ACCELERATED PHARMACEUTICAL

Product Development, Registration, Commercialization, and Life Cycle

CMC LESSONS, PART 2

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This article is Part 2 of a two-part series exploring what we can learn from examples of pharmaceutical products being approved using accelerated programs. The series focuses on challenges that chemistry, manufacturing, and control (CMC) development teams may encounter when a project is given accelerated development status. In Part 1, which was published in the July–August 2019 issue of *Pharmaceutical Engineering*, we introduced key considerations and themes in general terms and highlighted future opportunities in accelerated pharmaceutical product development. In this article, we provide more detailed discussion of the considerations and themes and present several case studies.

REVIEW OF KEY CONSIDERATIONS AND THEMES

As explained in Part 1, key considerations in accelerated pharmaceutical product development include:

- Teamwork and project planning
- Control strategy
- Process validation
- Pharmaceutical quality system (PQS) readiness
- Regulatory considerations

In the following sections, we expand on these key considerations and themes.

TEAMWORK AND PROJECT PLANNING

Initial Planning of an Accelerated Development Approach

When early clinical trial data indicate a potential accelerated development designation and a decision is made to pursue an accelerated development approach, it is critical for the CMC project team working with the whole development project team to:

- Build out development scenarios necessary to accommodate the accelerated timelines, dependencies, and interactions.
- Define options for the development strategy.
- Develop filing timelines for each proposed strategy.

During this phase, the development team should review options derived from the clinical strategy (i.e., what clinical data the regulatory authority will accept, what pivotal studies and clinical data are required, and the associated timelines). The CMC project team

should discuss development and supply chain options and analyze those options in close collaboration with the impacted sites (e.g., launch and commercial sites), external partners, and, where appropriate, regulatory authorities.

The development/validation data required to support each potential filing submission should be identified. These data include critical quality attributes (CQAs), critical process parameters (CPPs), process characterization and verification studies, cleaning studies, stability studies, and so on. It is important to identify critical path activities, early regulatory engagement opportunities, and resource requirements. For example:

- Evaluate the registration lot strategy, including site selection (launch readiness planning), and supply chain considerations.
- Evaluate the control strategy, including in-process, release, and stability testing.
- Assess CMC studies proposed for deferral during review and postapproval.

All of the preceding project analysis should also include iterative risk assessments to ensure that the strategy does not adversely affect patient safety priorities (e.g., purity, immunogenicity, viral clearance, and/or biological activity), product efficacy, or regulatory commitments. Application of risk management processes should allow teams to prioritize studies necessary to ensure patient safety and consider those related to process optimization as lower priority.

A comprehensive pharmaceutical product life-cycle strategy should be devised and agreed upon as early as possible in situations where the CMC timeline is potentially constrained by the accelerating clinical program and patient needs. However, early in the development life cycle, sponsors of accelerated programs cannot be prospectively certain which matters can be successfully negotiated with regulators. Therefore, decisions should be made that allow for maximum flexibility to key components of an accelerating CMC program including:

- Remaining agile in the face of clinical changes and regulatory input.
- Planning the process development and supply chain for pivotal supply manufacture to support filing and launch activities, and to potentially supply additional clinical materials.

The outcome of the preceding analysis should be captured in a project plan and approved by the appropriate CMC and quality teams and communicated to all internal stakeholders.

Next Steps After Receiving the Accelerated Development Designation

Upon receiving the accelerated development designation from the health authority, CMC development teams should further expand the project plan and gap assessment in close collaboration with the commercial site. The gap assessment focuses on supply chain, CMC, testing, stability, validation, and cleaning, as well as overall business risks. Multifunctional and multidisciplinary development teams should lead efforts to accomplish the following:

- Perform holistic risk assessments to identify quality system/compliance challenges and proposed deferred studies, including supporting rationale, interim controls, and definition of interdependencies.
- Update the project plan to document all deferred activities, associated rationale, and dependencies.
- Work with functional area leads to develop individual functional strategies for deferred activities. Details of this work will depend on the complexity of the specific issues to be addressed.
- Identify the need for bridging protocols. The content of such protocols will depend on the level of product and process knowledge, as well as the timing of the accelerated development designation (e.g., when launching at a smaller scale or using clinical material for commercial distribution).
- Connect with the clinical teams to identify opportunities to leverage clinical bridging studies.

In parallel with the accelerated development activities, the regulatory team should develop a global filing strategy, identifying expectations for comparability studies and supportive data required to meet those filing requirements. For an accelerated development designation, it should be anticipated that some CMC and Good Manufacturing Practice (GMP) activities typically completed prior to filing may be deferred and completed after filing, either during the preapproval inspection (PAI) or postapproval, based on completed risk assessments and control strategies, which, where possible, are developed in agreements with regulatory authorities.

This overall quality system strategy and rationale, including risk management planning, should be documented in a project plan and in function-specific project plans as needed. The project plan helps ensure transparency with regard to the various milestones and gating requirements.

The deferral approach should also be discussed with each health authority to reach a consensus during the accelerated development. The results of these discussions may impact the filing strategy or development plan.

Additional bridging/comparability studies may be required to address gaps identified during the risk assessments (e.g., releasing clinical material for launch, launching out of a clinical facility with transfer to commercial scale). Such studies may also be needed to update the control strategy as new knowledge is gained later in the product life cycle.

Resource planning is an important component of accelerated development planning. For many projects, the same personnel may be responsible for the following:

- Ongoing development activities
- Plant support
- Postapproval change management
- Regulatory filing/submission activities, including negotiation and responses to requests for information from various health authorities

If possible, separate teams should be designated for some of these activities. In addition, development work may be needed at multiple sites (i.e., clinical site vs. commercial site, drug substance site vs. drug product site), which puts additional constraints on the development team.

Accelerated development pathways are not well defined in many global regions. However, once initial marketing applications have been submitted with an accelerated development pathway in a major market, markets in the rest of the world may push to accelerate their submissions. This puts additional pressure on resources to manage the preparation and submission of global dossiers.

Teams taking a full life-cycle approach may wish to consider the advantages and disadvantages of the following product launch strategies:

- Using the fastest possible regulatory path and product launch with a comprehensive life-cycle plan for subsequent postapproval introduction of an optimized process. This approach could translate to launching with a "first-generation" process or product that potentially involves a higher cost of goods, more waste, inefficient processes, and decreased patient acceptability (e.g., multiple dosage units rather than a single unit, or a vial rather than a prefilled syringe). However, the tradeoff for inefficiency is that this strategy may have less impact on quality, safety, compliance, or the manufacturer's ability to consistently and reproducibly produce the commercial product.
- Limiting the initial number of launch markets (e.g., launch only in the United States and European Union). This approach will facilitate introduction of the preferred product, processes, controls, and so on, via postapproval changes, before submission in the remaining markets. In this manner, the approach should reduce the resource burden in CMC and regulatory affairs by limiting the process version management as postapproval changes are implemented, and may provide optimum value to the company.

Considerations when selecting the launch site include facility fitness in terms of its technical capability, position in the supply chain to support launch markets, compliance and pharmaceutical quality system status, and resource levels. Additionally, the impact of the change from a clinical site to a commercial site must be analyzed. Issues related to this transition include:

- Technical requirements such as comparability/bioequivalence (BE) studies, stability studies, and process validation approach
- Regulatory hurdles
- Change management
- Need for technical support

The team should also compare the options to scale-up a process by building more capacity at the same scale and make the appropriate decision.

CONTROL STRATEGY

Control strategy is defined in ICH Q10 as follows [1]:

> *A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.*

For accelerated programs, the compressed timeline challenges the sponsor to develop the appropriate degree of process and product understanding, and to manufacture many batches of both clinical- and production-representative lots commensurate with normal expectations of regulatory authorities. Hence, it is highly desirable to agree with regulatory authorities—based on risk assessment and risk control—on what control strategy could be achievable to meet patient-acceptable standards. These agreements between the sponsor and authorities are highly individualized according to the science of the specific program, as well as the sponsor's amount of prior knowledge and understanding of the product and production processes. Where possible, there is significant benefit in leveraging prior knowledge.

Process Control Strategy and Associated Specifications

When proposing or developing a process control strategy with associated specifications, platform processes should be used as much as possible. Their use should support process development, product- and process-specific understanding, and the proposed process validation strategy. ICH guidelines should be followed as closely as possible because deviation leads to complexity, offsetting the benefit of using platform technology.

Sponsors need different approaches to set acceptance criteria for large molecule vs. small molecule products. Small molecule acceptance criteria are based on ICH Q6A [2] and ICH Q3 series [3] guidelines for impurities, plus ICH M7 [4] for assessment and control of DNA-reactive (mutagenic) impurities and ICH S9 [5] for anticancer pharmaceuticals. Large molecules specifications are set using ICH Q6B [6].

For accelerated programs, it is challenging to set the specification because manufacturing and clinical experience are limited. Bercu and colleagues have published useful considerations for setting specifications for impurities [7]. They propose approaches that may be used for specification setting based on clinical relevance in the drug development, registration, and postapproval phases of a product life cycle.

To focus the prioritization of process characterization/validation experiments, it is helpful to establish early a control strategy summary linking the quality target product profile, CQAs, presumptive CPPs, and the raw material control strategy. Early identification of CQAs and development of suitable analytical methods

for process performance qualification (PPQ) and pivotal trials could help mitigate the risk of relatively few lots and assist in discussions with regulators. The evolution of the control strategy—justified by a combination of process development data, knowledge of platform process performance, and incorporation of risk assessment and proposed risk control output—will aid in the negotiation of the "must have" components at the time of file vs. those that can be completed in parallel to PPQ or even postapproval.

When a sponsor is relying on less-traditional validation approaches for a biological/biotechnological product, early investment in an applicable cell-based potency assay alongside more platform-based methods will bolster confidence in the process robustness. In other words, having the right methods in place with the justified acceptance criteria will help strengthen the rationale that process monitoring will be sufficiently reliable to overcome any perceived risks associated with less-traditional validation approaches or a less-comprehensive validation data package filed in the initial biologics license application (BLA) or marketing authorization application (MAA).

For accelerated development programs, the process control strategy will almost certainly be developed based on limited product-specific manufacturing experience and may need to include a postmarketing commitment to reevaluate and adjust specifications after a specified number of commercial lots. For example, the process control strategy could include:

- Tentative specifications (i.e., acceptance criteria and, perhaps, analytical methods) for release, stability, and in-process controls at the time of MAA submission that could be optimized postapproval.
- Filing of preliminary CQAs and/or CPPs that could be updated postapproval, as per agreements with health authorities.
- Filing with monitoring tests or an increased sampling plan and subsequently "sunsetting" some testing or reducing the sampling when more data become available to support a decrease in testing. For example, some attributes such as residual host cellular DNA and host cell proteins (HCPs) may be removed from the specification if sufficient data confirm the process is effective in removing these impurities.

Analytical Method Readiness

Sponsors should take a risk-based approach to determine the extent of method validation to be done prior to the initiation of the qualification campaign. Depending on the intended use and risks associated with a method (e.g., compendial methods, general methods such as pH or osmolality, or platform analytic methods where significant knowledge and experience exists), complete validation may not be necessary. Instead, it may be sufficient to demonstrate by other means the suitability of a method to achieve the intended purpose. However, suitability should be completed before qualification campaign testing begins. Using platform analytical methods and processes as much as possible should minimize risk and will assist with validation approaches, such as phasing of analytical validation, and justifications to regulatory authorities.

Sponsors should take a risk-based approach to determine the extent of method validation to be done prior to the initiation of the qualification campaign.

Methods associated with product CQAs or product safety (e.g., assay testing for contamination) should be validated, with issues being resolved concurrent with the qualification campaign. The risks associated with the level of method suitability assessment and/or validation should be linked to an evaluation of process understanding and the acceptability of the stability strategy and stability data package. Risks associated with limited manufacturing and method experience may require more frequent sampling and enhanced assay system suitability criteria. In all instances, method validation reports must be approved and appropriate retesting or method bridging studies completed prior to PAI and release of the product for commercial distribution.

During development for an accelerated program, sponsors must pay attention to the strategy to bridge early assays to potentially different commercial analytical methods; it is important to retain enough samples from early batches. Sponsors should also consider the potential impact of this strategy on specification, total analytical control strategy, and testing laboratory operations. For biologics, the common assay changes are potency assay and HCP assay. Although the platform assay (i.e., enzyme-linked immunosorbent assay [ELISA]), may be sufficient as a potency substitute for early-phase development, authorities require that a potency assay reflecting the mechanism of action be in place at the time of registration. Developing the appropriate potency assay early to generate enough stability data is key for a successful filing of accelerated programs.

For an expedited program for a biologic substance, the reference material strategy should be designed early and cover the lifetime of the product. The primary reference material is expected to be representative of the pivotal clinical study material to ensure that the commercial batches also represent pivotal clinical study material. For an accelerated program, however, the pivotal batch could be an early clinical batch, which may not have been made at a scale sufficient to provide clinical process characterization or enough reference material for long-term use.

The reference material should be sufficiently stable, and a strategy must be developed to monitor drift. The strategy to designate a lot as primary reference material should have qualification/requalification protocols in place, with criteria to evaluate the following:

- Storage and manufacturing requirements
- Stability to monitor the trend
- Maintenance of supply continuity in both quality and quantity
- Linkage of lots to maintain representation of reference material used in pivotal clinical studies
- Any changes to the analytical methods (changes in methods, especially for potency reference material, may require bridging studies)

Ideally, the primary reference material would be the same material throughout the development and life cycle of a product. Secondary reference material should preferably be prepared and used for routine analytical testing soon after a primary reference standard has been established.

Stability Data and Shelf Life

For some accelerated programs, the shortened development time and limited availability of materials may make it impossible to generate sufficient stability data to comply with ICH requirements at the time of submission. A practical shelf life must be requested. For accelerated development products, the long-term (real-time) stability data available from an appropriate scale may be limited. Therefore, it may be necessary to file with reduced long-term stability data on the commercial process (launch material) and/or clinical scale batches. Discussions with health authorities may be required to reach a consensus on the amount of real-time stability data from representative batches to be included in the filing before the submission and the likely shelf life granted at time of approval. The following stability approaches can be considered:

- Leverage use of stability data from representative pilot-scale lots.
- Add clinical batches to the stability program for supportive shelf-life data.
- Use forced degradation and accelerated/stress stability studies to model the stability profile; enhance understanding; support comparability studies of clinical, supportive, and commercial material; and predict shelf life.
- Provide periodic stability updates to the health authorities.

Experience indicates that the shelf life granted by regulatory authorities varies depending on the amount of supporting data from clinical batches, expectations of specific reviewers, types of molecules, the medicine's risks and benefits, and other factors. This likely variation for a drug product only adds complexity to management of the supply chain postapproval.

Raw Materials

For drug substance synthesis for small molecules, it is extremely important that internal stakeholders, regulators, and, if necessary, third-party suppliers agree on the choice of starting materials (SMs) in a synthetic sequence as soon as possible. This agreement clarifies the GMP requirements, including the validation strategy. For guidance for SM selection, refer to ICH Q11, Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) [8], as well as the ICH Q11 Q&A [9], which offers additional clarification. However, there may be insufficient time to complete all desired studies identified in that guidance.

Tighter timelines may lead to a more conservative approach to identifying SMs, in which SMs are designated further upstream than may be proposed using the ICH Q11 Q&A. This approach could introduce additional costs and controls in the process that may not be necessary. While mitigation strategies may be implemented (e.g., manufacturing the final steps in the SM manufacture under GMP conditions) in case health authorities do not agree with the identified SMs, launch supplies may still be jeopardized.

Accelerated development may limit the time to evaluate and/or qualify multiple suppliers of raw material or intermediates. Being single-sourced for key intermediates may impact assurance of supply.

PROCESS VALIDATION

For products with accelerated development timelines, time or materials may be insufficient to complete all traditional process validation studies (i.e., hold-time studies, mixing studies, process ranges, worst-case linkages) and batch manufacture before submission. For small molecules, it is not necessary in all cases to complete validation by the time of the new drug application (NDA) submission; however, for large molecules (and "nonstandard" products in the EU), satisfactory completion of at least three full-scale batches at the intended site of manufacture of both drug substance and drug product is currently required. Because accelerated development programs may not allow completion of these large-scale studies before submission, alternate phasing strategies have been employed. Given that process validation itself should take a life-cycle approach as discussed, for example, in FDA Process Validation guidance [10], a holistic life-cycle approach could be proposed. In this approach, data from stage 1 (process design) and similar processes could be leveraged to reduce initial stage 2 (process qualification) requirements. This is further supported by a robust stage 3 (continued process verification) monitoring plan, which provides added assurance of the quality of each batch.

A risk-based approach should be taken to determine the process validation strategy to be used before the qualification campaign begins (i.e., the extent of process design/development data to collect from stage 1). Process validation associated with patient safety must be complete (e.g., sterility, viral clearance, microbial control) at the time of launch to patients. Potential justifications to support a flexible process validation strategy include the following:

- Acceptance of a smaller scale of production
- Concurrent release of product
- Modeling and "scale-down" process design to study factors that impact CQAs and CPPs

If process validation is on the critical path to launch, some experiments can be viewed as more critical than others to process control strategy understanding. For example, for a given product's proven acceptable range series of experiments (and, therefore, reliance on appropriate small-scale models where applicable), it may be more critical to demonstrate that the process will reliably deliver a drug substance or drug product meeting the predetermined acceptance criteria and less critical to conduct column lifetime studies, which could be proposed as part of concurrent process validation or as part of the continued process verification protocol.

PHARMACEUTICAL QUALITY SYSTEM READINESS

An update and/or amendment to the PQS may be necessary because accelerated programs may not have historically expected data to readily support transfer of a process into a mature manufacturing PQS at a facility. Challenges are often experienced by development teams while navigating numerous development PQS requirements in a shorter than customary time frame. Challenges may also arise in the form of differing expectations between development and operations quality organizations. Such challenges are not unique to accelerated programs, but they do pose significant risk to the project's success given the aggressive timelines. For example, the use of a clinical manufacturing site for launch (which is unusual in a "conventional" development) may require a PQS upgrade to meet the standards of quality (i.e., documentation practices, deviation/change management) expected of a traditional commercial launch facility. In such cases, depending on the prior history of the facility, early engagement between the launch site and relevant operations' compliance teams may be necessary to ensure that the facility is positioned for successful execution of validation batches and prepared for inspection by health authorities.

There may also be differing interpretations of PQS requirements between local and global functions or between the company and contract manufacturing organizations. If such differences are not identified early in the process, they can result in rework or other project delays. It is important for the transfer team, launch site, and downstream parts of the supply chain (e.g., commercial filling) to communicate early and achieve alignment on standards for quality and compliance.

Forward planning of activities to manage PQS readiness is extremely helpful because the chosen launch site may not be familiar with the compromise between agility and formality required to support the early phases of launch from an accelerated development program. An operations site may be accustomed to more robust processes and having more data to support changes or deviations. Alternatively, a clinical site may not be familiar with the formality of PQS requirements for procedures in normal operations. Whichever site is chosen, considerable amounts of technical change management postlaunch are likely. Some factors to evaluate the level of agility and formality of the PQS are as follows:

- The PQS's ability to handle change management with agility. Careful planning and design of a proactive change management plan is a requirement for many accelerated development programs to address, for example, prospectively designed process changes. These proposed changes require a mature and potentially flexible change management system as a key element of the PQS.
- The appropriateness of standard operating procedures.
- The appropriateness of the levels and types of documentation.
- Staffing levels; for example, staff could be needed to handle the increased volume of investigations, which may be more intensive than usual. Additionally, in-process sampling/process monitoring activities will likely require more resources than a standard process would.

Quality risk management should be applied to identify and document risks to the accelerated program as they relate to PQS standards and to ensure appropriate control measures are in place to mitigate any accepted risks. Such assessments can then be used to prioritize activities and resources.

REGULATORY CONSIDERATIONS

Early, effective, and detailed communication between sponsors and regulatory authorities throughout development facilitates better and more informed CMC development decisions, which could lead to greater regulatory flexibility built upon a shared understanding of the risk-to-benefit profile. These discussions are particularly important when considering and developing a life-cycle approach.

When a life-cycle approach for a large molecule program is developed, it is most likely that use of comparability protocols and postapproval change management protocols (PACMPs) will be considered and proposed. Similar approaches should be considered for small molecule programs.

Some sponsors may find it useful to have discussions with authorities to reach consensus about the use of a product life-cycle management (PLCM) document as proposed in ICH Q12, Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, Step 2 [11]. The PLCM document outlines the specific plan for PLCM that is proposed by the sponsor.

Considerations for submission include dossier content and global filing strategies.

Dossier Content

Dossiers should be written concisely and clearly to facilitate review, and they should include well-structured and well-presented justifications to support the proposed positions and rationales. For example, the dossier should have justifications for the use of supporting data and platform technology, as well as brief explanations of the rationale for referring to prior knowledge. The CMC story, which may not be complete, should be logically organized and well written. Proposed future studies, the rationale for prioritization, and how results would be communicated to reviewers should also be clearly presented. For example, the use of regulatory processes such as comparability protocols and PACMPs should be clearly explained

and include references to any regulatory agreements. If a traditional approach to a control strategy has been taken, it may be beneficial to explain why this approach has been chosen.

Global Filing Strategies

Global regulatory filing strategies are complex and often not driven by CMC considerations. Issues such as the amounts and types of clinical data, as well as the enthusiasm of a regulatory authority for the drug product and its impact on disease in a regulator's country/region, will have an impact. Given that an accelerated development program will be targeted to at least one of the ICH regions, the sponsor is likely to focus, at least initially, on meeting the requirements of that region.

Furthermore, given the strong possibility that the CMC program will be phased with a life-cycle strategy, filings in regions beyond those proposed initially will depend on many factors. For example, the timing of applications could be affected by supplements and variations filed in the initial regions as well as by the amount of CMC data and information available from the still-evolving CMC program.

CASE STUDIES

The following case studies illustrate approaches that teams have taken to overcome their particular challenges related to the key considerations and themes noted in this series of articles. Notably, in every case study, teams observed that accelerated development programs run more smoothly when they have processes in place to ensure support by internal stakeholders. Furthermore, most, if not all, programs reported that they encountered significant regulatory challenges due to the lack of global regulatory harmonization particularly with (but not limited to) postapproval submissions. This issue is extremely important for accelerated development programs because, in almost all cases, a life-cycle approach is employed in such programs.

Case Study 1—Large Molecule

In case study 1, the sponsor had many postapproval commitments from various markets. Challenges included:

- Qualification of tests for certain in-process sample types
- Completion of drug substance and drug product container-closure leachable studies
- In-process hold-time revalidation
- Reevaluation of acceptance criteria after a certain number of lots (lot release, stability)
- Low endotoxin recovery remediation
- More detailed risk assessments
- Stability data

To resolve these issues, the sponsor had to conduct the necessary work and carefully coordinate postapproval supplements for:

- Change to an improved method: Supplements were needed for approximately nine markets; in the other markets, the original MAA was filed together with the supplements.
- Addition of a new site: Supplements were filed for around 20 markets.
- Method transfers and optimized testing strategy: Supplements were filed for most markets.
- Shelf-life updates.

The team used the life-cycle approach, deferring some CMC studies as postapproval commitments, with the regulatory authority agreeing to this strategy in advance, and articulating the risks and benefits of a selected approach. The sponsor also needed to consider supply chain options to add a new site of manufacture postapproval to maintain supplies to patients. Inevitably, shelf-life updates were required. Additionally, technical challenges were associated with the setting of acceptance criteria and the need to remediate low endotoxin recovery. In this case, a strategy to minimize process changes was employed to facilitate initial submission, approval, and supply to patients.

Case Study 2—Large Molecule

In case study 2, the sponsor pursued an accelerated submission process for a BLA for a new drug product with Breakthrough Therapy Designation (BTD). Key issues included the low commercial volume anticipated and the challenge of having different drug

product clinical and commercial manufacturing sites in the scope. Issues related to the latter challenge included:

- All clinical/stability experience to date would be from the clinical site.
- Shelf-life claims would depend on the bridge from clinical to commercial manufacturing (ensuring process comparability).
- Sufficient shelf life would be needed to effectively commercialize/distribute product.

Key facets of the life-cycle strategy used to address these challenges were to:

- Submit the BLA without a drug product PPQ at the commercial site and with limited or no commercial site experience (i.e., clinical or stability batches).
- Leverage a validation life-cycle strategy that relied heavily on prior knowledge from similar products manufactured in the same facility on the same manufacturing line. This strategy involved:
  - One PPQ batch to be provided at initial submission or during the review cycle
  - Two more PPQ batches to be performed/provided postapproval as clinical/commercial demand dictated the need for supply
  - Regulatory alignment pending

This team proposed to use a life-cycle approach to submit a BLA without a drug product PPQ from the commercial site and with limited experience of commercial site manufacture. The process validation and site selection strategies are heavily reliant on leveraging prior knowledge and platform processes. In both cases, risks and benefits were identified. In this case, a minimizing process changes strategy was also employed to facilitate initial submission, approval, and supply to patients.

Case Study 3—Large Molecule

In this case study, the sponsor also pursued an accelerated submission process for a BLA for a new drug product with BTD. Notable challenges included nontraditional comparability, the supply strategy, stability data, assay validation and utilization, and the reference standard.

To meet these challenges, the sponsor met with the FDA every 2 to 3 months to ensure alignment between the submission and regulatory expectations. Preapproval within a span of 1 year and the following interactions and content occurred:

- Type B: The sponsor sought FDA concurrence with the sponsor's proposed CMC strategy and proposed package for comparability.
- Type B: The sponsor provided an overview of its supply strategy.
- Type A: The sponsor and the FDA discussed the comparability strategy and data for Material B and Material B'; the use of B' in confirmatory trials; and the filing of B' as commercial material.
- Type C: The sponsor shared challenges in development, such as the potency assay, PPQ, HCP assay, and reference standards strategy, and gained the FDA's concurrence on strategy prior to finalizing the BLA.
- Pre-BLA meeting: The sponsor and the FDA discussed the CMC-specific content and format of the planned BLA submission, including the retrospective review of PPQ data, the updating of stability data, and the data's ability to support extension of shelf life.

Furthermore, at the postapproval (Type C) meeting, the sponsor sought the FDA's feedback on the control strategy and the agency's concurrence on the filing strategy for the proposed analytical method and specification changes.

This case study highlights the importance of communication between sponsors and authorities for many CMC issues, such as:

- Supply chain options
- PPQ strategy
- Provision of stability data and agreement about shelf life

All of the sponsor's justifications leveraged prior knowledge, and platform processes, identified risks and benefits, and the strategy obviously used a life-cycle approach. In this case, a strategy to minimize process changes was also employed to facilitate the initial submission, approval, and supply to patients.

Case Study 4—Small Molecule

Case study 4 involved a small molecule NDA submission after phase 2 clinical data. Submission after phase 2 clinical data was potentially 6 years shorter than a "typical" program based on historical experience.

Major challenges were:

- The solid-state drug substance form needed to be changed after phase 1 dose-finding studies so it would have a form that was compatible with proposed clinical and commercial tablet manufacturing processes and to ensure suitable long-term stability in global markets.
- The early drug substance synthetic route was not amenable to the scale of manufacture necessary to support rapidly enrolling clinical studies.
- Phase 2 tablet clinical formulation was an enabled tablet suitable for rapid entry to clinic, but it was not considered the image or strength necessary for commercial markets.

To address these challenges, the sponsor used the following strategy:

- A broad screen of solid-state forms was performed, supported by predictive tools and tabletability studies. Once narrowed to two options, a relative bioavailability study was conducted between the original phase 1 form and the proposed commercial form. Once relative bioavailabiity was shown, phase 2 pivotal clinical studies were started using the phase 2 clinical formulation and this selected commercial form.
- Synthetic route and manufacture, from 10 kg to 300 kg scale, were optimized to support commercial tablet development, drug substance ICH stability studies, and manufacture of commercial drug product stability and BE study materials.

- Commercial tablet formulation was developed in parallel with phase 2 clinical studies, evaluating formulation variants using predictive biopharmaceutical computational tools. A BE study was conducted to confirm the proposed commercial formulation is bioequivalent to the pivotal clinical study clinical formulation. This study was reported immediately before NDA submission. The commercial formulation was used in phase 3 confirmatory studies.

This case study had substantial risks beyond those expected in a conventional development:

- If another, more suitable (e.g., more stable), form were to be found later in development, the sponsor would have needed to redo the ICH stability studies and conduct another BE study. These additional studies would have involved significant delay and increased costs. Switching quickly and early from the phase 1 early drug substance form to the intended commercial form allowed for early commitment of the preferred drug substance form to clinical supplies for pivotal studies and to inclusion in the commercial tablet/ICH stability program.
- The impurity profile of the new drug substance synthetic route could not be qualified in time for NDA submission. If any new impurities were found in the optimized drug substance route, and the route were not qualified by virtue of their presence at some level in previous batches, the sponsor would have needed a toxicological qualification study (or studies) to qualify that impurity.
- The proposed commercial tablet formulation was not bioequivalent to the phase 2 clinical formulation. This could lead to a delay in launch supply and the need for an additional BE study of an alternate commercial formulation. Additional stability studies and process validation would be required for the alternate commercial formulation, resulting in a significant delay, added costs, and a risk to launch. Validation of clinical manufacturing facilities and process may have to be considered as a further mitigation step.

In this case, the company was able to deploy a skilled and knowledgeable workforce to understand the level of potential risk. With substantial resource commitment in terms of people and computational support, the sponsor managed to mitigate the highest risks successfully. This strategy was fully supported by internal stakeholders.

Interestingly, the total resources used for this 4-year (from first time in patients to filing) development program were comparable to the resources used for a typical 7-year program. In other words, the area under the curve is the same, but the peak of the accelerated program is higher over a shorter period of time.

Computational modeling, simulation, and predictions were used in all aspects of this program to minimize the risk associated with key decisions (form selection, drug substance synthesis scale-up, commercial tablet design, and prediction of BE performance). The program had no development "white space" (the time typically used to await a clinical decision point), which is used to to perform drug substance and/or drug product development activities and minimize risk. As a result, key development investments were made in parallel and at much greater risk than a "typical" program. These investments included the purchase of raw materials for the commercial drug substance route with commitment to a clinical supply with the selected commercial solid-state form of the drug substance for the pivotal study, the investment in ICH stability of the selected drug substance route before phase 1 ended, and the use of accelerated stability to predict long-term outcomes.

Case Study 5—Small Molecule

In this case study of drug substance synthesis, key challenges included:

- Supplier selection with respect to SM justification
- Purification strategy with respect to timing of route design and manufacturing route identification
- GMP strategy with respect to which steps to conduct or not conduct under GMP

The sponsor's strategy focused on the following:

- A commitment to purchase the SM before the control strategy was finalized and before data were generated (as recommended in ICH Q11 to select and justify a SM).
- The fairly aggressive choice for SM, which was considered risky for certain regional health authorities. SM selection should be determined by the technology required to manufacture intermediates.
- Use of an additional purification step (included in the common technical document) due to the conservative approach based on the tight timeline.
- The final few steps of SM being manufactured under GMP at vendors to mitigate risk.
- Inclusion of extra steps in the validation strategy (leveraging ICHQ7 Q&A for validation).

This case study exemplifies a strategy for selecting SM. In this case, an appropriate degree of process and product understanding was used to assess the risks and benefits of various approaches, and the sponsor took extra risk mitigation steps to minimize the harm to the project if a regulatory authority did not agree with the choice of SM. This approach, which required additional work compared to other strategies, had to be supported by internal stakeholders.

Case Study 6—Small Molecule

Case study 6 also involved drug substance synthesis. Three notable challenges were the development timeline (the sponsor sought to reduce it by 30% to 50%), the purification strategy, and optimization.

To address the acceleration of the development timeline, the sponsor used the following strategies:

- Choosing the commercial route with limited demonstration of processes at scale and limited time to investigate all multivariable effects, which is higher risk.
- Delaying process improvements during commercial route development.
- Compressing DOE studies, forcing a segmented study of process.
- Executing pivotal clinical studies before full analytical development was completed.

The purification strategy involved:
- Using a less-robust, higher-risk process due to time constraints.
- Manually stopping (cooling) the reaction when complete. This was necessary because overreaction leads to difficult-to-remove impurities.
- Submitting a comparability protocol for the development of control strategy for the catalyst.

Finally, the optimization strategies included:
- Delaying the pursuit of robust catalyst for reaction. The current catalyst ligand is very water sensitive.
- Placing multiple materials, representative API for drug product manufacturing, on stability due to a solvent switch in the middle of the API campaign.
- Choosing to not reduce the stoichiometry of reaction material to nearly 1 equivalents.
- Utilizing extra resources to develop the commercial route while managing clinical supplies (the route to be abandoned), and to challenge the impurity qualification utilizing dual campaigns.

In this case, the risks and benefits for the choice of the drug substance synthetic route were used to select what studies to perform to develop an appropriate degree of process understanding and to defer some obvious potential process improvements (e.g., choice of catalyst). Risks and benefits were evaluated by building redundancy into the program (e.g., multiple drug substance stability programs), with the approaches (e.g., investment of additional resources) supported by the internal stakeholders. A life-cycle approach was used to develop a control strategy for the catalyst through communication between sponsors and authorities.

Case Study 7—Small Molecule

In this case study of a drug substance solid-state form, the notable challenge involved selecting the ideal solid-state form for commercial manufacturing of the drug product. The sponsor's strategy was:
- Choosing the solid-state form while knowledge of the polymorph landscape was limited.
- Performing additional work to ensure that the chosen form would be obtained after a lower-energy form was discovered.
- Accepting that scale-up of API crystallization would be a high-risk endeavor due to incomplete process knowledge.

In this case, analysis of risks and benefits led to the conclusion that sufficient process understanding had been developed to support the scale of the chosen, higher-energy polymorph solid-state form and that the lower-energy polymorph would not be encountered on scale-up. This strategy required support from internal stakeholders.

Case Study 8—Small Molecule

In this case study, a notable challenge involved the drug product development timeline. Strategies to support the accelerated timeline included the following:
- Using the same clinical formulation and dosage form for the initial commercial launch of the drug product.
- Condensing brainstorming regarding the commercial route to submission.
- Focusing efforts on process reliability over yield and cost of goods.
- Deferring process optimization to postapproval.
- Submitting limited stability data.
- Utilizing single-source vendors.

In this case study, the sponsor evaluated the risks and benefits of using a less-efficient drug product formulation with single-sourced vendors for initial submission, approval, and supply to patients. An appropriate degree of process and product understanding was developed to support submission and launch, with a life-cycle approach used to advance process optimization postapproval. Communication between the sponsor and authorities was essential to ensure they were in agreement regarding the supply of limited stability data.

Case Study 9—Small Molecule

This case study highlights process validation challenges related to analytical development and the use of few full-scale validation lots. The sponsor's strategy was to:
- Focus on high-priority test methods.
- Use partially validated methods for qualification lots.
- Complete validation before commercial release.
- Negotiate acceptance to use clinical API for drug product validation.
- Build upon process and product platform knowledge and justification.
- Leverage continued process verification principles.
- Utilize clinical batch process data to enable the concurrent validation approach.

The sponsor evaluated the risks and benefits on the analytical validation approach to allow focus on the high-priority methods. Communication between the sponsor and authorities, the leveraging of prior knowledge and platform processes, and a life-cycle approach were used to develop the process validation strategy, which used data from clinical drug substance lots supported by data supplied during the continued process verification phase and submitted postapproval.

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