How to Avoid Last Minute CMC Roadblocks to Approval

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"We have to start over." Five words with heavy implications. When hearing this story, I could feel the impact those words must have had on the listeners. Months of work wasted. Months more of project delay. The simple fear of having to deliver the news to management that a simple, avoidable mistake would mean missing the filing date.

Problems can arise when sponsors face balancing available budget and time resources between clinical and chemistry, manufacturing, and controls (CMC) needs. Because of their high-profile importance in development, clinical needs get the emphasis, while the many CMC needs and risks may seem less critical. Unfortunately, as time passes, there is an increased risk of CMC issues becoming more complicated, time consuming, and expensive to fix.

The temptation to minimize or defer CMC activities while awaiting clinical milestones is understandable. Money and time are finite, and no one wants to spend either on CMC development activities that may turn out to be unnecessary if the desired clinical outcome fails to materialize. Such decisions, though, often contribute to delays, instead of accelerating development.

The simplest answer to this conundrum is to provide complete support to both clinical and CMC development, with a "keep everything up to date at all times, and verify or investigate everything" philosophy. Unfortunately, today's competitive environment does not lend itself to that solution. Timelines are too short, and expenses are too high to allow this approach to work. It is not helpful to have a fully developed and supported Phase 2 product if it takes a year too long, and you run out of funding or your competitor beats you to market.

A better, hybrid approach is to continue to progress with clinical development, while simultaneously giving metered attention to those CMC issues that pose the greatest danger of costly late-stage remediation.

This is a brief overview of the CMC information required by regulatory authorities and highlights why planning and budgeting for key CMC considerations early in the development process are essential for success.

CMC Documentation: Extensive and Exacting

CMC information provided in support of an IND, NDA, or ANDA filing must be presented in the electronic common technical document (eCTD) format and submitted via the electronic submissions gateway (ESG). In general, CMC content flows according to the following prescribed modules:

Quality Module 1

Module 1 provides administrative information including the FDA form 356h (application to market), field copy certification, patent certification(s), exclusivity claim, certificates of authorization, drug master file references, environmental assessment, and labeling information.

Quality Module 2

Module 2 contains the Quality Overall Summary (QOS), which provides an overview of the CMC for both drug substance and drug product. It highlights critical, key parameters and summarizes adherence to guidelines along with any important issues. The goal is to integrate quality module content with supporting information.

Quality Module 3

Module 3 provides the most comprehensive and detailed information of CMC subdivided into sections for drug substance (32S) and drug product (32P). Note that similar subcategories are required in each major section:

Drug substance

- General properties of the active pharmaceutical ingredient (API)
- API manufacture, including control of critical steps, process controls, and validation
- Elucidation of structure and impurities (polymorphs/ analytical results on impurities)
- Control of the API — specifications, analytical controls and validation, batch analysis, and justification of specifications
- Analytical reference standards, container closure documentation, and API stability

Drug product

- Description and composition
- Pharmaceutical development report
- Drug product manufacture, control of critical steps, process controls, and validation
- Control of excipients (compendial vs. animal/human/ novel) along with required TSE/BSE certifications
- Control of drug product, including specifications, analytical protocols and validation, batch analysis, characterization of impurities, and justification of specifications
- Analytical reference standards, container closure documentation, and finished drug product stability (including post-marketing stability commitments)

CMC information is not just supportive of your product in a way that can be completed at any time in development. In many ways, your CMC information forms the foundation for your product's clinical outcomes. It documents the chain of development that proves the work you have done and the data you have generated really are relevant to and support the final product for which you are seeking approval. The timing of this CMC work is often important. Changing aspects of CMC late in development — whether materials, composition, methods, or equipment — can make the clinical results from your earlier studies irrelevant to the final product. This can leave your final regulatory filing without sufficient supporting evidence as a basis for approval.

Real-World Examples: How CMC Can Help Avoid Problems

In the opening story, scale-up engineering was going well until the dissolution results did not meet expectations. Laboratory investigation confirmed the results. The equipment was checked, the operators were interviewed, and materials and batch records were reviewed. Investigation found nothing amiss with the equipment, the formulation, or the process. The correct batches and amounts of the correct materials were used. A repeat batch gave similar puzzling results.

Further investigation eventually yielded a disappointing discovery. For engineering use, the raw materials were received and accepted on review of their certificates of analysis. To save time and money, only identification testing for the API was performed on receipt. In-depth investigation eventually found that the lot of API received was the wrong polymorph. All the engineering work had to be repeated.

It was fortunate that the team discovered this error during the investigation. If the dissolution discrepancy had been small enough, it might have been possible to adjust the process parameters to obtain passing dissolution results with the wrong polymorph. This would have been disastrous as subsequent lots of API came in and the product again began to fail dissolution, because the process was now optimized for the wrong API polymorph.

This is just one example of a case where a simple and inexpensive action (confirming the polymorphic form of the lot of API), performed at the right time, could have avoided months of wasted effort.

Additional examples:

- **Raw material testing**

  Polymorphism is not the only risk to development posed by API. It's a common practice to move ahead in clinical assessment as quickly as API availability and quality allows. Frequently, this means minimizing the testing performed and going ahead once material "good enough for this phase" is obtained.

  In one case, this philosophy resulted in a costly clinical failure for the Phase 3 trials as the newly purified API eliminated an impurity that had been present during the Phase 2 studies. The impurity level had been deemed safe, and so the studies went ahead. Unfortunately, that impurity was also pharmacologically active, and when the Phase 3 trial failed to meet its primary endpoint, this impurity's absence was found to be the culprit.

- **Shipping temperature excursions**

  The risk of clinical trial materials being exposed to hot or cold temperature excursions during shipping is significant. Companies often include temperature-tracking devices (e.g., TempTales™) with their product during shipment to the clinical sites. This is an inexpensive way to assure yourself that your product did not suffer extreme conditions such as sitting for hours in a freezing truck or on a 100° F loading dock.

  If you do discover that your materials were overheated or frozen, what can you do? Having good data from a short stability study covering temperature extremes can make the difference between throwing that product away or starting your clinic on time. Newer temperature-tracking devices may include automatic, real-time alert messaging from material monitors while in transit, giving you a timely opportunity to determine the severity of the excursion and what corrective actions are needed to address clinical drug supply.

- **Implications of Maximum Daily Intake (MDI)**

  For one product, in late stage discussions, the FDA informed the sponsor that the MDI would be significantly higher than had been previously discussed, indicating that the MDI ranges weren't supported by the Pharm/Tox information in the application. This issue can occur at more than one stage of development with a variety of implications. During early stage formulation development, the formulator must make the effort to confirm that the MDI ranges for each excipient are acceptable based on the FDA Inactive Ingredient Database (IID) or supported by additional toxicology studies performed by the sponsor.

  MDI may also affect the expected specifications on impurities for the drug substance and drug product, elemental impurities, and residual solvents. Once the formulation composition is decided and provisional specifications are set, the development team must monitor the final expectations for daily dosing and confirm before filing that the product composition and specifications properly align with the MDI.

Ensure Site Readiness for Regulatory Inspections

To prepare for regulatory inspection and product launch success, strongly consider scheduling a mock pre-approval inspection (PAI) at both the manufacturing and analytical testing facilities. In addition to preparing for inspection success, these inspections, especially when conducted by experienced or former FDA inspectors, helps to alert the entire organization that a regulatory inspection is on the horizon and all inspection-ready activities must be completed.

Site Preparedness Means That:

- Site is able to manufacture product under cGMP conditions.
- Adequate controls are in place and manufacturing documents, such as batch records, validation reports, SOPs, etc., are readily available. Electronic systems provide a significant advantage to documentation availability.
- Descriptions of manufacturing steps and testing results for assay, stability testing, and the final dosage form are available for review.
- Methods validation documentation, a list of the analytical reference standard samples (include lot number, date of manufacture), and samples of the analytical reference standards themselves are readily available for shipment to FDA upon request after the regulatory submission.

In today's competitive environment, drug developers aiming for speed to market are compelled to focus available resources on achieving early clinical trial results while relegating development of the manufacturing process and analytical development to a lower priority. While it may be tempting to underfund CMC activities while waiting to attain clinical milestones, such decisions are more likely to delay, not accelerate, development.

CMC requirements, especially those critical to successful drug development, registration, approval, and life cycle management, require an appropriate share of the developers' attention and resources. The regulations relevant to CMC development are challenging, detailed, and time sensitive. As a developer, you must pay close attention to regulatory expectations to:

- Ensure drug substance/drug product dynamics are well characterized and understood.
- Write and assemble CMC sections of regulatory submissions.
- Prepare for productive and successful milestone meetings with regulatory agencies.
- Avoid noncompliance setbacks (FDA 483s, warning letters, or other regulatory notices of concern).

Product discovery, development, commercialization, and sustainability are all related. If you do not pay sufficient attention to regulatory expectations in the early stages, you may be forced to repeat or supplement previous development activities.

Final Recommendations

- **Maintain an issue log**

  It is easy during the months and years of drug product development to notice and consider many risks, gaps, and issues. Some will be immediately resolved, while others are deferred. These are often the things that come back at the most inopportune time. Keeping a log of issues, gaps, and risks, and revisiting it from time to time, will help ensure they aren't left unresolved until it's too late.

- **Keep regulatory affairs in the loop**

  Representatives from development and regulatory affairs should meet three to nine months in advance of the earlier phase regulatory submissions and collaborate with the FDA on the pre-NDA meeting, which should occur at least 12 to 18 months before the final NDA submission. These meetings will help ensure that critical path activities are initiated in time to deliver the required documents for filing. These internal milestone meetings will also provide an additional opportunity to ensure all necessary technical documentation has been produced to support the filing. Your team should also review the issues log and look for gaps in the development narrative.

- **Prioritize and plan**

  Agree to priorities. Quality will always top the list, but the relative importance of time versus budget will drive the prioritization in decision making. Performing an initial risk analysis will unearth any potential downsides of early, cost-saving decisions. Questions to be answered include: Have you left enough time for CMC development? Will there be an adequate supply of high-quality drug at first-patient-in? Have you ensured there will be enough clinical trial materials and final product when needed? What about formulations and packaging? Are the demands of the clinical design feasible?

  If you follow a quickly designed formulation and minimal CMC process, your team must be prepared for unexpected hurdles and delays. Disciplined and transparent risk assessment and decision making may seem slower at first, but it generally beats more haphazard approaches to success.

The goal of CMC preparation is to ensure that you successfully develop two things: a product and its means of production and testing, and a documentation package that brings together the full development path, rationale, and decisions in a way that fully supports and ties together the nonclinical and clinical results generated along the way. The requirements are complex, and any oversights by you and/or your CDMO could lead to deficiencies or repeat work, stall your development timelines, and increase costs.

For this reason, planning a CMC strategy and filing early in development is essential. The planning must be meticulous, and both the plan and the strategy must be rechecked and confirmed periodically during execution.

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