CERTARA

Best Practices for Developing High Quality, On Time Submissions

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BEST PRACTICES FOR DEVELOPING HIGH QUALITY, ON TIME SUBMISSIONS

Consolidating the scientific and regulatory information required to support a submission for marketing approval is a critical step for any drug development program. Yet many teams struggle with setting and adhering to a timeline for planning, drafting, reviewing, and editing the regulatory documents needed for the submission dossier.

Here are some of the most common submission planning mistakes and tips for addressing them:

1. **Not knowing what "done" looks like**: The experience gained by having been through the entire submission process from development through to defense, approval, and lifecycle management is invaluable. When you're starting a new submission, identify which (if any) team members know what "done" looks like because these individuals can anticipate potential difficulties to watch out for. Ideally, you have an experienced team. If your team is inexperienced, look for someone internal or external to your organization who has the requisite experience and can help guide your team through these challenges.

2. **Start at least 9 months prior to submission date**: Your company has spent many years and untold millions of dollars to get to this point—don't shortchange the submission and publishing milestones. While considering the type of submission (NDA and BLA versus IND, ANDA or other), begin the process of gathering documentation and calendaring all activities with enough slack time for when things go wrong (and they will!).

3. **Scheduling summary document preparation in parallel with source document preparation**: This pitfall refers to teams attempting to draft and review either non-clinical or clinical summaries in parallel with the supporting study reports. Trying to keep consistent messaging across documents that are undergoing simultaneous revision is difficult. Although this can be done, it's painful for everyone because this practice creates considerable rework and inefficiency. It's much more efficient for the team to separate source document prep from summary document prep—and you'll end up with a higher quality final submission with less stress. This is true even if it means shorter review or revision periods for those documents.

4. **Missing input from key stakeholders**: Solicit input from all key groups involved in your submission. Your core team may be limited to representatives from a handful of functions. But you want to include all stakeholders—drug metabolism and pharmacokinetics (DMPK), publishing, quality assurance, etc. If key people are sitting on the sidelines, try to engage them.

5. **Submission appropriate messaging**: Creating messaging, such as the 'forward-thinking wording in a target product profile is essential in drug development. However, such wording may not work in submission documents, which are used for regulatory approval and will likely require revision in scope and tone for use in the submission documentation.

6. **Ignoring dependencies**: Be sure to address dependencies. For example, you can't draft an integrated summary of safety (ISS) until you have the integrated pooled safety output. And that typically depends on getting to database lock on the last phase three study. Account for the time required to get from each submission development step to the next.

THE KEYS TO SUCCESS

Developing robust submissions with minimal disruption to people's lives and minimal stress is achievable. But it requires a lot of work, especially upfront.

First, do your homework. Start asking questions regarding the project before the kickoff meeting, and certainly before you start getting into the data and deliveries. Ideally that work starts 9 to 18 months before the submission date depending on the size of the program and the scope of the submission. You need this information to make a detailed submission timeline.

The team needs to meet regularly. In those meetings, document the minutes and actions and communicate relentlessly. You need to be the "calm in the storm", because there will be stormy times on the project! If you're in a lead role, be the person who helps move the team forward despite any chaos.

Many drug development teams struggle with submission planning.

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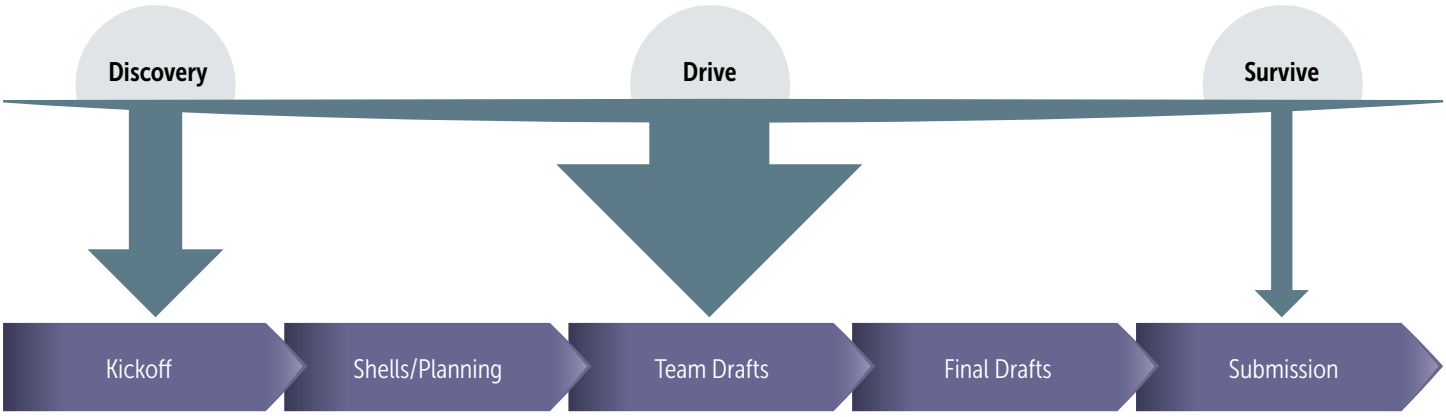
Every project has a beginning, middle, and end which can be thought of as a "discovery phase," the "drive phase," and the "survive phase." The discovery phase includes the kickoff meeting and planning the document shells. The drive phase is the longest and encompasses developing the team drafts and final drafts. The survive stage typically occurs at the time of the approvals and the actual submission.

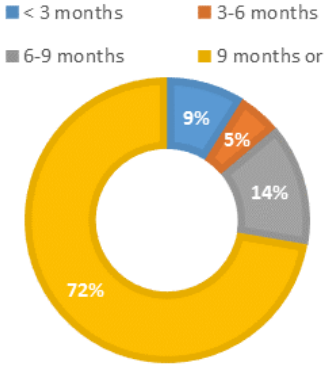
The Phases of a Submission Program



THE DISCOVERY PHASE

Many teams miss opportunities to be more successful in the discovery phase. Start by learning about the team and their personalities, skills, and experience levels. You also need to learn all of the associated processes. What's the document review and approval process? Are there templates for the documents and project planning? Obviously, you must know the product, the scope of the program, the type of submission being pursued, and the proposed indication(s).

In addition, learn whether any existing documentation or plans are already in place. Has someone already developed a submission plan that captures existing agreements about timing? If you know when deliverables are expected, you can build on that foundation, rather than starting from scratch.



The results of a market survey we conducted reinforces the need to start regulatory submission process early

Moreover, you need to determine the outstanding or rate-limiting documents or data. These key milestones will drive the submission date, which determines how much time you have at each step, especially towards the end.

One frequently overlooked, but critical, factor is the history of the program's regulatory interactions. At the start of a new submission, request copies of all of the minutes of the meetings that have been held with the US Food and Drug Administration (FDA), European Medicines Agency (EMA), or other regulatory bodies. Review these if the team hasn't already. If your team has this documentation assembled already, that is ideal.

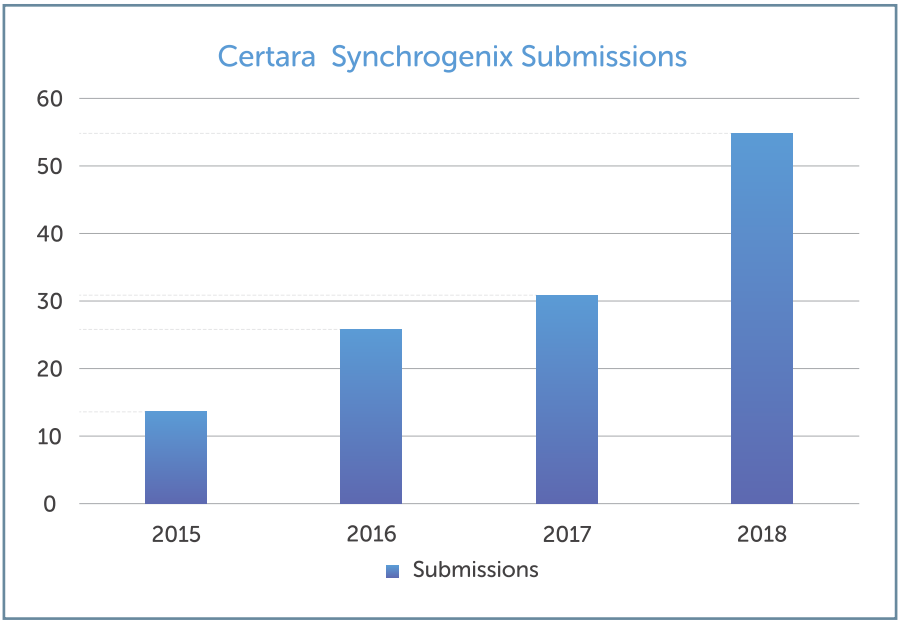
If your project doesn't have this information, review those minutes and create a summary document that captures all agreements with that health authority. Then check with the team to ensure that the agreement was actually followed through and implemented. Frequently, you will identify something that didn't get addressed or didn't get followed through, and therefore needs to be highlighted in the summary documents.

In addition, learn the strengths and weaknesses of the product and development program. Past interactions with health authorities provide some perspective on what they thought were strengths or weaknesses. Sometimes gaps or discrepancies develop between what you agreed on with the agency and the current situation. For example, team members, the target patient population, or the standard of care for the drug's indication could have changed. There may be good justifications for these changes. The recalibrations that were made to account for these changes in your drug's development path may not have been communicated to the agency. So, these changes must be accounted for in your documentation and submission.

ESTABLISHING YOUR CREDIBILITY AND REGULATORY WRITING PROCESSES

Now that you've learned about the drug program's team, processes, and regulatory history, establish your team and everyone's role on it. This is when you attain agreement on the specifics for this submission. Create a grid of the reviewers and approvers for each document so that team members know what's expected from them. It's helpful to agree on the approval process and signatories, so that everyone knows which documents need a signature and which ones just need a verbal or e-mail approval. Moreover, confirm which documents require a formal audit/Quality Assurance (QA) check versus just Quality Control (QC).

Don't forget to confirm and allot time for QC and publishing! Often, the regulatory operations and submission publishing aspects are missing from timelines. Consequently, the regulatory operations group gets squeezed at the end. But if you include them in the process and account for their time, you can avoid that stressful situation.



Over the past four years, we have written and published >125 global marketing applications for our clients, with 100% approval for completed submissions for which the agency has reached a decision.

DEVELOPING A ROBUST AND DETAILED PLAN

Based on everything that you've learned and the processes you've established, you're now ready to develop detailed plans. Identify "blackout" dates early that could affect the timeline—team members' vacations, key program milestones (final database lock, pre-NDA meeting), and external conflicts like scientific conferences that team members attend—so you can plan around them.

Then, you need to reach agreement on the detailed plan. The plan should be transparent to the team so that they know the expectations. Book document reviews and comment resolution meetings in people's calendars. It decreases the likelihood that they will double book themselves. Also, if meetings are in someone's calendar, you can send them reminders.

Failing to plan is planning to fail! If you don't have a timeline, there's no way you can expect people to follow it. Treat this timeline as something that doesn't change unless absolutely required.

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The team must be informed and know where things stand with the submission at all times.

CREATING A DETAILED TIMELINE

Ideally, develop the timeline for all documents at least six to nine months before the submission's due date. By creating a detailed timeline, you can see whether your reviews are staggered or whether they overlap. Or if you have three comment resolution meetings scheduled at the same time. It also helps you identify dependencies so you can make them clear to the team.

The timeline should include the following information:

- Holidays, vacation or other commitments
- Events or meetings—identify when the team needs to be available for external events
- Document deliverables for each step in the process, including drafting, reviews, comment resolution meetings (CRMs), and revisions

THE DRIVE PHASE

The next and longest phase in preparing a submission is the drive phase. The key here is to maintain your purpose and drive to the submission date. You want to reinforce and build upon the agreements reached upfront. Stick to your timeline and don't let things slip "because there's still time." It's easy to let a review slip one week at this point because it won't impact your submission. But it sets a bad precedent for when you don't have that option of delaying an activity.

You develop your team's trust with delivery during the drive phase. When the team completes those first few scheduled reviews, comment resolution meetings, and other activities and meets their deadlines, their confidence grows. Having this strong team rapport will be valuable during the more stressful, hectic end of the submission.

Anticipate delays and flaws in the data by meeting regularly and documenting the meeting minutes and actions. Don't let outstanding questions linger! The sooner you address them, the better. While meetings are a good way to keep everyone updated, you will also need additional communications between meetings.

If you've ever done a "lessons learned" on a submission, communication was probably identified as an area for improvement. Maybe the communication needed to be more frequent, clear, or widespread. Over-communication on a large submission project is generally not possible. The team must be informed and know where things stand with the submission at all times.

Potential differences between global regulators-considerations for global submissions

- Indication classification
- Health authority definition of 'standard of care'
- Dosing and dosing regimen
- Disease description and nomenclature
- Region-specific populations
- Risk management requirements
- Studies and data needs

THE SURVIVE PHASE

The final phase of a submission—the "survive phase"—occurs near the end of the project, often right as you need the first document approvals. Every submission reaches a point where things are just going wrong! Submission leaders have to adjust and help show the team the path to success. Provide or find extra support where it's needed.

What happens if you've been following a detailed timeline, and then a problem arises and database lock has to slip a week? Don't panic. You have an agreed timeline, so don't change anything that doesn't have to change.

If you've developed a detailed timeline, you can easily visualize your options. Maybe you can cut some documents' drafting time if the tables are also delayed by a week. Or perhaps the statistical group can deliver the tables a little earlier. Maybe the team can shave a few days off a study report's review. The inevitable delay arising doesn't need to disrupt the whole timeline. Being able to see the entire submission timeline allows you to minimize the tweaks needed to address issues that arise.

Often, teams avoid raising contentious topics. Staying quiet when everyone seems to be working well together is a tempting choice. But team members, and especially team leaders, need to raise these topics and encourage the team to do so because otherwise these almost always cause bigger problems later if not addressed and cause the submission (and the team) to falter.

"SIMULTANEOUS" GLOBAL SUBMISSIONS

Sponsors commonly submit applications for regulatory approval in multiple geographic regions. The plan for creating submissions for different health authorities should be baked into your detailed timelines. Discuss how to manage different global submissions at the kickoff meeting, not when you complete the first submission!

Pulling off simultaneous submissions requires heeding several considerations. Where are you planning to submit the marketing application? In how many different regions or countries? Which ones and when? Filing a submission in the US and Europe simultaneously poses different issues for the team than submitting to the FDA first and then three months later to Europe. This is because you start running into issues of cutoff dates for ongoing studies, changes in safety reporting, etc.

Submitting marketing applications to multiple countries also frequently requires altering how you write regulatory documents. The indications may have to be changed because of differences in standard of care or wording that the regulatory authority has for that indication. Likewise, the dosage form or dosing strategy may differ between regions. There is also variability in risk management requirements, especially between the US and Europe. Lastly, the disease description may vary in different regions of the world.

TAKE HOME MESSAGES

All submissions have discovery, drive, and survive phases. In the discovery phase, ask questions regarding the strengths and weaknesses of the program, its history, submission process aspects, the drug, and disease and indication. Have your submission kickoff 9 to 18 months before the submission date and create detailed plans that you then make transparent to the team.

During the drive phase, keep meeting regularly with the team, document minutes from those meetings, and follow up on those actions. These habits will help you hold team members accountable. Communicate relentlessly to keep everybody informed.

In the survive phase, submission leaders should be the "calm in the storm." Don't be afraid to speak up, and take control to help drive the team forward.

Many pharma companies put emphasis on "lessons learned" after a submission is completed. Ideally, you will gather these on an ongoing basis and then finalize them immediately after the submission is complete. Document any recommendations that the team would make for future submission teams. To maximize the benefit of lessons learned, a team member should present them at the kickoff meeting for the next submission. If the next project has an inexperienced team, having someone present the lessons learned from the last submission will help them have a good start.

Having a strong plan that is well communicated enables teams to have a smooth submission process that both minimizes project-related stress and chaos and optimizes your drug's probability of regulatory success.

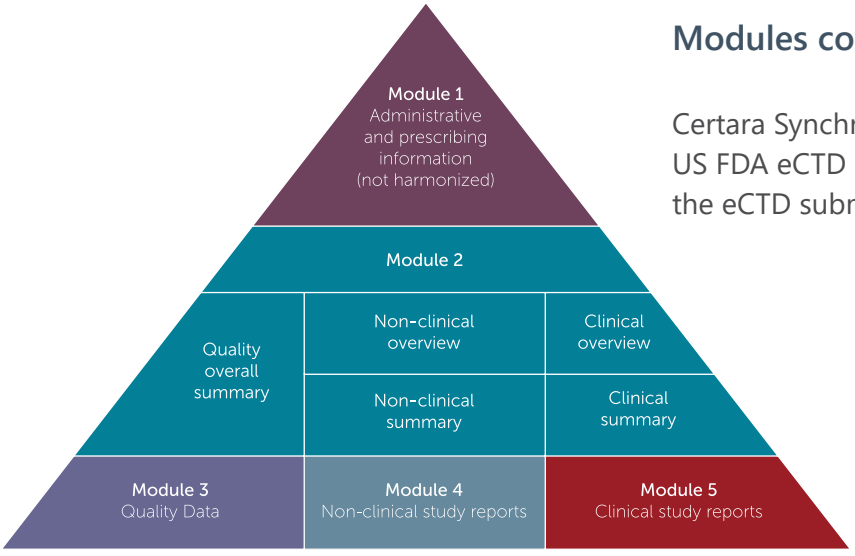
ELECTRONIC COMMON TECHNICAL DOCUMENT (ECTD)

Regulatory submissions must now conform to the electronic common technical document (eCTD) format to be successfully received and reviewed by health authorities. And while this might seem simple, this complex technical process is actually rife with risk if you lack expertise in medical writing and regulatory publishing.

The concept of the eCTD was developed by the International Conference for Harmonization (ICH). The concept was that the eCTD could be implemented by every health authority globally to streamline regulatory review of new drugs, and potentially all regulated products. The eCTD contains 5 modules:

1. Administrative information and prescribing information
2. Common technical document summaries
3. Quality
4. Nonclinical study reports
5. Clinical study reports

The FDA, EMA, SwissMedic and Health Canada require all submissions to be in eCTD format, while PMDA (Japan) is accepting, but not requiring compliance. Many other health authorities are considering and/or accepting some level of compliance.



Modules contained in the eCTD submission

Certara Synchrogenix has touched >95% of every US FDA eCTD submission ever created contained in the eCTD submission

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