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Best Practices for Qualification Success: A Statistical Analysis of Characteristics and Practices that Drive IQ and OQ Cost and Schedule

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This article presents a statistical analysis of planning and execution strategies for Installation Qualification (IQ) and Operational Qualification (OQ) activities carried out in 50 construction/ modification projects.

Introduction

Installation Qualification (IQ) and Operational Qualification (OQ)[1] are frequently on the critical path of activities in the construction or modification of pharmaceutical production facilities. Any delay during the IQ/OQ phase is a major problem if it prevents product from being delivered to meet market demand and/or regulatory approval.

This article outlines the research that was conducted on how pharmaceutical companies carry out IQ and OQ activities. The research resulted in three major deliverables:

- statistical models that can be used to benchmark cost and schedule performance in the execution of IQ/OQ
- a list of key project characteristics that affect qualification cost and schedule
- a list of key Qualification Best Practices that drive qualification success and minimize qualification failure

Methodology

In this study, using ordinary least squares statistical regression methods, "uncontrollable" project characteristics and "controllable" project practices were reviewed for statistically significant links between them and what IQ/OQ costs and schedules were achieved.

Uncontrollable project characteristics are those which are inherent in the project scope and cannot be altered by the behavior of the project team. An example is the type of facility being built (e.g., a bulk active pharmaceutical ingredient facility). Controllable project practices are those actions that the company management and the project team can choose to do or not to do. For example, the team could choose to develop a schedule of qualification activities during basic design instead of waiting until later in the project.

Table A. Characteristics of the research set.

Key Project Characteristic	Dataset(n = 50)
Facility Type	Bulk chemical active pharmaceutical ingredient: 21% Biological: 35% Oral dosage/Non-parenteral secondary: 25% Sterile formulation and finishing: 11% Other (incl. packaging facilities, pharmaceutical device facilities, etc.): 8%
Facility Scale	Production: 90% Pilot Plant: 10%
Project Type	Standalone (Greenfield or colocated): 57% Expansions: 33% Revamps/revisions/modifications of existing facilities: 10%
Geographical Location	North America: 49% Europe: 35% Puerto Rico: 8% Singapore: 8%
Product Description	Prescription: 94% Over the Counter: 6%
Project Engineering and Construction Cost (US$ millions)	Mean: $50 million Median: $25 million Range: $2.5-$191 million

By seeking statistically significant links between project characteristics or practices and cost or schedule outcomes, an attempt was made to uncover those characteristics and practices that "drive" IQ/OQ cost and schedule.

Project Dataset

For the purposes of this study, data on 50 projects was collected from nine major pharmaceutical companies. The choice of "major" or what is often referred to as "big pharma" companies was not a deliberate effort to exclude medium or small companies. It simply reflects the fact that the data was collected from companies that were interested in participating in the research, and all interested parties happened to be major companies. The companies are not named because they wish to retain their anonymity. Data was collected using a customized questionnaire.[2] Some key characteristics of the set are shown in Table A. In order to be able to conduct an "apples-to-apples" comparison, the data for all 50 projects was "normalized" to a common cost baseline (currency, location, and year). In addition to asking project teams to complete a detailed questionnaire, each team was interviewed to verify the reliability of the data provided. In addition, each company chose to participate in the study in order to receive advance notice of results that would help them improve their estimating, planning, and execution of Commissioning and Qualification activities. Consequently, it was in the interests of each company to provide data that was as accurate as possible.

Analysis of Qualification Cost

Cost Data Limitations

When the project teams were interviewed in the course of the data collection activities, it was discovered that they used a wide variety of approaches in the recording of qualification costs. Variations in accounting were seen across companies and from project to project within companies. Project teams rarely recorded charges and hours for individual qualification activities, and owner participation in qualification was often not tracked or charged to projects. In some cases, qualification charges were "hidden" within equipment/vendor costs, project management costs, or in other capital costs for the project. Every effort was made to trace the costs. Where these costs were expensed and traceable to a specific account, they were collected and included. The methodology was as follows: With the active advice and assistance of the study participants – it was decided what costs should be tracked and allocated as "qualification cost." There are numerous project costs associated with qualification that may or may not be captured, for example, owner costs associated with approving protocols - which is often captured in the project management account. Once the decision has been made as to what costs will be allocated to this account, the process of normalizing from project-to-project, company-to-company is more straightforward. Therefore, while project cost data can be "messy," the methodology used "forced" this messy data into defined "buckets" - a defined work breakdown structure that could then be analyzed in an apple-to-apples manner).

Key Drivers	t-score	P > t
ln (TIC)	8.54	0.00
Biological Facility(Biological facilities vs. API, Oral, Sterile, and Other)	3.19	0.00
Pilot Plant Facility(Pilot Plants vs. all other facilities)	-2.10	0.04
Stand-alone Project(Stand-alone projects vs. Revamp and Expansion Projects)	2.01	0.05
Qualification Schedule Definition (Critical Path Method or Milestone schedules vs. No schedule planning/ end-date only)	-3.03	0.01

Table B. Relationship between key characteristics and practices and IQ/OQ cost.

While "messy" cost information increases the variance in the data and the analyses, much of the error was essentially randomized across companies. Therefore, statistically significant industry outcome benchmarks still can be developed.

However, a major conclusion of this study is that the majority of project systems do not actually know exactly how much money is being spent for the completion of all the activities making up the total qualification effort.

IQ/OQ Cost Model

Given the limitations of the available cost data, the cost analysis for this study focuses on a single point of interest: the total cost required to complete IQ/OQ; (i.e., the cost to develop, write, and execute IQ/OQ protocols. All costs accrued by the owner, including internal and external (contractor/consultant) costs). While some commissioning and PQ cost data was available for some projects, the majority of projects were able to provide data for IQ/OQ only. Moreover, in the majority of cases, the IQ/OQ costs were not broken out from each other.

Project Size as an "Uncontrollable" Characteristic

IQ/OQ cost should be a function of basic project characteristics such as project size, project type, and facility type. It is reasonable to hypothesize that the size and/or complexity of a project will affect the IQ/OQ cost for a project. On a basic level, the total project size indicates the volume of work that will be required to complete IQ/OQ, which would then be directly related to IQ/OQ costs.

There are several potential measures of project size and complexity, including total project cost, major equipment costs, facility capacity (in terms of product count per year, etc.), or major equipment count. For this study, the total cost of engineering, materials, equipment, and construction (in other words the total installed cost – TIC)[3] serves as a proxy for the project size or complexity.

Table B shows the regression relationship between the natural log of the TIC and the natural log of the IQ/OQ cost. (Regression relationships presented in this study use student's t-test. In the tables illustrating the regression relationships, the "t-score" and "probability" (p>t) associated with each regression will be included. Both the t-score and probability

provide an indication of the statistical significance of an independent variable in the regression. For example, in Table B, the large t-score associated with ln(TIC) indicates that this independent variable is a statistically significant driver of ln(IQ/OQ cost), which is the dependent variable in our regression. (t-score varies with number of observations and has to be viewed in parallel with p>t, but generally, a rule of thumb is that if the absolute value (i.e., plus or minus) of the t-score is greater than 2.00, then the variable is a statistically significant driver.) The probability (p>t) also expresses the "confidence" with which a variable is regarded to be significant in the regression. The general cut-off for the analyses in this study is 90 percent confidence, or p>t=0.10. (i.e., there is 90 percent confidence that the correlation is not due to random chance). Note also that in cases where p>t is quoted as 0.00, this does not mean it is absolutely zero, but merely that it is zero to two decimal places, or put another way, it is smaller than 0.005).

The correlation between TIC and IQ/OQ cost was found to be very strong. Figure 1 graphically shows the strength of the relationship. Clearly, TIC is the single best predictor of IQ/OQ cost. (Note that the Figure uses log scales, hence the presence of minus numbers).

Other Significant "Uncontrollable" Characteristics

After controlling for size, other characteristics were examined for their significance in "explaining" variance in IQ/OQ costs.

- **Biological Facilities.**[4] For the facility types in the study dataset, a significant relationship was found between biological facilities and higher IQ/OQ costs. For biological facilities in the study, the average IQOQ cost as a percentage of TIC was twice as large as the average percentage for the other facility types.

- **Pilot Plant Facilities.** For the facility types in the study dataset, a significant relationship was found between pilot plant facilities and lower IQ/OQ costs. Although a first glance at this result suggests that pilot plant facilities may be less rigorous in their approach to IQ/OQ, hence driving lower costs, the overall data collected for this study does not support that finding. In fact, the pilot plant facilities, especially those making products to be used for clinical trial, appeared to perform the same set of qualification activities and apply the same set of quality standards as the other projects in the study database. However, the findings indicate that the qualification effort for these facilities may be smaller, if not less rigorous, relative to the total costs of equipment and materials being installed than non-pilot facilities.

- **Stand-alone Project Type.** A significant relationship was found between stand-alone facilities and higher IQ/OQ costs. As with the relationships between facility types and IQ/OQ cost, a first glance at project types suggests that stand-alone facilities would require more expensive IQ/OQ based on the requirements to execute qualification on all new facilities, including air-handling, utility tie-ins, etc. In contrast, expansion and revamp projects, by definition, are installed in existing facilities where it is likely that certain qualification activities have been performed previously. It is interesting that the significance of the relationship between stand-alone project type and IQ/OQ cost holds up even after controlling for total project size.

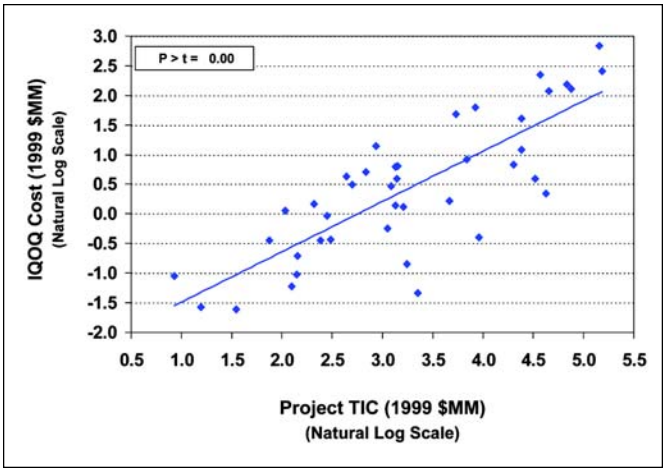

Figure 1. IQ/OQ cost is driven by facility Total Installed Cost (TIC).

For the drivers of IQ/OQ cost described above, each one is significant within a multilinear regression of all variables. Table B shows the regression relationship between the natural log of the IQ/OQ cost and the key "uncontrollable "project characteristics based on their fit within a multilinear regression analysis.

Key "Controllable" Drivers

A "controllable" driver that was found to have a major influence on IQ/OQ cost was qualification schedule definition.

- **Qualification Schedule Definition.** After controlling for project size, facility type, and project type, the following key project practice was seen as a significant driver of IQ/OQ cost: Qualification schedule definition at the time of authorization/detailed engineering start. The quality of schedule planning for the projects in the study ranged from Critical Path Method (CPM) planning to milestone schedules to schedules consisting of start and end dates only. For this analysis, the quality of the overall project schedule was broken out from the quality of the commissioning and qualification schedule. A statistically significant relationship was seen between the quality of the qualification schedule and IQ/OQ cost. For projects that had prepared a schedule to a critical-path or milestone level, IQ/OQ costs were lower than for projects that were working toward end dates only or had no schedule at all.

Even when a large portion of the variance in IQ/OQ cost is

accounted for by basic characteristics such as size, facility type, and project type (in other words, even when these characteristics are "held constant"), the quality of the qualification schedule accounts for some remaining variance in the data and is a statistically significant driver of IQ/OQ cost.

Table B shows the regression relationship between the natural log of the IQ/OQ cost and the "controllable" qualification schedule driver based on its fit within a multilinear regression analysis.

Other IQ/OQ Cost Drivers

In total, the "base" model, described by the variables above, explains approximately 80 percent of the variance in the cost of IQ/OQ for pharmaceutical projects.

Several project characteristics and practices explain some of the remaining variance in IQ/OQ cost as shown in regressions against the residual of the base model. Three of these factors are significant within a 95 percent confidence level and are described below:

- **Vendor Qualification Support.** For the purposes of this analysis, projects were classified into three categories: 1. projects for which there was no significant involvement of vendors in the qualification effort, 2. projects for which there was some vendor participation in the execution of IQ and/or OQ, 3. projects in which vendors executed entire protocols and/or delivered "prequalified" equipment or skids to the project team. The analysis shows that greater vendor involvement correlates with lower IQ/OQ cost.

- **Project Manager Assurance Team Development Issues**

- **Quality Assurance Team Development Issues.** The projects in the study were classified as to whether, during the life of the project, they experienced any "issues" with the key team members on the project. Issues include late arrival on the team, inability to participate as much as required, because of conflicting priorities, competing projects, etc., and turnover. Team issues related to the project manager and/or quality assurance representation were statistical drivers of higher IQ/OQ cost.

Three remaining practice or characteristics variables were found to correlate with IQ/OQ cost and were statistically significant within a 90 percent level of confidence when regressed against the "base" model:

- **Attendance by Qualification Personnel at Factory Acceptance Tests (FATs) and/or Site Acceptance Test (SATs).** The participation of qualification personnel corresponds with lower IQ/OQ cost.

- **Other Validation Group Requirements.** If qualification personnel had to divide their time between the qualification work on the project and a requirement to perform other tasks (such as writing Standard Operating Procedures (SOPs) or batch records and/or performing technical assessments), then this was found to increase total IQ/OQ costs.

- **New Technology.** Projects containing some aspect of new technology correlate with higher IQ/OQ cost.

Other Practices that Correlate with IQ/OQ Cost Performance

Other practices that correlated with IQ/OQ cost performance included:

- **Commissioning and Qualification Integration.** For the purposes of IQ/OQ cost analysis, many of the projects could be placed in two categories:

  1. projects with no planned or executed integration of commissioning and qualification

  2. projects in which the planning and execution of qualification included referrals to commissioning tests as part of IQ and/or OQ execution

Not surprisingly, the data suggest that increased integration of activities correlates with lower IQ/OQ cost.

- **Impact Assessment.** The occurrence and formality of Impact Assessment activities correlate with lower IQ/OQ costs for the projects in this study.

- **Project Team Status.** Two issues surrounding project team status at the time of authorization correlate with IQ/OQ cost. First, projects in which there is a clear understanding of the project objectives and target dates by all members of the project team have lower costs. Second, projects in which team roles and responsibilities are defined and understood by all members of the project team also have lower IQ/OQ costs.

- **Retest.** Not surprisingly, projects noting that changes and retest were required for qualification appear to have spent more on IQ/OQ costs.

- **Approach to Automation Qualification.** Projects relying on a separate approach to Computer System Validation (CSV), that is those project teams that wrote and executed separate IQ/OQ protocols for process equipment and utilities versus automation, appear to spend more on IQ/OQ costs.

Analysis of Qualification Schedule

Schedule Data Limitations

The IQ/OQ schedule represents a period of time during which resources are allocated and plans, schedules, and controls are put in place for the qualification effort. The "meaning" of the IQ/OQ duration varied somewhat from project to project. For some projects, this duration included a significant portion of

the protocol writing, review, and approval cycle; for others, it included only protocol execution and report writing. The defined start and end dates also varied slightly from project to project as the "boundary lines" between OQ and PQ were sometimes blurred. (As with the cost data collection methodology, the way this was resolved was to define what would be considered within the schedule boundaries. In this case, only protocol execution and report writing were considered in the IQ/OQ schedule. This is another example of how "messy" data was normalized across projects.) For the purposes of this study, these overlaps were essentially randomized, and while contributing to the overall variability of the cost and schedule data for these phases, they do not significantly impact the industry outcome benchmarks.

Qualification Schedule Models

There are several ways to examine qualification schedule performance of projects in the study database. As a broad analysis, the overall duration of IQ/OQ (from the start of IQ to the end of OQ) is renewed. Another means of studying qualification schedule performance is to examine the duration from the end of construction (mechanical completion) of a facility to the end of OQ.

Duration of IQ through OQ

To examine the duration of IQ/OQ (IQ/OQ schedule) the "start" of IQ can be defined as the date when the first IQ protocol is executed and the "end" of OQ as the date when the last OQ protocol is executed and/or the final OQ report is written.

An important reason to study the IQ/OQ schedule is the relationship seen between qualification cost and qualification schedule. The duration of IQ/OQ represents a period of time when resources must be allocated to the effort, including validation and quality assurance personnel, owners and contractors, and possibly plant operations and maintenance. In addition, plans, schedules, and controls must be in place for the duration of IQ/OQ. Therefore, the total IQ/OQ schedule in this analysis, was examined.

Duration of Mechanical Completion through the End of OQ

Another means of studying qualification schedule performance is to examine the duration from mechanical completion of a facility to the end of OQ (MC/OQ schedule). This is perhaps a more powerful way to consider schedule performance, as it is the best description of how much time is "lost" between the point when a facility is "ready" to make product from a mechanical basis and when it is "ready" to make product from a regulatory standpoint (of course, the completion of OQ is not actually the final step in the project process that is required for the regulatory approval to make product. Performance Qualification (PQ) often must follow and often overlaps with OQ, and all IQ, OQ, and PQ activities provide the basis for process qualification or validation. For the purposes of the analyses in this study, we will stop at the completion of OQ and examine the later stages of qualification/validation in future studies). Therefore, the MC/OQ schedule was examined in more detail in this analysis.

Key Drivers	t-score	P > t
Project Size: [ln(TIC)]	2.49	0.02
New Technology	-2.10	0.04
Percentage Overlap of IQ and OQ Schedules (months that IQ and OQ overlap divided by months of total IQ/OQ duration)	2.77	0.01
Engineering Definition at Authorization	2.01	0.05
Qualification Schedule Definition (CPM or milestone schedules vs. no schedule planning/end-date only)	-3.03	0.01

Table C. Relationship between key characteristics and practices and IQ/OQ schedule.

As with IQ/OQ duration and IQ/OQ cost, a relationship exists between MC/OQ schedule and IQ/OQ Cost. Although it is not obvious that one outcome is driving the other, the correlation is statistically significant.

The IQ/OQ Schedule Model

As with IQ/OQ cost, IQ/OQ schedule correlates with TIC, which may be seen as a proxy for overall project size and complexity. However, the regression relationship is not as strong as that seen for IQ/OQ cost, and other drivers are found to be just as influential as size. Therefore, rather than holding a single characteristic constant, as was done with project size when examining IQ/OQ cost, project characteristics and practices can be examined directly against the IQ/OQ schedule.

Table C shows the regression relationship between the natural log of the IQ/OQ schedule [ln(IQ/OQ schedule)] and the key project characteristics and practices that make up the IQ/OQ schedule model. The statistics presented in the table are based on the fit of the independent variables within a multilinear regression analysis.

"Uncontrollable" Characteristics

- **Project Size.** Greater TIC correlates with longer IQ/OQ schedules.

- **New Technology.** For the IQ/OQ schedule analysis, projects were grouped into three categories: 1. projects containing no new technology, 2. projects containing some aspect of technology, process, or product that can be considered new to the company or site, and 3. those projects incorporating technology new to the industry. Increasing "new technology" ratings correlate with increased IQ/OQ schedules.

Key "Controllable" Drivers

- **Percentage Overlap of IQ/OQ Schedules.** Increased schedule overlap *increases* the total IQ/OQ schedule. This is a very interesting finding given that one could reasonably assume that overlapping IQ/OQ would lead to a *shorter* overall duration. In fact, overlapping all phases within a project schedule is usually done to decrease the

overall duration of the project. In the MC/OQ schedule analysis, some schedule overlaps do, indeed, drive faster schedules, but the empirical data show that this is *not* true for IQ/OQ.

The reasonable explanation for why increased overlaps drive longer IQ/OQ schedules may be derived from an examination of why overlaps "fail" to produce the desired goal (faster schedules) for any phases within a project. The primary reasons are lack of planning in turnover from one phase to the next and repeated efforts. For example, a qualification team may complete IQ for one system and then start OQ. If upon review of the executed IQ protocol an error is discovered and retest is required, this can then have a subsequent effect on OQ, requiring retest in this phase as well.

Because the correlation between percentage IQ/OQ overlap and IQ/OQ duration is so strong, project teams may want to carefully examine their strategies for overlapping schedules and be sure that controls and contingency plans are in place so that the most efficient schedules are achieved.

- **Engineering Status at Authorization.** Our analyses found that as the status of engineering definition improved, the IQ/OQ duration decreased for projects in the study dataset. Earlier research has determined that Engineering Status is a critical parameter in the Front-End Loading (FEL) of projects and can be linked, along with other FEL activities, with improved absolute cost and schedule performance and predictability for pharmaceutical projects.[5] While Engineering Status appears to be important in and of itself as a driver of qualification schedule performance, it also may be standing in as a proxy for overall early definition efforts that can impact projects throughout project execution.

- **Qualification Schedule Definition.** For projects that had prepared a schedule to a critical-path or milestone level, IQ/OQ schedules were shorter than for projects that were working toward end dates only or had no schedule at all.

Other IQ/OQ Schedule Drivers

The IQ/OQ schedule variables mentioned above account for approximately 70 percent of the variance in the IQ/OQ schedules in the study database.

Other potential drivers of IQ/OQ schedule may be eliminated from the model, either because their relationship with the dependent variable does not hold up when key characteristics are controlled or because of strong co-linearity with other, more significant schedule drivers. However, their relationship to IQ/OQ schedule is suggestive. In addition, there is some overlap with the practices that appeared significant in our cost analyses.

Drivers	t-score	P > t
New Technology	5.77	0.00
Percentage overlap of Qualification with Construction schedule	-6.76	0.00
Percentage overlap of IQ and OQ schedules	3.51	0.00

Table D. Relationship between key characteristics and drivers and MC/OQ schedule.

- **Commissioning and Qualification Overlap.** As discussed for the IQ/OQ cost analysis, the data suggest that increased overlap of activities correlates with shorter IQ/OQ schedules.

- **Other Validation Group Commitments.** Projects in which personnel involved in qualification activities were required to perform other tasks, such as writing plant SOPs or batch records and/or performing technical assessments were found to have longer IQ/OQ schedules.

- **Overlap of Personnel Writing and Executing Protocols.** For the majority of projects in the study, the personnel responsible for writing protocols also were responsible for executing protocols. For those projects in which there was no overlap or overlaps were minimal, a correlation with longer IQOQ durations was seen.

The MC/OQ Schedule Model

Table D shows the regression relationship between the natural log of the MC/OQ schedule [ln(MC/OQ Schedule)] and the key project characteristics and drivers that make up the MC/OQ Schedule Model. The statistics presented in the table are based on the fit of the independent variables within a multilinear regression analysis.

"Uncontrollable" Characteristics

- **New Technology.** As with IQ/OQ schedules, increasing "new technology" ratings correlate with longer MC/OQ schedules. Based on the regression analysis, it is clear that the extent to which projects incorporate new technology is a very strong driver of the MC/OQ duration for pharmaceutical industry projects. New technology was determined to be the only significant project characteristic in the MC/OQ Schedule Model.

Interestingly, although total project size is a driver of both IQ/OQ cost and IQ/OQ schedule, this project characteristic is not a significant driver of MC/OQ schedule in a multilinear regression model. However, total project size correlates with MC/OQ duration in a simple regression analysis.

Key "Controllable" Drivers

The following schedule overlaps were significant drivers of MC/OQ duration in the MC/OQ schedule model:

- **Percentage Overlap of Qualification with Construction Schedule.** Not surprisingly, increased overlap drives *decreased* MC/OQ schedule.

The correlation between percent overlap of construc-

tion and qualification and MC/OQ duration is so strong that this appears to be a relatively simple strategy for project teams to decrease the time between when a facility is mechanically ready and when it is "ready" from a regulatory standpoint. Obviously, increased overlaps require increased coordination between construction and validation personnel in the field, as well as earlier planning, scheduling, and resource allocation. For the projects in the study database, it appears that project teams were able to prepare for and execute these overlapped phases and gain a schedule advantage.

Figure 2 shows the strength of the relationship between percentage overlap of construction and qualification and MC/OQ schedule. This schedule overlap is the strongest predictor of MC/OQ duration in the MC/OQ model. (Note that the Figure uses a log scale for MC/OQ schedule, hence the presence of minus numbers).

- **Percentage Overlap of Installation Qualification and Operational Qualification Schedule Phases.** Increased overlap drives *longer* MC/OQ schedules. This result is consistent with the relationship between IQ/OQ overlap and the overall IQ/OQ schedule.

Other MC/OQ Schedule Drivers

The above variables account for approximately 75 percent of the variance in the MC/OQ schedules in the study database.

Other potential drivers of the MC/OQ schedule may be eliminated from the model, either because their relationship with the dependent variable does not hold up when key characteristics are controlled for, or because of strong co-linearity with other, more significant schedule drivers. However, we want to note these drivers, whether characteristics or practices, because their relationship to MCOQ durations is suggestive, within the limits of the database.

"Uncontrollable" Characteristics

- **Project Size.** Greater TIC correlates with longer MC/OQ schedules.

- **Process Complexity.** For this analysis, process complexity is measured by the number of steps in a process required to perform all chemical and physical operations for the manufacture of product. For projects in the study database, our analysis shows that an increased number of process steps correlates with longer MC/OQ durations. This is not an unexpected result; and it is assumed that more complex processes take longer to complete qualification requirements, especially if the qualification strategy is to use a system-by-system approach.

- **CIP/SIP.** Based on regression analysis of a categorical (1,0) variable representing projects that were required to install Cleaning-In-Place (CIP) and/or Sterilize-In-Place (SIP) systems, this project characteristic was found to correlate with increased MC/OQ duration.

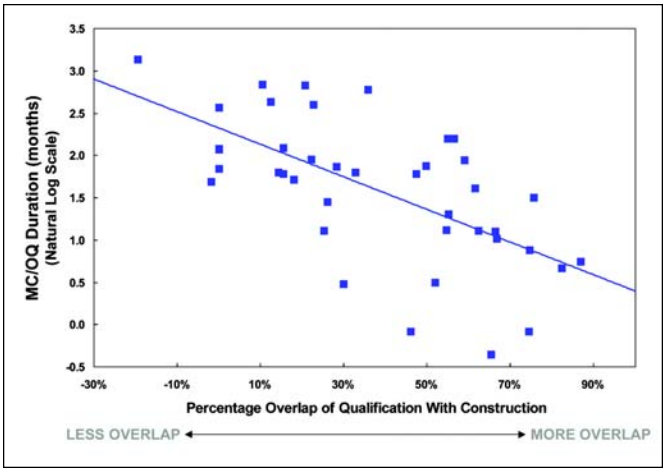

Figure 2. MC/OQ schedule is correlated with the percentage overlap of construction and qualification.

"Controllable" Drivers

- **Commissioning and Qualification Overlap.** The data suggest that increased overlap of activities correlates with shorter MC/OQ schedules. For this analysis, it was not possible to evaluate if there were schedule trade-offs between commissioning and IQ/OQ and/or MC/OQ. This may be examined in more detail in future analyses.

- **Overlap of Commissioning and Qualification Team Personnel.** In addition to the tasks required to complete commissioning and qualification, the personnel used to complete these phases varied among companies and among projects within companies. For the majority of projects, the same team was used to perform all activities under the commissioning and qualification umbrella, or there was active communication and crossover between teams. A minority of projects used different personnel to execute the activities described as commissioning versus qualification. Projects were placed into one of three categories describing the extent of team overlaps. Projects with increased overlaps of commissioning and qualification personnel achieved shorter MC/OQ durations.

- **Engineering Status at Authorization.** As described for the IQ/OQ schedule, as the status of engineering definition improved, so the MC/OQ duration decreased for projects in the study dataset.

- **Qualification Schedule Definition at the Time of Authorization/Detailed Engineering Start.** For projects that had prepared a schedule to a critical-path or milestone level, MC/OQ durations were shorter than for projects that were working toward end dates only or had no schedule at all.

- **Other Validation Group Commitments.** Projects in which personnel involved in qualification activities were required to perform other tasks such as writing plant

SOPs or batch records and/or performing technical assessments were found to have longer MC/OQ schedules.

- **Existing Corporate or Site SOPs for Commissioning and Qualification.** For projects in the study database, about two-thirds were able to use existing site and corporate standard operating procedures outlining the requirements and approach for commissioning and qualification. Projects were classified as to whether the majority of activities for qualification were covered by pre-existing SOPs. The remaining projects, approximately one-third of our project sample, had either no existing SOPs, limited SOPs, or there were major changes to the existing SOPs sometime during project execution. Projects in which teams had access to existing, unchanging, standard qualification procedures, completed faster MC/OQ.

- **Preparation of FAT and SAT Protocols.** The majority of projects in the study database prepared or had access to FAT and SAT protocols, which were executed as part of the project equipment procurement and construction effort.

Practice	Description
Qualification Schedule Definition at Authorization	Better-defined schedules in terms of milestone-level development or critical path analysis, resource loading, and integrated activities improve performance.
Commissioning and Qualification Overlap	Increased overlap between the Commissioning and Qualification activities is associated with improved Qualification cost and schedule performance.
IQ/OQ Overlap	Increased overlap between IQ and OQ dampens schedule performance.
Project Team Performance	Specific project team attributes are clearly associated with better performance. These attributes include avoiding key member turnover, eliminating the late assignment of key functions to the team, and avoiding multiple assignments with conflicting assignments. In addition, functionally integrated teams, well-defined project objectives, and documented roles and responsibilities improve performance.
Front-End Loading	Better-defined capital projects are clearly associated with improved absolute and predictable performance. These practices also apply to the execution of Commissioning and Qualification activities. In particular, improved Engineering Status and Project Execution Planning are important elements for Commissioning and Qualification project performance.
Existing Standard Operating Procedures (SOPs) for Commissioning and Qualification Activities	Procedures that are already in place facilitate performance. Companies without SOPs should consider developing them.
Reduce Other Validation Group Commitments	Projects with personnel who are dividing their time between activities outside of Commissioning and Qualification tasks and the Commissioning and Qualification tasks themselves, tend toward less effective Qualification performance.
Vendor Qualification Support	Vendor involvement improves Qualification costs with a neutral affect on schedules.

Table E. Qualification *best practices.*

This practice was shown to correlate with faster MC/OQ schedules and may be an indication of overall planning and controls for the projects.

- **Date When the Validation Master Plan (VMP) was Finalized.** Projects were assigned into one of four categories for "sign-off" date of the VMP. VMPs were finalized and signed off at 1. project authorization, 2. before the start of construction, 3. before mechanical completion, or 4. following mechanical completion. About two-thirds of the projects were in categories two and three. The remaining projects were equally divided between categories one and four. A regression analysis of the MC/OQ duration against the date of VMP sign-off shows that projects with earlier VMP approvals demonstrate faster MC/OQ schedules. This result is not unexpected, and may be correlated with an overall level of planning for IQ/OQ execution that results in faster delivery of the qualification effort.

  NOTE: The status of the VMP at the time of authorization or by the start of detailed engineering was examined for each project with the idea that the VMP may be used as a planning guide for other project definition activities and deliverables, such as cost and schedule estimates. Although it was reasonably expected that the early status of the VMP might affect later qualification outcomes, for projects in the study, VMP definition was not a significant driver of cost or schedule.

- **Changing Objectives.** Projects were categorized as to whether the objectives for the project were changed during project execution. Although cost or schedule predictability outcomes are expected to be affected by these changes, which are driven from outside the project team, it is interesting to note that changing objectives also can be statistically linked with overall longer MC/OQ durations.

Conclusions

Commissioning and qualification are significant phases in the overall project delivery system. Yet surprisingly, a large number of projects systems:

- are not accurately capturing the true costs in terms of labor and currency of the qualification effort

- do not put in the effort in the early, front-end phase of a project that is necessary to sufficiently plan and define qualification activities and ensure the future success of the qualification phase

However, this study has been able to determine those planning and execution practices that are found to be statistically significant drivers of qualification success, thereby providing companies with a potential focus for their activities as they work to refine and standardize the qualification process for capital projects. In summary, those *Best Practices* are listed in Table E.

References

1. Installation Qualification is defined as: "The documented verification that all aspects of a facility, utility, or equipment, that can affect product quality, adhere to approved specifications (e.g., construction, materials), and are correctly installed." As noted in the ISPE Baseline® Guide on Commissioning and Qualification, the activities that make up IQ correspond to the inspection requirements as noted per Good Engineering Practices (GEP).

   Operational Qualification is defined as: "The documented verification that all aspects of a facility, utility, or equipment, that can affect product quality, operate as intended throughout all anticipated ranges." As noted in the ISPE Baseline® Guide on Commissioning and Qualification, the activities that make up OQ correspond to the Setting-to-Work, Regulation, and Testing requirements as noted per GEP.

2. In developing the questionnaire, we would like to acknowledge the usefulness of the ISPE Baseline® Guide on Commissioning and Qualification in developing the questions. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 5 - Commissioning and Qualification,* International Society for Pharmaceutical Engineering (ISPE), First Edition, March 2001, www.ispe.org.

3. Project TIC includes design, engineering, procurement, construction costs up to mechanical completion. (In other words, it excludes commissioning, qualification, and validation costs).

4. Biological Facility – A production facility that uses cell culture (mammalian or bacterial) as the production method.

5. Lawrence, G.R., "Pharmaceutical Capital Investment: Time to Rethink Corporate Culture," *The Chemical Engineer* (*TCE*), August 2004, p. 28-29.

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