PARALLEL GLOBAL SUBMISSIONS

NAVIGATING THE SPACE BETWEEN SUBMISSION & APPROVAL

Development of a novel therapeutic takes several years of intense research and detailed planning. Because target populations are likely to be distributed over multiple regions globally, companies often plan for submission and approval in multiple countries at the same time, which adds a layer of complexity beyond development of the therapy. The likelihood of successfully launching a new therapy simultaneously in multiple geographic regions depends on thorough planning and disciplined execution from development through approvals.

Organizations need to consider both technical content requirements and company capabilities when developing a global submission strategy. Regulatory agencies and industry experts have collaborated and published harmonized guidelines on the scientific content for regulatory submissions, whether for one or multiple country approvals. Technical teams use this information to conduct appropriate studies and gather critical data to build dossiers that are compliant in several regions at once. However, many organizations are not as adept at factoring in company capabilities while planning for parallel submissions.

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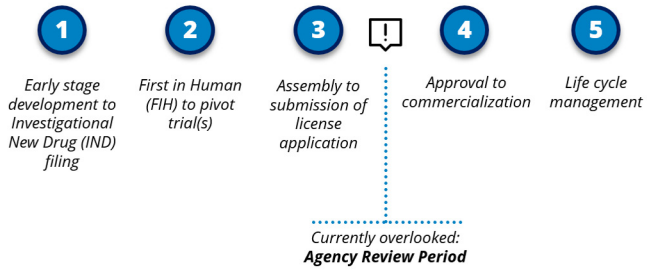
Figure 1: Stages Considered When Developing a Submission Strategy ▶



Careful planning is critical for success and includes, but is not limited to, factors such as awareness of regulatory, resource, and financial requirements for each submission. IPM's experience indicates that companies require and value effective planning for specific stages of the submission process, shown in Figure 1.

Regulatory and business operation leads often underestimate the level of planning and technical engagement that agency review periods require. During the period between submission and approval, companies must respond to agency questions and comments as they arise, while balancing daily functional responsibilities and other regulatory commitments. A program team may be able to develop a strategy, handle responses, and update the dossier for a single regulatory submission. However, the same team may struggle to execute those activities for several overlapping submissions—especially in multiple countries—with the same rigor. Inadequate planning for overlapping review periods could ultimately lead to resource burnout and missed projections.

RECOMMENDATIONS FOR MANAGING ONGOING, OVERLAPPING SUBMISSIONS

A holistic strategy incorporates the anticipated time, resources, and budget needed to support the review period ahead of submissions and enables teams to effectively manage the workload and mitigate risks. However, many pharmaceutical/biotechnology companies evaluate and establish review period requirements only after submissions are completed.

Over the course of managing such cases, IPM recommends the following best practices to maximize product team capabilities.

Understand agency requirements and timelines—and how they interact. Table 1 on page 4 summarizes the typical agency requests and response times for major market submissions. Ad-hoc agency meetings may be necessary to supply or clarify information. Responses provided during the review cycle can result in updates to the technical content in the original dossier. If the product and regulatory strategy includes overlapping submissions, changes to one filing may impact already approved or subsequent planned submissions, as reviewed material may be made public by agencies. Longer-term solutions proposed as post-approval measures or commitments must be recorded and tracked for timely delivery and may impact one or more submissions.

Assess the dossier and mitigate risk. Objectively review the complete dossier against agency requirements to estimate the volume and scope of expected queries. Identify weak areas or potential gaps that may prompt a major query, multiple post-submission questions, or high-risk post-approval commitments. Consider engaging subject matter experts or advisors to support the risk assessment and suggest strategies to mitigate potential agency concerns.

Classify gaps in the filing based on prior experience with and/or scientific advice from regulatory agencies. Prioritize the high risks and consider staggering submissions so approval in one major market is feasible before pursuing other submissions.

If several medium- to low-risk gaps are identified, consider a strategy that includes submission in one or two major markets simultaneously or with some lag in between; at the same time, pursue extensions or be prepared to withdraw if queries require actions beyond the planned scope or product team capabilities. If query responses are successful, continue with the rest of the global submissions as planned. Document the response strategy and make sure the product team understands it.

If a few low-risk gaps are identified, ensure you have a documented and well-understood response strategy.

Set expectations. Prior to the start of a review period, educate the team on the expected activities and then equip members with the tools and processes that will maximize efficiency. Conduct a kickoff meeting and outline the flow of activities and roles and responsibilities, as well as expectations for management engagement and approvals. Work through potential scenarios requiring varying levels of engagement to pressure test the team's readiness. For example, major objections from the EMA may result in a decision to conduct additional studies or the FDA may request quicker response turnaround times than originally planned.

Assign adequate resources. Put a rapid response team in place. Identify which submissions and responses require technical resources to be available continuously and assemble a backup team to manage off-hour requests. Consider allotting resources that are solely responsible for responding to product-specific post-submission requests. Assign roles and responsibilities to each activity, and ensure the team is aware of the expected workload. Consider the teams' competing priorities and assist them in prioritizing the work.

Implement standard processes and tools. Before the dossier is submitted to an agency, develop and train the submission team(s) on approaches, processes, and use of tools designed to efficiently manage events such as receiving a large volume of queries or ad-hoc information requests, documentation review and revisions, hand-offs, and post-approval commitments.

Incorporate the estimated cost of engaging in review activities when re-evaluating or planning for corporate goals. Companies should assume there will be heavy engagement required to support each submission. If the recalculated expenses are beyond company capabilities, the global submission strategy should be adjusted with a clear evaluation of tradeoffs.

THE BOTTOM LINE

Agency review periods may require a high level of engagement from the company. The learning curve for managing overlapping global review activities can be steep for organizations that overlook this period in the initial planning process. To increase the chances for successful approvals, consider therapeutic needs by region, evaluate submissions to predict queries and mitigate risk, and proactively budget resources and dollars.

Why Companies Start with Three Global Leaders

Product teams often juggle the overlapping review periods of three major agencies: the Food and Drug Administration (FDA) in the US, European Medicines Agency (EMA) in Europe, and Pharmaceuticals and Medical Device Agency (PMDA) in Japan. Pharmaceutical companies target these regions in parallel for several reasons, including:

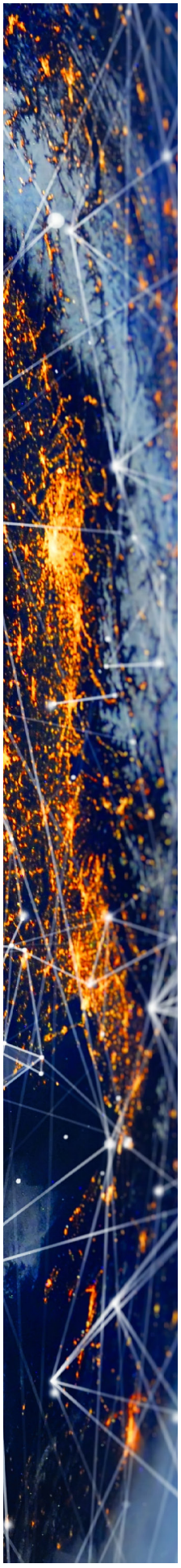
1. The International Council for Harmonization (ICH) developed a single set of guidelines, including safety, quality, efficacy, and multidisciplinary technical requirements, that regulatory experts use to build a core dossier. The ICH initially consisted of representatives from the US, EU, and Japan regulatory agencies.

2. Mutual Recognition Agreements (MRAs) enable pursuit of several markets simultaneously, including a more streamlined information exchange, leading to a reduction of redundant audits, decrease in overall expenses, and shorter lead times to approval. MRAs exist between the EU and the US, Japan, Canada, Australia, Israel, Switzerland, and New Zealand. (For companies considering submissions outside of the US, EU, and Japan, other initiatives to harmonize submissions include the Australia-Canada-Singapore-Switzerland (ACSS) consortium and Marketing Authorisation Holder (MAH) pilot program.)

3. Other global agencies may require a Certificate of Pharmaceutical Product (CPP), or prior approval, from the US, EU, or Japan. CPPs have been recommended by the World Health Organization to assist regions lacking quality assurance facilities. A CPP ensures that the product being imported meets the standards set by one of the three major agencies.

Agency	Standard Review Duration	Agency Requests	Risk Mitigation Considerations
FDA (US)	12 months: 2 months for validation + 10 months technical content	• Written Information Requests (IRs) are sent as technical content is reviewed. • Requests are ad-hoc. • Generally, a smaller volume of questions is sent per IR. • Turnaround times for responses range from 7 to 24 elapsed days.	• If the company has filed similar products in the past, reviewers may be aware and will look for consistency in responses. • Extensions may be requested per IR without impacting overall timeline.
EMA (EU)	Approximately 12 months (assuming three rounds of queries)	• Assessments are only sent after the entire dossier has been reviewed. • Companies are given a timetable with dates around the following activities at the time of submission. • Round 1 List of Questions (LoQ) is generally large in volume. • LoQs from rounds 2 and 3 are likely to be shorter if the responses address agency concern.	• Major objections are specified in the assessments and should be addressed thoroughly. • Extensions may be requested when final LoQs are received. Extensions will delay the approval date. • Final LoQs are published in the public domain and may impact business drivers.
PDMA (Japan)	12 months	• Companies are generally told at the time of submission when queries can be expected. • Questions are sent after the dossier has been completely reviewed. • Original LoQ is provided in Japanese. • Expected turnaround dates for responses are provided at the time the questions are sent. • Follow up questions to previous responses may be sent in subsequent rounds of questions.	• Additional time and resources are required for translation. • Japan has unique requirements, so the presence of a local expert at response strategy meetings is highly recommended. • Responses may require updates to the application form. • Extensions can be requested per round but will likely delay approval.

Table 1: Summary of Major Agency Review Period Activities and Risk Mitigation Considerations



HOW TWO PRODUCT TEAMS REACTED TO AN UNEXPECTED VOLUME OF AGENCY REQUESTS

IPM has worked with several pharmaceutical companies that were executing overlapping global submissions and encountered more complexity than they expected. Below are two cases, one where IPM guided the team in developing real-time solutions and another where an organization developed a strategy independently.

LEARNING FROM A PRESSURE COOKER

A large pharmaceutical company submitted oncology therapeutic approval applications to all three major regions within a 12-month period. Figure 2 illustrates the activities requiring product team engagement over the course of two and half years. The regulatory leads were aware of each region's approval expectations, but they were not prepared to manage and execute overlapping activities. Furthermore, expectations were not communicated to the technical team in advance.

Despite the aggressive nature of the FDA requests and large volume of queries from the EMA, the team did little to change their subsequent global submission strategy for this product, placing them at constant risk for missed deadlines and burnout.

As a first response, IPM applied change management strategies, developed novel tools and processes, and collaborated with the team to enable effective communication, resulting in on-time submissions. IPM also implemented ground rules for execution, back-up teams, and response tool optimization for subsequent submissions to alleviate the team from being overtaxed. Finally, the regulatory and commercial teams agreed to seek alignment and apply the approach to future submissions.

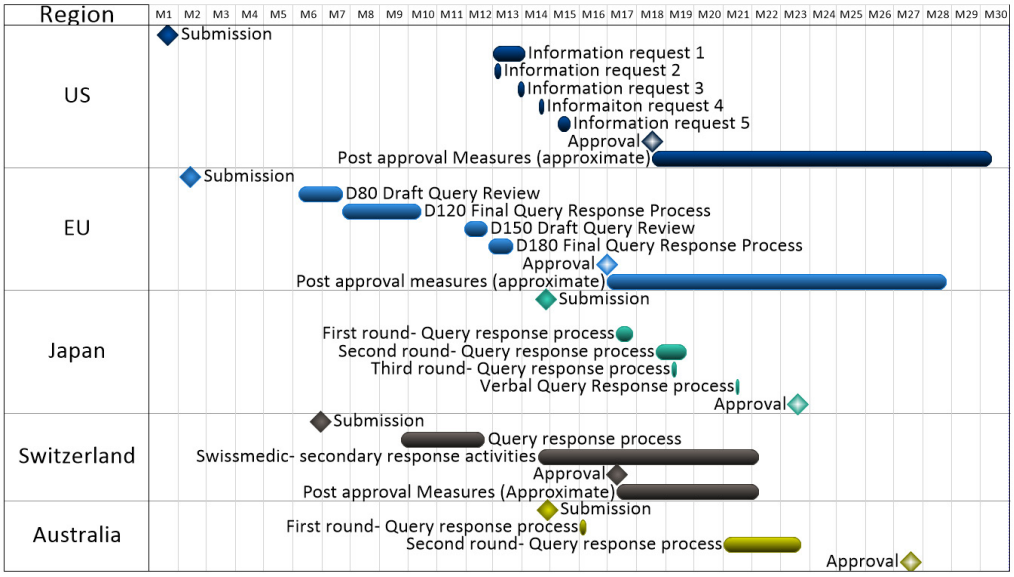


Figure 2: Overlapping Major Submission Scenario

PRIORITIZE AND ACCEPT DELAYS

A mid-size pharmaceutical company originally prioritized submissions to the US, EU, and Canada, followed by Rest of the World (ROW) countries (Figure 3). While FDA review activities were manageable, the depth and breadth of EU review questions were unexpected, thereby causing delays to subsequent submissions. The volume and scope of the queries received from the EMA placed an enormous amount of pressure on the company's overall global submission strategy. The company had limited resources and had to evaluate tradeoffs before deciding if they wanted to continue to pursue approval in the EU.

Ultimately, the team chose to focus their resources on obtaining EU approval first, before pursuing NDS filing (Canada) and ROW submissions. Assessing and reacting to the queries from the EU prior to pursuing other submissions allowed the company to strengthen the core dossier before presenting it to other agencies.

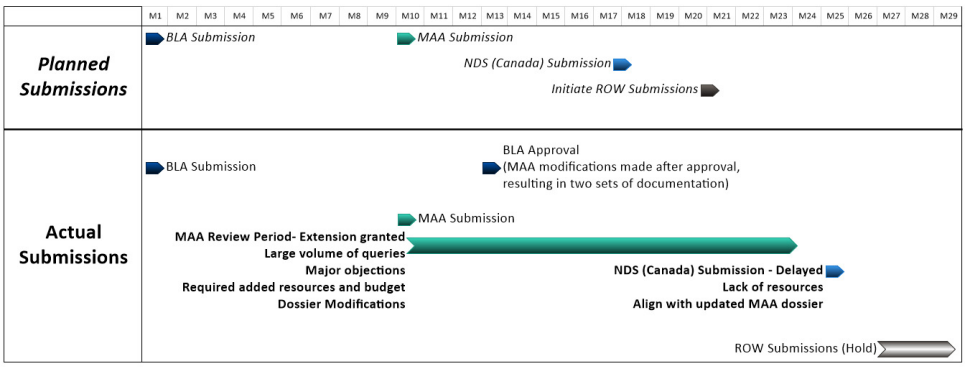


Figure 3: Delayed Submissions Due to Unexpected EMA Queries