A Project Delivery Perspective From Conceptual Design Through Operations

Chris Wernimont

INTRODUCTION
In the pharmaceutical and biotech industries, companies are often required to modify an existing facility or build an entirely new facility. These modifications and expansions are done to support the launch of a new product, increase production of a current product, or to add an additional product line using the same or similar equipment used to manufacture an existing product. No matter what the budget, size, or scope of the project may be, the concepts included in this article will help companies successfully complete the building project.

PROJECT EXECUTION PLANNING
As with any endeavor, the best place to start is to clearly visualize the desired endpoint. Proper planning can ensure cost effectiveness and time saved. The following are the four general criteria for a successful building project:

- **No unplanned downtime upon startup.** What is the cost to a company if a new life-saving drug is delayed even one day (not to mention the lives at stake)? There is no way to accurately determine what that cost may be, but it can be significant, particularly if the delay is long enough to allow a competitor to get to the market first or to capitalize on an advantage the research and development department has worked hard to achieve. As the time is projected out 5 or 10 years, the cost can certainly be in the hundreds of millions of dollars.

- **No factory losses upon startup.** Factory losses as a result of a building project are not as significant as the possible loss of opportunity cost given in the previous criteria, but the cost of a batch of product or partial lot can be very high. It may also be relatively low and as such should be defined and understood to best assess the business risk and cost of focusing resources on this issue.

- **Well-organized documents for FDA inspection.** This one speaks for itself. If the inspection is not passed then product cannot be sold and this can contribute substantially to “unplanned” downtime. There are numerous examples of documents that have had to be re-executed because the planning and foresight of the entire project team was not brought to bear early in the project. Within our industry, documentation has improved much in the last 10 to 20 years because of more stringent and enforced expectations. Table I provides a list of typical documents required for US Food and Drug Administration inspection.

- **Well-organized documents for future reference by operations staff.** Proper documentation for future reference is often overlooked in the haste to deliver a project on time, on budget, and per FDA requirements. A focus on only having the immediate FDA-required documentation can cause another missed opportunity. As an example, developing properly organized engineering calculations as part of the design qualification (DQ) exercise that are then clearly referenced by the DQ document can greatly assist process engineering sup-

ABOUT THE AUTHOR
Mr. Chris Wernimont, P.E., is principal of Project Technologies, Inc., a company dedicated to enhancing major capital project delivery and execution in the pharmaceutical and biotech industries. He can be reached at cwernimont@project-technology.com or 317.498.4375.
Table I: A sample of typical documents for FDA inspection.

- Project Master Plan or Validation Master Plan
- User Requirements
- Design Qualification
- Installation Qualification
- Operational Qualification
- Performance Qualification
- Cleaning/Sterilization Validation
- Process Validation
- Computer System Validation
- Contractor Training Records

Table II: A sample of typical documents of value to the manufacturing support staff. *(Sometimes required for FDA inspection.)*

Commissioning Documents
- Factory Acceptance Testing (FAT)
- Site Acceptance Testing (SAT)
- Weld logs and Welder Certifications for process piping
- Process piping slope verification and heat number maps

Maintenance Program Deliverables
- Preventative Maintenance schedules
- Failure Modes and Effects Analysis
- Spare Part Stocking Strategies and Schedules
- Computerized Maintenance Management System Updates

Piping, Equipment, and Instrumentation Specifications

Vendor Equipment, Skid and/or Modular System Operation, and Maintenance Manuals

Design Engineering Calculations (Process & Utility)

Design Review Documents for non-process related systems
Port staff long after the equipment has been installed, qualified, and the project closed out (See Table II). There is sometimes resistance to this because of fear that FDA will somehow ask for this documentation. This fear can be exacerbated by inspectors who do not know engineering fundamentals or understand the often-changing dynamics of project delivery; or by quality unit representatives that are not engineers themselves or are not experienced enough to clearly explain the technical aspects to the inspector’s satisfaction. Faced with these challenges, data are sometimes not included in the final reports or not adequately referenced so that a fellow engineer can follow them. Nothing is more valuable to the process engineer who is supporting the ongoing manufacturing than to quickly get a solid understanding as to what the original design engineer was thinking. When supporting a billion-dollar-a-year production facility, finding a solution to a significant problem quickly can save millions a day, greatly reduce organizational strain, and increase supply chain confidence.

How do these four areas of success criteria get on the radar screen of everyone involved? After defining the best plan to get to the desired end result using these criteria, work backwards so that the schedule and budget can be based on the best possible assumptions and determine actions required at each project phase to achieve success criteria.

**PROJECT ANATOMY**

It is not practical to list every required action at each stage in this article; therefore, the discussion will focus on user requirements, acceptance criteria, and other key considerations. A typical project has the following eight distinct phases:

1. Conceptual design
2. Schematic design
3. Detailed design
4. Procurement
5. Construction
6. Commissioning and qualification
7. Validation

**Conceptual Design**

The first three phases are often understood by the A/E firm and corporate engineers that frequently work with these projects but not well understood by the manufacturing site representatives. A simple review is helpful to all project stakeholders. As part of the conceptual design exercise the user must define what needs to be done (not how) and it is essential to define the acceptance criteria in this exercise as well (see Figure 1). Considering Figure 1, the requirement is to have a unit operation(s) that will concentrate a 10,000 L batch of 40% acetone/water solution with 1g/l of product into a 10g/l solution with less than 1% acetone. These requirements may be based on pilot-scale data.
or actual commercial-scale data that suggest that the product solution needs to be concentrated by a 10X factor and the acetone needs to be removed in order to be further processed by subsequent purification steps. Other typical requirements would include cycle time, which would be based on an analysis of the production steps and marketing projections. In this example, for throughput reasons the cycle time cannot exceed four hours. Temperature is another common requirement because many pharma/biotech products and processes are temperature sensitive. In this example (for product degradation reasons) process temperature cannot exceed 27 degrees Celsius. Defining these types of acceptance criteria is essential for a successful design solution and one of the first steps of the overall project delivery process. Any deficiencies will domino through the subsequent procurement, construction, commissioning, and qualification steps. If a change is required in the acceptance criteria, the later in the project delivery cycle the change is required the more costly and more schedule consuming it is to remedy. These same acceptance criteria will be used in the design qualification step, and once the equipment is purchased and installed they will be used in the testing steps (i.e., commissioning and qualification). There are two schools of thought when it comes to design qualification, one is that it is done at this step and a subsequent final qualification (or review) is done after detailed design. The other thought is to do design qualification after detailed design. It is the author’s recommendation that it be done per the first school of thought for more complicated systems as often seen in active pharmaceutical ingredient (API) processes. The latter approach may be more appropriate in vendor packaged systems that are not custom designed.

**Detailed Design**

In this phase the CAD designers take the information from the process designers and instrument engineers to create the final process and instrument diagram (P&ID).
The instrument engineers also have worked with the process designers to develop control strategies and size control valves and other instrumentation in schematic design in this phase. The P&ID is ready for the final review by the site manufacturing process engineering representative or facility engineer. This review is paramount for a robust design qualification document. Once the site review has taken place and any changes updated, the P&ID is ready to be issued for construction. Also, during detailed design the piping designers will take the information from the P&ID and develop the piping schematics that show detailed placement where the piping and instrumentation must go in the field. Constructability considerations are also now included in the final design. It is not necessary to wait until the final version of the P&ID to start the piping schematics but they must be updated after the final review. This is then issued to the construction contractors so that they can do their work.

**Procurement**

Once the system is designed, the equipment and instrumentation can be purchased. Many manufacturers have corporate engineering departments that have specifications for common process and utility equipment, instrumentation, and piping. These specifications define items such as surface finish, control logic, equipment types for application (e.g., positive displacement pumps for chromatography process steps), material of construction, and documentation and testing requirements for vendors. For startup or smaller companies, using the engineering firms’ specifications is sometimes leveraged. Care must be taken in these cases to assure that the specifications are appropriate for the pharma/biotech application, and it is recommended that they be checked with industry references such as ASME bioprocessing standards. Once the specifications have been checked for appropriateness (which includes a review or approval by the site engineering manufacturing representative) and the equipment, instrumentation, and piping have been sized appropriately by the design effort, the items can be purchased or sent out for bid by the procurement specialists. The specifications and design information are sent to the vendor(s) for bidding or estimation. Actually receiving the equipment and instrumentation is the next step of the procurement process. An additional step in the process, receipt verification, is beneficial. Receipt verification is documented evidence that what was received complies with the purchase order specifics and the purchase specifications. This is the commissioning or qualification step that checks the procurement business process. This simple check can save significant time and money. Otherwise a mistake in the procurement phase may not be detected until later in the project delivery cycle.

**Construction**

Once the detailed design team has finished the piping schematics and final P&ID, they submit this along with the appropriate specifications (e.g., piping) to the construction contractor. If it is to be bid out then these items are given to the various contractors for the bidding process. Once a construction contractor is chosen, one of their initial steps is to purchase the small items such as manual valves, pipe lengths, and fittings. Also, the construction contractor requires significant planning before any thing is done in the field. Assessment of the number of trades needed (e.g., pipe fitters, electricians, welders, etc.) and the corresponding staffing models, allows the contractor to begin getting the team together and to work with local and regional labor pools to get the right skill set and number of crafts personnel. Creating a robust training plan and executing it is also important. Often the laborers, especially on larger projects, may not have experience with pharma/biotech projects and may require additional training to be sensitive to the compliance nature of the business. The final step is to install the equipment.

**Commissioning and Qualification**

The sixth phase of project delivery is commissioning and qualification. These testing steps are often separate activities. Refer to Table I for documents that are qualification related and Table II for documents that are sometimes considered commissioning related. The line between what activities are considered commissioning and which are qualification is often different for each project and is based on a number of project specific factors such as the technical (i.e., equipment) knowledge of the quality unit representative, complexity of process and equipment operation, operator training, schedule, and budget constraints. In general, this phase of the project is about proving the assumptions of the preceding business processes. For example, DQ is the check of the design process. Receipt verification is the check of the procurement process. Installation qualification (IQ) is the check of the construction process. Operational qualification (OQ) and performance qualification (PQ) are the checks of the design process in the field. Whereas DQ checks the design process in theory, OQ and PQ test it in the field, answering the question: “Does the system actually work as designed?” Let us consider the example given previously using the evaporator system. The design solution, equipment arrangement, and sizing are based on VLE, fluid dynamic, and heat exchange calculations. These calcula-
tions have been reviewed by and approved by the site process engineer or third party engineer in design qualification. The equipment has been purchased and receipt of equipment and associated instrumentation has been checked against the purchase specifications. The system has been installed and the installation checked with appropriate installation drawings, such as a P&ID. Piping is then hydrotested to assure that the system will not leak when the acetone solution needed for subsequent testing is added. The installed system is now ready for field testing and since it is an evaporator system, it is necessary to use the acetone water solution it was designed to process. The acceptance criteria for the testing are the same as those developed in the user requirements. The test is written so that 10,000 L of a 40% acetone/water solution is charged to the evaporator, the temperature never exceeds 27 degrees Celsius and the solution is concentrated to 10X within four hours. If the time is not taken to develop good acceptance criteria in the conceptual design phase, the entire project is at risk. The entire project delivery cycle from schematic design through qualification is based on these assumptions.

Process Validation

Often, but not always, process validation is the first step that product is committed to the equipment for testing. Let us consider the example of the evaporator system. As with many API applications this involves some complicated chemical engineering design. The designers made an assumption during schematic design that the VLE of the solution would behave as acetone and water solution. This is a fair assumption as it is difficult to determine the impact of the product solution on the VLE data. When it comes to this stage of the process and product is introduced, the system will behave differently than modeled. The system will behave differently, how differently will be determined in this step of project delivery, and it is important for the project stakeholders to understand the implied business risk from the beginning. There may be some tweaking of the parameters developed during the commissioning and qualification phases (typically executed with water) and, in some more rare cases, slight equipment changes and retesting. These contingencies need to be understood so that some project resources are available to address these concerns quickly and not disappear from the project once the equipment is qualified. Bottom line is that no matter how well the conceptual design through qualification phases are executed, there may be challenges in the process validation phase due to the difficulty in modeling the effect of product on the mass and heat transfer effects of the commercial scale. It is important that the quality unit representative and FDA understand these challenges.

Operations

There has been much written about the validation life cycle and how it starts once a project is completed and the initial documentation is delivered. These concepts will not be repeated here, but the operations stage is mentioned as the last phase of the cycle because this is the initial objective: to create or modify a facility so that product can be made.

SUMMARY

By following this systematic approach and communicating that approach to all project shareholders, a project will have a greatly enhanced probability of achieving the success criteria of no unplanned downtime upon startup, no factory losses upon startup, well organized documents for FDA inspection, and well organized documents for future reference of the manufacturing staff. If these criteria are successful, the manufacturer will achieve production quality more quickly and cost effectively.

REFERENCES


ARTICLE ACRONYM LISTING

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>DQ</td>
<td>Design Qualification</td>
</tr>
<tr>
<td>FAT</td>
<td>Factory Acceptance Testing</td>
</tr>
<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
</tr>
<tr>
<td>IQ</td>
<td>Installation Qualification</td>
</tr>
<tr>
<td>OQ</td>
<td>Operational Qualification</td>
</tr>
<tr>
<td>P&amp;ID</td>
<td>Process and Instrument Diagram</td>
</tr>
<tr>
<td>PQ</td>
<td>Performance Qualification</td>
</tr>
<tr>
<td>SAT</td>
<td>Site Acceptance Testing</td>
</tr>
<tr>
<td>VLE</td>
<td>Vapor/Liquid Equilibria</td>
</tr>
<tr>
<td>VLS</td>
<td>Vapor/Liquid Separator</td>
</tr>
</tbody>
</table>