Pharmaceutical Engineering

Commissioning and Time-to-Market

Author: Wael Allan

Extract from Pharmaceutical Engineering | July/August 2004

spgl
Managing Quality
Improving Performance

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
July/August 2004, Vol. 24 No. 4

Commissioning and Time-To-Market

by Wael Allan

This article describes how a properly planned and executed commissioning strategy can eliminate downstream problems and accomplish much of the data required for qualifications and plant delivery.

Introduction

Quality, risk management, and time-to-market are probably the most important aspects of a biopharmaceutical project. These elements seriously impact the viability of a drug. Missing a launch date for a product or losing a race to market may result in serious loss of revenue and/or market share.

Quality of a drug is a prerequisite for success and it must be built in at every stage during development, design, construction, manufacturing, and distribution. Quality must be established at the outset and the appropriate level of quality must be determined for all phases of a project.

As in all industries, anticipation, analysis, and management of risks are a constant challenge requiring appropriate proven methodology.

The above elements are critical to the success of a project.

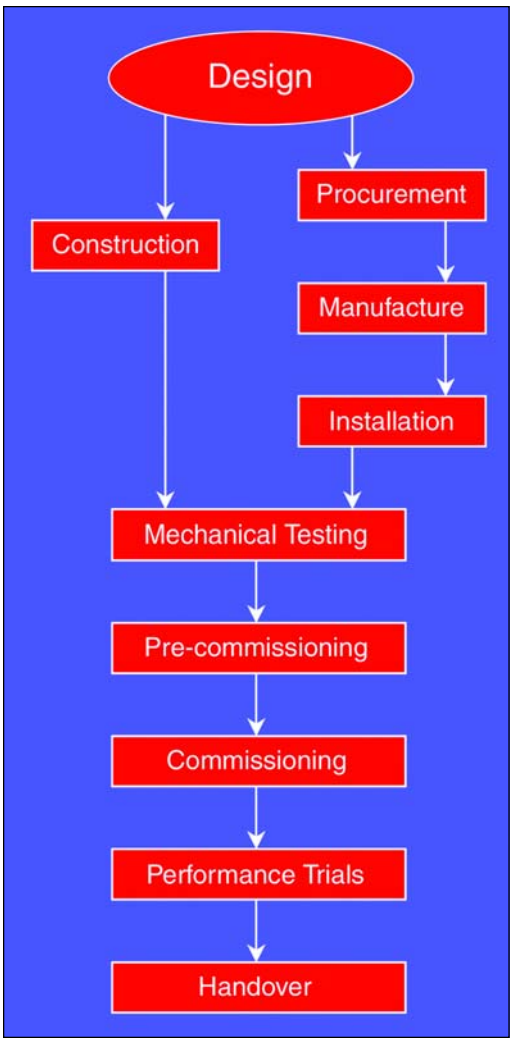

Figure 1. Typical phases of a project.

Background

The biopharmaceutical industry is one of the most regulated industries, due to the nature of the products and the regulations that govern their usability. A drug is heavily controlled from the point of molecule discovery to the point where it reaches the patient either via a prescription distributed through a pharmacy/chemist or in hospital. This has made biopharmaceutical companies cautious and conservative with regard to the scope awarded to a contractor in an Engineering, Procurement, and Construction (EPC) project. Most industries would feel comfortable awarding a project to a contractor and having them conduct construction, mechanical testing, commissioning, and performance trials ready for handover and production - *Figure 1*. In the biopharmaceutical industry, handover is normally performed at "mechanical completion." This approach has put pressure on cost, time-to-market (as integration becomes more difficult), and also has placed more pressure on clients to participate extensively throughout the whole project.

Many engineering firms have developed "integrated approaches" to EPC, but the key is achieving a reduced time-to-market and a better quality product, while managing client risks appropriately and cost effectively. The success of this is still being debated.

Construction companies have a good track record in risk management by nature of their

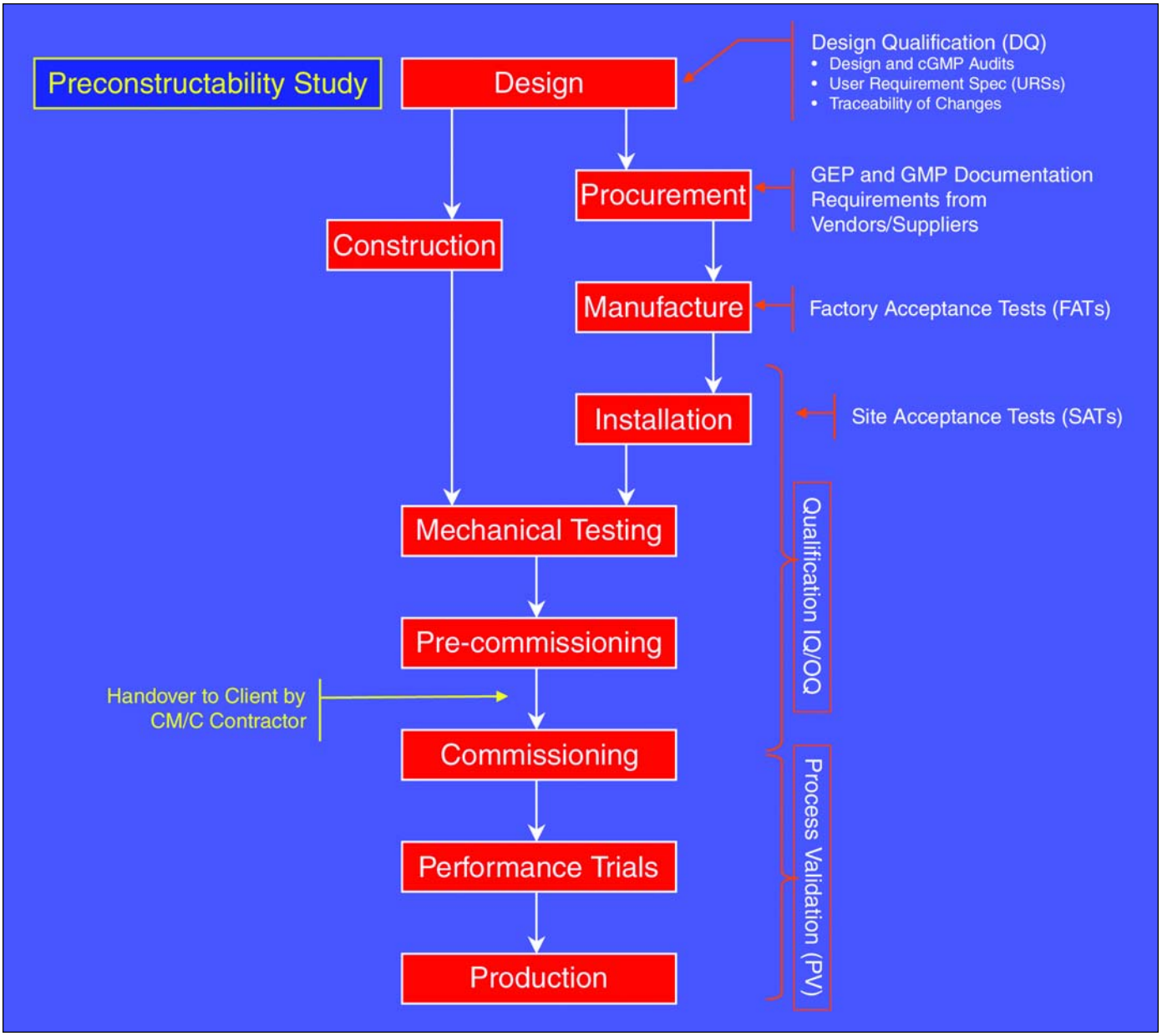

Figure 2. Typical phases of a pharmaceutical project.

work. Are such firms more suited to integrate installation, commissioning, qualification, and validation? And through this integration, can they reduce time-to-market, provide a quality facility, and manage the client's risks effectively?

For the last 15 years, the industry, led by many engineering firms, has marketed the concept of integrating engineering, procurement, construction, and validation for new pharmaceutical/biotechnology facilities. Certainly, the idea is a commendable one; however, in reality, it has no significant impact on time-to-market or cost. In many cases, the cost escalated and the schedule was extended due to the failure of integration and the lack of quality documentation by the constructor.

In the last 15 years, engineering design has come a long way in terms of Good Practice (GP) compliance through properly documented and executed GP audits. Advances have been made to the point where the work product of any major engineering firm specializing in this business can be deemed to be GP compliant.

The Mystique of Validation

Commissioning and validation have become a costly and time-consuming exercise. For large, new capital expansion projects, an owner's cost for validation, inclusive of both internal and external services, includes spent labor and materials, and is on the same order of magnitude as typical costs for engineering or construction management services. While actual validation costs will vary depending upon an owner's approach and the nature and location of the project, the range of costs are shown in Table A.

In the majority of cases, much attention has been paid to qualification/validation at the expense of commissioning.

The effectiveness of commissioning as a proven method to expedite plant delivery has been overshadowed in the phar-

maceutical industry by the emphasis on qualification/validation. Often the problems encountered in qualification are due to incomplete commissioning.

A properly planned and executed commissioning can eliminate many downstream problems and accomplish much of the data required for qualifications and plant delivery.

Construction Qualification

In light of the "Risk-Based Approach to Validation" and the increasing pressures on cost and time-to-market, a new methodology is needed to ensure the true and successful integration of construction, commissioning, and qualification.

Many API producers in Europe were not familiar with qualification/validation some 15 years ago; however, they knew that in a regulated industry they needed to ensure quality and competitiveness so they relied on GP and risk analysis as part of a methodology, namely Design Qualification (DQ).

In Europe, bulk producers regarded DQ as "qualification" for a long time before installation and operational qualifications were enforced. Typically, Design Qualification encompassed:

- Design and GP/Audits
- Risk Assessment and Criticality Analysis
- User Requirements Specifications (URSs)
- Traceability of Changes

This methodology worked well from a design perspective, but was not extended effectively to the field - *Figure 2*. Thus, providing design compliance without much impact on cost and time-to-market. Extrapolate this methodology to the field and you have Construction Qualification (CQ).

The CQ methodology is aimed at reducing cost and time-to-market through a number of critical steps as follows:

- Risk Assessment and Criticality Analysis
- Construction Audits at Approved For Design (AFD), Approved For Construction (AFC), and during field activities (based on Risk/Criticality Analysis)
- Turnover Package Organization
- GP construction forms
- Control and traceability of field charges

See Figure 3 (CQ Approach).

"CQ is a prerequisite to successful integration with Commissioning."

The activities stated above are key to expediting a project to conclusion and delivery. They impact commissioning, as many of the final construction activities (for mechanical completion) are entwined with pre-commissioning/commissioning activities.

Mechanical completion is the phase between installation and commissioning, in which components of the plant/facility are proved to be mechanically fit for their duty. It can be considered as a specialized part of the pre-commissioning activity in which each component is prepared for process commissioning. Since installation may be continuing in some areas of the plant while others are being tested and commissioned, site safety must be given detailed consideration. For example, component suppliers and sub-contractors must be carefully controlled during this phase since areas can change classification during the course of construction and commissioning.

Generally, pre-commissioning refers to preparing the facility/plant for the introduction of process materials, and its main purpose is to eliminate any problems which might arise at later and more critical stages of facility/plant operations.

The sequence of mechanical completion is governed by the overall program, but usually starts with electrical power and utilities. The objective of mechanical completion is to prove that an installed plant component is suitable for commissioning.

	Engineering	Construction Management	Validation[1]
Bulk Chemical API	10 - 14%	5 - 11%	5 -7%
Bulk Bio API	14 - 18%	5 - 11%	10 - 15%
Secondary Pharmaceuticals (Solid Dosage, Liquids, and Ointments)	7 - 10%	4.5 - 8%	5 -9%

[1] Includes owner spent material and plant labor costs up through qualification costs.

Table A. Typical Engineering, CM, and Validation Costs (% of Total Installed Cost "TIC").

Commissioning

Properly planned commissioning begins during the pre-construction phase of a project. During this time, the parameters for commissioning and qualification turnover documents are identified. Also, Factory Acceptance Test (FAT) plans and Site Acceptance Test (SAT) plans are developed for pre-purchased equipment and systems.

The goal is to have the commissioning and closeout documentation requirements identified in outline form prior to the start of construction. Specific requirements for long lead equipment and modules require definition and will be fully developed for incorporation into the bid documents.

Overall, it is the intent to utilize the project's commissioning process to enhance and reduce the time taken for qualification, hence reducing time-to-market. Properly documented commissioning can be leveraged into qualification by systems and completing the process in phases, allowing for early production and manufacturing.

Commissioning is defined as a well planned, documented, and managed approach to the start-up and turnover of systems and equipment to the end-user that results in operational, safe, and functional systems, which meets established operational requirements and end-user quality expectations.

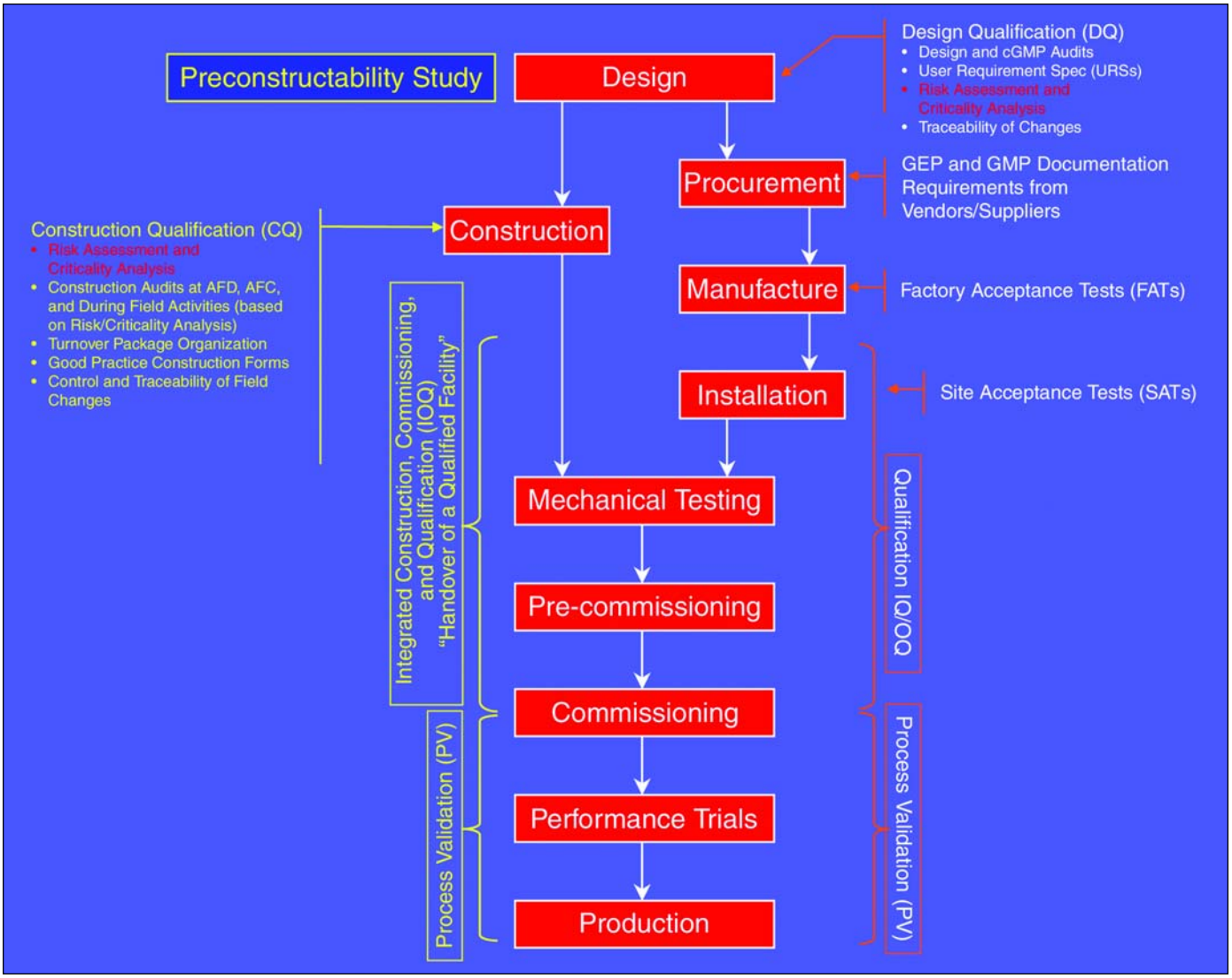

Figure 3. Construction Qualification (CQ).

Commissioning can be accomplished through different phases and methodologies. There are a number of proven methods to achieve commissioning in the biopharmaceutical industry. For purposes of illustration, it will be broken down into six phases to reflect the various tasks that will be executed through the project. These phases and tasks are summarized below and described in detail in the following sections.

1. Design Phase
   - Kick-off of Commissioning Activities
   - Focus Design Review (System Impact Assessment)
   - Documentation Requirements
   - Commissioning Protocol Writing (toward the end of detailed engineering)

2. Procurement Phase
   - Vendor selection
   - Long lead
   - Equipment Modules
   - Qualified Subcontractors

3. Construction Phase
   - Component Impact Assessment
   - Commissioning Protocol Writing and Approval
   - Construction Quality Control Activities
   - Owner Quality Assurance Activities

4. Start-Up Phase
   - Construction Quality Control Activities
   - Trade Contractor Pre-Commissioning Checks
   - Owner Quality Assurance Activities

5. Inspection, Testing, and Documentation Phase
   - Construction Quality Control Activities
   - Owner Quality Assurance Activities
   - Installation Commissioning/Verification "IC"
   - Initial Calibration
   - Operational Commissioning/Verification "OC"
   - Training

6. Handover to End-User Phase
   - Closeout Reports/Deviation Resolution

Design Phase

This is the phase of the project when the scope of commissioning is defined, the commissioning team is assembled, responsibilities are assigned, information is obtained, and protocols drafting is planned.

Kick-off of Commissioning Activities

The project manager assigns a commissioning team for the project. The project has a basis of design, a control level schedule and control estimates, and a preliminary equipment list available to assist the commissioning team in defining the commissioning activities. The commissioning team breaks the project into a series of systems, which formulates the basis for the commissioning plan.

The first draft of the commissioning plan is produced as outlined by the team. The commissioning plan is distributed for review and comment. Subsequent team meetings are held to review and resolve comments.

Focus Design Review (System Impact Assessment)

The team conducts a System Impact Assessment using the system list. The systems list covers the entire scope of the project, broken up into manageable segments. Typically, these are by equipment package, distribution or piping systems, and architectural items.

The team assesses each system with regard to its effect on product quality. In effect, the systems will be categorized into one of three categories.

- Direct Impact on Product Quality
- Indirect Impact on Product Quality
- No Impact on Product Quality

The Direct Impact Systems require further qualification after commissioning and the Indirect Impact and No Impact Systems will not require further qualification after commissioning. However, this is dependent on company policies, for example, some companies will further qualify some Indirect Impact Systems depending on the criticality of the interface with a Direct Impact System. These categories and the assessment criteria are further defined by the commissioning team and are usually documented in the System Impact Assessment Report.

Documentation Requirements

During the design phase, the User Requirement Specification (URS) and Design Specifications for Good Manufacturing Practice (GMP) critical systems and equipment should be reviewed with regard to the vendor/contractor documentation required to support commissioning and qualification as well as operations and maintenance. Where appropriate, documentation numbering, layout, formats, etc., should be specified. In most instances, the equipment/system vendor is best placed to provide the documentation required to support the commissioning and qualification effort. Therefore, this must be stated during the design phase of the project so that the documentation becomes one of the key deliverables for the vendor/contractor.

Commissioning Protocol Writing

The team will decide how to generate the commissioning protocols and who will execute them. Two approaches exist.

1. The equipment manufacturer (vendor) provides a Site Acceptance Test (SAT), which is incorporated into the commissioning protocol. The vendor also executes the SAT.

2. The commissioning team writes the commissioning protocol for engineered systems, such as utility distribution systems. Subject matter experts are consulted as required. The commissioning team also executes the protocol.

Procurement Phase

The procurement of subcontractors, vendors, and equipment design and fabrications systems could potentially have "added value" to the overall schedule and cost of a project. Without proper integration of design, prefabrication, and construction, the maximum benefit may not be obtained. In addition, without a rigorous implementation strategy, not only will inefficiencies result that erode the schedule and cost benefits, but the end product may be viewed as a compromise and fall short of expectations.

A successful approach must influence the project from the early stages of preliminary engineering. This early involvement will yield dividends for every phase of the project.

1. Objective

- Maximize the use of 'Equipment Modules" to provide the optimum combined schedule and cost benefit value while increasing the overall quality and improving the project's schedule.

2. How Implemented

- Assemble a team of individuals who possess a unique combination of pharmaceutical/biotech design and construction experience.
- A team with the design, construction, and integration of skidded process equipment.
- A team with know-how in project turnover requirements for Good Practice facilities.
- A team with experience in the start-up and commissioning of pharmaceutical/biotechnology facilities.
- Empower the team to be part of the up-front engineering

3. Engineering and Design Recommendations

- Develop module boundaries for the project.
- Lead in the development of an "Equipment Module Design, Fabrication, and Installation Standard" (EMDFIS).
- Review and critique layout and general arrangement studies in regard to module implementation.
- Develop engineering and design boundaries between process engineer/design firm and equipment module manu-

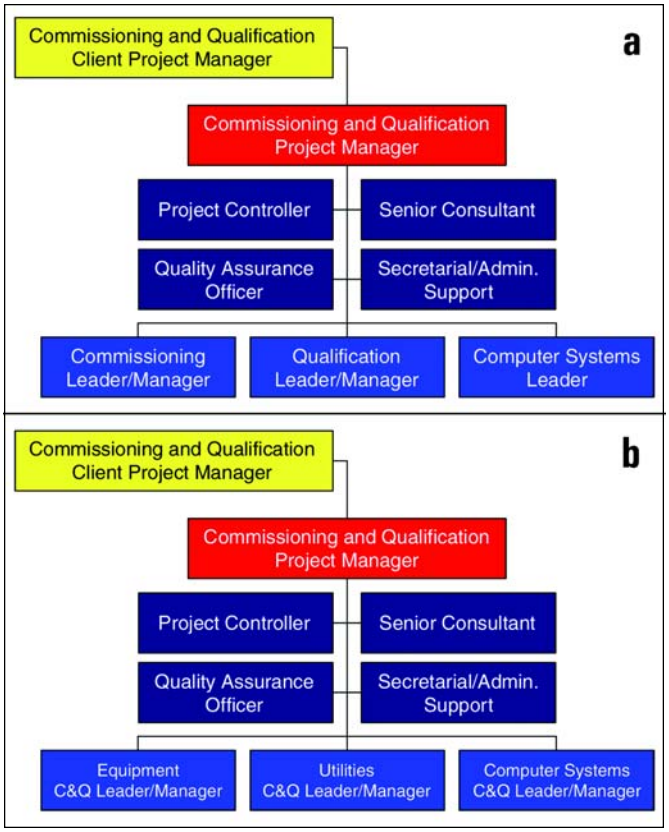

Figure 4a. Proposed organizational chart.
Figure 4b. Alternative organizational chart (C&Q = Commissioning and Qualification).

facturer to optimize design schedule and cost.
- Prepare a construction strategy that identifies field versus shop work and interface requirements as well as standards for controls, piping, electrical, etc.

4. Procurement Strategies

- Conduct pre-qualification visits to potential suppliers of equipment modules.
- Evaluate best methods of design and construction that may influence the EMDFIS.
- Evaluate integration options of module boundaries.
- Develop options for the field and module scope boundaries.
- Review overall shop capabilities in regard to projected workload, shop capacity, quality program, maximum assembly size, technical capability, turnover documents, etc.
- Develop a procurement strategy to maximize buying power and scope distribution across vendor availability.
- Evaluate major equipment, instrument, and controls procurement with drop ships to equipment module vendors versus turnkey approach.

Construction Phase

Subcontractors, vendors, operations, maintenance, and engineering develop support documentation that will be reviewed during commissioning.

Component Impact Assessment

To evaluate the impact of system's components on product quality, the team meets to review the details of each system. Similar criteria that were used for the System Impact Assessment are used to judge a component's effect on product quality. Although all systems undergo a component impact assessment, emphasis is placed on the direct impact systems. The spirit and principle of risk analysis and management plays a vital role here, and this information also is recorded in the Component Impact Assessment Report.

Commissioning Protocol Writing and Approval

It is the commissioning team's responsibility to ensure that the proper information is getting to the individuals who are writing the protocols with the operations and maintenance representatives on the team serving as the focal points of this information flow.

The data for these protocols is gathered from end-users, the construction manager, third parties, or subject matter experts as required.

The commissioning team reviews and approves all protocol submittals and then signs the protocols prior to execution according to the document approval matrix.

Note: If commissioning is to be leveraged into qualification then the involvement of the clients' Quality Assurance (QA) organization is a pre-requisite. The level of involvement is critical as this impacts the approval times and the overall schedule.

Construction Quality Control Activities

At this stage of the project, construction groups and equipment vendors review documentation and drawings for design completeness and adherence to building codes and practices. As construction progresses, the quality control activities become more physically orientated to ensure installation complies with approved design. Deviations are tracked in the project worklist/punchlist.

Owner Quality Assurance Activities

Similar to the construction control process, but with owner participation along with the construction groups and engineers who review documentation and drawings for design completeness and adherence with regulatory requirements, operational requirements, and best practices. As construction progresses, the quality control activities will become more physically orientated to ensure installation complies with approved design. Deviations are tracked in the project worklist/punchlist.

Start-Up Phase

Vendors and system representatives power-up the systems and perform necessary procedures to make the systems fully operational. This phase culminates in the handover of systems to the commissioning team.

Construction Quality Control Activities

The construction manager and the commissioning team conduct periodic reviews of the construction progress and the

quality of the installation (walk downs). Deficiencies are tracked in the project worklist/punchlist, which contains commissioning, qualification, and general items still requiring completion.

Trade Contractor Pre-Commissioning Checks

Prior to system or equipment start-up, the trade contractor is responsible for performing valve/equipment line-ups to ensure that all equipment is in the proper operating condition and no equipment or system damage will occur.

Continuity checks also are performed and documented in accordance with the specifications.

Turnover of a system from construction to commissioning is based on the acceptance of a system by the commissioning team. The following items are typically required to define construction process as being complete:

- Construction manager, contractors, vendors or system representatives, engineering, and operations sign off on the construction turnover package.
- All installation documents required to support commissioning are complete and available.
- Required utility services are available in adequate supply to properly operate the system.
- All controls signals from external sources are available or can be reliably simulated.
- Equipment/system start-ups requiring lockout/tagout for equipment or personal protection are performed using owner procedures.
- After the system has been checked, the construction manager assembles the completed forms and provides them to the commissioning leader for review. The construction manager provides copies of the completed forms to the commissioning leader and keeps the originals for inclusion in the turnover package.

Owner Quality Assurance Activities

System walkdowns, which begin when installation of a system is approximately 90 percent complete, are coordinated with the owner representative. The construction manager informs the owner representative prior to system/equipment start-up, and coordinates times when the equipment could be available for certain activities, should the owner representative need or wish to access the systems/equipment at any time.

Coordination with the owner representative is critical to ensure that start-up of the equipment does not affect areas outside of the scope of specified project.

After a successful start-up and commissioning has been completed, plant personnel including facilities engineering, operations, and safety are notified that the system is ready for them to prepare, execute, and issue plant specific readiness reviews or an Operational Readiness Report (ORR) indicating it is safe to be turned over to operations for regular use.

Start-Up

The equipment vendors and/or contractors review their own internal installation complete checklist to make certain the equipment/system has been properly installed and is ready to be safely activated.

The equipment vendors/engineers will activate the equipment, and perform all necessary activities required to make the equipment/system fully functional. This includes checking liquid/lubrication levels, checking motor rotations, tuning loops, debugging installation problems, confirming installation against as shipped drawings, setting system specific parameters, and making the equipment/system ready for testing.

Calibrations also are performed during this phase, which vendors require to finish their start-up procedures. Full loop checks are performed (field device through software to console or vice versa) and documented.

Inspection, Testing, and Documentation Phase

The commissioning team executes the commissioning protocols in this phase. The executed protocols, system closeout, and handover reports are then reviewed by the team. Execution of the commissioning protocols confirms that the installation was performed according to the approved design. The acceptance criteria are defined in the approved design documents.

Installation Commissioning/Verification

The commissioning team reviews the available documents comparing them to the requirements outlined in the Engineering Turn Over Package (ETOP). The commissioning protocol execution ensures that the required documents are complete and available.

The installation is checked against the approved drawings. This process includes such activities as P&ID verification, general arrangement drawing verification, and nameplate verification.

Initial Calibration

Proper documentation of the calibration is referenced back to a traceable standard depending on the country, e.g., USA: NIST. The initial calibration is performed as part of the vendor or system start-up activities. The documented evidence is reviewed at this stage.

Operational Commissioning/Functional Testing

The commissioning team system representatives execute the commissioning protocols to ensure proper operation of the machine as defined in the approved project documents. The commissioning team signs off the executed protocols accepting the results of the execution.

Training

The commissioning team ensures that operator and maintenance training has been addressed to the end-user's satisfac-

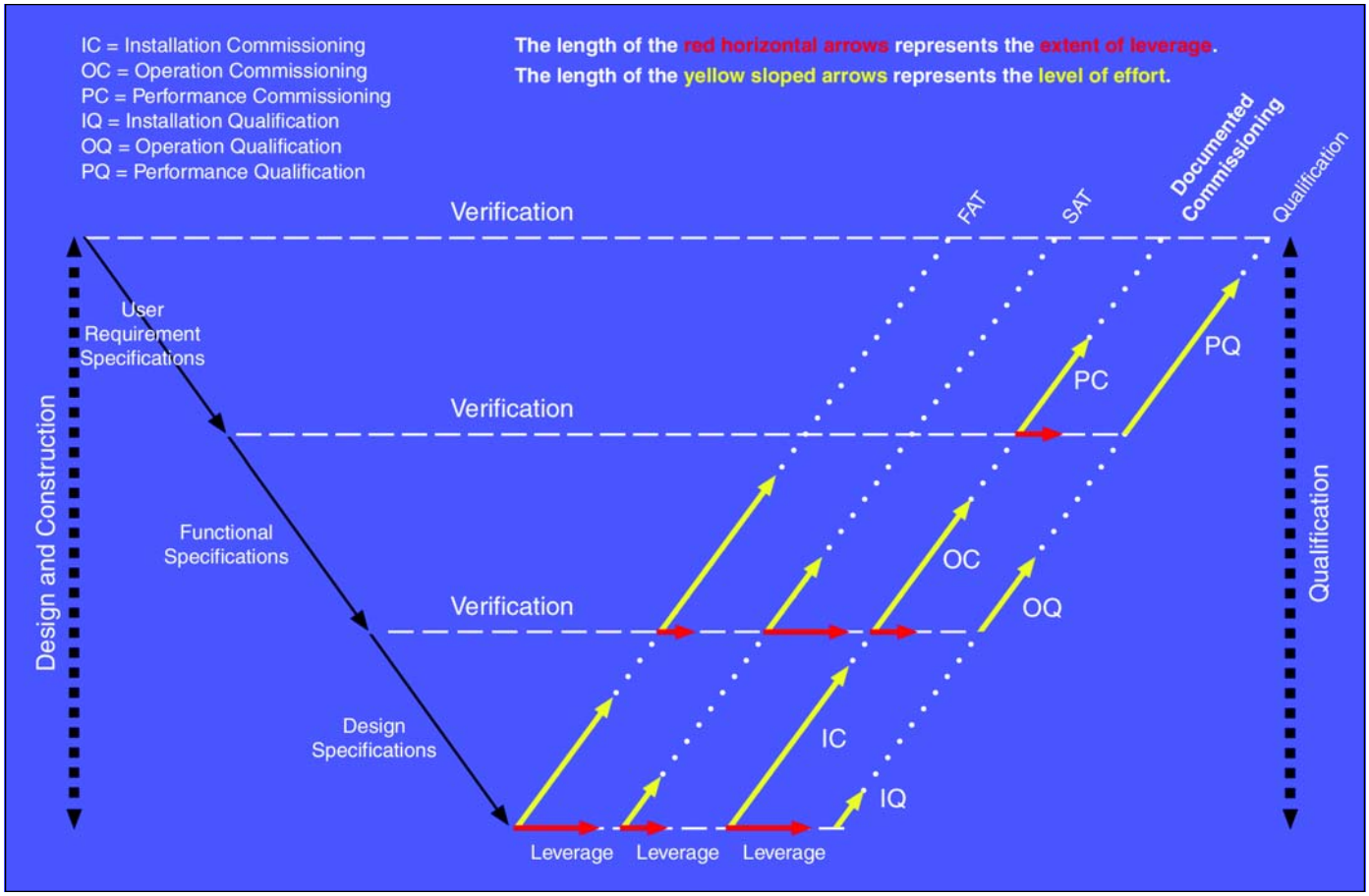

Figure 5. Leveraging commissioning into qualification.

tion. The commissioning protocol ensures that training documentation has been provided to the end-user and that training has been scheduled.

Handover to End-User Phase

Commissioning is complete; the system end-user formally accepts the systems. Plant maintenance is responsible for the preventative maintenance of systems, some of which undergo further qualification.

For true integration to take place and in order for commissioning to be leveraged into qualification, it is strongly advised to have the same team members perform qualification for the systems they commissioned.

Closeout Reports/Deviation Resolution

Closeout reports address open issues, identify corrective actions required, the responsible party, and dates for completion. Deviations, documented on the project worklist/punchlist, are reviewed to ensure that all remaining open issues are transferred to the closeout report.

Project Organization and Execution

There are many different ways to organize a commissioning team, but the most time and cost-effective is when commissioning and qualification activities are integrated.

It is not the intent of this article to offer details with respect to project organization and execution; however, the following structures are proposed as examples - *Figures 4a and 4b*.

Commissioning in Support of Qualification

Earlier in the article, reference was made to the fact that overemphasis on qualification/validation has overshadowed commissioning, resulting in problems during validation due to incomplete commissioning. Some of these problems can be detrimental to cost and time-to-market since fixing them requires a high level of backtracking and mending of installation and documentation.

Commissioning performed in new construction and existing facilities helps to ensure that systems are installed, functionally tested, and capable of being operated and maintained to perform in conformity with the design intent and the owner's needs. This ensures that a new facility begins its life cycle at optimal productivity. Commissioning also can result in restoring an existing facility to optimal operation. Furthermore, when commissioning is repeated periodically throughout the life of a facility, it improves the likelihood that the facility will maintain a higher level of performance.

Placing more emphasis on Documented Commissioning (DC) may have cost and schedule consequences. In general, qualification costs can be at least twice as much as that of commissioning. Reversing the emphasis will make the cost of documented commissioning higher. However, the cost of qualification could come down significantly as documented

commissioning can be the lion's share of the effort required for qualification. More significantly, by adopting documented commissioning as the basis of qualification, clients could significantly reduce the risk of non-compliance and serious problems affecting the delivery of a qualified facility, hence reducing time-to-market.

In order for DC to work effectively as the basis for qualification, early active participation of the client's quality unit is key to ensuring that various commissioning activities are eventually accepted for inclusion in support of the installation and operational qualification. These protocols, along with any performance qualification protocols that are required, form the basis of the qualification/validation effort. This is in accordance with the framework set forth in the ISPE Baseline® Pharmaceutical Engineering Guides for New and Renovated Facilities, Volume 5, Commissioning and Qualification. It is worth referencing the ISPE definition of commissioning as a well-planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user that results in a safe and functional environment that meets established design requirements and stakeholder expectations.

DC must be treated as a unique and discrete activity in accordance with the above definition to be used as the basis of qualification/validation. In many cases, where attempts were made to mix commissioning and qualification together serious delays and shortfalls occurred - *Figure 5*.

The Future

The new order for our industry is, as always, driven by pressures on cost and constant changes to meet market demands. The new industry drivers are risks (analysis and management), cost, and time-to-market. If you agree that those stated above are the real drivers in our industry, would it make sense to expect C/CM contractors to deliver a qualified facility rather than a mechanically complete facility. Clearly, the goal is to be cost-effective, fast, as well as comprehensive. Redundancies in testing may be eliminated through the implementation of a smart and efficient approach to installation and operational qualification of systems and equipment. This logic, or "Qualification Rationale" as it is called by the ISPE Baseline® Guide, can be achieved through the integration and implementation of Construction Qualification (CQ) and Documented Commissioning (DC).

Finally, the next decade may see Documented Commissioning replacing Qualification and/or Qualification becoming the QA function for Documented Commissioning.

About the Author

Wael Allan is a Senior Vice President of the Skanska Pharmaceutical Group, leading its commissioning, validation, and regulatory compliance services globally, and serving as Managing Director of the Pharmaceutical Group's U.K. entity. Allan has extensive experience managing a wide range of commissioning and validation businesses in the pharmaceutical and biotechnology realm. He is responsible for developing the group's global strategy as well as focusing on operations, business development and growth. Allan holds a MSc. in biochemical engineering and B.Eng. in chemical engineering, graduating with honors, from the University College of Swansea in the United Kingdom. He can be contacted by tel: 1-973/390-9219 or by email: wael.allan @skanskausa.com.

Skanska USA Building Inc., 1633 Littleton Rd., Parsippany, NJ 07054.