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Primer of Design and Construction Delivery Methods for Today's Modern Pharmaceutical and Biotech Facilities

This article presents four common project delivery methods and discusses the significant features of each approach.

by Brian Sirbovan, Dave DiProspero, and Brian Larson

Introduction

Pharmaceutical and biotech companies undertaking capital construction and improvement projects are often faced with considering several different project delivery options or contracting approaches based on project size, timetable, risk, or a range of other factors. Choosing an inappropriate project delivery approach can be costly and may ultimately adversely affect the project economics and business case the company was relying on to provide a satisfactory return on the capital invested.

The selection of the most appropriate project delivery option is dependant upon a number of factors such as time constraints, risk limitations, cGMP/containment issues, budget/cost issues, quality/functional objectives, project complexity, cash flow constraints, and even owner internal job creation.

This document reviews the four most common project delivery methods, namely:

- Design-Bid-Build (traditional approach)
- Construction Management (Owner assumes certain cost risks)
- Guaranteed Maximum Price (Owner and Contractor share certain benefits, Contractor assumes cost risk)
- Design-Build (single source responsibility)

The analysis discusses the significant features of each approach, including strengths/weaknesses, typical contractual arrangements used, and the conditions under which each type is appropriately implemented. A timeline comparing the various project delivery options is included, and compliance issues also are discussed.

Hybrids of these project delivery approaches also can be discussed.

The Design-Bid-Build approach is the most traditional and well-known project delivery method used and should be considered the base case for comparative purposes.

An experienced project management consultant can assist the Owner in choosing the most appropriate project delivery approach.

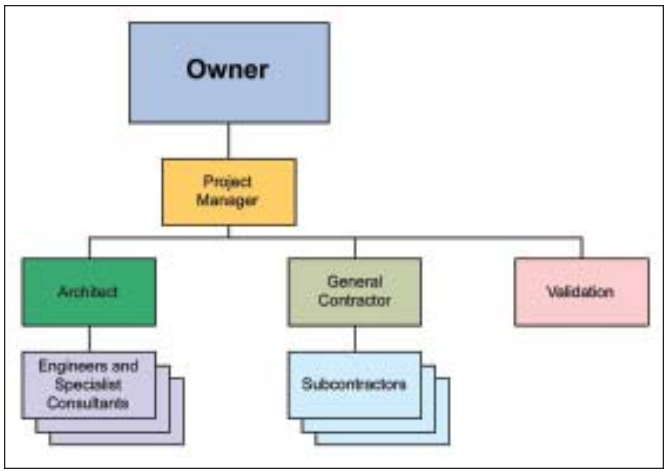

Figure 1. Organizational structure for the Design-Bid-Build (traditional) approach.

Design-Bid-Build (Traditional)

Description

- Owner acts as Project Manager or retains a project management firm as its representative (Project Manager).
- The Owner/Project Manager retains an architect, engineers, and other specialist consultants, who initially prepare a program, then subsequently prepare drawings and specifications for the total project scope under the overall

direction of the Owner/Project Manager, and consistent with defined scope, time, cost, and quality objectives.
- The Owner/Project Manager, or sometimes the architect, retains cost consultants to monitor the project scope and provide cost advice as the design develops.
- Competitive lump sum tenders are typically solicited and received from a selected short list of pre-qualified General Contractors; a single General Contractor is selected based on the lowest price, compliant with the tender documents.
- The General Contractor constructs and commissions the facility under a single lump sum/stipulated price contract, which is administered by the Owner/Project Manager, assisted as required by the architect, engineers, and other specialist consultants particularly with respect to issues of construction quality and compliance with contract documents.
- The Owner/Project Manager performs oversight and due diligence with respect to the General Contractor's ongoing activities.
- The Owner retains a validation firm or executes validation internally.

The organizational structure for the traditional approach is shown in Figure 1. The strengths and weaknesses for the traditional approach are shown in Table A.

Contractual Arrangements

The contractual arrangements typically include a lump sum stipulated price based upon industry standard contract format.

When Used

This contracting strategy is typically used on a well-defined project of a routine nature where there is no requirement for a fast-track schedule overlapping design and construction and an Owner risk requirement exists for a fixed price prior to starting construction.

Construction Management

Description

- Sometimes called Construction Management – Agency or "CM for Fee".

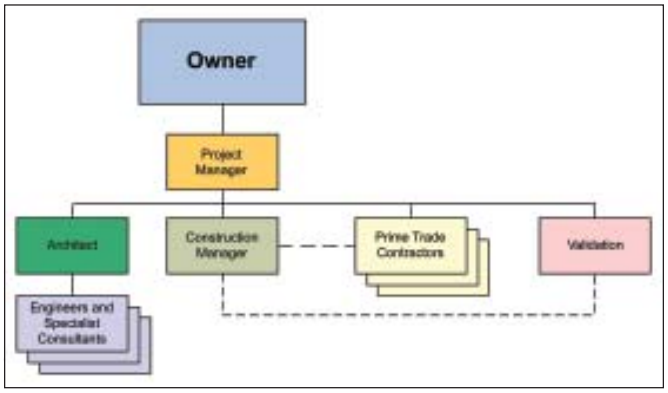

Figure 2. Organizational structure for the Construction Management Approach (Agent for Owner Model).

Strengths
• Time tested and a well understood traditional project delivery approach. • Competitive market pricing with minimal contingency in the contractor's price. • Scope of project and quality requirements of the Owner is usually well defined. • Contract price is "theoretically" known prior to construction start. • Owner transfers full construction performance risk to the contractor. • Construction health and safety risk is clearly with the contractor.
Weaknesses
• Often minimal or no contractor input to design. • Minimal opportunity for value engineering and constructability after tenders are received. • Costly to incorporate major changes or revised Owner requirements into the project and may lead to impact or delay claims. • Longest overall project schedule with limited overlap of design, tender, and construction activities. • Owner and Contractor are potentially in adversarial roles from the outset. • Contract price and hence budget performance are not known until drawings completed and tendered; risk of cost overrun and re-design to reduce costs exists. • Any cost savings or unspent contingencies revert to the contractor. • Competitive market forces may encourage "low ball" contractor pricing which may ultimately not be in the best interest of the Owner.

Table A. Strengths and weaknesses for the Design-Bid-Build (traditional) approach.

- Owner acts as the Project Manager or retains a project management firm as its representative (Project Manager).
- Owner/Project Manager retains an architect, engineers, and specialist consultants who initially prepare a program, then subsequently prepare drawings and specifications under the direction of the Owner/Project Manager for a series of separate and sequential trade contract tenders in such a manner that design and construction activities run concurrently and are overlapped.
- The Owner/Project Manager retains a construction management company (Construction Manager) on a fee for services basis, who is responsible for compliance, constructability, and value engineering input during the design, arranging competitive trade contract tenders, scheduling and cost control, as well as managing all construction activities to meet the Owner's scope, cost, time, and quality objectives.
- The Owner/Project Manager may retain an independent cost consultant to work closely with the Construction Manager in establishing and monitoring the construction cost budget for the project.
- Competitive separate trade contract tenders are issued and received by the Construction Manager sequentially throughout the course of the project as per the project schedule. Trade contracts are awarded, generally on the basis of the lowest price, based upon the recommendations of the Construction Manager. The separate trade contractors may be pre-qualified by the Construction Manager.
- The Construction Manager manages and administers the various separate trade contracts required to construct and commission the facility with oversight and inspection relating to quality issues from the architect, engineers, and other specialist consultants.

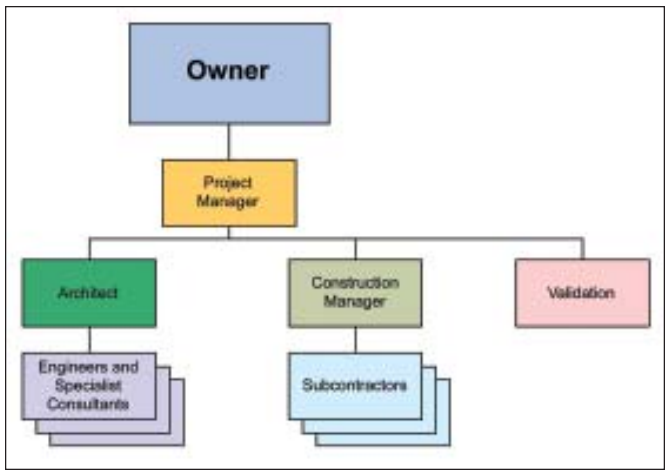

Figure 3. Organizational structure for the Construction Management Approach (At Risk Model).

- Contracts may be between the Owner and the individual trade contractors, wherein the Construction Manager is acting as an agent for the Owner with limited liability risk and virtually no financial risk. Alternatively, the contracts may be between the Construction Manager and the individual trade contractors, in which case the Construction Manager is acting in a similar manner to a general contractor and in an "at risk" situation. See Guaranteed Maximum Price description in the next section.
- The Owner/Project Manager performs oversight and due diligence with respect to the activities of the Construction Manager.
- The Construction Manager manages commissioning and validation activities, either with internal or external resources.

The organizational structure for the Construction Management Approach (Agent for Owner Model) is shown in Figure 2. The organizational structure for the Construction Management Approach (At Risk Model) is shown in Figure 3. The strengths and weaknesses of the Construction Management Approach are shown in Table B.

Contractual Arrangements

This contract strategy would typically have the Construction Manager acting as an extension of the Owner, compensated on the basis of a fee for services rendered. The risk assumed by the Construction Manager is generally low and hence the management fee for this service is lower than other approaches.

All construction trade contracts would generally be fixed price stipulated sum trade contracts, administered by the Construction Manager.

When Used

This contract strategy is typically used when the Owner is not risk averse and prefers a hands-on involvement in the project working closely with the Construction Manager or doing the construction management directly with his own people.

It allows for an overlapped design/construction schedule with maximum flexibility for Owner-initiated changes at the lowest cost. It is typically used on complex projects by Owners with a high degree of skill and confidence in managing projects, especially with an existing operations environment or projects where the transfer of cost and schedule risk to a contractor would result in excessively high contractor risk premiums.

Guaranteed Maximum Price (GMP)

Description

- This approach is a variation of Construction Management and sometimes called Construction Management – At Risk.
- The Owner acts as Project Manager or retains a project management firm to act as its representative (Project Manager).
- Owner/Project Manager retains an architect, engineers, and specialist consultants who initially prepare a program, then subsequently prepare drawings and specifications under the direction of the Owner/Project Manager for a series of separate and sequential trade contract tenders in a manner that the design and construction activities run concurrently and are overlapped.
- As a parallel activity, the Owner/Project Manager retains a construction management company (Construction Manager), initially on a fee for services basis during the pre-construction phase to provide constructability and value engineering input during the design phase and subsequently for construction phase services acting as a general contractor under a Guaranteed Maximum Price form of contract. The GMP Construction Manager (GMP CM) arranges for competitive trade contract tenders, scheduling, and cost control, as well as manages all construction activities to meet the Owner's scope, cost, time, and quality objectives.

Strengths
• Design process can be managed to control scope and quality. • Flexibility exists during the design and construction phases to overcome problems, incorporate changes and vary schedule requirements. • Design and construction overlap to reduce the overall schedule and achieve an earlier construction start and hence occupancy. • Construction Manager provides compliance, value engineering and constructability input to the design. • Cost savings due to budget under-runs, favorable market conditions, design, and construction innovation revert to the Owner, in whole or in part. • Owner retains and manages project contingencies as he/she sees fit. • Rigorous change control process implemented after completion of concept design.
Weaknesses
• Total project costs are not firmly known during the early stages of the project. • Contract administration of individual trade contracts, as it involves the Owner, is more complex and onerous. • The Owner may assume some construction health and safety risk. • The Owner must exercise a great degree of "due diligence" in selection of the construction management firm, as the Construction Manager is typically acting in a relationship that involves trust and confidence. • Risk of project cost and/or schedule overrun rests with the Owner. • Incentives may need to be introduced to ensure the CM's and the Owner's cost and schedule goals are aligned.

Table B. Strengths and weaknesses of the Construction Management Approach.

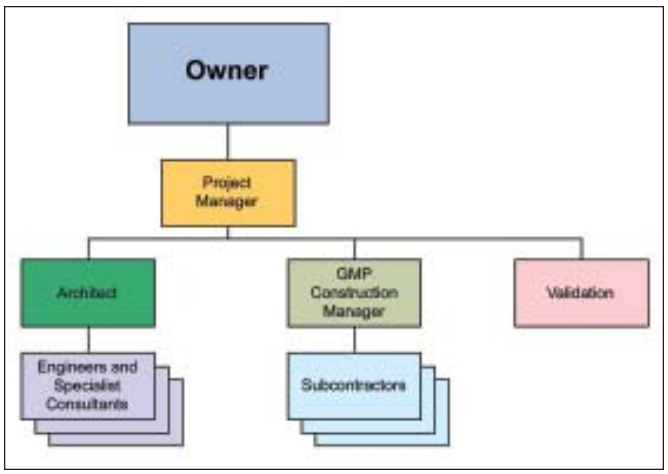

Figure 4. Organizational structure for the Guaranteed Maximum Price Approach (Construction Management - At Risk Model)

- GMP CM is selected by the Owner/Project Manager from a pre-qualified list of general contractors who specialize in GMP construction management. The GMP CM is typically selected based upon qualifications and their respective CM fee for overhead and profit. The fee is quoted as a percentage of direct construction cost and is to be applied to the project cost estimate to determine the Guaranteed Maximum Price (GMP) for the project. The GMP approach can involve establishing a cost sharing formula under which an incentive is provided for the GMP CM to reduce cost and schedule and share any savings with the Owner.
- The selected GMP CM develops a detailed budget for the project, based upon a combination of subcontractor/supplier quotations and his own estimates, which is used to finalize the GMP price target. The GMP CM works with the architect, engineers, and other specialist consultants to control the finalization of drawings and specifications in accordance with assumptions contained within the GMP price and compares the individual sub-trade tenders against budget as they are awarded.

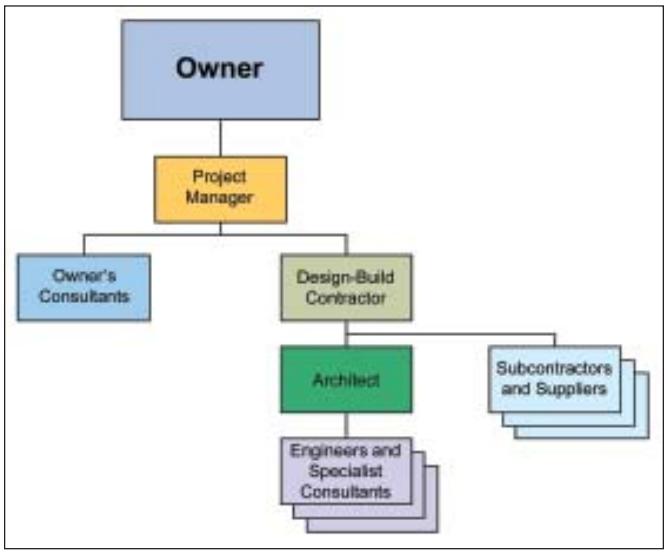

Figure 5. Organizational structure for the Design-Build Approach.

Strengths
• Advantages similar to construction management with the following additional benefits: - Owner has the benefit of a not-to-exceed cost figure during project development, assuming no changes are made to the scope of the contract. - Risk of cost performance is transferred to the Contractor after the GMP is established.
Weaknesses
• Owner and Contractor share in any costs savings regardless of reason. • Owner is reliant on the ability of the Contractor to develop a GMP and negotiate competitive sub-trade prices. • Owner must have confidence in the Contractor's integrity as well as auditing and cost control systems in place to assure that the GMP is not padded or overly inflated. • Owner requires a strong and knowledgeable Owner's team to review and approve/accept the initial GMP price and administer the GMP contract. • The Owner and Contractor run the risk of haggling over changes (i.e. changes inside or outside the original GMP amount). • The Contractor may propose to do some of the work with own forces, hence reducing the competitive advantages of sub-trade tendering. • Fee for overhead and profit, which is part of the GMP, is higher, due to additional risk assumed by the Contractor.

Table C. Strengths and weaknesses of the Guaranteed Maximum Price Approach.

- The Owner/Project Manager may retain an independent cost consultant to assist and provide advice when finalizing the GMP with the GMP CM.
- Architect, engineers, and other specialist consultants complete drawings and specifications under the direction of the Owner/Project Manager, but in conjunction with the GMP CM for separate sequential sub-trade contract tenders.
- GMP CM obtains competitive sub-trade tenders for all elements of the work and obtains Owner's/Project Manager's approval to award each separate sub-trade contract progressively throughout the course of the project.
- Owner/Project Manager administers the GMP contract, assisted by the architect, engineers, and other specialist consultants who monitor quality of the completed work.
- At the conclusion of the project, the Owner/Project Manager reconciles the final cost of the project with the GMP CM based upon the actual costs incurred by the GMP CM plus the GMP CM's fee including all approved changes with the GMP price originally established. Any cost over-run beyond the GMP contract price is absorbed 100% by the GMP CM. Any cost under-run below the GMP reverts to the Owner or is shared between the parties based upon the cost sharing formula. Any incentives to meet schedule also are applied.

The organizational structure for the Guaranteed Maximum Price Approach (Construction Management - At Risk Model) is shown in Figure 4. The strengths and weaknesses of the Guaranteed Maximum Price Approach are shown in Table C.

Contractual Arrangements

This contract strategy typically involves an "open book" approach with the GMP CM, where the GMP CM will buy-out the various elements of the project at the lowest cost on a

competitive basis and charge the Owner a separate fee for the service. The fee is commensurate with the value of the costs managed by the GMP CM and his risk in the GMP not-to-exceed figure. The later in the design process the GMP is established, the lower the cost risk for the contractor. The GMP is usually established through negotiation with the GMP CM in advance of construction start.

Trade contracts are typically lump sums between the GMP CM and Subcontractor and obtained on a competitive basis. Competitive sub-trade pricing is waived on all components the GMP CM is authorized to approve. A general expense account is typically hard for the Owner to effectively control under this approach and can be 10-20% of the direct cost of the construction, depending upon the type of project, and is often a source of disputes.

When Used

This contracting approach is typically used where the project is straightforward and not overly complex, and the Owner is somewhat risk adverse, but wishes to enjoy many of the same benefits of the Construction Management approach with the added benefit of "a not to exceed" figure before construction proceeds.

Design-Build

Description

- The Owner acts as Project Manager or retains a project management company to act as its representative (Project Manager).
- Owner/Project Manager retains an architect, engineers, and other specialist consultants (Owner's consultants) to establish space program and develop a project concept and performance specifications (statement of owner's requirements).
- Owner/Project Manager selects a short list of pre-qualified design-build contractors to submit designs and corresponding fixed price tenders for the project based upon the Owner's stated requirements. Each design-build contractor retains its own architect, engineers, and other specialist consultants to assist in the development of its own unique design solution.
- Owner/Project Manager selects the design-build contractor on the basis of the design, schedule for completion, and price (not necessarily the lowest price), which best meets the Owner's requirements and represents best value with the assistance of the Owner's consultants.
- The successful design-build contractor completes the design, drawings, and detailed specifications, using its own architects, engineers, and other specialist consultants, and constructs and commissions the new facility.
- Owner/Project Manager administers the design-build contract and the Owner's consultants continue an active involvement in a compliance role with the review of the detailed design, drawings, detailed specifications, and construction quality.

The organizational structure for the Design-Build Approach is shown in Figure 5. The strengths and weaknesses of the Design-Build Approach are shown in Table D.

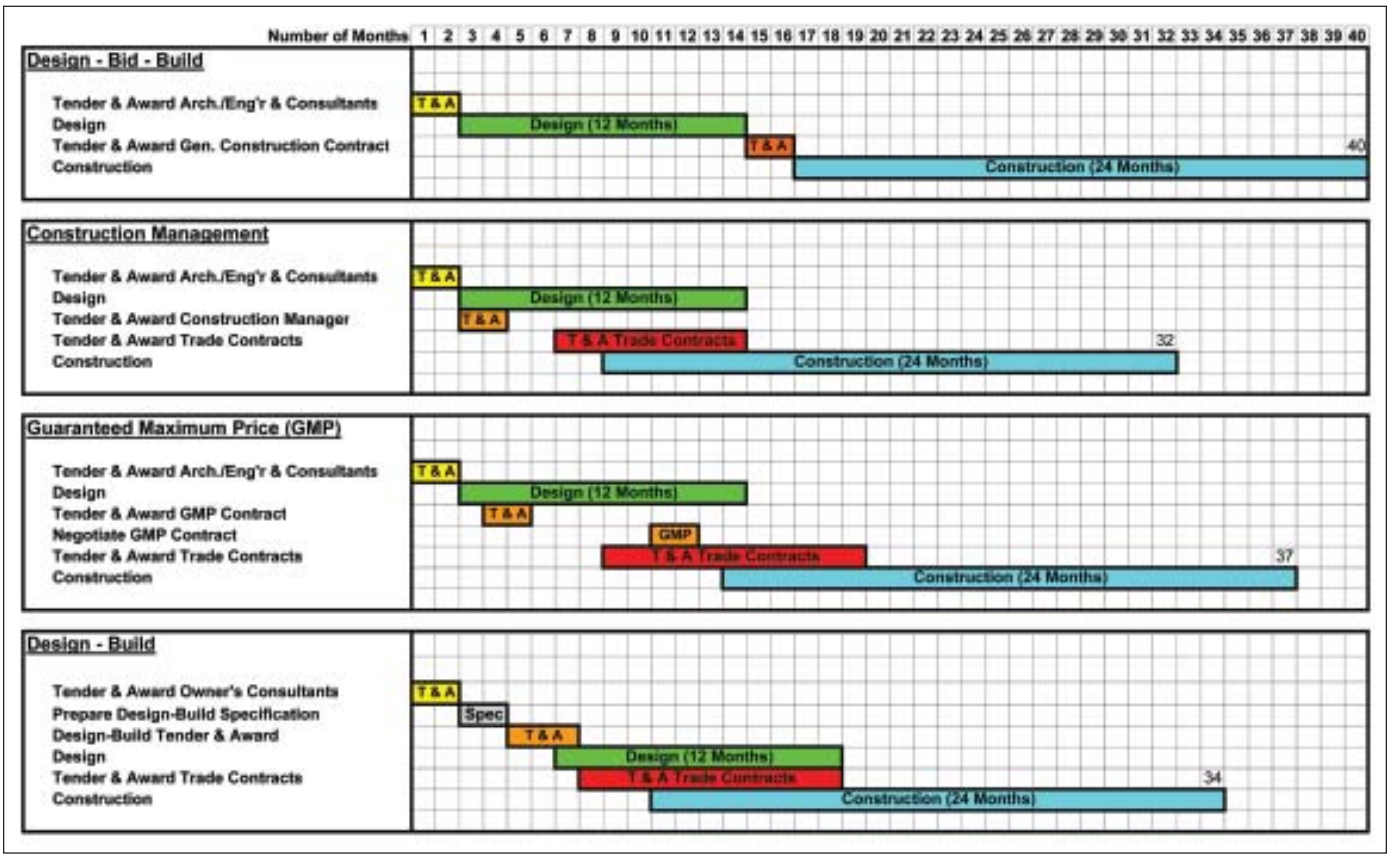

Figure 6. Project delivery options - timeline comparison.

Strengths
• Design and construction are overlapped to reduce the overall schedule. • Total design and construction costs are theoretically fixed prior to design and construction start subject only to changes in the Owner's requirements. • Allows more than one design solution to be developed to fulfill the intent of the Owner's requirements. • Competitive design-build process can result in creative and cost-effective design solutions. • Single source responsibility for delivery of the total project. • Design and construction risk is theoretically transferred to the contractor. • Compliance issues are typically owned by DB contractor.
Weaknesses
• Owner does not have direct control over the design team. • Owner's requirements must be very well defined at the outset. • Limited flexibility for the Owner to introduce changes in requirements. • Savings resulting from value engineering during the design phase or favorable market conditions accrue to the contractor. • Evaluation and comparison of the various design build solutions is difficult to ensure best value in terms of price, performance and function, including accounting for lifecycle cost. • Owner requires a strong consultant team to be actively involved to enforce requirements of the contract and perform adequate due diligence through the process. • Design build tendering process is costly to the bidders. Some form of compensation may be required to losing design-build teams. • Design innovations developed by the losing teams remain the respective "copyrights" of the losing contractors.

Table D. Strengths and weaknesses of the Design-Build Approach.

Contractual Arrangements

The contractual arrangements typically include a lump sum stipulated price based upon the design solution developed to respond to the Owner's stated requirements. Cash allowances may be included for items not able to be defined. The form of the contract is based upon industry standard design-build contract.

When Used

This contracting strategy is typically used when the Owner can develop his functional and performance requirements to a high degree and requires single source responsibility for total project delivery on a fast-track schedule.

It is typically used for projects when the Owner would like to deal with a single party or where the financial institution lending the money to finance the project requires a single party in an "at risk" situation for total project delivery. The Owner's requirements and project scope must be well-defined from the outset.

Risk premiums built into the contractor pricing may adversely affect the project economics and the ability to secure third party financing. A timeline comparison is shown in Figure 6.

Summary

Selection of the appropriate Project Delivery Method is critical to every project. No project is identical to the previous project. Thus, there is no single delivery system that works best for all projects. Unfortunately, there is no single "silver bullet" for executing projects.

Individual companies possess different internal capabilities as it relates to the execution of capital projects.

However, the characteristics of capital projects in the biopharmaceutical industry generally have many similarities, including:

- Speed to market driven
- Cost, quality, schedule, and safety drivers
- Owners are typically knowledgeable in capital projects, but resources constrained.

As outlined in the body of this article, there are many pros and cons as they relate to the differing execution strategies. Companies need to not only review their capital project execution strategy, but the need for assessment of contract and financial strategies should be blended into the overall Execution Plan.

When selecting the appropriate project delivery system, companies must carefully consider their internal resources capacity and competency, level of scope definition, project cost, and schedule as well as regulatory and overall business strategies.

About the Authors

Brian Sirbovan is responsible for the overall direction and development of Stantec's Program and Project Management (P&PM) practice area. Sirbovan also provides expert consultation and advice to clients on all aspects of project and construction management. He possesses nearly 30 years of project management and construction management experience and is recognized as a leading authority in the field of professional project management. Sirbovan has an extensive knowledge of all aspects of project and construction management, particularly in the areas of project management best practices, pre-project services, and project controls. Specific areas of expertise include pre-project planning, project definition and implementation planning, and project organization. His extensive project experience encompasses a diverse array of industrial, commercial, institutional, and municipal projects. His experience includes senior project oversight and management roles on numerous projects exceeding $100 million in capital value. He is a graduate of the University of Waterloo, mechanical engineering, Waterloo, Ontario, Bachelor of Applied Science (1976). He serves on the Board of Directors for the Consulting Engineers of Ontario, is a member of the Project Management Institute, and is a registered Professional Engineer. He can be contacted at telephone: 1-416-229-4000 x232, fax: 1-416-229-4889, or e-mail: bsirbovan@stantec.com.

Stantec, 100 Sheppard Ave. E., Suite 700, Toronto, Ontario M2N 6N5 Canada.

Dave DiProspero is responsible for the growth of the biopharmaceuticals practice area and is involved in the front-end planning, strategizing, and project set-up/implementation for Stantec's biopharmaceutical clients. DiProspero provides expert consultation and advice on various aspects of pharmaceutical processes, facility layout and project planning, and interrelation to the construction process. He possesses 25 years of pharmaceutical experience and is well versed in oral solid dose form facility design with a strong process and equipment expertise. DiProspero has been involved in design, installation, commissioning, and qualification for contained material handling, transfer and ergonomics, ingredient dispensing, formulating, weighing and batching, OSD unit operation process feed and receipt, blending, wet and dry granulation, fluid bed processing, roller compaction and milling, tablet encapsulation, compression and coating, fill/finish and packaging, as well as integrated processing trains. DiProspero completed his undergraduate studies at the Rochester Institute of Technology. He is an active member of ISPE and is the current Chair of the Certification Training Task Team. He can be contacted at telephone: 1-856-218-7987, fax: 1-856-582-5553, or e-mail: ddiprospero@stantec.com.

Stantec, 39 Daytona Ave., Sewell, NJ 08080.

Brian Larson has more than 20 years of engineering and management experience and has directed a vast array of multi-million dollar planning, design, and compliance projects for pharmaceutical clients in the US, Canada, and the Caribbean. As a corporate practice area leader, Larson oversees the division's strategic vision and critical project programming along with the practice area's management and performance. In addition, he has direct hands-on involvement with various projects in their development stages. Larson provides expert consultation for his clients in business strategies as they relate to capital project planning. With a diverse range of project experience in biopharmaceutical processing and facilities, he manages significant projects from concept through validation. Larson has completed projects in the sterile, OSD, vaccine, and API market sectors. A licensed professional engineer, Larson is Vice President of Stantec's biopharmaceutical group. He holds degrees in mechanical and industrial engineering. Larson is a member of ISPE and the Society of Manufacturing Engineers. He can be contacted at telephone: 1-607-755-9805, fax: 1-607-755-9850, or e-mail: blarson@stantec.com.

Stantec, 1701 North St., 40-4, Endicott, NY 13760.

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Achieving Faster Project Delivery – More Haste, Less Speed

by Gordon R. Lawrence

This article discusses how implementing proven Best Practices can help get products to market quickly and more competitively.

Introduction

When introducing a new drug to the marketplace, pharmaceutical firms need to move fast. This means not only moving fast in research, clinical trials, and marketing, but also in designing, engineering, constructing, and validating new production facilities capable of producing the drug in the quantities required.

Whereas there has been a lot of discussion within the pharmaceutical industry on how to improve efficiency in research and clinical trials, there has been less discussion of how to improve efficiency in the management, design, engineering, construction, and validation of facility capital investment projects.

The study[1] presented in this article shows that by incorporating some fairly basic project management Best Practices into their project systems, pharmaceutical firms can improve the speed of project execution by more than 40 percent. The study presented in this article also shows that the barriers to implementing these Best Practices lie outside the project/engineering group. The key to advancements in project execution practices lies with business and manufacturing managers; fresh thinking about project practices on the part of senior management could go a long way to seeing improvements take root.

Research Questions and Answers

Research that we have carried out over the past 19 years,[2] including analysis of more than 550 pharmaceutical industry projects,[3] shows that most pharmaceutical firms share some common characteristics in the way that they execute capital investment projects. These characteristics include, most commonly, a focus on speed of project execution rather than minimizing project capital cost.[4] Another frequent characteristic is a lack of knowledge outside the project/engineering department about Best Practices in project management that would allow projects to be executed quickly and efficiently.

In this study, we posed the question, "Are pharmaceutical firms achieving their aim of executing projects quickly - and, if not, what working practices should they change to decrease time to market?"

In this study we found that, although pharmaceutical firms generally execute projects just as fast as the general process industries, when pharmaceutical firms try to accelerate their projects (e.g., schedule-driven projects to bring new drugs to market), they are far less successful than their counterparts in other process industries in meeting their schedule goals.

When we looked at the Best Practices that are routinely used in other process industries to accelerate schedules, we found that these practices were viewed with some doubt by pharmaceutical management outside the immediate project/engineering group. There was a misconception that Best Practices developed outside the pharmaceutical

Table A. Comparison of the two datasets for the pharmaceutical project study.

Key Project Characteristic	Bulk API Pharmaceutical Dataset (n = 38) *(±1 standard deviation)*	Non-Pharmaceutical Batch/Specialty Chemical Dataset (n = 398) *(±1 standard deviation)*
Mean Total Installed Cost (US$ millions)[8]	32.75 *(0-88.78)*	46.49 *(0 – 117.56)*
Mean Year of Project Authorization	1997 *(1992-2001)*	1997 *(1994-2001)*
Project Type	Greenfield or co-located (brownfield): 32% Expansions and add-ons: 46% Other revamps: 22%	Greenfield or co-located (brownfield): 36% Expansions and add-ons : 39% Other revamps: 25%

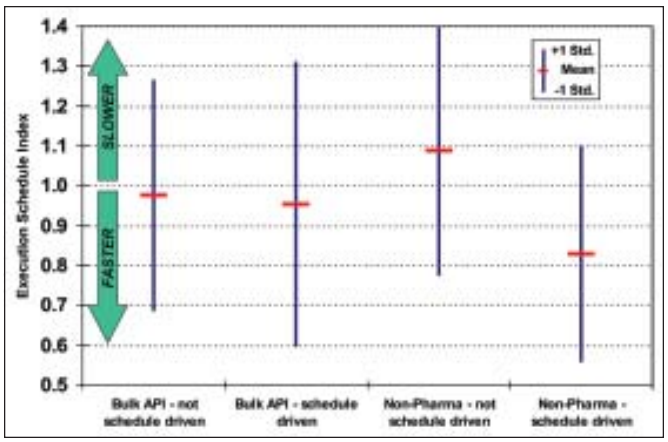

Figure 1. Schedule-driven projects: pharmaceutical project teams do not accelerate their projects by much beyond the overall average.

industry were focused solely on minimizing cost, and therefore had no applicability in an industry that prized speed over cost. However, this study demonstrates that these Best Practices are just as effective at shortening project schedules in the pharmaceutical industry as they are in other process industries.

We looked at the reasons these Best Practices were not being adopted for pharmaceutical projects. What we often found was that, although the project/engineering groups usually understood the rationale for Best Practices, they were prevented from implementing them by the actions of other stakeholders within the firm, but outside the project/engineering group. Typical problems observed were:

- *The business was unclear as to the rationale and objectives of the project* – leading to confusion and inefficient working on the project.

- *Frequent changes to the business objectives* – also leading to inefficient working.

- *Lack of involvement from end-users during the early design stages* – leading to late (and hence costly in terms of time and money) changes to the design when the end users did become involved.

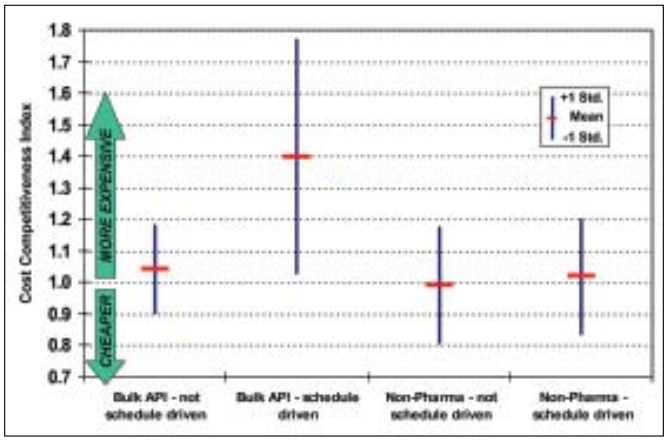

Figure 2. Schedule-driven projects: pharmaceutical project teams expend money in their efforts to accelerate.

- *Construction work started as soon as project approval was received* (and prior to completion of basic design work) purely because management outside of the project team wanted visible evidence of progress in the field – leading to inefficient working as construction either outstripped the supply of engineering drawings or re-work when the design changed after construction had started.

- *Projects being approved on the basis of rough estimates, without any basic design work being completed* – leading to lack of accurate estimates with which to control the project.

All of these problems appear to stem from incorrect information and/or poor understanding of project management basic theory and practice on the part of stakeholders external to the project/engineering departments of pharmaceutical firms. With training of senior management in some of the basic Best Practices, capital investment will become more efficient in the pharmaceutical industry.

Methodology

In looking for the root causes of success and failure in capital investment projects over the past 19 years, we have gathered data on several thousand projects across the process industries. We have then applied statistical methods to identify why some projects succeed and others fail. This has allowed us to develop statistical models for calculating the industry average outcome of a given project. It has also given us an empirically based view of what constitutes Best (and worst) Practice for promoting project efficiency.[5]

In this particular study, we examine:

- whether pharmaceutical firms achieve their stated aim of being able to execute projects quickly.[6]

And if they do not achieve that aim, we examine:

- whether the Best Practices used in other process industries to affect the "controllable" factors of a project have a similar effect on pharmaceutical project.[7]

And hence:

- whether pharmaceutical firms could improve their project execution efficiency by adopting these Best Practices.

Do Pharmaceutical Firms Execute Projects Quickly?

For this research, we need a study set of pharmaceutical projects and a comparison set of projects from the wider process industries. We then need a method of calculating the "industry average" schedule for each project to see if pharmaceutical projects are faster or slower than similar projects in other industries.

Comparison Datasets

In order to ensure as far as possible an "apples for apples" comparison, we chose to compare:

- Bulk Active Pharmaceutical Ingredient (API) facilities and utility projects (tank farms, piperacks, etc.) on pharmaceutical sites

- Batch specialty chemical and utility type projects executed outside the pharmaceutical industry

From our database of more than 550 pharmaceutical projects, we drew a sample of 38 bulk API and utility projects. From our database of more than 8,000 process industry projects, we drew a comparison set of 398 non-pharmaceutical specialty/batch projects. The characteristics of the two sets are shown in Table A.

"Industry Average" Schedule Model

If we are to examine whether (and how) project teams took longer or shorter than the "industry average" to execute their project, we first need a way to calculate what the "industry average" schedule would have been for each project. We can then compare the actual schedule time taken to the "industry average" to decide whether the project was fast or slow. (Note that this is an entirely different concept from schedule predictability. Predictability simply examines whether the team met its original planned schedule; it says nothing about how fast the team was in comparison with industry.)

In previous research a model was developed using least squares regression techniques that is based on a data sample of more than 1,000 projects. The model is based around "uncontrollable" project factors such as overall project size.[9]

For this study the model was cross-checked against both of our current sample sets (shown in Table A) to confirm that the model was still valid for these particular sets.

An industry average schedule was then calculated for each individual project. Next, by dividing the actual project schedule by the industry average schedule, we then get an index value with which we can compare results from different projects.[10]

Are Pharmaceutical Projects Fast?

We compared the average execution schedule index of our bulk API dataset to our dataset of non-pharmaceutical projects. Giving the non-pharmaceutical set an average index of 1.00, we found that the bulk API average was only three percent faster in executing a project (i.e., taking it from start of detailed engineering to mechanical completion).

However, the picture changes if we take account of the difference between those projects that were deemed by the teams to be "schedule-driven" and those that were not. In Figure 1, we divide the projects into two groups: those labeled by the teams as being "schedule driven" and those that were not. This time, we can see that schedule-driven bulk API projects typically do not achieve as much execution schedule acceleration as the non-pharmaceutical projects. We also can see that "schedule-driven" bulk API projects are only a couple of percentage points faster than the non-schedule-driven bulk API projects. In other words, pharmaceutical project teams are not able to accelerate the execution phase of their

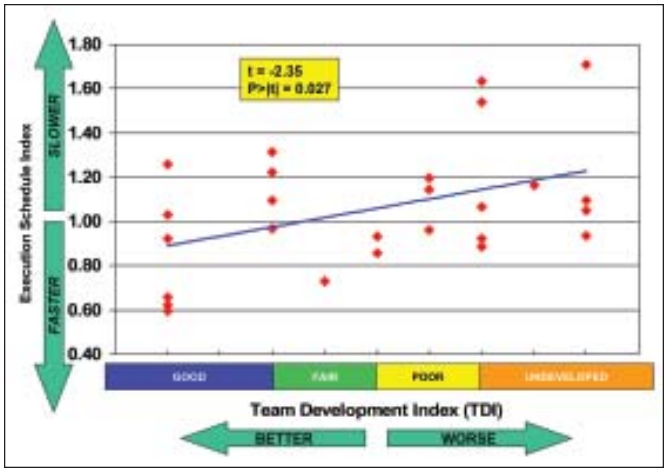

Figure 3. Better team development correlates with shorter execution schedules.

projects beyond the industry average speed, but non-pharmaceutical project teams can achieve execution schedules that are around 14 percent faster than the average, and more than 20 percent faster than the execution schedules on non-schedule driven projects. (Remember that we are looking here at execution time; in other words detailed engineering, procurement, and construction up to the point of mechanical completion. We are not including commissioning, qualification, and validation in this measure.)[11]

Using a model for project cost, we also were able to make a comparison of project cost between schedule-driven and non-schedule-driven projects.[12] In Figure 2, we can see that the pharmaceutical project teams achieve their minor schedule acceleration at the expense of a significant increase in cost, whereas the non-pharmaceutical teams achieve their acceleration with only a slight increase in cost.

So, in answering our first question, "Do pharmaceutical firms achieve their stated aim of being able to execute projects quickly?" The answer is no when we compare them with speed of execution in other process industries. Project teams in other process industries are able to achieve much greater schedule acceleration—and for less of a cost penalty.

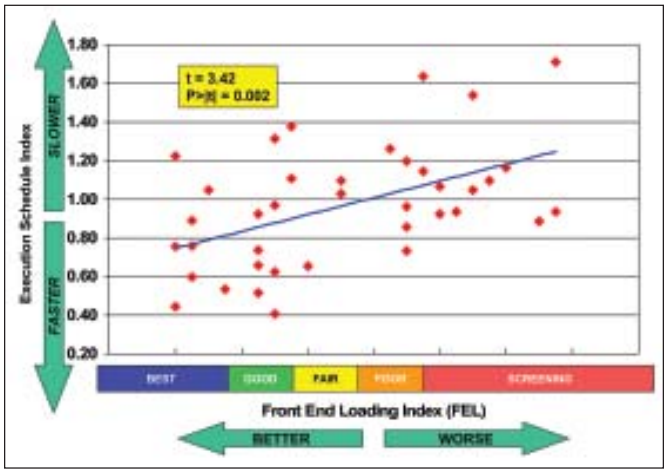

Figure 4. Better front-end loading correlates with shorter execution schedules.

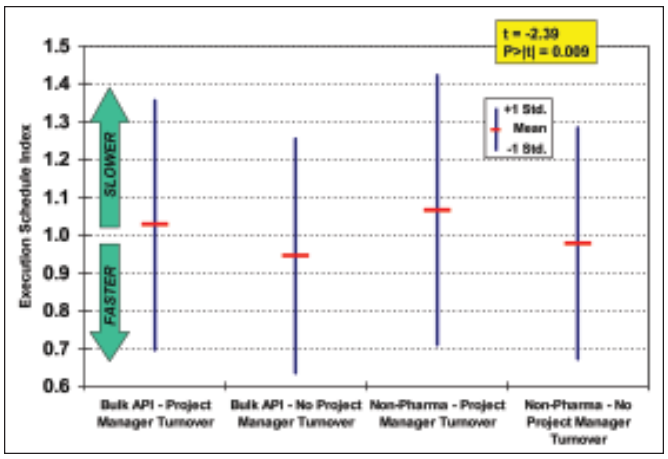

Figure 5. Changing the project manager... causes delays to the project.

Schedule Acceleration Methods Used

We next looked at what pharmaceutical project teams did to accelerate their "schedule-driven" projects. In talking with the pharmaceutical project teams, typical responses were:

- "*We order long-lead equipment items before the project is approved and before the basic design is complete*." This is a common schedule acceleration activity across the process industries. But it does carry risks. Early ordering is risky because, for example, the project might be cancelled or as the basic design develops, it might be found that order specifications are wrong.

- "*We start construction before detailed engineering is far advanced*." Projects commonly overlap detailed engineering and construction. An overlap between engineering and construction in the region of 28 percent of execution time is typical and is good practice for an efficient project. However, if the overlap is increased - some pharmaceutical projects start construction before even basic design is complete - then this carries a risk. For example, work could become inefficient if construction gets too far ahead of the issue of engineering drawings; and, the risk of late changes increases because construction begins on the basis of drawings that are not yet frozen. Interestingly, teams often cite their reasons for starting construction early as being not only to speed up the project, but also to "demonstrate" progress to those outside the project team who "could not understand design development, but could understand a man digging a hole."

- "*We use overtime and shift work*." This is an expensive option. Several studies have shown that not only does productivity decline rapidly as the workday is lengthened, but also that productivity declines further, the longer those extended workdays continue.[13]

Do Industry Best Practices Work For Pharmaceutical Firms?

We know from previous research across the process industries that several "controllable" factors have a positive effect in reducing schedule time and that they achieve shorter schedules at little or no extra cost; in fact, they frequently result in reduced cost as well as faster schedule.[14] These factors include (1) the level of team development achieved during the early concept/basic design phases of the project; (2) the level of Front-End Loading (FEL) achieved (the level of definition in the basic design package PRIOR to full authorization of project execution funds); and (3) the amount of turnover of key project staff during the execution of the project. We wanted to examine whether these three factors also had a positive effect in the pharmaceutical industry.

Team Development

In previous research in other process industries, we have developed a quantitative measure of the level of "development" of a project team.[15] We assess team development in five main areas. These areas cover issues such as clarity of objectives; composition of the team, and clarity of roles. This assessment gives us a quantitative measure or a Team Development Index (TDI) in the range from *Undeveloped* to *Good*.

Each of the five areas has been shown to individually have a statistically significant effect on project outcomes, such as schedule and cost, when applied to various process industry projects. We now wish to see whether TDI has an effect on our bulk API project sample.

Does Better Team Development Reduce Pharmaceutical Project Schedules?

When we plot the execution schedules of our bulk API projects against the TDI that each project achieved, (Figure 3), we note a clear correlation between execution schedule and TDI. Better TDI (i.e., better team development) leads to faster schedules.[16]

Taking a closer look at the bulk API projects that did not achieve a *Fair* or *Good* TDI, we see pressures from outside the project/engineering group that ran contrary to Best Practice. These projects had issues such as:

- Business objectives were not clearly defined to the team.
- End-users and business sponsors did not make the time to get involved in the early stages of the project.
- The project team was directed to skip the company approval gate process "in the interest of speed."

Each of these issues affects the assessment of TDI, and is largely outside the control of the project department.

Front-End Loading

In previous research in other process industries, we also have developed a quantitative measure of the level of front end definition detail in a basic design package.[17] We assess this measure in three main areas. The resulting index we have called the Front-End Loading (FEL) Index. The three main areas are:

1. **Engineering Design:** How well developed are the basic design package engineering documents? Have they been approved by the end-users?

2. **Site Factors:** Have the factors external to the project been taken account of in the design? (e.g., "As-built" checks of existing drawings, soil surveys, environmental authority approvals, health and safety regulations, etc.)

3. **Project Execution Planning:** Has the team developed a plan for project execution (including schedule, contract strategy, etc.)?

This gives us a quantitative measure, or an FEL Index, in the range from a *Best* rating of a complete "issued for construction" package to a *Screening* rating for a project that has not progressed far beyond the basic business idea.

As with TDI, each of the three areas has a statistically significant effect on project outcomes, such as schedule and cost, when applied to various process industry projects. We now wish to see whether FEL has an effect on our bulk API project sample.

Does Better FEL Shorten Pharmaceutical Project Schedules?

When we plot the execution schedules of our bulk API projects against the FEL that they achieved (i.e. the level of definition they achieved in their basic design packages) prior to full funds authorization (Figure 4), we see a clear correlation between execution schedule and FEL. Better FEL (i.e., better definition of the basic design package prior to authorization) leads to faster schedules.

If we look at those bulk API projects that achieved only a *Fair*, *Poor,* or *Screening* level of FEL to determine why they did not achieve better FEL ratings, we can again discern the influence of stakeholders from outside, driving the project team to:

- Start detailed engineering (or even construction work) before the basic design work is complete. (Because management outside of engineering wanted visible evidence of progress in the field.)

- Neglect to employ specialist planners and cost estimators to develop good schedules and estimates during basic design. (Because management outside of engineering wanted to keep down the "head count" in the project/engineering department, because this department is seen as adding little to the company bottom line.)[18]

When we discussed these findings with the pharmaceutical firms involved, we often met with the comment that, although developing an excellent FEL package might help speed up execution, the teams believe it would lead to slower overall project cycle time because of the time required to develop the FEL package. However, this is simply not the case. We found that there is no correlation between longer front-end schedules and better FEL. In fact, the need to focus on the key requirements for good FEL can help teams to keep the front-end schedule (and hence the overall project cycle time) short.

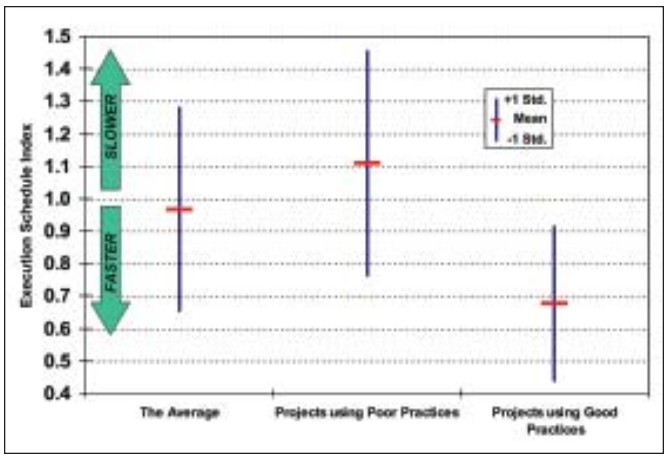

Figure 6. Use of best practices is reflected in results: almost 45 percent faster.

We also noticed that the schedule-driven projects in our bulk API set had extremely slow front-end phases. Anecdotal evidence from the teams suggested that this, again, was driven by influences from outside the project/engineering department. Business managers were unable to make firm decisions in the early phases, leading to recycle of the project.

Turnover of Core Project Staff

From previous research in other process industries, we have confirmed the common-sense view that turnover in "core" staff positions during the course of a project negatively affects project schedules.[19]

Does Turnover in the Project Manager Role Affect Pharmaceutical Schedules?

Figure 5 shows the effect on execution schedule when the project manager is changed part way through the project. Our bulk API set shows the same trend as our non-pharmaceutical set. Changing the project manager in mid-project has a detrimental effect on project schedule.

Clearly, there may be times when a project manager may need to be dismissed (e.g., due to under-performance), or leaves the position for other reasons. However, moving the project manager to another project or into a different role in the firm (e.g., as career development) comes at a price that senior management should carefully consider.

Can Pharmaceutical Firms Improve their Project Schedules by Adopting Best Practices?

We showed earlier (Figure 1) that pharmaceutical teams that describe their projects as "schedule-driven" achieve only slightly faster schedules than those projects that are not schedule-driven.

This time, instead of focusing on whether the team treated the project as "schedule-driven," we now focus on those teams that employed Best Practices versus those that did not.

In Figure 6, we compare projects that used Best Practices with those that did not. As illustrated, the projects that did use Best Practices achieved schedules almost 45 percent faster than the projects that did not use Best Practices. Hence, the answer to our question is that pharmaceutical firms could dramatically improve their project schedules if they routinely employed project Best Practices rather than adhere to the more typical (and more high risk) schedule acceleration methods, such as starting construction early and using overtime.

Conclusion

Activities such as starting construction very early and using high levels of overtime are visible and obvious schedule acceleration methods that are easy for non-project staff to understand and they can improve project schedules slightly. However, they do not offer dramatic schedule improvements, they carry a risk of having the opposite effect, and they come with a risk of an increase in overall project cost.

This study shows that implementing Best Practices, such as effective team development and Front-End Loading on bulk API projects are a low risk way to drive improvements in project execution schedules, and also can reduce overall project installed costs. However, they are not easy for pharmaceutical business managers who do not have a background in capital projects to understand. Nevertheless, if pharmaceutical business managers can be persuaded that *"More Haste – Less Speed"* applies to capital projects as well as it does in other walks of life, then a distinct improvement in pharmaceutical project efficiency should result.

Below are the 5 key areas where pharmaceutical business managers need to change their typical working practices. They will come as no surprise to seasoned project professionals, but we hope that the data in this article will help those project professionals in convincing management of the efficacy of basic project management principles.

1. *Stating the business objectives unambiguously in the early phases of the project* – clear objectives help avoid confusion and help to focus the team on the task in hand.

2. *Engaging end-users and business sponsors to become involved in the project in the early stages* – engaging these people in the early stages allows them to comment on (and change) the design before the design is frozen and changes become dramatically more expensive in time and money terms.

3. *Refraining from demanding late changes to the design* – the same change made after the basic design has been completed is more expensive in terms of time and money than if it had been made in the early design phase.

4. *Allowing project teams the time and space to develop a basic design package, before starting detailed engineering or even construction* – using the correct sequence of design, engineer, construct is more efficient than starting construction before the design is complete.

5. *Avoiding unnecessary changes to project personnel during the life of the project* – changes in key personnel are disruptive to a project and can adversely affect both cost and schedule.

By using these basic practices, pharmaceutical business managers can greatly assist their project teams in achieving a significant improvement in project performance.

References

1. For a full listing of public domain articles and conference publications related to this research please either contact the author or go to http://www.ipaglobal.com/pubs/publications.html. A listing of additional proprietary research also is available on request.

2. Ibid.

3. This database covers the range of pharmaceutical industry activities, including offices, laboratories, primary/bulk active pharmaceutical plants, biopharmaceutical plants, secondary/formulation and finishing plants, warehousing and site utilities. Projects are drawn from around the world and from more than 25 companies. They range from greenfield facilities to small revamps of existing facilities. Project sizes range from less than $0.5 million to more than $360 million.

4. An example of this research is: Lawrence, G.R. "Pharmaceutical Capital Investment: Time to Rethink Corporate Culture," *TCE (The Chemical Engineer)*, August 2004, pp. 28-29.

5. An introduction to this methodology is given in: Merrow, E.W. and Yarossi, M.E. "Assessing Project Cost and Schedule Risk," *Transactions of American Association of Cost Engineers*, pp. H6.1-H6.7. Morgantown, West Virginia, USA: American Association of Cost Engineers, 1990.

6. In this study, we have looked at two schedule measures:
   - Project Execution Schedule – from the end of basic design to the point of mechanical completion.
   - Project Cycle Time – from the start of concept design, through basic design, engineering, procurement, and construction to the end of startup (in other words, installation and operation qualification, but not the end of process qualification).

7. In other words, project factors that are within the control of the project team. Controllable factors might include: having everyone on the team who should be there; avoiding turnover of project staff; developing a detailed basic

design package, etc. Uncontrollable factors that can affect project schedule might include overall project size; number of unit operations; number of reactor units, etc.

8. Total installed cost includes design, engineering, procurement, construction costs up to mechanical completion. (In other words, it excludes commissioning, qualification, and validation costs). The average cost of a project in the set is shown in US$, de-escalated to a common baseline year and adjusted to a common baseline location.

9. The general methodology used is outlined in: Merrow, E.W. and Yarossi, M.E. "Clothing the Emperor: A Plea for Scientific Discipline in Project Evaluation," presented at the *American Association for Cost Engineers*, 34th Annual Meeting. Boston, Massachusetts, USA, 26 June 1990.

10. For example: a project with an actual schedule of 12 months and an industry average schedule of 10 months would have an index of 1.20, making it 20 percent slower than industry. Conversely, a project with an actual schedule of five months and an industry average schedule of six months would have an index of 0.83, making it 17 percent faster than industry.

11. However, we also know that Best Practices such as Team Development and key team member turnover also have an effect on qualification cost and schedule performance – as discussed in Aschman, A.J., "Outcomes and Best Practices for Commissioning and Qualification," November 2003 – a proprietary research study developing cost and schedule models as well as a view on best practices for commissioning and qualification.

12. This model was developed using a similar methodology to the schedule model described earlier. The cost model for bulk API plants and batch/specialty plants is based around Lang factors. For an example of this methodology in developing a laboratory cost model, refer to: Lawrence, G.R., "Laboratory Cost Modeling," presented at the ISPE *Continuous Advancement Conference – Development and Analytical Laboratory Design*, Copenhagen, Denmark, 1-4 December 2003.

13. One example is: Merrow, E.W., "Labor Productivity Research-Phase II: Understanding Labor Productivity in High Wage Regions," presented at the *Industry Benchmarking Consortium*, McLean Virginia, USA, March 2002.

14. For an example of how this research applies to the pharmaceutical industry see: Merrow, E.W., "It's Time for Capital Excellence in Pharma Projects," presented at the *Pharma Summit on Aseptic Technologies*, Cork, Ireland, 1-3 June 2005.

15. Biery, F., "Enhancing Team Effectiveness to Improve Project Outcomes," presented at the *Industry Benchmarking Consortium*, McLean, Virginia, USA, March 2001.

16. The two statistical values shown in this Figure are t and P>|t|. These are defined below. However, for the purpose of this article, a rough guide for those engineers whose statistics knowledge may be a little rusty is – if P>|t| is less than 0.05 then there is a correlation and vice versa.
    - t = A statistic that measures the significance of an independent variable in a regression equation.
    - P>|t| = The statistical confidence you have that the population coefficient you are approximating is not really zero.

17. Merrow, E.W. and Yarossi, M.E., "Managing Capital Projects: Where Have We Been – Where Are We Going?" *Chemical Engineering*. 101 (10): 108, 1994.

18. This is despite the fact that there is no link between reducing the engineering cost (as a percentage of total project cost) and improved pharmaceutical project cost competitiveness – as described in: Lawrence, G.R., "Has Engineering Percentage had its Day?" *The Chemical Engineer (TCE)*, June, 2005, pp. 40-41. And also despite the fact that project departments in manufacturing firms across the process industries frequently do not employ sufficient cost controllers and schedulers – as discussed in: Findley, D. and Jochmann, M. "Organizational Effectiveness," August 2005 – a proprietary research study into the link between project department staffing levels, project portfolio size, and project effectiveness.

19. Parodi, F., "Why Do Good Practices Produce Non-Competitive Results?" presented at the *Industry Benchmarking Consortium*, McLean, Virginia, USA, March 2000.

About the Author

Gordon Lawrence is a Senior Project Management Analyst at Independent Project Analysis (IPA), working from the Netherlands office of this US firm. IPA is a consultancy specializing in analytical research into the root causes of success and failure of capital investment projects and project systems. Prior to joining IPA, Lawrence was a project manager with the general service contracting firm, Jacobs Engineering. He has degrees in chemical and biochemical engineering and in business administration. He is a chartered engineer and a member of the ISPE Membership Services Committee. He can be contacted by e-mail: glawrence@ipaglobal.com; telephone +31-70-315-1080.

Independent Project Analysis (IPA), Koningin Julianaplein 30, 4B Babylon, 2595 AA The Hague, The Netherlands.

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Capital Costs for Biopharmaceutical Process Retrofit Projects

by Stephen R. Higham

This article presents cost data and analysis from several recent large process retrofit projects inside an active manufacturing plant. It also provides cost data for several types of process equipment and digital fieldbus DCS systems. It compares retrofit costs with greenfield construction costs.

Introduction

Genzyme's Allston, Massachusetts, biopharmaceutical production facility is a 132,600 square foot (12,300 sq meter) building completed in 1994. It is a three story building with interstitial mezzanines - *Figure 1*.

It was originally outfitted with media, buffer, cell culture, and purification capabilities for one process, as well as lyophilization and fill-finish functions. The building was constructed with two separate cell culture suites. The main (larger) suite was outfitted, started-up, and validated in 1994. The second suite (the smaller of the two) was partially outfitted, but not completed at that time. Each suite was designed with dedicated gowning rooms/airlocks, inoculum prep labs, and air handlers.

Starting in 2000, Genzyme embarked on a series of projects that completed the second cell culture suite, additional purification rooms, and ancillary media, buffer, and utilities capacity. These projects have added 50% to the plant's throughput, and added multi-product capability. These projects were retrofits of existing space within the building, implemented while all other manufacturing processes were ongoing.

Figure 1. Genzyme's Allston, Massachusetts facility.

Most construction cost articles do not adequately cover this type of project. Most articles tend to focus on greenfield construction. However, in pure retrofit projects, the "bricks and mortar" are partially or totally in place, thus, greenfield estimation methods do not apply. The goal of this article is to:

- provide actual cost data for various construction costs divisions for both cell culture and purification retrofits.
- provide cost data on process equipment.
- show costs for digital bus based process instrumentation and wiring.
- compare retrofit costs with greenfield cost estimates from the literature.

Project Descriptions

For the purpose of this article, the projects can be broken into two sub-projects or phases. First, there was the build-out of the second cell culture suite. This covered about 3100 square feet (290 sq meters) and involved demolishing and rebuilding two mezzanine levels. New structural steel for the mezzanines was installed to accommodate the new "through the floor" tank geometries - *Figure 2*.

The old tanks were removed, two new production bioreactors and one new seed bioreactor were installed, and all were designed and purchased skidded. A process microfiltration system also was designed and purchased, as well as six cell-culture process tanks ranging in size from 2500 liters to 8000 liters (660 to 2100 gallons). There was extensive field installed process and clean utility piping, both within the suite and as interconnections to existing processes and utilities. A new city water feed

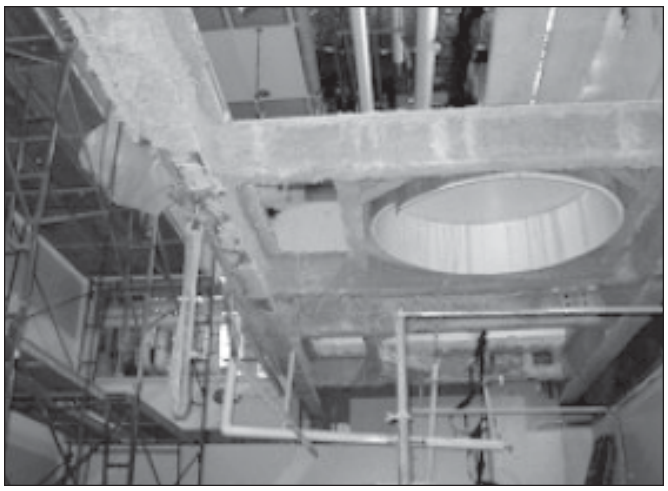

Figure 2. New structural steel for mezzanine, cell culture suite.

Figure 3. Field piping and tanks in purification buffer hold, during construction.

and skid-mounted deionized and reverse-osmosis water systems were provided as an addition to the building's centralized utilities, as well as a separate new Clean-In-Place (CIP) skid and CIP distribution piping. Finally, a 900 square foot (84 sq meters) renovation to the cell culture equipment prep area was undertaken. The approach taken here was to add a new glassware washer dedicated to the new process. On the clean side of the washers, the room was split into two with separate outflow paths for personnel and clean components for each process.

The other project phase was a build-out of three purification coldrooms, totaling about 2900 square feet (270 sq meters). It also included creating three small formulation rooms, as well as an equipment prep room renovation similar to that described in the cell culture section above. This project phase also involved designing, purchasing, and installing purification process equipment. This encompassed the use of the coldrooms described above, as well as several new buffer preparation rooms. The total area affected in this project phase was 6800 square feet (630 sq meters). The process equipment in the scope of this phase included a large depth filtration skid, two ultrafiltration/diafiltration systems, and five chromatography skids. In addition, 20 purification buffer and eluate pooling tanks in the range of sizes between 500 liters and 3800 liters (130 and 1000 gallons) were purchased, as well as a number of smaller portable tanks. All purification process equipment was designed for use in hazardous atmospheres, utilizing US National Electrical Code Class I, Division 2 compliant construction. Clean utility systems included a vapor compression WFI still, a Clean System Generator (CSG), a new CIP skid, and CIP supply and return piping. The still and CSG were needed to increase generation capacity for the new processes, and were tied into existing storage and distribution systems. Finally, a 1000 ton (3.5 MW) process chilled water centrifugal chiller was purchased and installed to complement the building's existing 2000 tons (7 MW) of absorption chillers. For all of the projects considered in this article, the total affected floor space was 12,700 square feet (1182 sq meters).

In these projects, space was constrained by existing building conditions. This often necessitated the use of tanks with unusually high or low L/D ratios, as well as increased complexity and density of field-erected piping. In many cases, field piping approached the complexity and density of typical skid piping - *Figure 3*.

In addition, skid geometry had to be carefully thought through with skids in several cases being designed in multiple sections. Rigging of tanks and skids had to occur in many cases through a second floor window - *Figure 4*.

Since the plant was in operation in adjacent spaces around the clock, there were profound schedule implications for the construction projects. Often, only small windows of time were available to take down and tie into existing utility and process systems. The same constraints were in place for

Figure 4. Tank rigging through second floor window.

Construction Division		Division Description
2	Sitework	Core drilling, demolition, temporary walls and doors, cleaning
3	Concrete	Floors, equipment pads
4	Masonry	
5	Metals	Structural steel, permanent fall protection and retrieval equipment, decking, pipe racks, permanent metal platforms and mezzanines
7	Thermal and moisture protection	Roof work, fireproofing, fire-stopping
8	Doors and windows	
9	Finishes	Drywalls, painting, epoxy floors, architectural detailing, suspended and drywall ceilings
10	Specialties	Special architectural items
11	Equipment	Rigging, storage, shipping
11a	Process equipment	All bioprocessing tankage and skids, not including field erected piping. All utility and clean utility equipment.
13a	Coldrooms	
13b	Process instruments	All field installed sensors and automated valves
13c	Process controls	Controls hardware except that provided on skids and for HVAC and building systems. All controls software, software licenses, and software development except that for HVAC and building systems.
14	Conveying systems	Materials handling, forklifts, elevator repairs, dumbwaiters
15	Mechanical	Fire protection systems, chillers, HVAC systems, HVAC controls, plumbing, duct insulation, utility and waste piping, safety and waste systems
16	Electrical	Labor, supplies, motor controls, variable frequency drives, substations, controls and power wiring
17	Process mechanical	Process piping, manual valves, non-destructive examination, insulation, passivation, turnover documentation.
18	Special conditions	Includes permitting

Table A. Construction divisions.

access into rooms in order to do installation work. In some cases, temporary partitions were created to separate a given room into clean and construction zones. Both piping and electrical installation are more costly than in new construction since work must be done behind existing walls and through cramped interstitial spaces. These types of schedule and construction constraints are easy to underestimate, and must be built into any upfront cost estimates for retrofit projects within active manufacturing plants.

For all project phases, most process engineering was done in-house, including most P&ID development and equipment specification and design. Instrumentation and Control (I&C) equipment specification also was done by Genzyme engineering personnel. An outside engineering company supplied piping design, structural engineering, electrical engineering, and some P&ID development.

Project Costs

To analyze the project costs, invoices were categorized using a modified version of Construction Specifications Institute (CSI) divisions.

For the overall project's costs analysis, cost corrections were made to third quarter, 2005 by using the Chemical Engineering Plant Cost Index. This data is presented in Table B. Note that this table presents divisional costs as both a percentage of the total direct cost for each project, as well as a cost per unit area. The cost per unit area for coldrooms uses the coldroom area, not the total project area.

Equipment Costs

There were two types of process equipment that were purchased in sufficient quantities so that cost-versus-size curves could be developed. These are chromatography columns and large process tanks. That data is presented in Figures 5 and 6. The chromatography columns are 316L stainless steel construction and are ASME pressure vessels. The tanks have 316L stainless steel wetted surfaces, 304L stainless steel insulation covers, and are ASME pressure vessels. They have internal surface finish of 20 micro-inch Ra, maximum (0.5 micron) and are electropolished. The tank cost also includes magnetic-drive bottom agitators. The cost curves are for equipment only (uninstalled). For both types of equipment, costs were corrected to third quarter, 2005. Since this equipment is fabricated entirely of stainless steel, a "blended cost index" was used to account for the materials escalation. The blended index consisted in equal parts of the Marshall and Swift Equipment Cost Index and the CRU Steel Price Index for stainless steel.

An estimate was developed for the costs associated with typical installations of fixed process tanks. Above and beyond

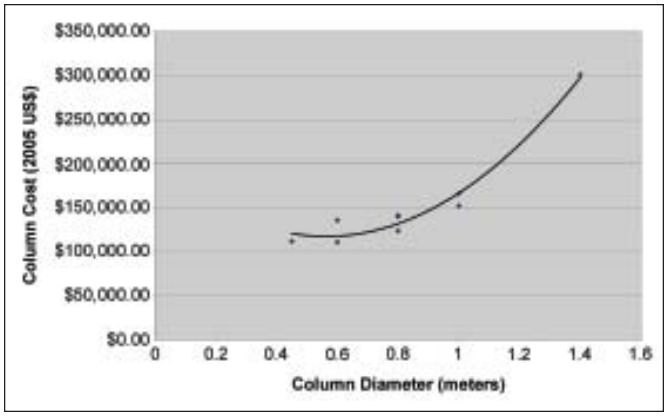

Figure 5. Chromatography column cost versus diameter.

the costs for the tank and agitator themselves, we have estimated that the installed cost of all instruments, valves, utility, and process piping surrounding a typical buffer or eluate tank is $160,000. For the range of tank sizes in question, this equates to a total installed cost of $2.4 to $3.2 for each dollar of tank cost. This does not include runs of pipe interconnecting a tank with the rest of the process. For transfer panels around 1-1/2" tubing OD size, costs are about $700 per nozzle and $200 per proximity switch.

Control System Description and Costs

Controls architecture and integration was delivered by a combination of an outside systems vendor/integrator and Genzyme I&C and automation engineering personnel. Genzyme used a new Distributed Control System (DCS) for these projects since the legacy DCS for the rest of manufacturing was no longer fully supported, and nearing its I/O capacity limit. We also decided to standardize on digital bus technology for DCS communications with instruments and actuated valves. Foundation Fieldbus was used for most continuous-signal devices, and AS-i bus for most discrete-signal devices. Profibus DP and DeviceNet were used for certain proprietary devices or those that were not supported by the other bus technologies. For the cell culture build-out project, the DCS input/output (I/O) count was approximately 380 field I/O points, and 270 on-skid I/O points. The DCS I/O count for the purification project included 900 field installed I/O points and 330 skid I/O points.

Networks using bus technologies should be more expensive to implement on a small scale due to increased hardware and cabling costs, but there should be cost savings at a certain larger scale due to the simpler wiring topology. In addition, Foundation Fieldbus presents other cost savings in electrically hazardous atmospheres due to certain intrinsic safety aspects inherent in the design. The issue of utilizing several bus technologies, due to instrument support issues, and the complications this caused with respect to explosion-proof construction, meant some initial cost uncertainties with process skids. Since identical projects were not run using both two-wire and bus technologies, a direct cost comparison cannot be made here. However, it is known that about 65% of all electrical time on the projects were spent on controls related work. This allows calculations that show that the controls wiring and hardware installation cost in these projects was between $1400 to $2000 per field installed I/O point. This seems surprisingly high. Lesnik[1] had DCS costs in 1996 at $200 to $300 per I/O point. The higher cost range for the Genzyme projects can be explained by the fact that an entire new DCS infrastructure was installed. The incremental costs of wiring another I/O point into an existing system would certainly be less than the cost range determined here.

	Cell Culture andAssociated Projects			Purification and Associated Projects		
DIRECT COSTS		**% of Total Direct Costs**	**Cost/Area ($/sq ft)**		**% of Total Direct Costs**	**Cost/Area ($/sq ft)**
Sitework	$262,043	2.4	84.5	$481,480	1.8	70.8
Concrete	$43,420	0.4	14.0	$102,549	0.4	15.1
Masonry	$5,333	0.0	1.7	$23,416	0.1	3.4
Metals	$156,159	1.4	50.4	$1,393,740	5.1	204.9
Thermal and Moisture Protection	0	0	0	$64,395	0.2	9.5
Doors and Windows	$44,615	0.4	14.4	$86,942	0.3	12.7
Finishes	$319,499	3.0	103.0	$575,035	2.1	84.6
Specialties	0	0	0	$7,610	< 0.1	1.1
Equipment	$10,881	0.1	3.5	$447,224	1.6	65.7
Process Equipment	$2,608,512	24.1	841.4	$5,385,531	19.8	791.8
Coldrooms	0	0	0	$1,179,612	4.3	406.8
Process Instruments	$549,112	5.1	177.1	$1,744,982	6.4	256.6
Process Controls Hardware, software, software development, licenses	$1,979,475	18.3	638.5	$3,777,121	13.9	555.4
Conveying Systems	$5,441	0.1	1.8	$39,790	0.1	5.8
Mechanical	$262,352	2.4	84.6	$2,513,692	9.2	370.1
Electrical	$802,859	7.4	259.0	$2,742,462	10.1	403.7
Process Mechanical	$3,753,836	34.7	1211	$6,620,152	24.3	974.8
Special conditions	$19,192	0.2	6.2	$69,579	0.3	10.2
TOTAL DIRECT COSTS	$10,811,847	100.0	3488	$27,266,192	100.0	4010
INDIRECT COSTS						
Engineering	$896,631	8.2		$5,727,590	19.3	
Construction Management	$826,503	7.6		$954,339	3.5	
TOTAL INDIRECT COSTS	$1,723,134			$6,681,929		
TOTAL COSTS	$12,534,981		4043	$33,948,121		4992

Table B. Total project construction costs.

Total overall controls software and hardware implementation costs were difficult to estimate in advance throughout the project. Depending on the phase of the project, Genzyme's integrator had some or all of the following deliverables:

- systems engineering and configuration
- field technical service for controllers and bus
- on-site operator training including hardware mockup
- off-site component validation
- service contract
- Functional Requirement Specification (FRS) development
- design and construction of system enclosures, field termination boxes and I/O cabinets
- software licenses and scaleups
- controller hardware
- controller I/O hardware
- workstations
- O&M manuals
- project management and administration
- process skids FAT support
- engineering of interfaces between legacy DCS and new DCS
- systems startup support

Total controls hardware and software costs (minus process instruments) were in the range of 70 to 76% of process equipment costs. However, note that process skids were specified and constructed with all required instrumentation installed and wired. The skids did not have on-board controllers, and were instead tied into the plant's DCS system upon installation in the facility. Thus, on the costs breakdown, the instrumentation and electrical costs for the skids themselves are absorbed into the process equipment line item. Thus, while it is valid to compare controls hardware and software costs against total process equipment costs, it is a better comparison to compare instrumentation costs against only fixed tankage costs. When that is done, instrumentation costs come in as 80% to 140% of fixed tankage costs.

Future project managers would be well advised to address the costs of all these items early on in the project. However, even if the initial controls integrator project scope is well-defined, client project scope changes in both process design and project implementation can have radical cost implications for controls.

Other Cost Data and Literature Comparison

There are other interesting facts that can be gleaned from the cost data. Metals cost for the purification build-out was several times that for the cell culture build-out. This is due to the extensive structural steel needed to install the large chiller in a penthouse.

Process equipment costs were approximately $800 per square foot ($8600 per sq meter). This high number is to be expected due to the high density of the installations. By way of comparison, Pavlotsky[2] estimated this parameter at $255/sq.ft. This high density of process equipment is perhaps a hallmark of most retrofit projects.

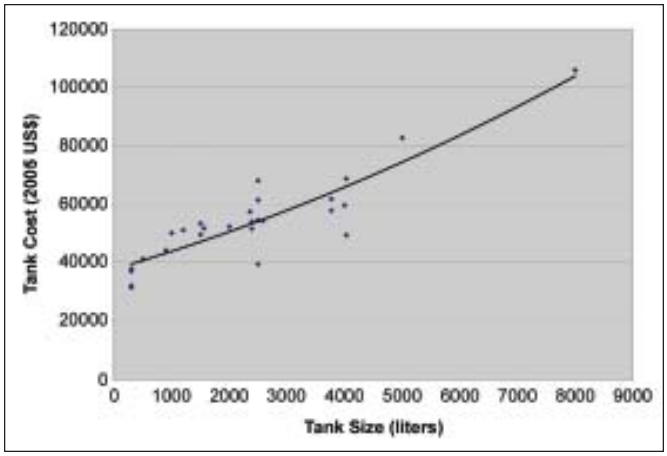

Figure 6. Stainless steel sanitary process tanks cost versus capacity.

For both projects, total process mechanical costs came in at about 150% of the cost of overall process equipment and at about 540% of the cost of fixed tankage.

The cost of mechanical work for the purification project was several times higher than that for the cell culture project. The purification area had several air handlers spread over a greater area, as well as the installation costs for the process chiller. The cell culture job, on the other hand, had no new air handlers, and ductwork changes were concentrated in a smaller area. Electrical costs for purification also were higher than those for cell culture. Again, this is probably due to the longer distances involved in purification, especially since all controls and power wiring had to be run in conduit.

The Construction Management (CM) fees declined substantially between purification and cell culture since Genzyme began to self-perform more CM tasks as time went on.

Only limited information is available to compare the costs of renovations described in this article with the original building costs. The total direct construction cost of the Allston facility, converted to 2005 US dollars, was $1252/square foot. This is in contrast to the equivalent number for the new projects (including both process and utilities areas), which is $3660/square foot. The comparison is limited since the old number includes not only process and utility space, but also offices, hallways, labs, conference rooms, and the empty spaces which later were retrofitted.

Table C shows more comparisons between other cost estimate work done for greenfield biopharmaceutical facilities and the Genzyme retrofit projects. The increased factored costs for some construction divisions can be explained

Cost Item	Cost Range as Multiple of Process Equipment		
	Petrides[3] (greenfield)	Pavlotsky[2] (greenfield)	Higham (retrofit)
Process piping (assume includes utility piping)	0.3 – 0.6	0.34	1.23 – 1.44
Instruments and control system	0.2 – 0.6	0.17 – 0.23	0.96 – 1.03
Electrical	0.1 – 0.2	0.14	0.31 – 0.51

Table C. Selected cost comparisons.

by the increased equipment density, smaller footprint, and the construction and scheduling constraints needed when working inside an active plant.

Conclusion

To summarize, certain factors contribute to driving up construction costs in retrofits projects. These include manufacturing schedule constraints, rigging complications, the necessity to isolate areas with temporary partitions, and to work in tight spaces behind and above finished spaces. Also contributing to costs are limits on available process space, necessitating dense skids and process installations. Finally, work is spread around the building, connecting "islands" of renovation within the building.

However, these are offset by the advantages of retrofitting inside an existing manufacturing facility. These advantages include potential reduced regulatory hurdles, lower permitting costs, and lower "bricks and mortar" costs. In addition, some or all clean utilities are in place, trained personnel are available for start-up, validation, and operation, and existing utilities infrastructure (chilled water, electrical, waste systems) can continue to be used.

Actual capital cost data from retrofit projects within an active biopharmaceutical plant show dramatic differences in several respects from greenfield estimates. Capital managers must be aware of these differences. It is hoped that the data and analysis presented here can be used as a guide for cost estimation for similar projects in the future.

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About the Author

Stephen R. Higham is a Principal Project Engineer in the Engineering Services Group at Genzyme Corporation. He has a BS in chemical engineering from the University of New Hampshire and has done graduate work in biochemical engineering. He is a Professional Engineer in the state of Massachusetts. Higham has 21 years of experience in the diagnostics, biologics, and biotechnology industries. He has held positions in project and process engineering and facilities management. He has been at Genzyme for eight years in a project engineering and capital projects management role.

Genzyme Corp., 500 Soldiers Field Rd., Allston, MA 02134.

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Efficient Qualification: A Holistic Approach to Effective Project Execution

by Anna Kälvemark and Gordon Leichter

This article addresses an innovative development in project delivery that utilizes a risk-based integrated qualification approach based upon the effectiveness of off-site construction.

Introduction

In somewhat questionable grammar, project management experts agree, "…if you do what you've always done, you'll get what you've always got…"[1] This analogy is undoubtedly a fitting mantra for the pursuit of excellence exhibited within the pharmaceutical industry. Without question, there have been demonstrated advancements within the pharmaceutical industry in the project management execution for new facilities and renovations through creative innovations and process re-engineering over the past few years.[2]

Recognizably, the project delivery of a pharmaceutical manufacturing facility involves additional complexity compared to other construction projects.[3] One of these complexities is the validation efforts needed to comply with the regulations of the US Food and Drug Administration (FDA) and other regulatory bodies. A well known consultant acknowledges that validation efforts are not only a significant differentiator in project delivery complexity in our industry, but ranks that effort as the critical path to successful project delivery.[4] Comparatively, "Validation is the most crucial step in realizing the completion of a pharmaceutical construction or update project. Simply, without adequate validation, multi-million dollar pharmaceutical facilities become nothing more than over-priced real estate."[5] Furthermore, according to the same consultant, the average project is set back five months for finalization of Operational Qualification (OQ) which brings additional attention to refining the validation effort.[6]

There have been notable advancements in improving the validation effort in project delivery management, which have spanned from re-engineering of the design process,[7] to a risk-based project management focus,[8] to integrating validation,[9,10] to better turnover package planning.[11] In addition to these achievements in the management process, there have been considerable gains in technology that have aided the project delivery process and validation effort. Innovations in constructability have dramatically improved the project delivery process. Specifically, the utilization of off-site construction has produced major advancements in project delivery.

This article addresses an innovative development in project delivery that utilizes a risk-based integrated qualification approach based upon the effectiveness of off-site construction. This new approach was developed to provide a new level of efficiency in qualification of a pharmaceutical manufacturing project. Where validation is still recognized as the most volatile use of resources in project delivery,[5] the process described in this article is an approach that increases project efficiency.

This efficient qualification approach is described in three sections within this article. First, there is a discussion of the underlying philosophy behind the drivers and goals of the concept as well as leveraging of a risk-based assessment. Second, the workflow is described and the critical integration aspects are identified. Finally, examples of off-site testing criteria are described.

One aspect that differentiates this initiative from other efforts is that the efficiency is tied to off-site construction. The concept of off-site construction has been embodied in the widely and sometimes overused term modularization.[12] While this article discusses some of the advantages off-site construction contributes to Com-

Project Start	Activities by Project Team	Activities by Project QA/ Qualification Team
	Basic Design	Impact Assessment Enhanced Basic Design Review Development of QMP/CMP[B]
	Detailed Design Population of Database	Enhanced Detailed Design Review Development of Test Protocols, Generation of Test Record
	Production in Factory	Execution of Commissioning
	Shipping	QA Review of documentation generated during execution in factory
	Assembly at Site	Completing Commissioning and Qualification
Hand Over	**Hand Over**	

Table A. Integration of commissioning and qualification activities with the project design and execution.[14]

missioning and Qualification (C&Q) efficiency, the main focus is on innovations that bring a new level of effectiveness to 'modularization'. Specifically, the advancements discussed in this article are directly associated with the modularization of the entire facility, which results in the complete project delivery of a new pharmaceutical manufacturing facility inclusive of the C&Q. The concept involves the design and fabrication of large steel modules that are built in a factory, assembled for pre-testing, and then shipped and re-assembled at the end users' location - *Figure 1*. However, the disciplines and technologies discussed in this article could be applied in part on a conventionally built project with the proper attention to protocols and database design.

Efficient Qualification Philosophy

Vision

Most project managers dread the conclusion of a project because of the unpredictability and volatility of the C&Q effort. This has led companies to proactively integrate C&Q efforts earlier in the project. The objective is straightforward, but rarely quantified. Therefore, applying efficiency principals to the concept provides gains similar to those achieved through streamlining manufacturing by utilizing Total Quality Management (TQM) type philosophies. The efficient gains targeted by this efficient qualification program include:

- shorter schedule
- predictable results and time frame
- reduced costs
- tighter and increased accuracy of C&Q execution

Quantifiably, each gain complements each other. A shorter schedule is realized through integrating C&Q with engineering from day one, which results in reduced costs. Comparatively, the project processes and controls utilized to achieve a shorter schedule will result in predictable results and execution time frame. Ultimately, the accuracy and administrative control over the C&Q effort will increase. Holistically, these efficiencies are realized through a reduction of the commissioning and IQ/OQ costs by as much as 60%[13] and associated schedule reductions of up to six to eight months - *Figure 2*.

Strategic Approach

The first step to increasing the efficiency of the C&Q effort is by taking an integrated approach -*Figure 2*. Though there have been a number of articles written about this topic, there are still numerous accounts of the concept not being followed or embraced.

Integrating qualification requires that the end result is the focus from the beginning. Simply put, the project goal is to turn over a qualified facility within budget and schedule so that products can be manufactured and sold. Without starting from day one with that goal as the focus, achieving the desired end results can be compromised. Starting the risk assessment and proper planning of the qualification activities during the initial design phases (conceptual, basic) allows for protocols and test plans to be incorporated effectively and efficiently through subsequent steps of the project. Early identification, assessment, and differentiation of risk-based items allows for utilization of standardized protocols and designs to be integrated through a common database.

One key aspect is that it is critical at this initial stage to have the involvement of the end user's Quality Assurance (QA) team. While most design and fabrication activities are run in parallel to save time, having the QA team's 'buy-in' early in the project eliminates delays later in the project, -

Figure 1. Modular fabrication of an entire facility (A - Facility modules fabricated in a factory, B - An entire facility assembled and pre-tested in a factory, C - Facility modules rapidly assembled at site).

Table A. Traditionally QA has not been involved early in the project. However, the time spent by these individuals early on in a project will have a significant return on investment for the project.

Efficiency

The efficiency of the qualification effort is greatly enhanced by utilizing off-site construction, particularly from the synergies realized through quality manufacturing practices, as well as applying the philosophies of risk-based assessment in practice early in the project.

Reliability, repeatability, and consistency are inherent to the practice of manufacturing in lieu of on-site construction. Procedures and protocols that have been developed over a number of executed projects with different end users provide a significant foundation to guide projects. Direct experience from user groups along with lessons learned is perpetually incorporated to capture best practices and current regulatory requirements. The manufacturing approach further provides the basis for standardized documentation, while retaining a high level of flexibility to meet specific user requirements.

Primary Principles

The primary principles employed in the efficient qualification approach provide a clear initial process for C&Q, which reduces overall costs by improving and developing work processes and administration tools. These work processes are developed in accordance with governing guidelines, regulatory requirements, and specifically Volume 5 of the ISPE Baseline® Guide for Commissioning and Qualification.[15]

Developed C&Q tools include:

- improvement of terminology and execution consistency for C&Q
- development of a commissioning database
- wireless system for commissioning of indirect and no impact systems

Terminology can be a significant obstacle to comprehension in a project, which can further become an obstacle to consistency of execution. This can materialize as communication and handover inefficiencies. Not only is terminology different between owner organizations, as it varies between design and supplier organizations, terminology varies within organizations, also.

Combining semantics with the learning curve of handover and one of the major inefficiencies of the qualification becomes evident. Focusing on thoroughness and consistency of terminology is one part of increasing effectiveness. The other is continuity from one discipline to the other. Continuity is inherent to the factory approach achieved through sound standard operating procedures, SOPs, quality procedures, and experience that are realized in a manufacturing environment.

A commissioning database serves as the central nervous system enhancing the efficiency of the process. Information about components and systems automatically populates pro-

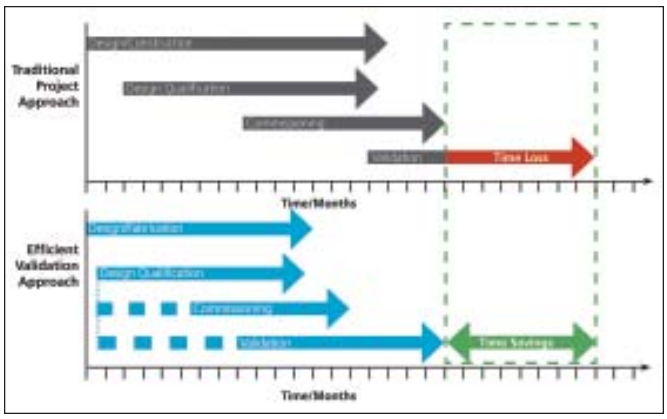

Figure 2. Integrated qualification time savings.

tocols for Receipt Verification (RV), and Installation Verification (IV), further reducing transcription errors and establishing a respective tracking record. Standardized specifications for packaged equipment[16] and engineered systems[17] are maintained and updated for guidance and use. Customized requirements are then easily inserted into the protocols without causing disruption to the format.

Standardized specifications allow for identification of critical qualification aspects from the initial design stage. This provides visibility, continuity, and consistency for all disciplines and sub-suppliers as to what documentation and testing will be needed, and at what stage of the qualification process it will be required - *Figure 3*.

Title	Subtitle/Description	Rev	
Technical specification Autoclave		01	

Criterion No.	Description	Criteria	Class
3.1.5	Chamber size (width x height x depth)	Chamber should be of X Y Z size	IQ
3.1.6	Gas detector	There shall be an automatic gas detection for measuring of non-condensable gases.	IQ
3.1.7	Condensate control	No condensate in the drain system is allowed, a drain bleed valve that prevents this shall be included.	IQ
3.1.8	Filter, process air	1. Redundant filters There shall be two redundant filters (0.2 µm) on the process airline. 2. Sterilizing in place It shall be possible to sterilize the filters in place. 3. Drainability The filter housing shall be fully drainable. 4. Integrity testing A valve shall be fitted between the filter and the sterilizer chamber to prevent steam penetration from the chamber into the filter.	IQ

Figure 3. Standardized requirement specification.

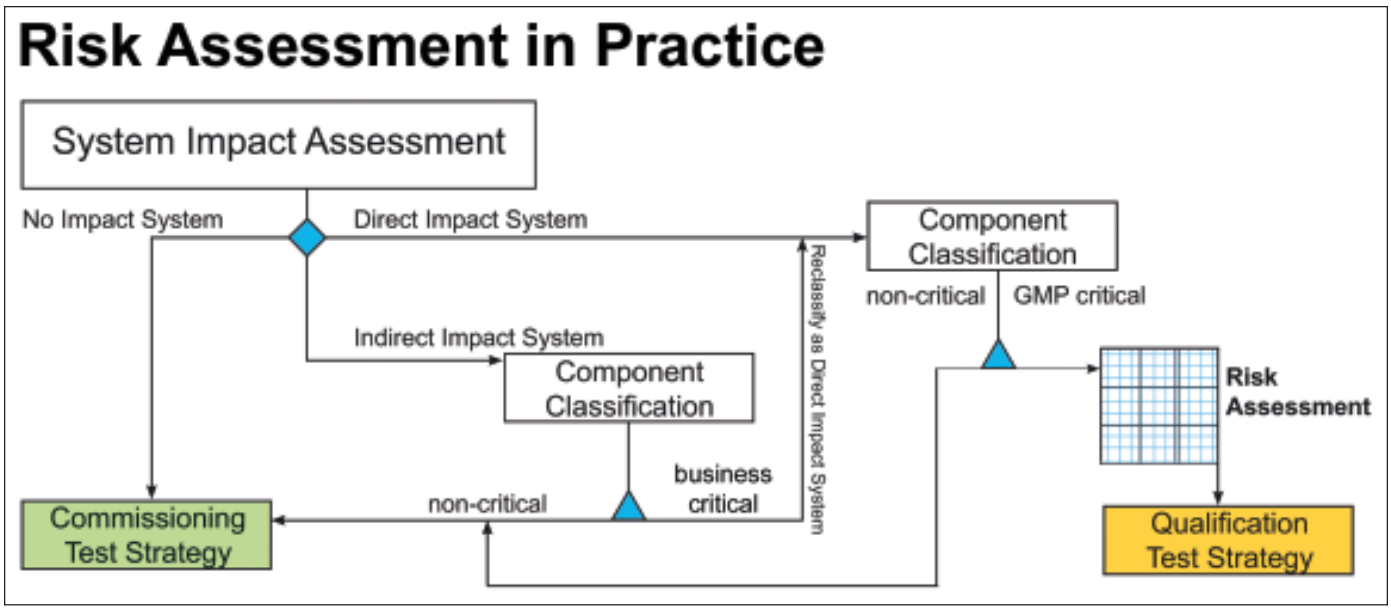

Figure 4. System impact assessment based upon ISPE Baseline Guide Vol. 5: Commissioning and Qualification and GAMP 4.[15]

Risk Assessment in Practice

The other key aspect involved with optimizing the efficiency of the qualification effort is to only do qualification on systems that require qualification, hence limiting the burdensome GMP documentation to direct impact systems. Thorough and effective risk assessment of each respective system, as identified in Volume 5 of the ISPE Baseline® Guide for Commissioning and Qualification[15] and Good Automated Manufacturing Practice (GAMP®) Guide, see Figure 4, provides the basis for leveraging the inspection and testing performed. Each respective system is evaluated for impact on the quality of the final product, which forms the basis for the approach discussed in the proceeding qualification workflow section.

Drilling down into impact assessment identifies component criticality and functionality. Critical components and non-critical components are defined and identified through the impact assessment. This risk assessment is conducted early in the design phases. SOPs, which comply with Failure Mode Effect Analysis (FMEA), ISPE's GAMP® guide, as well as other methods, including ICHQ9, define the risk assessment standards for early attention.

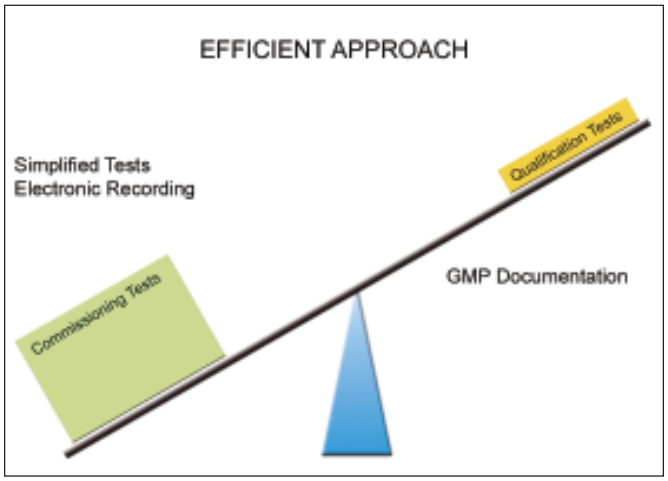

Figure 5. Efficient approach – less tests ▶ focus on quality and performance where it matters.

An efficient approach is achieved by not performing redundant and unnecessary testing. Testing criteria and records are generated to identify the specifics of what will be tested, to what extent, and if re-testing will be required after shipment where shipment can be from the vendor to the modular provider or from the modular provider to the final job site - *Figure 5*.

Figure 6 is a sample of a packaged equipment test plan for a Water For Injection (WFI) still. The objective is to utilize the Factory Acceptance Test (FAT) at the OEM's facility to the furthest extent possible for qualification purposes. The respective tests and inspections performed during the FAT that will not be impacted by shipment are not repeated after the equipment is installed, as identified in the system test plan and agreed to by the client. Further installation and operational tests are performed after the packaged equipment is installed in the modules, which is similar to tests that would be performed much later in the project at a final conventionally built facility location. Early installation and operational testing in the final location provides more time for updating as-built information, developing SOPs, transferring of data/information for equipment to the client's calibration and maintenance systems, as well as initiating user training. These respective tests are not repeated unless they are affected by shipment or if they do not fulfil the predetermined acceptance criteria, see "Pre-testing Efforts."

Efficient Qualification Workflow

Efficiency is achieved through a well developed and mapped out process. Figure 7 depicts the qualification workflow of an integrated project. It exemplifies the parallel paths followed through a project and the utilization of database sharing

between design and C&Q efforts.

The qualification workflow maps out critical project steps from left to right in a timeline format. Project design steps run along the top of the diagram, while client interaction milestones run along the bottom. The center portion depicts the C&Q project steps, along with additional steps for design and qualification activities for automation. Reduction of the classic qualification bottleneck - Transfer of information from engineering to qualification - is eliminated. Critical client interactions as well as critical internal interactions are identified and mapped out. Activities, e.g., A1 for design teams, B1 for automation, C1 for clients, etc., are assigned dates and incorporated into the overall project schedule where it becomes an integral responsibility of the project team with the proper level of visibility. Thoroughness is achieved by mapping out the decision process and identifying responsibilities of whom, what, and when decisions will be needed.

Major timeline steps are identified on the X-axis of the Qualification Workflow diagram regarding initiation of change control, shipment from the factory, and final handover after completion of OQ. The workflow diagram clearly identifies the difference between 'Start of Change Control' for engineering changes, and 'Start of cGMP[8] Change Control' for changes that will require qualification documentation. This provides an effective understanding of when changes will become more involved and helps to minimize the qualification documentation trail for further efficiency.

The next major timeline step is the shipment of the facility from the modular fabrication factory. The workflow depicts the amount of commissioning completed while respective systems are being manufactured. The focus is divided into three systems. First, indirect and no impact systems are commissioned to the furthest extent in the factory and finalized in the field after shipment and re-assembly. Second, engineered systems that are direct impact systems, e.g.,

X=Execute, A=Audit/Accept FAT, PR=Partial Repeat, R=Repeat, I=Inspection

System Test Plans

WFI Still		Commissioning		Qualification			
No:	Test Description	FAT	FACTORY	IQ	OQ (automation)	OQ	Notes
	Test of security and access	X			A		
	Mechanical Documentation • Equipment List • Operational and Maintenance Manuals • Drawings etc. • Piping • Component • Certificates • Pressure Vessel Rating • Passivation	X		A/PR			
	Hardware is installed and labelled according to drawings and specifications	X			A		
	Test of interlocks	X			A		
	Materials of construction (MOC)	X		PR			
	Leak Test	X		R			
	Slope Check & Documentation and dead leg verification	X	PR	A/PR			

Figure 6. Selected tests from a sample packaged equipment test plan.

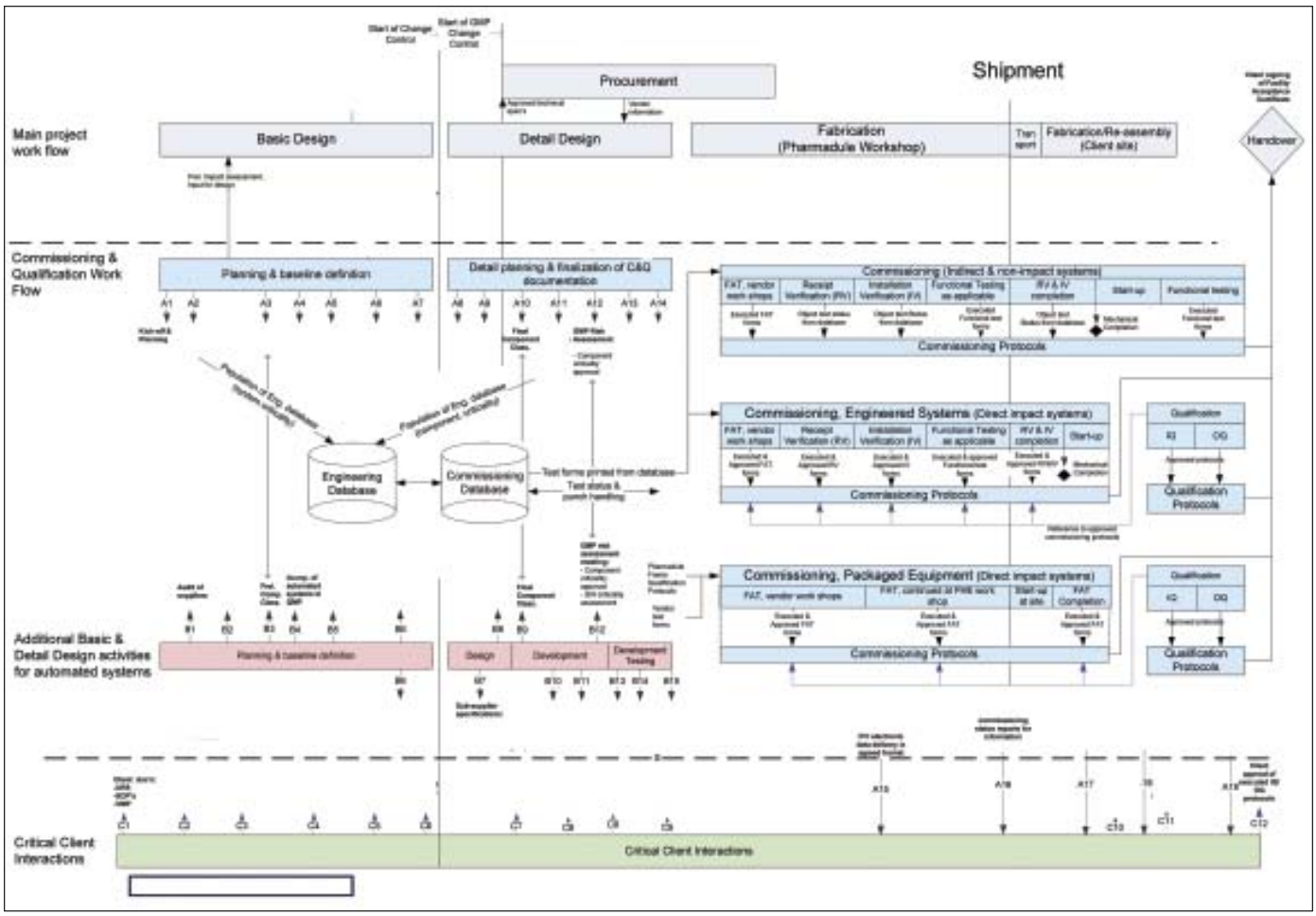

Figure 7. Efficient qualification workflow.

HVAC,[19] process distribution, automation, etc., also are commissioned to the furthest extent in the factory. As noted in the ISPE C&Q Guide and according to Good Engineering Practices (GEPs), all systems, including direct, indirect, and no impact must be commissioned. Additionally, the testing performed in the factory is leveraged toward qualification performed after reassembly of the facility. Finally, the packaged equipment is commissioned thoroughly during the FAT, at the OEM's locations, and further commissioned after being set inside the facility module. As with the direct impact engineered systems, the commissioning for the packaged equipment is leveraged toward the final qualification.

Commissioning Database

At the center of the qualification execution is the key relationship between the engineering database and the commissioning database. This information relationship allows for seamless and efficient transfer of key parameters from design documents into testing forms. Additionally, testing status, document tracking, deviations, and punch-list are effectively tracked and maintained within the commissioning database. The engineering database serves as the residence and historian for system and component criticality levels defined through risk assessment steps.

The commissioning database pulls design data from the engineering database, inclusive of information about component and equipment tags for a project. This automatic transfer of information provides full traceability of design changes and updates to tag information. Additionally, the status of checks and tests performed are tracked and maintained. Changes or additions are smoothly incorporated into the system providing a high level of assurance that nothing is missed or overlooked. A Web-based interface provides easy access to the database during OEM and site execution. Furthermore, it is necessary that the commissioning database is qualified for reliability and repeatability to be utilized for this application. Final tag information in the database can be transferred to the end user for maintenance records as part of a turnover package.

From a manufacturing perspective, commissioning of the facility starts as soon as material is received at the factory. Pre-populated documents are printed from the database for immediate at point of use execution. As materials (e.g., valves, instruments, pipe-work, etc.) are received at the factory RV is initiated through the commissioning database to assure specification adherence. After the respective materials are installed in their final location within the modules, IV is executed and recorded in the commissioning database. Hardcopy executed records are collected and completed and punch-list items are tracked in the database. The commis-

sioning work performed for each facility at the factory typically can support about 90% of the Installation Qualification. Effectively, this leaves only a fraction of the IV commissioning work to be performed on the connections between the modules after being set on site - *Figure 8*.

Another advancement enabled through the commissioning database technology is the utilization of wireless pocket Personal Computers (PC), devices - *Figure 9*. The wireless pocket PC enables further efficiencies through the reduction of paper, and the real time entry of data and progress monitoring, while eliminating possible errors and time expended through manual transfer of information. Recognizably, this innovation is only valid on indirect and no impact commissioning. However, it has proved to be a very effective use of technology.

Pre-Testing Efforts

The off-site testing leveraging is based upon the tests being performed utilizing pre-approved protocols or in accordance with pre-approved check record templates regulated by SOPs. All acceptance criteria of the specific test must be met, and the tests must be documented in accordance with good documentation practices. As an example, established off-site testing criteria can include the following:

- The test was performed in pre-approved protocols or in accordance with pre-approved check record templates regulated by SOP.
- All acceptance criteria of the specific test were met.
- Site utilities used for the test were of equivalent quality and output as at final site, such that there would be no impact to the result of the test.
- The item tested was not dismantled in a manner that may impact the test result.

Conclusion

Though feared by many project managers, the qualification effort can become an efficient and cost effective part of any project. Reduction of C&Q costs by as much as 60% and associated schedule reductions of up to six to eight months can be realized. This is a dimension that modular facility technology lends to the efficacy of the qualification effort through manufacturing efficiencies. However, the disciplines and technologies discussed in this article could be applied in part on a conventionally built project with the proper attention and database design.

The 'Efficient Qualification' approach can provide a shorter and secured schedule, predictable results and time frames, as well as reduced costs. Shortened and secured schedules are achieved by starting the commissioning and qualification activities during the manufacturing process in the factory and allowing for testing and FAT of the facility much earlier in the project. Predictable results and time frames result from the development of qualification protocols early in the project allowing significant time for client review and approval. Finally, costs are greatly reduced by gains through effective knowledge transfer and lower demands on resources.

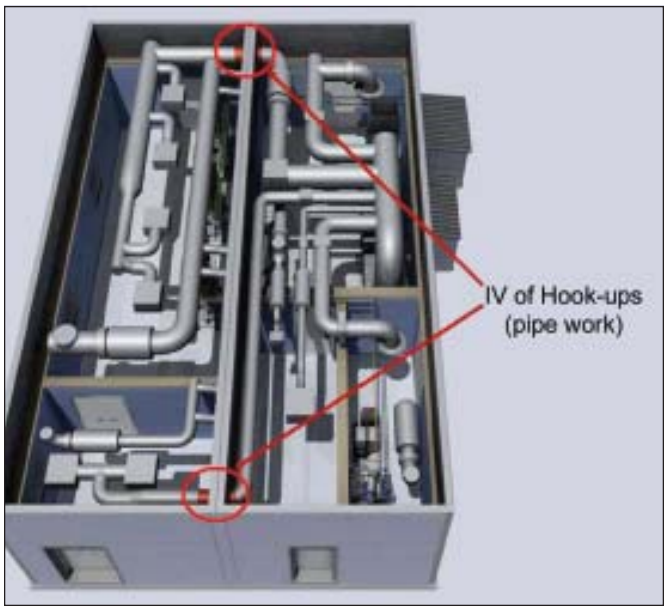

Figure 8. Only minimal Installation Verification (IV) is required after modules are assembled on site.

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About the Authors

Anna Kälvemark is the Vice President of Quality and Validation for Pharmadule-Emtunga in Sweden. She has worked in the validation and inspection field within the pharmaceutical industry for AstraZeneca and US Filter. Since joining Pharmadule, she has worked as project validation manager on a number of pharmaceutical construction projects before taking over the qualification and validation group where she developed the Efficient Qualification Approach. She has a Masters degree in industrial engineering management from Luleå University of Technology, Sweden.

Pharmadule Emtunga AB, Danvik Center 28, SE-131 30 Nacka, Sweden.

Gordon Leichter is the Director of Business Development for Pharmadule USA, Inc. focusing on the design and delivery of pharmaceutical manufacturing facilities. He has more than 20 years of experience working in the pharmaceutical industry with equipment suppliers. He has extensive experience with manufacturing, design, and engineering of sterilization and clean utility systems. Some of his previously held positions were director of operations for Getinge and product manager for AMSCO/Finn-Aqua (now Steris Corp). He holds a MS degree in management and is a candidate for a PhD in marketing. Leichter has been an active member of the ISPE throughout his career, serving on a number of Chapter boards and giving technical presentations. He can be contacted at e-mail: gordon.leichter@pharmadule.com

Pharmadule, Inc., 500 Hills Dr. Bedminster, NJ 07921.

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This interview was conducted by Gloria Hall, Editor, *Pharmaceutical Engineering*.

PHARMACEUTICAL ENGINEERING Interviews
Ron Branning, Vice President, Commercial Quality, Genentech

Ronald Branning is Genentech, Inc.'s Vice President, Commercial Quality. He is responsible for the quality organizations in South San Francisco, Oceanside, and Vacaville, California and Porriño, Spain. Branning has more than 35 years of experience as a quality professional in the biologics, biotechnology, device, pharmaceutical, and plasma products industries. He has held positions as quality assurance manager for Johnson & Johnson, QA director for G.D. Searle (Pfizer), Boehringer Ingelheim and Ares-Serono, quality systems director for Genetics Institute (Wyeth Biotech), VP QA/Regulatory Affairs for Somatogen (Baxter) and vice president of quality assurance for Aventis Behring (Behring ZLB). Branning received a BBA in Industrial Management from The University of Texas, Commerce, in 1973 and was enrolled in the MBA Program at the University of Dallas in 1974-1975. He has presented numerous papers and seminars on a wide range of compliance management, computer systems, production, quality, and validation issues. He is currently a member of ISPE's International Leadership Forum (ILF).

Q What type of training and preparation best prepared you for your current career in global quality at Genentech?

A First and foremost, it was my life long interest in science. While studying science and industrial management at the University of Texas at Commerce, I joined Johnson & Johnson's Surgical Specialties Division as a Quality Control technician. My J&J experience gave me a very good foundation in Quality management and production operations. The Operations Management courses at the University of Dallas MBA program helped me understand the necessary balance between the science-based Quality assessment process and business priorities and turnaround time requirements. I've used these fundamentals throughout my career.

Q What led you into the biotech industry?

A It's been a tortuous path that I didn't realize would lead to biotech; since J&J I've taken opportunities to either get companies out of trouble with FDA, or, as in Genentech's case, to build quality systems that ensure a continuing good compliance position. Johnson & Johnson manufactured devices and sterile products, G.D. Searle and Boehringer Ingelheim were traditional ethical pharmaceutical manufacturing companies with a broad range of dosage forms; Ares Serono, Genetics Institute and Somatogen were part of the fledgling biotechnology revolution; Aventis Behring (Centeon) was one of the FDA's blood plasma product casualties.

Interestingly, in 1987 when I was director of QA at Boehringer Ingelheim we developed a strategic plan "QC 2000" to predict the future of QC in the pharmaceutical industry. At that time we projected that biotechnology would be replacing traditional pharmaceuticals and that by 2000 Genentech would lead that effort based on initial successes and the strong science base. And 20 years later here we are.

When I look at those old strategic planning notebooks, it's amazing to see what we predicted and how accurate our predictions were just from the information that we pulled together at Boehringer. It was a very good exercise. I didn't realize at the time that I was charting my own course.

Q What experiences best prepared you for your current position?

A It's an accumulation of all my experiences. It started with a good foundation at Johnson & Johnson. When I worked for them in the 60s and 70s it was recognized by Fortune Magazine as being one of the best managed companies; looking back on it, that was very true. I had many Quality and management mentors at J&J who helped shape my view of Quality. The fundamental lesson from my experience at Johnson & Johnson was to look at everything you do as systems and processes and continuously improve them. And once again, it's balancing science and business, learning how different processes fit together into systems, and how those systems work most efficiently.

My career has been built on the J&J foundation; the successive positions helped build my experience base through increasing scope and responsibilities in QA and QC, more varied interaction with FDA and learning new technologies. The greatest challenge and best professional experience was joining Aventis Behring six months after it entered into a consent decree with FDA and spending the next four years successfully working through the issues with a great team of people in the Kanakee Illinois plant. Rebuilding the facility operations and production and quality control systems was challenging and required the use of all my quality management tools.

Q Overall, what significant changes have you seen in the industry in the last five years?

A A significant change is the move from stand-alone pharmaceutical companies to large mega companies and their cycle of merger, acquisition, and consolidation. Fortunately, for pharmaceutical professionals there's a resurgence in biotech, which almost died back in the early 90s because of the lack of productivity. I think there is also a change in traditional pharmaceutical companies turning to biotech to fill their product pipelines while biotech is developing a healthy interest in small molecules. There are many therapies out there waiting to be discovered, and they lie in all areas, and we simply need to apply our science and intelligence to bring to fruition.

Q What are some of the quality issues with your collaborators? How do you enforce and maintain quality when working with partners?

A At Genentech, we match our quality systems and standards up with those of our collaborators and ensure that they operate together. We have (using NASA terminology) "a docking collar" between companies so that systems have a way of interfacing and we understand each other. I've worked for eight different companies in my career and every one of them have different terms or use their own acronyms to describe the same thing so it's necessary to put a mechanism in place for companies to communicate with each other effectively.

Q What are your views on managing quality, and what methods do you find successful?

A The tagline in Commercial Quality is, "Comprehensive Quality Management and Assessment Systems," and I think that pretty well sums it up. We look at everything we do as interlocking systems. Quality Management means making sure that management at all levels including our executive committee and board of directors, is aware of Genentech's quality and compliance status. Assessment means that we address anything that impinges on product quality and we make certain that it's included in the final disposition decision. The net result is a compliant monitoring and control system.

Q In your opinion, how can engineering and manufacturing improve their relationships with the quality organization at Genentech?

A I think we've established a superb working relationship between the three organizations at Genentech. We've learned that all of us need to wear our respective hats and understand our respective roles and responsibilities, but also to be able to view things from the other person's perspective.

Q Do you have any advice or recommendations for people who would like to work in the QA area?

A People who want to work in biopharmaceutical QA need to have a good understanding of the science behind the applicable GMPs. They need to be able to view the GMP regulations as principals of production and Quality that require knowledge of the process and appropriate monitoring and control to assure consistent compliant product. From my perspective, there is no conflict between what the regulations say you should do and good business practices; the benefit in my experience is that compliant companies are also profitable.

Another piece of advice is to continue to learn, grow personally and professionally and build good working relationships with your colleagues. This will give you a good personal base and a network to call on when you need help.

About Genentech

Genentech, Inc. was founded in 1976 by venture capitalist Robert A. Swanson and biochemist Herbert W. Boyer, PhD. In the early 1970s, Boyer and geneticist Stanley Cohen pioneered a new scientific field called recombinant DNA technology.

Genentech was the first company to bring a biotechnology drug to market and the first to become profitable.

Genentech is headquartered in South San Francisco, California, which is the only location where research and development occurs for the company, and has locations in Vacaville and Oceanside, California, and Porriño Spain.

Q Does Genentech have global quality standards?

A Yes we do; they are embodied in our quality policies and quality systems.

Q How do you enforce and maintain those quality standards when dealing with your partners?

A It goes back to the discussion we had about the docking collar approach. We have our systems, we assess their systems, and we find a way to fit them together.

Q The FDA believes that developers and manufacturers need to increase efficiencies and recently issued the guideline on Process Analytical Technologies (PAT) which aligns with their Initiative for the 21st Century. What is Genentech doing to increase manufacturing performance?

A PAT may seem like the latest buzzword, but there's nothing new in what the FDA has proposed. The fundamental standards of validation within the GMPs are what PAT rests on, and when FDA talks about design space, what they mean is looking at a robust picture of what the process is actually capable of, what its variabilities are, and what impact that has on product quality. Design space in statistical terms means a response surface, a topographical picture, of how process variability affects product quality and yield. Genentech has an active approach to PAT which is being incorporated into our production operations.

Q How do you measure performance increases or efficiencies?

A Genentech uses a standard industry approach of monthly and quarterly key metrics reviews for safety, compliance, production, budget, leadership development and operational excellence and project management.

Q What type of management strategy works best in a biotechnology company? How do the quality and regulatory groups manage engineering and manufacturing quality? What is the organizational strategy at Genentech?

A Genentech takes a matrix management approach to operations. The various groups have traditionally defined roles and responsibilities and they also work together on projects and leadership teams.

Q How does Genentech work with the FDA enforcement policies with respect to their manufacturing establishments and products?

A Genentech has a superb working relationship with the FDA thanks to our Regulatory Affairs department. We believe in being open with the FDA, addressing anything we believe is of significance with them, and asking their advice and counsel; the best word I can use to describe it is transparency.

Q How do Genentech's future expansion plans affect the quality of the organization?

A Genentech's recent growth to include the purchase of the Oceanside, CA facility and building a major addition to our Vacaville, CA site have been incorporated into Commercial Quality's strategic and tactical plans. While these new facilities have increased the size of the organization and the complexity of our operations, we have established a Quality Operations group that will extend our quality systems, policies, standards and governance across the four manufacturing facilities in Oceanside, Vacaville, South San Francisco, and Porriño, Spain.

Q How can industry, government, academia, and other professionals such as those in ISPE work best to interact and develop new methods, sensors, processes, and controls that will benefit pharmaceutical or biotech consumers?

A The important role ISPE has played from its inception is being a forum for industry representatives, academia, and suppliers to address common issues and how they can work together on solutions. It has also evolved into being a catalyst for maintaining good relations between the industry and regulators. Most importantly, ISPE plays a leading role through guidance documents, training and seminars to help the industry understand how to comply with existing regulations and how to develop new technologies.

Q Do you find that ISPE's training has helped you in any significant way to succeed in your career and in this industry?

A I attended an ISPE Pharmaceutical Water seminar in 1983 and for the first time in my career I really understood pharmaceutical water; from how you assess water sources, system design to monitoring and control - it was a complete and thorough explanation about water systems, and something I could take back and use immediately. That's been my consistent experience with ISPE; courses and seminars have practical application.

Q What do you think ISPE needs to do to grow in the biotech industry? What can we do better?

A I think it's incumbent upon us to realize that there is a transition in industry where biotech is developing small molecules and traditional big pharma buying into biotech. ISPE needs to continue to reassess the needs of its customers – industry, the regulators, suppliers and academia – in this transition and be prepared to support them all. The ISPE strategic planning process should address how to bring traditional pharmaceutical and biotech professionals together to address common issues but also be flexible enough to meet the specialty needs of biotech. While process validation principles are the same its application to special technologies will be different.

Q Can you tell us about your involvement with ISPE's ILF?

A The International Leadership Forum is a great place for the heads of manufacturing, engineering, and quality to get together and to address common issues and identify topics on

the horizon. We're currently determining how ISPE can take a leadership role in risk assessment, qualification/validation, the drug shortage issue, and developing a model for the pharmaceutical manufacturing professional of the future. A major issue for us now is how to ensure that ISPE adds value, both to individuals and companies that support ISPE. We would like them to continue to attend conferences, continue the collaborations with the regulators, and volunteer for the various committees to keep the Society strong. I think the leading indicator of that is that ISPE has steadily grown over 25 years. I applaud Bob Best's statement that he wants to continually reinvent ISPE for the future.

Q Is there anything else you want to share with the readers of *Pharmaceutical Engineering*?

A The ISPE strategic plan, to be unveiled at the 2006 ISPE Annual Meeting in November in Orlando, should be a call to arms for all of us to look at the Society in preparation for its next 25 years, to incorporate what we believe it needs to deliver, and to be willing to participate in molding and shaping that future. We the industry, suppliers, regulators and academia need to be leaders within the Society developing the standards, guidelines, courses and seminars to help make the tran-sitioning biopharmaceutical industry remain strong, not only in the US, but worldwide. I think this would be a great platform from which to launch ISPE into the next 25 years.

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Facility of the Year

This case study provides a behind-the-scenes look at the making of Baxter BioPharma Solutions' Phase IV Vial and Syringe Filling Facility, winner of the 2006 Facility of the Year Award. It highlights the global innovation, ingenuity, teamwork, and challenges involved in the design and construction of an unconventional, cutting-edge facility in just 22 months.

An Innovative Mix of Science, Technology, and Architectural Engineering –

A Look at Baxter BioPharma Solutions Cutting-Edge Facility

by Rochelle Runas

A Time to Fill

As pharmaceutical companies have become increasingly focused on the R&D pipeline and its impact on sales and marketing, contract manufacturing has become a cost-effective alternative to large capital projects – especially if production volumes don't warrant the investment. With changing demands and market pressures on pharmaceutical companies to get products to market at the most cost-effective and expedient way possible, the contract manufacturing services market has exploded and continues to steadily skyrocket.

Baxter BioPharma Solutions (BPS), a unit of Baxter Healthcare Corporation, is a full service contract manufacturing organization that continues to stay steps ahead of the fast-changing manufacturing needs of the pharmaceutical and biopharmaceutical industries. Soon after opening its Bloomington, Indiana facility 15 years ago, BPS quickly evolved into a formidable one-stop shop for form, fill and finish services. Today, BPS provides manufacturing on both clinical and commercial scales, producing a variety of sterile product dosage forms. These products include solutions, suspensions, and freeze-dried powders encompassing human and veterinary small molecule, biologic, biotech, vaccine, and protein pharmaceuticals.

BPS is nestled in the middle of a $1.2 billion US parenteral dose contract manufacturing services market. This market, which includes vials, ampoules, syringes, bags, and bottles, is projected to grow 15-20% annually over the next 10 years. BPS' major competitors in this market are Abbott Laboratories, Cardinal Health, BenVenue Laboratories and DSM Pharmaceuticals.

The market preference for pre-filled syringes also continues to grow. For consumers, pre-filled syringes have advantages over traditional packaging in vials, including reduced microbial contamination risk due to less manipulation and exact dosing for greater patient safety and compliance. From a manufacturing perspective, pre-filled syringes im-

Exterior view of the completed facility.

Module ready for outfitting and process equipment and utility installation.

prove a client's bottom line as less overfill is required than with vials. Plus, a variety of customized features can be used to meet end users' needs, potentially resulting in product differentiation and market share expansion.

Recognizing this emerging market niche, BPS re-evaluated its position as a contract manufacturer and in 2003 embarked on a strategy to expand their Bloomington facility. It would be a challenging race against time to respond to an under-served market and against competitors to claim market share. But their construction plan would not be typical, nor would their facility's technology. And according to the Facility of the Year Judging Panel, that's what made it – intriguingly – so successful.

BPS Project by the Numbers

The total project was approximately 162,000 square feet (15,000 square meters) of which 37,500 square feet (3500 square meters) utilized the modular approach. The project was initiated with the basic design starting in March 2003. Performance Qualification (PQ) began in January 2004 and was completed in April. The overall detail design and construction schedule was 17 months. After completion of Operational Qualification (OQ), performance qualification and media fills were performed in an unprecedented duration of four months by BPS, resulting in the facility being satisfactorily inspected by the FDA in June 2005. The total project schedule from design to licensing was 22 months.

The final project cost was $116 million, which was 93 percent of the budgetary estimate prior to start of the basic design. The cost increase for the modular process scope of the project was controlled at +0.2% from start of the detailed design, demonstrating tight budget control and effective project execution. The completion date was within the original estimated schedule.

The Strategic Blueprint

Located about 50 miles south of Indianapolis, the Bloomington facility transformation would include a partial demolition, new construction, and renovation of an existing building. The project would be a mix of conventional construction for support areas, utilities, office space, a cafeteria, and a fitness center, combined with state-of-the-art modular construction of the manufacturing areas. Another off-site building would be renovated for expansion of packaging operations, and BPS would add large-scale cold storage capacity for temperature sensitive products.

The driver for the project was to provide the most leading edge, yet reliable technology that would provide the flexibility and speed needed to meet the demand for the emerging market niche. A business plan was devised that would recognize a significant Return On Investment (ROI) if the facility was able to be completed 12 months sooner than if conventionally built.

Equipped to Deliver Science

A design collaboration between BPS and INOVA produced an innovative new high-speed syringe-filling system, which can fill 500 syringes per minute, a considerable improvement over the 300 syringes per minute capacity of existing technologies. One of the key attributes of the machine that has increased throughput is the tub handling system, which now handles tubs in parallel instead of serially. The increased throughput of the filler has saved considerable capital costs on the project by alleviating the need for two machines and additional clean space and gowning room.

Another focus of the facility was to provide a new formulation and filling service for manufacturers of insoluble or unstable drugs. The new technology revolves around BPS's Nanoedge process, which increases solubility and reduces excipient side effects in formulation. Drug particles are reduced to 100 nanometers in diameter, and then coated with a thin layer of proprietary excipient, creating drug particles that dissolve more rapidly when injected or infused.

Nanoedge has allowed BPS to solve seemingly intractable formulation problems. This is based upon the dilemma of current formulation situations that would ordinarily take one part drug to 10,000 parts of water to dissolve. Instead of requiring a patient to endure a 10 L infusion, Nanoedge would allow for formulations in 10 ml doses. The flexible formulation space included as part of this facility enabled BPS to commercialize this technology.

In addition, the facility incorporates a large capacity of aseptic compounding for formulation of final products, which meets a market need for most newly developed vaccines and

products that cannot be sterile filtered.

With Nanoedge and a new high-speed syringe-filling system, BPS was ready to deliver. But they needed advanced infrastructure to compliment and facilitate their advanced science and equipment.

Facility modules built in a workshop environment.

A Turn-Key Decision

BPS chose Pharmadule AB as their design/build partner for the manufacturing portion of the facility. The Stockholm, Sweden company is a provider of modular facilities for the pharmaceutical and biopharmaceutical industry. BPS pursued modular technology because it provided the quickest ROI with minimal risk to cost and schedule and with a minimal demand on internal resources from BPS. Modular technology allowed for expedient design and construction of the facility under controlled conditions. Weather, labor, and material logistics that are unpredictable conditions on conventional construction sites were eliminated. Integrating conventional construction with modular technology enabled the construction of the manufacturing areas to happen concurrently with the conventionally constructed portions of the project, saving months to the overall project timeline had the entire facility been built conventionally.

The remaining three-fourths of the project included renovation of an existing warehouse and demolition of an existing building replaced by conventional construction of offices, laboratories, and support utilities. The conventional construction was managed by Turner Construction Co. of Indiana and designed by Raymond Professional Group of Chicago, Illinois.

The Modules of Facility Design

Modular technology and delivery used for design and construction involved the off-site fabrication of the entire manufacturing process facility, inclusive of structural steel, poured concrete floors, internal finishes, process and utility equipment, and systems. The modular facility was fabricated in a factory in Sweden, pre-assembled, tested, pre-qualified, disassembled, packed, and shipped across the Atlantic Ocean, then reassembled, and commissioned and validated at the Bloomington site.

Three-Dimensional (3D) design was used to develop the blueprints of the manufacturing portion of the facility, which facilitates any later remodeling or expansion of the facility by the owner. Airflow patterns in the critical areas such as the filling suites were stimulated before finalization of the 3D design. This allowed for the design to be changed before start of construction in order to optimize airflow patterns. All internal finishes, including flooring, gypsum board walls, wall covering, electrical wiring and fixtures, instrumentation loops, HVAC units, and ductwork, were installed within the boundaries of the modules. Plant and clean utility piping,

Finished preparation area.

Service area for HVAC and utility systems.

To avoid environmental impact, electric and gas utilities were tunneled under the creek.

process piping, and selective equipment also were installed and pre-qualified.

Modularization in combination with the use of 3D design assured a high level of accuracy in the placement and access to equipment and services. Time and efficiency gains of modularizing the manufacturing areas were realized in Phase II and III expansion projects, which drove the decision to again pursue modularization for the Phase IV project.

The Phase IV facility was designed with foresight to minimize any impact for expansion of the vial filling and lyophilization capacity related to the market demands. The facility modules are designed with 12' x 14' removable panels that are bolted with gaskets allowing clean and quick access to the building. Equipment can be added or removed easily, as well as the quick addition of manufacturing modules for a fast response to market demand without disturbing the ongoing production.

The facility was designed to add a mirror manufacturing suite on the opposite side of the building, which will then utilize the personnel and material corridors as a central spine. Wide-open rooms allow for ample working space and flexibility within the facility.

An Early Foundation for Validation

One of the key cost and schedule drivers for modularizing the manufacturing portions of the facility was the integration of the commissioning and validation processes. Total on-site critical path commissioning and qualification preparing for licensing was four months compared to 12 months anticipated by BPS for a similar conventionally built facility.

The integrated commissioning and validation with design, procurement, and installation was initiated during the front end design phase, which contributed greatly to the speed, smoothness, and predictability of execution during pre-qualification at the fabrication factory and final qualification on site.

Final OQ was conducted at the Bloomington site, but most facility systems were tested before shipment from the factory in Sweden. Total on site commissioning and OQ took five months compared to the 12 months anticipated for a similar conventionally built facility. PQ was completed in four months after handover, mainly due to the integrated validation efforts.

A River Runs Through It

Great care and detailed planning was required to avoid any environmental impact, especially to a natural creek that runs through the campus. One of the drivers for renovating parts of the existing facility in lieu of completely demolishing it was to reduce the environmental impact on the creek. Electric and gas utilities were tunneled under the creek so as not to

Project Schedule

The project schedule was based upon a 24-month turn around of the facility expansion from start of front-end design to the completion of Performance Qualification (PQ). The project schedule was developed to minimize disruption of the existing plant site operation. The modular portion of the building, which was 25% of the project, was erected in five weeks. The highlights of the project schedule were:

- Basic design began April 2003.
- Permitting was approved November 2003.
- Long lead equipment orders were placed July 2003.
- Module fabrication began October 2003.
- Assembly of the process part of facility in Sweden began April 2003.
- Demolition of existing building starts.
- Ground breaking for the new construction.
- Factory Acceptance Testing (FAT) of the facility and the process equipment systems in Sweden April 2004.
- Arrival of process facility modules in Bloomington first week of August 2004.
- First module was set first week of August 2004.
- Last module was set four weeks later.
- Reassembly of the facility was complete end of October 2004.
- Commissioning and IQ/OQ qualification was complete mid-January 2005.
- FDA approval of the facility May 2005.
- Operation began May 2005.

Exterior view of the final packaging facility, located off-campus.

disturb fish and wildlife and silt fences and other erosion control methods were employed.

By constructing the modular manufacturing facility off-site in a dedicated factory, BPS was able to greatly reduce the project's impact on the local environment.

Using Advanced Technology to Track Success

The facility uses a new ERP/MRP enterprise planning system to facilitate the tracking and management of material throughout the manufacturing process, providing 100 percent accountability of product tracking from raw materials through packaging. The platform features a production-scheduling program that will monitor constraints and anticipate potential problems, which is a task that previously required six full-time managers.

A machine vision system designed and developed by Frakes Engineering of Indianapolis is utilized to track syringe accountability. Filled syringes are counted in a nested configuration, resulting in a printed label barcode with human-readable lot numbers, tub numbers, and count information. The system is tied into the enterprise planning system, and production information is stored in the compliant historian for lot tracking.

In addition to the vision system, an automated inspection system designed by Eisai Machinery Co. of Hackensack, New Jersey is utilized to inspect for defects in syringes. The system can sort out defects such as particles in the solution, as well as glass and stopper defects. The system can inspect 300 syringes per minute, which would take 70 people at the rate of four syringes per minute each to achieve. Additionally, consistency of quality is dramatically increased by the elimination of human error.

Interior view of the final packaging facility, located off-campus.

The final advancement incorporated into the Phase IV expansion is a sophisticated final packing line, which provides for automated "kitting" assembly of final products for different client requirements. For example, the line can combine a syringe, a lyophilized vial, an insert, reconstitution/mixing devices, and alcohol pads all automatically.

Vision Becomes Reality

In 2003, BPS embarked on a fast-track construction project to provide contract manufacturing services to a demanding pharmaceutical market calling for pre-filled syringes and lyophilized vials. But through a creative and innovative mix of science, technology, and architectural engineering, the project has propelled BPS to become the world's largest supplier of pre-filled syringes.

At its award-winning, state-of-the-art facility, BPS provides large-scale syringe filling, aseptic formulation, vial filling, lyophilization, terminal sterilization, and flexible formulation capacity for a variety of challenging products such as insoluble solutions and vaccines. These services had never before been available all "under one roof" from other contract manufacturers.

"BPS, in conjunction with design/build partner Pharmadule AB, has demonstrated true leadership in the rapidly growing contract manufacturing sector," said Peter Bigelow, Senior Vice President of Consumer Healthcare Manufacturing for Wyeth and Chairman of the 2006 Facility of the Year Award Judging Panel.

"It is rare to find such an impressive array of cutting-edge filling technologies all within one facility. We were also very impressed with BPS's use of bolt-on removable components, 3D design throughout, and the combination of innovative technology and practical functionality – a difficult balance for an aseptic environment. These are among the many qualities that make this a truly world-class facility."

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Country Profile

A look at the Pharmaceutical Industry in

TURKEY

Produced in collaboration with ISPE Turkey

ENGINEERING PHARMACEUTICAL INNOVATION

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Dear ISPE Members,

On behalf of ISPE Turkey Affiliate, it is a pleasure for me to have the opportunity to make you more familiar with our country, our pharmaceutical industry, and our rather young Affiliate.

The roots of the Turkish pharmaceutical industry date back to the beginning of the 19th century. Today, the pharmaceutical industry represents nearly 300 companies in Turkey, of which 135 are major, and employment is approaching the 25,000 mark. It is in this context that we have launched the new ISPE Turkey Affiliate. One of the Affiliate's primary objectives is to contribute to the development of a common platform representing various manufacturers and suppliers of the industry, including academia, public authorities, and government agencies. The aim of such a platform is to foster progress within the industry. This cooperation among parties is to be supported by three to four educational seminars per year to promote dissemination of current knowledge and best practices.

In addition to these activities, we also are planning with the overall support of ISPE at large to promote the concept of the "professional pharmaceutical engineer." This goal shall be pursued in cooperation with Educational Foundations and as a response to the current high demand for training for pharmaceutical technicians by both industry and academia.

The enthusiastic support we received from the pharmaceutical industry at the inaugural seminar of our Affiliate last December reinforced our confidence and strength in the pursuit of the established milestones.

I hope this profile will fulfil its mission of giving a good picture of the Turkish pharmaceutical industry.

Sincerely,

Ünsal Hekiman

Chairman
ISPE Turkey Affiliate

This feature in *Pharmaceutical Engineering* is designed so that you can tear it out, three hole drill (if desired), and keep it with other Country Profiles as they are published.

Chronology of Turkey's Pharmaceutical Industry and its Outlook for the Future

by Selim Seyhan, Manager of R&D and Training, PharmaVision

Highlights

Turkey is considered to be one of the 35 pharmaceutical producing countries in the world. With preparations being offered as early as the beginning of the 19th century, large scale manufacturing started before the Republic (1923). Starting in 1915, mainly in drug stores and laboratories, around 30 products, ampoules, drops, syrups etc. were produced. After the establishment of the Turkish Republic, between 1928 and 1950, manufacturing was conducted in laboratories and small plants. After the Second World War, manufacturing capacity was increased with the establishment of local and foreign invested plants commencing in 1952. From 1984 onward, investments of foreign capital companies have increased. Especially after 1990, many foreign capital firms have entered the Turkish pharmaceuticals market. According to the last available data, about 300 entities are operating in Turkey, including 85 Drug Product (DP) plants and 11 API plants.

- Two of the plants are owned by the state.
- Eight foreign capital firms have their manufacturing facilities in Turkey.
- 27 foreign capital firms are supplying their products by imports or using subcontractors' manufacturing facilities in Turkey.
- There are 97 local capital firms.

Year	Raw Material (tons)	Finished Product (million boxes)
1998	7076	923
1999	5552	1005
2000	4980	1094
2001	4382	952
2002	3909	969
2003	circa 3900	circa 1129
2004	circa 3000	circa 1321
2005	circa 3000	circa 1366

Table A. Pharmaceutical production in Turkey.

After the official application of the GMPs in 1984, the Turkish Pharmaceutical Industry, making necessary investments, reached a technological level which can almost be compared to EU countries except in biotechnology and a few state-of-the-art technologies.

Consumption of Finished Product

Latest figure for the Turkish pharmaceutical market size is around US $6.6 billion (close to

Professions	Number Employed
Administrative staff	3,969
Workers	3,366
Skilled workers	2,338
Other engineers	1,600
Economists	1,255
Biologists	1,113
Chemical engineers	910
Chemists	853
Technicians	615
Pharmacists	514
Doctors	374
Laboratory assistants	212
Other personnel with university degrees	4,695
Total	**21,814**

Table B. Pharmaceutical employment in Turkey - 2005.

Continued on page 78.

General Information on Turkey

With a yearly growth rate of 9.9 %, currently one of the highest in the world, a market of 70 million people, a well established pharmaceutical manufacturing base and EU accession talks underway, the establishment of an ISPE Affiliate in Turkey is more relevant than ever before.

Investments by foreign capital companies have steadily increased in the past 20 years with this trend expected to continue, taking into account the country's proximity to European markets and its qualified and relatively inexpensive workforce. According to data provided by the Ministry of Health, there are 300 companies in the Turkish pharmaceutical market, of which 52 are foreign owned. 85 companies have their own manufacturing facilities, 11 are API producers. The rest of the companies are supplying their products by means of imports or by using subcontractors' production facilities in Turkey. A general overview of the scope of the Turkish pharmaceutical industry is further detailed in later sections of this profile.

With an area of nearly 800,000 square kilometres spread between Europe and Asia, the country's strategic geographical location between East and West is further emphasized by its cultural and political closeness to several governments in the region with conflicting political views.

Chronology of Turkey's Pharmaceutical Industry...

Continued from page 77.

Year	Exports (US$ million)	Imports (US$ million)	Export/Import Ratio (%)
1998	129	1181	10.9
1999	128	1337	9.6
2000	140	1511	9.3
2001	149	1534	9.7
2002	157	1716	9.2
2003	246	2419	10.2
2004	248	2710	9.2
2005	282	2850	9.9

Table C. Export/import ratio in the pharmaceutical industry.

half of it accounted by imports), making it the 12th largest drug market in the world.

Projections for 2023

Market worth is estimated to reach US $25 billion; US $100 per capita annual spending on drugs; US $800 million export; 55% import share in the market according to available recent data from various sources.

Statistical Data[1] about the Industry

In this section, you will find information, statistics, and other relevant data and graphics giving an accurate picture of the Turkish pharmaceutical industry.

Year	Total: Manufacturer Prices (US$ billion)	Of which, import (US$ billion)
2005	6.6	circa 3
2023 (projected)	circa 25	circa 12

Table D. Size of the Turkish pharmaceutical market (Source: Pharmaceutical Manufacturer's Association of Turkey).

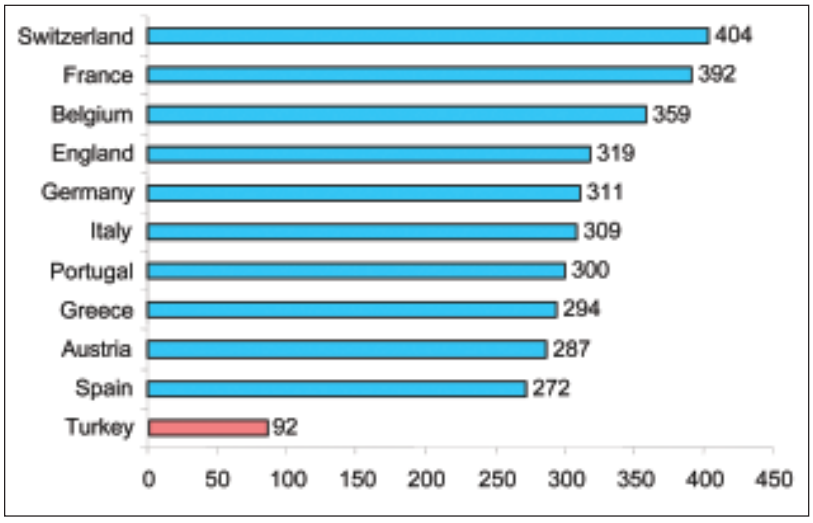

Figure 1. Per capita consumption rate in US$ of pharmaceuticals according to treatment groups - 2003 / data for Turkey is 2005.

Consumption

On a comparison based on Year 2004 figures, it can be concluded that per capita, pharmaceuticals consumption in Turkey (US $92) is quite lower than EU and other developed countries. A graphical comparison with several countries is given in Figure 1.

In treatment groups, according to 2005 figures, antibiotics are leading with a 17.8% consumption rate, anti-rheumotismals are second with a 12.4% consumption rate, followed by pain killers, cold treatment pharmaceuticals, and vitamins. The complete breakdown is illustrated in Table E.

Treatment Pharmaceuticals	Market Share (%)
Antibiotics	17.8
Pain-killers	9.5
Anti-rheumotismals	12.4
Cold and cough treatment pharmaceuticals	8.5
Vitamins, minerals and anti-anaemic pharmaceuticals	6.1
Skin diseases pharmaceuticals	4.9
Digestive system pharmaceuticals	5.2
Cardiovascular diseases pharmaceuticals	7.3
Hormones	4.0
Ear, nose, throat, and ophthalmic preparations	4.3
Nervous System pharmaceuticals	3.4
Diabetes pharmaceuticals	1.4
Others	15.2

Table E. Market share by pharmaceutical product category - 2005.

Country	US$ million
Ireland	12.945
Switzerland	11.073
France	6.674
England	5.939
Sweden	4.373
Denmark	3.511
Germany	2.995
Netherlands	1.356
Austria	63
Belgium	-700
Norway	-710
Finland	-733
Turkey	**-1.019**
Italy	-1.157
Portugal	-1.306
Greece	-1.534
Spain	-3.007

Table F. Trade balances in finished goods - 2003.

Chronology of Turkey's Pharmaceutical Industry...

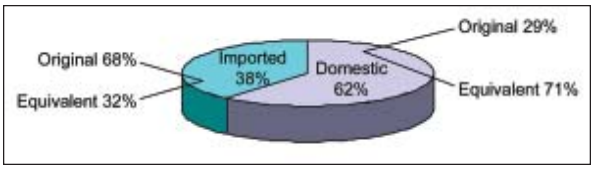

Figure 2. Market pharmaceutical distribution in terms of sales forms - 2005.

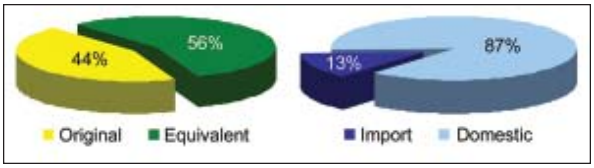

Figure 3. Original/equivalent and import/domestic distributions (packs) in pharmaceutical market - 2005.

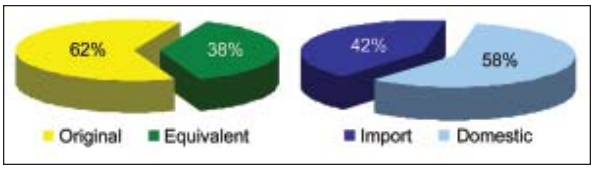

Figure 4. Sale amount ratios for original/equivalent and import/domestic - 2005.

The information in Figure 2 represents the market distribution in terms of local manufacture vs. imports, further divided into original preparations against generics.

Foreign Trade/Investments

The Turkish pharmaceutical industry, with the quality, efficiency, and reliability of its products has reached a level where it can compete with many countries. As a matter of fact, the industry performed exports to more than 50 countries including Germany, US, Austria, Belgium, Finland, Netherlands, UK, Switzerland, Italy, and Japan.

On the other hand, the industry faces certain obstacles. To compete more successfully in foreign markets, The Turkish pharmaceutical industry is increasing both its technical and marketing investments on a continuous basis. The foreign trade volumes are on the rise as shown in Figures 5 and 6.

One of the Affiliate's missions will be to increase the cooperation between the industry and the authorities to reverse this trend. With a well educated workforce and relatively cheap manufacturing costs, the stumbling block appears to be inadequate investments.

It is estimated that in order to closely align the technological developments in the world and the evolving GMP rules, the Turkish pharmaceutical industry must invest at an average rate of $100 million per year. The graph below indicates that the industry is steadily approaching this value.

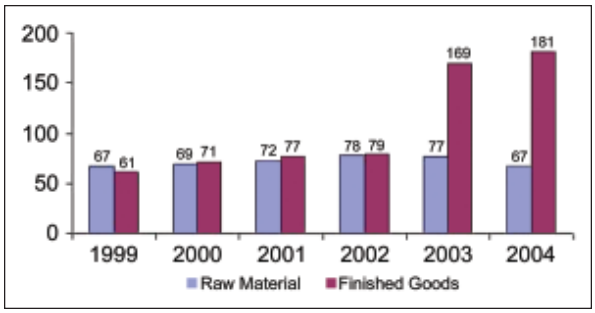

Figure 5. Exports in millions US dollars.

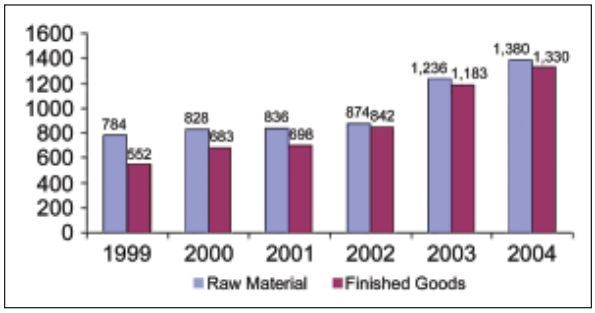

Figure 6. Imports in millions US dollars.

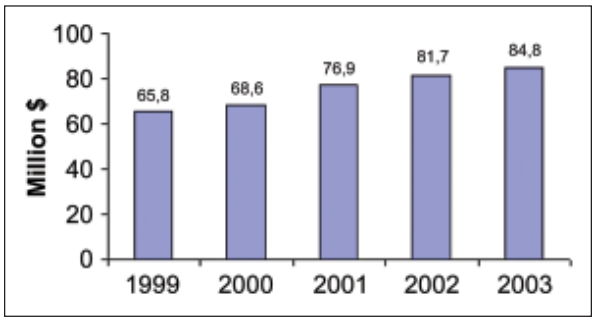

Figure 7. Turkey's investment growth rate in the pharmaceutical industry.

Investments in the Turkish Pharmaceutical Industry

With already planned measures showing their effects in the coming years, the industry is confident of surpassing its goals.

[1] Sources: European Federation of Pharmaceutical Industries and Associations (EFPIA), Pharmaceutical Manufacturers' Association (IEIS), The Scientific and Techonological Research Council of Turkey (TÜBITAK), and various company reports.

Case Studies

by Selim Seyhan, Manager of R&D and Training, PharmaVision, Nuran Varolan, Technical Director, Pfizer Istanbul Site, and Suat Kumser, Aseptic Operations, Liquid, and Ointment Area Production Manager, Pfizer Istanbul Site

In this section, two case studies will be presented of companies demonstrating the level of manufacturing understanding reached in Turkey. PharmaVision is a pure contract manufacturing entity in Istanbul, and Pfizer Istanbul is a well established manufacturing site of the global Pfizer organization also in Istanbul. Many other leading Turkish manufacturing companies are also competing successfully on the international level.

PharmaVision

A Successful Management Buyout Case

PharmaVision, a leading Contract Manufacturing Organization (CMO) in Turkey, has a long history in the country, its roots going back to Türk-Hoechst Sanayi ve Tic. A.S, the Turkish subsidiary of the German Hoechst AG, was established in 1954 as one of the first foreign investments in our country. Through various mergers at the headquarter level over the years, the site became part of Hoechst Marion Roussel followed by Aventis, this transformation culminating in a management buyout in December 2002 with the creation of PharmaVision.

Over 50 years on its 51-acre manufacturing site in the Topkapi region of Istanbul, the company has witnessed various GMP upgrading in line with ever increasing regulatory and customer demands. A 12-year long multi-stage remodelling project commencing in 1987 has resulted in a technologically advanced factory with its computer supported, closed system, and uninterrupted manufacturing lines. Adapting to new technical advancements, further investments are in progress in an intensive manner.

Located on 51,000 m^2 campus, PharmaVision aspires to become a preferred partner in contract manufacturing to the pharmaceutical industry. The company's vision is in complete toll manufacturing partnership without any own licensing. Maintaining and continuously improving its high Good Manufacturing Practice (GMP) standard is attained by adhering to strict, effective, and updated Standard Operating Procedures (SOPs) as well as quality standards by continuously investing in its facility and equipment and by recruiting, properly training, and retaining top talent in the country. In line with current regulatory trends, and in addition to general non-betalactam manufacturing encompassing all galenical processing except lyophilization, PharmaVision has also separate production facilities for cephalosporin (sterile powder), penicillin (tablets, oral powder), and enzyme products (oral form).

The quality and compliance level reached through these modifications is further supplemented by continuous education and training of the staff, integration of modern quality management systems encompassing EHS, and risk assessment procedures. Such continuous efforts and a constant benchmarking of industry standards are all aimed at the mission of becoming the "preferred toll manufacturing business partner" not only on a national level, but a global one as well. In this roadmap, PharmaVision has collected several certificates, such as ISO 14001, OHSAS 18001, TS 13001 (HACCP-Risk Assessment), on several occasions as pioneers in the industry. Similarly, PharmaVision has been recognized with many awards such as the Responsible Care and Environmental Awards of the Istanbul Chamber of Industry as well as those by CEFIC, the latest being the European Environmental award. The company has demonstrated its social responsibility on several occasions, but most notably through the construction and maintenance of an elementary education school in Düzce, an earthquake damaged region of the country.

Consequently, several multinational companies have chosen PharmaVision as their manufacturing partner in Turkey for their local and export markets.

Pfizer Turkey

Integration to New Pfizer "Right First Time" Initiative

Pfizer Turkey was established in 1957 in Istanbul which is the industrial capital of Turkey. At the beginning, the plant was designed to manufacture only a few products. In parallel to the pharmaceutical market growth in Turkey, the Pfizer plant also has extended its manufacturing capacity to satisfy the increasing demands in years.

In 1993, penicillin and cephalosporin plants became operational; within a short period of time, these two facilities became the most important driving forces of Pfizer Turkey in its export business mainly to the Eastern European markets.

In 2005, the company exports 17 different pharmacy and animal

Case Studies

health products to 24 markets around the world. Ninety percent of export sales go to the Eastern European Region countries which are mostly EU members such as Poland, Czech Republic, Hungary, Slovakia, and Lithuania.

In 1995, the non-penicillin manufacturing facility also was renovated to ensure current GMP compliance requirements. The company continues to invest in maintenance and quality improvements to assure its constant compliance status.

In 2004, Pfizer Turkey made export sales of $19 million. This alone constituted 7% of Turkey's annual export sales in the sub-sector of pharmaceutical products, declared to be amounting to $272.5 million by the Exporters' Union, Istanbul. With this figure, Pfizer Turkey ranked the third biggest exporter of the sector overall in Turkey and received an award in February 2005.

The export sales have been showing upward trend over the last few years. In 2004, the figure grew by 60% compared to 2003 and exceeded last years' performance by export sales of $23 million in 2005. Regarding the manufacturing capacity for the local markets, 37 different products are locally manufactured with the 148 presentations.

Taking in account the imported and toll manufacturing products, Pfizer Turkey supplied 121 different products with 356 different presentations with the total supply volume of 44 million packs in year 2005.

As an extension of various quality improvement tools applied over the years, the Right First Time (RFT) Strategy is a Pfizer Global Manufacturing (PGM) driven strategic initiative that will enhance effectiveness of the Pfizer Manufacturing core processes by quality and performance improvement projects.

Being a data driven strategy, RFT utilizes some statistical models. One of the basic tools of this strategy is the Six-Sigma, which has been widely used by the manufacturing and non-manufacturing industries as a problem solving, business process development, and a decision making technique based on real data.

Pfizer's Right First Time Strategy is established around Five Strategic Mission Elements

Organizational Initiatives

RFT will concentrate attention on relations within the Pfizer Global Manufacturing (PGM) organization between Active Pharmaceutical Ingredient (API) and Drug Product (DP), or between PGM and another Pfizer Division - Pharmaceutical Global Research and Development (PGRD), or external as in the case between PGM and their suppliers.

Paradigm Shift

Fundamental to RFT is the recognition that there is a paradigm shift occurring in the pharmaceutical industry. This is a shift that will move organizations from an empirical to a science-basis for manufacturing operations.

Colleague/Culture

Basing all actions on good scientific and risk-management principles, Pfizer Turkey believes that product quality and performance is foremost achieved and assured by design of effective and efficient manufacturing processes. Therefore, product specifications are based on a mechanistic understanding of the relevant formulation and process factors.

The recognition of the need for the right persons in this project led to a major effort in Pfizer Turkey to select and develop suitable colleagues for this project. The result has been the achievement of the Right First Time culture on a broad basis.

Process Understanding

Process Analytical Technology (PAT) is the driving force for process understanding.

Because the process understanding was one of the most important key factors for the successful completion of the RFT projects, Pfizer Turkey has started to use several PAT applications in RFT projects. One major example is the use of NIR spectroscopy for better process understanding and more effective and efficient incoming material analysis for quality control purposes.

Performance

Pfizer's Right First Time initiative was started primarily to increase the quality of services and products. Within the past two years with the successful integration of new global initiative several Right First Time projects were successfully completed which contributed to increase the effectiveness and efficiency of Pfizer Turkey's manufacturing and supply operations.

With the help of global performance metrics and knowledge sharing activities, sites in different countries find a chance to compare and improve the capability of the processes.

Pharmaceutical Associations and Organizations in Turkey

ISPE Turkey Affiliate
Kusbakisi sok. No: 29 B Blok
Altunizade/Uskudar Istanbul,
Turkey
Tel: +90-212-482 0000 (2601)
Fax: +90-212-482 0086
E-mail: info@ispe.org.tr
www.ispe.org.tr

The Republic of Turkey, Ministry of Health
Mithatpasa Cad. No: 3
Sihhiye Ankara, Turkey
Tel: +90 (312) 435 6440
Fax: +90 (312) 4339885
E-mail: info@saglik.gov.tr
www.saglik.gov.tr

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8 December 2005

Chemical, Petroleum, Rubber, and Plastic Industries Employers Association of Turkey
Kusbakisi sok. No: 29 B Blok
Altunizade/Uskudar Istanbul,
Turkey
Tel: +90-216-651 4900
Fax: +90-216-474 9192
E-mail: kiplas@kiplas.org
www.kiplas.org

Pharmaceutical Manufacturers' Association of Turkey
Talatpasa Cad. 98/B Gultepe
Istanbul, Turkey
Tel: +90-212-278 8540
Fax: +90-212-2787007
E-mail: info@ieis.org.tr
www.ieis.org

Turkish Pharmaceutical Industry Association (TISD)
Yildiz Posta Cad. İs Bankasi
Bloklari B Blok D: 1
34349 Esentepe Istanbul, Turkey
Tel: +90-212-275 9630
Fax: +90-212-274 5024
E-mail: info@tisd.org.tr
www.tisd.org.tr

AIFD (Research-Based Pharmaceutical Companies Association)
Barbaros Bulvari No: 121, TEV
Orhan Birman İs Merkezi
Balmumcu Istanbul, Turkey
Tel: +90-0212-267 1600
Fax: +90-212-273 1179
E-mail: aifd@aifd.org.tr
www.aifd.org.tr

YASED (Foreign Investors Association)
Barbaros Bulvar1 Mürbasan Sok.
Koza Is Merkezi
B Blok Kat.1 Balmumcu /
Beşiktaş Istanbul, Turkey
Tel: +90-212-272 5094
Fax: +90-212-2746664
E-mail: yased@yased.org.tr
www.yased.org.tr/

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Site Master Planning

by Richard Larkin

This article presents a methodology for the delivery of a Site Master Plan (SMP) for a pharmaceutical facility. It describes a three step execution and presents a list of issues that appear regularly during the development phase.

Pharmaceutical manufacturing and research sites are complex investments, which must provide a cost-effective environment for a company to conduct its activities.

Often the site has developed in a piecemeal fashion over the years with new capital projects being subject to short term goals and pressures. This can result in a site which is no longer operating at peak efficiency (in terms of equipment utilization, utility supply and overall movements) and where the layout of individual buildings or the whole site needs improvement. Overall, the site may look very different from the ideal arrangement for a new site. However, there comes a point when a more fundamental reorganization and rationalization of the site becomes essential. This may be triggered by one of the following reasons:

- overall age of assets
- GMP deviations
- manufacturing cost pressures
- logistical issues and flows
- changes to product portfolio
- change of ownership (merger or acquisition)

This is the point at which a site will benefit from a Site Master Plan (SMP).

An SMP for an overall site or facility has to identify the business drivers and future site strategy for a defined period (say five to ten years), convert this into a technical brief (technology, space, support functions, etc.), and select the best overall arrangement to meet these objectives. It is of no value if the plan satisfies one activity (for example, production) if at the same time, it compromises other activities (such as logistics, QC space, etc.).

The SMP must be a holistic plan that addresses every issue and yet manages to obtain consensus agreement with both site and corporate management. A thorough SMP will encompass the following operational needs:

- production departments
- logistics, warehousing and material flows
- cost of goods and operating efficiency
- utility systems

It will also encompass the following site support features:

- personnel flows and practices (such as gowning)
- laboratories and QC compliance
- archives
- office and canteen areas
- site security and parking
- environmental and planning issues

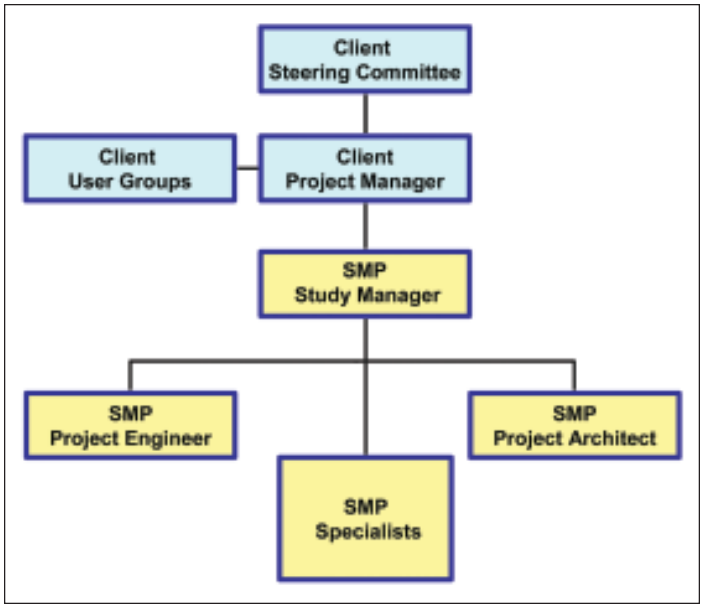

Figure 1. A typical SMP team organization chart.

As the SMP will be a key document for the future of the site, the execution of the study must follow a well structured and transparent methodology in which competitive schemes are compared and analyzed in an objective way. A record of the decision-making process is vital

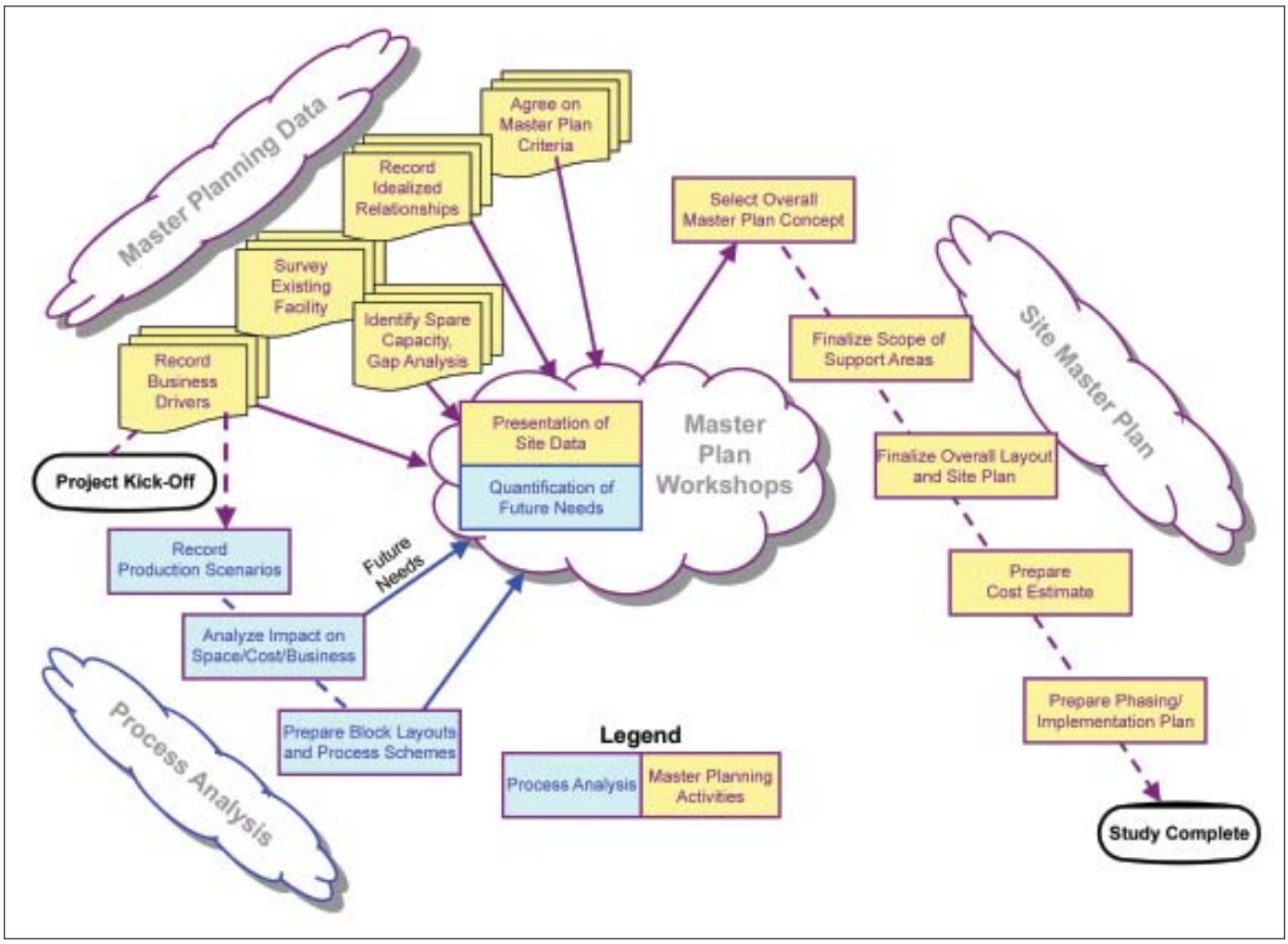

Figure 2. The overall steps of the SMP execution plan.

for reference, and to demonstrate this objectivity and 'best value' solution.

Many clients prepare their SMP 'in-house,' but others wish to use an external company to provide independent input.

This article outlines the author's experience in developing SMPs, including some of the typical issues encountered at pharmaceutical sites around the world.

The term Site Master Planning can be used to cover three distinct types of plan:

- **Green Field** Site Planning
- **Facility** Planning of an Existing Mature Site
- Individual **Building** Planning

The techniques described in this article are applicable to all three types of plan, but the examples are drawn from Facility and Building Planning.

The Vision

The bedrock that underpins any SMP is the future vision for the site. This must be provided by the client or owner, who will have a specific vision regarding the role of the site within the overall corporate strategy. The vision also must incorporate the long range production plan.

Many sites have a stated vision for internal publicity and marketing, but often this requires further definition to form the basis of a detailed site plan. For instance, a site may declare a vision:

> *"To be a center of excellence for production of a certain product range."*

However the SMP may need this vision to be further developed into:

> *"To be the center of excellence in sterile manufacture within the corporation with an annual capacity of xx million units/yr on a two-shift, six-days-per-week basis, but readily expandable to yy million units/yr by operating a third shift. The site is to have the flexibility to back up production from zz site, and be able to accept transfers from other sites. All obsolete equipment is to be replaced within a certain period. The site must target a 20% reduction in the cost of goods and site inventory is to be reduced to a target of ww days. The site is to address*

all high and medium risk GMP issues..."

The Final Deliverable

A well structured SMP report will typically contain the following elements:

- Site Strategic Vision/Mission Statement

- Executive Summary, including:
  - critical issues addressed in the SMP
  - critical assumptions
  - key selection criteria used in the SMP development
  - overall site plan showing key phases of implementation
  - summary of key projects
  - overall cost and schedule, including key steps/trigger points
  - implementation plan
  - inclusions, exclusions, and outstanding issues

- Report on each department, including current status, future plans, and implementation strategy:
  - process operations (production, packaging, clean utilities)
  - GMP compliance
  - quality operations
  - flows and site infrastructure, including security
  - buildings and building services
  - site support areas
  - warehousing and logistics
  - utilities
  - environmental systems

- Project listing of all the significant capital projects required to deliver the SMP, including cost estimate (+/- 30%), implementation plan, and schedule

- drawings of the overall site, production building block layouts, and other more detailed plans to illustrate the SMP concept

- appendices, including a summary of the methodology used, and details of the alternative schemes that were adopted and rejected

The Execution Plan

The most critical element leading to a successful SMP is the team.

The study manager for the SMP consultant must have facilitation skills as well as a good technical knowledge of current industry practice. He or she also must be able to interface with the client's management team at the highest level and be able to present concepts and ideas in a simple and yet authoritative manner.

The study manager will need to be able to call on the support of technical experts in key disciplines including:

- GMP Compliance
- Automation
- Production Equipment
- Civil/Structural Engineering
- Environmental Engineering
- Architecture and Local Planning

However, the greatest threat to a successful SMP may come from a team that is drawn into excessive detail in the analysis of technical issues. Therefore, specialist input has to be carefully managed to focus on the key issues affecting SMP development.

A typical SMP team organization chart is shown in Figure 1. Note how the organization chart identifies the key client users who must represent key departments and guide the study to a result that will be acceptable to the overall client organization.

The SMP execution plan itself must be built on:

- a sound knowledge of the existing facility
- a clear and approved strategic vision for the site
- involvement of the key client representatives from every site department
- a clear and approved methodology for identifying and comparing different solutions

The overall steps also are illustrated in Figure 2. Essentially, the plan is executed in the following three phases:

- Phase 1 - Data Collection and Presentation
- Phase 2 - Development of Master Plan Options, Concept Identification Screening and Selection
- Phase 3 - Delivery of the Completed Plan

Phase 1 - Data Collection and Presentation (Current Operations)

The first phase of an SMP is devoted to data collection and analysis. This is a rather laborious, but vital, part of the study, as it provides the sound foundation for the development of the actual SMP.

Data should be collected from each site department, including key performance statistics such as:

- process utilization and equipment efficiency
- logistics, including current inventories and material flows
- GMP gap analysis
- utility capacity, utility demand (peak/average), reliability, and redundancy
- major site constraints, such as planning rules, environmental limits
- QC requirements and sample release statistics
- personnel flows and gowning issues
- site security and car park limits

Bear in mind that in this phase, the client team will be fully committed running the ongoing operation so the SMP team must target the information that it collects.

As a general rule - if the data in the SMP cannot be used,

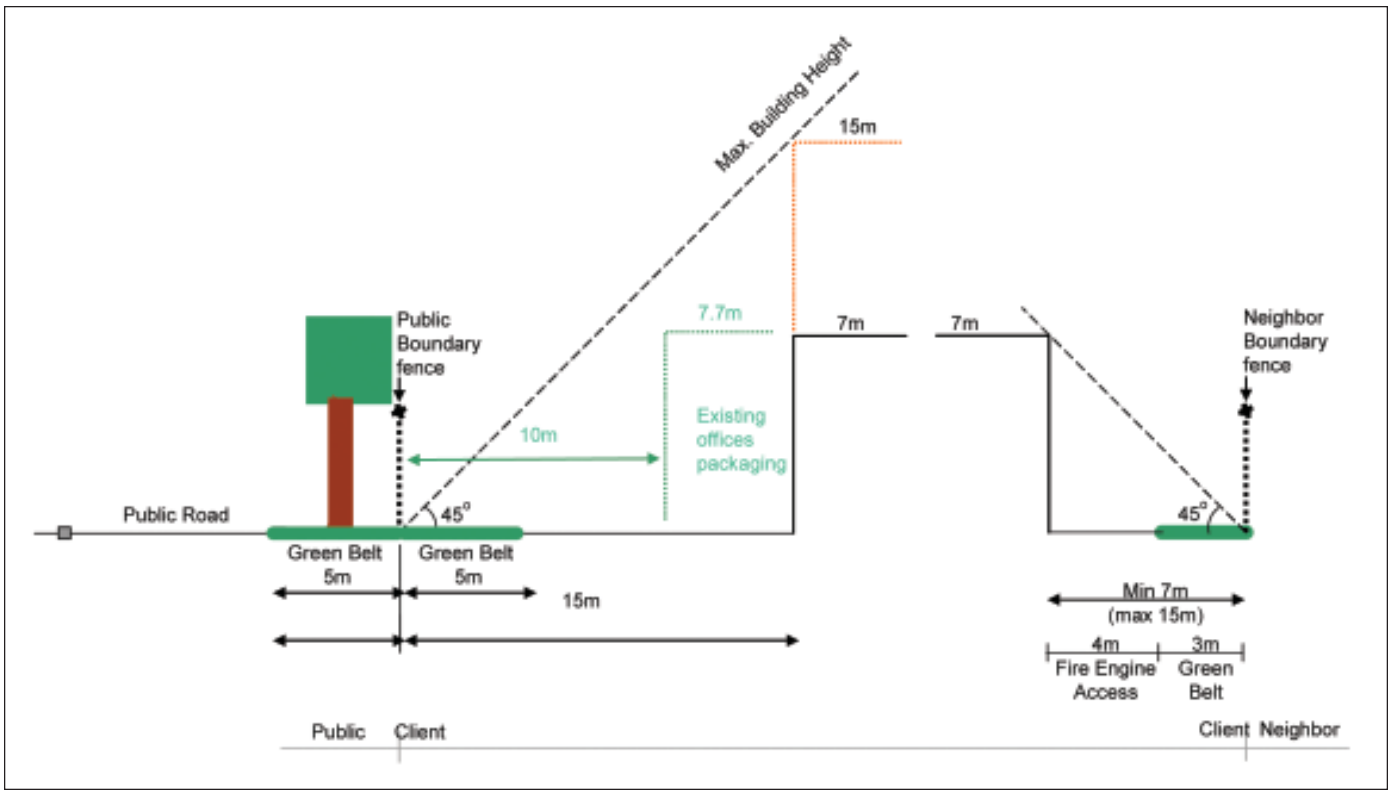

Figure 3. Typical presentation of boundary limitations.

then don't ask for it! For this reason, a set of generic data collection templates is invaluable to collect the information quickly and efficiently.

The best method of collecting the data is to plan a series of interviews with each individual department, and use the templates as the agenda for the meeting. In many cases, data will already be available in existing site reports and drawings, and this can be handed over to the consultant to extract the key data. It is not unusual that a follow-up meeting is required to collect more information on a specific topic that impacts on the SMP, but good preparation for the interview will ensure that this is infrequent. Clearly, during this phase, the consultant must be based at the site to be able to tour the site and respond immediately to unavoidable changes in the client interview schedule.

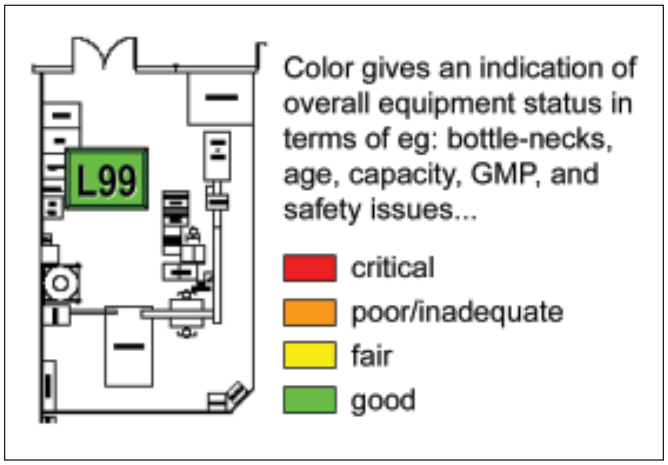

Figure 4. Example of a standard graphical format to show line performance.

Another key requirement for a successful SMP is the ability to present the data in a clear graphical manner so that all parties can assimilate the key issues. It is important to present the data to the client's team to gain confirmation of the key issues to be resolved in the SMP. Therefore, a 'presentation style' is essential with maximum use of illustrations and graphics.

The following examples may illustrate this approach:

Planning Rules

Planning setbacks and height restrictions can be shown in an illustration for easy reference - *Figure 3*.

Layout Issues and Constraints

Mark-ups of existing layout drawings can be used, not only to show the conventional issues such as materials and personnel flows, but also the location of significant issues such as:

- opportunities and constraints
- GMP compliance issues
- structural limitations, etc.

Production Issues and Efficiencies

When analyzing production departments, line performance must be presented in a simple graphical way. The following format proved useful on a recent SMP of a secondary pharmaceutical facility.

First, each line is coded to summarize its overall age and

Equipment Features	Line #	L99
	pharmaceutical form	
	production complexity	
	age	
2004 Performances	volume	
	measured efficiency	
	efficiency target	
2006 Forecast	volumes	
	utilization	

Table A. Example of a standard table format to show line operating parameters.

condition, based on the site records and a visual inspection, using a standard format - *Figure 4*.

The operating parameters of the line are then summarized in a standard table - *Table A*.

Using this format, the available spare capacity and efficiency improvements can be readily identified as a basis for future planning.

Site Potential

An existing site may offer limited potential for extending existing buildings in certain directions, due to structural or space constraints - *Figure 5*.

Site Flows

Material and personnel flows are often the first items to be compromised as a site develops. The existing flows are best shown superimposed on the site or building layout so that the cross flows or areas of intense flow can be identified - *Figure 6*.

Utility Status

The demand and capacity of each utility system can be represented graphically for easy reference.

Scheme Selection Criteria

At this point, it is important to recognize that the SMP team will identify many potential options for the site, and that a structured selection methodology must be agreed with the client. This normally requires the team to identify the key issues and sort them into:

- Key issues (must have) - issues that must be resolved by any scheme
- Preferred (nice to have) - issues which the site should aim to resolve as far as possible

One proven method of identifying critical issues to be addressed is to hold a Strengths, Weaknesses, Opportunities, and Threats (SWOT) analysis where the site's future outlook can be categorized against the four parameters:

- Strengths - to be built on
- Weaknesses - to be addressed
- Opportunities - to be exploited
- Threats - to be mitigated

SWOT analysis is best prepared in a workshop environment where the consultant and client user groups are encouraged to think laterally regarding the issues affecting the site.

The SWOT analysis provides a very useful basis on which to judge the success of a scheme.

Finally, the plan needs to review the status of any ongoing projects on the site and categorize them into:

- approved projects - assumed complete
- unapproved projects - which may be modified by the outcome of the SMP

Phase 2A - Development of Master Plan Options

The data collected during Phase 1 describes the existing site situation, and provides the base reference for Site Master Planning.

Before any SMP concepts can be generated, it is necessary to convert the strategic site vision/mission statement into its technical implications. For example, increased production may require not only more efficient production, but possible new production lines, additional or modified storage, extra QC samples analysis, more canteen and car park spaces, etc.

It also is vitally important that the SMP provides real cost savings for the site. For this reason, the SMP must generate production efficiencies by, for example, increasing the utilization of the existing equipment, and eliminating wasteful activities.

Significant costs can be built into site operations from inefficient flow patterns, such as long distances between gowning areas and operating departments and multiple handling of materials. For this reason, it can be useful to generate a series of idealized relationship diagrams that will guide the study team toward the most effective arrangement of functions. Figures 7 and 8 illustrate two typical drawings.

At the end of the data collection phase, the SMP team will have all the basic reference material that they will need to generate and compare alternative SMP schemes.

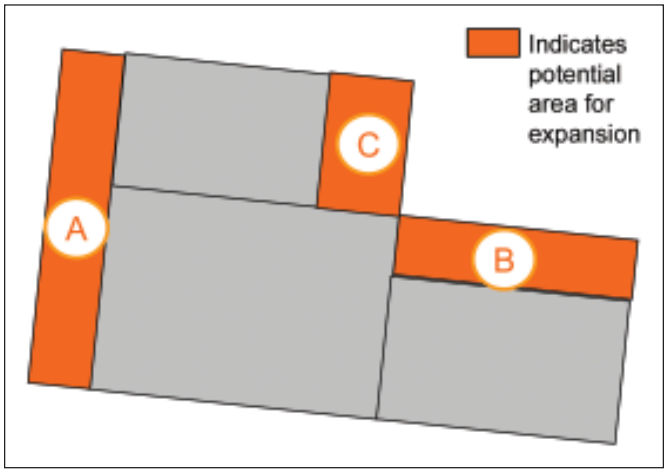

Figure 5. Sample diagram to show potential area for expansion.

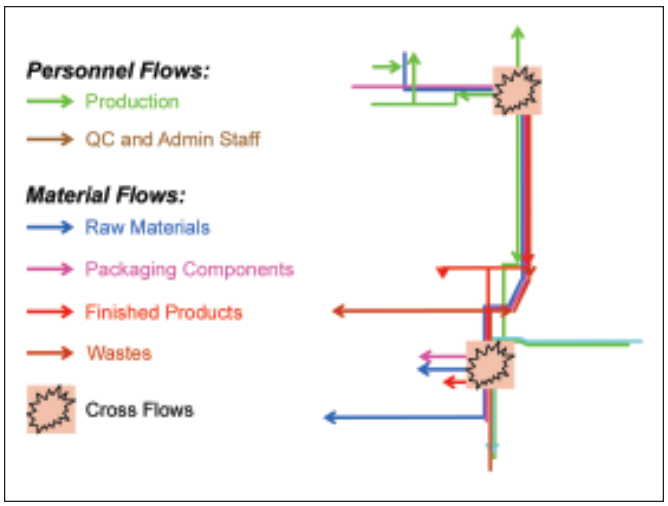

Figure 6. Existing flows shown superimposed on the site or building layout.

Phase 2B - Concept Identification Screening and Selection

During Phase 2, potential schemes are identified and screened with the intention that a single scheme will be selected at the end of Phase 2 for final development.

Generation of Alternate Schemes

Typically, the first activity is a brainstorming session when the team members identify all the potential alternatives. In the true tradition of brainstorming, no scheme is rejected at this stage unless it clearly fails to satisfy one or more of the 'must have' criteria, or fails to provide the basic functionality that is required.

A good way to involve all team members in a brainstorm session is to develop alternate layouts on a physical site plan; for an overall facility plan a 3D layout is very useful to show any significant topographical constraints.

Alternate facility layouts can then be developed using the following technique:

1. estimated footprints are calculated for all new buildings or departments

2. blocks (to scale) are created to represent these new footprints

3. alternative arrangements are created by locating the blocks on the layout and photographed for review and comparison against the success criteria

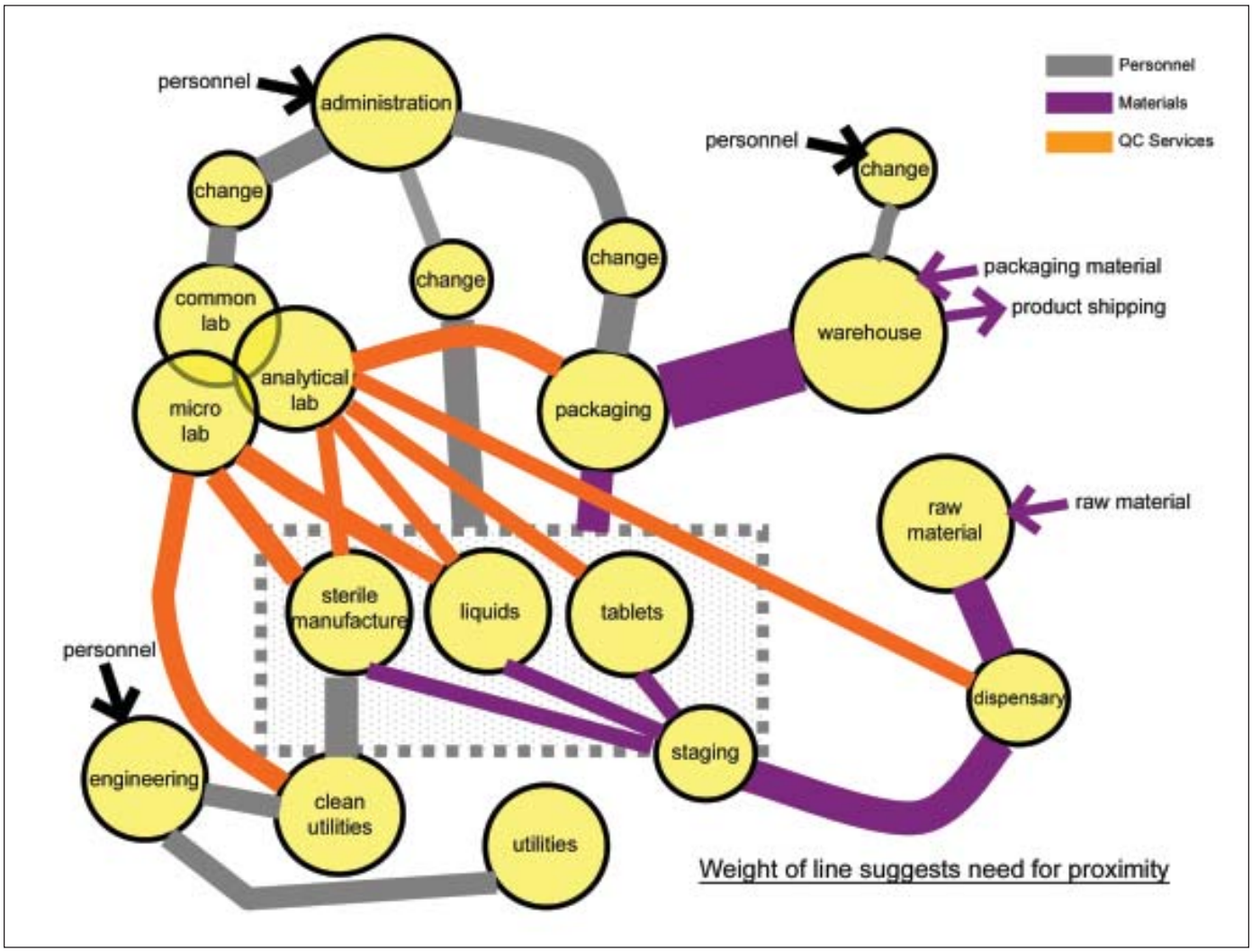

Figure 7. Overall site relationships diagram.

At this stage, it is quite acceptable and indeed preferable that the schemes are represented by simple blocks on the layouts. Typically, five to ten substantially different options would be generated.

Screening of Potential Schemes

The next step is to screen the preliminary options against the 'nice to have' criteria.

Some indication of comparative capital cost, operating efficiency, and schedule also are required at this stage to review the schemes.

There will undoubtedly be some individual features that appear in all the options, and these can be taken as 'fixed.' This will leave a number of open issues that require more detailed analysis before a final scheme can be agreed. For each open issue, it may be necessary to prepare one or more of the following supporting documents:

- dimensioned layout plans
- technology assessment
- materials and personnel flows
- block layouts of new or expanded departments
- projects listing and cost (+/- 30%)
- schedule and draft implementation plan

These open issues are then presented again to the site team in a workshop forum with an analysis and recommendation for client review and approval. At this point, it should be possible to select the SMP scheme.

Phase 3 – Delivery of the Completed Plan

As the concept for the SMP has now been established, the final phase comprises the development of the concept into final quality deliverables. This will include a project listing, identifying all the individual projects that together make up the whole plan, plus a level 1 schedule to show the overall links of the projects and the projected dates for achieving various milestones. Most schemes will include phasing that must be clearly and logically presented. Each project also should typically be costed to an accuracy of +/- 30%.

The impact of development on utility systems is best represented as a series of charts showing the future predicted demands and the trigger points for future capacity increases - *Figure 9*.

The final SMP report must be a high quality document, suitable for presentation at the highest management level, including presentation style drawings to demonstrate:

- overall site plan
- production building floor plans
- personnel and material flow diagrams
- staged implementation drawings
- 3D CAD architectural impression of the site development - *Figure 10*

How Long Does a Master Plan Take?

There is no standard schedule for the completion of an SMP,

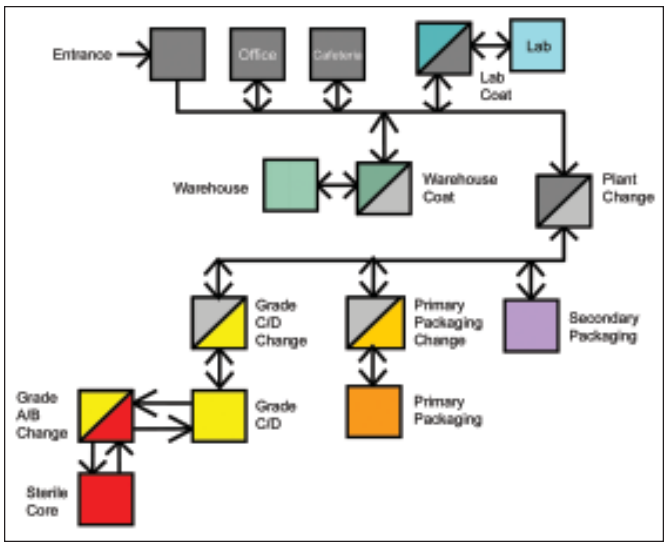

Figure 8. Ideal change regime.

as the duration will be influenced by both the extent and complexity of the SMP and also the availability of key client resource to participate in the key workshops and presentations. What is important is that the key steps in the SMP must be followed in a logical, sequential manner, and that a reasonable schedule is agreed in advance. Once the dates for key management reviews have been fixed, these will be difficult if not impossible to reschedule once the SMP has started.

Durations of between six weeks and six months are quite possible, but a reasonable starting point for a SMP is a three

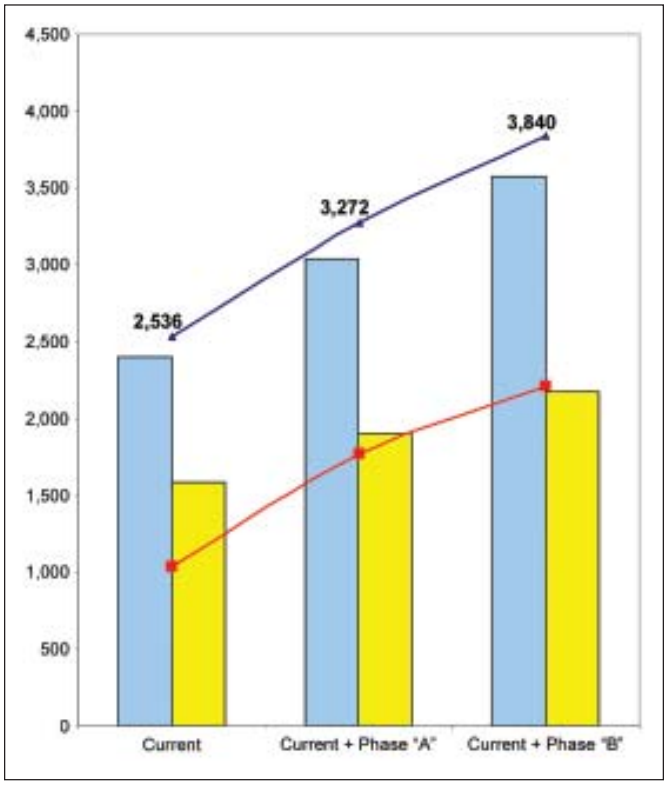

Figure 9. Chart example to show future predicted demands and trigger points for future capacity increases.

Figure 10. 3D CAD architectural impression of the site development.

to four month duration split equally between the three phases - *Figure 11*.

Experience (It's Not Rocket Science, But...)

It is often said that, "Master planning isn't rocket science," and this is certainly true.

What it takes, most of all, is a sound knowledge of issues affecting pharmaceutical research and manufacture, an interest and ability to analyze information and extract the key issues, and the desire to listen to opinions and facilitate the 'best overall' scheme.

This article concludes with the following 'top ten' issues that appear regularly in master plans:

1. the need to improve operating efficiency and reduce cost of goods
2. poor material and personnel flows
3. excessive inventory of materials stored on site
4. the need to plan future expansion and replacement of ageing assets without disrupting ongoing operations
5. GMP compliance issues
6. space for expanding QC activities and archives
7. lack of suitable space for meeting rooms and training
8. eating and rest rooms within the 'pharmaceutical zone'
9. environmental impact, for example, boundary setbacks, on-site waste water treatment, and solid waste collection/ disposal
10. site security and insufficient car parking spaces

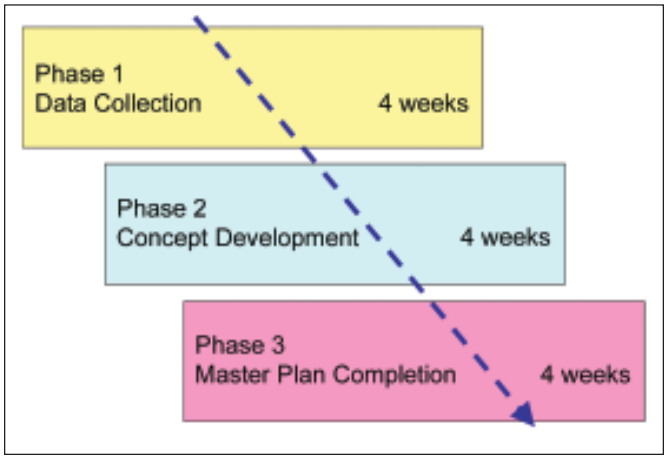

Figure 11. Typical master plan duration.

About the Author

Richard G. Larkin, MA, FIChemE, is Principal Consultant and Co-founder in 1987 of the Pharmaceutical Division of Foster Wheeler, the international engineering, procurement, and construction contractor based in Reading, UK. In this role, he has provided pharmaceutical engineering design and consultancy to many of the world's leading pharmaceutical companies, including Pfizer, Glaxo SmithKline, Sanofi-Synthelabo, and Eli Lilly. He has personally developed the site master planning expertise for Foster Wheeler, and regularly manages site master plans for pharmaceutical clients. Larkin has been an active member of ISPE for more than15 years. A member of the South-East UK Chapter, he has presented papers on containment and engineering topics at ISPE seminars and led the Pharmaceutical Innovations course for ISPE in 2002 in Birmingham, UK. He can be reached at e-mail: richard_larkin@fwuk.fwc.com.

Foster Wheeler Energy Limited, Shinfield Park, Reading, Berkshire RG2 9FW, United Kingdom.

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Developing and Implementing a Certification Program to Drive Change in the Pharmaceutical Industry

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ENGINEERING PHARMACEUTICAL INNOVATION

ISPE

This article describes the credential development process utilized by the ISPE-PCC and the results obtained from the CPIP™ international practice analysis.

Developing and Implementing a Certification Program to Drive Change in the Pharmaceutical Industry

by Jerry Roth, PE, Dr. Russ Somma, Dr. Sandra Greenberg, and Alexander P. Demos

Purpose and Context

The global pharmaceutical industry is facing needed change to improve drug product safety, quality, and consumer cost effectiveness while providing new drug therapies to the market more quickly and in a streamlined manner. Government regulators support this movement and encourage new science- and risk-based innovative approaches for drug product development, manufacturing, and distribution. This was emphasized by Janet Woodcock, MD, Deputy Commissioner for Operations, U.S. Food and Drug Administration (FDA), during her keynote address at the International Society for Pharmaceutical Engineering (ISPE) Annual Meeting (November 7, 2005).

To facilitate change in the industry, the ISPE, a not-for-profit, membership-based organization with a global membership of 23,000, has worked with government regulators, academia, and pharmaceutical industry stakeholders. Initiatives include collaboration with the University of Florida and the North Carolina Community College System to develop curricula to train a biotechnology workforce, and co-sponsorship of good manufacturing practices (GMP) workshops in China with the USFDA and Peking University (see www.ispe.org for descriptions of these activities).

In 2004, ISPE formed the ISPE Professional Certification Commission (ISPE-PCC) to govern the development and administration of credentialing programs for pharmaceutical industry professionals. The ISPE-PCC maintains autonomy and administrative independence from the ISPE International Board of Directors regarding credentialing decisions and is composed of 14 Commissioners representing Asia, Oceania, Europe, and North America. The first group of Commissioners (serving terms of 1, 2, or 3 years), represents large and small global pharmaceutical organizations as well as academic and regulatory stakeholders. The Commissioners each have more than 25 years experience in the industry and collectively embody pharmaceutical industry and biotechnology practice, from drug product development through manufacturing.

The ISPE-PCC mission statement is twofold:

- To serve the global pharmaceutical and biotechnology industry by establishing competency standards for professionals involved in drug product development through manufacturing
- To elevate the status of industry professionals, provide employers with competent workers, facilitate development and manufacturing innovation, and enhance drug product quality

Recognizing the eminent challenges associated with industry innovation, the ISPE-PCC set out to develop and implement a pharmaceutical industry credential, the Certified Pharmaceutical Industry Professional™ (CPIP™), for professionals who demonstrate the competencies and knowledge required to become the "change agents" needed to realize the vision of the industry's leaders assembled within the ISPE-PCC.

The purpose of this article is to describe the identification and validation of those competencies and the underlying knowledge base.

Development of a Description of the Pharmaceutical Professional

The ISPE-PCC was charged with developing and validating a contemporary description of a pharmaceutical industry professional that was consistent with the mission of the ISPE-PCC and its goal of developing a certification program that would positively impact the profession.

Background Work of the ISPE-PCC

The initial task of the ISPE-PCC was to operationalize the vision of the CPIP™; that is, to create a narrative description of what these professionals can do and know in terms of both depth and breadth of subject-matter expertise.

To facilitate the development of the narrative description, the Commissioners participated in a critical-incidents analysis process whereby they interviewed 11 managers and technology experts from the industry to understand how these professionals went about solving a realistic problem. In analyzing their responses, the Commissioners identified as many as 17 knowledge and 7 skill sets. They described a professional capable of:

- Identifying and analyzing problems, including problems that were both internal and external to the experts' areas of immediate responsibility and/or expertise;
- Pinpointing causes;
- Generating and evaluating alternate solutions;
- Demonstrating techniques for resolving problems, including the conduct of risk analyses; and
- Communicating across various disciplines within the organization.

Moreover, the narrative description included a competency component that highlighted a fully engaged individual—one with a "get it done" attitude, able to take action and work across many disciplines in order to resolve situations.

The narrative description articulated by the Commissioners provided the framework for the next effort, which was to codify the competencies of the pharmaceutical industry professional, including all of the key knowledge and skill elements that would be expected to be in the CPIP™-credential holder's toolbox.

Refining the Vision

In August 2005, the ISPE-PCC contracted with Professional Examination Service (PES) to enhance and validate the narrative description of practice that had been developed by the members of the ISPE-PCC. The conduct of the study to develop and validate the practice description complied with current testing and measurement requirements for the validation of certification and licensure examinations. The overall process is described in the 1999 revision of the *Standards for Educational and Psychological Testing* (AERA/NCME/APA) and the *Guidelines for the Development, Use, and Evaluation of Credentialing Programs* (PES, 1995). The work products of the study were consistent with the requirements set forth in ISO/IEC 17024, *Conformity assessment—General requirements for bodies operating certification of persons* (ISO, 2003). The documents emphasize the concept of content validity and the need to conduct an analysis of practice to ensure that what is assessed is required for competent performance and serves a public protection function. Practice analysis becomes an important basis by which a professional association or credentialing agency such as the ISPE-PCC establishes, maintains, and defends the validity of its credentialing program requirements, in general, and its assessment program, specifically.

Using the preliminary results obtained by the members of ISPE-PCC, the Commissioners developed a revised description of professional practice at a 2-day meeting of the ISPE-

Competency	Components	
Technical Competency	**Elements and # of Knowledge Statements**	**#**
Technical Knowledge	1. Product development	13
	2. Facilities and equipment	17
	3. Information systems	3
	4. Supply chain management	10
	5. Production systems	14
	6. Regulatory compliance (includes drugs, environmental, health and safety)	7
	7. Quality systems	7
Non-Technical Competency	**Category Sets (Exemplars) and # of Behavioral Descriptors**	**#**
Leadership and Professionalism	1. Leadership	7
	2. Decision making	5
	3. Communications and interpersonal behaviors	4
	4. Professional development	2
	5. Professional conduct	1
Integration/Innovation/Change Advocacy	1. Innovation and problem solving	5
	2. Cross-functional integration	5
	3. Risk-based, cost-effective approaches	3
Quality and Continuous Improvement Focus	1. Continuous improvement mindset	5
	2. Quality by design	3

Exhibit 1. Framework and Components.

Competency 1 — *Technical Knowledge*

Knowledge Element 1 — *Product Development*

Formulation, Clinical Phases, and Manufacture
1. Knowledge of functions and pathways involved in product development
2. Knowledge of the purpose and conduct of clinical trials Phases I, II, and III
3. Knowledge of the impact of decisions (for example, dosage forms, batch size, production method, outsourcing) during drug development on product lifecycle viability and success
4. Knowledge of the production process and the role of interactions of ingredients/materials employed in pharmaceutical development and manufacturing
5. Knowledge of the impact of the processing, storage, and transport environments on ingredients/materials and semi- and finished goods
6. Knowledge of the impact of methods of measurement and control on product and process quality and stability
7. Knowledge that the physical and chemical attributes of the product have implications in production

Technology Transfer
8. Knowledge of the critical activities and success factors required for an effective and efficient technology transfer
9. Knowledge of requirements for planning, execution, and assimilation of technology and knowledge transfer

Production Scale-Up and Optimization
10. Knowledge of the options to increase and/or optimize production
11. Knowledge of the critical factors (for example, rate change, mechanistic properties, equipment design) of scale-up and their impact on manufacturability
12. Knowledge of the impact of factors that can positively or negatively affect scale-up
13. Knowledge of modeling techniques for optimization of product cycle time

Knowledge Element — *Facilities and Equipment*

Design and Construction/Installation
1. Knowledge of requirements for product protection and containment
2. Knowledge of requirements for personnel and environmental safety and protection
3. Knowledge of the importance of personnel flow and materials flow and their implications for layout
4. Knowledge of the materials and methods of construction of equipment and facilities, particularly from the perspective of cleanliness, functionality, and maintainability
5. Knowledge of critical process equipment and utility systems' attributes (performance, functionality, construction, instrumentation) and their impact on personnel and product
6. Knowledge of cleaning systems including CIP/SIP
7. Knowledge of the fundamentals of good engineering practice

Commissioning and Qualification as a Risk Management Strategy
8. Knowledge of factors that can impact the commissioning and qualification process
9. Knowledge of requirements for executing and documenting the commissioning and qualification
10. Knowledge of concepts, sequencing, and documentation of commissioning and qualification activities required by design intent
11. Knowledge of critical systems impact assessment and implications for the product

Operation and Maintenance
12. Knowledge of equipment and facility reliability and predictability models to establish a maintenance and calibration program
13. Knowledge of equipment operability and maintenance (location and access, type, and frequency of maintenance)
14. Knowledge of linkage of product and process development to operation and maintenance of process equipment and facilities
15. Knowledge of continuous operations improvement

Controls and Automation
16. Knowledge of building management systems
17. Knowledge of types of process automation and associated controls

Knowledge Element 3 — *Information Systems*

1. Knowledge of data management systems with product and financial impact (for example, manufacturing execution systems [MES], laboratory information management systems [LIMS], electronic document management systems [EDMS], and enterprise resource planning [ERP] or manufacturing resource planning/material requirement planning [MRP])
2. Knowledge of the basic computer system life cycle model and the activities and software quality assurance practices in each phase
3. Knowledge of data integrity and security measures, such as back-up, archiving, and retention requirements

Knowledge Element 4 — *Supply Chain Management*

Materials Management
1. Knowledge of the key components of the supply chain
2. Knowledge of supply chain and inventory models (for example, Kanban, JIT, APICS)
3. Knowledge of supply chain constraints that impact material and product throughput and their mitigation strategies
4. Knowledge of contributors to market projections and supply chain strategy for product

Operational Economics
5. Knowledge of the controls required for purchasing, receipt, storage, and dispensing of raw materials, and packaging materials and their related impacts on costs
6. Knowledge of industrial engineering standards and application to capital investments, facility and equipment utilization, and operational efficiencies

Warehouse and Distribution Management
7. Knowledge of warehouse and distribution management systems
8. Knowledge of transportation and logistic systems
9. Knowledge of environmental storage and transportation controls for hazardous and non-hazardous materials
10. Knowledge of distribution chain security and product disposition controls

Knowledge Element 5 — *Production Systems*

Production Unit Operations – Drug (small molecule) and Biologics
1. Knowledge of manufacture of active pharmaceutical ingredients, components, and excipients
2. Knowledge of unit operations
3. Knowledge of labeling and packaging operations
4. Knowledge of critical process equipment and utility systems' attributes (performance, functionality, construction, instrumentation) and their impact on personnel and product
5. Knowledge of the controls required for receipt, storage, and dispensing of raw materials, and packaging materials
6. Knowledge of industrial engineering standards, facility and equipment utilization, and operational efficiencies

Production Management
7. Knowledge of production management
8. Knowledge of storage requirements, production logistics, and RFID
9. Knowledge of environmental conditions, security, and status requirements

Production Control
10. Knowledge of batch records
11. Knowledge of contamination controls (for example, cleaning, segregation, HVAC) and changeover
12. Knowledge of critical factors that impact quality and how to control
13. Knowledge of methods and tools for data manipulation and analysis
14. Knowledge of critical quality attributes and process controls

Knowledge Element 6 — *Regulatory Compliance (includes drugs, environmental, health and safety)*

Government Regulations
1. Knowledge of the role of regulatory bodies worldwide and their structure and operations
2. Knowledge of the role of legislation, regulations, guidance, and MRAs worldwide (for example, types of regulatory filings, GMPs)
3. Knowledge of the use of global compendia
4. Knowledge of the common base in requirements of regulating bodies around the world and awareness that differences exist

Standards, Practices, and Guides
5. Knowledge of the role of industry-generated guidance relating to international harmonization (ICH guidance documents; ISPE Baseline Guides, GAMP, and Good Practice Guides; and the PDA technical reports)
6. Knowledge of the role of common environment, health, and safety standards
7. Knowledge of the role of consensus standards (ISO, ANSI, ASTM)

Knowledge Element 7 — *Quality Systems*

Risk Management and Quality Management System (QMS)
1. Knowledge of purpose, elements and implementation of a QMS
2. Knowledge of risk management strategies
3. Knowledge of purpose, elements and implementation of change control programs
4. Knowledge of purpose, elements and implementation of CAPA programs
5. Knowledge of the elements of an internal assessment program

Systems Validation
6. Knowledge of purpose, elements and implementation of product, process, facility, equipment, computer system, analytical method, and contamination control programs
7. Knowledge of impact of emerging process development and control strategies on traditional validation practices

Exhibit 2. *Technical Knowledge*, including 7 Knowledge Elements, and 71 Knowledge Statements.

PCC, facilitated by PES, in September 2005. Their goal was to codify the attributes of the professional as well as the breadth and depth of the essential knowledge base, and to inform the process by which all key aspects of the CPIP™ program were to be developed and implemented.

After detailed discussions, the Commissioners crafted an organizing framework for the practice description, including one technical competency and three non-technical competencies. The technical competency was structured into knowledge elements and knowledge statements, and the three non-technical competencies were structured into sets of competencies (exemplars) and behavioral descriptors. Key questions guided the development of the practice description:

- Does the practice description include a comprehensive list of the knowledge required and the skills demonstrated by pharmaceutical industry professionals?
- Is each aspect of the description clear and concise?, and
- Does the practice description address in all key aspects the narrative description developed by the Commissioners?

During the meeting, the Commissioners identified potential gaps in the representation of subject-matter experts (SMEs) contributing to the development of the practice description and identified specific *categories* of individuals to fill the gaps; for example, representatives from Europe and Japan, and experts in supply chain management and information database management. Subsequently, the Commissioners nominated more than 60 additional SMEs to contribute to the refinement of the practice description, including experienced industry professionals representing all areas of expertise from drug product development through manufacturing, as well as academics, regulators, and other key stakeholders representing the global pharmaceutical industry.

Following the September 2005 meeting of the ISPE-PCC, PES implemented two complementary data-collection initiatives to augment the practice description: an independent review of the description and critical-incident interviews to verify the comprehensiveness of the description. Twelve SMEs participated in the independent review, and 18 SMEs participated in the critical-incident interviews. Feedback from the SMEs participating in the independent review and the critical-incident interviews was summarized by PES and the results were used by the Commissioners at a follow-up meeting in November 2005, at which time a final description of professional practice was drafted. Exhibit 1 contains an outline of the framework for the description of practice, including all key components.

Exhibit 2 includes a list of the 71 technical knowledge statements related to the technical competency—*Technical knowledge*, and Exhibit 3 includes a list of the 40 behavioral descriptors related to the three non technical competencies—*Leadership and professionalism, Integration / Innovation / Change Advocacy*, and *Quality and Continuous Improvement Focus.*

Competency 2 — *Leadership and Professionalism*

Leadership
1. Leads by example, delegates appropriately, and commits self and team to achievement of goals
2. Creates an environment that motivates and enables innovation and high performance
3. Recognizes knowledge gaps and facilitates their resolution
4. Encourages others to evaluate their work and consider alternatives to the status quo
5. Encourages open feedback on own performance
6. Values cultural differences and uses effective dynamics and motivation within the business context
7. Conceptualizes and thinks strategically

Decision Making
8. Defines authority, responsibility, and accountability for decision making
9. Facilitates broad and innovative thinking and fosters an environment for debate while participating in interdisciplinary teams
10. Demonstrates meeting management skills
11. Facilitates effective decision making
12. Assumes accountability for performance of the team members and decision making

Communications and Interpersonal Behaviors
13. Communicates clear, concise, accurate information in timely way
14. Uses critical analysis tools to ask the right questions
15. Adapts reports and presentations to intended audience
16. Demonstrates respect for people, diversity of thought and ideas

Professional Development
17. Stays current with industry and regulatory trends and applies this learning to the benefit of customers and the organization
18. Shares knowledge through mentoring and coaching of others

Professional Conduct
19. Adheres to industry, ethical, and professional standards

Competency 3 — *Integration/Innovation/Change Advocacy*

Innovation and Problem Solving
1. Defines and formulates problems within a clear purpose, frame of reference and scope
2. Collects, selects, verifies, and evaluates information relevant to the defined problem
3. Chooses the appropriate statistical and management tools to analyze data patterns, relationships, and trends
4. Considers alternative solutions and stimulates innovation
5. Identifies and uses techniques from other industries that are applicable to pharmaceutical industry

Cross-Functional Integration
6. Ensures potential changes take into account all possible upstream and/or downstream effects, both short and long term
7. Draws on knowledge, tools, and resources from within and outside the industry for possible solutions
8. Benchmarks best practices across industry
9 Identifies key steps, milestones, critical systems, and organizational relationships; and uses project management skills that are needed for success
10. Builds support with stakeholders and team members

Risk-Based, Cost-Effective Approaches
11. Identifies, recommends and evaluates enhancements, including policy, program and process changes to effect efficiency and significant cost containment or savings
12. Recognizes issues that could impact the business and sets priorities for action
13. Utilizes risk-based management for products and processes

Competency 4 — *Quality and Continuous Improvement Focus*

Continuous Improvement Mindset
1. Acts as a change agent
2. Anticipates where problems are likely to arise and takes preventative action
3. Conducts reviews of existing systems, processes and controls within the organization to identify and drive opportunities for continuous improvement
4. Applies knowledge of regulatory requirements and industry best practices to develop pragmatic interpretations and approaches based on science and sound analysis
5. Strives for harmonization to enable more efficient global operations

Quality by Design
6. Understands systems, products, and processes at a mechanistic level and designs quality from the outset
7. Promotes a quality mindset as opposed to one of compliance
8. Incorporates risk-based prioritization when involved with quality initiatives

Exhibit 3. *Leadership and Professionalism*, *Integration/Innovation/ Change Advocacy*, and *Quality and Continuous Improvement Focus*, including 10 Competency Sets, and 40 Behavioral Descriptors.

Description of Practice	Version 1	Version 2	Version 3
***Technical Competency – Technical Knowledge*: 65 knowledge statements**			
Frequency Ratings	✓		
Importance Ratings		✓	
Proficiency level Ratings			✓
Open-ended questions about Knowledge statements	✓	✓	✓
***Technical Knowledge*: 7 Elements**			
% of Time	✓	✓	✓
Importance	✓	✓	✓
***Non-Technical Competencies – Leadership and Professionalism, Integration/Innovation/Change Advocacy,* and *Quality and Continuous Improvement Focus*: 40 behavioral descriptors**			
Frequency Ratings	✓		
Importance Ratings		✓	
Essential Ratings			✓
***Non-Technical Competencies – Leadership and Professionalism, Integration/Innovation/Change Advocacy,* and *Quality and Continuous Improvement Focus*: 10 competencies sets**			
Acquisition Ratings	✓	✓	✓
Verification Ratings	✓	✓	✓
Demographic and Professional Questions	✓	✓	✓
Open-ended Questions			
The value of the development of the ISPE-PCC credential	✓	✓	✓
Knowledge and skills recently acquired	✓	✓	✓
Changes to occur over the next three years	✓	✓	✓

Exhibit 4. Content of ISPE PCC Practice Analysis Survey Versions.

Validation of the Practice Description

In order to validate the description of professional practice developed by the ISPE-PCC, a large-scale survey was conducted. First, a draft survey was developed by PES and reviewed and revised by the Commissioners. Second, the survey was piloted tested by 11 SMEs nominated by the ISPE-PCC. Results of the pilot test were used to clarify the instructions, revise the rating scales, and augment the description of professional practice. Then, ISPE-PCC staff and a subset of Commissioners reviewed and finalized the survey instrument.

The survey included multiple sections that facilitated quantitative and qualitative data collection. Respondents rated:

- the frequency, importance, and proficiency level of each knowledge statement;
- the importance and percent of time spent in association with each knowledge element;
- the frequency, importance, and essentiality of each behavioral descriptor; and
- the verification and acquisition of each competency set (exemplar).

Respondents were also given the opportunity to provide open-ended comments regarding the comprehensiveness of the description of professional practice, and to respond to questions about the value of the proposed certification initiative.

To reduce the time required to complete the survey, three versions of the survey were created—each containing all of the components of the practice description but a subset of the rating scales applied to two of the four components. Exhibit 4 contains an outline for the contents of each version of the survey, and Exhibit 5 contains a description of the rating scales used.

Results Related To the Validation Survey

The validation survey was emailed to a sample of 1200 pharmaceutical industry professionals selected from a list of over 4500 professionals with 5 to 15 years of pharmaceutical-industry experience included in the ISPE database. A two-stage sampling plan was implemented so as to ensure (a) the representation of SMEs from Asia/Pacific Islands, Europe, and North America, and (b) participants with expertise in each of the seven knowledge elements.

Each member of the sample received an email invitation from the ISPE-PCC in early January 2006, including a cover

Section 1	65 Technical Knowledge Statements
Frequency	How frequently do you use this knowledge? *1 = Never, 2 = Rarely, 3 = Occasionally, 4 = Frequently,* or *5 = Very frequently*
Importance	How important is this knowledge in producing a quality product? *1 = Not important, 2 = Minimally important, 3 = Moderately important, or 4 = Highly important*
Proficiency Level	Which proficiency level best represents your usage of this knowledge? *Not used in practice, General awareness and background, Comprehension,* or *Mastery*
Section 2	**7 Technical Knowledge Elements**
% of Time	Overall, what percentage of your work time required this knowledge?
Importance	How important is this knowledge to individuals functioning at the level of a newly ISPE-PCC credentialed professional? *1 = Not important, 2 = Minimally important, 3 = Moderately important, or 4 = Highly important*
Section 3	**40 Behavioral Descriptors related to Competencies**
Frequency	How frequently do you demonstrate this competency? *1 = Never, 2 = Rarely, 3 = Occasionally, 4 = Frequently,* or *5 = Very frequently*
Importance	How important is this competency in producing a quality product? *1 = Not important, 2 = Minimally important, 3 = Moderately important, or 4 = Highly important*
Essential	Is it essential that a newly ISPE-PCC credentialed professional demonstrate this competency? *Yes (Essential)* or *No (Not essential)*
Section 4	**10 Competencies Sets (Exemplars)**
Acquisition	At what point should the competencies in this set be acquired? *Never (The competencies in this set are not necessary)* *Primarily before ISPE-PCC certification* or *Primarily after ISPE-PCC certification*
Verification	In your professional judgment, how should this set of competencies be validated? Experience: *Verified through a practical experience questionnaire* Education: *Verified through education-related performance* Exam: *Verified through formal assessment*

Exhibit 5. Survey Rating Scales.

note describing the credentialing mission of the ISPE-PCC, and signed by the ISPE Director of Professional Certification. The email included a unique URL, linked to the web-based survey. Special features of the survey ensured that respondents could start and stop the survey, as necessary, and that they were randomly routed through one of the three versions. As an incentive, participants completing the survey were offered the chance to participate in a drawing for one of seven prizes. Two reminder emails were sent to each participant not previously completing the survey approximately 5 business days after the invitation email and the subsequent reminder.

In mid-February 2006, the ISPE-PCC met for 2 days to review the results of the validation survey and develop recommendations related to the development and implementation of a certification program for pharmaceutical professionals, if warranted by the results of the survey.

Demographic and Professional Characteristics of the Respondents

The overall response rate for the survey was 17%—relatively high given that a certification program did not exist at the time of the survey and the potential participants in the sample may not have been aware of the ISPE-PCC's intentions regarding the development of a certification program.

Consistent with the sampling plan, 56% of the respondents worked in North or South America, 35% in Europe or Africa, and 10% in Asia/Pacific Islands. About two thirds of the respondents indicated that they had worked in the industry from 6 to 15 years—reflecting the experience level of the target audience for the certification. About 80% of the respondents had earned either a Bachelor's degree or a Master's degree, while 10% had earned a doctorate.

Slightly more than one half of the respondents worked in organizations with fewer than 500 employees. Respondents were most likely to describe themselves as working in validation (24%) or engineering and technical support (20%), and less likely to indicate that they worked in project management (16%) or regulatory/compliance/QA (11%). Two thirds of the sample described themselves as working in traditional pharmaceuticals, biopharmaceuticals/biotechnology, or consulting. When asked to indicate their primary area of expertise, the responses of the survey respondents were virtually identical to the profiles of the nearly 30,000 individuals in the ISPE database.

The respondents to the survey were more likely to spend significant amounts of time (64%) in pharmaceutical product manufacturing and less time in pharmaceutical product development (17%). A closer inspection of the time estimates revealed that 25% of the respondents spent no time in product development, whereas only 6% of the respondents spent no time in product manufacturing.

Respondents indicated that they had expertise in one or more of the seven technical knowledge elements identified in connection with the *Technical Knowledge* competency area—providing some indication that these elements might provide a useful mechanism for describing professional practice.

	n	%
Product Development	24	18%
Facilities and Equipment	98	73%
Information Systems	25	19%
Supply Chain Management	7	5%
Production Systems	62	46%
Regulatory Compliance (includes drugs, environmental, health and safety)	49	36%
Quality Systems	58	43%
Other	7	5%

Table A. Knowledge Elements Expertise.

Table A indicates the percentage of respondents indicating expertise in each of the seven technical knowledge elements.

Finally, the ISPE-PCC reviewed the demographic and professional analyses of the respondents and confirmed that these individuals were similar to the membership of the ISPE and to other pharmaceutical professionals in regard to every key demographic and professional variable.

Quantitative and Qualitative Results Related to Competencies

Quantitative and qualitative analyses were performed on the sections of the survey related to the *Technical Knowledge* competency and the three non-technical competencies (*Leadership and Professionalism*, *Integration / Innovation / Change Advocacy*, and *Quality and Continuous Improvement Focus*) using the survey ratings of the total sample of respondents—regardless of the survey version to which they had responded.

Results Related to Technical Knowledge Competency—Knowledge Elements and Knowledge Statements

For each of the seven Technical Knowledge elements, the mean, range, and standard deviation were reported for the *% of Time* and *Importance* scales. The knowledge element results are presented in Table B, which also includes the definition of each element. The percentage of time ratings show that, on average, respondents spent about 25% of their time calling upon knowledge related to Facilities and equipment. They spent somewhat less time calling upon knowledge related to Production systems, Quality systems, and Regulatory compliance (includes drugs, environmental, health and safety), and even less time with regard to the remaining three knowledge elements, Information systems, Product development, and Supply chain management.

The knowledge elements related to Facilities and equipment, Production systems, Regulatory compliance, and Quality systems received an average rating indicating that the knowledge associated with these elements was at least moderately-to-highly important to individuals functioning at the level of a newly credentialed professional. The remaining four knowledge elements received an average importance rating indicating that the related knowledge was at least minimally-to-moderately important.

For each of the 65 knowledge statements, the mean and standard deviation of the respondents' ratings were reported for the *Importance* and *Frequency* rating scales, along with

	% of Time	Importance
1. **Product Development:** Through the interactions of multi-disciplinary functions and the scientific application of experimental design methodologies, implement a process to reproducibly and economically manufacture a product of (a) the desired formulation, dosage form, and specifications that meets predicted quality; (b) is optimized for purity, potency, and efficacy; and (c) facilitates continuous improvement.	8.9% *0 – 100* (14.8)	2.8 *1 – 4* (.8)
2. **Facilities and Equipment:** Knowledge required to ensure (a) that the critical physical and chemical requirements of drug products are properly understood and managed; and (b) that the selection of process equipment and the design of facilities and support utility systems will consistently deliver those requirements and all other aspects of the product specification (including quantity and timely delivery).	24.8% *0 – 90* (19.7)	3.5 *1 – 4* (.7)
3. **Information Systems:** Knowledge of (a) the types of information and data management systems that are integral to successful drug development, manufacturing, and distribution; and (b) the controls and methods necessary to maintain data integrity and security.	9.3% *0 – 60* (10.2)	2.8 *1 – 4* (.7)
4. **Supply Chain Management:** Knowledge of (a) the key components of the supply and distribution chains and their financial impact; (b) the systems required for dynamically controlling and automating receipt, storage and dispensing of raw materials, and packaging materials; and (c) storage and distribution of finished products, so that the integrity of the product is not impaired by any of these processes.	5.5% *0 – 100* (10.2)	2.5 *1 – 4* (.7)
5. **Production Systems:** Knowledge of (a) the full range and scope of unit operations and production steps for manufacturing APIs and both small molecule and biologic pharmaceuticals; (b) the building and critical process utility systems that support the manufacturing process; and (c) the means of managing and dynamically controlling and automating manufacturing and warehousing operations.	18.7% *0 – 80* (16.0)	3.4 *1 – 4* (.7)
6. **Regulatory Compliance (includes drugs, environmental, health and safety):** A fundamental understanding of (a) international regulations and guidance issued by regulatory bodies and coalitions which shape the world's current pharmaceutical-related requirements and future directions, and (b) the application of regulations and industry-generated guidance for global harmonization of compliance and product registration.	15.8% *0 – 75* (12.4)	3.4 *1 – 4* (.7)
7. **Quality Systems:** Knowledge of the role and elements of a quality management system and its impact within the overall risk management approach, as well as its implementation in a scientific and pragmatic manner.	16.9% *0 – 70* (13.7)	3.4 *1 – 4* (.7)

Table B. Mean, Range, and (Standard Deviation) of % of Time and Importance.

the percentage of respondents indicating each scale point on the *Proficiency* scale. With few exceptions, the average rating of each knowledge statement indicated that the knowledge was moderately-to-highly important to producing a quality product. The average frequency that knowledge was used was more varied. In general, knowledge related to Facilities and equipment, Information systems, Production systems, Regulatory compliance, and Quality systems was called upon more frequently than knowledge associated with Product development and Supply chain management. The knowledge statements with the highest frequency ratings were in the areas of Regulatory compliance and Quality systems and received among the highest importance ratings.

The percentage of respondents indicating each scale point on the *Proficiency* scale indicated that each of the knowledge statements delineated in connection with five of the seven knowledge elements was used at some level by more than 80% of the respondents. Only in the areas of Product development and Supply chain management did as many as 24% and 49% of the respondents, respectively, indicate that the related knowledge was not used in professional practice. Respondents indicated that knowledge related to Product development, Regulatory compliance, and Quality systems was most frequently used at the Comprehension level; and knowledge related to Facilities and equipment was most frequently used at the Comprehension and Mastery levels.

Respondents were provided the opportunity to identify additional knowledge that may have been omitted from the description of practice. A review of all the qualitative comments of the respondents indicated that the delineation of 65 knowledge statements associated with the *Technical Knowledge* competency was comprehensive.

Results Related to Leadership and Professionalism, Integration/Innovation/Change Advocacy, and Quality and Continuous Improvement Focus Competencies—Competency Sets (Exemplars) and Behavioral Descriptors

For each of the 10 competency sets, the mean and standard deviation of the respondents' ratings were reported for the *Acquisition* and *Verification* rating scales. As seen in Table C, a majority of the respondents indicated that 9 of the 10 sets of competencies be acquired primarily *before* certification. In the case of one competency set, Cross functional integration, associated with the *Integration / Innovation / Change Advocacy* competency, the respondents were about as likely to indicate that this set be acquired primarily *before* and primarily *after* certification. The verification ratings of the respondents indicated that they supported the verification of the non-technical competencies through multiple methods, including experience, education, and examination. In general, respondents were most likely to support the verification of the sets of competencies related to *Leadership and Professionalism* through experience requirements, and the sets of competencies related to both *Integration / Innovation / Change Advocacy* and *Quality and Continuous Improvement Focus* through experience and education requirements. Thirty percent or more of the respondents indicated that three sets of competencies could be verified through examination requirements.

For each of the 40 behavioral descriptors, the mean and standard deviation of the respondents' ratings were reported for the *Frequency* and *Importance* rating scales, along with the percent of respondents indicating each scale point on the *Essential* scale. The average frequency rating indicated that 39 of 40 behavioral descriptors were demonstrated at least

occasionally. Behavioral descriptors associated with *Leadership and Professionalism* were most likely to be demonstrated frequently-to-very frequently, and behavioral descriptors associated with *Quality and Continuous Improvement Focus* were most likely to be demonstrated occasionally-to-frequently.

Without exception, the average importance rating for each behavioral descriptor indicated that it was moderately-to-highly important to producing a quality product. In general, two thirds or more of the respondents indicated that each behavioral descriptor should be demonstrated by newly credentialed professionals.

Results Related to Open-Ended Questions—The Value of Certification, Recently Acquired Knowledge or Skills, and Changes in the Profession

Respondents identified the possible benefits of certification. For the profession as a whole, they indicated that the implementation of a credential would establish and clarify a uniform standard for the profession, drive innovation, contribute to the development of "best practices," and lead to an internationally recognized benchmark for pharmaceutical professionals. On an individual level, they indicated that the credential would facilitate hiring, recruiting, and job mobility, while providing a useful tool for understanding one's own knowledge base.

Members of the ISPE-PCC reviewed the open-ended comments made by the respondents regarding recently acquired knowledge or skills. Respondents were most likely to have participated in learning related to regulatory standards; technical and information systems; risk analysis and risk management; project management, leadership, and quality management; key performance indicators, process improvement, and process control; safety; facilities; non-pharmaceutical manufacturing processes; business knowledge, finance, and business strategy; and problem solving.

Members of the ISPE-PCC also reviewed the respondents' comments regarding industry changes they perceived would occur in the next three years.

- Respondents were most likely to describe the increased focus on global regulatory health authorities' (RHAs) requirements and process analytical technology (PAT) concepts;
- Respondents were also likely to indicate an increased focus on: accountability for capital effectiveness; increased process-improvement, lean manufacturing, Six-Sigma, continuous improvement; automation; and validation requirements.
- Respondents indicated that the industry will face downsizing and cost cutting at the same time as it contends with the drive for enhanced production to move the industry forward.

Results Related to Hypothetical Specifications for the Assessment of the Technical Knowledge Competency

Assessment specifications are outlines or blueprints that are used to construct certification examinations. In February, 2006, at a 2-day meeting of the ISPE-PCC, the Commissioners reviewed all of the quantitative and qualitative results of the validation survey and a set of hypothetical assessment specifications. The hypothetical assessment specifications were derived by weighting equally the percentage of time and the importance ratings of the respondents on the seven knowledge elements associated with the *Technical Knowledge* competency.

Based on extensive discussions of the survey results, final assessment specifications were developed for the proposed certification program. In proposing recommendations for adjusting the hypothetical assessment specifications, the Commissioners considered the following:

Non-Technical Competencies and Competency Sets (Exemplars)	Acquisition			Verification		
	Never	Primarily *before* ISPE PCC certification	Primarily *after* ISPE PCC certification	Experience	Education	Examination
	%	%	%	%	%	%
Leadership and Professionalism						
Leadership	8%	58%	34%	92%	34%	6%
Decision making	4%	73%	23%	84%	37%	18%
Communications and interpersonal behaviors	5%	76%	20%	79%	47%	12%
Professional development	2%	60%	39%	63%	68%	30%
Professional conduct	2%	79%	18%	79%	33%	17%
Integration/Innovation/Change Advocacy						
Innovation and problem solving	2%	68%	30%	68%	50%	24%
Cross-functional integration	5%	48%	47%	73%	41%	15%
Risk-based, cost-effective approaches	3%	60%	37%	52%	59%	39%
Quality and Continuous Improvement Focus						
Continuous improvement mindset	3%	63%	34%	75%	47%	22%
Quality by design	1%	74%	25%	54%	60%	36%

Table C. Acquisition and Verification Ratings for Competency Sets (Exemplars).

- the potential overlap between knowledge elements (for example, Product development, Facilities and Equipment, and Production systems; Regulatory compliance and Quality assurance);
- the impact of the under-representation of respondents engaged in product development;
- the impact of the over-representation of respondents engaged in activities related to facilities and equipment;
- the open-ended comments of the respondents in regard to upcoming changes in practice; and
- the mission statement of the ISPE-PCC regarding fostering industry innovation and quality improvement.

ISPE-PCC Decisions Regarding the Implementation of the Certification Program

After much discussion, the Commissioners determined that the sample of survey respondents represented a robust cross-section of professionals in the pharmaceutical industry, and that their quantitative ratings and qualitative comments were consistent with how industry professionals currently function. The Commissioners discussed the differences between the empirical ratings and ISPE-PCC's vision of professional practice.

Then, the Commissioners identified both initial and ongoing requirements for the CPIP™ program candidates that were consistent with the vision of the ISPE-PCC. These requirements were crafted so as to align with the results of the validation survey and acknowledge the key role that both technical and non-technical competencies play in competent professional practice. Based on the practice analysis data collected and psychometrically analyzed, and tempered by the vision of the pharmaceutical industry professional needed to drive change in the profession, the ISPE-PCC established eligibility criteria and the form of assessment required for the CPIP™ credential.

Education

Based on all of the quantitative and qualitative ratings, the results of the validation survey strongly supported a focus on a scientifically-educated person. Accordingly, the Commissioners determined that all candidates for certification, regardless of geographical location, must demonstrate that they had earned at least a Bachelor's degree or globally equivalent university degree from an educational institution accredited by a generally recognized accrediting body (e.g., ABET, SACS, UK Science and Engineering Research Council).

Technical Knowledge	% of Assessment
1. Product Development	14%
2. Facilities and Equipment	20%
3. Information Systems	8%
4. Supply Chain Management	8%
5. Production Systems	21%
6. Regulatory Compliance (includes drugs, environmental, health and safety)	13%
7. Quality Systems	16%
	100%

Table D. Assessment Specifications for Technical Knowledge.

Experience

Based on all of the quantitative and qualitative ratings, the results of the validation survey strongly supported a focus on technical as well as non-technical competencies. Accordingly, the Commissioners determined that candidates for the certification must document specific experiences that illustrate competency in each of the four major competency areas, in general, and a subset of competencies related to *each* major competency area, in particular.

- *Technical Knowledge*—via formal assessment;
- *Leadership and Professionalism*—experience in any 2 of the 4 competency sets: Leadership, Decision making, Communications and interpersonal behaviors, Professional development;
- *Integration / Innovation / Change Advocacy*— experience in any 2 of the 3 competency sets: Innovation and problem solving, Cross-functional integration, Risk-based, cost-effective approaches;
- *Quality and Continuous Improvement Focus*—experience in any 1 of 2 competency sets: Continuous improvement mindset, Quality by design.

In addition, the Commissioners determined that candidates with educational backgrounds in science, technology, engineering, or mathematics (STEM) must document 5 years of relevant pharmaceutical-related work experience, while candidates with non-STEM backgrounds must document 10 years of pharmaceutical-related work experience.

Examination

Based on all of the quantitative and qualitative ratings, the results of the validation survey strongly supported a focus on technical knowledge demonstrated in the context of both technical and non-technical situations. After being determined eligible by the ISPE-PCC, the CPIP™ candidate may register for the CPIP™ examination. The examination will cover the 7 knowledge elements associated with the *Technical Knowledge* competency. The CPIP™ credential will be awarded upon successfully passing the examination.

As shown in Table D, the final specifications for a written knowledge-based examination give greatest weight to two knowledge elements—Facilities and equipment (20%) and Production systems (21%); somewhat less weight to three knowledge elements—Quality systems (16%), Product development (14%), and Regulatory compliance (13%); and least weight to two knowledge elements—Information systems (8%) and Supply chain management (8%).

In considering the specific content of the written knowledge-based examination, the Commissioners determined that since all 71 knowledge statements had been validated, they

might all be used as the basis of item writing and examination construction initiatives. Accordingly, all written knowledge-based examinations developed in connection with the proposed certification program will be identical with regard to the testing emphasis associated with each knowledge element, and will draw upon the entire knowledge base.

Commissioners discussed recertification requirements related to education, experience, and examination, and determined that these requirements should be developed and implemented in a manner that focuses on assuring the continuing competency and currency of the technical knowledge of the CPIP™.

Conclusion

Innovation is the new industry buzz word. The pharmaceutical industry and the professionals employed in it must be proactive in pursuing innovative concepts to improve overall drug product development and manufacturing efficiency and quality. The ISPE-PCC believes that recognition of "change agents" and certification of those professionals will become a catalyst for innovation. As technology advances and the global regulatory environment moves towards harmonization, the ISPE-PCC must respond to these stimuli by creating professional certification programs for enhancing the professional practitioners' career and for the benefit of their employers. It will be key that the ISPE-PCC ensures the ongoing validity of its certification program requirements by examining academic, industry, and regulatory-environment drivers with an eye to the future. To that end, the ISPE-PCC will conduct an analysis of practice for the CPIP™ on a periodic cycle to keep pace with change.

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Ali Afnan, PhD
Process Analytical Technologist
FDA/CDER/OPS
Silver Spring, Maryland, USA

Mr. Wim Bolink
VP Chem and Pharmaceutical Development
Solvay Pharmaceuticals
Netherlands

Mr. Lou Capalbo
Director Investigational Supplies
Boehringer Ingelheim Pharmaceuticals, Inc.
Danbury, Connecticut, USA

Mr. James Durkin
Consultant
United Kingdom

Mr. Tomiyasu Hirachi
Representative Director, President
Shionogi Qualicaps, Co., Ltd.
Japan

Mr. James Hubbard
President
The Massbury Group Inc.
Gaithersburg, Maryland, USA

Peter Kilpatrick, PhD
Department Head of Chemical Engineering and Biomolecular Engineering, Director of the Biomanufacturing Training and Education Center
North Carolina State University (NMO)
Raleigh, North Carolina, USA

Mr. Larry Kranking
President/CEO
Lang Medikament, Inc.
Raleigh, North Carolina, USA

Ms. Barbara Mullendore
Director, Corporate Quality Systems
Watson Pharmaceuticals, Inc.
Corona, California, USA

Russ Somma, PhD (PCC Chairman)
President, SommaTech, LLC
Affiliate of IPS
Somerset, New Jersey, USA

Ms. Nancy St. Laurent
Senior Engineer – Sterile Fac/Pkg Systems
CH2M HILL Lockwood Greene
Omaha, Nebraska, USA

Ms. Melody Spradlin
Senior Manager
Genentech Inc
South San Francisco, California, USA

Mr. Ronald Stellon
VP Quality Assurance
AstraZeneca Pharmaceuticals
Wilmington, Delaware, USA

Mr. Steve Williams
Director
SeerPharma Pty. Ltd.
Melbourne, Victoria, Australia

About the Authors

Jerry Roth, PE is ISPE's Director of Professional Certification. He has 44 years of experience in the life sciences industry, and has been involved in developing strategic alliances with operating companies and equipment suppliers worldwide. Roth is a registered professional engineer and has an engineering degree from Purdue University. He served as chairman of the ISPE International Board of Directors and has been chairman of the Education Committee and a course leader and speaker for ISPE educational programs.

Dr. Russ Somma has been involved in production support, scale-up, pilot plant, as well as early and full development activities of pharmaceutical products, which include novel as well as traditional dosage forms during his 29 year tenure with Novartis. He has provided support for 21 NDAs in the chemistry, manufacturing and control area from submission through the pre-approval inspection phase. As president of SommaTech, an affiliate company of IPS, his focus is on pharmaceutical technology and helping clients achieve their FDA regulated product goals for a fast submission, seamless approval as well as assuring a cost effective product and a secure supply chain. He is the past chairman of ISPE's SUPAC Equipment Guidance Steering Committee. He currently chairs the ISPE-PCC. Somma earned his PhD in pharmaceutical technology under N.G. Lordi at Rutgers University College of Pharmacy in 1987. Prior to this, he earned his BS in pharmacy in 1974 and an MS in 1980 from Rutgers University.

SommaTech, LLC , 3 Executive Dr., Somerset, NJ 08873, E-mail: rsomma@sommatechconsulting.com.

Dr. Sandra Greenberg is Vice President for Research and Development at Professional Examination Service, a not-for-profit organization specializing in creating, implementing, and enhancing quality credentialing initiatives for clients across a broad range of occupations. She conducts feasibility studies and large-scale international practice analyses, develops practical examinations and outcomes-based assessments, and consults on a variety of credentialing related initiatives. She has recently co-authored a chapter on the use of computer-based testing for credentialing assessments. She received her PhD in special education from Yeshiva University in New York, and has been at PES since 1984. She can be reached by telephone at +1-212 367 4271 or via e-mail at sandy@proexam.org.

Professional Examination Service, 475 Riverside Dr., New York, NY 10115.

Alexander P. Demos earned his Bachelor's degree in psychology from New York University, and expects to complete a Master's degree in psychology at NYU in the summer of 2006. He is a Research Analyst at Professional Examination Service (PES), specializing in survey design and quantitative analysis. During his time at PES, Demos has worked on international practice analysis studies for diverse professions including information security management, pharmacy technicians, and human resource management. He may be reached at demos@proexam.org or +1-212-367-4207.

Professional Examination Service, Research and Development, 475 Riverside Dr., Suite 600, New York, NY, 10115.

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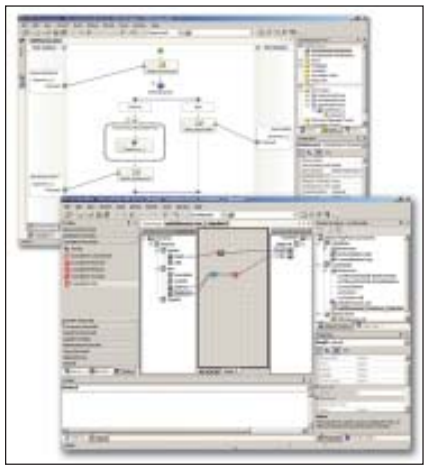
Connector



GE Fanuc Automation, Inc., a unit of GE Industrial, has announced the release of Proficy™ Enterprise Connector 1.5, which provides bi-directional enterprise integration between Proficy and Enterprise Resource Planning (ERP) systems, such as SAP. As an extension of GE Fanuc's Proficy Plant Applications integrated suite of Production Management Solutions, Enterprise Connector enables the mapping of the external Business Systems requests to/from the Proficy Information Architecture. The information from manufacturing facilities is now available to the business to make more rapid, informed, business decisions. The Proficy Enterprise Connector leverages the ISA-95 standard to define the interface between an enterprise's business and manufacturing systems through the XML-based B2MML (Business to Manufacturing Markup Language) schema.

GE Fanuc Information Center, P.O. Box 8106, Charlottesville, VA 22906, www.gefanuc.com.

Remote Airborne Particle Counters

Hach Ultra has announced the availability of Met One 4500 Series Remote Airborne Particle Counters, offering a minimum sensitivity of 0.3 or 0.5 microns and a flow rate of 2.83 LPM (0.1 CFM). Designed for electronics, life sciences and industrial environments, the 4500 works remotely to monitor cleanrooms, sample inert gases and verify mini-environments. Modbus and pulse communication protocols available for the 4500 make the instrument easy to integrate with an existing FMS. The 4500 Series may also be combined with Ultra Vision Online software to monitor a cleanroom from a single desktop console.

Hach Ultra Analytics, 481 California Ave., Grants Pass, OR 97526, www.hachultra.com.

System Suitability Standards for TOC Sensor

System suitability testing is a critical requirement in qualifying instruments used for Total Organic Carbon (TOC) measurements in pharmaceutical applications. The new System Suitability Standards Set from Mettler-Toledo Thornton provides the reference standard solutions necessary to perform testing for the 5000TOC Sensor in conformance with USP (643) and EP 2.2.44 for System Suitability Testing. The System Suitability Standards Set is packaged in 500 mL containers and includes one bottle of 500 ppb p-Benzoquinone, one bottle of 500 ppb Sucrose and two bottles of Reagent Water. Mettler-Toledo Thornton uses only USP Reference Standards, thereby assuring consistent quality and compliance.

Mettler-Toledo Thornton, 36 Middlesex Turnpike, Bedford, MA 01730, www.thorntoninc.com.

Air Filter

The Camfil Farr "Riga-V™"air filter, available in three ASHRAE efficiencies (MERV 11, 13 and 14), offers greater dust holding capacity and lower pressure drop than most comparable filters at a significantly lower first cost. It may be used in commercial buildings, schools, healthcare facilities, industrial plants, utilities and other applications. The key to the Riga-V filter's economical performance is a high-lofted synthetic media in a proprietary V-pleat configuration that produces optimized performance. Benefits include superior dust loading and airflow characteristics, for longer service life and lower average energy costs.

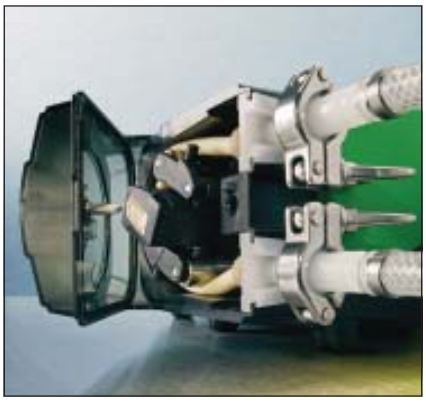
Camfil Farr, One North Corporate Dr., Riverdale, NJ 07457, www.camfilfarr.info.

CD Catalog of Dust Collectors

Farr Air Pollution Control has published a new CD that provides a comprehensive electronic catalog of the company's dust, mist and fume collection equipment. The CD contains in-depth information on dust collectors for all types of applications, including the popular line of "Gold Series®" cartridge collectors with patent-pending HemiPleat™ filter technology. Product literature, technical data, application guidelines, photos and drawings, and PowerPoint presentations are included for key products. The CD also contains a library of technical papers and case studies on dust collection topics.

Farr Air Pollution Control, 3505 S. Airport Rd., Jonesboro, AR 72401, www.farrapc.com.

Pumpheads



Watson-Marlow Bredel, a leading manufacturer of peristaltic pumps, has launched the 520 LoadSure® elements range. The combination of the tube element and pumphead design provides pressure performance up to 100 psi, allowing the 520 pump to be utilized in applications that require the accurate metering, dosing and transferring of corrosive or sensitive fluids in sanitary environments. Sanitary process users can now have the functionality of the best-selling 520 pumps with expanded pressure capability. The new 520 LoadSure® pump offers flows of 3,500 ml/min at 30 psi to 450 ml/min at 100 psi and covers a wide range of applications including low shear feed for ultrafiltration and diafiltration, chromatography, transfer of viscous media and high-pressure spray coating of tablets.

Watson-Marlow Bredel, 37 Upton Technology Park, Wilmington, MA 01887, www.watson-marlow.com.

Hot Plates, Stirrers, and Stirring Hot Plates

Corning Incorporated, a global supplier of scientific laboratory and drug discovery products for more than 90 years, has announced the addition of digital displays to its hot plates, stirrers and stirring hot plates. The new digital display features include: a digital temperature display adjustable in 5 degree increments and set temperature indicator; optimum digital stir speed display indicator; and an external temperature controller for precision accuracy "inside the beaker." Digital display hot plates and stirrers help scientists to be more precise in their experiments by providing outstanding clarity, functionality, and brightness through easy-to-read LED indicated temperature and stir speed settings. The new stir and heat displays are also Underwriters Laboratories, Inc. (UL) approved and allow for specific settings that enable labs to establish routine protocols.

Corning Life Sciences, One Riverfront Plaza, Corning, NY 14831, www.corning.com.

Servo-Driven Rotary Capper

NJM/CLI has introduced Equatorque, a servo-driven rotary capper that improves the precision of the capping operation to maximize product quality. Featuring Elau brushless servomotors at each capping head, Equatorque accurately controls torque from zero to 35 lb/in (four Nm) and enables on-the-fly torque adjustments to be made without slowing the machine via the local operator interface or remotely via an optional Ethernet connection. NJM/CLI can design Equatorque with one to 24 capping heads to achieve line speeds from 10 to 600 containers per minute. Handling containers from 30 ml to 5 liters, Equatorque achieves faster tool-free changeovers by eliminating the mechanical adjustments required with traditional magnetic clutch systems.

NJM/CLI, 56 Etna Rd., Lebanon, NH 03766, www.njmcli.com.

Infrared Detectors

TT electronics OPTEK Technology has developed a silicon phototransistor in a miniature surface mount package (0.10" [2.5 mm] x 0.08" [2.0 mm]) with a variety of lead options. Designated the OP570 Series, the NPN phototransistors feature an integral lens that enables the devices to operate with higher performance at lower cost. Electrical performance of the OP570 Series NPN phototransistors is characterized at collector-emitter breakdown voltages of 30V, emitter-collector breakdown voltage of 5V, collector current of 20mA and power dissipation of 130mW. On-state collector current is 2.5mA (min.), and the collector-emitter dark current is 100nA (max.).

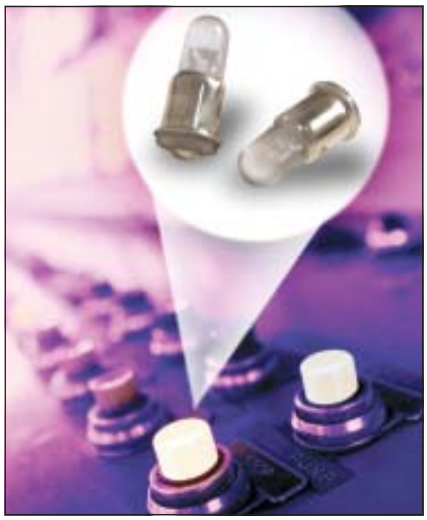
OPTEK Technology, 1645 Wallace Dr., Carrollton, TX 75006, www.OPTEKinc.com.

Continuous Conveyor Test Loop

Priority One announces the availability of its new Conveyor Test Loop, a continuous container handling system that has been added to the company's extensive demonstration facility. Designed to give prospective customers the opportunity to identify the behavior of their specific containers on a wide variety of conveyor types prior to system design and installation, the Conveyor Test Loop helps assure risk free start-ups. Conveyor Test Loop handles full and empty, round and non-round, stable and unstable containers made of plastic, metal, glass and composite materials at speeds from 100 to more than 1000 containers per minute. With a combination of table top and mat top conveyors as well as tab corners, magnetic corners and dynamic transfer corners, the Conveyor Test Loop provides valuable real-world information about container behavior.

Priority One Packaging Ltd., 815 Bridge St., Waterloo, Ontario N2V 2M7, Canada, www.priorityonepackaging.com.

Midget Flange Based LED



DDP, a leader in engineered LED solutions, has developed a warm-white midget flange LED lamp designed to retrofit and replace incandescent light bulbs. The T1 ¾ midget flange based LED is ideal for indicators used for backlighting switches, pushbutton rockers and panel builders in harsh conditions including off-highway, transportation, military/aerospace and industrial applications. DDP's midget flange based LEDs ensure a clean white light without any color mixture, a requirement for many applications that demand specific color and brightness levels such as railroad stations and trains as well as military/aerospace applications. The subminiature T1 ¾ size midget flange based LED features an industry standard mount and is available in 6V, 12V, 14V, 24V, and 28V versions. It also works with a variety of color lenses.

DDP, 445 S. Douglas St., El Segundo, CA 90245, www.datadisplay.com.

Guide to Bag Filtration Systems

Eaton Filtration's new Guide to Bag Filtration Systems describes recent advances that Eaton Bag Filtration Systems can bring to a wider range of filtration applications than in the past. Innovations in both the filter housing and the bag filtration media now make it possible for Eaton Bag Filters to be used in applications that previously required more costly types of filtration equipment. The new full color guide provides detailed information on Eaton Filtration's products, including the new patent pending HAYFLOW™ Filter Element and Eaton's PROGAF™ Filter Bag. Advances in bag filter housings are detailed in a special section of the guide that covers both single bag housings and multi-bag housings for high flow rate applications.

Eaton Filtration, LLC, 900 Fairmount Ave., Elizabeth, NJ 07207, www.filtration.eaton.com.

Well Freeze Drying Systems

SP Industries™, a leader in freeze drying technology, has introduced the VirTis® 96 Well Freeze Drying Systems for high throughput applications. These new systems include either glass or plastic vials set in an aluminum vial holder with an exclusive LyoCap™ 96 Well Capmat Lyophilization Stopper. The solid aluminum 96 well vial holders provide efficient and even heat dis-

tribution to ensure fast and consistent freeze drying results for every sample. The fluted LyoCap 96 Well Capmat Stoppers enable samples to be quickly freeze dried and then sealed under vacuum or inert gas after the lyophilization cycle is complete.

SP Industries, 935 Mearns Rd., Warminster, PA 18974, www.SPindustries.com.

Free Tablet Press Buyers Guide

Fette, a leading manufacturer and supplier of tablet presses for both pharmaceutical and industrial applications, has prepared a 12-page booklet to help tabletting buyers make an informed decision about tablet presses. The material presents more than 50 key questions prospective buyers need to ask before buying a tablet press, and includes the corresponding answers.

Fette America, 400 Forge Way, Rockaway, NJ 07886, www.fetteamerica.com.

Cartoner with Servo-Controlled Operation

Uhlmann, a worldwide leader in pharmaceutical packaging, offers the C 2155 Cartoner. The C 2155 features intermittent processing with the precision of servo-controlled carton pick-up and erecting. Visual instructions via touch screen monitor allow for ease of operation and quick start-up. With an output from 25 to 150 cartons per minute, the C 2155 is self-cleaning, has GMP-compatible cantilevered construction, and features an outstanding ergonomic design for operator comfort and safety. With its continuous automatic system alignments, the C 2155 Cartoner provides ultimate production reliability.

Uhlmann Packaging Systems LP, 44 Indian Ln. E., Towaco, NJ 07082, www.uhlmann-usa.com.

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FDA and Sweden's Medical Products Agency Sign Confidentiality Arrangement

The US FDA and Medical Products Agency (MPA) of Sweden have signed a mutual Confidentiality Arrangement, effective April 2006. The agreement allows the two agencies to share certain nonpublic information, including law enforcement information and internal pre-decisional information. According to Director General Gunnar Alvan of the Swedish MPA, the Confidentiality Arrangement is "useful when it comes to sharing drug safety data, potentially resulting in regulatory measures we want to implement globally in a concerted manner. The difficulties experienced in simultaneous risk communications, due to the time-difference between North America and Europe have effectively been alleviated."

Dave DiProspero Appointed Principal at Stantec

Dave DiProspero was appointed to the position of Principal in the BioPharmaceuticals Practice Area of Stantec. DiProspero will provide industry leadership, vision, business development strategies, and communication within and outside regional borders in order to expand and grow the Bio/Pharmaceuticals Practice Area. In addition, DiProspero will provide technical expertise on Oral Solid Dose Form (OSD- Pharmaceutical Tablets and Capsules) and containment projects. Dave has more than 20 years of pharmaceutical engineering experience in Oral Solid Dose Form (OSD), Active Pharmaceutical Ingredients (API), and biotech processes. His specialty is in the areas of process, material handling, systems integration and containment, with a strong background in equipment.

Millipore to Acquire Serologicals

Millipore Corp. and Serologicals Corp. have announced that their boards of directors have approved a definitive agreement whereby Millipore will acquire Serologicals in an all cash transaction. The acquisition will transform Millipore into a company with combined annual revenues of approximately $1.4 billion, based on 2006 full year projections. Assuming stable foreign exchange rates, Millipore believes 2007 revenues for the combined company will grow between 9 and 11 percent over 2006 pro forma revenues. The strategic combination of Millipore and Serologicals will significantly strengthen Millipore's Bioscience Division by giving it leading positions in a broad range of high growth segments such as drug discovery products and services, antibodies, cell biology reagents, and stem cell research. The combined organization of approximately 5,800 employees will have significantly expanded R&D capabilities and a worldwide sales, sales support, and service organization of approximately 1,200 professionals selling a broad portfolio of complementary products.

Gilbane-Tarlton Selected as Construction Manager for Pfizer's Research Building

Gilbane Building Co., in a joint venture with Tarlton Corp., is the Construction Manager for Pfizer's new research facility in Chesterfield, MO. The new research building is part of a nearly $200 million expansion of Pfizer's Chesterfield Campus site. The four-story, 330,000-square-foot building will add to the pharmaceutical company's existing research and development facility, which currently operates four buildings at the site. Gilbane's Chicago office and Tarlton's St. Louis office will oversee the project, alongside the design team of Kling Architects. This expanded capacity, expected to be completed by the end of 2008, will allow the company to relocate approximately 250 employees from throughout the St. Louis region to its Chesterfield campus, bringing the total workforce at the site to just over 1,000.

Sartorius and ProMetic Announce Collaboration Agreements

Sartorius AG and ProMetic Life Sciences Inc. announced the signing of a collaboration agreement utilizing bioseparation systems to recover proteins from human blood plasma, between Sartorius and ProMetic's subsidiary ProMetic BioTherapeutics, Inc. ProMetic has developed with its partners, an innovative proprietary process, the "Plasma Protein Purification System" (PPPS), to fractionate blood plasma, which it licenses out to the blood-processing industry. Within this alliance, Sartorius will be a preferred supplier and technology provider to ProMetic's PPPS licensees for filtration equipment and consumables. In addition, Sartorius and ProMetic BioSciences Ltd have agreed to collaborate on the development of ligand-membrane composites for the isolation of the proteins from blood plasma and other sources. These affinity composites will be based on ProMetic BioSciences Ltd's Mimetic Ligand™ technology and Sartorius' membrane chromatography technology Sartobind®.

CDM Acquires Metrix

CDM has acquired Metrix Inc., enhancing CDM's resources and service offerings in site remediation, environmental compliance, litigation support, and environmental business services. Metrix focuses on site remediation, environmental management and compliance, litigation support and expert witness testimony, and environmental business services, with specialized expertise in design-build remediation programs, as well as sediment remediation and geotechnical services. The employees of Metrix—experts in civil, environmental, and geotechnical engineering, as well as geology, environmental science, and related disciplines—will be located in Denver, Golden, and Basalt, Colorado.

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Mark Your Calendar with these ISPE Events

June 2006

5 - 8 ISPE Washington Conferences, Crystal Gateway Marriott, Arlington, Virginia, USA

7 UK Affiliate-Southern Region, "Meeting the Challenges in the R&D Environment," Pfizer Ltd. Plant Visit, Sandwich, Kent

8 San Diego Chapter, CEO Night, La Jolla, California

9 The Fifth Pharmaceutical Quality Forum Symposium, Co-Sponsored by ISPE, featuring ICH Q8 and QoS, Yokohama Municipal Education Hall, Yokohama City, Japan

14 Chesapeake Bay Area Chapter, 2006 Summer Social, Baltimore, Maryland, USA

15 France Affiliate, Conference, ATEX, France

15 New Jersey Chapter, Chapter Day and Multi-Tract Event, Holiday Inn, Somerset, New Jersey, USA

15-16 Poland Affiliate, Conference on Process Improvements, Poland

20 On-line Seminar: Effective Training of CTM Personnel

22 Greater Los Angeles Area Chapter, Social Event, California, USA

22 Midwest Chapter, Golf Outing and Executive Panel Discussions, Tiffany Greens GC, Kansas City, Missouri, USA

25 - 27 ISPE Singapore Conference in association with INTERPHEX Asia, Suntec Convention and Exhibition Centre, Suntec City, Singapore

27 - 29 INTERPHEX Asia, Suntec Convention and Exhibition Centre, Suntec City, Singapore

27 - 30 INTERPHEX Mexico, Centro Banamex, Mexico City, Mexico

28 UK Affiliate-North West Region, Seminar, "Introduction to the Pharmaceutical Industry: HVAC and Cleanrooms for the Pharmaceutical Industry Seminar," United Kingdom

29 Greater Los Angeles Area Chapter, Golf Tournament, Fullerton, California, USA

29 - 30 DACH Affiliate, Workshop, Linz, Austria

July 2006

27 Greater Los Angeles Area Chapter, Grifols Facility Tour, Los Angeles, California, USA

August 2006

10 San Francisco/Bay Area Chapter, Golf Tournament and Winery Tour, Chardonnay Golf Club, Napa, California, USA

22 Greater Los Angeles Area Chapter, Commuter Conference, California, USA

30 Nordic Affiliate, Conference, "New Concepts for Commissioning and Qualification," Copenhagen, Denmark

31 Puerto Rico Chapter, Members Night, Puerto Rico

September 2006

11 - 15 ISPE Boston Classroom Training and GAMP Americas Forum, Hyatt Regency Cambridge, Cambridge, Massachusetts, USA

12 Nordic Affiliate, Conference, "Operating Efficiency joint with Mentor Communications," Malmo, Sweden

12 Delaware Valley Chapter, Program Meeting, USA

12 - 14 Great Lakes Chapter, Education Event, Plant Tour, and Golf Outing, Eagle Crest Conference Resort, Ypsilanti, Michigan, USA

14 Ireland Affiliate, Seminar, "R&D Pilot Plant Commercialization," Ireland

14 UK Affiliate-North West Region, Joint Seminar with IChemE, United Kingdom

18 - 22 ISPE Vienna Congress, InterContinental Wien, Wien, Austria

20 - 21 DACH Affiliate, Fachdiskussion, Water and Steam, Basel, Switzerland

28 Puerto Rico Chapter, Medical Device and Pharmaceutical Combo, Puerto Rico

Update on FDA Pharmaceutical cGMPs for the 21st Century - A Risk-based Approach

by Joseph X. Phillips

The US Food and Drug Administration announced a significant new initiative in August 2002. The announcement, titled Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century, was made to enhance and modernize the regulation of pharmaceutical manufacturing and product quality. It was made to bring a 21st century focus to this critical FDA responsibility.

The objectives of the new initiative included:

- encourage early adoption of new technological advances by the industry
- facilitate application of modern quality management techniques
- encourage implementation of risk-based approaches that focused both industry and Agency attention on critical areas
- ensure that regulatory review, compliance, and inspection policies are based on current good science
- enhance the consistency and coordination of the FDA's drug quality regulatory programs by further integrating quality systems approaches into the Agency's business processes and regulatory policies

Over the past four years, the Agency has released periodic reports documenting its progress and plans.

- February 20, 2003 - listed accomplishments and first steps toward achieving FDA's goal in the initiative
- September 2003 - outline of Agency implementation plan for achieving objectives announced previously

The Agency formed a number of multidisciplinary working groups to continue to shape the initiative, under the oversight of the cGMP Steering Committee. In addition, the Agency has formed a Council on pharmaceutical quality, which has been charged with policy development, coordination, and continuing change management, including the ongoing implementation of specific quality management systems within the FDA. Summarized here are a number of the specific accomplishments under the initiative, thus far:

- adoption of quality systems model for Agency operations
- development of quality systems guidance for cGMP regulation
- implementation of a risk-based management plan
  - developed a strategic action plan
  - developed a risk-based model for inspectional oversight
  - conducting an ongoing data analysis
  - issued in 2003, Guidance for Industry Part 11, Electronic Records, Electronic Signatures - Scope and Application. Many barriers to scientific and technological advances were removed, and the risk-based approaches to managing computer systems were encouraged.
  - ONDC Pharmaceutical Quality Assessment System developed
- science-based regulation of product quality
  - PAT team and the Manufacturing Science Working Group have continued their collaboration and significant progress has been made in building consensus on
    - the principles of manufacturing science and process understanding
    - PAT guidance has been issued
    - A support structure for the PAT guidance was reported in FDA's earlier reports to be evolving in the pharmaceutical community including the American Society of Testing Materials (ASTM) E55 Committee on pharmaceutical application of process analytical technology.
    - Additional progress has been made as reported below.
  - International Collaborations: the FDA continued its collaboration with international health and regulatory partners. They continued to collaborate within the ICH framework. The FDA is seeking membership in Pharmaceutical Inspection Cooperation Scheme (PICS).
  - implementing the Future of Pharmaceutical Manufacturing regulation
    - Risk-based approaches: the FDA has implemented a risk based approach to regulating pharmaceutical manufacturing. The approach will be applied to the review, compliance, and inspectional components of FDA regulation
    - Quality Systems Approach: the FDA has issued Quality Systems Approach to Pharmaceutical cGMPs.
    - Enhanced internal regulatory coordination - the Agency has developed a staff of highly trained individuals, known as the Pharmaceutical Inspectorate, to conduct inspections of highly complex operations
    - Analysis of cGMP requirements is ongoing.

Since the 2003 progress Report, the Agency has:

- developed a risk-based approach for manufacturers to use to comply with Part 11 electronic records requirements
- developed a technical dispute resolution process
- changed procedures for drug cGMP warning letters to give greater consistency and uniformity to the letters
- Continued to be engaged in the ICH process. ICH Q8, dealing with pharmaceutical development and Q9 dealing

Concludes on page 4.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

Staff News

Departures

Both sadness and joy accompany our announcement that **Susan H. Klein**, Vice President of Administration and CFO, will retire from the Society on 30 June 2006. Susan has provided us with her contributions and wisdom for more than 16 years, and it goes without saying that she will be missed. We are fortunate that Susan has agreed to remain in a part-time capacity for the foreseeable future. We wish Susan all the best as she continues to formulate her plans for retirement to spend time with her family.

Susan Pazera resigned from her position as Director of Marketing Communications. Her husband accepted a position with another company and they will be moving to Portland, Oregon. Susan's last day at ISPE was 28 April 2006.

Sara Welte resigned from her position as Membership Services Coordinator to pursue other opportunities. Sara's last day at ISPE was 10 February 2006.

Becky McConnell resigned from her position as Membership Services Coordinator. Her fiancé accepted a position which requires a transfer to Raleigh, North Carolina. Becky's last day at ISPE was 28 April 2006.

Valerie Kestner-Marcy resigned from her position as Public Relations Manager. Valerie's last day at ISPE was 4 May 2006.

Susan K., Susan P., Sara, Becky, and Valerie will be missed and we wish them the best in their future endeavors.

Promotions and Transfers

Victoria Smoke has been chosen as Susan Klein's successor as Vice President of Administration and CFO and will assume full responsibilities in her new role effective 1 July 2006. Victoria has been with ISPE for more than 10 years and has been a very valuable asset to the team.

Lynne Richards was selected as Connie Muia's successor as Director of Affiliate and Chapter Relations effective 1 February 2006 and assumed complete responsibilities for the position on 1 April 2006.

Effective 24 April 2006, **Coleen Fisher** transferred from her position as Customer Services Coordinator to her new position as Membership Services Coordinator.

Please join us in congratulating Victoria, Lynne, and Colleen and wishing them well in their new roles.

New Hires

Effective 18 January 2006, **Heather Fortson** joined ISPE as Marketing Communications Associate. Heather came to us from WellCare Health Plans where she was a Copywriter/Editor and Project Manager for the Marketing-Communications department. Prior to WellCare Health Plans, Heather served as Public Relations Coordinator for St. Joseph's-Baptist Health Care, an alliance of five hospitals in Tampa, Florida. Heather attended Florida State University in Tallahassee, Florida, where she obtained a Bachelor of Science in Communications, and The American University in Washington, DC, where she obtained a Master of Arts in Film and Video.

Effective 23 January 2006, **Rochelle Runas** joined ISPE as Technical Writer for the Publications Department. Rochelle came to us from the University of South Florida (USF) in Tampa, Florida where she was the Communications Manager for the Office of the President. Prior to USF, Rochelle served as Interactive News Indexer/Editor for Dow Jones and Co. in South Brunswick, New Jersey. Rochelle attended The College of New Jersey where she obtained a Bachelor of Arts in Journalism.

Effective 3 April 2006, **Cindy Cesani** joined ISPE as Part-Time Affiliate & Chapter Relations Coordinator. Cindy came to us from Syniverse Technologies, Inc. in Tampa, Florida where she was the Human Resources Manager for the Benefits and Wellness department. Prior to Syniverse, Cindy served as Human Resources Generalist for Switch and Data also in Tampa, Florida.

Effective 25 April 2006, **Danielle Shelton** joined ISPE as Event Operations Coordinator. Danielle came to us from Jessica McClintock in Tampa, Florida where she was the Store Manager and Allen Wedding Company where she served as Creative Director. Prior to Jessica McClintock, Danielle worked for Primos Catering/Signature Flight Support in the Catering and Events department. Danielle attended Ohio University in Athens, OH, where she obtained a Bachelor of Arts in Creative Writing and English.

Effective 8 May 2006, **Alison Matherly** joined ISPE as Director of Marketing Communications. Alison came to us from the National Association of Underwater Instructors (NAUI Worldwide) in Tampa, Florida where she was the Marketing Manager. Prior to NAUI Worldwide, Alison served as Director of Marketing Communications for The Flying Hospital, Inc. in Virginia Beach, and as Regional Media Relations Manager for The Coca Cola Company in Atlanta, Georgia, for the 1996 Olympic Torch Relay project. Alison attended Temple University in Philadelphia where she obtained a Bachelor of Business Administration in Marketing and Finance.

Effective 15 May 2006, **Marsha Strickhouser** joined ISPE as Public Relations Manager for the MarCom Department. Marsha came to us from the University of South Florida (USF) in Tampa, Florida where she was the Media Relations Coordinator. Prior to USF, Marsha served as Media Relations Specialist for the University of Miami, School of Medicine. Marsha attended the University of Miami where she obtained a Bachelor of Arts in Communication/Journalism.

Please join us in welcoming Heather, Rochelle, Danielle, Cindy, Alison and Marsha to the ISPE Team!

Pharmaceutical Regulatory and GMP Structure in Russia

by Mike Bennoson

This article provides an overview of the pharmaceutical regulatory structure and GMP organization in Russia. It also provides details on the establishment of a National Pharmaceutical Inspection unit.

The National Pharmaceutical Inspection (NPI) unit was recently established. Plans are to recruit 60 inspectors for GMP, and eventually 200 to 300 inspectors for GDP. A General Director of the NPI has been appointed. The Pharmaceutical Regulatory Structure is as follows:

- Ministry of Health - Legislation
- Federal Service - Russian healthcare supervision and control
- Federal Agency - Management of Property

Federal Service has two areas, the Executive Branch (government policies and decision making) and Experts (pharmaceutical, medical devices, and healthcare). The Pharmaceutical Section employs experts who may be independent consultants and work on a contract basis. This section has responsibility for:

- Registration of Drugs
- GMP/GDP Inspections through the NPI
- Clinical Trials
- Laboratories
- Certification

Training of NPI inspectors is undertaken by both organizations within and outside of Russia.

About the Author

Michael J. Bennoson joined ISPE in May 1996 and supports the European office in the development of European educational programs and ISPE links with regulatory authorities. Bennoson obtained a Bachelor of Technology degree in industrial chemistry from the University of Bradford, England. He emigrated to Montreal, Canada where he spent four years in quality assurance at Ayerst Laboratories. He then emigrated to New Zealand and established GMP inspections for the government as head of inspection for the Department of Health. Upon his return to the UK, he joined Wellcome (now GSK) in quality assurance, retiring as director of quality assurance operations, UK in December 1995. Bennoson was chairperson of the UK industry GMP Committee for 13 years and participated in a number of European working groups.

Update on FDA Pharmaceutical cGMPs

Continued from page 2.

with quality risk management, have been signed off at Stage 4.

- science-based policies and standards to facilitate innovation
  - aseptic processing final guidance has been issued
  - PAT Guidance - a framework for innovative pharmaceutical development, manufacturing, and quality assurance has been issued.
  - The FDA PAT team has worked with ASTM International to establish the technical committee E55 on pharmaceutical application of PAT. Focusing on process monitoring and control, instead of testing, requires process control standards consistent with guiding principles of the control theory. The E55 Committee is tasked with developing standards related to process analytical technology with the primary focus on process understanding and control.
  - The Agency has developed a system to use comparability protocols for the review process for post approval changes.
- improved the integration of the pre-approval and cGMP inspection programs
- implemented its quality management systems
- The Agency is updating its current thinking on validation.
- The Agency has developed a risk-based inspection site selection procedure.

The above is a brief summary of most of the accomplishments by the Agency on the progress of its cGMP initiatives. To read a complete and detailed summary, please visit the FDA Web site.

About the Author

Joseph X. Phillips joined ISPE in 2003 as Regulatory Affairs Advisor and was appointed to the US Food and Drug Administration (FDA) as a special government employee on the Pharmaceutical Science Advisory Committee that is involved in the Agency's new "Risk-Based Approach to Pharmaceutical current Good Manufacturing Practices (cGMPs) for the 21st Century" initiative. Previously, Phillips was vice president, Pharmaceutical Services for Quintiles Consulting following a 44-year career with the FDA. At the FDA, he served as Deputy Regional Director of the Agency's Central Region. He was heavily involved in training of FDA Investigators and in planning and managing pharmaceutical programs including the Pre-Approval Inspection program and the Scale-Up and Post Approval Changes (SUPAC) for field operations. Phillips was a principal negotiator for the US/EU Mutual Recognition Agreement and was the FDA Lead to the International Conference on Harmonization (ICH) Expert Working Group for GMP Guidance for Active Pharmaceutical Ingredients (ICH Q7A Guidance).

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Architects, Engineers - Constructors

CH2M Hill, PO Box 22508, Denver, CO 80222, www.ch2mhill.com. See our ad in this issue.

CRB Consulting Engineers, 7410 N.W. Tiffany Springs Pkwy., Suite 100, Kansas City, MO 64153. (816) 880-9800. See our ad in this issue.

IPS – Integrated Project Services, 2001 Joshua Rd., Lafayette Hill, PA 19444. (610) 828-4090. See our ad in this issue.

NNE US, 7868 Hwy. 70 W., Clayton, NC 27527. (919) 359-6600. See our ad in this issue.

Parsons, 150 Federal St., Boston, MA 02110. (617)-946-9400. See our ad in this issue.

Stantec Consulting, 201 Old Country Rd., Suite 301, Melville, NY 11747. (631) 424-8600. See our ad in this issue.

Cleanroom Products/Services

AES Clean Technology, 422 Stump Rd., Montgomeryville, PA 18936. (215) 393-6810. See our ad in this issue.

Employment Search Firms

Jim Crumpley & Associates, 1200 E. Woodhurst Dr., Bldg. B-400, Springfield, MO 65804. (417) 882-7555. See our ad in this issue.

Filtration Products

US Filter, 125 Rattlesnake Hill Rd., Andover, MA 01810. (978) 470-1179. See our ad in this issue.

Hoses/Tubing

AdvantaPure, 145 James Way, Southampton, PA 18966. (215) 526-2151. See our ad in this issue.

Label Removal Equipment

Hurst Corp., Box 737, Devon, PA 19333. (610) 687-2404. See our ad in this issue.

Passivation and Contract Cleaning Services

Active Chemical Corp., 4520 Old Lincoln Hwy., Oakford, PA 19053. (215) 676-1111. See our ad in this issue.

Astro Pak Corp., 12201 Pangborn Ave., Downey, CA 90241. (800) 743-5444. See our ad in this issue.

Cal-Chem Corp., 2102 Merced Ave., South El Monte, CA 91733. (800) 444-6786. See our ad in this issue.

Oakley Specialized Services, Inc., 50 Hampton St., Metuchen, NJ 08840. (732) 549-8757. See our ad in this issue.

Sterile Products Manufacturing

Tanks/Vessels

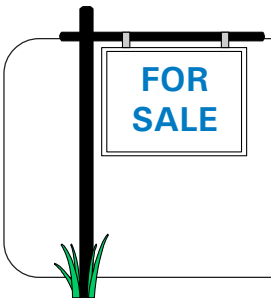
Validation Services

cGMP Validation, 5800 Foxridge Dr., Suite 402, Mission, KS 66202. (913) 384-2221. See our ad in this issue.

ProPharma Group, 10975 Benson Dr., Suite 330, Overland Park, KS 66210; 5235 Westview Dr., Suite 100, Frederick, MD 21703. (888) 242-0559. See our ad in this issue.

Water Treatment

Christ Pharma & Life Science AG, Haupstrasse 192, 4147 Aesch, Switzerland. +41 617558111. See our ad in this issue.



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Manuscripts Due: 1 Sept 2006
Publishes: 23 Jan 2007

MARCH/APRIL 2007
Theme: Automation
Manuscripts due: 3 Nov 2006
Publishes: 23 Mar 2007

MAY/JUNE 2007
Theme: Commissioning and Qualification
Manuscripts due: 3 Jan 2007
Publishes: 21 May 2007

JULY/AUGUST 2007
Theme: Outsourcing and Contract Manufacturing
Manuscripts due: 2 Mar 2007
Publishes: 23 Jul 2007