PRA Health Sciences

WHITE PAPER

Lessons Learned From Preparing and Submitting an IND Application for a COVID-19 Treatment Candidate

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Executive Summary

The coronavirus disease 2019 (COVID-19) pandemic has undoubtedly impacted many aspects of drug development, including the preparation process for electronic regulatory submissions. After the decision was made to evaluate a potential therapy to treat COVID-19 respiratory complications, an Investigational New Drug (IND) application needed to be submitted to the US Food and Drug Administration (FDA) to enable a clinical trial to begin following the FDA's green light.

Given the urgent environment, a submissions team was formed to prepare the IND application as quickly as possible. While the IND submission package typically requires several months of preparation, the team exceeded previously established benchmarks and submitted the IND application in less than four weeks! The high quality of the IND submission package led to the FDA providing a "safe to proceed letter" 21 days after submission. The importance of rapidly submitting the IND forced us to evaluate which steps in the end-to-end submission process were more significant than others and make bold decisions. Using the lessons learned from this experience, we assessed the success factors and identified areas for improvement to specify best practices, increase operational effectiveness and efficiency, and apply learnings to subsequent submissions.

This paper provides insights into:

- Challenges we faced as we prepared the pre-IND and IND submission package and how we overcame them
- Risks we were willing to accept and mitigate based on decisions made early on, and what could have been done differently
- Why cross-functional team alignment, submission coordination, and effective communication and collaboration across stakeholders are essential
- Best practices for submission readiness and how these led to our success

We are excited to share our experience to help colleagues in the industry optimize their IND submission preparation process and allow clinical trials to begin faster.

Milestones Overview

Winston Churchill once said, "Perfection is the enemy of progress," which is true when working on a high-priority application under tight deadline pressure. Specifically, one of the most significant challenges we faced was balancing the attained progress at any point in time with the ticking clock.

Shortly after the business case for the COVID-19 IND project was approved by the sponsor in early May 2020, a dedicated PRA regulatory project and submission manager (RPSM) was appointed to manage the IND deliverables and oversee the submission preparation. There was already an existing parent IND to cross-reference this IND, and we would not include any new non-clinical or Chemistry, Manufacturing, and Controls (CMC) data. The parent IND holder was based in a different country and time zone than the sponsor, which added complexity. While the IND submission package typically requires several months of preparation, we exceeded previously established benchmarks and submitted the IND application in less than four weeks. The high quality of the IND submission package led to the FDA issuing a "safe to proceed letter" 21 days after submission!

Figure 1: Key milestones

Lessons Learned: Successes

Submission coordination and meeting management

The sophisticated planning of an experienced and dedicated RPSM was recognized as one of the key contributors to our success. The RPSM's strong regulatory experience allowed us to build critical interdependencies for discussion with the submission team. The RPSM quickly translated the IND filing strategy into a clear and detailed operational plan that pointed out how functional area representatives should work together to achieve a high-quality and on time IND submission. Also critical to our success was using clear and transparent tools for communication such as dashboards and Gantt charts.

Communicating task relationships, document interdependencies, and expectations regarding the timing of specific outputs to be used as inputs to subsequent processes/documents helped us exceed our stretched timeline targets and minimize unnecessary rework resulting from unmet deliverables.

Teamwork and collaborative team culture

Teamwork and a collaborative team culture were also instrumental to our success. Unplanned changes are likely to be requested when working under tight timelines. The team, especially those with document reviewer and approver responsibilities, stayed aware of unplanned changes and remained available to sign off on documents after regular business hours to ensure our submission targets stayed on track. It was also beneficial to have strong support from senior management that endorsed a flexible working schedule and kept the team motivated along the way.

Importance of activity front-loading (where possible)

While preparing a BD for a pre-IND submission, there may be sections dependent on other documents and data, and other sections that do not have dependencies. In our case, the regulatory lead provided a well-populated BD shell that enabled the Medical Writing team to make a head start with drafting questions and company positions. Identifying and prioritizing activity front-loading, such as creating document shells and aligning with the team on aspirational key messages, before data become available proved to be a valuable strategy for meeting aggressive timelines.

Increased productivity by front-loading tasks early

In more complex scenarios where you are working with a partner and a cross-reference IND, it is essential to check both your organization's and the partner company's corporate policies governing the Investigator's Brochure (IB). Having one single IB for all indications enabled us to provide necessary information to regulators even though data were not final through Module 2. Obtaining the IB from the partner company as early as possible in an editable format may help eliminate a potential rate-limiting step and reduce risk to the critical path.

Partnership between regulatory project and submission manager and publisher

The partnership between the RPSM and the publisher was another key contributor to the team's success. Our publisher was involved early and remained flexible to accommodate last minute strategy and content changes, so our timelines were not impacted. The publisher and the RPSM were well-connected and in complete alignment to ensure a full understanding of incremental handover and any risks for the reopening of documents. We greatly benefited from this submission framework where the RPSM and the publisher were two distinct roles. This framework enabled the regulatory strategist and other team members to remain focused on their deliverables while the RPSM guided the team to complete their tasks on time and the publisher built the electronic Common Technical Document (eCTD) application and added files on a rolling basis.

Submission Table of Contents (ToC)

The ToC submission was made available in a shared environment where the IND submission preparation was initiated. The ToC was the operational tool we used to we used to ensure the team was clear on which sections/modules of the eCTD would be part of the IND application and the expectations for these deliverables from a functional area and timeline perspective. The technology automation that we implemented removed previously accepted manual tasks, helped us easily identify the status of documents, and allowed the team to focus on outstanding documents while final documents were delivered to publishing on a rolling basis. We recommend that sponsors consider having this level of automation ingrained in their processes and tools.

Leveraging global working time zones within Global Regulatory Operations

Having a Global Regulatory Operations team based in different countries and time zones worked to our advantage. It allowed us to extend working hours by utilizing the time difference across several time zones.

Lessons Learned: Challenges

Stakeholder identification

Because the IND holder was a separate company from the sponsor and located outside of the US, additional time was needed to identify all of the required stakeholders. It is critical to identify all stakeholders early for streamlined communication.

Pre-IND BD timeline

The initial BD timeline was developed before the RPSM was assigned and focused only on a single deliverable. The initial timeline failed to consider all of the required steps and interdependencies that would have otherwise been identified by the RPSM since they are responsible for managing the end-to-end submission process.

Senior leadership availability

Senior leaders had prior commitments during the first draft review of the BD that could not be rescheduled. The team was able to accommodate and resolve their delayed input at Round Table Review meetings to keep timelines on track. However, the late review led to extended working days and weekends, which could have been avoided.

Technical issues with collaboration sites

And of course, we had our share of technical challenges! Technical issues occurred that resulted in corrupted documents. No content was lost, but additional rework was needed.

Limited access to regulatory systems

As mentioned previously, due to the high priority and urgency of this submission, we had several senior leaders who are not typically tasked with project responsibilities at the submission level. They did not have access to regulatory systems required to author, review, and approve documents. This resulted in having to rely on workarounds that caused some delay in finalizing a few key documents.

Tips

Whenever possible, make sure all stakeholders are identified on time especially if partner companies are involved.

Ensure that the project manager is assigned early on to assess task relationships and interdependencies for a realistic timeline.

Alternate processes may need to be mobilized when working under such tight timelines to ensure senior leaders are available to fulfill their responsibilities at the project level.

It is strongly advised that a point of contact is available to resolve technical issues quickly if required. Also, check for any potential standard operating procedure waivers that may apply on certain occasions.

Identify all required stakeholders responsible for reviewing and/or approving documents early on and ensure they have access to appropriate regulatory systems.

Corrupted figure and other formatting issues

While the BD was in approval workflow, a figure was found with corrupted formatting. This error would have been detected by routine quality check (QC), which was not performed because of our tight timelines. The delay was brief because the entire team was available to assist, and the figure was quickly corrected.

Consider having an abbreviated checklist identified from the beginning to ensure clarity of critical items such as key messaging and style throughout the IND development.

Last-minute content changes

On the morning of the BD's planned approval date, senior leaders requested a content change. This change led to additional rework, such as team review and operational tasks and workflows that had to be repeated in the electronic document management system. This was one example where we had to decide whether the change was necessary or a "nice to have" because the overall submission timeline could have been jeopardized. It is critical to communicate risks clearly and transparently across the entire team so they can make an informed decision.

Ensure that decision-making and risk management procedures are documented and communicated clearly.

Incorrect use of escalation pathways

When timelines are tight, risks and issues must be escalated to the appropriate points of contact who can quickly resolve problems. Having the right points of escalation in place can save valuable time.

Ensure that the right points of escalation (along with any delegates) are identified and available throughout the submission preparation.

Key Takeaways

To summarize our key takeaways from this case study:

- Communication is critical to a well-managed submission.
- Having an RPSM responsible for all of the operational moving parts of the submission is key. The RPSM will leverage tools to provide the team with visibility into the current status, risks, and the critical path. We highly recommend that our clients have a dedicated RPSM in these scenarios who will focus solely on the end-end submission process.
- Ensure the team understands competing priorities. It is important for the team to balance time constraints for agreed deliverables and not spend longer than needed on any one task, document, or activity.
- Avoid making changes after the agreed timelines. It is essential to establish criteria early on defining what would be "nice to have" vs a necessary change that may put the target submission date at risk.
- Finally, being agile in your project management approach has been proven to be very beneficial for engaging people and building processes to accelerate results.

About the Author

Efi Sergi is an Associate Director within PRA's Regulatory Project and Submission Management group. The group consists of accredited project managers primarily responsible for the strategic planning, management, and coordination of regulatory filings, of all complexities, in all geographies.

Efi has been in the pharmaceutical industry since 2008 and has held various regulatory roles in the US and the UK. Efi has international regulatory project management and strategic planning experience in key markets/regions including the US, EU, China, Latin America, Middle East, Asia Pacific, Russia, and South Africa. She has in-depth knowledge of location regulations and best practices in electronic and paper submissions. She has project managed several submission types, including but not limited to New Drug Applications (NDAs), Marketing Authorization Applications (MAAs), INDs, sNDAs, Type II variations, and China clinical trial applications (CTAs).

Her key skills are communication and meeting management. She plays a critical role in facilitating cross-functional teams to identify appropriate submission deliverable dependencies and generate optimized and accelerated filing strategies to meet business objectives. Efi is also overseeing a team of regulatory project and submission managers who are supporting a partnership with a top pharma client in the US as part of PRA's Embedded Solutions™ model.

Efi is a pharmacist by training and holds a Master of Science in Regulatory Affairs from Northeastern University, Boston, MA. Efi is also PMP-certified by the Project Management Institute (PMI) and a member of the Drug Information Association (DIA) and the Regulatory Affairs Professional Society (RAPS).

Contact Information

For further information regarding PRA's approach or to discuss any aspect of PRA's services, please contact your PRA account director or the PRA employee below:

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