



TECHNICAL FACT SHEET

Insights from Belgium's Clinical Trials Regulation experience

Health Inspired, Quality Driven.

In pursuit of advancing medical research and drug development, we conducted a comprehensive analysis of the impact of the new Clinical Trials Regulation (CTR) on clinical trial submission timelines in Belgium.

This report provides a detailed examination of the specific factors that contribute to Belgium's reputation as a hub for early-phase trials.

About the Clinical Trials Regulation

Since its enactment on January 31, 2022, the CTR has proven to be a pivotal development, aiming to standardize and simplify clinical trial processes across EU member states.

Since January 31, 2023, all new trials are now mandated to be submitted in accordance with the CTR.

This regulatory milestone seeks to enhance patient protection, increase transparency, reduce administrative complexities and bolster the competitiveness of the EU's clinical research.

Belgium's leading role in early-phase trials

Belgium has established itself as a global front-runner in the field of early-phase clinical trials. The country currently holds second position in Europe for approved clinical studies per capita and for actively enrolling First-in-Human (FIH) studies (Deloitte, 2022; Pharma.

be, 2023). This achievement can be attributed to the exceptional quality of its centers, experienced investigators and streamlined regulatory authorities (Deloitte, 2022).

NR. 2

In terms of approved trials per capita

12,5%

Increase in FIH trials over the last 5 years



Belgium's expedited review process

Belgium has streamlined the validation review, completing it in just five days – half the time stipulated by the CTR.

Furthermore, Belgium is aiming for a swift review process for monocentric early-phase trials, capping them at an impressive 15 days, compared to the 50 days observed in other regions. This accelerated timeline will be facilitated by the open and transparent

collaboration with authorities, showcasing Belgium's leading role in advancing medical research and innovation.

Remarkably, Belgium achieves the cumulative maximum timeline from submission to approval in just 20 days (if there are no Requests for Information, or RFIs). This far surpasses Europe's set standard of 66 days.

Global comparison

When compared with other countries such as Germany, the Netherlands, the UK and the US, Belgium's CTR timelines showcased its sustained efficiency throughout the first year after CTR implementation.

For example, while Germany (BfArM) normally completes its initial reviews in 26 days (BfArM, 2024), Belgium (FAMHP) accomplishes the same reviews twice as fast. Specifically, when examining the data from the SGS Clinical Pharmacology Unit (CPU) in Belgium, the average time for reviewing submitted protocols is just 13 days.

Similarly, the Netherlands (CHDR) reports total approval and turnaround times of 43 days, as observed by our SGS CPU (CHDR, 2023). In comparison, the UK (MHRA) requires over 62 days on average for approval, without considering additional

time for questions or RFIs (MHRA, 2023).

The US is known for its swift reviews, which take somewhere between one and four weeks, making the Institutional Review Board process in some cases faster than in Belgium.

However, it's essential to have Investigational New Drug (IND) approval to enter the US market, which can take up to 30 days. In FIH trials specifically, Belgium outpaces the US in overall efficiency, as the Clinical Trial Information System (CTIS) application includes both regulatory and ethical reviews within a single application.

Despite minor increases in timelines with the introduction of the CTR, Belgium remains one of the fastest countries globally.

SGS clinical pharmacology unit data review

This report offers a detailed exploration of the operational insights derived from our experiences at the SGS CPU in Belgium. Leveraging real data aggregated over the span of one year following the

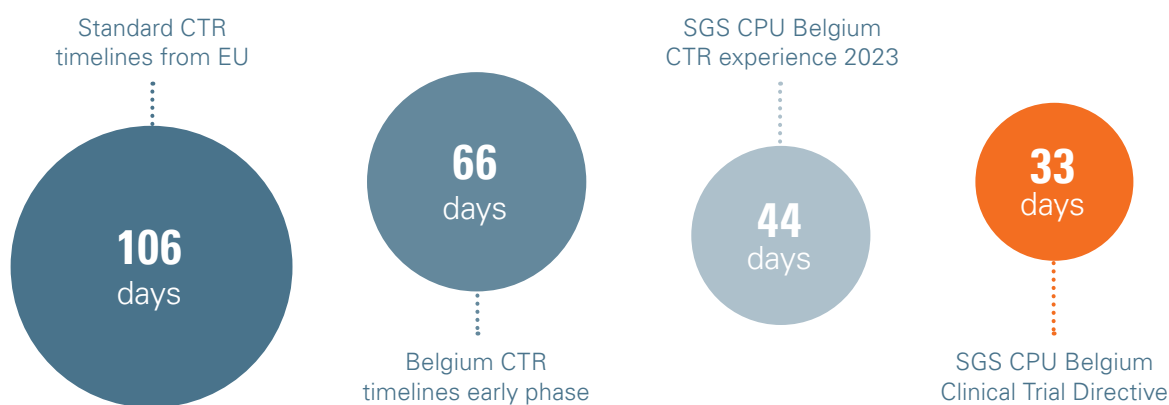
implementation of the CTR, we conducted a thorough analysis of submission-to-approval timelines for our early-phase trials.

Operational efficiency

Delving into the real data from the SGS CPU in Belgium, we observed that the actual timelines significantly outperformed the statutory maximum of 66 days.

The entire process, including trials with various complexities in design, needed just over 44 days on average.

Cumulative timeline from submission to approval



Examining the timeline breakdown

Notably, the validation phase – including any necessary revisions – averaged out at a remarkable 5 days. Approvals for trials without additional questions were achieved in a mere 1.6 days.

The initial review of the dossier was performed within 13 days on average for small molecules and most biological products. Extended timelines for assessment were required for monoclonal antibody trials.

Additionally, there was an extension in timelines for trials submitted before the end-of-year closing period of the regulatory agencies of 14 days.

However, the response to RFIs poses a potential area for improvement, with sponsors taking an average of 9 days to provide their answers and clarifications. Responding to these RFIs in a swift and efficient way is a key leverage point for potential efficiency improvements in the process.

Experience in FIH studies and regulatory review plays a pivotal role in reducing authority questions and shortening timelines. This impact is particularly significant when all questions are anticipated, eliminating the need for RFIs. As a result, choosing a knowledgeable facility is imperative for optimizing efficiency.

74%

Faster timelines for initial review with SGS vs. Standard EU CTR timelines

41%

Faster submission-to-approval timelines with SGS vs. Standard EU

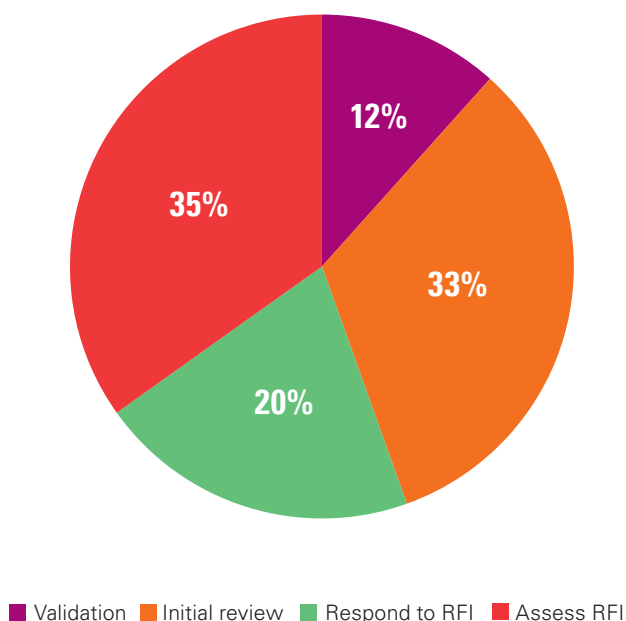
Comparison with the Clinical Trial Directive

To gain perspective, we compared the CTR timelines with the previous Clinical Trial Directive (CTD). The CTR had an average timeline of 44 days. The CTD, although slightly shorter at 33 days, demonstrated more variability in the approval process with a maximum of 114 days.

Notably, amendments were swiftly processed under the CTR, with an average approval time of 29 days, even for more complex changes.

Initial submissions*

AVERAGE CTR TIMES

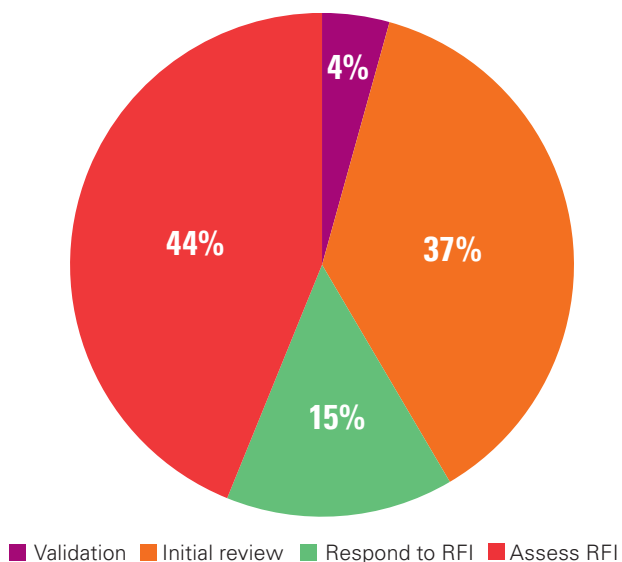


	Average (calender days)	Minimum (calender days)	Maximum (calender days)
Submission to Validation Approval	5.30	0	21
Validation Approval to RFI	15.00	11	32
RFI to Response	9.40	4	12
Response to Approval	15.89	4	31
TOTAL Submission to Approval	44.44	29	56
TOTAL Clinical Trial Directive **	33.00	14	114

* Initial submissions performed at CPU. Total number of submissions = 13
 ** submissions performed by SGS, N=38.

Amendment submissions*

AVERAGE CTR TIMES



	Average (calender days)	Minimum (calender days)	Maximum (calender days)
Submission to Validation Approval	2.17	0	5
Validation Approval to RFI	18.67	11	31
RFI to Response	7.33	4	11
Response to Approval	22.00	10	34
Submission to Approval	29.17	11	61

* Amendment submissions performed at CPU. Total number = 6

Overview – timelines (in calendar days)

		Percentage in comparison to CTR timelines	SGS CPU Phase 1 experience 2023 (n=13) *	Phase 1 single site BELGIUM timelines **	STANDARDCTR timelines ***
	Initial review	84% faster	1.6 days (0 – 5 days)	5 days	10 days
	Respond to RFI			10 days	10 days
	Assess RFI	78.8% faster	5.3 days total validation phase (0 – 20 days)	5 days	5 days
Part I/II assessment	Initial review	73.8% faster	13.1 days (11 - 14 days)	15 days	45 (review) + 5 (decision) = 50 days
	Respond to RFI		9.4 days (4 - 12 days)	12 days	12 days
	Assess RFI	26.3% faster	14 days (9 - 19 days)	19 days	19 days
Total		59.3% faster	Average: 43.1days Min: 29 days Max 56 days	Max 20 days in case of no RFIs Max 66 days in case RFI to both validation and part I/II decision	Max 60 days in case of no RFIs Max 106 days in case RFI to both validation and part I/II decision
* Results originating from SGS CPU - ** Belgian CA (FAMHP) implemented timelines - *** CTR timelines					

Outliers and considerations

We identified two factors contributing to longer timelines.

Firstly, the performance of Controlled Human Infection Model (CHIM) trials relies on inherently more complex protocols, and trials of this nature are therefore more challenging to adequately review, approaching the maximum 66-day timeline.

Secondly, products falling under the annex medication category, such as ATMPs and monoclonal antibodies, allowed for an extra 25 days of review time, resulting in occasional extensions. According to the CTR, this extension can be a maximum of 50 days. The Belgian authorities have now made a commitment to reduce this timescale.



Review of part II documents

Part II of the CTR contains the national and patient-level documentation. In Belgium, these documents are mainly reviewed by ethical committees (ECs). For early-phase clinical trials, several ECs are accredited to perform these reviews.

Under the CTD, SGS submitted all patient-facing documents to the same EC, making the reviews consistent and reliable. Having more than one EC performing this review scatters the focus and aggregated knowledge of the ECs in early-phase trials, which has an impact on the predictability and consistency of this review.

Focus areas and trends in requested information

Overall, 142 Requests For Information (RFIs) were raised in the trials reviewed, the majority which were focused on the Subject Information Form and Informed Consent Form (ICF).

The primary comments revolved around requests for additional information or clarification, as well as incorrect lay language. As understandability of the ICF is one of the most important objectives, it is expected that this is consistent with the number of comments.

On Recruitment Arrangements, most comments were related to advertisement. Comments on Proof of Insurance, Financial Arrangements and Suitability of the Principal Investigator were scarce.

Addressing challenges through collaboration

Progress has been made and several measures have been taken to enhance the review of early-phase documents. The early-phase units in Belgium are collaborating in the Healixia Early Development Group. This group has facilitated constructive discussions with Belgian agencies, early-phase ECs and the CT-College – the organization that oversees the Clinical Trial Application Review. Three key fronts are being addressed:

1. Pre-approval recruitment guidelines

These guidelines provide the option to start recruiting for early-phase trials before approval with non-study-specific information – approved by local ethical committees – for entry into the clinical trial unit’s own database. This translates into a smoother transition to the trial phase once authorization is granted, shortening the timeline to the first participant’s first visit by approximately two weeks.
2. Standardized informed consent forms

Collaborating with the EC working group, Healixia created a standardized ICF tailored specifically for healthy volunteers, aiming to minimize RFIs in consent forms and expedite reviews.
3. Advertising guidelines

The working groups are developing clear advertising guidelines. These guidelines will enhance the efficiency of the review process by providing clarity on acceptable advertising content, reducing comments and improving overall submission efficiency.



Conclusion

Belgium, previously celebrated as one of the fastest countries under the CTD, continues to be a leading force in early-phase trials under the CTR. While timelines have seen a modest increase, Belgium remains a highly efficient and attractive destination for clinical research, offering a balance of speed and

predictability in the drug development process. The Belgian agencies and ECs are open to constructive meetings and helping to provide solutions for review predictability within the boundaries of ICH GCP, the CTR, and Belgian legislation.

How SGS can help

We are SGS – the world's leading testing, inspection and certification company, with decades of experience in the medical and pharmaceutical sector. SGS Health Science has one core mission: improving patient health by safeguarding the quality and efficacy of medicines.

By choosing SGS, you will be working with leading experts who will collaborate with you throughout every stage of your clinical submissions. You can leverage our industry-leading, fully accredited facilities featuring state-of-the-art equipment, and consult our knowledgeable specialists throughout the clinical trial process.

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The SGS logo consists of the letters 'SGS' in a bold, sans-serif font. To the right of the letters is a vertical line that extends from the top of the 'S' down to the bottom of the 'S', with a small horizontal tick at the top and bottom.

When you need to be sure