

APPLIED CLINICAL TRIALS

Drug Development on Rails

Managing the drug development process entails project planning, management, and the right tools.

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By: [Timothy A. Wurst](#), [Brock G. Guernsey](#)

Applied Clinical Trials

The drug development process would rarely be described as being on rails, unless roller coasters were included in the metaphor. However, with integrated project team planning, good project management, and the right tools it is possible to guide the process within narrow boundaries or, remaining true to the metaphor, put it on rails. Key benefits of a well-guided project are efficiency and rapid progress.



Project team and plan

Managing drug development is a complex undertaking. The activities of an individual functional domain or department are often so complex that it is difficult to marry one department's intricate schedule with those of a different functional domain. For example, the chemists and product formulators not only isolate the active substance and create a usable dosage form, but they also provide technical reports for the chemistry, manufacturing and controls (CMC) section of an investigational new drug (IND) submission and manufacture the investigational product (IP) in time to have it available for clinical trials.

On the other hand, toxicologists should not start long-term and expensive carcinogenicity trials until there are positive clinical results. Then again, they should not wait too long or these studies will be on the critical path and hold up the new drug application (NDA)/common technical document (CTD) filing for FDA approval. Figure 1 shows a general overview of how the domains of discovery, CMC, nonclinical, clinical, and regulatory integrate their drug development activities.

This is Part One of a two-part article on managing a drug development project from discovery through final regulatory approval and product launch, which can be a 12-year process. Part One describes the structure of a comprehensive project plan template and four aspects where the template can facilitate project progress. In Part Two, we explore how the template can infuse a project with best practices and how it can be used to accelerate a project's timeline.

Project manager

When considering the unique knowledge in each of the five major domains of drug development, one quickly realizes that it takes a magician to coordinate the independent functional activities into a coherent and usable timeline. Yet, that is what good project managers are supposed to do: magic.

Drug development is generally a slow process. Entire careers may be spent on just a few drug development programs. Resident departmental experts rarely have the decades of experience necessary to intrinsically know how their work product dovetails with the requirements of other functional areas. Good project managers are schedule coaches, and they understand how departmental plans integrate into the overall project plan. Departmental leads or

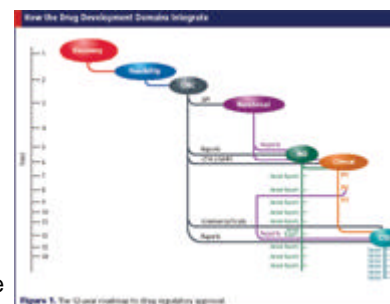


Figure 1. The 12-year roadmap to drug regulatory approval.

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representatives who participate in the project team negotiate, but they eventually accept the coach's prioritization and overall integration of each departmental plan into one project plan.

The project plan

A competent coach starts with a plan. A complete, detailed, and integrated project plan is the best place to begin when focusing the valuable energies of functional departments. The plan should be started early. A project plan should be visible to the entire company as soon as discovery has a viable compound/lead or when a licensing agreement is being considered for an external compound.

This article describes a fully integrated template of a project plan used to accelerate NDA-related activities, milestones, and deliverables for a New Chemical Entity (NCE) during an estimated 12-year development cycle. The project template utilizes a regulatory backbone based on the IND and CTD tables of content.

The NCE project template covers the broadest possible array of development milestones. It was built in 13 modular sections, utilizing the five functional domains of Discovery, CMC, Nonclinical, Clinical, and Regulatory. The complete plan contains approximately 8400 tasks. The modularity enables rapid customization for varying projects. The 13 plan modules are: pharmacology discovery and efficacy proof of concept; project initiation; CMC development; nonclinical development; IND preparation; clinical development; CTD preparation; 120-day safety update; final labeling safety update; FDA approval and launch preparation; IND annual reports; CTD periodic updates; and product development and strategy.

The NCE model assumes the compound to be a chemically synthesized IP. From a project planning perspective, biologicals, new indications (sNDA), and generics (ANDA) have differences that would justify a modified template, particularly in the Nonclinical module and commonly in the CMC and Clinical modules. Templates of those variants have also been developed; however, for simplicity, only an NCE example is illustrated. The putative disease for this template is one that can be studied for efficacy in a 60-day "on-study" window in Phase II and III studies. The estimated times used in the NCE project template are customized in case different assumptions need to be made by the project team, or if actual protocols become available with final estimates.

Utilizing the Microsoft (MS) Project® software application, the template takes full advantage of the software's native functionality to properly organize, track, and present a complicated list of operational tasks and timelines. The project timeline self-adjusts based on the project's actual progress.

Project plan rationale

The project plan may be used in many different roles. It serves as a planning tool. It can be a benchmark of company or team performance. It can provide a template that acts as an expert system for how things should be done. It creates a forum for project team member interaction and communication. It may even provide a means for controlling development costs.

Better performance tool

There are always those in an R&D organization who resist being held to a plan. "My work is too dependent on factors outside my control" is a common perspective. Behavioral studies show that productivity dramatically improves if there is some expectation of a deadline.¹ Even with the creativity required within a function such as discovery, the department can benefit from having a rough guideline of how long it is allowed to experiment with a molecule before the company expects to have a lead compound to transition into nonclinical and CMC development. It is difficult to operate efficiently in an environment where there are no expectations.

Strategic template and expert system

Executives make better decisions when presented with realistic expectations. A project manager who begins a plan based on a complete and fully integrated template can help position senior management's expectations to minimize surprises.

A 12-year development timeline is far too unwieldy for even the best manager to remember in detail. While creating a customized project plan de novo might be one option, it is more reasonable to use the knowledge embedded in a project plan template. For any IP, the project manager uses whatever information is available

from the functional domains, blends it into the project plan template, and modifies it as required. This method provides a far better visualization of what might be required during the multiyear development process for an NCE.

By using a template, senior management has an immediate overview of the entire program, its timeline, resourcing, and costs. Without the aid of a template that provides estimates for timing and resources for the complete project plan, there is great risk of having an R&D program evolve from a limited and inexpensive venture into an open-ended and resource-consuming enterprise. Figure 2 illustrates a collapsed high-level overview of the NCE 12-year development template.



Figure 2. A collapsed, high-level overview of the NCE 12-year development template.

Interaction and communication

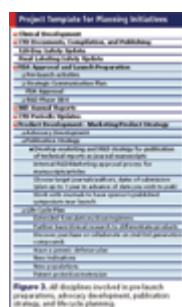


Figure 3. All disciplines involved in pre-launch preparations, advocacy development, publication strategy, and life cycle planning.

Getting an NCE to market requires more than the simple execution of operational work steps by the project team. It takes intelligent interaction, creativity, and interdisciplinary communication over the course of the development cycle.

The NCE template includes tasks that prompt marketing assessment and planning, financial evaluations, and management decisions. For example, the template identifies the timing and prompts the team to evaluate technical criteria for graduation of a lead compound from Discovery to CMC and Nonclinical development. It initiates team discussion on how to integrate clinical protocol endpoints with marketing labeling targets. It suggests appropriate timing for clarifying and implementing the strategy for technical and marketing publications, product advocacy development, prelaunch logistics for sales force and training, continuous evaluation of ROI from detailed cost planning and sales projections, and product life-cycle planning. Figures 3 and 4 show examples of how the project plan template prompts the project team to consider these types of cross-functional interactions at appropriate times in the development cycle.

Controlling costs

Risk of study failure and study costs are often inversely related to the linear progress down the development process. When risk of failure is high (e.g., in early preclinical stages), the experiments are cheaper to perform. This pattern remains true during clinical, where only a few healthy volunteers are tested in Phase I, while more subjects are enrolled in Phase II and even more in Phase III.

If a compound fails to meet expectations, the project should be terminated, and the earlier a candidate is eliminated from development, the fewer penalties the company pays in investment and opportunity costs. A proficient project team creates stringent technical and clinical criteria designed to eliminate a potentially unsafe or ineffective compound as early as possible in the development cycle.

Aside from prompting the project team to create stringent stopping criteria, the project template times the initiation of certain studies to either maximize cost savings or accelerate development. In the current NCE template, CMC waits for positive clinical results before making larger production scale batches; expensive nonclinical carcinogenicity tests also await demonstration of clinical efficacy. Conversely, it is logical to invest in a battery of tasks when the cost is relatively low.

In the template, all the relatively inexpensive nonclinical safety tests are run in parallel rather than sequentially. The Phase I trials are implemented in a rolling fashion only two weeks apart, and several of the Phase II studies are run in parallel. Even though it is possible to receive technical results that would terminate the drug immediately and save downstream expense, the hundreds-of-thousands saved probably do not merit the millions in lost Net Present Value (NPV) if patent time is wasted. By keeping all these elements organized, linked, and integrated in the project plan, the project team can help enforce a sensible and cost-effective approach to govern development.

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Figure 4. All disciplines in project initiation and financial and marketing review.

Wesley, Boston, 1997).

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Drug Development on Rails: Part Two

Using a template both accelerates a project's timeline and infuses it with best practices.

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Developing an integrated project plan requires the involvement of experts from each of the functional domains. It is always good to set benchmarks from industry best practices within those domains. Best practices identified from wide experience in numerous clinical trials were incorporated in the New Chemical Entity (NCE) template described in Part One of this article (ACT, August 2006). Naturally, some task times

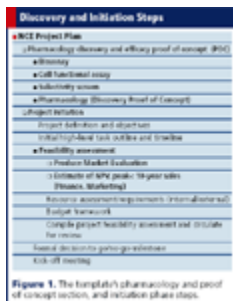
will vary widely by product and indication, but a starting framework is a useful baseline from which to then later modify using more specific assumptions. Even with the variation from product to product, a standard best practices timeline can help set general expectations even before the detailed aspects of the preclinical or clinical development plan are known. Particularly in the clinical area, many tasks are fairly standard from one study to the next (e.g., four months to initiate a trial).

Discovery and project initiation

Discovery research is by nature the most creative aspect of the process and is best managed with modest schedule constraints and maximum flexibility. The project template allows one year for Discovery activities. Following Discovery, the first detailed part of the project plan template is the Initiation Phase. Before a project can transition from research to development, it must be critically evaluated in the Initiation Phase for overall feasibility from the technical, financial, marketing, and resource perspectives. Once the project is approved to advance into the development domains [Nonclinical; Chemical, Manufacturing, and Controls (CMC); and Clinical], the work on manufacturing and formulating the Investigational Product (IP) may begin. Figure 1 shows a breakout of the Discovery pharmacology and proof of concept section of the template, and an overview of the steps for the project Initiation Phase.

This is Part Two of a two-part article on project managing a drug development project from Discovery through final regulatory approval and product launch, in what can be a 12-year process. Last month we explored the structure of a comprehensive project plan template and four aspects where the template can facilitate project progress. In Part Two, we explore how the template can infuse a project with best practices and how it can be used to accelerate a project's timeline.

Chemistry, manufacturing, and controls



The CMC effort requires several years to produce IP at Good Manufacturing Practice (cGMP) standards, but early Nonclinical safety testing may be conducted using non-cGMP product that is usually produced within 12 months. Another 12 months are allowed for manufacturing to reach pilot scale process. The toxicology and early Phase I clinical studies require cGMP investigational product from pilot scale batches. CMC is often plagued with long lead times that can compromise development schedules and delay critical Nonclinical and Clinical milestones if there is inadequate advanced planning. As a result, it takes a dedicated effort to assure that manufacturing responds to development initiatives in a timely fashion. Getting into the queue for manufacturing the various batches of IP (laboratory scale, pilot scale, and production scale) can create months of delays if not addressed early. In addition, the manufacture of pilot and production scale batches involves extensive validation and quality control procedures that add significantly

Figure 1. The template's pharmacology and proof of concept section, and initiation phase steps.

to the overall time requirements. An overview of the CMC section of the template is illustrated in Figure 2.

Nonclinical

Once CMC has initiated its plan and there is confidence that the IP can be manufactured at the required scale and on time, more specific details from the Nonclinical and Clinical plans supplant the automatic defaults in the project plan template. The safety studies in the Nonclinical module of the template are planned for completion in a few months and assume the use of unformulated, laboratory scale IP. Toxicology studies begin only after preliminarily formulated cGMP IP is available.

CMC commonly is on the critical path for early Nonclinical studies, particularly toxicology studies. Once cGMP investigational product is available, most of the toxicology studies are finished within two years. Toxicology studies that are not required for Phase I and/or are very expensive (e.g., definitive carcinogenicity studies) are delayed in the template until they logically fit into the project plan timeline. In Figure 3, the major studies and elements of the Nonclinical template module are detailed.



Figure 3. Major elements of the Nonclinical template module.

Clinical

Subject enrollment in the clinical program is initiated 30 calendar days after IND filing. (All other days described below are work days per MS Project®.) Human dosing at an investigational site begins when the following predecessor steps are completed: 1) protocols are written and approved; 2) the IND is accepted; and 3) IP is available at the site (requires completion of essential regulatory documents).

Clinical studies usually follow the same basic operational tasks, no matter what product is being studied, and the template was designed with that assumption. Start-up tasks are generally similar between studies, although timelines expand with the number of sites involved. In practice, a single-site Phase I study could be scheduled and initiated with a single phone call, while a large global trial involving 300 sites would require more time. A complicated protocol or one in which investigative sites are not readily available might also require substantially more time. There are, of course, many other design variations other than the number of sites that might occur and affect study start-up timelines. For template consistency the Study Start-up module allows two variations in duration of time required to identify and select investigative sites: 1) a Phase I and pharmacokinetic-type trial is set at 23 days; and 2) a longer Phase II and III timeline is set for 52 days. An example of the Study Start-up module in a Phase I trial is shown in Figure 4.



Figure 4. Example of the Study Start-Up module in a Phase I trial.

In the Study Conduct module, two enrollment rates and three "on-study" durations were allowed for subject enrollment and treatment defaults. This keeps the template for the Study Conduct module standardized and reusable, but modifiable when more specific study information becomes available.

- Phase I and pharmacokinetic-like studies allow for enrollment over 20 days from "First Subject In" (FSI) and "Last Subject In" (LSI) and one day on-study.
- Most other studies (Phase II and Phase III) use a 60-day enrollment window for FSI to LSI and 60 days on-study.
- Safety studies are usually longer term and the module provides for 60 days for FSI to LSI and 260 days on-study.

A breakdown of the Study Conduct module for Phase II and III studies is illustrated in Figure 5.

operational drug development strategies, including project acceleration through outsourcing and establishment of fast-cycle performance.

Project planning and outsourcing

Outsourcing is an acceleration tactic that especially benefits smaller companies. A detailed and fully integrated project plan (or evolving plan in a completed template) is a key to outsourcing any project activity effectively and communicating clear expectations to outsourcing partners. Outsourcing may be strategic or tactical. Strategic outsourcing implies that outsourcing decisions are made for the entire R&D portfolio to assure that priority projects receive appropriate internal and/or external resources. Tactical outsourcing is transacted by the project team or functional department. It usually involves only certain elements of the operational activity, which is delegated to specific outsourcing partners. These partners perform narrower functions and have developed an expert niche, such as nonclinical studies, specialized manufacturing, designing pharmacokinetic protocols, recruiting and prequalifying clinical study sites, data collection and analysis, auditing/QA or medical writing.

An evolving project plan embedded in a complete and detailed template assists the project team, or functional departments appropriately delegate blocks of project activities to appropriate outsourcing partners and still manage those activities successfully. In the template, the tasks have standardized names, which facilitate communication inside and outside the outsourcing company. The template alerts the project team to minute detail where the partner must perform per timeline to stay off the critical path, where the partner and company need to communicate and interact, and where achievement of milestones allows comparisons of the partner and the company's own internal performance against recognized industry benchmarks.

Project planning and fast-cycle performance

Another strategy to accelerate projects that requires a very detailed, complete, and integrated project template is fast-cycle performance. Fast-Cycle Teams (FCTs) are usually implemented to surmount normal company processes that would otherwise delay a critical project. FCTs work outside the traditional company hierarchy and are empowered to make project decisions that will move the project forward.² In the "tiger team" variant of FCTs, team members typically come from the highest ranks in the company: vice presidents and directors. They take sabbaticals from their R&D functional responsibilities for the duration of the project and streamline Standard Operating Procedures (SOPs) to maintain project quality and increase project speed; tiger teams are not required to operate within the company's traditional network of functional management. Getting the job done is the goal, and normal corporate constraints that help keep less experienced employees on the right track are relaxed when using tiger teams. The techniques these teams use to compress timelines are:

Immediate decision making. There is no waiting for senior management attention that can often take 30 days or more to occur in typical corporate environments.

Start with firm draft of the final labeling. Everything works more efficiently if the project team starts with the end labeling in mind. Protocols are designed to address the desired label, data is analyzed to prove the defined labeling targets, and reports are written to support the draft labeling. Everyone from Marketing to Research & Development have the same goals for the product.

No rework. Work is done once because all the normal checkpoints, Clinical Quality Assurance (CQA), and Regulatory are involved in process during the origination, conduct, and completion of the operational activity. As team participants, the departmental Quality Control (QC), CQA, and Regulatory assure in-process quality and compliance. When the final work product or document emerges, sign-offs happen immediately.

Team members retain accountability throughout the entire process. There is no multiple level of management sign-off, since the functional representatives on the project team are the departmental vice presidents and directors. If someone is accountable for writing a report and sends it to another team member, their accountability does not end once the next responsible person has received the report (i.e., "throwing it over the wall"). The writer remains accountable and is expected to follow-up and set the time for getting return feedback and completion of the activity. While responsibility can be delegated, accountability cannot.

Parallel activity and advance work. Many activities are undertaken in parallel rather than waiting for serial results and everything that can be done in advance is done as early as possible. Advanced planning and prework are the keys to speed. Prework is completed and ready for integration when the final pieces become available. For instance, report shells can be written very early, practically at the same time the protocol is written.

Constant management and participation. Management by the tiger team functional representatives (i.e., leads) is conducted through daily short briefing meetings with other team members to identify problems or bottlenecks and develop immediate solutions.

Highly visual project management tools. The project team operates from a war room that contains graphic depiction of the plan and progress. All submission documents are posted on walls with color coded status from origination through publishing status and final submission.

This fast-cycle approach can cut normal development times by 25%–50%. A detailed project plan (in template format) is of particular benefit to FCTs since the whole project is already laid out before them. They can predict the next steps, know immediately where other work product dovetails with their tasks, and make decisions quickly with full knowledge of the priority and timing required of them. Less consultation is required so decisions are made quickly and confidently, resulting in accelerated development.

Summary

Full transparency of the NCE project plan (critical milestones and functional interdependencies) from Discovery to NDA submission is the primary advantage of using a NCE template. From the beginning of the development process, the template visually creates the entire project plan for full examination by project team members and senior management. The template shows activities of all functional domains and how the activities integrate, and provides a focus on achieving the product labeling targets. The plan provides a solid visual reference that enables the project manager to keep the project team and senior management attuned to the project status. As project assumptions change or milestones are reached, the project plan template can be easily modified.

The fully integrated, 12-year project plan template developed in MS Project for use with NCEs provides a common scheduling platform with standardized modules. The modules are clearly documented, and have plainly delineated key predecessors/trigger events. Event lead times derived from industry best practices are integrated into the template to benefit resource planning and scheduling. Departmental QC organizations, CQA, and Regulatory compliance all benefit from a composite plan, as found in the NCE template. Working from the template, a project team can identify wasted time and poorly matched tasks. By reducing the inefficiency of a project, costs are reduced and the return on investment is enhanced.

Outsourcing is simplified with a project template. Partner and internal performance is monitored using industry-accepted benchmarks. Attempting to integrate multiple independent plans from various departments or outsourcing partners without an acceptable template is very difficult. Starting with a complete plan in a template format eliminates future complications. A project template provides a highly visible roadmap for fast-cycle performance, and FCTs are able to make quick, accurate decisions and accelerate project development.

Drug development projects can be compared to a freight train with five different engines and engineers. The idea is to keep everyone on track and to arrive safely at the destination at the appointed time, or earlier if possible. Good project management and a fully integrated, detailed project plan from a template can keep all that energy focused and pounding on down the rails. All aboard!

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