionate Use (CU), Named Patient Supply (NPP) and Early Access Programs (EAP) in the EU.

Dr Shawn Murtough

Qualified Person

Shawn Murtough is an EU Qualified Person. Having graduated with a doctorate in pharmaceutical microbiology, he has worked in various roles within the pharmaceutical industry for the last nineteen years. He has over ten years' experience working as a qualified person with both traditional small molecule drug products and novel therapies. In recent years he has specialised in cold chain logistics for clinical trials. This has entailed handling a wide range of product types including, cell therapies, viral vectors, monoclonal antibodies and vaccines.

*If you are interested in learning about PCI's **Water Cooler Chat** series where our experts answer questions in real-time, please visit us **here** to see the schedule and register for this complimentary series.*