
On the Fast Track: Project management and FDA interaction when an NDA is Fast Tracked

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For a new drug, every day lost waiting for approval is a day of lost profits for the marketer. In the case of drugs intended to treat serious or life-threatening conditions such as cancer, it can literally be a matter of life and death for the patients seeking treatment. To facilitate the approval of these important drugs, the Food and Drug Administration (FDA) Fast Track program exists to expedite the review of new drugs that are intended to treat serious or life-threatening conditions, as well as those that address unmet medical needs.

The average approval time for a new drug is currently more than 18 months, and each application is under increased scrutiny to ensure drug safety, as a result of recent high profile drug safety issues. A successful Fast Tracked drug application can cut that time down to a year — or even less — with excellent project management, talented technical resources, experience with regulatory requirements, hard work and maybe a little luck.

Definition and benefits of Fast Track development

Firms may request Fast Track status any time from submission of the original Investigational New Drug Application (IND) until the approval time of the New Drug Application (NDA). Firms will usually make the request during clinical trials, after safety has been demonstrated and after preliminary efficacy data show encouraging results. The FDA will determine whether to designate the drug for Fast Track within 60 days of the request. Typically, the Fast Track designation will be awarded during Phase II of the clinical trials.

Once Fast Track designation is granted, the submission process is greatly accelerated. First, and most important, the sponsor is encouraged to meet with the FDA several times throughout the drug development process to reach agreement on the Agency's expectations for the NDA submission. Also, the Fast Track designation allows for submission of the NDA in sections rather than all at once, as in the case for new drugs not so designated. Often firms will submit the Chemistry and Manufacturing Controls (CMC) section before submitting the Clinical section. Further, the FDA may agree to accept sections without full data or full reports, which are required for non-Fast Track drugs. For example, the FDA may accept the section with limited stability data contingent that the application will be amended with additional data as it becomes available. If the FDA agrees, this significantly reduces the time between the initiation of the stability study and submission time by many months.

There are, however, risks with the Fast Track submission. During the development process, much is learned about the drug and about its performance in the clinical setting. When the time to submission is so dramatically reduced, some of the knowledge normally gained during development is lost. Fewer manufacturing replicate batches can result in less manufacturing knowledge. Unpleasant surprises, such as unanticipated impurities, can arise with materials, processes or test methods. More dire consequences may result from less experience in the clinic. As the number of patients treated becomes larger, unanticipated adverse events may occur; some can be serious. But if you or one of your loved ones has a life-threatening disease such as cancer, the potential benefits often outweigh the risks. There are many cases of people

who, told that they had untreatable cancer, were given only a handful of months to live, but went into remission after treatment with a new drug that had been Fast Tracked to approval.

The compressed timeline of the Fast Track application further narrows the already razor-thin margin for error of a standard NDA. A successful Fast Track drug will depend upon the sponsor's and contractors' ability work together to anticipate and mitigate any and all complications in development, manufacturing and regulatory matters.

I. Customer Relationship

In one instance, a sponsoring company reported that the submission timeline was compressed from 36 months to 12 months. Still, the same amount of work had to be done to satisfy regulatory requirements. Even without the added complications of an accelerated timetable, the task facing the sponsor's project manager is formidable. The chemistry and clinical "to-do lists" fill entire textbooks.

Although the submission and review process is accelerated, all of the work required for a "non Fast Track" drug is still required for a Fast Track drug, and careful design of the project plan will make or break a sponsor's application. While each project plan is specific to its unique drug, sponsors should know that they will need the following critical path items:

- * Processes must be developed, challenged and validated for both the drug substance and for the drug product.
- * Analytical methods must be developed and validated.
- * Reference Standards have to be prepared and characterized.
- * It may be necessary to prepare impurities for use in analysis.
- * Specifications for all materials and components must be developed and justified.
- * Drug substance and drug product must be put on stability.
- * Microbiological concerns must be addressed.
- * If new facilities or equipment are installed, they must be qualified.
- * Equipment cleaning procedures and analytical methods must be developed and validated.
- * Manufacturing process hazards must be evaluated.
- * Operating personnel need to be trained.

Finding the right contractors to fit these jobs is absolutely essential. A given new drug may require on the order of half a dozen different contractors. There is plenty of work to go around, from the development of the drug substance (the Active Pharmaceutical Ingredient or API) synthesis, development of the formulation and packaging for the drug product (the dose unit used in the clinic), analysis of materials, stability and toxicology, clinical trials administration, and preparation of regulatory documentation. To reduce the number of contractors needed, sponsors are often well served to seek out providers that can handle multiple duties. Conversely, a sponsor should also consider adding a contractor to audit all of the other contractors.

Due to the extreme time crunch, the relationship between the sponsor and its contractors is of vital importance in order for a Fast Track approval to be successful. While the advantages of a Fast Track designation are innumerable, all requirements for submission must be met in a compressed timeline.

The project manager from the sponsor side must work carefully with project managers at the contractors to be sure that all of the work is performed on schedule and complements the work being done at the various sites. From the beginning of the process, communication at every level will facilitate a smooth approval process. Primary contact between sponsor and contractor project managers will drive the project. For a successful Fast Track, dialogue between sponsor and contractor chemists, analysts and quality management (QM) must be developed and maintained. Weekly or bi-weekly contact either through reports or conferences may be held early in the process while communication will increase as the drug approaches approval. In some cases, brief daily teleconferences may be appropriate to maintain a tight schedule. A flexible contractor lets the sponsor determine how much communication they need to feel comfortable with a given application, whether daily or only as the contractor needs information to continue work. A responsible contractor will also tell the sponsor if more communication is needed.

II. Technical experience and expertise

In choosing contractors, there are several factors to consider. What experience does each have with Fast Tracked applications? Do they have experience with materials of a similar chemical class to the new drug? Do they have experience with approval in international markets?

A good contractor will leverage its experience and share knowledge and expertise with the sponsor, making recommendations where appropriate. A responsible contractor will not take undue risks. If needed, the project will be provided with additional manpower to ensure approval. On the other side of the coin, a good sponsor will not ask contractors to cut corners, take risks that put employees or facilities in danger or break or bend any laws or regulations. A responsible contractor will not sacrifice its compliance record and reputation to save the client a little money.

When evaluating contractors, sponsors should also consider the markets they will be entering in both the short and long term. The European regulatory agencies have different expectations than those in the U.S. A sponsor that expects that its product may eventually be marketed in Europe may wish to choose contractors that have such experience to help accelerate approval down the line. Even very early in the process, data can be collected that will be important in the E.U.

The application process is the same regardless of the compound, meaning a contractor's staff experience will be transferable to any NDA. The chemistry can be radically different, but the regulatory process and data and reporting are the same. Lessons are learned project to project, in project management, process development, analytical work and documentation. A question raised by the FDA for one compound is likely to be raised for others, so having a response prepared in advance will save time. Having gone through the process allows one to anticipate possible issues and address them early on.

III. FDA relationship and understanding

The FDA's Guidance, "Fast Track Drug Development Programs," specifies that the sponsor can have meetings before the IND submission, at the end of Phase I, at the end of Phase II and right before the NDA submission. Sponsors may choose to have their contractors participate in these meetings. This is especially valuable if the contractor possesses expertise that the sponsor does not. Even with the best of communication between the sponsor and contractor, the contractor has a more complete and thorough knowledge of the processes and systems and will be able to answer questions about them.

After submission, any and all of the contractors and clinical sites are subject to Pre-Approval Inspections (PAI) from FDA. It is wise for the sponsor to retain auditors to review work at the manufacturing contractors and the clinical sites to ensure that all are complying with the regulations and that all comply with procedures and protocols in the submissions.

If a drug is declared non-approvable, most often it is because it fails in the clinic, but another significant reason for non-approval is a lack of compliance with the filed procedures or protocols at the manufacturing or clinical sites. One contractor firm reported that it failed a PAI because the sponsor had made major changes to the filing and did not provide the contractor with current processing, sampling and testing procedures. Ultimately, the sponsor's application was approved, but patients were left untreated and significant sales revenue was lost.

Before you host a PAI, you should have at least one lot of API completed under the Process Validation protocol. Inspections may be waived at the discretion of the FDA, and this decision is based in large part on the contractors' inspection profiles, when they were last inspected, and if the material under review is similar to material from a prior inspection. While no contractor is immune to inspections, a good inspection history increases the chances that they will not slow down the approval process with additional questions from the FDA.

The broader the range of APIs a contractor has worked on, the more likely it will have worked on a similar material and be more likely to facilitate the approval process. When a contractor is inspected, there is a likelihood that issues will be raised. They must be responded to promptly to minimize delays in approval. A responsive contractor will work with the sponsor to turn around a response to FDA quickly.

One of the first documents that FDA will want to review during the PAI is the Development Report. This document provides the basis for the intended commercial process and provides data from process challenges ("parametric studies"), which define the critical process parameters and define and justify the processing operating limits. A thorough, complete, well-written development report will set the tone for the rest of the inspection. The contractor should also be prepared to present documentation for analytical methods validation, cleaning validation and equipment qualification. Any batch failures or discrepancies must be thoroughly investigated and corrective / preventative measures should be in place.

At the conclusion of the inspection, the Investigator may issue a citation (an FDA-483), which lists any areas of non-compliance identified. It is imperative that responsible personnel who will actually be preparing the response — department heads, directors, vice presidents — understand the observations. While a formal response is not required, it is strongly recommended. Responsible personnel should assess the observations and commit to provide a formal response with all due haste. Whenever possible, the issues should be addressed and closed (for example, procedural rewrites or additional training). In some instances, the planned corrections are described and commitments are made as to when the remedial action will be complete. Any commitments must be met. Once a timeframe has been agreed upon with the

FDA for a response, that deadline simply cannot be missed. If further data must be supplied to supplement the available data, the sponsor risks the very real possibility of having their approval revoked unless it complies.

During the NDA review, the FDA may ask chemistry questions of the sponsor. Here again, the contractor's support is critical to the approval process. One of the more common questions will relate to the specifications and request that the limits be tightened. It is important that the contractor know its systems and processes thoroughly to know whether to tighten the limits or to explain why they are justified as submitted. If you can't make the product to meet the new specifications, you must defend your existing specification. One approach is to indicate that the specification has been developed based on limited data and to commit to review the specification after completion of additional lots. Other issues that may appear in the FDA chemistry questions may necessitate development and validation of new analytical methods. As with the PAI response, a formal response to the chemistry questions should be submitted as soon as possible. Depending on the nature of the questions, it may be appropriate to request a meeting with the reviewer to discuss options for remediation. If the issues are not too serious, the FDA may be willing to discuss matters in a teleconference. Again, the contractor's assistance can be invaluable, particularly if it has experience responding to FDA questions.

IV. Preparation, Anticipation and Mitigation

A good contractor will report good news to the sponsor quickly and bad news immediately. Any problems left unattended will only serve to increase delays, or worse, sink approval altogether. Validation lots may not meet specifications, new impurities may be discovered and there may be a loss of quality when scaling up the process. Humidity, temperature, pressure and countless intangibles have a very real effect on processes and must be managed appropriately.

While there will always be some unexpected issues along the way, a successful Fast Track application will have anticipated as many potential problems as possible and be prepared to mitigate them as they arise.

A major area of concern from regulatory authorities will be the specifications of the materials (API, drug product). The more a sponsor can anticipate questions on the specifications and have a prepared response, the faster it will be able to come to terms with the FDA and the faster it will be able to achieve approval. One cannot overprepare when it comes to identifying potential questions and developing responses and justifications.

The Fast Track approval process has accelerated the delivery of a number of vital drugs to the market to meet the needs of serious conditions. While the FDA works just as hard to help get these drugs to market, it is the agency's responsibility to ensure that the public's safety is not compromised. A successful Fast Track relies on the experience and expertise of the contractors to prepare for and work with the FDA to ensure a smooth process from PAI to approval.