Plant Start-Up, PAI and Licensure

by Ian L. Uydess, Ph.D.

Tunnell
STRONGER PERFORMANCE AHEAD

More pharmaceutical companies today – challenged by the rapidly changing business environment – are compelled to make pivotal decisions regarding how best to provide new facilities or added capacity for their new and/or current products. That alone is a daunting task! However, once such decisions are made – and the resultant sales projected – attention must turn to assuring the on-time and on-cost delivery of those facilities to meet the forecasts made. Sadly enough, many companies find out too late in the game that this is frequently easier said than done – all too often resulting in costly over-runs, rework and delays.

Anyone in the pharmaceutical industry who has ever been involved in the planning and start-up of a new or refurbished production facility knows there are literally thousands of details that must be planned for and checked – and an equal number of opportunities for disaster.

When first conceived, such projects are frequently treated as routine initiatives that – while representing significant investments ($50MM - >$100MM) – can be executed in a relatively straightforward, reliable and uncomplicated manner.

So, what's the big deal? All you really need to do is . . .

- Come up with a good business reason for a new, modernized, or re-purposed facility
- Project an exciting level of new sales so you can get Corporate Management to support it and, while they're still enthusiastic about what you've promised them, convince them to give you a hefty little budget to cover all the costs
- Get a high-paid architect to help you design a state-of-the-art facility and a world-renown construction/engineering firm to build it
- Order lots of neat materials and equipment
- Develop a really complex-looking project plan and an unreasonably aggressive schedule (timeline) to show management just how quickly you can 'do the build' and get the product to market
- Hire a bunch of contractors/consultants to help you install all the neat materials, utilities and equipment you ordered
- Commission the building, qualify the utilities and equipment, and validate the process
- Make a few batches of product to show everyone how well the process works, and take a few stability and other analytical or microbiological samples along the way to make the FDA folks feel confident about what you have done.

Then, when all that is accomplished, all you need to do is submit some process diagrams, analytical and environmental data, production records and other easily-obtainable information so you can get the FDA to inspect and license the facility. From that point forward it's 'full speed ahead!' It's that simple! . . . Or is it?

The Sobering Reality

Whether building a 'green field' facility or modernizing ('re-purposing') an existing facility, Tunnell Consulting has found that even the most experienced organizations tend to default to the "I'm sure it will take care of itself one way or another" paradigm. After all, that's what our procurement, project management, engineering, and technical services folks are for. They identify the right partners (architects, construction and engineering firms, etc.), purchase the right materials and equipment, and find the right contractors/consultants to get the job done. Then it's up to our quality and regulatory folks to get the right paperwork to the FDA in a timely manner so we can get the facility inspected (PAI), approved, and our product(s) can get to market.

*There are **literally thousands of details** that must be planned for and checked – and an equal number of opportunities for disaster.*

***The path** from 'concept' to 'licensure' **must be looked upon as a continuum** – rather than as just a series of steps.*

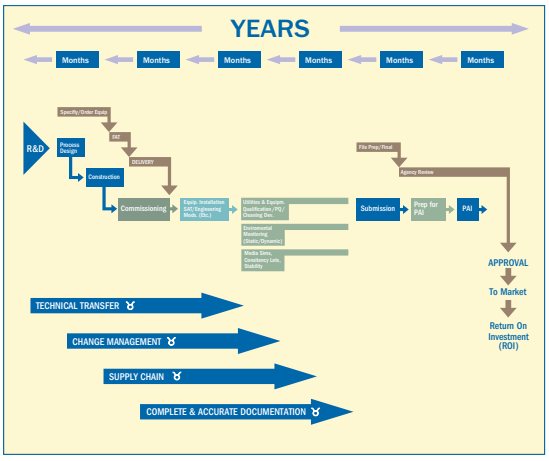
The truth of the matter is this doesn't always go quite as smoothly as planned – particularly when specialized operational and/or process requirements have to be considered – such as the need for aseptic operation, use of exotic materials or unusual production steps, or extensive control/automation systems integration.

To make matters seem even worse, there is no one panacea – as much as we would like to believe there to be one – to help avoid plant start-up issues or to remediate them once they have occurred. Instead, the answer lies in having an in-depth understanding of the path that lies ahead – as well as in meticulous planning from day one.

This includes assuring a high and reliable level of supervision, diligence, perseverance and communication with all participants and stakeholders throughout the inception, design, build, commissioning, equipment qualification and process validation phases – right through submission and PAI.

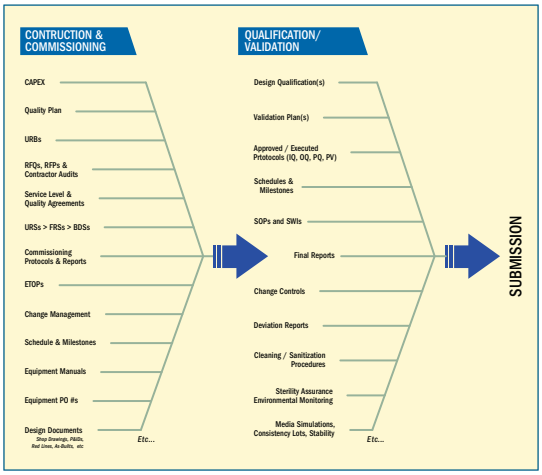
So, Where Do We Start?

As with most things, the best place to start is in the beginning – in this case with a clear picture of all the steps/requirements that lie ahead. Fundamental to this is the development of the critical requirements and specifications documents that will form the foundation for everything that will follow.



No one understands your technologies, processes, and/or products as well as you do! But understanding the "big picture" – as well as the highly tangled web of pre-requisites ('predecessors') and inter-dependencies that will have to be managed along the way is critical to the successful outcome of your organization's facility start-up and licensure efforts.

That is why the path from 'concept' to 'licensure' must be looked upon as a continuum – rather than as just a series of steps. The origin of this continuum lies in the founding documents that describe the purpose and functional requirements of the process and facility, as well as the user's requirements for that process/facility.



These include, but are not limited to:

- Functional Requirements Brief (FRB),
- Functional Requirements Specifications (FRSs)
- User Requirements Specifications (URSs)

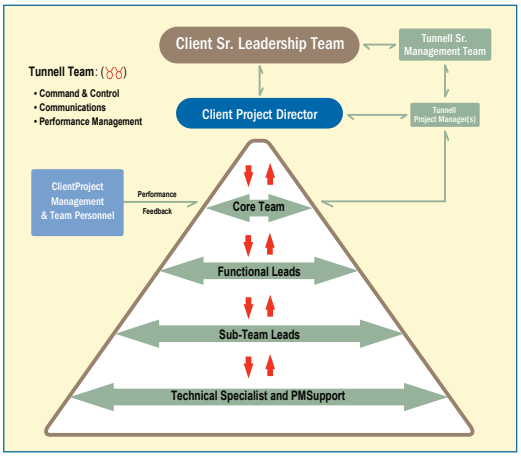
Supporting this informational infrastructure must be a well thought-out and collaboratively agreed-upon Quality Plan, Commissioning Plan (Protocol) and Change Management Plan (among other guiding processes, principals and documentation).

An effective and centralized documentation control strategy is also critical to an undertaking of this size and complexity – as

are well understood processes, resource requirements and cycle-times for document generation, review and approval (SOPs, protocols, etc.). If overlooked, underestimated, or not adequately supported, these quality elements can result in significant 'bottlenecks'/delays/lost time and, in the worst case, an organization's inability to successfully obtain licensure for their facility.

Planning the Work and Working the Plan (The Devil is in the Details)

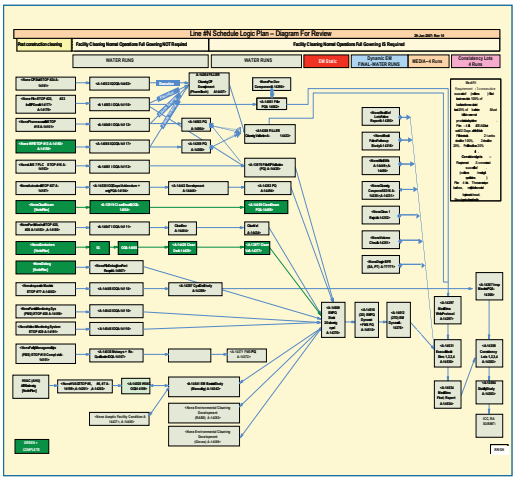
Once the fundamentals are in place the work can begin. Again, the "big picture" has to be kept in mind as well as a healthy understanding of – and respect for – all the details that need to be planned for and executed correctly ("right 1st time"), completely, cost-effectively and in a timely and high-quality manner.



As pointed out earlier - this is more easily said than done. And to do this successfully requires the right approach (methodology) and tools.

The Process Logic Diagram (or Logic Plan) – when developed and used appropriately – is one of the key tools enabling the successful implementation of a facility start-up project.

Having a nice Project Plan (Scheduling Diagram) is a good and wonderful thing! However, it's just that – a tool that can help



you schedule what has to be done, by who and when. Not that this isn't very important and useful information – it is!

The Process Logic Diagram, on the other hand, describes the relationship (dependency) each element in the process has to other elements – particularly with regard to what 'predecessors' are required prior to execution of that step or task.

Such 'predecessors' may include the successful completion of another step or tasks – or – the completion (development, review and approval) of a document or set of data required to support the execution of that step in the plan.

One of the major advantages of the Logic Diagram is that it compels the developers to work out the details of how long it actually takes to conduct (initiate and complete) the process steps represented in the diagram.

Tunnell finds this exercise works best when done through a collaborative effort involving multiple project members (functional area SMEs) who can use their knowledge and experience to help develop this information – either from their own personal experiences, from available 'historic' data or, as a result of virtual 'walk-throughs' conducted by the project team under the guidance of

Not only does the Logic Plan depict the various tasks/activities that have to be conducted to arrive at a functioning process or operation, but it also provides critical information.

There may well be times when compromises may have to be made to help overcome what seem to be unsurmountable obstacles.

the project manager (PM). At times, some of these determinations may have to be made from 'best guess' estimates provided by the appropriate SMEs and then updated with more precise data as they become available.

Each step in the Logic Plan must be agreed upon by the appropriate participants/SMEs **prior to execution of the Plan** with regard to the times, resources and dependencies identified – and then reviewed periodically by the team to assure continued accuracy/currency.

Herein lies the power – and efficacy – of the Process Logic Plan. Not only does the Logic Plan depict the various tasks/activities that have to be conducted to arrive at a functioning process or operation, but it also provides critical information about the order, time-to-do, and interdependencies of those tasks – as well as what other ancillary 'predecessors' may have to be taken into consideration – such as the drafting, review and approval of an SOP or other controlled document, (etc.).

When developed properly – the Process Logic Diagram helps PMs better understand what steps/tasks in the process may be totally dependent on the successful completion of a predecessor (or predecessors) vs. which steps may actually be more flexible and allow alternative approaches to be undertaken in a compliant and defensible manner (such as the ability to execute some steps in parallel – instead of in sequence, etc.).

Of course, some judgment must be exercised regarding the level of detail that will be addressed during the construction of such diagrams – thereby insuring that the resultant product won't itself become an obstacle (too complicated to deal with).

Over the years, Tunnell PMs have found the following hints to be helpful in guiding the development of an effective Logic Diagram:

- Start the diagram off simply – then build in detail as you go
- Focus on the most critical equipment, documentation requirements, processes and/or resources
- Focus primarily on those tasks that are inter-disciplinary – requiring cross-functional input and coordination
- At each linkage ask yourself "is this the best way to do this or are there other viable alternatives?" (Suggestion: Keep a record of the alternatives that are identified, prioritized in order of their perceived applicability or effectiveness.)
- Be sure to foster the engagement and active participation of whatever stakeholders are needed

Also, as complex projects like these progress, there may well be times when compromises may have to be made to help overcome what seem to be unsurmountable obstacles (in, of course, a compliant and non-compromising manner). The Logic Diagram can be used proactively to help prepare for and address such contingencies. It is also an organizational engagement and learning tool – the benefits of which can further strengthen the project team's ability to plan, execute and manage a start-up project – as well as to successfully operate the resultant process and operation once it is completed.

Don't Underestimate the Resources – Particularly for Project Management

It's probably no secret that another critical element in executing successful plant start-up and licensure projects is having a critical core of knowledgeable and experienced resources to support the implementation of the work at all needed levels (from planning and process development to the hands-on task execution level). While it goes without saying that many of these resources must

be technical in nature (supporting utilities and equipment qualification, process validation, etc.) – others need to be highly skilled and experienced project managers who have successfully navigated their way through previous start-up projects.

Through interviews Tunnell has learned that many senior executives believe that virtually any 'good' project manager can oversee an initiative of this kind. And sometimes that may be true. However, we have also found that every start-up/licensure project has its own set of challenges – some less familiar to the average project manager than others. That's when experience counts – and counts big! It can often mean the difference between significant and costly delays and cost over-runs and the successful and on-time delivery of a new manufacturing line or plant.

In addition to knowledge and experience, the organization needs to assure that: (1) their project managers have the time and availability to devote to the project, and (2) sufficient numbers of experienced project managers are available to cover the great variety of activities that must be planned, overseen and implemented.

Recent experience has proven that while many organizations believe they have both these bases covered – (1) their PMs are being multi-tasked to the point they do not have sufficient time to devote to these projects, and (2) there aren't enough experienced PMs to 'go around' to support the various projects that have been conducted.

The shortage of qualified and experienced internal resources is one of the greatest deficiencies Tunnell has observed in this industry – a deficiency that adversely impacts the outcome of such projects – and one that is frequently overlooked by many pharmaceutical organizations when planning such challenging and business-critical initiatives.

Quality at the Core of the Plan

Needless to say, compliance is fundamental to the successful approval and licensure of any new operation or facility (no need to belabor that topic here). Yet like PMs, the quality resources needed to support such complex and challenging projects are frequently underestimated by many organizations which all-too-frequently focus on the executable technical tasks and timelines, and not the documentation that must be created (either as a prerequisite to the execution of those tasks, or as evidence that the task was successfully executed and completed).

The sad outcome of this can be that critical documentation required to execute some phase in the project may not be available (formally approved) at the time it is needed – precipitating one of three potential outcomes:

- The task is executed anyway
- The documentation is rushed through the review and approval process
- Everything stops until someone can decide what to do (hours, days, more?)

Each one of these actions has risk – some more than others – and are the result of poor planning. No organization should put themselves – or their staff – in such an avoidable and potentially hazardous predicament. This is yet another example of how a well developed Logic Plan could have helped identify and plan for this 'dependency' – as well as the time and resources needed to assure availability of the required documentation – and timely and compliant execution of that phase in the plan.

External Resources as a Temporary and Flexible Solution

One viable alternative to helping insure successful plant start-up and licensure is to engage an experienced external resource that can provide a flexible, tem-

The shortage of qualified and experienced internal resources is one of the greatest deficiencies Tunnell has observed in this industry.

porary workforce of PMs and SMEs to work hand-in-hand with your PMs and project team members.

Judicious selection and use of an appropriate external partner can supply your organization with a flexible, temporary workforce to help get your project done – while also providing an additional source of mentors to help increase the skills and capabilities of your staff. The broader the knowledge, experience and capabilities of the resource, the better. This goes equally for the depth of that resource's 'bench' – and the ease with which that resource can provide additional SMEs when needed – and then remove them once their assignments are done.

Key to making this all work properly is knowing that the organization you select to assist you with these needs can provide you and your organization with:

- The number, breadth of experience and quality of resources/SMEs needed to support the project at hand
- Effective on-boarding and integration with your team members
- A thorough and reliable quality and performance management (governance) infrastructure to assure successful outcomes and provide remediation when needed
- Project Managers who understand the importance of effective coordination, communication and planning – and are experienced in the tools and approaches needed to support that
- A culture centered on quality, reliability, and "right 1st time"
- A partner who understands the key business and operational needs of your organization, and the impact that successful project execution has on those goals

Summary of Key Issues

There are few things worse than seeing millions of dollars of your investment sitting idle and non-productive over protracted periods of time – not to mention the lost sales opportunities that result!

Looking over our many years of experience with a number of excellent pharmaceutical organizations, Tunnell has found that the same key issues are frequently at the root of many facility or plant start-up disappointments, including:

- Lack of organizational understanding of the true complexity/nature of undertaking a plant start-up project – particularly when specialized equipment, facilities and/or processes are involved
- Insufficient attention to the planning, quality, completeness and continuity of foundation documentation (FRBs, FRSs, URSs, etc.) – and the importance and impact these documents have on successful project execution (both technically as well as on quality/compliance)
- Lack of the appropriate number and/or quality of internal resources (knowledge, experience, etc.) – particularly with regard to sufficiently 'field-seasoned' project managers
- Lack of centralized and highly coordinated oversight and control – including performance and quality management over both internal and contract personnel
- Lack of effective and regular communication
- Lack of understanding of effective risk management, mitigation, and problem solving approaches and tools
- Lack of effective supervision and management of contractors (their qualifications, activities, and quality of their 'deliverables')
- Failure to take into account and plan for the impact such projects will have on other departments/operations within the organization (Quality, Labs, etc.)

The good news is that each of these issues can be effectively dealt with – and their problems minimized, if not totally avoided – if the proper level of consideration is given to all the challenges, risks, and contingencies, when planning a start-up project.

About the Author

Ian L. Uydess, Ph.D.

Managing Consultant

Dr. Ian L. Uydess is a managing consultant at Tunnell Consulting. He specializes in enhanced regulatory compliance, plant start-up and technology transfer programs. Dr. Uydess' expertise includes: cGMP, GLP, quality systems development (including SOPs, APRs, and training program development and implementation) as well as culture change.

Dr. Uydess previously worked in a broad range of training and compliance positions at Smithkline Beecham (now GlaxoSmithKline), Genzyme Transgenics, Inc., Primedica Corporation, Purdue Pharma LP, Astra Zeneca Pharmaceuticals to name a few.

Dr. Uydess was a post-doctoral fellow in immunology and toxicology at the University of Rochester Medical Center, Strong Memorial Hospital, Department of Medicine, Infectious Diseases Unit in Rochester NY. He received his Ph.D. in Microbiology from the University of Rochester; his M.S. in Molecular Biology/Oncology at State University of New York at Buffalo (Roswell Park Division) where he also did cell membrane research and served on the NASA Mars-Viking Steering Committee.

He received his B.S. in pre-med biology at Fairleigh Dickenson University.