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Science to Life

White Paper

# The Impact of the New EU Clinical Trial Regulation 536/2014 on CMC Activities

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Authored by: 2 Bridge

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## Introduction

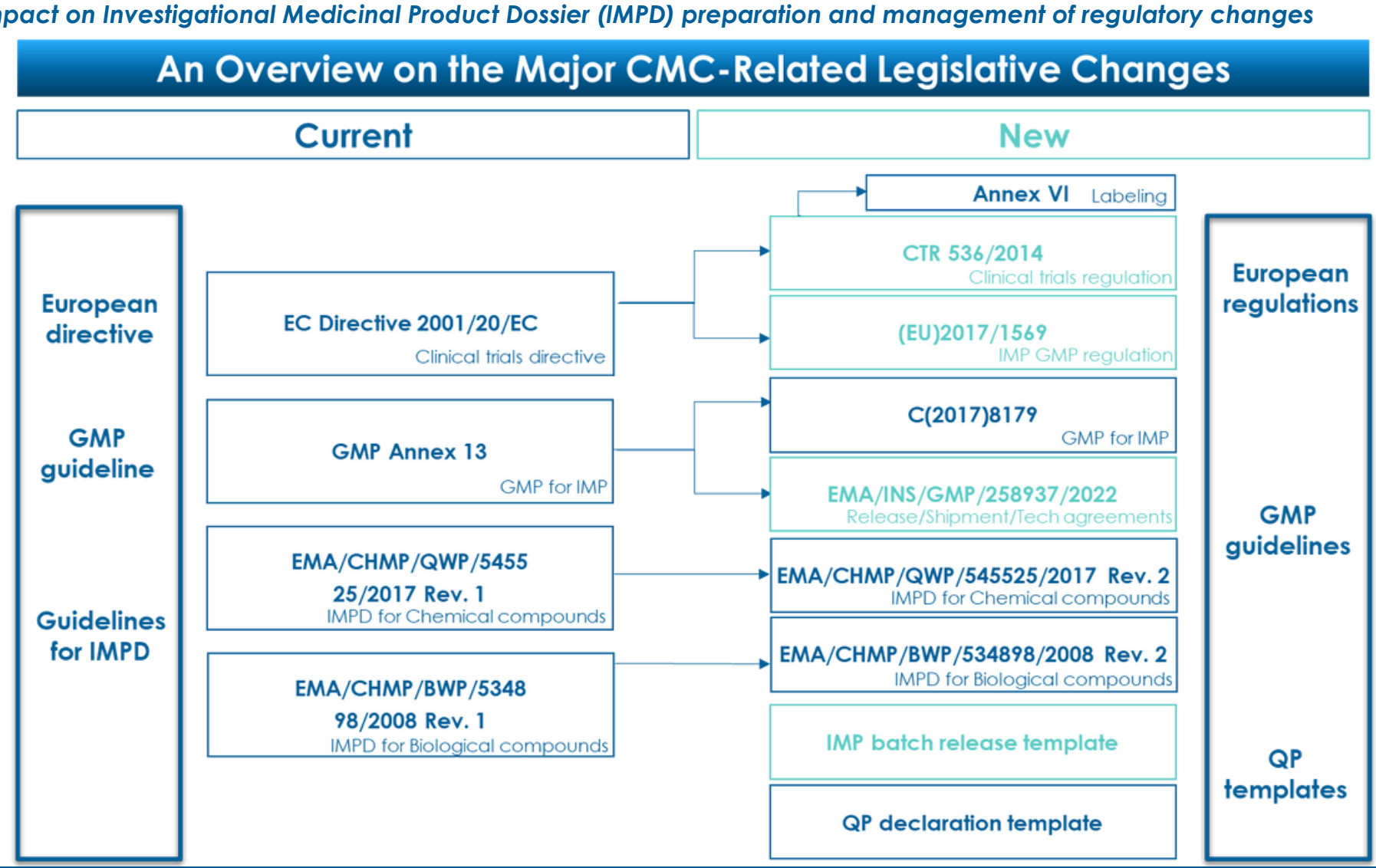
After many years of anticipation, the new Clinical Trial Regulation (CTR 536/2014) supplemented by (EU)2017/1569 which defines GMP requirements for Investigational Medicinal Products (IMPs) was finally implemented on 31 January 2022. This new CTR will replace the European Directive 2001/20/EC. The transition period where studies can be submitted under the directive or the regulation will end on 31 January 2023.

This new regulation will significantly impact how clinical studies are set up, submitted, and conducted within the EU/EEA.
At 2 Bridge, our Clinical Operations, CMC, and Regulatory and Quality experts have been evaluating this impact to ensure we can continue to deliver up-to-date advice to our clients.

***In this white paper, our CMC and Quality experts will discuss the impact of the CTR on our CMC activities including:***

- ***Impact on Quality aspects including the responsibilities of the Qualified Person (QP)***
- ***Impact on Clinical Supply set-up and management***
- ***Impact on Investigational Medicinal Product Dossier (IMPD) preparation and management of regulatory changes***

## An Overview on the Major CMC-Related Legislative Changes



## Quality and QP Responsibilities


Annex 13 of the EU GMP guidelines (Eudralex Volume 4) is being replaced by the Detailed Commission guideline on Good Manufacturing Practice (GMP) for Investigational Medicinal Products (IMPs), published on 17 December 2017.

Additionally, the EMA/INS/GMP/258937/2022 Guideline on the responsibilities of the sponsor with regards to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice is introduced.

In this section, we will discuss the most important changes and additions in this guideline as compared to Annex 13 and summarize the quality impact on the manufacture of IMPs.

The requirements of the documentation to be captured in the **Product Specification File (PSF)** are being expanded in the new guideline so existing processes are to be reviewed and updated.

A PSF is an important tool and requirement for every production site with QP release responsibilities to ensure full traceability of GMP activities from DS to released IMP. Some major changes are listed below:

- The requirement to ensure that the QP has access to all **clinical trial application approvals and amendments** in view of IMP release is new and will require adjustment to our current practices and interaction with QPs in an outsourced operating model.

- The PSF should be in place **at the start of the manufacturing** of the first IMP batch for a clinical trial and needs to be retained for **at least 5 years** after the end of the clinical trial. This may require changes to existing quality agreements with CMOs.

Another documentation-related update concerns the **order for IMPs**, defined by the guideline as the sponsor's request for processing and/or packaging of a certain number of units and/or their shipment. The manufacturer should retain the order as part of the batch documentation.

Although GMP requirements have always been in place for products in clinical development, it is noted that the new guideline puts a lot of emphasis on the need to prevent **cross-contamination**. Quality risk management is an important tool to monitor and prevent cross-contamination. The availability of adequate cleaning processes using appropriately qualified analytical methods is mandatory and need to be checked as part of batch certification by a QP. The ultimate goal hereby is to always protect the patient.

For companies working in an outsourced model, it is relevant to mark the guideline's emphasis on the need for **written agreements** (quality agreement and technical agreements) between the sponsor and the manufacturer(s) defining mutual roles and responsibilities.

## Clinical Supply: (RE)labelling and AxMP

Whereas Annex 13 to the EU GMP guidelines (Eudralex Volume 4) also describes the labelling requirements for IMPs, these are not covered by the Detailed Commission Guideline. Instead, labelling requirements are included in Annex VI to the CTR.

In general, the new requirements are more restrictive than those in Annex 13. The regulation instructs to add the **period of use** on both the immediate and the outer packaging.

In view of the complexity of this additional requirement and appeals by industry, an annex (Annex C(2022) 6240) was issued in September 2022 stating that for unauthorized investigational medicinal products where immediate and outer package remain together or with small immediate packaging, the period of use can be omitted on the immediate packaging.

Another novelty is the introduction of **Auxiliary Medicinal Products (AxMPs)** replacing Non-Investigational Medicinal Products (NIMPs).

**Definitions** are included for AxMPs.

- 'Auxiliary medicinal product' means a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product;
- Authorized auxiliary medicinal product' means a medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an auxiliary medicinal product;

The labelling requirements for unauthorized AxMP are **almost identical** to those for unauthorized IMP, including the new additional requirements listed in Annex VI of the CTR.

In the case of authorized AxMPs, **no additional labelling** is required if the authorized AxMPs commercial label is compliant with Title V of Directive 2001/83/EC.

## Regulatory CMC and CMC Development Strategy

An Investigational Medicinal Product dossier (IMPD) is a key document in every Clinical Trial Application (CTA). It summarizes the proposed control strategy of drug substances and drug products/placebos under clinical investigation.

Regulatory requirements generally become stricter as a product reaches later phases in product development. It is expected that additional controls are implemented and listed in the IMPD updates as a project moves from an early phase development to late-stage development.

**Updated versions of the regulatory guidelines** listing the requirements of chemical/biological and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials were implemented in January 2022.

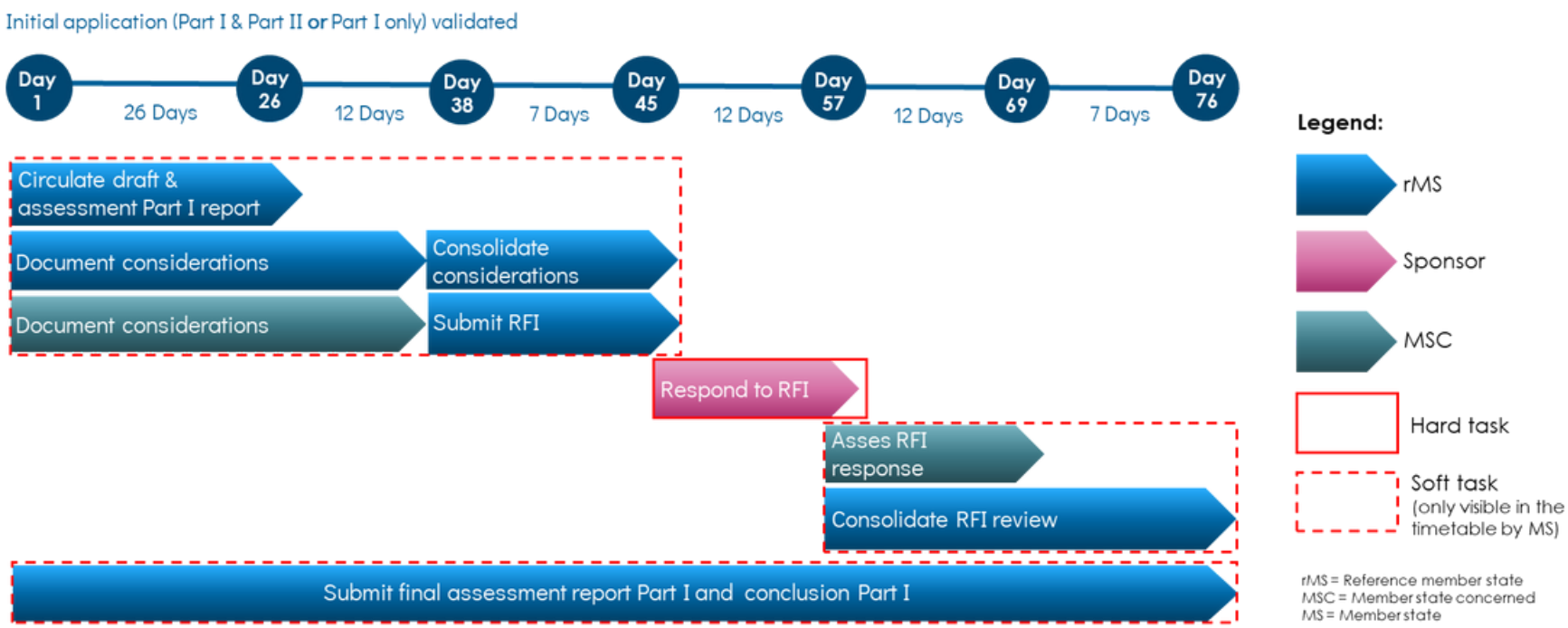
Although strictly speaking there are no new regulatory requirements in these updated versions, they do contain a lot of **additional clarifications** on several CMC topics. For instance, what is considered 'acceptable extrapolation of shelf life' based on available stability data is clearly listed in the new guideline versions.

A very useful addition to the regulatory guidelines is the new section on what is considered **a substantial versus a non-substantial amendment.** This will alleviate a lot of ambiguity on what changes require prior approval.

An important additional consideration, linked to regulatory submissions and CMC productions strategies, is of course the change from national CTA submissions to an harmonized EU CTA submission process and linked to this **very strict review timelines** for Sponsors to respond to regulatory questions. In the past there was a big diversity of how member states reviewed CTA submissions, so it is to be seen how this will evolve in the new harmonized process.

It is important to note that the **response time** in case of additional 'requests for information' (RFI) is **limited to 12 days**. Careful project planning and risk management will therefore be critical to anticipate potential regulatory questions prior to any CTA submission.

**New transparency rules** will also warrant careful consideration to avoid that proprietary information will be made available to the public.



## 2 Bridge Can Support

- AxMP sourcing, label development and strategy for IMP and AxMP
- Vendor qualification and oversight, quality agreements and EU QP certification
- Writing of the IMPD, filing strategy and Q&A's
- CMC development strategy and execution

In this paper, we discussed some notable changes in new CTR with impact on CMC. As the transition period will pass, the impact will become even more clear. With these operational challenges lying ahead, it is of major importance to be well prepared and if needed, our 2 Bridge consultants can offer their support.

This paper highlights that the new CTR will not only impact how clinical studies are submitted and managed, it will also significantly impact CMC activities and it is critical to prepare CMC teams for the transition to the CTR.

The 2 Bridge CMC team is there to support this transition!

## ABOUT US

The CMC team at 2 Bridge consists of experts in multiple domains of CMC, all passionate and motivated to contribute to the success of our Tiger Teams. We have junior and seasoned Product Development leads, Clinical Supply Management experts, CMC Regulatory experts, GMP/GxP Quality Experts, and European Qualified Persons in our team.

Our team has a joint track record in small molecules, large molecules, ATMP, and medical device development, covering the preclinical phase up to late-stage clinical development, registration, and post-approval life-cycle management.

Our CMC experts can oversee, manage or support the entire - or part of the - production supply chain from drug substance starting materials to delivery and administration of medication at the clinical site.

To ensure efficiency and consistency in our CMC activities, we have developed standardized methodologies, templates, and procedures for relevant oversight activities such as vendor selection, CMC project management, regulatory documentation, and quality management oversight procedures.

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## Meet the Authors

**Emilyne Blattes, PhD**
**R&D Leader, Scientific development & CMC**

Emilyne has experience in early-stage development, managing CTA-enabling trajectory of a new drug, including preclinical and CMC activities oversight and regulatory writing. She has insight in the new ATMP regulation and MD regulatory landscape. She has a global view on development as she combines the biological and medical sides of a project, as well as its technical CMC dimension.

***"We have a lot of experience in writing IMPDs for clinical trial applications and in the design and execution of CMC regulatory strategies."***

**Ilse Bollaerts, PhD**
**R&D Manager, CMC & Quality**

Ilse has gained experience in quality assurance and regulatory compliance in R&D and commercial GMP environments, where she supported CMC processes as quality representative. She is involved in the management of quality agreements, audits, deviations and change controls. She also participated in the development and continuous improvement of quality management systems.

***"A Sponsor PSF will help companies to retain good oversight on all GMP activities. We have a lot of experience with GMP vendor qualification and in general on GMP vendor oversight."***

**Geertje Van Beeck , MSc**
**Managing Partner & CQO**

Geertje has over 25 years of experience in a pharmaceutical development, registration and production for multiple early and late-stage development projects. As a CMC regulatory and development expert, she has authored multiple IND/IMPDs, MAA/NDA, post-approval variations, and response dossiers and has had direct interactions with regulatory authorities (FDA, EMEA).

***"Our team of CMC experts are accustomed to develop and execute CMC development strategies and to select and manage GMP vendors. With 2 QPs in our team, we have a strong quality mindset that combines GMP knowledge with regulatory compliance."***

**Charlotte Van Spaendonck, MSc**
**R&D Leader, CMC**

Charlotte is experienced as clinical trial supply manager with activities including distribution, packaging and labelling for early and late-stage development projects and early access programs. She also has experience in CMC support for drug product manufacturing and compatibility studies with products for SC and IV administration.

***"We are facing technical challenges for design and execution of packaging and labelling but a thorough regulation on use of AxMP was a real gap and the CTR will help us with the correct use in clinical studies."***