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Project Management Best Practices: Improving Schedule Using a Distributed Workforce

by Mark Albano, Bruce Kane, and Robert Thomas

This article presents more than a decade of project management learning about distributing a project workforce and the limits and risks of over distribution.

When it comes to project management, speed is king and the drive is to maximize work efficiencies to deliver projects under cost and ahead of schedule. It is actually a very simple equation: the longer it takes for a facility to start up and produce product, the longer it takes for the company to start producing a profit. With the competitive landscape getting more crowded by the day, everybody is rushing to be first to market.

With all of this in mind, the pressure resting on the shoulders of project management teams might be heavier than ever in the life sciences industries where project managers are constantly tasked with the challenge of meeting construction deadlines that only a few years ago would have seemed insurmountable.

The successful solution for situations like this is achieved through a combination of organization and experience. Every project management organization has – or should have – a well tested and established set of best practices and procedures gleaned from working multiple projects in various industries and independently certified professional project managers. Having the foresight and experience to recognize what works and what does not, leads to insight to implement successful strategies in future projects. The easiest way to make a great project manager is to utilize the lessons learned from one project and adapt them for use in the next. Doing these things facilitates the meeting of these challenges – and in some cases exceeding them.

Recent case in point, a 200,000-square-foot, $250 million biopharmaceutical production facility (one of the world's largest single use sites) was brought online to first production in record time with only two years elapsing from groundbreaking (April 2008) to mechanical completion (early 2010). However, the typical timeline for a facility like this is five years. The company had a great need to finish construction and begin production in order to meet the demand for much-needed medicine. The installation incorporated extensive single-use technologies on a commercial scale, a more complex process, but profoundly beneficial in that it contributed to a reduced build time of nearly 50 percent.

Many different methods and activities have been attempted in the pursuit of an ever-improving project execution and reduced time lines. Opportunities for improvement in the execution have dramatically increased in the last decade, due to changes in the regulatory environment and more importantly in the technology used by the engineering workforce. The regulatory environment has allowed testing methods to evolve allowing a decoupling of logic and software testing from the target systems, and the introduction of less prescriptive methods. A tremendous opportunity with respect to establishing a virtual workforce has been facilitated by changes in technology.

The successful project manager prides him or herself on having a record of finishing on schedule, under budget, and meeting requirements. When faced with unexpected obstacles, they should demonstrate flexibility and ingenuity in solving complex issues with speed and grace. However, the best tool for a project manager is to plan projects beginning with the lessons learned of the previous project and end projects with the lessons learned to be applied to the next project.

Following a series of major biotech facilities, the automation project management team shares their learning about staffing and project man-

agement information systems. What does this latest iteration of the Project Management Institute (PMI)*, lessons learned process tell us about these topics? The following examines some of the key learning from the latest iteration of this process.

Achieving a Common Vision

One of the key lessons learned is the value of appropriate staffing models. By relying on proper staffing procedures, project managers provide enhanced value to the customer. Working with the right staffing model significantly increases efficiency, speeding up the construction process and eliminating unnecessary work. Having the right people on the team is essential to meeting project goals, but it is also a matter of how many people, when they need to start contributing, where they are located, and how to organize them. With the right management practices and staffing models, the diverse network of teams comprising a project can be a project manager's greatest strength.

The greater the interaction required between vendor and customer, the greater the need for co-location. Interaction between the end user and the implementation teams is used to transfer process knowledge and requirements and to clarify the "intended use" of the equipment and facilities. Clearly, if the teams are in regular contact, clarity is increased and knowledge transfer is facilitated. Co-location provides these benefits, but has higher travel and living costs. Often, in order to minimize the costs involved, only key individuals are asked to co-locate. In addition to the fiscal cost associated with co-location, there is a morale issue with asking people to be away from home for extended periods. For these reasons, a project is seldom fully co-located, and there is a significant degree to which this middle ground optimized by trying to identify the optimal use of co-located assets.

However, trying to integrate many teams to work as a cohesive unit on a multi-million dollar project is not for the faint of heart. Oftentimes, the scope of a project requires the capabilities of a global workforce. A distributed global workforce creates a new set of complexities, as directing resources and equipment across multiple time zones can often feel like a juggling act. With people all over the world working on a single project, the sun never sets on a distributed work force. Progress can be made around the clock, which makes meeting tight deadlines easier and having a distributed and global workforce allows you to staff projects quickly.

However, the difficulties of a distributed workforce can sometimes seem as significant as the benefits. Remote team coordination has proven to be quite challenging. Sharing knowledge and managing work flows require that status, monitoring, and communication tools be developed and incorporated into daily work habits. The simple process of speaking face-to-face and establishing priorities and responsibilities becomes difficult at times due to time zones.

One tool available that facilitates a distributed workforce is the use of virtualization. Virtualization use has increased as the infrastructure for cloud computing has increased. Virtualization is the set of collaborative tools that enable real time communication, information transfer, and global access. This has enabled teams in multiple work locations to not only report their status and share information but to work on the same configuration simultaneously. Consolidating a project's information into a single database reduces repetition and provides for development that is more consistent and testing. Additionally, virtualization of the physical control layer allows development and testing without the limits imposed by bulk physical equipment.

Striking the right balance of work locations via virtualization is a delicate, but crucial process, because all of the work must ultimately appear as if it was completed by a single author. Early in the aforementioned biotech project, it was identified who would make up remote teams and where they would be located. Then, representatives were selected for each remote location. This representative spent three to four weeks with the leadership team, learning the detail of the manufacturing process, project procedures, and responsibilities for their team, as well as others. This forged a single vision and cohesiveness within the project leadership team. They then took that information back to their remote teams and managed the responsibilities there. Having someone at each location versed in the proper guidelines maintains consistency throughout all the teams involved in the project. Not only does this prevent a remote team from veering off the established plan, it also prevents time zone hang-ups, as remote teams are not reporting problems and waiting 12 hours for the management's answer the next business day.

The perfect work force balance applies to both staffing size and staffing location. Debate over the correct ratio of local and distributed workers is an exercise in futility. The truth is that there is not a single correct ratio that applies to every project, because each project has its unique needs and challenges. However, there are a few rules of thumb to follow that can guide a project manager to finding the right ratio for a specific project.

First, co-location is critical during the design phase. The design phase typically requires significant collaboration between the various stakeholders in the success of the project. The design phase has such an impact on the rest of the project that it makes co-location a necessity. Detailed design plans require face-to-face interaction with management and the customer and development of a solid work relationship based on mutual understanding. Explaining nuances, educating, and influencing each other are accomplished much easier when team members work alongside each other. The simple act of working in proximity makes a huge difference.

Co-location also reduces work redundancies. Having process knowledge experts in the same room as control knowledge experts solving the same problems eliminates repeating work activities and information sharing. Having a good definition of what needs to be completed and only executing it once streamlines execution. With a good understanding of the role and responsibilities, work can then be distributed to different places.

Once the design is agreed upon, the workforce location distribution can shift. However, it is critical that the customer facing team has adequate capability to handle the informa-

tion flow from the customer to remote work locations and adequate capability to perform quality checks on the output of the remote work locations. It is also highly imperative that both the vendor and the customer have this capability. Pushing this distribution too much can cause bottlenecks as information is delayed waiting to be approved or reviewed. However, staffing should be sufficient to handle appropriate quality reviews. Companies should move gradually and evaluate the process as it continues. If possible, as benefits of further workforce distribution are identified, steps should be taken in that direction, but managers must be willing to scale back if necessary.

Co-location may have a critical mass – that is, a minimum size and skill set required to run projects successfully. Shorting on these responsibilities will undoubtedly lead to problems down the line. At a minimum, the on-site team needs representation from all key knowledge areas. Generally, project management including the project manager and lead engineer will spend significant time co-located.

Ultimately, there is no magic number to achieve the proper balance. Some project managers might claim that they have the formula figured out, though in reality the ratio is entirely subjective. Projects change, the people working on them change, and there are simply too many variables in new projects to pinpoint the universal proportion of work dispersal. However, those in need of a good baseline can estimate that a fair starting point is somewhere around one-third local, two-thirds virtual.

When managers can find the right dispersal ratio for a project, teams can more-easily fire on all cylinders, and progress can steadily hum along. Seamless integration between distributed teams means that all know their place and their responsibilities, greatly enhancing efficiency.

Project management has a constant struggle to come through within budget. Distributing work has scheduling benefits, and when properly handled it can help control costs. Nobody wants to cut back on a project's scope, and work distribution is a way to deliver greater value. Distributing work may require more logistical oversight, but properly utilizing it results in considerable labor cost savings. Conservatively, the percent savings can range from 15 to 25%, but can rise to as high as 30 to 40% when truly optimized.

Team Building

The concept of team bonding may seem cliché, but it truly is an integral part of the proper staffing model. Instill a sense of camaraderie and a value of "getting the job done" in the work force. The team that gets work done right – on time, the first time – is the team that shares a common goal. It sounds obvious, but each member of the team knows and understands their roles and that there needs to be an open dialog between the members of the team. Every choice that is made should be made with the ultimate goal of the project in mind. Creating a sense of unity also helps people work together. It should come as no surprise that people work a lot better together when they get along. Teamwork and agility are the defining characteristics of workforces that can deliver, repeatedly, even when faced with remarkable challenges. Less integrated teams shy away from these challenges and look for the easy way out; others meet these challenges head on and often find new opportunities by doing so.

Establish a culture of safety and productivity by creating a communication plan that encourages feedback, honesty, and openness. A major part of the communication plan for the biopharmaceutical facility was routine field walkthroughs, during which subcontractor owners and senior managers walked around the site and actively engaged the workforce. The goal of this practice is to examine the well-being of the workers by recognizing and rewarding safe work practices, sharing safety messages, and soliciting feedback on safety and management performance. Such conversations reinforce the priority on worker safety, which not only saves time by reducing work stoppages, but also means all workers go home safely to their families at night.

Field walkthroughs also foster a sense of ownership of the project in the on-site workers. This level of personal involvement with the management often means workers develop a new perspective of their roles in meeting goals. It leads to improved honesty and candor between workers and supervisors. The feedback managers receive can be used to evaluate the project and identify areas for improvement. This can generate fresh solutions and raise potential issues that may have otherwise been overlooked. One time saving solution resulting from this process makes it all worthwhile.

Having a good team environment helps to support continuity of personnel. Management must also support the continuity of a team as retraining causes delays due to lost skills and knowledge. Having a consistent team cannot be undervalued. Key individuals should be committed to supporting the project for its duration. The continuity of personnel is a key consideration in choices for team membership and leadership positions. Continuity of team membership and well thought out transition management plans are essential to the dissemination and consistency of the project vision.

Project Management Information Systems Supporting the Common Vision

The same electronic tools that support a distributed workforce also facilitate increased efficiency and reduction in cost. With team members scattered all over the globe, housing documents in a common, easily accessible location is paramount to success. In these biopharmaceutical projects, teams relied on an elaborate digital filing system of cloud storage. This system consolidated every document into one place, provided all revision tracking, and reduced the need for a document control person.

In addition, the team utilized a cloud-based project tracking system to monitor every stage of deliverable development. This system was fully integrated with deliverable work flows requiring minimal manual data entry and supplying real time progress tracking and reporting information on all deliverables. This system helped the team focus on the most critical paths and warned of problems before they became critical. At any point in time, any team member (vendor or customer) could access the system to find out exactly what a team halfway

across the globe was working on at that precise moment. This benefit cannot be overstated; every worker had a clear vision of the project status at any given time. The entire team could implement and test from anywhere in the world, as long as they had access to the cloud. Such great success was had by the team with this application that they extended the concepts to such project management tasks as change management, requests for information, and action items.

This electronic workflow removed the dead time associated with moving physical documents from place to place. Depending on the type of document, it was estimated that review and approval cycles in an electronic workflow resulted in schedule savings of 30 to 50 electronic reviews and tracking of comments along with electronic document approvals provided a more traceable and consistent system to assure all issues got resolved and their status tracked in the documents.

During the course of the project, these processes saved more than one million pages of paper. In addition to the costs of the actual paper, this eliminated the costs associated with managing a mountain of paper. There was no need for printers, ink, shipping, and time saved on the organization of punching and collating materials. Instead of having several people inputting the same information and keeping track of the same records multiple times, all progress was saved online. If someone else had already updated a project tracker, that freed up time to work on something else.

Conclusion

Meeting time lines, staying within budget, and meeting requirements are all goals of any project manager. Falling short in one area can cause problems in the others. Schedule can be maximized by distributing work across several locations, but over distribution also can cause issues. One must be careful to assure that both customer and vendor resources are sufficient to deal with the amount of work produced by distributed work locations. In addition, work systems must be established to assure all project team members can easily follow the project's processes.

There are important points to consider when using a distributed workforce. Upfront planning is critical, and project leadership must be diligent to assure continual alignment. Extra planning for team building and a hand on management style also contribute to the project success. Co-locate early to assure good information transfer and plan for consistency and continuity of team members. Sufficiently train distributed team leaders on the project's processes and requirements. Utilize automated electronic document workflow processes to increase efficiency and traceability; look for and leverage new enabling technologies like virtualization and cloud technologies.

Accelerating schedule is not simply a matter of throwing more people on the job; in order to accelerate a schedule a Project Manager must get the right resources to the right place while balancing cost versus the benefits of co-location.

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**The Project Management Institute (PMI) is a leading not-for-profit membership association for the project management profession, with more than half a million members and credential holders in more than 185 countries. PMI recommends practices and processes for the successful management of projects. Project Management Information Systems (PMIS) is defined as systems that are used to organize and distribute the project specific information. It includes a variety of things that document objectives, schedules, and responsibilities.*

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The article presents the implementation of a suite of software packages that together provide a total Enterprise project management system.

The Science of Project Management: Project Controls Systems Integration

by Frederick Cramer, Susanne Keller, Christopher Law, Thomas Shih, and Britton Wolf

The concepts in this article were applied to the ECP-1 Facility, Overall Winner of the 2010 Facility of the Year Awards. For further information on this project, see "Case Study: Genentech's ECP-1 Bacterial Manufacturing Facility, Overall Winner, 2010 Facility of the Year Awards" in the March/April 2011 issue of *Pharmaceutical Engineering*.

Background

Genentech is among the world's leading biotech companies with multiple products on the market and a drive to discover, develop, manufacture, and commercialize new medicines to treat patients with serious or life-threatening medical conditions.

In 2005, Genentech was ramping-up a build program due to increased demand for existing and new medicines about to come to market. By that time, Genentech had grown from a small biotech company with less than 3,000 employees in 1995 to more than 9,000 employees.

It quickly became apparent that an ad hoc approach to project management of capital construction projects would no longer be sufficient. To keep pace with growth, an intensive effort was launched to investigate and then implement a set of integrated tools and approaches to facilitate project planning and execution.

Investing in a full suite of project planning, monitoring, and control mechanisms is a prudent and necessary step to ensure project delivery. This investment must start in the front end planning stage to ensure the most appropriate execution strategies are selected and to put into place the necessary software platforms and resources to provide support during the entire project life cycle. A special focus on end-to-end project planning, cost, and schedule integration with comprehensive feedback is an absolute necessity if project goals are to be met. In addition, an integrated estimating and cost control scheme must be developed in tandem with the execution plan and early phase schedule development to ensure costs remain within the original authorized amount.

The result of this effort was a suite of tools and approaches known as Project Controls System Integration, which was spearheaded by a newly formed Project Services group.

This article presents the implementation of the software packages and covers:

- Estimating and Benchmarking
- Cost Management
- Schedule and Risk Management
- Small Project Portfolio Management

Challenges are discussed, such as organizational resistance to change, and advantages are listed for having an integrated Enterprise wide project management system.

Introduction to PCSI

Project Controls System Integration or PCSI (pronounced Pixie) was the vision of the head of Project Engineering in 2005. The basic idea formed from a desire to bring together discrete tools that dealt with cost control, estimating, benchmarking, change and risk management, and moving from a series of misaligned spreadsheets to a database driven model.

One of the goals of PCSI was to avoid manual re-entry of data when moving from one spreadsheet to another, consequently reducing human error. Furthermore, having all the project information in a common tool based on real-time data would enable management to make better decisions.

As the idea germinated and additional detail was developed, the decision was made for the modules to be "off-the-shelf" solutions that could be supported by the in-house IT department. A concept map shown in Figure 1 was developed with a holistic approach.

The concept map was developed to provide an overall vision for the capital planning and project delivery teams. The "Project Controls" and "Benchmarking" sections of the map were to be considered as a suite of integrated, off-the-shelf tools that would communicate and pass data. A set of requirements for these tools was identified

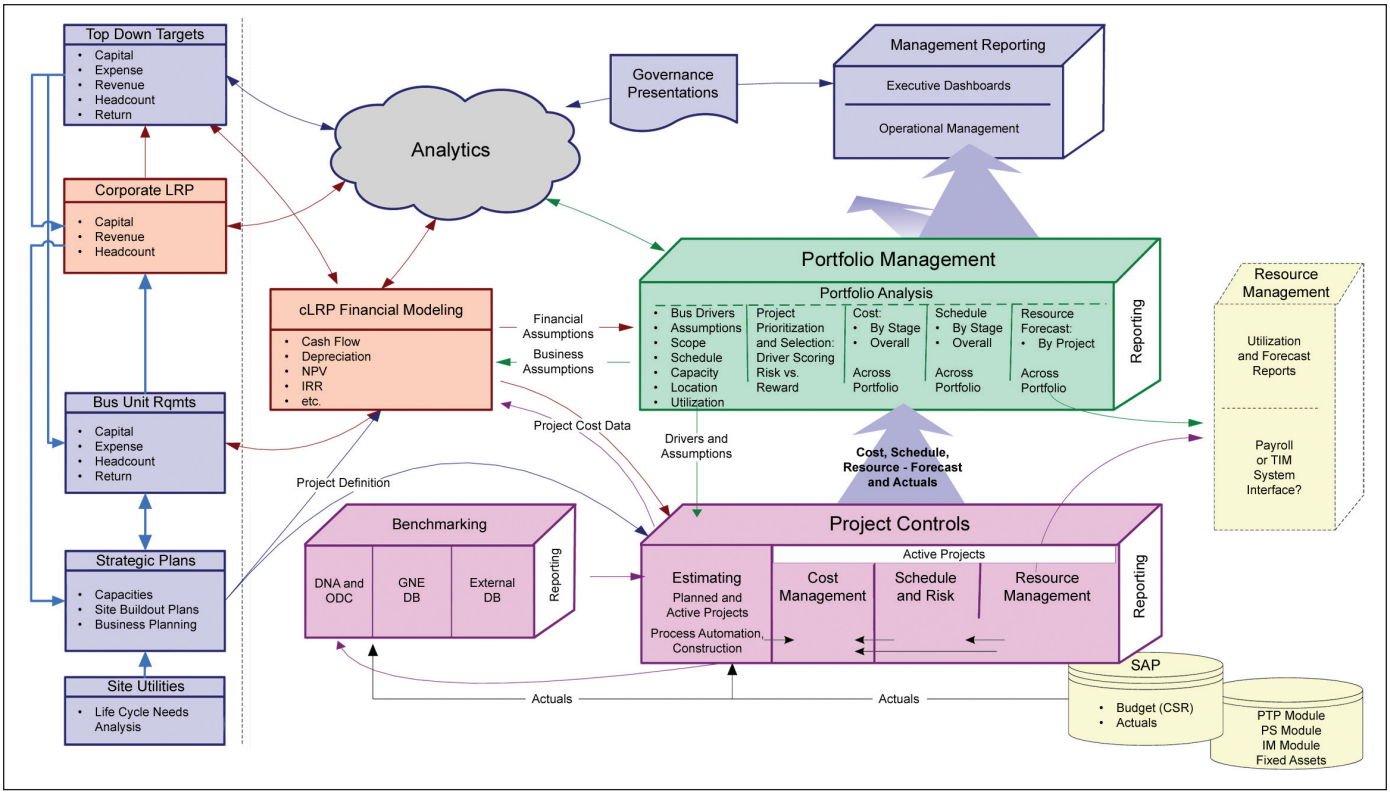


Figure 1. Functional tools concept map.

and the project was initiated.

Concurrently, a cross functional team developed a set of Good Engineering Practices (GEPs) that detailed all of the business processes underlying the Project Services functions of estimating, scheduling, cost, change, and risk management. The GEPs incorporated much of the native knowledge of the Project Management group along with industry best practices. After intensive vetting by an extensive review process, these practices served as the basis for engagement of PCSI.

After considering these requirements and implementing a strict bid and award phase, the solutions chosen were Skire Unifier for cost and change management, Primavera and Microsoft Project for project and portfolio planning, Timberline for estimating, and Advisor for benchmarking - *Figure 2*.

Estimating and Benchmarking

During Genentech's rapid growth period, a focus on capital efficiency and planned, predictable performance required the development of accurate cost estimates. Two major considerations were examined to meet these needs. The first was an increased competency in development of high level cost ideas/options with a +/- 50% accuracy for long range planning. The second required a flexible way to develop detailed internal estimates or review/challenge external costs estimates for large projects in execution.

This requires both a tool that develops, stores, and reports information in a

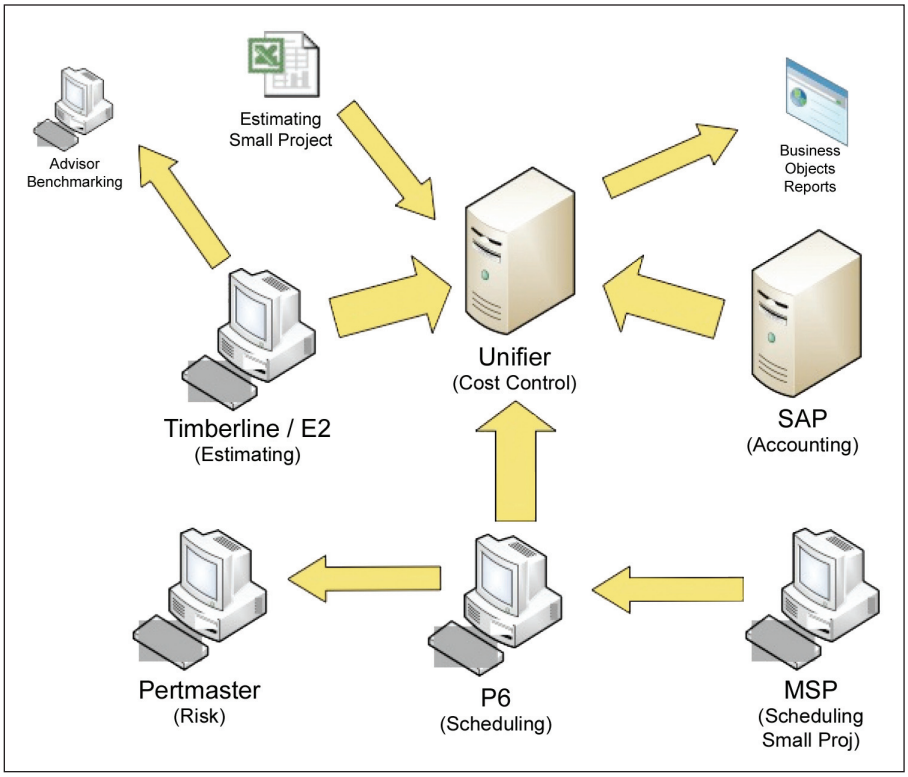


Figure 2. Tool implementation.

flexible, but consistent manner, as well as staff that understand the concept and methodologies of estimating.

Senior management bases business decisions on accurate cost data. It is important to develop cost estimates with the highest possible accuracy at any stage of the project lifecycle. Taking this into account, the following needs were identified:

- flexibility in cost breakdown structure to analyze options for financial feasibility
- options to develop estimates with a fast turn-around time
- credible in-house resources to work on confidential project studies
- build credibility with customers through a consistent and accurate reporting format used throughout the project life cycle

Before focusing on the tool to support estimating and benchmarking services, a small team of experienced estimators and project controls specialists developed business processes and common guidelines. The selected tools included Timberline as the detailed estimating tool with a standard RS Means database and an internal custom process database, E2 as the filing and information set, and Advisor as the global online benchmarking tool. Timberline has a direct connection to Advisor to move cost estimates for benchmarking and a direct Enterprise Service Bus (ESB) connection to the Unifier to transfer the latest estimate.

To perform fast and flexible alternative costs sorting, Timberline can show data in different breakdown structures. Four standard Work Breakdown Structures (WBS) were developed for estimating, benchmarking, financial asset allocation, and senior reporting. The system also provides the capability to map costs to any custom categories (e.g., cost breakdown for process steps for option analysis). This flexibility aids in supporting both customers and the internal Finance Department with data analysis.

To ensure a structured and consistent way to document and store estimating and benchmarking data, a server based database file structure was developed that allows controlled access to a large group of users and is consistent with the official Portfolio structure.

In building and modifying several first of their kind biotech manufacturing facilities, the challenge of a lack of standard processes and equipment databases became apparent. To account for this, Timberline provides the flexibility to use multiple cost databases, including an internal custom library based on historical data and off-the-shelf solutions. Additionally, standardized formats to develop estimates, collect benchmark data, and create reports aid in comparing project information.

Most early project cost studies or alternative analysis use the detailed data from Advisor from similar projects. The tool allows online access 24/7 at any location with multiple standard and custom reports based on high level metrics.

Requests for high-level ROM estimates frequently come from senior management. To provide information with a quick turnaround time, it is important to have a benchmarking tool, like Advisor, that is accessible online and provides custom reports for any special needs. Benchmarking is crucial to avoid losing valuable historical information, which improves the quality of future estimates.

Of high importance were clear and consistent reporting options from all tools spanning high level to detailed information. These outputs have increased credibility with the entire client base.

Cost Management

Cost management procedures and change control are fundamental building blocks of controlling costs on projects. When common definitions and procedures are coupled with a standard toolkit, accuracy and confidence is increased. The information can be aggregated across projects and provide actionable intelligence and visibility across the entire portfolio. Ultimately, the analysis of the common data can be used to improve performance on future projects. If the tool is based on the corporate network or the internet, the added convenience of remote access is possible.

When an organization has reached a high maturity level, the requirement for improved efficiencies in business processes and a corresponding reduction in duplicative work becomes a focus. Once the organization becomes committed to standardization, project cost forecasting becomes increasingly transparent and more real-time, in turn facilitating effective executive management decision-making. Enterprise reporting re-packages content for a variety of purposes, and single sources of data become a governing principal. This initiative at Genentech was referred to as "Class A."

There are several related concepts that, when applied together, multiply in value to a business, including: 1. one set of numbers, 2. workflow processes aligned to actual work, 3. common cost codes across all accounting/PM systems, 4. standardization of individual business processes, 5. one process for change control, and 6. one format for each standard report.

Data exists in many locations throughout a company. Whenever individuals query different financial systems and find differing answers, the credibility of the numbers is called into question, or worse, severe errors occur. Off-the-shelf software often requires that company business processes and procedures change to match the terminology and workflow of the selected system. An advantage of tools that are configurable is that the workflow can be set up to match exactly how teams do their work. Applying common cost coding across the corporate systems from accounting, estimating, project management, and benchmarking enables all arms of the company to speak the same language and data to be consistently exchanged or compared.

There are many ways to approach cost control and various project team members may have perfectly valid methods of performing individual cost management tasks. Unfortunately, by not utilizing the same business processes, it cannot be guaranteed that values displayed mean the same things across the project or organization. A workflow ensures a standard business

process is followed and that project data are comparable.

Change control on a project touches many facets of execution from the legal contract modifications through the delegation of approval authority to commit funds, as well as the impacts to the project forecast. Utilization of the system means that all changes can be seen and tracked exactly the same way. Standard sets of reason codes and root causes allows aggregation of data across all projects for analysis, potentially leading to improvements in execution on future projects as trends may be corrected early.

Issuing standardized reports from enterprise systems ensures that each project is measured identically and that management can have confidence in the accuracy of the project results and forecasts. The same data can be repackaged easily for multiple purposes such as project reports, management dashboards, and executive summaries.

The primary key success factor to cost management is to understand every business process that the system is intended to control. To set up the tool, the level of detail required is imposing as the configuration extends from the names of each individual field to the values on every drop down menu as well as the roles of personnel that take action at each step. The benefits are that each option exactly matches how you want the business processes to work. The second key factor is to have a common cost coding structure to enable the communication and transmittal of information in a common way.

Genentech adopted a Common Estimating Structure (CES). This coding exists in the corporate accounting systems (SAP), the estimating system, the project management system, and the benchmarking systems. At the highest level, the codes include:

1. Site Works
2. Building
3. Equipment
4. Process Installation
5. Internal Labor
6. External Labor
7. Indirect Costs and Expenses
8. Validation

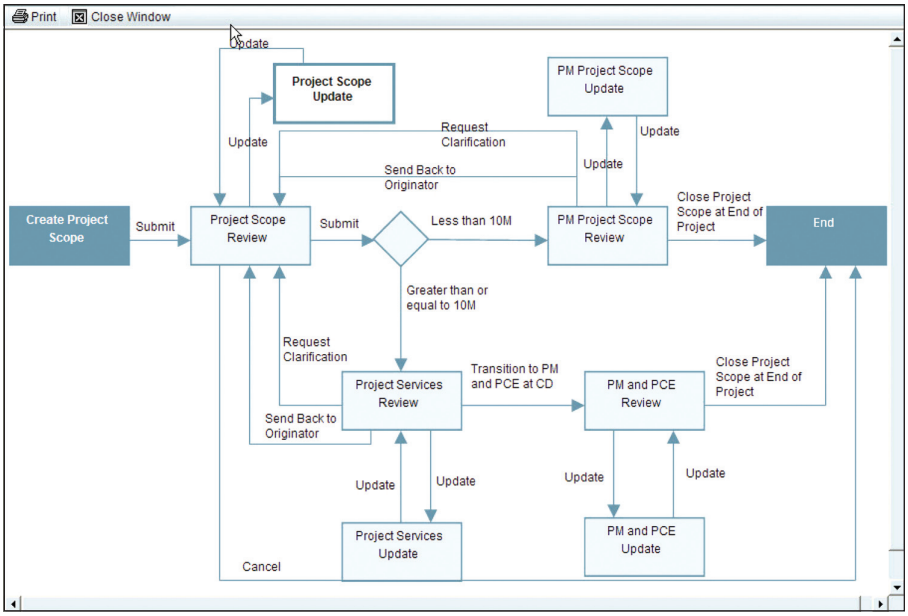


Figure 3. Workflow.

9. Contingency

The Cost Management and Change Control processes were divided into five sub-processes. Each sub-process has several business processes that collect and manage the data required for control, including:

1. Estimate Control
2. Budget Control
3. Commitment Control
4. Expenditures Monitoring
5. Forecasting

Each of the sub-processes are managed via a set of custom business processes with formal data collection and workflow - *Figure 3*. A separate module was implemented to manage the Planned Capital Portfolio for the company in terms of projects included in the plan, the approved (updated quarterly) scope and budgets, and the planned cash out forecast.

Once data collection begins in the project management system, it needs to be made available for use via reporting. Reporting is done at several levels within the organization with differing needs and levels of detail. At the project level, highly detailed transaction reports are required to manage the work. These include items like detailed cost reports, change order logs, purchase requisition reports, etc. Genentech's system produces these day-to-day reports in a simple tabular log format that can be output in many formats and automated to run and e-mail on a fixed schedule.

The next level of report is more complex, either crossing multiple business processes or requiring advanced formatting. Genentech utilizes Business Objects and Crystal Reports for this type of report. An example would be project monthly reports, which have multiple tables and charts along with period progress reporting. In addition, many reports that cross multiple projects or portfolios are used for Capital Planning or other functional business units such as Capital Finance and Corporate Risk Management - *Figure 4*.

The final level of reporting is for senior management. At this level, dashboards, traffic lights, and summary reports are made for reviewing exceptions. Highly formatted and suitable for presentations, these reports apply standard business rules across all projects ensuring all are evaluated in a similar fashion.

An additional benefit was that many corporate functions became aware of the value and type of data collected. Standard reports are requested for items, such as asset allocations, cash flows; and in service date reports for calculating future depreciation. Risk management utilizes construction schedule reports to

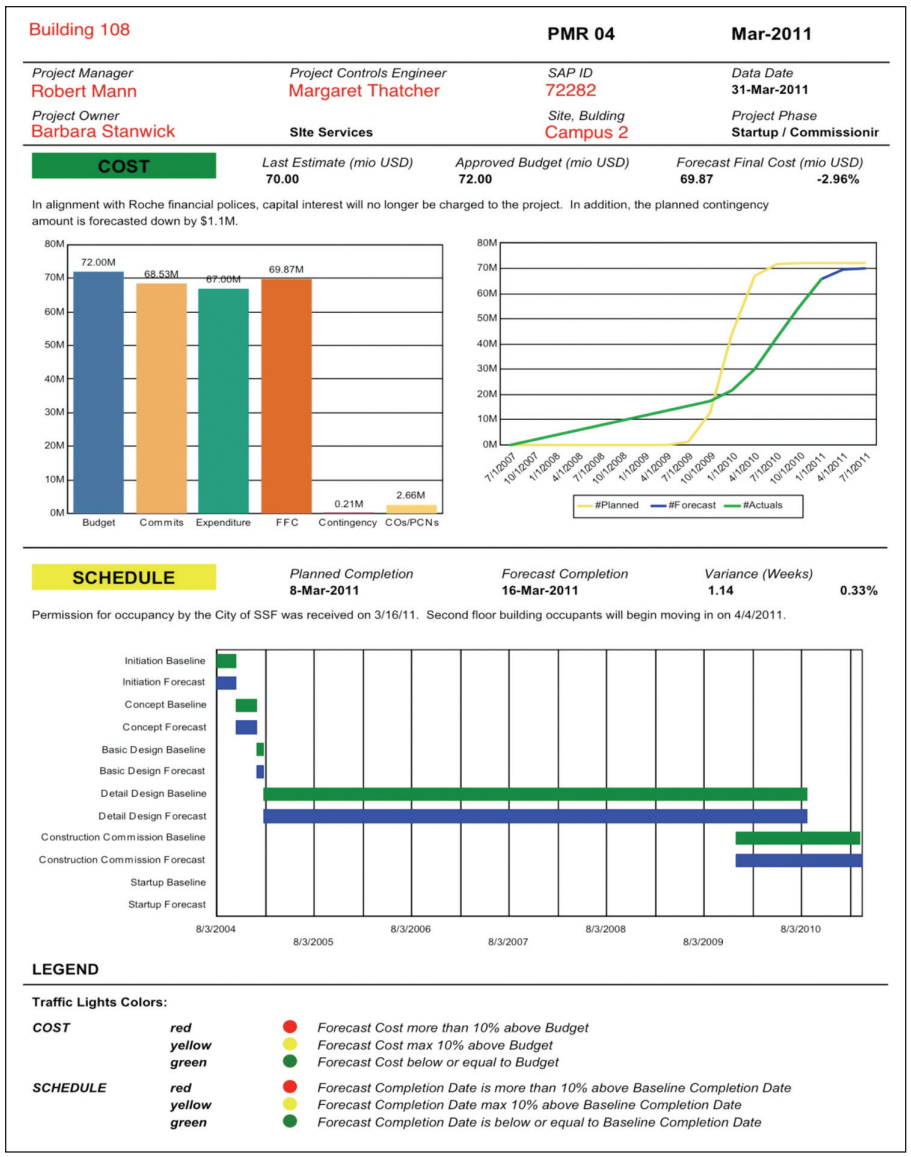


Figure 4. Project report.

procure the proper insurances for the duration of the portfolio of projects.

Scheduling and Risk Management

In the areas of project planning, schedule control, and risk management, the simple premise was to strive for planned, predictable performance. This was enabled by clear, consistent, and accurate reporting using a single enterprise source of planning and scheduling with portfolio capability that communicated key milestones for management review. Obtaining the targeted project schedule performance required an increase in collaboration and end-to-end project planning by driving more robust planning by all sub-teams, including Corporate Engineering, operational support groups as well as AEs, CMs, and subcontractors. Other areas that needed to be addressed to meet the performance objectives were a standard project risk toolkit, optimization in the area of resource planning, and some enhancements in the project front-end planning process.

For system implementation, the chosen platforms are a Primavera P6 database (hereafter called "P6") and Microsoft Project in which the project schedules, resource libraries, and all associated schedule data are constructed and stored. The major projects are scheduled on the P6 platform with dedicated planners, while some of the smaller projects and operational sub-teams utilize Microsoft Project, which is linked to the P6 database via Project Link or exported directly. The corporate database includes some 500 manufacturing projects and more than 300 non-manufacturing projects with schedule milestone data transferred from the P6 database to Unifier via an ESB for consolidated management reporting. Pertmaster, which is a software package that "bolts on" to P6, is used to execute both cost schedule and risk simulations for project risk management.

For the large project portfolio, dedicated planners build-out the details on the shared P6 platform drawing on proven logic libraries, or "fragnets," to ensure consistency. A common standard WBS for all projects allows for summarization of the schedule data under projects or other pre-defined portfolio structures. The level of detail is dependent on project requirements with the larger, more complex manufacturing projects requiring significant detail, while the office and lab projects less so. Figure 5 displays a roll-up by the major functional areas under the manufacturing and non-manufacturing groups. Each area is comprised of numerous small and large projects, which can be highlighted or grouped in any way required. The active project schedules are updated at a minimum of monthly intervals in the scheduling platform, and the resulting critical reporting milestones are "pushed" to Unifier. The resulting schedule information is matched in Unifier with the cost data and project status for monthly management reporting. This seamless data flow presents accurate and timely information to management with a minimum effort.

One area of emphasis has been end-to-end project planning. Major projects have successfully knitted together typical project execution schedules (i.e., engineering, module fabrication, construction, and Commissioning, Qualification and Validation [CQV]) with business infrastructure functions. While all engineering and construction schedules are in P6, business infrastructure or operations sub-teams often work in Microsoft Project, as this is the platform with which they are most comfortable. On one of the large

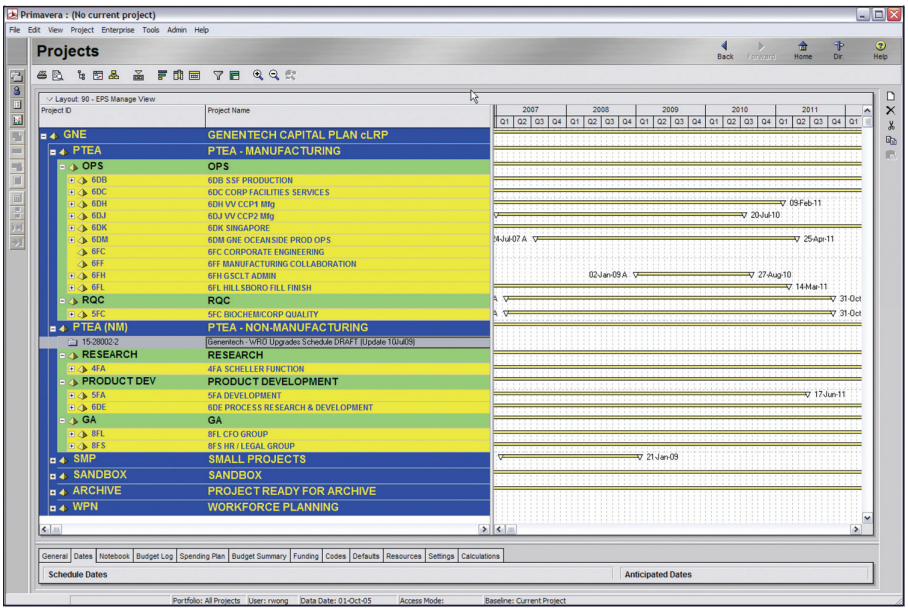


Figure 5. Schedule project portfolio.

complex projects, all data was pulled together in the P6 platform with a total of some 20 separate sub-schedules and 16,000 activities over several continents, including detailed design in Cincinnati, OH, module fabrication in Charleston, SC, site construction in Singapore, and process design and overall integration in South San Francisco, CA. This tight level of integration contributed significantly to a project that went from design to qualification lots in just 24 months.

Rigorous CQV scheduling has been extremely important for project success. Some CQV sub-schedules have included as many as 4,000 activities and utilized techniques such as resource and equipment leveling to verify achievability of completion dates. This planning and status is typically aggregated in the project master schedule with numerous exhibits generated weekly from the schedule data to ensure the project is on target. Often exhibits display consolidated planned vs. actual vs. forecast progress for CQV of critical systems with progress weighted by man-hours, while displaying percent completes and identifying which system is critical.

Document progress is another key activity to track in an integrated schedule. Quality documents and SOPs are required for project completion (i.e., the project is not complete until the paperwork is done). All the details were developed and updated in the schedule and linked to the "impact systems." Some projects have tracked the progress of as many as 600 critical documents with 2,800 activities and publish a family of curves with status of the draft through approved stage of all documents. This approach has successfully ensured that all documents are complete and ready to support licensure of a facility.

To increase productivity, Workforce Planning needed to be enhanced. Loading all of the corporate engineering resources – including project management, project services, design, automation, process engineering, quality, and procurement – as part of the work plan allows management to "see" the peaks and valleys of required staffing based on both actual and potential projects. This ensures that the resources are in place to properly support the projects, including considering alternative project timings. The intent is to ultimately load craftsmen to ensure the project sites are not exceeding available local resources so as not to experience additional labor costs.

Ref #	Area / Category	Description of Risk	Impact	Risk Type (Threat / Opportunity)	Risk Status	Risk Trigger Date	Probability Factor	Cost Impact	Schedule Impact	Risk Rating
1	Construction	Underground condition with firewater loop	Cost & Schedule	Threat	Active	6/15/2010	VH	M	L	50
2	General	End user identified changes	Cost & Schedule	Threat	Active	8/15/2010	H	M	M	48
3	Engineering	Need to finalize finish design and standards.	Cost & Schedule	Threat	Active	8/15/2010	L	M	M	24
4	CIT	New AV requirements may not be adequately incorporated into the current design	Cost & Schedule	Threat	Active	4/15/2010	H	L	L	32
5	Operations	Facilities support during commissioning	Cost & Schedule	Opportunity	Active	5/1/2010	M	L	L	24
6	General	Union labor negotiations (disruption)	Cost & Schedule	Threat	Active	4/20/2010	VL	L	L	8

Figure 6. Risk log.

Another area targeted for enhancement was project front end planning. Historically, there have been issues with the discipline of the front end planning process with the early activities not taking place in a timely and robust manner, examples being strategy and contract development, scope review meetings, etc. In order to address this, standard logics have been developed and published to guide and track progress. This process engages groups from procurement, project management, legal, and engineering support groups who may be only partially engaged during the early phases of the project, especially given their workloads on active projects. This approach has helped illuminate the early project phases, allowing both the teams and management to make those critical early decisions.

To manage project execution risk, a straightforward methodology was introduced that starts with a standard risk log to capture discrete project risks, rate these risks for cost, and schedule impact and assignment of a responsible risk owner - *Figure 6*. A formal session is held with the extended project team to brainstorm and capture the risks following up with development of mitigation and responses as well as follow-on updating on a monthly basis. Based on this data, a risk rating is calculated for each item, which is flagged on the log. This simple approach provides the team with a consistent and reliable basis for continuous risk management throughout the life of the project. The risk log feeds discrete risks to Pertmaster software. Coupling these risks with a cost loaded schedule allows for the generation of "Monte Carlo"

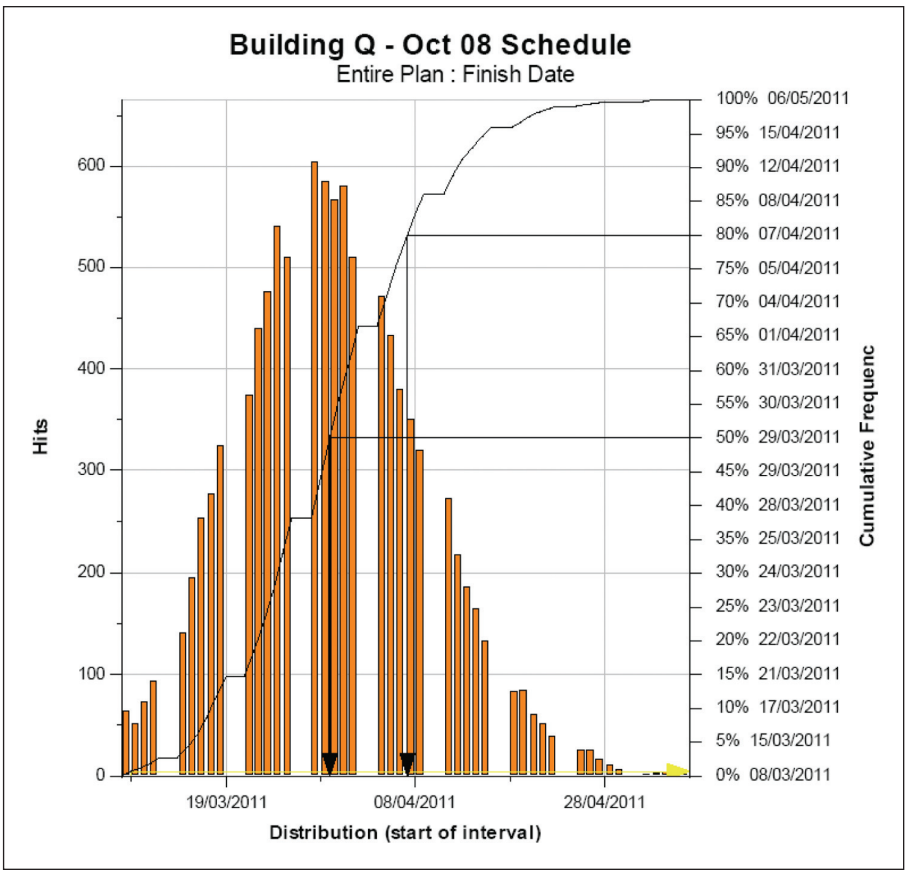


Figure 7. Risk simulation.

cost and schedule simulations. For the schedule simulations, it is typical to generate probable project completion dates, while for cost simulations, generation of probable project final costs is the norm, both given a level of certainty - *Figure 7*. Simulations are often produced as the project moves toward final funding and at other important inflection points. This information is used to verify project funding, develop potential contingency levels, and to review possible project completion dates. Management often requests simulations when issues arise during execution that may affect project outcome.

Small Project Portfolio Management

The original PCSI vision was to develop a suite of best in class tools to control and manage cost and schedule for large individual capital projects greater than $5 million. The implementation of these tools for the Facilities Engineering group to manage an $80 million small project portfolio of over 300 projects, ranging in value from $20,000 to $5 million, required thoughtful consideration of adjusting tools and processes to ensure standard processes for managing individual projects at the appropriate level of detail that feeds into a portfolio rollup.

The implementation of PCSI to manage a portfolio of small projects required a few adjustments in the application of the tools, as follows:

- Estimating – since most of Facilities Engineering projects are small and less complex, the group chose to continue to use Excel for estimates, which are manually uploaded into Unifier. As a project goes through different phases, the estimate is updated in Unifier directly.
- Scheduling – due to the less complex nature of small projects, Microsoft Project is used as the primary scheduling tool, and Project Link pushes the schedules into Primavera. A standard template was developed for all projects that have the 14 reporting milestones with a baseline, forecast, and actual that are pushed from Primavera into Unifier monthly.
- Cost Management – Unifier is the key central repository that all information feeds into and is used to report out information. The latest estimate, budget, change orders, PO commits, actuals are managed within Unifier. The level of detail was simplified by reducing the potential number of WBS codes used to track small projects from approximately 1200 codes to a standard list of 35 codes. SAP actuals are fed into Unifier once a month and a reconciliation process is put in place.
- Reporting – while Unifier has user defined reports that can be run from within the system to report on the projects and portfolio, a Business Objects Universe has been created against the Unifier database that allows for powerful customized ad hoc reporting of project information across the portfolio of projects.

Establishing a reporting cadence is critical to provide the structure for ensuring the data integrity on a portfolio. It sets expectations on the timing of when information should be updated in the system and the quality of the information at various times within the month. That coupled with regular management review of the information is critical to ensure accurate data. If the information is not being used and reviewed at the appropriate level, it quickly goes stale. Figure 8 displays report build up used for small projects.

The reporting foundation starts at the individual project level. Each Project Manager (PM) in conjunction with

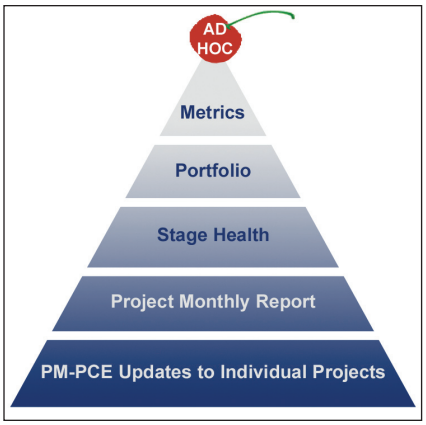


Figure 8. Small project reporting buildup.

their Project Controls Engineer (PCE) must update the cost and schedule information for their individual projects by the first week of the month.

The Project Monthly Summary Report pulls together four discrete data elements that indicate whether a project is under control. This is reviewed by the PM and provides an update on the project status and first level data integrity check. The four elements included are:

- Project Metadata Data – basic project information such as project number, name, current phase, project team members, key vendors, plus key data fields that drive report logic.
- PM Narrative – a monthly narrative entered by the PM into Unifier to provide commentary on project status and highlight any key issues.
- Cost Summary Info – the latest information on estimate, budget, change orders, commits, actuals, trends, and forecast from the cost sheet. Also included is monthly cash flow forecast information and cost variance stop light color status.
- Schedule Info – reporting on 14 key milestones that are incorporated into the standard schedule template used for all project schedules and schedule variance stop light color status.

The combination of Project Metadata, PM Narrative, Cost, and Schedule should tell an aligned story. If elements are not aligned, it is usually a sign of poor data integrity. For example, if a project is in Construction Phase, but the budget is much less than the estimate and there is no actual completion date on Detailed Design Phase, there is a misalignment of the information. That usually warrants investigation to determine if the data has been properly updated. Perhaps the project should still be Detail Design Phase.

A Stage Health Report provides a manager/director view of all active projects filtered by the PMs reporting to them. It provides a snap shot view of current stage forecast completion milestone against a baseline variance that drives a stoplight color. For fully funded projects, it calculates a current stage cost forecast against approved budget cost variance that drives a stoplight color. The calculations behind the stoplight color match the Project Monthly Report. This information allows the manager to focus on addressing issues on projects not on target (stop light yellow or red) and serves as a second level data integrity check.

A Portfolio Report is meant for use by portfolio owners and organized to filter for projects that make up their portfolio spend. It provides overall cost and schedule information, but also breaks up the cost into capital and expense dollars (which are separate budgets). The report also provides cash flow information on actuals and allows for forecasting against portfolio budgets.

Metrics are used to measure cost and schedule performance on active and completed projects, and measures how the portfolio is performing against a Class A goal of 95% within process metrics tolerance.

Ad hoc Reports that answer various business intelligence questions is the cherry on top. You get this information essentially for free by having a robust database of accurate project data. Some examples of leveraging the database would be to answer Business Intelligence questions, such as Status on Project in Closeout, Contingency Setting and Usage across Portfolio, General Contractor Workload/Volume, Analysis of Hard vs. Soft Cost %, Review Planned Project Start, List of Projects that Impact Key Stakeholders. The possibilities are limited only by the data and its accuracy within the system.

Conclusion

The introduction of the PCSI enterprise system has provided a holistic and integrated project management solution. The solution bridged from the earliest phases of estimating, through detailed planning and budgeting, to scheduling, cost reporting and risk management, and finally to close-out and benchmarking.

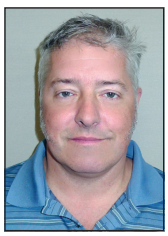
Although the implementation of a database of project management tools requires a significant commitment, it is only part of the solution. The organization must have robust processes that define roles and responsibilities as well as definitions around data required and clear reporting objectives.

As with any changes in organizations, workflows, or the implementation of new systems, it is very important to have strong senior management support and to be transparent with the extended organization.

One of the biggest challenges to the success of PCSI was the organizational resistance to both the new procedures and the new system that would enforce compliance. A significant effort was required to bring the organization to a maturity level that embraced both the new disciplined approach to Project Control and the new Enterprise system.

To manage and report on a large portfolio of projects requires resources, effort, and discipline. When coupled with the PCSI suite of tools, which has a central repository for all project cost and schedule information, an organization can truly work to "One Set of Numbers." Combined with the implementation of robust processes and regular management review of the information, this becomes the right formula to effectively manage a portfolio of projects.

About the Authors



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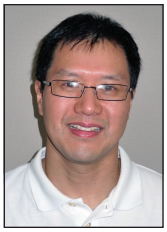

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Project Management Strategies for Multi-Company Project Teams

by Mark Mathis

This article presents methods and tools for successfully managing projects where team members are from multiple and sometimes competing organizations.

Introduction

With the growth of smaller, single-industry focused corporations and single-employee regionally based companies, clients in the pharmaceutical/biotech industry have come to enjoy the advantages of assembling project teams with exactly the individuals they need from multiple sources. There are risks and liabilities that accompany such decisions, but overall, this helps keep the market competitive for all service providers. This shift in resource availability brings a paradigm shift in how all companies must execute projects.

For those who have worked in large and small Architecture and Engineering (A&E) firm environments, there is a significant adjustment made when switching between the two. Larger firms have more established guidelines on how work is to be performed and by what criteria specific deliverables are completed. These work practices can span several industries that the larger firm services with the idea of creating continuity in a diverse, more project flexible workforce. Smaller firms have the flexibility and freedom to cross over inter-disciplinary boundaries and by necessity, must sometimes execute work outside of their comfort zones or technical background.

What seemed a great divide 10 years ago in the two operating philosophies has now been pulled together to form the hybrid project team. This is the team where several players from different organizations are made to work together to complete projects as a group. While it does happen that these hybrids form at the larger $100 million plus projects, it is more common to see it at the less than $50 million Total Installed Cost (TIC) jobs. The rationale is simple, smaller, more diverse, and focused teams will bring a wide breadth of experience without significantly adding overhead costs. By "cherry picking" individuals with backgrounds best suited to the scope, clients can offset the risks of a single company's shortfalls in personnel.

This scenario does not always provide for a lower capital cost for services. To the contrary, choosing select professionals from multiple firms will result in the highest Time and Materials (T&M) rates per person. What is diluted is the need for excessive overhead and administrative cost. Clients with a solid administrative infrastructure can offset this cost by including direct personnel to help with establishing and managing travel guidelines and expense reimbursements. Also, integrating members of a client's internal project team with the group will result in increased efficiency in communications and schedule alignment among all team members.

In this environment, projects can be derailed by taking the wrong approach to managing the team early on. Risks include larger firms trying to force their own governing work protocols on everyone else, individuals acting as lone-wolfs working in bubbles and not communicating with the group, and an increased likelihood of defection from key personnel. Much of this comes down to the personalities of those involved, but there are practical and successful strategies that if implemented early on will result in more managed scope control, higher retention of the core team, and a significant reduction in encountering the aforementioned risks along the way.

The concepts address in this article are as follows:

1. Identify Team Players
2. Identify the Project Culture
3. Identify Technical Resources
4. Communication

Strategy 1 – Identify Team Players

Encountering non-qualified individuals on project teams and realizing it a little too late is one of the more common risks all clients try to avoid. Overstated or embellished resumes can appear from large and small companies alike. Be on the lookout for inter-corporate nepotism as well. This can be especially common in projects where large project teams are relocated to jobsites. Corporate teams will naturally want to surround themselves with friends and their own known quantities. Don't assume that educational background was verified and check if the background seems appropriate for the positions held within the company or on the project. There can be managers of engineering staff who do not have an engineering degree, or other applicable experience other than the relationships with senior staff. In some states, you cannot add "engineer" to a title unless there is a relevant engineering degree and in some cases a regional license. This is not to say that all positions require degrees, but be discriminating with relocating project teams. The A&E's goal is to provide the right person, but often has to choose from a shallow pool of those employees who are willing to relocate. Set a project standard for background checks and degree verifications for everyone regardless of affiliation. This helps minimize what has become known as "empire building" on projects where the priorities tend to shift away from the project and more toward the individuals involved.

Another risk common in this scenario is personnel hired solely for the purpose of relocating. If you are considering a contract with any firm that includes relocating staff, you should expect personnel that are experienced with that company's policies and loyal to representing them even when away from the corporate home front. A senior executive brought on to pad a job with years and years of experience but no ties to the organization and a history of jumping companies can quickly poison the well for other members of the team. This too can turn into empire building which will only serve the goals of the empire and not the project.

Smaller firms will have every motivation to put their best face forward, but may not realize the advantages of integrating with others. It is easy to default to posturing and exaggeration of capabilities instead of identifying areas where they need support from others. Be aware of those that would propose to hold any technical role on a project. A small firm or individual should be flexible, but should have some area of expertise and a willingness to shore up the places where they are not as experienced. In fact, this is the primary advantage of assembling a team from multiple organizations.

There should be one flag for any project team. Since team members may originate from several different entities, a single governing set of directives that is aligned with the project objectives should be in place and managed by the team leader. If possible, become familiar with what the internal goals or employee incentives that may be in place at the different firms. Make sure these will align with project expectations. There are several technical strategies to defining the way a project will be executed but first, the hard part; identifying the project team's culture.

Strategy 2 – Identify the Project Culture

What is it about our industry that remains constant regardless of the company you work for or the products you help produce? It is the culture of that organization that defines, enhances, or limits the ability of the group to achieve success. There are many unique characteristics of the pharmaceutical, and more specifically, the biotech arena that set it apart from other multi-billion dollar industries. One that stands out is the fact that biotech itself is still an ever expanding and new marketplace. Having not been around near as long as the food and beverage, polymer, semiconductor and a host of other similar product driven groups; biotech has quickly set the pace of continually redefining itself every few years. Existing drug products are being manufactured more efficiently and becoming safer to produce and consume; and new drugs are pushing the envelope of what manufacturing and design tools are out there to formulate the product and increase speed to market.

If a hierarchy of culture were assembled for the biotech industry, it would include the fact that our media age continues to be one of the youngest, second only to Ecommerce; our workers and service providers can quickly set themselves apart as generators of new ideas and specialists in new areas of expertise; that the very core products are themselves a generous payback to those that work in the industry, striving to better the quality of life for friends, families and in most cases strangers around the globe. When speaking to those still in school, this culture is the easiest to convey because there are just a few professions that are as exciting and fulfilling as the pharmaceutical/biotech industry. No student can resist even the very basic principles of GFPs Green Fluorescent Protein (GFPs) and watching mice and other mammals glow under a black light. Combine that and other exciting technological advancements with the fulfillment of serving the sick and reducing the spread of disease worldwide, and you have an interested and engaged pupil.

Underneath the culture of the industry resides the culture of the individual company. This can be a manufacturer, a consulting group, or any number of service providers that work in the field. The first major challenge of working with a new client is determining what their culture is. This is more than a mission statement, it defines their community and ultimately what their priorities are. There are vast differences between company cultures that become evident after spending time with many of the larger drug makers. There are regional influences in west and east coast businesses and depending on the drugs produced; there are differences in attitudes about manufacturing; there are campuses that resemble colleges and parties and events that would impress even the coolest Facebook employee. Working at an acetaminophen plant will highlight the extreme difference between making aspirin additives in large bulk quantities and making a drug that only applies to a select market of consumers. The employees, the packaging, and very processes are all very distinct to the culture of the company where the drug is made.

The reason all of this becomes important to consider as part of a Team Leadership paradigm is that the culture of operations extend throughout all unique companies, but none is more

challenging and ever changing than that of the small business consultant. Larger engineering firms that service multiple industries where biotech is but a small sector, cannot afford to greatly deviate the process by which they execute projects. An engineer or manager working in the biotech sector one day may be working in the petroleum group the next, especially those who work on the infrastructure or non-process driven side. However, the smaller companies, specifically those that choose to focus on the pharmaceutical/biotech industry alone, must constantly reevaluate the respective client's culture with every project. This is a more intimate environment where more often than not, consultants are brought into the fold of a clients operating group. Even going so far as to integrate them into site specific training, access to facilities and perks, and internal metrics by which performance is rated along side of full time employees.

So in this rapidly changing environment, how does a small company navigate the different modes of operation within a changing client roster, while simultaneously establishing a unique identity in this environment? Something that becomes apparent when an engineer leaves the fold of a big company, is that the workload and responsibility matrices begin to flatten. The lines of segregating interdisciplinary tasks and objectives are no longer clearly marked. A process engineer must now understand equipment and procurement; a mechanical design engineer must now route pipe and duct alike; a controls engineer has to step outside of the programming bubble to consider people and material flow and locate shared, multi-purpose operator interface stations or OITs.

Identifying and understanding the client's culture is a key first step in any team's success. It is equally the responsibility of the client to communicate this to the group, understanding that those not in the fold may not be aware of what happens behind the scenes. The leadership of the team should take an active part in making sure everything is communicated and consider it a primary responsibility to keep the team involved and engaged with a client's culture.

Strategy 3 – Identify Technical Resources

This article considers the challenges of smaller jobs, those under $50 million. These are the projects where overhead and administrative support is cut extremely thin. The project manager also may hold a technical design lead role in addition to managing the client interface and schedule.

For these type of jobs, efficiency in operation is everything. There is no time to waste on shoving the metrics and tools for $100 million plus projects down the throat of the team who is not staffed to manage those tools and whereby the larger output is not relevant to the smaller project needs. The team needs tools that are designed appropriately for smaller, faster paced jobs with flattened levels of communication throughout.

Common challenges that surface on almost all of these projects are how to manage the project's technical deliverables with the design and procurement of material. Often a smaller team that would include a process engineer, an architect and a project manager will conceptualize the project with the owner's team. This results in a rough budget and general plan for facility and equipment. Material and personnel flows, square footage and throughput are critical to establish and set the groundwork for the preliminary and detailed design teams to gather information for their respective disciplines. Where large groups of engineers maintain a respectable catalogue of past projects, computer programs, and other resources to draw from, it may be cost prohibitive for a client to bring them on board, or more likely, teams are now cherry picked from a variety of organizations where issues of intellectual property prohibits an open and sharing environment. In the absence of more traditional resources, coming up with unique project tools for the team can be challenging. These tools need to not only streamline the more mechanical operations (like datasheet and specification assembly), but make communication of technical and commercial data more efficient.

The relative cost of failure was mentioned in one of this year's earlier articles on risk assessment and also has great relevance for this topic. The primary goal of a project team is not to execute perfectly, but to properly evaluate risk and identify problems as early in the project as possible, knowing that failure costs increase exponentially with time.

A. Multi-User Project Database

For process engineers who must now manage equipment, a customized database application can be a good place to start. The days of Excel's large, multi-layer worksheets with countless embedded calculations referencing obscure and sometimes hidden cell locations are phasing out. As these programs are passed on or reused, they can't help but bring the old project problems into the new project. Too often there is only a single individual who may no longer be with the organization that even knows the details of the programs design, fudge factors, or macros. While creating a database management system does come with its own set of challenges and frustrations, a very powerful advantage is the ability to properly name variables and protect formulas from modification –accidental or otherwise. After all, there are certain laws of fluid dynamics that will never change with regard to line hydraulics as there are other constants and calculations that can be placed into a controlled environment.

Many of the project deliverables can be rolled into a common database management tool to not only provide a single source location of information, but act as a gate check for shared properties. As an example, Figure 1 is a flow path for acquiring the information regarding the HP load for a CIP Return Pump. Assumption is that for this return pump there is only a tank and line circuit.

This is simplified and meant to demonstrate a linked chain of communication and output from three disciplines working on a common piece of information. If the horsepower changes, process may have trouble returning the CIP fluid back to the skid, equipment may have undersized the pump, and electrical may not have accounted for the load. Instead of these groups acting in individual bubbles, they are working from a common technical matrix where each has a part to update and maintain. It is not to say that large companies don't communicate well. More to the point is that on a project with a small amount of

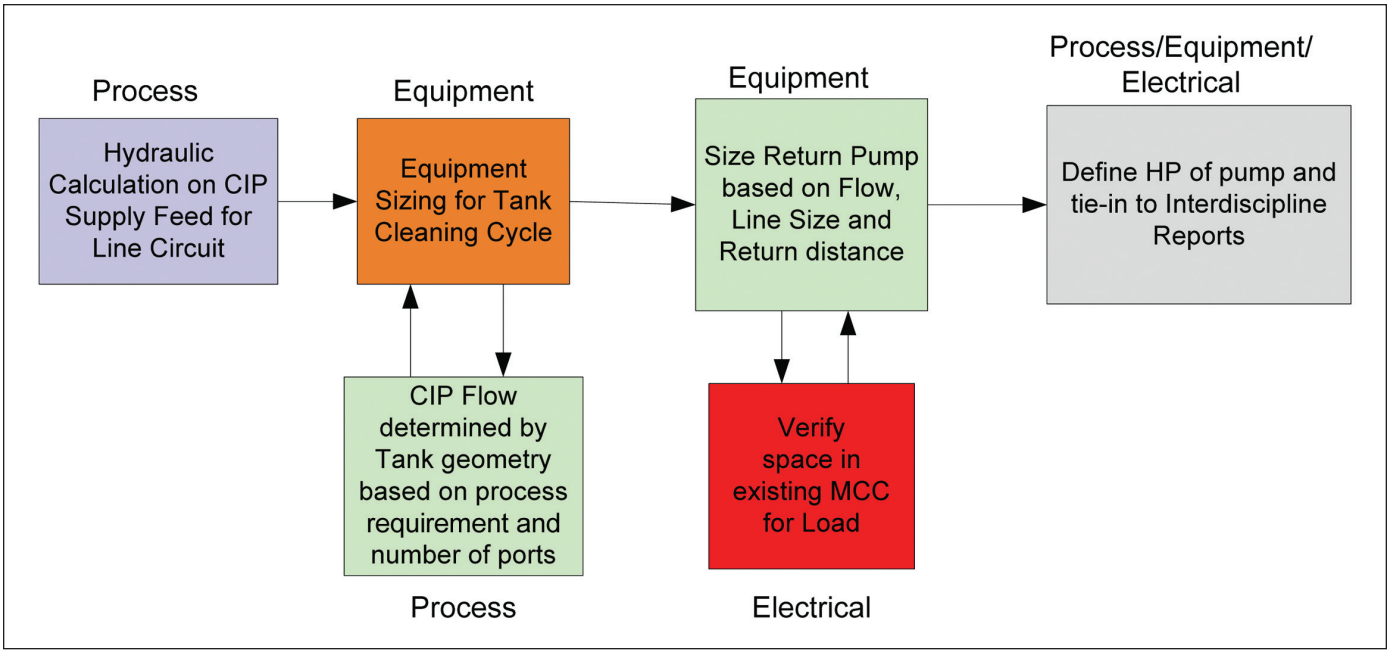

Figure 1. HP Calc for CIP return pump.

equipment resulting in a smaller electrical scope, there may not be a budget for a design lead to remain on the project full time throughout its duration. This lands the detail in a common room with links to quickly coordinate design impact when project changes occur.

With a database application such as Microsoft Access or Oracle based products, it is common to have a primary interface screen or "Main Menu." Projects should be divided by tasks or a minimum by discipline lead. The separation can be as simple as process, equipment, and electrical. For each of these primary categories, subcategories will fall per the deliverables of the project. It may look like this shown in Figure 2.

In practice, the main discipline categories will be populated with many more subcategories, most of which may not be interconnected, but all of which should serve as a data resource area for the project team.

B. Technical Design Templates

Something that works well with one discipline may not be successful in another, but from a process perspective, design templates are a must have. Design templates are meant to identify and define boiler plate technical areas that would be repeated several times through the course of a project. As an example, P&IDs can be split up into many different categories

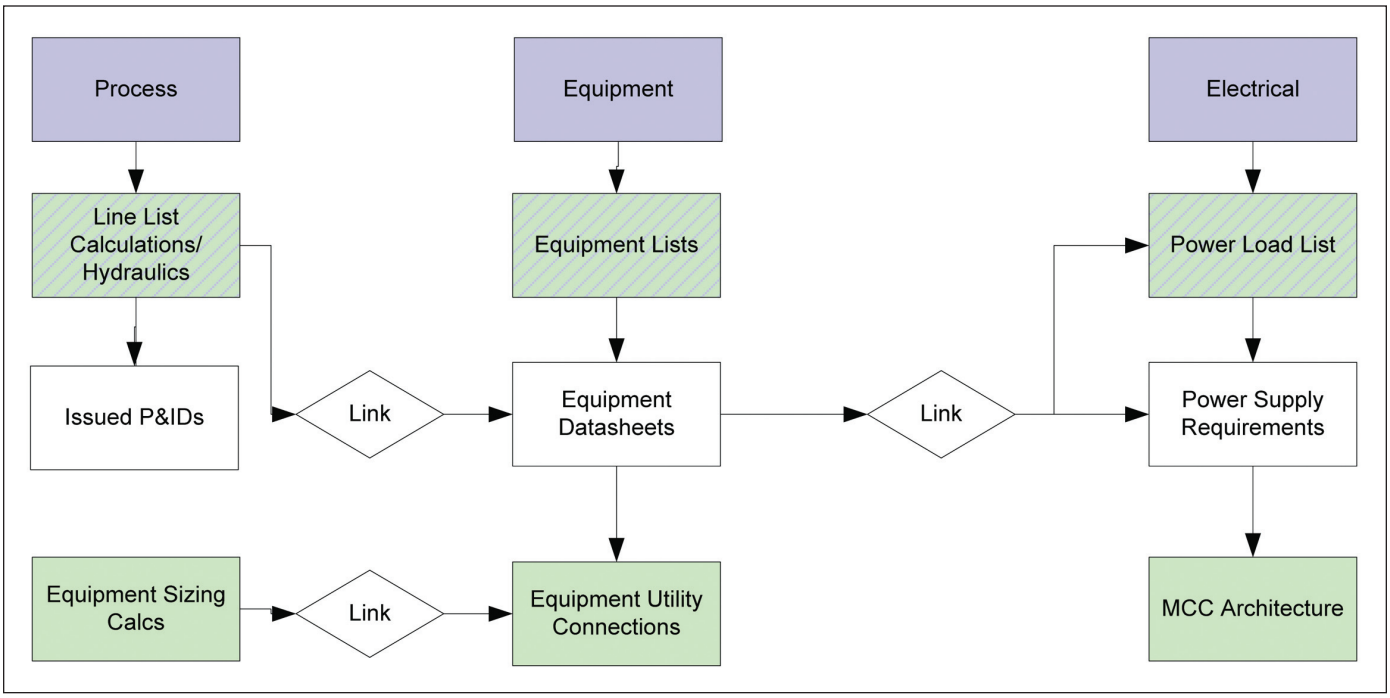

Figure 2. Inter-disciplinary project database flowchart.

such as upstream, downstream, process support equipment, utility, etc. The foundation of these drawings can have several design modules in common. A trick brought over from the automation side is to find groups of valves, instruments, components, or equipment that serve a common function and keep the operation and representation of those items consistent. This allows the automation team to easily reproduce and troubleshoot areas of their program that were similar.

From the process side, keeping the grouping of small components consistent is also an advantage, but branching out into larger modules of tanks, heat exchangers, and pumps can not only simplify the entire flow of the P&IDs, it can help bring consistency of operation to the finished product. Low hanging fruit would be things like vessel temperature control whereby buffer tanks, media tank, fermentation vessels, product pool tanks, and other similar vessels can all represent the respective heating/cooling operation the same way. There may be different setpoints, but the component cast of characters is often identical. This also branches out into instrumentation choices. There will be times when to preserve consistency, a common manufacturer or instrument model number may be used even though it is overqualified for its operation.

Plant steam and process steam traps are another area where consistency will add a lot of value. Producing the design template for each type of steam system along with the slight variations of horizontal, vertical, and high/low flow trap installations will not only make it easy for multiple P&ID owners to have similar drawings, but the piping designer doing the CAD work will have a lot less guess work to do when interpreting markups.

Here are some other design templates to consider:

- media feed through a filter
- dual CIP Sprayball arrangement for a vessel
- shell and tube heat exchangers
- chilled water/glycol inlet and outlet valves and instruments to a room or tank
- vent line drip legs
- transfer panel jumper design
- block and bleed arrangements

There are more, and the nice thing is that you can make use of these on future projects also. There are differences in design philosophies around equipment, but the basic mechanics will remain constant.

Note that this is not the same as just using an old set of P&IDs, to the contrary, this should protect against inheriting the mistakes of previous jobs and setting a design standard for future projects.

C. Simulators and File Share Software

One of the first considerations on a process driven project is how best to define scale. Defining this for the small project team is critical since the schedule is shorter and the need for consistency in deliverables is of greater importance. Give a centrifuge design to three different companies and you will get three different designs back. Documenting scale in the conceptual phase serves as the foundation for process equipment sizing, what options are needed, required utility services, and production support equipment. A popular method is to use a simulator and/or time and motion study to define and document scale. It would be good to research whether there are existing industry products out there that may serve the same purpose as an internal or custom program even if it is done with Excel worksheets. A turnkey software product sounds like a good idea; however, in practice, tends to implement more successfully on larger jobs. These types of tools are often designed for use in multiple industries and sometimes lack the necessary customization options to form fit to a smaller work protocol.

A good example is looking at the simulation platforms that are out there. Regardless of which platform used, Aspen, SuperPro, etc., each of them could be manipulated in some way to produce the desired result or graphic and more often there were very few people trained to make use of the available customization for their respective disciplines. It sometimes results in bringing a nuclear weapon to a knife fight. By keeping it simple and multi-use, each discipline lead can create and manage their deliverables and information on a common database platform with links for high priority detail throughout. The current versions of software for Access and Oracle have very good HTML options for reporting whereby weekly updates can be sent automatically through email or on a secure Web site for the whole project team. This negates the need for everyone to service the database for common and frequently updated information. This will not take the place of communication, but will bridge the gap between multiple disciplines on a small fast-paced job.

A software platform that is increasingly popular at job sites is that of the fileshare. Products like Autodesk's Constructware and many others profess to provide the kind of seamless information exchange on a common interface, but can easily morph into an endless sea of data in an even more endless sea of structured file folder locations. Constructware is no longer manufactured; whether this is due to user problems or a lack of market demand is debatable. This type of program does serve a purpose and is instrumental in the review, distribution, markup, and archiving of project documents, but tends to favor the construction teams more so than the early design teams. It becomes too easy to simply throw a document out there supposedly for everyone to have input on only to find out that if collected intranet dust for weeks without moving forward. The proposed database tool in this article will not take the place of a service like Constructware. However, it will fill in the need for a fluid design tool interface which serves the discipline lead's calculations and sizing of equipment and components during the design phases of the project. The reporting structure of the database can still be archived in a platform like Constructware or a simple project folder on the intranet.

Another positive aspect of this type of tool is the similarity between a typical PLC/DCS interface and the database interface itself. By keeping the database user friendly and implementing push button functions on the main screen and sub screens, it should serve as familiar territory for anyone

who has run process or utility equipment in the field.

In keeping with the "less is more" aspect of smaller projects, it is important not to overload your project database with ancillary functionality that is already done better elsewhere. A good example of this is smart P&IDs. If properly managed, smart P&IDs can be effective in managing the valve, instrument and material lists for the project. These lists can be produced from the Smart P&ID platform in a database format which can either stand on its own or sync with your project database. The advantage of syncing this data is reducing the chance of double dipping on procurement with regard to equipment boundaries, such as: where does the shutoff valves scope lie? It also would allow related discipline leads to append to the information things that may be important to them, such as unusual power supplies for instrumentation, or special conduit requirements.

Strategy 4 – Communication

Communications within small project groups tends to have both advantages and disadvantages when compared to the larger teams. The advantages are that it spreads quickly and by companies being small and/or having a small role on the project, there is inherent motivation to stay in the loop. Small project teams can push the boundaries of current technology using smart phones and Web based protocols for faster and more seamless interface with the team. Disadvantages are case dependent, but problems can arise in the event where team members are remote or perhaps not full time on the project. Engineers with several projects going on at the same time are often forced to place a pecking order for their projects to meet their respective deadlines.

This forces the need for a more frequent and standing interface between the team. During FATs Factory Acceptance Tests (FATs), the small project scenario plays out in short periods of time. Here exists the likelihood of team members who are from different firms and backgrounds, interfacing with a vendor's sub-team and working remotely sometimes for several weeks. The first thing a successful FAT team sets up is the schedule and tasks to complete per the protocol. This may involve starting off with a daily safety meeting, followed by splitting up to inter-disciplinary protocol sections, touching base at lunch, and doing a final wrap up at the end of the day to set the next day's agenda.

For small project work, while it does not necessarily have to be this packed with meetings, the basic theory is sound. More communication will equal better alignment and performance by all team members. For the first few weeks of the job, having a standing morning meeting for your project team on site with telecommunication video capability. If people can't attend due to schedule conflicts, or move the meeting earlier until you can guarantee attendance, make it mandatory. This helps set the priorities and allows team members from separate companies to get to know one another better. Spread out the meetings throughout the week as deliverables begin to fall into place, but try not to just meet once a week. With people juggling travel schedules, remote operations, and other project workloads, it won't take much to hit a conflict. As a project manager, don't fall into the trap of being reactive and calling the fire brigade every time something goes astray. Things will go wrong. Put in a system of regular, but brief meetings, email/text updates, and one-on-ones with team members to help anticipate problems and respond accordingly.

Clearly communicate the chain of command. Clients and consultants alike can tend to break out the corporate org chart and use this as a guideline for how the project is going to run. If a person two bars up is never going to be present at the meetings or play an active daily role on the job, they should not be listed in the chain. Let your team have one point of contact for communication and keep your org chart as flat as possible. This will encourage doing what needs to be done instead of what team members are just supposed to do as a scope or contractual requirements.

Encourage communication by applying incentives to shared deliverables between different leads within the team. Incentives should be built around time spent on the job to help with mid-project defection. When single employees are seconded to a jobsite, they are more at risks for taking the next best thing in job opportunity. Straddling a time and milestone type incentive will help identify the advantageous to sticking with the project until completion.

Case Study

Here is an example of a executing a job in a multi-company project team. In 2008, Biotech Company A and Biotech Company B partnered to produce a Biotech Company A product using production capacity from one of Biotech Company B's plants. The project's engineering company had approximately 17 process engineers on site, from two office locations that assumed responsibility for project management, process, commissioning and validation. Working side by side were multiple firms, including a large A&E firm and several one-person contract employees selected by Biotech Company B to manage the engineering and construction side of the project. Total project team size between all organizations involved was approximately 50 engineers and commissioning staff.

The clients also provided their own project staff to manage the technology transfer and to establish continuity in the drug's manufacture. Culturally, there could not be a more different match up. California with New England; large engineering firm with small; and several one-person 1099s to fill in the staff where needed; and nice heavy snowstorm filled winter to be based out of for a year. What appeared disastrous from the onset went very smooth. Strong client team leaders on both sides kept the staff meetings to a minimum and utilized technology to communicate pertinent information to the team. Each client provided an A-team of players who were intimately familiar with the product and the process and shared information through a common internet based fileshare platform. All project staff worked and housed in the same trailers and many travelled back to their home base every week or every other week. Per diems for travelers were kept consistent and fair and non-discriminate based on the company you worked for or your position. By establishing uniform project directives from the client's leadership and filtering priorities across all companies on the job, a common

focus (flag) was maintained and executed as a seamless team. Project staff were screened prior to joining the project for all stated education credentials through a common background agency that everyone utilized. Teams were purposely divided to include several people from different companies in each group. This helped to ensure no silos could form and become cut off from the team or project communication.

Daily safety meetings and client regimented regular training protocols provided a platform for continuity among the project team and eliminated much of the concerns over intellectual property between competing firms. Social functions were common and designed to be non-exclusive.

Conclusion

The culture of our industry is ever changing and impacts everything from the latest drug on the market to the way small projects are executed with multi-company teams. By thoroughly vetting the proposal team ahead of time, utilizing a flexible, custom, but powerful tool like an interdisciplinary database, project design templates, and a good fileshare platform, a small, multi-company project team can be more efficient in execution and identify problem solutions much sooner in the timeline. Creating a culture of collaboration to align with project goals will build trust amongst the team members and help to retain valuable resources for longer durations on the job.

About the Author

Mark Christopher Mathis is Regional Vice President of Integrated Process Technologies, Inc. and for the past eight years has managed the Southeast operations of their Engineering and Skid Fabrication division. Mathis holds a BS in chemical engineering and has 19 years of experience in the pharmaceutical/biotech industry. He has performed as both Senior Project Manager and Senior Process Engineer in the design, construction, and validation of large scale multi-product manufacturing facilities with a specialty and focus on design of large scale bioreactors and chromatography systems. Mathis has designed and Commissioned process equipment for a worldwide list of clients. As a member of ISPE for the past 13 years, he has held several local positions including Chairperson of Programs and Communications Committees, Treasurer, Vice President and President of the Carolina South-Atlantic Chapter. He currently serves on the ISPE CASA Board as Past-President and Chairs the Industry Advisory Council for the region. He also has just been elected as Chair of NASAAC for 2010-2011. Mathis is blessed with a wonderful marriage and two boys, Ryan and Connor. He spends his free time fishing, camping, and performing music at local Raleigh events. He may be contacted by telephone: +1-919-345-4044 or email: mmathis@intprotech.com.

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John Honey provides insight into Genentech's approach to delivering capital projects and shares his own perspectives on important issues in the field of project management.

PHARMACEUTICAL ENGINEERING Interviews

John Honey, Associate Director of Facilities Engineering, Genentech, Inc.

by Keith Gibbs, ISPE Project Management Community of Practice (PM COP) Chair

John Honey is the Associate Director of Facilities Engineering at Genentech, Inc. In this role, Honey provides leadership to a team of capital project professionals. He is responsible for the delivery of capital projects up to $10 million throughout the South San Francisco campus. Prior to joining Genentech in 2006, Honey spent 12 years at Merck & Co., Inc. where he held positions in engineering, manufacturing, supply chain, and operational excellence. He is currently a member of the ISPE Project Management Community of Practice (PMCOP) Steering Committee where he serves as the Project Management Application Chair. Honey has a BS degree in chemical engineering from Michigan State University and an MBA from Lehigh University.

Q What led you to a career in Pharma/Biotech?

A Working in an industry with a mission to save lives is definitely something that attracted me early in my career and what continues to motivate me.

Q What is your current role with Genentech?

A I currently lead the Facilities Engineering group at the South San Francisco campus. My team implements facility related capital projects up to $10 million that support the five million sq-ft campus.

Q What is your current involvement with ISPE? What attracted you to that role and what keeps you involved?

A I've been a member of the Project Management Community of Practice (PMCOP) Steering Committee for three years now. As the Project Management Application Chair, I participate in developing project management educational content for conferences, publications, etc. I enjoy working with colleagues that share common objectives and challenges.

Q What sets ISPE apart from other organizations?

A ISPE fosters a culture of best practice sharing, which is a benefit to the Pharma/Biotech industry. There is a tremendous amount of diversity and breadth of content that ISPE takes on and coordinates.

Q Has your management and leadership style changed as your career developed? In what ways and for what reasons?

A My management and leadership style has changed as a result of my own growth and development through years of experience. Sometimes that means adapting to different

individuals, team members, and organizational cultures to inspire and find effective ways to motivate and get the most out of a team. It doesn't change who I am or what I believe in. Simply having flexibility in the approach.

Q What are your biggest concerns for the future of the Pharma/Biotech industry – if any?

A As an industry, we are facing tremendous financial pressures. Although healthcare coverage in the U.S. is still under debate, we in the Pharma/Biotech industry should prepare ourselves to deliver our medicines to a wider patient base without adding costs. The expectation to operate our business more efficiently is higher than ever.

Q If you were to devise a "mantra" that industry could use in regard to its approach to Project Management, what would that be?

A Project Management is a service that is provided to the business/industry that we serve. Our customers are typically those that discover, develop, manufacture, and market life-saving medicines for patients. Project Management services can be thought of as an enabler of our industry. Successful Project Management translates to success for our customers and their ability to deliver on their business commitments.

Q How would you define the value of Project Management?

A Project Management includes so many components that it is often difficult to summarize value or criticality. That said, I define the value of Project Management as managing all attributes of a project or initiative, balancing the critical components, and making appropriate trade-offs when required. The key is to understand the business objectives and the customer expectations and coordinate the project in such a way that it completely fulfills these two requirements.

Q What are your views on managing a successful project?

A A project is successful if the value defined above is maximized. If a project meets or exceeds the business objectives and customer expectations, then success is achieved. We often talk about meeting scope, schedule, and budget as key success criteria and yes those are important. But if you miss the business objective or the functionality of the project does not meet the customer's expectations, then it's hard to claim success.

Q How can government, academia, and ISPE work with the industry to help address some of these concerns and also provide excellence in training, education, and knowledge to advance the Pharma/Biotech industry?

A Currently, there is a lot of content available through organizations such as ISPE that is broadly targeted to individuals and organizations throughout the Pharma/Biotech industry. In addition to the current approach, it would be helpful to develop material that targets leaders in the industry who are decision makers for their organizations and can influence change. This targeted audience can take best practice material back to their organizations and incorporate into their business systems. By taking this approach, best practices can be implemented in a systematic way throughout industry and have a wider spread benefit.

Q What are some of the biggest risks in biotechnology projects that face a Project Manager?

A Projects implemented in the cGMP environment carry the highest level of risk. Any impact to the cGMP environment can have significant consequences to the downstream supply chain. That's why there is so much rigor put around these projects and why we have more robust project requirements, deliverables, and governance in the cGMP area.

Q What are the advantages to putting in place a scalable project delivery process? Describe what is in place at Genentech.

A A one-size fits all process for project delivery has its limitations. No two projects are exactly alike in terms of scope, complexity, business drivers, cost, etc. So whatever the approach to project delivery, there needs to be flexibility and scalability. At Genentech, we have taken the approach to put separate processes in place – one to execute projects that are greater than $10 million and one to implement projects that are less than $10 million. The less than $10 million process is essentially a framework that provides a structured approach to implement projects ranging from $50,000 to $10 million. There are required and recommended deliverables at one or more stage gates that can be tailored to meet the needs of the project based on complexity and risk.

Q What are some of the key metrics used in your organization to gauge project performance or success?

A We use the traditional adherence to budget and schedule to monitor the overall health of projects and the portfolio. We also evaluate cycle time, contingency management, and portfolio resource efficiency. Moving forward, we will be putting in place a more robust measurement system that measures a combination of quantitative and qualitative measures, such as customer service and relationship management to ensure a more holistic gauge of performance and success.

Q Do you think that having project standards for equipment, instrumentation, and test methods will result in reduced capital costs and project delivery timelines?

"By continuing to streamline our project delivery model, we will help drive value in capital spend today and mitigate depreciation expenses tomorrow."

A Absolutely. Standardization drives efficiency by removing repeatable work from the process. For instance, the IQ and OQ for an autoclave should have similar elements that can be utilized from project to project. If the project team does not have to re-invent the similar elements for each project, work has been removed from the process translating to reduction in capital costs and schedule. Of course, the challenge is to identify the right level of standardization since although there are similar elements across projects, there are also very different elements – no two projects are exactly alike.

Q What is your definition of Operational Excellence (OE) and how have you applied it?

A Operational Excellence is the application of continuous improvement in a structured, disciplined way that ensures sustained improvements and results. The key here is sustainment of the improvement. There are a lot of good ideas that come from all parts of the organization and a lot of effort is spent designing and implementing those ideas. Successful OE projects or initiatives are those that are fully operationalized and become part of the everyday business process. For example, we've established effective project delivery processes using simple OE techniques and tools, such as Suppliers-Inputs-Process-Outputs-Customers (SIPOC), Responsible-Accountable-Consulted-Informed (RACI), and process mapping. A system is in place to measure and report on "project health," which ensures that projects adhere to the process and consistency is sustained over time. As these measures are rolled up across the portfolio, we begin to understand where there are opportunities for improvement. A commonly used lean tool called "Kaizen" (which means "change for the better") is employed to implement improvements quickly. A successful Kaizen includes a control plan to ensure that the change sticks. We've successfully applied Kaizen techniques to reduce project cycle time, drive efficiency into the project close-out process, and improve project contingency utilization.

Q What primary business initiatives are you focused on in your current role?

A The way my current organization is structured, nearly all project management and project execution activities are outsourced. My team and I are looking to transform the current outsourcing approach into a turn-key project delivery model that incorporates performance based contracting concepts. This new approach will translate into a streamlined project execution and contracting system that will allow my internal team to focus more on aligning the capital portfolio to the business objectives.

Q What are some of the concerns or issues you have today in your operations? What kind of improvements do you think that you can make to mitigate those concerns?

A The current financial climate brings focus to how we direct our capital investments and to ensure that the value of our capital spend is maximized. Capital spending has long-term impacts – a capital investment today translates into future depreciation expenses. By continuing to streamline our project delivery model, we will help drive value in capital spend today and mitigate depreciation expenses tomorrow.

Q What do you see as emerging methodologies in Project Management? What are you implementing?

A Putting more focus in managing outcomes as opposed to the task. Performance based management is an emerging concept in the project delivery sector. The Facilities Management industry has successfully implemented these concepts and I believe that there are elements of this philosophy that can be successfully applied in the project delivery service model.

Q Do you have any advice or recommendations for current or future Project Managers?

A Project Management is such an exciting field because every new project brings a new set of challenges and opportunities. It never gets old, unless you let it. My advice is to not be complacent in how to approach your projects. Look for better ways to accomplish the goal. No matter how much process, requirements, deliverables are out there, it still boils down to the people doing the work. The Project Manager has the opportunity to be innovative on every project in how to use those processes, tools, etc. Maximize the value you provide!

Q Is there anything else that you might want to say to our readers? Any last thoughts on the industry you serve?

A I think that despite all the challenges that our industry faces, we will continue to innovate, become more efficient, and ensure that we continue to deliver life-saving medicines to the patients we serve. Stay tuned because the best is yet to come!

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Cleaning Validation for the 21st Century: Acceptance Limits for Active Pharmaceutical Ingredients (APIs): Part II

by Andrew Walsh

This article discusses how to establish true science-based limits using data from clinical and toxicological studies, a risk-based approach to evaluating cleaning validation data, and guidance on setting statistical process control limits from that data.

Introduction

Part I of this article[1] discussed the history of Cleaning Validation Acceptance Limits for Active Pharmaceutical Ingredients and where the currently used industry limits came from, analyzed the current approaches to setting acceptance limits, and discussed some of the problems and weaknesses of these approaches. Part II will discuss how to establish true science-based limits using data from clinical and toxicological studies, a risk-based approach to evaluating cleaning validation data, and guidance on setting statistical process control limits from that data.

Establishing Science-Based Limits

As discussed at the end of Part I, setting cleaning validation limits based on all available safety data is much preferred over an approach that considers only one factor (therapeutic dose). ISPE's recently published Risk-MaPP Baseline Guide[2] goes into great detail in describing how to set health-based limits using all the toxicological and clinical data available. Although Risk-MaPP is new and is structured to align with the principles described in the recent ICH Q9 document, much of its contents are based on long-existing principles and long-used procedures in toxicology. The following discussion will summarize some of the guidance on determining health-based limits provided in the Risk-MaPP Guide.

Before attempting to set limits of any kind, it is important to understand what hazard an API may actually present to a patient. Risk-MaPP states that a…

> *"…hazard describes the inherent property of a compound to produce adverse effects, e.g., in patients that may be exposed to the compound as a trace contaminant in another pharmaceutical product."* and *"Each compound has its own inherent ability to cause adverse effects (i.e., toxicity) – effects that may be well documented in the case of the API….."*

Once the hazard is identified, the hazard should be characterized by examining its dose-response relationship and the consequences of exposure. The consequence is then considered in the establishment of an Acceptable Daily Exposure (ADE). In Risk-MaPP, the ADE is defined as:

> *"The daily dose of a substance below which no adverse events are anticipated, by any route, even if exposure occurs for a lifetime."*

Although it should be obvious, I will point out here that, from Risk-MaPP's definition, the ADE is a very conservative value.

During the identification of the hazard, a formal review of all available data for the compound is performed. For an API, the data used in this analysis would be the data submitted in the company's regulatory filing. By definition, this includes all of the preclinical and clinical data required for approval of the drug. Through review of these data the "critical effect" can be identified. The critical effect is the first significant adverse effect that is observed as the dose increases. For every hazard there is a dose

below which no effects are expected and this can be the basis for determining an ADE. Exposures below this ADE will not lead to any other adverse effects.

The next step is to define the no-observed-adverse-effect level (NOAEL) for the critical effect to be used for derivation of the ADE. The dose at which a significant adverse effect is first observed is the lowest-observed-adverse-effect level (LOAEL). The application of uncertainty factors and other adjustment factors results in ADEs that are unlikely to produce any undesirable compound-related effects.

The ADE is derived by dividing the NOAEL for the critical effect adjusted for body weight (e.g., 60 kg) by various uncertainty or adjustment factors to extrapolate to the "true" no-adverse effect level. Uncertainty factors have been defined for each of the main sources of uncertainty as described below.

Calculation of the Acceptable Daily Exposure (ADE) Value:

$$\textbf{ADE}\ (\text{mg/day}) = \frac{\text{NOAEL} \times \text{BW}}{\text{UF}_C \times \text{MF} \times \text{PK}}$$

Where:

ADE = Acceptable Daily Exposure (mg/day)
NOAEL = No-Observed-Adverse-Effect Level (mg/kg/day)
BW = Body Weight (kg)
UFC = Composite Uncertainty Factor
MF = Modifying Factor
MDD = Maximum Daily Dose (mg/day)
PK = Pharmacokinetic Adjustment(s)

The calculation of the ADE takes into consideration all of the available data and applies corrections (UFC, MF, and PK) to the data for Intraspecies Differences, Interspecies Differences, Subchronic-to-Chronic Extrapolations, LOAEL-to-NOAEL Extrapolations, Database Completeness, Modifying Factors, Pharmacokinetic Adjustments, and any additional factors that may need to be considered. The procedures used in calculating the ADE have been well established for decades and Risk-MaPP cites a number of existing guidance documents and peer-reviewed articles on setting health-based exposure limits in this manner.

Suffice it to say, that well established tools already exist to develop a truly science-based limit for exposure to pharmaceutical APIs and this limit (ADE) is not only appropriate for, but can easily be used in, cleaning validation. Choosing the ADE as the starting point for calculating cleaning validation limits ensures that all subsequent values are truly safe. So how does using the ADE fit into current cleaning validation practices?

Using the ADE is simply a matter of replacing the value "Lowest Dose (A)/Safety Factor" with the ADE value. All other currently used calculations discussed in Part I would remain the same; for example:

"New" Swab Calculations using the ADE

1. $\dfrac{\text{ADE (mg/day)} \times \text{Batch Size}}{\text{Max Daily Dose (B)}} = \textbf{MSC}^*$

   *Maximum Safe Carryover (Note: MSC is equivalent to the term Safe Threshold Value (STV) found in Risk-MaPP)
2. **MSC**/Total Surface Area = Surface Residue µg/cm^2
3. Surface Residue/cm^2 × Area Swabbed = Residue on Swab (µg)
4. Residue on Swab (µg)/Dilution Volume (mL) = Residue level in swab sample (ppm)

(Note: Although the calculations are the same, another distinction that this author believes should take place is the change of terminology from "Maximum ***Allowable*** Carryover" to "Maximum ***Safe*** Carryover." Just because we in industry can calculate a limit that is high does not mean that it is an ***allowable*** carryover to a regulator. Basically, no cross contamination should be allowable if you can easily prevent it; the goal should be to minimize cross contamination.)

Setting the acceptance criteria to a health-based limit such as the ADE offers many advantages. The ADE is toxicologically and pharmacologically derived based on data generated by commissioned or published studies and not simply based on a dosage calculation. All the appropriate safety factors have already been applied in deriving the ADE. Using a health-based limit such as the ADE also has the benefit of being presented in the drug filing and reviewed by regulators.

The ADE is now an appropriate starting point to set a "safe level" for cleaning residues. However, while swab sample limits calculated from an ADE will definitely be safe, they will still suffer from the wide ranges shown in Table C in Part I. Some ADEs will result in lower swab sample limits, but many will result in higher swab sample limits. Take, for an example, the low dose (81 mg) Aspirin used for prevention of heart attack. The ADE will in all likelihood be much higher than

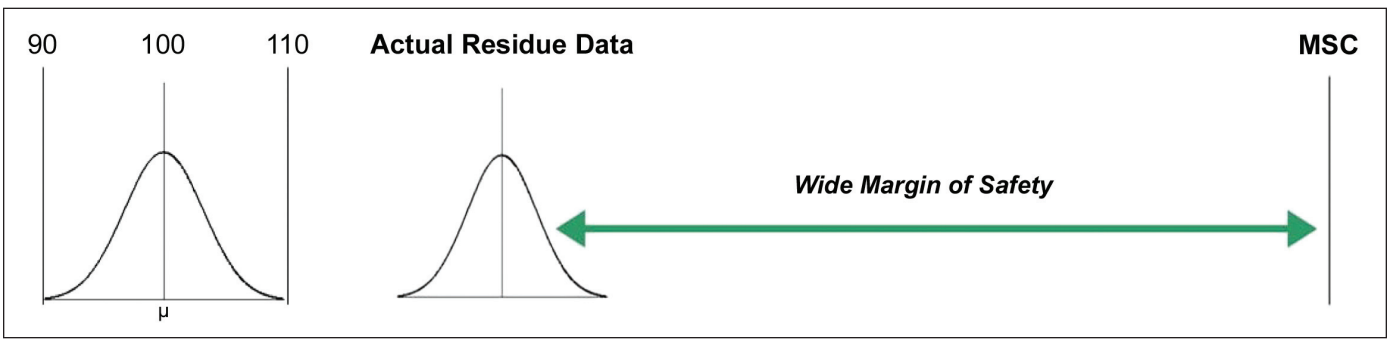

Figure 1. Relationship of cleaning data to "safe" levels (MSC).

Drug Compound	Drug Type/ Adverse Effects	Lowest Therapeutic Dose	1/1,000th of Therapeutic Dose
Low dose Aspirin	NSAID/low side effects	81 mg	0.081 mg
Ribavirin	Anti-viral/teratogen	600 mg	0.6 mg
Capecitabine	Chemotherapy/ numerous side effects	1150 mg	1.15 mg

Table A. Comparison of 1/1,000th limits for low and high risk compounds.

0.081 mg. So this brings us back to square one – how can we use the ADE if it suffers from the same failings discussed in Part I as the 1/1,000th approach? What it brings this author to ask is:

Why Are We Calling These "Limits"?

A definition of a "limit" that would be commonly understood in the pharmaceutical industry is "a point or line beyond which data may not exceed." For example, the upper monograph "limit" for Content Uniformity may be 110 and a tablet data point at 109.9 would be considered to pass this limit and be acceptable as visualized on the left in Figure 1. For cleaning validation we consider the calculated "limits" as being a "safe" level. Higher levels than these would potentially present a risk to a patient. Therefore, theoretically, residue data for cleaning validation should really be as far away from the "safe" level as possible as shown on the right in Figure 1.

Cleaning procedures should strive to reduce residues to the lowest levels that are possible to consistently achieve (without heroic efforts) regardless of what levels the calculated limits may seem to allow. As seen in Table A, the limits for the chemotherapy product suggest that residues 100X higher than for the NSAID product would be acceptable. This should not be, even from a cleaning standpoint.

In our daily lives, I believe none of us have higher standards for peanut butter residues remaining on our dishes than for jelly because jelly is easier to remove, or require our forks to be freer of egg residue than a plate. Regardless of the residue type our dishes and utensils should be equally clean. Pharmaceutical equipment should be equally clean regardless of what drug product was manufactured on it, the type of equipment it is, or which company is using the equipment; all pharmaceutical equipment product contact surfaces should be cleaned as well as possible. It is not logical or reasonable or even compliant to clean one piece of equipment less than another simply because "the calculated limits say we can."

As discussed in Part I, the calculations for swab samples results in limits that are either grossly too high or too low. Can we really use these ADE-derived "safe" levels as "limits"? My answer is no; limits based on safety data alone may result in acceptance criteria that are well above the actual ability to clean the equipment. However, I would then add that these calculated "safe" levels can still be very, very useful. We should not use these calculated "safe" levels as "limits," but rather use them for assessing "risk." The "risk" to a patient can be assessed if these calculated "safe" levels are used for:

Statistical Evaluation of Cleaning Validation Residue Data

One of the primary principles of ICH Q9 is that:

> *"The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient."*

This principle can be employed in the evaluation of cleaning validations. As discussed in Part I (see Figure 2), the distance between a "Safe" Level and the actual drug residues after cleaning can be viewed as a "Margin of Safety." It should be quite obvious that the larger this distance, the safer the patient is from developing an adverse health effect from any residues that may get into the next product. It is equally obvious that from a regulator's perspective the larger the "Margin of Safety" the greater the confidence in the degree of control in the cleaning process. Thus, the application of a science-based limit and a significant Margin of Safety is a powerful demonstration of process control and patient safety compared to the application of arbitrary safety factors and a small Margin of Safety (due to arbitrarily low limits).

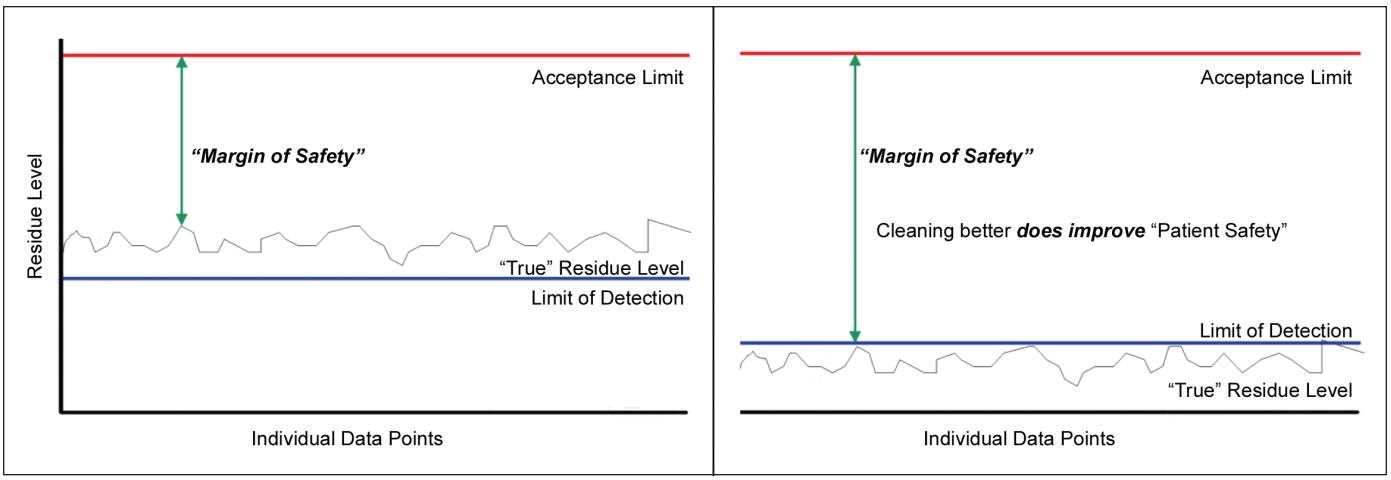

Figure 2. Effect of cleaning better on Margin of Safety.

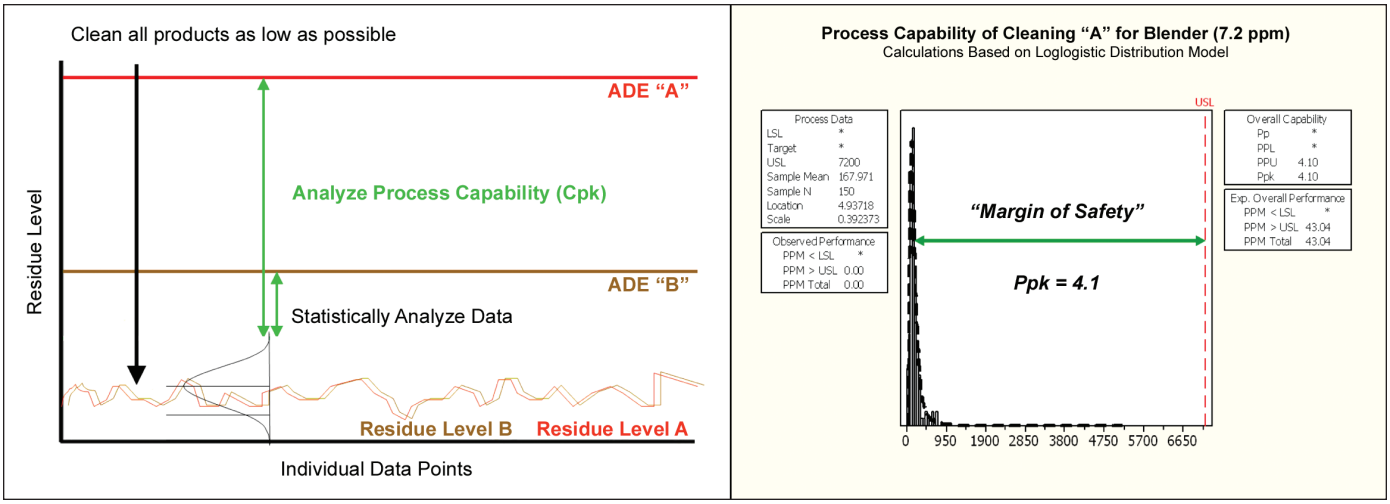

Figure 3. Graphical representation and actual process capability graph of "Margin of Safety."

The residue data collected for cleaning validations should be statistically analyzed to determine how effective the cleaning has been and if greater efforts are required. The residue data for each product can be evaluated against its ADE to measure the relative risk to the patient posed by the residues remaining on the equipment. This is shown graphically in Figure 3 on the left. The residues for products "A" and "B" have both been reduced as much as possible and are then compared to their respective ADE values.

While this graphically shows the relative safety of the cleaning process, the question remains. How safe is it? Well, the residue data can actually be evaluated statistically in terms of Process Capability using readily available statistical software packages. The graph on the right shows the results of statistical analysis of residue data using Minitab Statistical Software and how the "Margin of Safety" can be quantified as the Process Performance Capability Index. These software packages are also capable of calculating the number of potential failures based on the residue data (see Exp. Overall Performance on right chart in Figure 3). This approach is simple to perform, can quantify the level of risk, and also predict the possibility of failures. ICH Q9 points out that:

> *"Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight."*

When a company can show an inspector that the residue data demonstrates that the cleaning process is highly capable of providing a wide "Margin of Safety" and patient safety is clearly not an issue, the inspector can move on to consider more risky operations. Therefore, the acceptance criteria for API residues should consider the cleaning process capability of the manufacturing equipment or equipment train. This cleaning process capability should include an evaluation of the difficult to clean areas and the history of the "cleanability" of the equipment or equipment surface. Once the cleaning procedures have been statistically shown to pose no or little risk, it is then possible to move on to:

Setting Statistical Process Control Limits

The FDA recently posted their new Guide to Process Validation.[3] Its rationale and nearly all of its elements are directly applicable to cleaning validation. In the Guide, they point out that:

> *"Valid in-process specifications .....**shall be derived from previous acceptable process average and process variability estimates** where possible and determined by the application of **suitable statistical procedures** where appropriate. This requirement, in part, establishes the need for manufacturers to analyze process performance and control batch-to-batch variability."*

This is not a new requirement and the Guide referred to 21CFR 211.110(b). This concept can be directly applied to cleaning also and as we will see allow us to set valid specifications for cleaning residues. After the residue data have been collected and evaluated against the ADE and the level of risk found to be acceptable, the residue data can then be used to calculate a Statistical Process Control (SPC) Limit. The calculation of an SPC Limit is simple; the mean +3 or +4 standard deviations of the residue data. A CpK of 1.33 is obtained when using 4 standard deviations. Figure 4 shows an SPC Limit (green line) that has been set at the mean +4 standard deviations based on the underlying residue data.

Setting SPC Limits based on process data is a long established practice dating back to Walter Shewart in the 1930s.[4] While SPC has been used extensively in many industries for years, the practice is relatively new to the pharmaceutical industry. However, this simple and powerful tool has started to make inroads. An article in BioPharm International was published in 2006 showing how specifications for impurities could be derived in this manner which could easily be applied to cleaning validation data.[5] More recently, in 2008 a presenta-

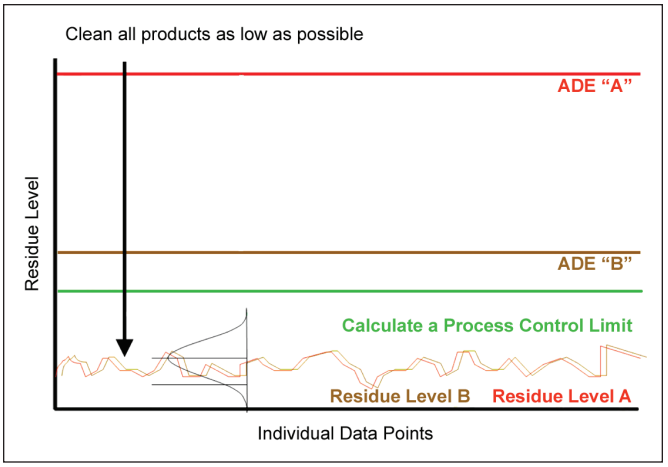

Figure 4. Process control limits and comparison to ADE-derived "safe" levels.

tion was given at an ISPE conference showing how a Process Control Limit could be derived from cleaning validation data for a fluid bed dryer.[6] This technique should see much more use in Process Validation in the near future and its use in Cleaning Validation should follow as well.

One of the benefits of setting a Process Control Limit is that the cleaning of subsequent products simply needs to meet these statistically derived limits. New product introductions typically trip over cleaning validation and can slow the launch of the product. The ADEs of new products can be quickly evaluated against such a Process Control Limit to determine whether the current cleaning procedure is capable of safely cleaning the new product before it enters the facility.

Summary

The ADE is a value based on ***ALL*** of the available safety data, not simply the lowest dose, and provides a clearly safe starting point for subsequent cleaning validation calculations. Using the ADE eliminates much of the guess-work involved in using the dose-based criterion and employs all of the science at hand in the company.

The use of the ADE also will provide a scientific basis for the "Margin of Safety" when evaluating cleaning residue data, and from an operational standpoint, this will allow much greater flexibility than with the dose-based criterion. As stated earlier, the ADE is a very conservative value and using it in cleaning validation will result in very conservative "safe" levels.

In a large number of cases, we have been overly restrictive using the dose-based criterion and this has resulted in the unnecessary dedication of parts, equipment, and even whole manufacturing trains and packaging lines. In some cases the flexibility to manufacture products is severely restricted based on the order of products manufactured as it appears they cannot be cleaned well enough. These overly restrictive dose-based limits also have led to the unnecessary development of "disposable" equipment. Use of the ADE should help alleviate some of these issues.

We have seen the progression of the development of cleaning validation limits based on pesticide levels in food, to fractions of the therapeutic dose, and now on to the calculation of ADEs, risk analysis based on residue data and limits based on Statistical Process Control. The older paradigms, while clearly providing a platform to work from for cleaning validation in the past, should now yield to a newer science-based, risk-based, and statistical paradigm.

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Andrew Walsh is an Industry Professor at Stevens Institute of Technology in their Pharmaceutical Manufacturing Program where he teaches courses on validation and Lean Six Sigma. In 2009, Walsh founded the Stevens Pharmaceutical Research Center (SPRC), a research lab focusing on Pharmaceutical manufacturing topics, such as cleaning process development, total organic carbon analysis and method development, visual inspection method development and automation of GMP systems. A current Chair of an international task team to write a cleaning Guide for ISPE and ASTM, he was one of the contributors to the ISPE Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP) Baseline® Guide. He has more than 20 years of diverse validation experience in pharmaceutical and biotech companies, including Johnson & Johnson, Schering-Plough, and Hoffmann-La Roche. Walsh has given numerous presentations over the past 15 years with IIR, Barnett, WorldPharm, IPA, IVT, and ISPE. He can be contacted by telephone: +1-201-216-5533 or email: andrew.walsh@stevens.edu.

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This article presents strategies to engage in life science projects from a schedule, quality, and budget standpoint – all with "speed to market" in mind.

Fast-Track Life Sciences Projects: When to Use Design-Assist and Why It Works

by Raj Vora, P.E.

Introduction

End-user organizations are constantly searching for the "best" ways to engage in life science projects from a quality, schedule, and budget standpoint, while keeping "speed to market" in mind. In this article, the benefits of design-assist project delivery versus design-bid-build delivery will be examined. The article will demonstrate how design-assist project delivery contributed to the success of a fast-track life science project. Examples of project execution tools utilized to overcome specific challenges will be provided and the article will conclude with an itemized list of the "rules of engagement" for successful design-assist life science projects.

The selection of a proper construction delivery method for capital construction projects can ensure successful execution, while simultaneously meeting overall business goals. While choosing the right approach needs to be evaluated on a case-by-case basis, selecting the right delivery method should be based on a number of factors, including budget, schedule, cash flow, project complexity, risk, project goals, and most importantly, project team composition. Due to the weak economic climate, companies that had large in-house engineering and project management staffs have reduced resources and are opting to outsource these critical project roles. This is a key consideration in selecting the right project delivery method.

Project Delivery Methods

The most commonly used project delivery method is Design-Bid-Build (DBB.) In DBB, the owner functions as the overall project manager and hires external engineers, consultants, and contractors to deliver the project. The owner typically starts by retaining an architect to program and develop a scope of work. The architect then hires a consulting engineering firm, who is the engineer of record, to develop the project plans and specifications. Once the detailed design effort has been completed, mechanical and plumbing contractors are invited to submit pricing to meet the owner's competitive bid requirements. Although this seems like the most cost-efficient method for securing a specific scope of work, design-bid-build has several pitfalls as follows:

1. Quality: the goal of the competitive bid process is to get the lowest upfront cost for the owner's scope of work and the general contractor may invite several mechanical contractors to bid on the project. As a result, the quality of the project could suffer if the owner/general contractor selects the mechanical contractor only on the basis of low price.

2. Design Safety Factors: in design-bid-build projects, the design usually includes safety factors, some as high as 20% excess capacity to ensure that the engineering design is adequate for the project scope. In traditional design-bid-build projects, designers don't want the liability of a design that may not work so they often overcompensate by incorporating excess capacity into the scope of the project. These safety factors lead to oversized building systems and equipment and unnecessary cost to the project. In fact, oversized building systems can lead to underperforming buildings through lack of efficiency and high energy consumption. In a design-assist, the approach is collaborative from the start

with all parties working toward the same goals, allowing them to design based on actual project scope, and avoid costly changes down the road.

3. Change Orders: in design-bid-build, the contractor, based on the construction plans and specifications, assumes all construction and performance risks. Any scope variations from the bid documents result in change orders and schedule delays. The mechanical contractor does not influence the project design and opportunities for alternative approaches at bid time are minimal. Design-bid-build procurement by its nature is set up to create an atmosphere of silo entities with little contractual reason to collaborate to solve design gaps or resolve cost issues.

4. Schedule Impacts: in addition to the scope impacts mentioned above, the submittal review process can impact the project schedule. The mechanical contractor is required to submit shop drawings for each component of work per plans and specifications for formal review and approval by the architect, engineer, and owner. This process takes time and has to be repeated should there be scope changes or additions. All of this can negatively impact the owner's project schedule, leading to additional cost throughout the duration of the project.

5. Project Harmony: the nature of design-bid-build projects can lead to adversarial relationships among the owner, architect, designers, and contractors, especially if the owner's intent is not fully captured in the bid documents. Owners run the risk of expending significant project funds and time for detailed design only to find out the final project does not meet the project budget and schedule parameters.

Conversely, a highly successful delivery method is design-assist, which is becoming more commonly used. A design-assist project allows the owner to maintain control over his project, but key contractors are selected early in the project's lifecycle to achieve schedule and budget goals. Design and construction are integrated in the design-assist method, rather than compartmentalized, as is the case in design-bid-build. The owner still procures the general contractor, architect, and engineer of record, but instead of completing the design documents before soliciting pricing and procuring contractors, the mechanical contractor is brought on board early, usually as part of schematic design, to help finish the design process while simultaneously providing real-time pricing feedback.

There are many advantages to utilizing the design-assist project delivery method in lieu of design-bid-build:

1. Reduction of system cost through:
   a. Correct system application
   b. Use of innovation
   c. Right-sizing of systems
   d. Intelligent procurement
   e. Early coordination with other trades
   f. Enhancement of field productivity
   g. Near elimination of change orders
2. Early firm cost with updates at design revisions
3. Single source accountability for mechanical and plumbing system cost and performance
4. Quality installed system and equipment
5. Time/schedule savings through:
   a. Doing things right the first time
   b. Integrated design and coordination
6. Reduced administrative burden through reduced change order processing
7. Improved risk management

The goal of the design-assist method is to totally integrate the design and build processes in order to design, build, and commission high-quality systems within budget and on or ahead of schedule through designing things once. This collaborative approach reduces design costs and time, in addition to encouraging the design of systems that fully meet the owner's requirements. Design-assist also produces constructible documents that allow design errors to be detected and corrected early in the process, maximizing productivity in the field and saving time. Design-assist enables projects to ramp up to a completion date faster than traditional design-bid-build.

Case Study – Private Lab Facility

A national design-build and design-assist mechanical contractor teamed with a general contractor on a private lab facility project located in Maryland. The building is specially designed for breeding rodents for research purposes. The 54,000-square-foot facility is primarily used for animal holding, but it also includes administrative space, mechanical equipment spaces, lab support areas, and future tenant fit-out space. Specialized HVAC, plumbing, and process systems include 100% outside air handling units, lab exhaust, industrial and animal watering systems, compressed air, vacuum discharge, humidification steam, and services to several cage washers and autoclaves.

This project commenced in early 2007 based on a traditional design-bid-build project delivery. However, problems quickly arose. The owner had budget concerns, the facility design was incomplete and tenant leases had already been signed for May 2008. This created the need for an extremely aggressive project schedule of eight months. With critical time constraints facing the project, the mechanical contractor was brought on board in August 2007 in a design-assist contract delivery.

The project team held weekly meetings to complete the design while developing early cost guarantees. Due to the compressed schedule, construction had to begin while the design was still being finalized. The mechanical and plumbing design was completed in phases to best support the fast-track schedule. As the aboveground services were being finalized, design and installation of underground plumbing got underway. The team was able to keep the mechanical and plumbing equipment off of the critical path by procuring the equipment during the detailed design phase. Simultaneously, the entire project team held regular coordination meetings to ensure a smooth installation of services in the field. Frequent meetings

EXAMPLE PROJECT DELIVERY PLAN
"UNDERGROUND PLUMBING"

PROJECT NAME	Project Anywhere
SHORT PLAN SCOPE	Underground plumbing – all systems
PROJECT NUMBER	7118273
LOCATION/ADDRESS	Anywhere, USA
GENERAL CONTRACTOR	General Contractor, Inc.
MAILING ADDRESS	
BILLING ADDRESS	

PROJECT DIRECTORY (MAIN POINTS OF CONTACT FOR SHORT CP)

NAME	COMPANY	ROLE	TELEPHONE	E-MAIL
John Doe	GC, Inc.	Project Manager	703-555-1212	jdoe@gcinc.com
Cara Doe	Mechanical Contractor	Project Manager	703-555-2433	cdoe@southlandind.com

SAFETY/EMERGENCY INFORMATION

CONTACT	COMPANY	ROLE	TELEPHONE
Joe Safety	Mechanical Contractor	Division Safety Manager	703-555-7748

ACTIVITY HAZARD ANALYSIS (AHA)

SI AHA	GC JHA	DESCRIPTION OF ACTIVITIES ASSOCIATED WITH THIS SHORT PLAN
X		Excavation
X		Inhalation

DIRECTIONS TO NEAREST MEDICAL EMERGENCY TREATMENT FACILITY

FACILITY NAME & ADDRESS	
DIRECTIONS FROM PROJECT	1.
LINK TO INTERNET MAP SITE	

LOCATION OF JOB-SPECIFIC SAFETY PLAN

GC, Inc. - Trailer

SOUTHLAND SCOPE OF WORK (SHORT PLAN)

SHEET METAL	None
PIPE FITTING	None
PLUMBING	Underground sanitary, storm, water and industrial waste piping.

OPTIMUM SEQUENCE OF INSTALLATION (SHORT PLAN)

SHEET METAL	1. N/A
PIPE FITTING	1. N/A
PLUMBING	1. Start at mains exit point on building working towards east wall. Complete A side first before moving down to B side.

OPEN ITEMS OR TASKS TO COMPLETE TO MAKE STATED PLAN

WHO?	DESCRIPTION OF ITEM, TASK OR PREDECESSOR ACTIVITY	DATE CHECKED
Detailing	Drawings for Area A to be completed by Friday	09/04/07

CREW SIZE & MANPOWER

TRADE	CREW SIZE	# OF CREWS	START	COMPLETE	WEEKS	FOREMAN
Plumbing	2	2	09/10/07	10/11/07	5	Mike Plumber

SCHEDULE & CPM ACTIVITIES

COMPANY	MAJOR CONTRACTUAL MILESTONES FOR THIS SCOPE	FINISH DATE
SI	Complete UG before concrete pours	10/11/07

PRE-FABRICATION PLAN

SHEET METAL	N/A
PIPE FITTING	N/A
PLUMBING	N/A

PROCUREMENT

EQUIPMENT/MATERIAL TYPE	TAG NO.	QTY.	SUBMITTAL STATUS	REQ'D ON-SITE
Chem Drain Pipe Material	IW	1976	Approved	09/11/07

OUSTANDING DESIGN OR COORDINATION ISSUES

SHEET METAL	N/A
PIPE FITTING	N/A
PLUMBING	Coordination drawing from detailing (SIDE A COMPLETED)

POTENTIAL ROAD BLOCKS (RISKS) THAT SHOULD BE WATCHED

SHEET METAL	N/A
PIPE FITTING	N/A
PLUMBING	1. Power – We may need to rent a generator if no power present. (COMPLETED)

OPPORTUNITIES

VALUE ($)	TRADE	DESCRIPTION

COST CODES REQUIRED FOR THIS SCOPE

TRADE	SCOPE		HOURS	
Plumbing	Detailing		299	
Plumbing	Supervision		239	
Plumbing	Material Handling		131	
Plumbing	Underground – PVC (Including Drains)		373	
	Underground – Chem Drain (Inc Drains)		1054	
Plumbing	Material (UG Portion Only)		N/A	
Subcontracts	Excavation – T&M Subcontractor Only		N/A	

APPLICABLE DRAWINGS & SPECIFICATIONS

TRADE	SPEC SECTIONS	DRAWINGS
Plumbing	Standard Submittals	P-101 and P-102

CONTRACT OR SPECIFICATION ITEMS OF INTEREST

CONTRACT/SPEC CLAUSE	APPROVED INTERPRETATION

Figure 1. Project Delivery Plan: document used to plan and organize execution of projects by compartmentalized specific scopes of work into deliverable portions of work.

and daily communication led up to the bulk of the mechanical and plumbing rough-in occurring in just four months, between February 2008 and May 2008. This equated to 11,000 hours of sheet metal labor, 15,000 hours of piping labor, and 11,000 hours of plumbing labor performed within this time frame.

How did the team achieve their goal of delivering the project within eight months? As outlined below, it was the combination of design-assist, frequent communication, and project execution tools that made it possible:

a. Project Delivery Plan: this is a document developed to detail the "plan-of-attack" for executing specific scopes of work for the project. This document contains all of the relevant project information; key personnel, safety contacts, etc., in addition to the project's milestone schedule dates, prefabrication opportunities, and tasks lists. This document compartmentalizes and plans the execution of the project into deliverable portions of work - *Figure 1*.

b. Equipment Delivery Log: this is a spreadsheet that captures all of the equipment on the job, associated lead-times and delivery dates. By understanding when equipment is needed on site, the project team can drive design decisions to achieve associated construction milestones.

c. Trend Log: in a design-assist delivery, owner generated scope changes will occur as the design progresses. The trend log is a tool used to capture owner design decisions that increase scope or cost in addition to capturing contractor ideas that help maintain a net zero impact of those changes. The project team uses the trend log to make educated decisions with an understanding of project schedule and budget impacts. It is a great communication tool that is used by the owner to realize the value in the design-assist process and to ensure involvement of the project team in maintaining project budgets. The log includes a description and the quantity of an item, its location, critical dates – planned/actual including lead times, plus the vendor name, contact person, and phone.

d. Prefabricated Racking of Services: the project contained an extremely congested service corridor running down the

Figure 2. Prefabricated Racking of Services: prefabricated racks in the service corridor that includes all major utilities and services.

center of the facility. All major utilities and services were located in this corridor and hung from several different locations along the route. The team utilized coordination and modeling capabilities in conjunction with weekly coordination meetings with the project team to design the building to allow prefabricated racks for all the utilities, rather than individual piping distribution for each utility service. The coordinated racks were built off-site and delivered to the site in 20-foot sections for field installation, which helped meet the aggressive schedule - *Figure 2*.

Conclusion

The selection of the right project delivery method and the right configuration of roles, responsibilities, and relationships are more crucial than ever. The ability to define and develop project requirements and scope early, in order to deliver a successful project, is the key challenge that will continue to face project teams today. Choosing a collaborative delivery-method will ensure a good project experience by all.

These "Rules of Engagement" should serve as a guideline for determining when design-assist should be considered.

Design-Assist "Rules of Engagement"

1. Schedule: the project has an accelerated timeline that cannot be achieved by using the traditional design-bid-build method.

2. Budget: the project's budget is in jeopardy or the owner wants cost certainty and needs early cost validation.

3. Risk: minimize owner's and mechanical contractor's risk through early involvement in the design process.

4. Owner's Team: the owner wants to utilize their architect and engineer from past projects.

5. Project Complexity: a more complex greenfield or renovation project requires early mechanical contractor involvement and more team collaboration to meet the overall project goals.

Outcome: the owner's quality requirements are met more efficiently through the design-assist project delivery process because design-assist is more collaborative – the budget is shared up front and either through an open-book or lump sum process, the contractors and project team are working together toward a common budget goal as opposed to the negative competitive aspects of design-bid-build.

About the Author

Raj Vora, P.E. has more than 12 years of industry experience ranging from campus-wide master planning and manufacturing expansions to renovation and retrofits of facilities during operations. His background includes experience in client consultation, collaborative design and construction projects, and start-up for a variety of projects within the biotechnology/pharmaceutical manufacturing sectors and bio-containment and R&D laboratories. Vora currently holds the position of President of the ISPE Chesapeake Bay Area Chapter. In his role, he is responsible for the strategic growth and oversight of the 450-member chapter through educational events, facility tours, charity events, and business functions. Vora earned his Master's of Architectural Engineering from Penn State University and is a licensed Professional Engineer in the State of Maryland. Vora is also an Industry Mentor to a 4th year student in Penn State University's Architectural Engineering program, providing coaching and guidance through personal and professional interaction. At Southland Industries, Vora is responsible for the strategic growth of the enterprise through new project and customer development by guiding the company on the type and size of projects to pursue. His extensive customer base has been developed on the principals of repeat business through the execution of projects at a high rate of client satisfaction. Vora frequently leads project pursuit teams, ranging in size from five to 15 people and is one of Southland's technical experts in the areas of life sciences and healthcare. He can be contacted by telephone: +1-703-834-5570 or email: rvora@southlandind.com.

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Using Operational Excellence to Meet the New Process Validation Guidance

by Bikash Chatterjee, Peter Rafa, and Wai Wong

This article presents a framework for executing the three stages of process validation, employing the philosophies and methodologies of Operational Excellence (OpEx).

Introduction

In January 2011, the FDA issued its new guidance regarding Process Validation (PV). This revised guidance represents a radical departure from the 1987 definition of process validation which, to determine process capability and reproducibility, relied heavily on inspection and testing. The new guidance defines a staged approach designed to demonstrate process understanding as a product moves through its development lifecycle. While this guidance has been under discussion since 2008, adoption of its principles has been limited. Industry is still struggling with the paradigm shift away from a highly prescriptive guidance to one that is flexible and based on a case-by-case scientific quality argument. While the days of *"three lots and you're done"* are more than likely over, the considerations for moving through the three stages have yet to be standardized. This article presents a framework for executing the three stages of process validation, employing the philosophies and methodologies of Operational Excellence (OpEx). The methodologies employed and the challenges encountered will be described based on the adoption of an OpEx framework as part of a recent PV exercise executed for a client organization, with references to the business unit and development team assembled for the project.

Operational Excellence

Within the industry, the concept of continuous improvement as a foundation for product performance predictability and quality assurance became part of the strategic lexicon with the FDA's Critical Path Initiative in 2004. The critical path initiative spawned a number of key guidance documents that advocated a more scientific approach to product development and quality assurance without specifying how to achieve this new level of scientific rigor.

One response by Pharma has been to turn to established improvement methodologies such as Operational Excellence (OpEx) as a framework to meet these new directives. OpEx

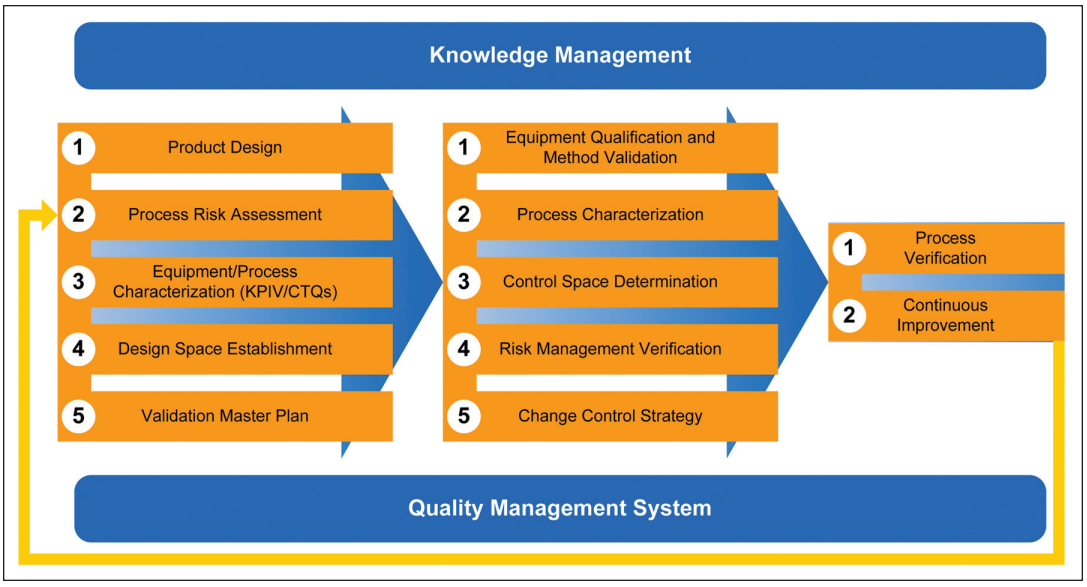

Figure 1. The roadmap.

Deliverable	*Activities/Tools*	*Rationale*
Stage 1		
Formulation Review	• Review existing suppliers/agreements • Evaluate suitability of excipients and functional raw materials • Review final formulation • Define Charter-Product Requirements Specification (PRS), other business success metrics	• Leverage strong existing relationships • Develop understanding of product design • Understand CTQs based on PRS
Process Risk Assessment	• Swim-Lane Diagram • Value Stream Mapping • Pareto Charts • Fishbone Diagram • Force Field Analysis • Check Sheets • Concentration Diagrams • Failure Mode and Effects Analysis (FMEA)	• Understand process requirements early compared to PRS • Identify sampling, testing and control considerations early
Equipment Characterization	• GRR • Calibration review	• Make sure equipment variability is acceptable • Analytical and in-process test method resolution is acceptable
Process Characterization (Knowledge Space)	• API diagnostics • Raw material diagnostics • Design of Experiments • ANOVA • Storage and handling studies • Summary report	• Build a baseline profile for API and Raw Materials (RM) • Identify KPIV/KPOVs • Identify facility and container requirements to protect API, RM, WIP, and FP • Summarize knowledge base to support CMC development report
Design Space Establishment	• Equipment Characterization (GRR) • Process Map • Value Stream Map (VSM), 5S • FMEA • Rapid Changeover • Poke-Yoke Equipment • Sampling and Testing GRR • DOE • ANOVA • Correlation • Process capability • Statistical Process Control (SPC) • QFD • Pull Methodology/Cellular manufacturing • Process Tolerance Analysis	• Establish equipment, facility, process, and operational requirements
Validation Master Plan	• KPIV/KPOV summary • Process capability • Sampling and testing	
Stage 2		
Equipment Qualification and Method Validation	• Equipment IQ, OQ, and PQ • Facility FQ • IP and FP Method Validation • Computerized System Validation	• Demonstrate measurement resolution is acceptable • Ensure equipment stability before control space activity
Control Space Process Characterization	• DOE • ANOVA • Correlation • Process capability • Statistical Process Control (SPC) • Stability Program	• Establish control space limits
Control Space Confirmation/PPQ	• Commercial Sources of Variation • Confirmation Studies	• Capture uncontrolled sources of variability
Risk Management Verification	• pFMEA	• Update pFMEA with final controls
Change Control Strategy	• Summarize KPIVs and KPOVs	• Create roadmap for planned improvements and simplify quality impact assessment
Stage 3		
Process Verification	• Data collection protocol • Control Charts	• In addition to product performance metrics monitor KPIV/KPOVs
Continuous Improvement	• Create production dashboards • Integrate into OpEx program	• Build upon knowledge from PV exercise to catalyze business

Table A. Operational excellence tools applied by process validation stage.

is not limited to a single methodology or approach and includes proven business performance methodologies such as Six Sigma, Lean Manufacturing, TRIZ, and Right the First Time (RFT) to name a few. In principle, they share similar characteristics that account for their success. They all require clear definition of the success metrics and cross-functional organizational engagement within a well-defined framework to objectively evaluate and measure both data and program progress. Often, the key to these programs is not in the tools themselves, but how they are applied.

The Roadmap

The new PV guidance defines three distinct stages as part of the new definition of process validation:

- **Stage 1 Process Design:** the commercial manufacturing process is based on knowledge gained through development and scale-up activities.
- **Stage 2 Process Qualification:** the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- **Stage 3 Continued Process Verification:** ongoing assurance is gained during routine production that the process remains in a state of control.

The roadmap uses a milestone-driven framework creating a phase gate process for each stage of the new process validation lifecycle. This framework was designed to leverage the intrinsic expertise of the development group while integrating ICH Q8, Q9, Lean, Lean Product Development, and Six Sigma principles. The roadmap used for this project is shown in Figure 1.

The potential suite of tools, methodologies, and rationale for their application are shown in Table A. The thought processes and application are discussed in detail in the subsequent sections. The key areas of emphasis for the team to navigate this framework were the prerequisites for moving from stage to stage within the new PV lifecycle.

The Development Team Strategy

The business unit had an established continuous improvement program with many of its employees receiving Six Sigma and Lean training. While the concepts of objective data evaluation and unbiased statistical experimental design were present in the existing organizational thinking around process control, the organization had many pockets of more traditional pharmaceutical thinking that required buy-in to a new approach. Organizationally, Stage 1 was the joint responsibility of R&D and the Technical Services group. For this project, the firm's consultants recommended a project team approach based upon a Design for Manufacturing or Design for Six Sigma (DFSS) philosophy in which downstream customers and key stakeholders were accountable along with R&D and Technical Services for the development of the product. For Stage 1 the development process utilized a Define-Characterize-Optimize-Verify (DCOV) approach. A comparison of the four different Lean DFSS development approaches is shown in Figure 2.

The team strategy was to utilize Stage 1 to determine the critical process parameters called the Key Process Input and Output Variables (KPIV/KPOV) for the process at small scale then bridge to full scale. This would simplify the final Process Performance Qualification (PPQ) to an evaluation of the uncontrolled sources routinely encountered in commercial manufacturing.

The cross-functional project team used this strategy to establish internal project success metrics and project development timeline commitments in addition to product performance requirements defined in the Product Requirement Specification (PRS) as part of the project chartering process.

Product Design Requirements

The business unit was developing a new controlled release anti-hypertensive tablet. A PRS was given to the development team defining the critical to quality attributes for the final tablet. Key criteria from the PRS included:

- greater than 50 percent Active Pharmaceutical Ingredient (API)
- round 200 mg tablet
- coated to mask taste
- 12-hour drug release with the following specifications:
  - 4 hour dissolution 20 to 40 percent
  - 8 hour dissolution 65 to 85 percent

Process Validation Framework

Stage 1

Product Design

During the formulation activity, the team defined baseline raw material and API activity that could benefit downstream commercial production. Specific emphasis was placed on excipient and raw material selection with the goal of leveraging existing suppliers and materials that have shown to be consistent performers in commercial manufacturing. Information on current suppliers and materials was summarized as background for the formulation process to be used as a guideline for excipient

DMADV	IDOV	DCOV
Define – What is the new process, product or service? Why is it needed?	**Identify** – What are the needs and requirements of the customer?	**Design** – What are the needs and requirements of the customer?
Measure – What are the customer requirements? How do we translate these into design requirements?	**Design** – How do we translate customer needs and requirements into a product design?	**Characterize** – How do we translate customer needs and requirements into a product design? What are the key process input variables (KPIV) that affect customer requirements (KPOV)?
Analyze – What are the design alternatives? How do we select the best concept (High Level Design)?	**Optimize** – How can we optimize the design to minimize variability and meet customer requirements?	**Optimize** – How can we optimize the design (KPIV) to minimize variability and meet customer requirements (KPOV)?
Design – What is the design realization (Detailed Design)?	**Verify** – How do we verify the design meets customer requirements?	**Verify** – How do we verify the design meets customer requirements?
Verify – How do we verify the design meets the customer requirements?		

Figure 2. Lean DFSS models.

Raw Material	%w/w	Function
API	60	Active ingredient
Microcrystalline cellulose	20	Excipient filler
Hydroxypropycellulose (HPC)	7	Granulation binder
Lactose	12	Excipient filler
MG Stearate	1	Lubricant
Purified water	QS	Solvent
Coating Solution Raw Material	**%w/w**	**Function**
Eudragit Coating Solution	12	Controlled release polymer
Triethyl Citrate	1	Plasticiser
Talc	1.5	Glidant
Water	QS	Solvent

Table B. Final tablet formulation.

selection. The final formulation for the product, along with each component's functionality, is shown in Table B.

The final product design revealed two key considerations for the downstream process characterization studies. First, the product has a fairly large loaded dose. This translates to a potentially lower risk of content uniformity issues. Second, the primary controlled release component is limited to the coating step, which means if the upstream process steps can be shown not to impact the final drug release profile, this will simplify the final process validation argument.

Process Risk Assessment

Once the formulation was established, the team went through a Process Risk Assessment prior to developing the characterization plan. As part of the exercise, the team developed a process map by unit operation, listing all controlled and uncontrolled variables along with any proposed in-process testing. This was used as the common baseline process flow, along with the risk ranking charts developed by the team for the Process Failure Mode and Effects Analysis (pFMEA). The overall process stream is shown in Figure 3.

The small-scale equipment used for the process development is listed below:

- 5 L Jacketed SS Tank with High Shear Mixer
- Laboratory Scale Fluid Bed Granulator GPCG-2 with 7' column
- Mill
- 16 qt P-K V Blender
- Tablet press
- 24" coating pan

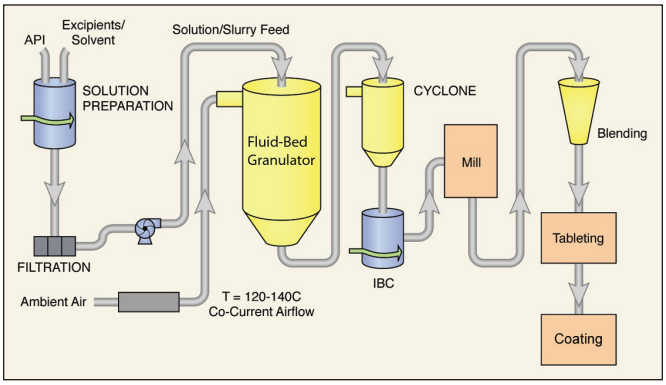

Figure 3. Manufacturing process stream.

Using this equipment stream and the baseline manufacturing process, the team performed a pFMEA to identify areas that could add to the process variability during a commercial process. This information was used as a basis for the process characterization studies at small scale. The pFMEA highlighted several areas as potentially important to the process predictability - *Table C*.

Equipment/Process Characterization

Before performing any characterization work, each raw material and API was characterized per the pFMEA summary.

Unit Operation	Factors	KPIV-Parameter	KPOV-Parameter
API/Raw Materials			Raw Material (RM) PSD-d_{10}, d_{50},d_{90} Raw Material Bulk Density API PSD-d_{10}, d_{50},d_{90} API Solubility with Temp. API and T_g and T_m Polymorphs Solubility
Compounding	Tank Geometry Baffling Mixer Impeller Design Sampling Accessibilty	Mixer Speed Mixing Time Addition Rate Water Temp. Control	Fully Dissolved-Visual
Fluid Bed Granulation/ Drying	Insert Size Nozzle Uniformity	Spray Rate Dewpoint Inlet Air Velocity Inlet Air Humidity Atomization Pressure	Granulation PPD-d_{10}, d_{50},d_{90} Moisture Content
Milling		Feed Rate Screen Size RPM	PSD-d_{10}, d_{50},d_{90}
Blending	Sampling Scheme	Mixing Speed Mixing Time	Content Uniformity Potency (% Label Strength)
Compression	Material Transfer	Compression Force Speed Granulation D50	Tablet Thickness Tablet Weight Tablet Hardness Dissolution Profile Potency Content Uniformity
Coating	Airflow Across Pan	Pan Load Spray Rate Atomization Air Pressure Inlet Air Temp. Inlet Air Humidity Spray Gun Position/Angle Drum Speed	

Table C. Factors and key input and output variables identifies from the pFMEA.

Based upon this data, a working specification was set up for the API and raw materials.

Analytical method resolution was established before beginning any processing studies to ensure the measurement sensitivity was acceptable for characterization work. Also the small-scale equipment was characterized to ensure the equipment controls were suitable to address the planned process characterization activities. This included verifying that the critical factors identified in the pFMEA could be measured.

Experimental Approach

Per the ICH Q8 guidance, the first step in establishing process understanding is to define the knowledge space. The knowledge space constitutes describing the contribution to process stability of the total set of variables for each unit operation across a practical range of variability. The process team needed to understand both linear and interaction effects which could affect the process stability. Typically, the first set of studies conducted on each process unit operation were screening studies. The team used a Design of Experiments (DOE) approach ensuring all investigation experimental designs were orthogonal. Screening studies do not look for interaction effects, but do allow non-critical variables to be dropped from follow-up studies, simplifying confirmation studies. The coefficient of determination (r^2) measures how much of the data is explained by the model. A poor r^2 means that there could be interaction effects between variables or other sources of variability that have not been captured by the experiment and must be studied. The data from each DOE were regressed against each unit operations' KPOVs with the objective of identifying which variables could steer the process. In all cases, the null hypothesis $\alpha = 0.05$ was used to determine significance. An example of the Pareto Regression Chart for the Fluid-Bed Granulation (FBG) process is shown in Figure 4. Based upon the study, only linear contributions are important for spray rate, atomization pressure, and inlet air humidity. Similar experiments and analyses were conducted for the other unit operations.

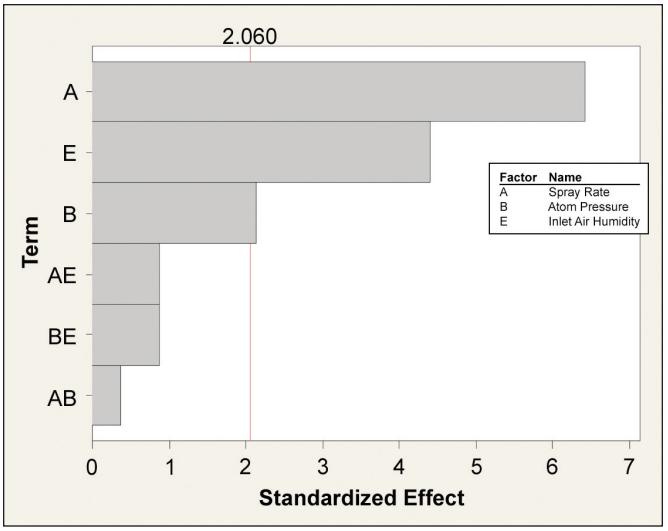

Figure 4. Pareto chart of the standardized effects FBG/drying process (response is LOD, Alpha = .05).

Commercial process challenges also were introduced at this stage to try and limit the variability during scale-up. For example, layer-on-layer loading of the blender vs. side-by-side loading were compared to determine if there was impact. In the former approach, the blend uniformity is dominated by convective forces, while the latter relies on diffusion as the primary driver for blend uniformity.

For the compression unit operation, compression force was found to be a critical parameter but turret speed was not as it pertained to the critical output parameters, tablet thickness, weight, and hardness. There were many Critical to Quality (CTQ) factors in terms of the final product release criteria including content uniformity, potency, degradation products, etc. Of these, the primary CTQ the team concentrated on in the process development was achieving a reproducible drug dissolution profile. In this study the CTQ specifications for the coated tablet were 20 to 40 percent dissolution at four hours and 65 to 85 percent dissolution at eight hours. Dissolution was tested at every hour for up to 16 hours to establish the uncoated tablet dissolution profile. Although there was no controlled release coating, the full dissolution profile gave us a good idea of what the contribution to the final tablet dissolution profile of the uncoated tablet would be across the full knowledge space. In all cases the uncoated tablets were at 100 percent dissolution within three hours. Hence, the most critical operation for the final dissolution product specification would be determined by the final coating step.

The baseline process capability for the coating process was established at Cpk = 1.46 as it pertained to drug dissolution at four and eight hours, which was above the team success metric of 1.33 (4 sigma) set during the chartering process.

Sampling and Testing

One challenge with the new guidance is how to determine a defensible sampling and testing plan for the characterization activity. The team used several criteria for determining sample size. Leveraging information from the product design and pFMEA output, the sampling and testing plan was modulated to ensure adequate resolution of the behavior of the specific KPIV, KPOV, and CTQ of interest. In some cases, the ANSI Z1.4-2008 tables were used, in others, a power calculation was used. For several unit operations at small scale, an Operating Characteristic (OC) curve was developed allowing the team to bounce between Acceptable Quality Level (AQL) and Lot Tolerance Percent Defective (LTPD) based upon whether producer risk or consumer risk was of concern.

Storage and Handling

The last set of studies concentrated on the impact of storage and handling on product performance. The critical raw materials based upon the product design are the binder HPC and the controlled release polymer coating solution. In terms of intermediate product, granulations from each unit operation and uncoated and coated tablets were put through temperature and humidity studies, including cycling studies to determine if the functionality changed from baseline. Both protected and open container materials were used as part of the study. This

data was critical to ensuring that the facility was suitable for commercial production of the product. The granulations and the uncoated tablets were found to be hygroscopic and both intermediates were stored along with desiccant in their secondary containers.

At the end of the knowledge space development activity, the team reviewed the conclusions of the characterization studies and summarized all findings in a report that would become supportive data for the final product development report. Following the framework, the number of critical input variables had been significantly reduced as the process moved through each unit operation.

Design Space Characterization

The next step was to verify behavior of the identified KPIVs in the scaled-up process as well as identify, *a priori*, sources of variability that could stem from the new large-scale operation. Business performance and compliance performance often stem from departures from the planned procedure and/or Quality Management system. For the process definition, with the KPIVs identified at small scale, the scale-up activity concentrated on defining the design space.

The activity was divided into two phases with the first phase concentrating on operability sources of variation and the second phase focusing on bridging from small scale to large scale and defining the final design space. In terms of the operation, the team looked at the proposed use of the equipment, facility, and raw materials for each operation. The team developed a Value Stream Map (VSM) for the process train, including sampling and testing. Next, each area went through a 5S (Sort, Set-In-Order, Shine, Standardize, and Sustain) exercise to eliminate unnecessary material and equipment from each area. Each unit operation was compared against the original pFMEA and updated for the new areas and controls. Based upon this analysis, several of the unit operations went through a rapid changeover exercise. These activities had the added benefit of characterizing the equipment stability before beginning the design space determination.

The improvements were performed prior to the design space activity with the intent of completing all activities before the equipment qualification phase in Stage 2. This greatly clarified the roles and responsibilities for the operation and laid the foundation for standardized work practices, equipment setup, sampling, and testing for the process train. These ultimately became baseline metrics for the Operations and Quality organization.

With the operability elements addressed, the team turned to the scale-up activity to establish the design space. Before beginning the design space confirmation studies the sampling methodology was qualified.

Sampling Methodology

These studies were used to pre-qualify the sampling technique. This involved developing a standardized procedure for sampling each unit operation of the process and assessing their suitability for pulling a representative sample. A simple crossed Gage Reproducibility and Reliability (GRR) study was performed to demonstrate that the resolution of the method was acceptable for characterization and validation activities later. The metric evaluated was potency. A GRR of 20 percent with NLT 5 distinct categories was used as minimum acceptance criteria for each sampling technique and test method evaluated. The residuals for each GRR were evaluated as well for data bias or anomaly. The resulting GRRs for each unit operation sampling evaluation were less than 10 percent with the number of distinct categories ranging from 5 to 17. Based upon these qualification studies the techniques for sampling were capable and qualified.

Sampling Plan

The design space determination represents the major risk reduction opportunity in terms of moving to final Process Performance Qualification. Sample sizes were chosen to provide the necessary resolution to have confidence in moving into the final control space determination and PPQ. In evaluating Acceptable Quality Levels (AQL) and Lot Tolerance Percent Defective (LTPD), the resulting sample sizes were too large and impractical to implement. Instead, the team used power calculation to establish the sample size. A power of 80 percent was used with a five percent variation as a meaningful difference to calculate the final sample size. However, to bolster understanding of the true process behavior, the sample size was applied to multiple sampling points within the process. This created a strong database that could be used for defending the sampling plan at the control space/PPQ exercise downstream in Stage 2. More importantly, the combination of Process Capability (Cpk), which measures the overall process variation, and a statistically based sampling plan, which measures inspection risk, provided a clear picture of the process predictability before moving to the PPQ.

The equipment used in the commercial process:

- Fluid Bed Granulator GPCG 60
- Mill 196-S, square edge impeller, 0.175" shim, 0.040G screen
- 45 cu ft PK Blender with Vacuum Loader
- 61 Station Tablet Press
- 60" Coating Pan

The design space establishment focused on bridging the information determined during small scale modeling with the new commercial scale process. The critical process parameters identified during the small-scale characterization activities and their commensurate CTQs are shown in Table D.

The range-finding studies determined the scale-up process limit cognates for the critical process parameters identified at small scale. Studies were designed based upon equipment and process experience and considering manufacturers' recommended scale-up algorithms for each unit operation. These range-finding studies were compared back to the small-scale model to determine where the corresponding KPIV limits fell for the design space.

The design space establishment was achieved using a much smaller set of statistically orthogonal experimental

runs using the data from the range-finding studies and the small-scale model. The design space limits were narrowed by 1 sigma to move away from the potential edge of failure of the knowledge space limits. Additional sampling and testing was performed on several key unit operations. For the Fluid-Bed Granulation (FBG) process, samples were pulled during the granulation process to measure the granulation growth curve. In addition, the final granulation was evaluated using a RoTAP sieve analyzer with each fraction tested for potency and Content Uniformity (CU). Finally, the coated tablets were pulled at 94, 96, 98, and 100 percent of theoretical weight gain to determine the drug dissolution sensitivity to final coat weight. The results are shown in Figure 5.

This additional characterization work allowed the team to have a high level of confidence that Content Uniformity (CU) was not going to be an issue in the final tablet. These samples were placed on stability as supportive data for the registration lots. At the end of the design space development activity the team reviewed the conclusions of the characterization studies and summarized all findings in a report that would become supportive data for the final product development report.

Validation Master Plan

Based upon the Stage 1 studies, the KPIVs and KPOVs of interest and their relationship to the product CTQs was clearly understood. It was essential to capture this development and justification in the Validation Master Plan for two purposes. First, this provided the necessary insight into why certain parameters were not challenged in the final control space and PPQ. It also helped frame the final compliance argument in terms of process predictability. Process capability and sample size resolution justification could be introduced to reinforce the VMP strategy going forward. The Validation

Unit Operation	KPIV-Paramater	KPOV-Parameter	CTQ
Compounding	Mixing Speed Water Temp. Additional rate	Full Dissolved- Visual	
Fluid Bed Granulation/ Drying	Spray Rate Inlet Air Humidity Atomization Pressure	Granulation PSD- d_{10}, d_{50},d_{90} Moisture Content LOD Bulk/Tapped Bulk Density	Content Uniformity Potency
Milling	Screen Size	PSD	
Blending	Mixing Speed Mixing Time		Content Uniformity Potency-Assay
Compression	Pre-compression Force Compression Force	Tablet Thickness Tablet Weight Tablet Hardness Friabilty	Dissolution Profile Content Uniformity Potency-Assay
Coating	Spray Rate Atomization Air Pressure Inlet Air Temp.	Percent Weight Gain Appearance	Dissolution Percentage at 4 and 8 hours Potency-Assay

Table D. Small scale critical process parameters and CTQs by unit operation.

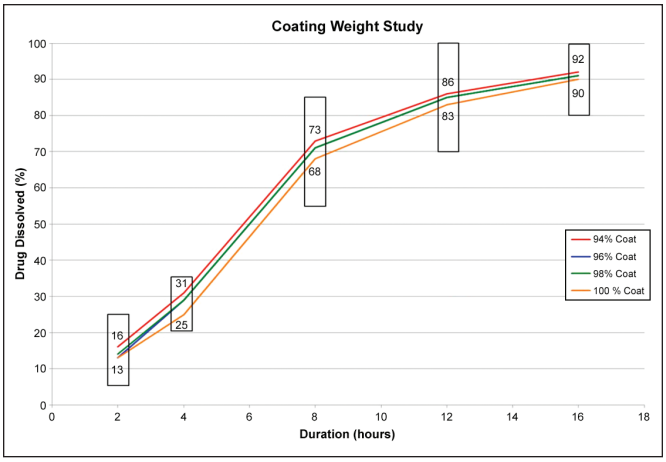

Figure 5. Drug dissolution dependence on coating weight.

Master Plan was written to outline the approach and strategy for the facility, utilities, and equipment. The plan defined the production equipment and facility, the supporting utilities, and critical process parameters (defined previously in product development and analysis) within the scope of the validation effort.

Stage 2

Before moving into the final Control Space demonstration and PPQ, all supportive precursor elements required to support commercial production must be in place. The equipment, supporting facility and utilities must be qualified and suitable for use. Standard IQ, OQ, and PQ protocols have to be completed for the supporting utilities, including air handling systems (process and facility) and the clean dry air system to establish documented evidence of control, alarming and suitability of environmental parameters such as cleanliness, temperature, and relative humidity. It also must be established that an effective Environmental Monitoring program is in place to monitor, review, and archive key environmental data. In addition, the cleaning validation program must be complete as well as any supportive analytical method validation required for process characterization and product performance testing.

Control Space Process Characterization

With establishment of the design space at the end of Stage 1, the process characterization work for the control space in Stage 2 concentrates on identifying a practical range for the KPIVs that will support consistent process performance. Using the contour plots identified in the design space established at the end of Stage 1, the control space was established by narrowing the design space limits by 1 sigma again. Confirmation runs at these new limits were used to demonstrate process predictability and consistent drug dissolution performance. The process capability (Cpk) for drug dissolution at four and eight hours was determined to be 1.67 and 1.43, respectively, which are above the target metric of 1.33 (4 sigma) set as the success metric during the chartering process at the outset of the development program.

Process Performance Qualification

The demonstration phase of the Process Validation cycle begins in Stage 2. With the necessary equipment, facility, and utilities validation completed, the final process capability is demonstrated by the Process Performance Qualification (PPQ). Given the rigor of the development and characterization work performed in Stage 1 and early Stage 2, the relationship between the KPIVs and KPOVs in terms of process predictability is well understood. Similarly, the relationship between KPOV variability and the product's CTQs is also well understood. The PPQ is intended to capture the variability of uncontrolled sources of variability that will routinely be encountered in commercial manufacturing. This will establish the baseline monitoring data for Stage 3 of the new Process Validation lifecycle.

Because the contribution of each critical process parameter has been characterized at the boundary limits of the process control space in Stage 1 the contribution of the uncontrolled sources of variation became the focus of the PPQ. Uncontrolled sources of variability include supplier process variability, process interruptions, non-steady state operations, such as loading and unloading of equipment during manufacturing and sampling. There is no statistical justification for the number of lots required; rather, the number of PPQ lots required were based on the number of lots required to capture this set of uncontrolled variables.

In this case, the PPQ protocol was able to capture this commercial variability over six lots. API lots were selected based upon the widest possible PSD d50 values for material in inventory. Cleaning validation studies had demonstrated the equipment could be run back to back based upon a minor cleaning with no statistical impact on process stability. Given that the final dissolution CTQ was based upon the final coating process, the PPQ lots utilized different vendor lots to try and capture Supplier capability data. For drug dissolution testing, the sample size determination was made the same power calculation used in the Design Space calculation using a five percent level of significant difference. The five percent provides some assurance that data that are nearing the upper or lower control limits are accurate. Based upon these assumptions, the dissolution sample size was 18. Samples were pulled randomly from across the lot. For content uniformity, ICH USP 29-NF 24 testing sample sizes were established using Bergum's method.

The six-pooled lot process capability analysis based upon four-hour dissolution is shown in Figure 6. A similar analysis was performed on the eight-hour dissolution to yield an eight-hour Cpk of 1.77. All data met release criteria. While Cpk is an indicator of process variability, it is greatly influenced by the number of lots evaluated. A comparison of the PPQ lots to the control space characterization lots concluded that there was no significant statistical difference compared to the six PPQ lots. The PV final report recommended monitoring the FBG Granulation PSD-,Bulk/Tapped Bulk Density and LOD,

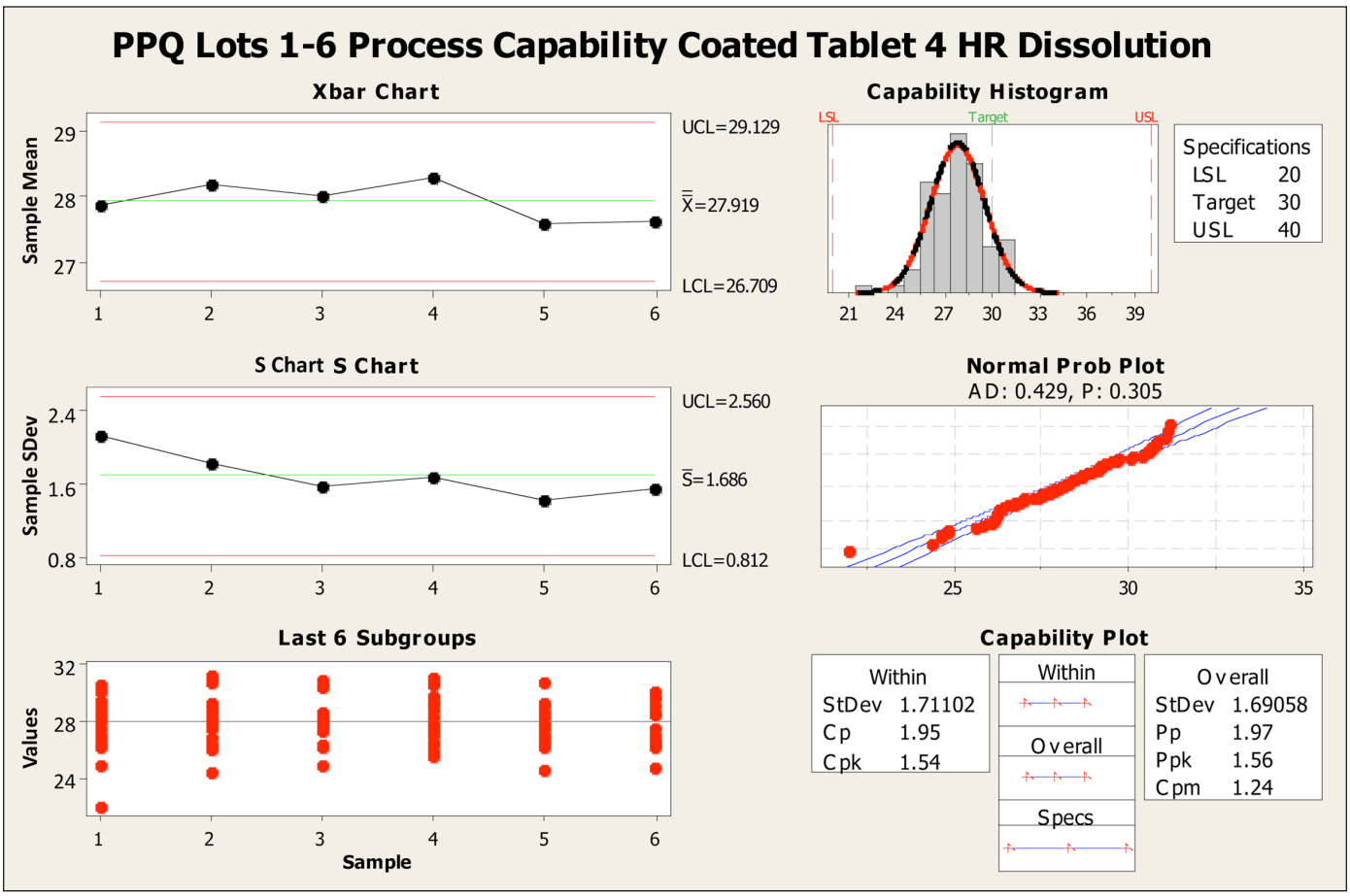

Figure 6. Process capability – pooled lots 1 to 6 – 4 hour dissolution.

the uncoated tablet dissolution at two and four hours and the coated tablet weight gain in addition to the final product CTQs for Stage 3. Continuing to monitor process capability in Stage 3 will provide a longer-term insight into the process stability.

After completing the PPQ analysis, the team revisited the pFMEA to update the final process and controls risk assessment for the commercial operation. This data was included in the Stage 2 final report.

Stage 3

The last stage of the new process validation lifecycle is process monitoring. This concept is common to most OpEx methodologies. While monitoring has been part of the normal drug quality management system (QMS), the new guidance advocates moving beyond the normal CTQs reported in a product's Annual Product Review (APR) and extending them to include the KPOVs which have been identified as critical to process stability. As with all monitoring exercises, the more data gathered, the greater the likelihood of capturing a snapshot of the true process performance. For this product, a protocol was drafted to gather data over the next 30 lots to establish alert and action limits relating to process variability. This data was intended to be reported as part of the product scorecard and included in the APR.

Conclusion

In integrating OpEx principles to satisfy the requirements of the new PV guidance, adopting a cross-functional project team was key to managing knowledge across the organization. Including commercial QA/QC as part of the project team during the first knowledge space definition was instrumental in establishing a comfort level early. This, in turn, greatly simplified the process validation argument in Stage 2.

The milestone-driven framework defined the roles and responsibilities during each stage of the PV lifecycle and went a long way to breaking down the organizational silos that often impede cross-functional characterization activities. Despite the pockets of OpEx in the organization, deploying the lean VSM, 5S, and rapid changeover required perseverance to get all the key stakeholders to participate in the process. However, the efficiency gains made during manufacturing bore out the investment in time.

The thoughtful integration of OpEx tools also was very effective in identifying the sources of variability and the critical process parameters. Revisiting the process risk assessment as the process moved through PPQ ensured there was a clear understanding of what risks had been reduced and which risks remained. Along with the summary reports developed during the three stages, the pFMEA was the foundation for assessing the impact of continuous improvement or remediation activities through the company's change review board. While there is no one solution that will fit all processes, the framework and tools utilized in this case study are a practical and defensible solution for meeting the new PV guidance requirements.

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A Novel Process Analytical Technology Approach to Automated Pharmaceutical Container Closure Integrity Testing

by Emiliano Niffoi and Andrea Simonetti

This article provides an overview of Process Analytical Technology (PAT) methodology application to an automated equipment developed for 100 percent Container Closure Integrity Testing (CCIT) of pharmaceutical items.

Introduction

This article provides the overview of Process Analytical Technology (PAT) methodology application to an automated equipment developed for 100 percent Container Closure Integrity Testing (CCIT) of pharmaceutical items.

PAT is a scientific approach which is designed to facilitate continuous process improvement in terms of reliability, effectiveness, and efficiency. PAT is based on process understanding and in particular it looks at the identification, determination, and management of all critical sources of variability to guarantee that the expected quality is compliant with its requirements from the start (right first time).

The CCIT is based on ASTM F-2338-09 "Standard Test Method for Non-Destructive Detection of Leaks in Packages by Vacuum Decay Method,"[1] and is a proven integrity testing technology that can be applied to all possible containers. CCIT, as all other physical processes, is affected by variability, resulting both in common and special causes. While common causes are predictable and removable through equipment improvements, special causes and effects are intermittent and unpredictable, therefore can be mitigated through user direct actions only.

The article describes the methods and controls to be used while implementing and managing the CCIT process to consistently ensure the required level of quality, stability, and repeatability. It proposes the Statistic Process Control Algorithm (SPCA) as a solution for improving production rates, minimizing downtimes, and quickly identifying the root cause behind failures or anomalies.

In the following sections, a specific case study, developed from a MSc thesis,[2] is presented.

Equipment Overview

The equipment under analysis is of the "in line" type at continuous operation to test 100 percent of the production by using the Vacuum Decay Method, and is designed to be installed:

- downstream of a Blow-Fill-Seal machine for aseptic primary packaging providing a 60 Containers Per Minute (CPM) output rate
- upstream of a secondary packaging machine

The infeed and outfeed of Blow-Fill-Seal (BFS) containers is to be carried out by means of automatic systems as conveyors and transfer devices. The equipment was set to work at a speed of 60 cpm, to comply with the BFS primary packaging machine output rate.

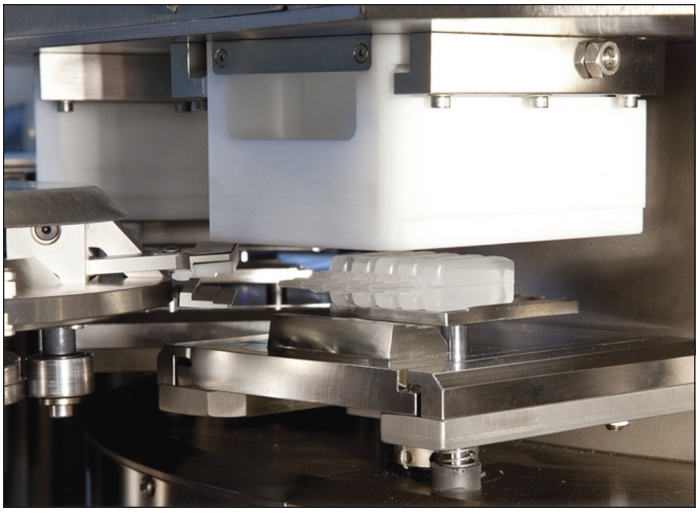

Figure 1. Test chamber.

The case study refers to a scenario in which the equipment was installed in the supplier's factory, where a production-like environment was simulated with the aid of a closed loop conveyor, continuously feeding the equipment with a suitable set of 500 conforming BFS containers. The reference time frame for the case study was 50 hours, comprising of:

- 45 hours of uptime
- 5 hours of downtime for:
  - periodic replacement of the 500 conforming BFS looping in the conveyor
  - failures simulation and management
  - data collection and preliminary review

The study included resulting in approximately 150,000 closure integrity tests.

Test Chamber

Ten test chambers with the same characteristics are installed on the equipment central turret; test chambers are mounted on shafts which are vertically actuated by a mechanical cam. A test chamber (Figure 1 and Figure 4) is made up of:

- a fixed top part which is connected with pneumatic actuators and vacuum transducer
- a mobile bottom part for BFS holding, which is lifted and lowered by means of the mechanical cam in phase with BFS loading and unloading. The mobile bottom part stroke provides for the test chamber closure.

Each test chamber performs a CCIT cycle composed of the following steps in correspondence to one complete rotation of the central turret:

1. loading of BFS in the test chamber
2. hermetic closure of test chamber
3. CCIT process execution and decision making on BFS closure integrity
4. opening of test chamber
5. unloading or rejection of BFS
6. arranging the next operation

Container Closure Integrity Testing

The CCIT is performed while the BFS is held within the hermetically sealed test chamber. The principle underlying the CCIT is that, as a consequence of the application of vacuum within the test chamber and hence of a differential pressure between the inside and the outside of the BFS, the air moves from the high pressure zone (within the BFS) to the low pressure zone (outside the BFS), causing a progressive increase of the pressure (that is a vacuum decrease) outside the BFS. A vacuum decrease greater than a given threshold at end of the testing phase points out a failure in the BFS closure integrity (leakage).

The CCIT process comprises the following phases - *Figure 2*:

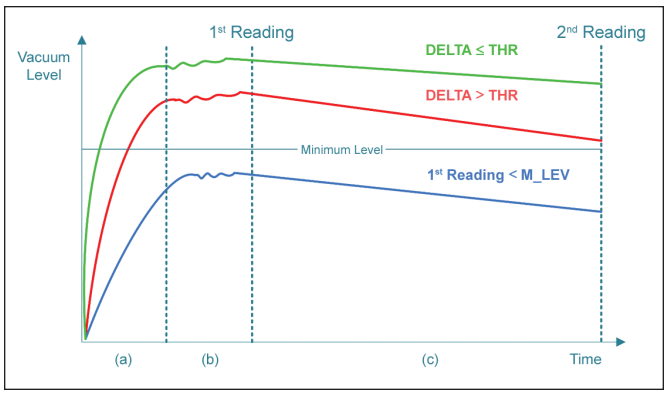

Figure 2. Vacuum curves during CCIT process execution.

a. Vacuuming: the period of vacuum setting within the test chamber.
b. Stabilization: the time necessary to get a homogeneous vacuum distribution within the test chamber.
c. Testing: the time frame in which the vacuum level is monitored by means of a dedicated transducer; two measurements are taken respectively at the beginning (1st reading) and at the end (2nd reading) of this phase.

Following the testing phase, the CCIT decision-making is performed by means of comparing the vacuum variation Δ (Δ = 1st – 2nd reading) to a previously determined threshold THR:

- If Δ ≤ THR, the BFS is accepted.
- If Δ > THR, the BFS is rejected (a micro leakage is detected).

In case that a preset minimum level (M_LEV) of vacuum is not reached at 1st reading time, the BFS is rejected as well (a gross leakage is detected).

DMAIC Strategy

Six Sigma uses a problem solving methodology known as Define opportunities, Measure performance, Analyze opportunity, Improve performance, Control performance (DMAIC).[3] SPCA works within the application of a specific DMAIC strategy (Table A and Figure 3) to provide means to successfully carry on the "Analyze" and "Improve" phases.

The DMAIC strategy is arranged as a cycle showing two main sections: the stability and capability stages; the latter being performed only following the former successful completion. SPCA's main objective is the monitoring and management of the following CCIT process:

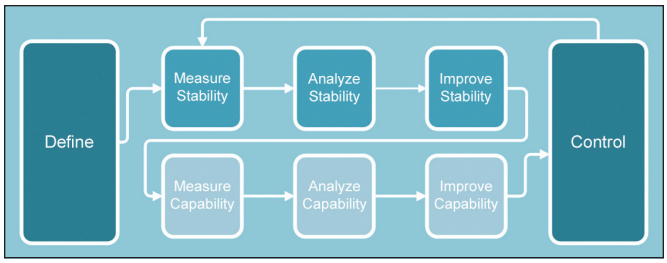

Figure 3. DMAIC cycle.

Define Phase	Measure Phase	Analyze Phase	Improve Phase	Control Phase
Definition of: 1. CCIT Critical Quality Attributes (CQA) as: • stability • reliability • repeatability 2. CCIT Critical Process Parameters (CPP) as the measurable variables having impact onto CQA: • 1st reading • Δ	1. Characterization of the natural variation of CQA and CPP, the purpose being monitoring the overall CCIT process behavior over a length of time appropriate for allowing the detection of relevant changes. 2. Setting the Control Limits (CL) for CCIT stability acceptance. 3. Setting the Specification Limits (SL) for CCIT capability acceptance.	Control charts based process stability analysis aimed at detecting special causes for CPP values non aligned with the reference CL.	In case: 1. CCIT is In-Control: continuous monitoring is performed 2. CCIT is Out-of-Control: corrective actions are implemented for removing the identified special causes (see the considerations arisen in the Preliminary Experiments section) and preventing them.	Control the improved CCIT process over time to ensure keeping it on track and correcting any outstanding variation before negatively affecting the process itself.
		Process capability analysis aimed at estimating common causes for CCIT outcome non compliant with the reference SL.	If capability does not fulfill the SL the process is to be adjusted and common causes reduced according to the desired cost-benefit trade-off.	

Table A. DMAIC phases.

- stability (including special causes detection)
- capability (including common causes effects estimate)

Preliminary Experiments

The background for the SPCA integration within the process stability stage was the performance of a Preliminary Experiments phase, during which the equipment was exposed to a focused and exhaustive set of standard failures affecting the CCIT process and the reference Critical Process Parameters (CPP) indicators. The resulting data were subsequently analyzed with the aim of:

- identifying the impact of mechanical, pneumatic, electrical, and configuration anomalies
- isolating the effects of each failure on the CPP indicators curves, modeling such effects as "noise sources" superposed to the CPP data - *Figure 5*.

The Preliminary Experiments phase observed the presence of special causes and determines a process drift that gradually brings CPP indicators Out-of-Control (OOC), causing test outcomes alteration and equipment, as well as CCIT process, performance degradation.

Furthermore, as a result of this analysis, a one-to-one correspondence between subsets of standard failures and the mathematical models describing their effects as noise sources affecting the CPP data was set, allowing SPCA to leverage it for the timely detection of anomalies: if CPP curves match one of the models, SPCA infers that one of the corresponding failures is present. The Stability Management section of this article provides more detail on how SPCA establishes this relation.

Table B enumerates the standard failures and the corresponding mathematical models. (Figure 4 provides an overview of the test chamber components whose possible failures were taken in account).

Stability Management

SPCA provides the CCIT process stability monitoring by means of tracking a continuous stream of incoming CPP values on Control Charts (individually for each test chamber) and analyzing the resulting data, triggering a suitable alarm in

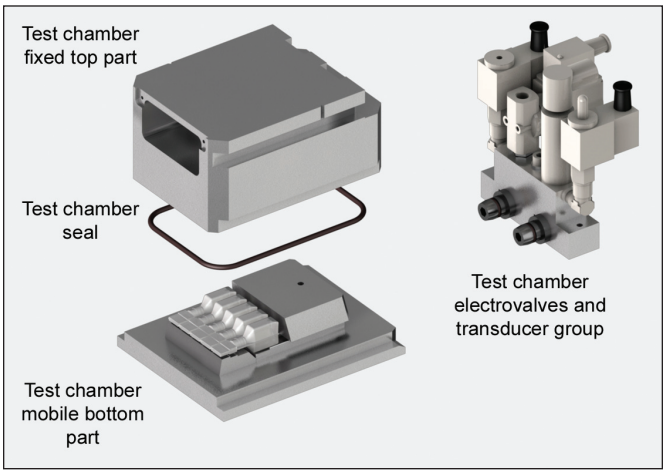

Figure 4. Test chamber main components.

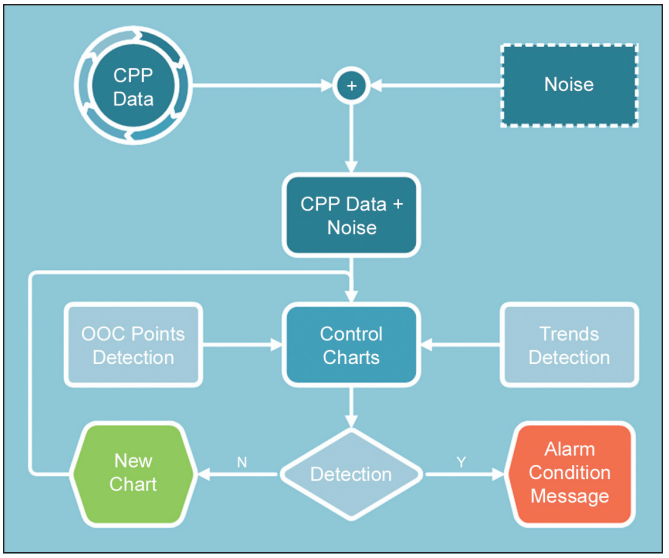

Figure 5. SPCA flowchart.

Standard Failures		Noise Source Model
1st Reading	Δ	
Test chamber seal loss or significant physical damage	Electrovalves/transducer support seal(s) wrong positioning or absence	Step
Electrovalve failure	Cut/scratch onto test chamber seal	Linear (Long Duration)
Dust and other materials (glass, debris, plastic) presence onto closing seals	Dust presence onto test chamber mobile bottom part	Linear (Short Duration)
Vacuum supply downfall		
Transducer failure		
Liquid presence in test chamber		Linear + Offset

Table B. Failures affecting CPP indicators and the corresponding mathematical models.

case a deviation in the form of a trend or a set of OOC points is detected.

If the deviation pattern is recognized by SPCA as corresponding to a given subsets of standard failures, the triggered alarm provides the user with specific information on the equipment components to be troubleshot; on the contrary a generic alarm is displayed.

Trends Detection

On the one hand, SPCA provides the detection of potential trends by means of the least squares method. The user may choose the Confidence Interval (CI) between one of the following values: 90%, 95%, 99%, 99.5%, 99.7%. The current case study had shown that a CI value of 99.7% is the optimal solution for a timely detection of most of the expected anomaly conditions.

OOC Points Detection

On the other hand, SPCA provides OOC points detection, taking advantage of the Western Electric Rules (WER);[4] only the first four WER are applied to minimize the likelihood of activating false alarm conditions.

The WER were chosen due to their relevance in the statistical process control field, where they are widely adopted to determine the detection of OOC points and anomalous data trends.

Following is a list of the WER, reporting for each rule the violation condition and the corresponding score (a partial score is assigned to the violation of each of the WER):

WER1: a single point more than three standard deviations from center line (score is 3)

WER2: two out of any three consecutive points more than two standard deviations from center line on one side of center (score is 1)

WER3: four out of any five consecutive points more than one standard deviation from center line on one side of center (score is 1)

WER4: eight consecutive points on one side of center (score is 1)

1	(N+1)	…	(x*N+1)	K*N - (N-1)
2	(N+2)	⋮	⋮	⋮
⋮	⋮	⋮	⋮	⋮
N	2*N	…	(K-1)*N	K*N

Table C. Matrix for CPP data storage and control charts update.

Once the analysis is completed, the sum of the partial scores for all the violations occurred in the reference time frame (that is the period in which the measurements reported in Table C matrix are taken) is compared with an acceptance threshold (WE_THR). The WE_THR parameter is set by the user and when the scores sum exceeds it the reference CCIT process is deemed OOC.

Since the CCIT process is based on continuous data, X, S, and R Control Charts are taken into account. The CPP data is acquired in real time from the CCIT process and is organized dynamically within a matrix before being provided for analysis to the Control Charts. The Control Charts are evaluated only when the matrix filling process is completed.

The matrix is of the N-by-K type, with N (number of rows) standing for the number of measurements for a given set and K (number of columns) for the number of measurements sets; the CPP data is inserted one column at a time, from left to right, from top to bottom.

The N and K parameters are to be configured by the user, and an adequate choice of their values is required for SPCA optimal behavior. The choice of N is based on evaluating the best trade-off between the following criteria:

- *responsiveness* ("quick variation" detection time: SPCA should detect possible CCIT drifts as fast as possible; responsiveness increases as N decreases)
- *robustness* (SPCA should avoid false detections: robustness increases as N increases)

The empirical analysis of the SPCA behavior in the reference case study shows that N = 10 is the best solution for CCIT; as a consequence the control charts choice is narrowed to a combination of X and R charts (for N < 12 the standard deviation method S loses efficiency).[3]

The choice of K is based on finding the best compromise between the following criteria:

- *regression accuracy* (increases with K)
- *time performance* (short chart calculation time: decreases with K)
- *responsiveness* (decreases with K)

A static choice of K that satisfies the criteria is not possible so K needs to be adapted dynamically or chosen on a case by case basis.

Deviations Analysis

Figure 5 shows how the CPP data being processed by SPCA may be altered by a failure occurrence and how the failure effects are modeled as the addition of a noise source causing

a process deviation; SPCA processes the resulting data by means of Control Charts, performing Trends and OOC points detection. The patterns shown in the detected deviations are in turn analyzed to ascertain their correspondence with the standard failures mathematical models, to provide the user with detailed information on the troubleshooting actions to be undertaken or start equipment automatic corrective actions. The following sub-sections give an overview of:

- the simulation, for a given test chamber, of a failure from each of the standard failures subsets (refer to Figure 4)
- the SPCA performance corresponding to different K values

The 1st reading CPP was the object of the analysis, nevertheless all conclusions reported for 1st reading are fully applicable to Δ as well.

Failure Modeled as "Linear + Offset"

A failure showing these features was induced contaminating the test chamber with liquid. This may occur in a production scenario when a defective BFS was tested during the previous test cycle, being that holes or damaged seals may cause liquid leakages from BFS. During the CCIT, vacuum is established within the test chamber, leading to liquid evaporation and subsequent CPP variation.

Figure 6 shows that this anomaly caused a 1st reading quick variation (10 mbar decrease) followed by a progressive increase toward the former value (owing to Automatic Drying System (ADS) algorithm action, as detailed hereinafter). In this case, the X-Chart was effective in detecting the OOC points, allowing SPCA to recognize the deviation pattern as belonging to the "Linear + Offset" class and trigger the corresponding alarm.

At this point, the user may stop the equipment and provide to manually clean the test chamber. Otherwise, the anomaly may be automatically managed by the equipment by means of ADS for excluding and drying contaminated test chambers until the complete restore of the optimal condition (this automated option avoids the possibility of testing conforming BFS into contaminated chambers, causing their possible false rejection). The correct management of a failure modeled as Linear + Offset is successfully completed with the capability of detecting wrongly configured equipment parameters (e.g., if the M_LEV threshold is mistakenly set too low, the ADS is not activated).

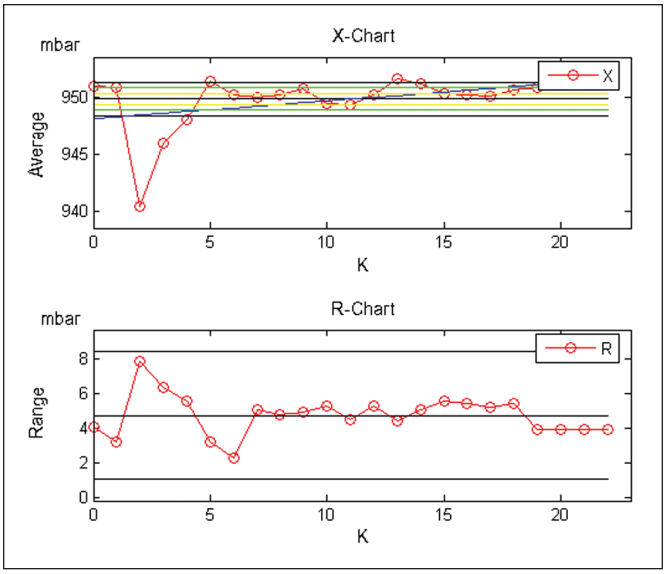

Figure 6. Linear + Offset failure charts.

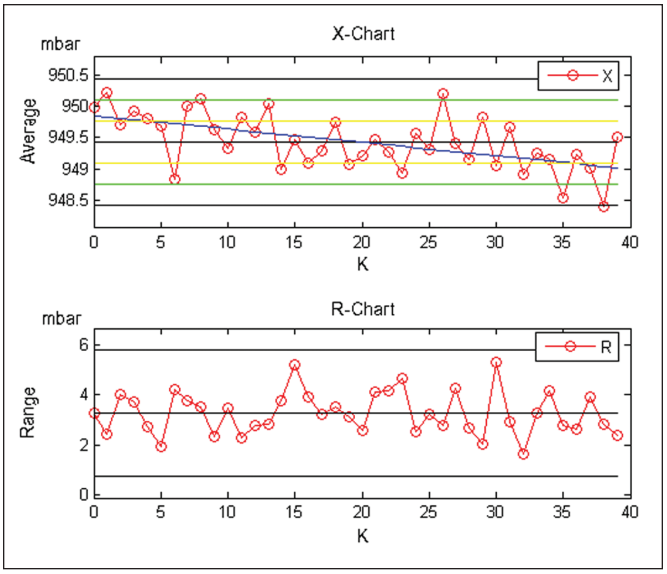

Figure 7. Linear (Long Duration) failure charts.

Failure Modeled as "Linear (Long Duration)"

This noise source model was simulated with an electrovalve failure causing a 5 mbar decrease of the 1st reading. Figure 7 shows that SPCA detected the trend (highlighted in blue) by means of the X-Chart. The collected data (Table D) shows that SPCA needs at least a value of K = 40 for each chart to detect effectively noise sources of this type.

The simulation was designed to consider the worst case scenario, hence the failure was conventionally started at the half of the measurement sets (e.g., when working with K = 50 and N = 10,500 measurements were needed, hence the noise in this case started at the 250th measurement).

Failure Modeled as "Linear (Short Duration)"

This noise source model was simulated contaminating the test chamber seal with tiny plastic particles to compromise its airtightness during the CCIT cycle and cause a 5 mbar decrease of the 1st reading CPP.

Figure 8 shows that SPCA detected the trend (highlighted in blue) by means of the X-Chart. This type of failure causes a greater slope on the X-Chart curve with respect to the ones

K	Noise Start	Number of Charts	Detected Trend	Result
20	100	16	-	X
30	150	11	8	X
40	200	8	2, 3, 4, 5, 6, 7, 8	OK
50	250	6	2, 3, 4, 5, 6	OK

Table D. Linear (Long Duration) failure collected data.

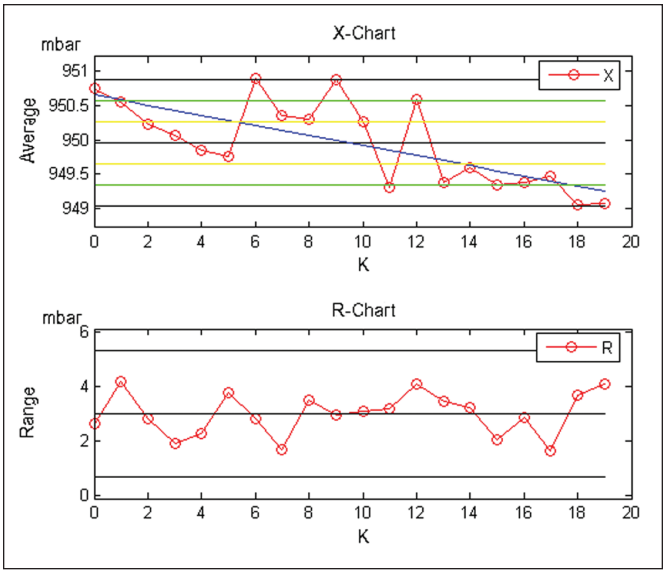

Figure 8. Linear (Short Duration) failure charts.

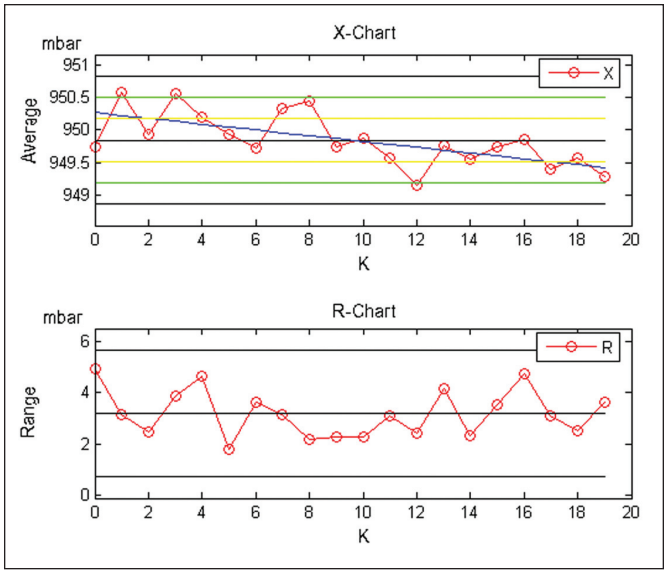

Figure 9. Step failure charts.

of the Long Duration Linear class, making K = 20 enough for a correct failure identification - *Table E*.

Failure Modeled as "Step"

This noise source model was simulated damaging a test chamber seal to cause a sudden decrease (step-like) of the 1st reading CPP. The minimum relevant value for the step amplitude is 0.5 mbar and is determined according to the equipment THR parameter (step amplitudes lower than THR are not able to influence the CCIT process outcome and are not taken in account).

The collected data (Figure 9) had shown that K = 20 is an appropriate value for effectively detecting this type of failures.

Results

SPCA provided the possibility to perform quick data-driven decision making and identified the root cause behind CCIT process stability alterations with a high degree of certainty.

In particular, following the detection of OOC variations, SPCA pointed out clear indications toward the needed corrective actions to be implemented for removing special causes; therefore avoiding a time-consuming and unnecessary troubleshooting phase. SPCA worked in the direction of complementing the equipment standard tools for runtime diagnostic of pneumatic actuators, and mechanic and electronic components (algorithm for Autodiagnostics), helping the CCIT process to perform reliably and predictably.

Capability Management

Once special causes have been detected and removed and the CCIT process stability assured, SPCA estimates the common causes impact and provides feedback about the improvements to be made to the equipment and the configuration of its computerized system, to attain compliance with the established SL. Therefore, a continuous process capability analysis is performed in order to achieve this goal: CPP values are taken as input and C_p e C_{pk} indicators values[5] are returned as output.

K	Noise Start	Number of Charts	Detected Trend	Result
10	50	9	-	X
20	150	4	1, 2, 3, 4	OK
30	200	3	1, 2, 3	OK
40	250	2	1, 2	OK

Table E. Linear (Short Duration) failure collected data.

The desired quality and the common cause variability are generally deemed acceptable for such pharmaceutical equipment when the condition $C_p \geq 1.33$ is satisfied; in case the C_{pk} value is close to C_p we can infer that the process CCIT is capable of producing within the SL and moreover that it is centered on the target value. In case SPCA finds that these conditions do not hold true, the CCIT process is affected by common causes which must be investigated (in particular the $C_p < 1$ condition is symptomatic of unacceptable performance behavior).

C_p will remain constant unless there is a clear change made in the process or the equipment. In cases where the CCIT process is not centered on the SLs means a substantial deviation of the CQA expected behavior, actions should be planned to get improvement on both capability indicators value.

The parameters to be optimized and the actions to be executed for improving process capability are to be determined according to a preliminary choice on the desired trade-off between process performance and quality on one side and the corresponding costs on the other.

Results

The information derived from the SPCA analysis with a broad range of conditions, combined with the historical know-how of the CCIT process, allowed us to create a list of actions to perform for process capability and equipment efficiency improvement:

- test cycle:
  - recipe configuration and set-up parameters adjustment

  - equipment hardware fine-tuning
- equipment sub-systems:
  - routine use of embedded diagnostic tools
- pneumatic system:
  - optimization of the test vacuum generation system (pipes routing and sizing, pressure regulators calibration)
- test chamber:
  - choice of materials and seals, mechanical tolerances refinement
  - calibration of compensator springs on test chamber mobile bottom part shaft

Conclusion

A method for process improvement and variability management has been presented with a focus on the following:

- identifying possible process weakness allowing proactive remedial
- making respectively failures identification, resolution, and prevention possible
- driving the design of suitable and robust solutions based on thorough knowledge of processes and possible sources of variability
- achieving excellence as long as preventing variability is the key for producing high quality

SPCA proved its effectiveness in:

- attaining a stable, repeatable, reliable, and robust CCIT process in the context of a productive environment
- providing means for enhancing production quality, improving the equipment performance, and extending its operative life span

Possible future developments for SPCA include its full industrialization and the ability for dynamically adapting the K value for maximizing the likelihood of anomalies detection.

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Project Managers as Mediators

by Leo Hura, PM COP Steering Committee Member (Mediation), and Keith Gibbs, PM COP Chair

Introduction

Over the last several years, a key component of Project Management training offered by the ISPE Project Management Community of Practice is the topic of Conflict Resolution, including contractual obligations in procurement, alternative dispute resolution boards, and appropriate use of mediation. This is a key Project Management skill and therefore addressed in the upcoming ISPE Project Management Good Practice Guide. Every project should include plans for dealing with conflict, and those plans should be communicated to all members of the project team. Additionally, the PM COP recognizes that conflict also can be found within other areas of organizations outside of the project infrastructure. This also may be identified within program teams and working groups or committees, even within volunteer driven organizations such as ISPE. Therefore, the PM COP has expressed within its charter the availability of trained mediators within its membership to serve as facilitators for conflict resolution to any and all ISPE groups, committees, task teams, boards, or other Communities of Practice. This activity is managed by Leo Hura, the current PM COP Steering Committee Member (Mediation). In addition, Hura has provided the following editorial to define the topic.

Editorial

Disagreements are inevitable in any group endeavor. The key is to avoid, prevent, and resolve disagreements before they grow into conflicts, disputes, and post project complaints. Whether it's within a project team where assignments are made by organizations or among volunteers working in a non-profit endeavor like ISPE, the objectives and principles defined to mediate disagreements should be the same, although methods may vary. The critical point is that in the knowledge that disagreements are unavoidable, comes the need to define a way to manage those disagreements.

Organizations are established for multiple business and/or professional objectives, including the need to protect against the negative impact of conflict. This requires the establishment of a set of processes and training for anticipating, preventing, and resolving conflict. Usually covered within a project are terms for dealing with conflict and dispute in a contract, through defining clear contractual obligations and specifying such potential actions as mediation and/or litigation if those obligations are not met. However, no contract can foresee the various types and tenor of disagreements, conflicts, disputes, and post project complaints. More needs to be done at the initiation of any endeavor by gaining a commitment from all engaged parties to do a better job of identifying the foreseeable types of conflict which may arise in a particular relationship, and in the training and communication of how to deal with that conflict.

Foreseeable risk may be defined as:1 a danger which a reasonable person should anticipate as the result from his/her actions. This definition assigns personal responsibility to each individual in an organization. Even one person's conflict can materially and adversely impact a project. In an organization such as ISPE – almost totally dependent on volunteerism – conflict can result in alienation of conflict-phobic members and totally disrupt volunteer relationships.

Knowing the objective of an organization defines what that organization is supposed to do. To get a sense of the types of what types of conflict are foreseeable comes from many sources. Key reference areas in defining what is foreseeable are track history, lessons learned and individual past experience. Track history of others involved in a project come from organizational experience on past and current projects, reviews of litigation history, and interviewing former members associated with the organization in question. In terms of lessons learned – every organization should have a system of creating, cataloging and using lessons learned for future projects. Individual experiences can be utilized through topical survey, interviews, and focus groups. All of these activities can result in clear catalogue of the conflict risk that faces planned endeavors, whether they be partnerships, projects, programs, or policies.

Once foreseeable conflicts are identified, emphasis must be turned to identify and put in place applicable systems, processes, and resources which are appropriate to meet the mediation needs of the group. This must be followed by definition and implementation of a training plan which instills the practice in the team. In consideration of efforts to avoid, prevent, and resolve conflict, organizational management and responsible department policies should permit flexibility and adaptation to meet the objective of a specific project or activity, as agreed to by all affected parties subject to review and approval by responsible organizational authorities (e.g., legal, procurement)

Training needs are often underappreciated and sometimes even ignored. In today's complex organizational environments, this creates risk. Bringing together people from different organizations and organizational cultures requires active efforts toward formation of a common goal based infrastructure and integration of best practices. A critical component of training is participant interactivity in training exercises and particularly so in that training which deals with conflict resolution. Training should encompass putting participants in role playing exercises that deal with foreseeable situations and having them work through those situations using the

Concludes on page 2.

Project Managers as Mediators

Continued from page 1.

systems, processes, and resources meant to be applied on the project or activity. Given today's multi-media culture, it is helpful to include appropriate entertainment value in training. Although there is disagreement about the value or futility of using role plays and videos in the conflict resolution arena, these methods should be embraced when training on foreseeable conflicts. To draw an analogy, reflect on airlines which use simulators to train their pilots on how to deal with emergency situations and by degree, all training is more impacting through the use of simulation. Nothing can crash a project more quickly than unresolved conflict. Training facilitators, who also may be actively involved in a project or activity, should be utilized – this is a confidence builder to participants if the facilitator is a known quantity when later "real life" project or activity situations arise.

Ultimately it is how trained behavior is maintained and how utilization of conflict avoidance training fit in to a project or an activity. As a result, the system selected to monitor and respond to conflict must be utilized. Ignoring conflict always leads to greater conflict, but ineffectively addressing conflict will have similar results. The selected system must be embraced by all participants and the focus needs to be a clear understanding that turning to the processes established for dealing with conflict is a positive and not a negatively perceived activity.

Two components in conflict resolution processes are critical. The first is to strike a balance between confidentiality and transparency. The argument behind holding what is said in a conflict resolution process confidential, is to ultimately increase the openness among the people involved in conflict or dispute. The argument for transparency is that management may want to understand what has happened. The second critical component is the sacrosanct "neutrality" of the facilitator. Neutrality has to be real; if not participants may avoid, resist, or object to participation and/or be less open in their discussions. If disputants believe there's a conflict of interest between neutrality and allegiance to a particular element in an organization – the results will negatively impact future participation. These two components must be clearly embraced, not just in theory, but in practice.

Monitoring a project or volunteer activity for conflict should include periodic interviews with individuals and facilitators and reports on the state of collaboration/conflict resolution activities as part of situational reports. If and when disagreement grows into conflict the established processes need to include resources assigned and aligned to deal with the issues being disputed. There are a number of processes adaptable to a conflict management system including negotiation, facilitation, mediation, mediation arbitration, and arbitration. System policies and procedures should be clearly articulated so that participants in the process know an organization is serious about and committed to avoiding, preventing, and resolving conflict.

Realizing that there may be contrary opinions on the above defined need to establish systems to deal with conflict is proof that a difference of opinion within an organization can exist. If conflict exists at any level of the ISPE organization, the PM COP is willing to apply our leadership and network of local Chapter/Affiliate liaisons to help work through the steps required to move past dispute and achieve the goal to bring the best value ISPE can to our global membership. Contact any PM COP Steering Committee Member for assistance.

Dispute Resolution Session at the ISPE 2011 Annual Meeting:

In addition, the PM COP "Real World of Project Management" Track at the 2011 Annual Meeting will conclude with a session titled, "Keeping the Peace: the Project Managers role in Dispute Resolution." This entire track explores how Project Management is like the Wild, Wild West; a period in American history where expansion was eminent, resources were undiscovered, and the rate of innovation was on a sharp rise. However, lawlessness prevailed, as those outside the direct oversight of authority lived life in any way deemed fit. Cattle were rustled, stakes were claimed, jumped and reclaimed, and whoever had the biggest gun and fastest horse was usually the one who made the rules. That is, until the Sheriff came to town. Larger than life stories of these "enforcers" are commonplace in the American legend, and their counterparts exist in examples from other cultures throughout the world. They maintained order. They enforced the law. They were leaders in their community. They were tasked with a scope to end the chaos and lawlessness, given a schedule to meet that goal and a budget of men, horses, weapons and tools to do it. They wanted to keep the law abiding citizens safe, and do it all without bringing the US Marshalls or other "regulators" into the matter. In short, the Sheriff was the Project Manager of the Wild, Wild West.

References

1. http://legal-dictionary.thefreedictionary.com/foreseeable+risk. PE

We look forward to seeing you at this year's Annual Meeting!

Pharmaceutical Engineering
2010-2011 Article of the Year Finalists

We are pleased to announce the 2010-2011 Roger F. Sherwood Article of the Year Award Finalists. The winner will be selected from this group and recognized at ISPE's 2011 Annual Meeting.

September/October 2010, Volume 30, Number 5

Lean Maintenance – A Risk-Based Approach

by Gerard Clarke, Gerry Mulryan, and Padraig Liggan

November/December 2010, Volume 30, Number 6

IT Outsourcing and Offshoring: Recognizing and Managing Risk

by Arthur D. Perez, PhD and Glenn Morton

January/February 2011, Volume 31, Number 1

Risk Management – A Key Requirement for Project Success

by Brett Schroeder, John Alkemade, and Gordon Lawrence

March/April 2011, Volume 31, Number 2

Business Process Management (BPM) Based Pharmaceutical Quality Management Systems: A Win-Win Between Compliance and Competitiveness

by François Versini

May/June 2011, Volume 31, Number 3

Standardizing Equipment Maintenance Outsourcing

by Martin van den Hout

July/August 2011, Volume 31, Number 4

Quality Risk Management (QRM) Tool Selection: Getting to Right First Time

by Kristin S. Murray and Stephen Reich

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For further information, please visit us on the Web site at **www.ISPE.org/pharmaceuticalengineering**, then connect the following links: How to Submit an Article, and then Author Guidelines.

Practice What You Preach!

The Project Management of the Project Management Good Practice Guide (PM GPG)

by Dr. Trish Melton on behalf of the Core Team

When the PM GPG became a reality what was the first thing we did:

- Appoint a Chair (effectively the Project Director) and a Project Manager
- Form a core steering team of key stakeholders
- Develop a vision of success for our 'project'

With this key structure in place we all agreed that if we were to achieve success that a fundamental concept was that we had to behave as project managers, use our combined project management expertise, and deliver excellent content in an effective value add way: we had to 'practice what we were about to preach' – good practice project management.

"The Guide was managed using a risk-based approach. All areas of uncertainty were identified and managed."

People

Key to our success was the engagement of a variety of stakeholders: Guide chapter writers and other contributors; reviewers and those involved in the governance of such documents within ISPE (the Guidance Document Executive Committee – GDEC).

Our chapter teams were all led by a member of the core steering team and contained ISPE members with both interest and expertise in selected subjects. The desire to share knowledge was critical to effective management of the content generated.

Benefits

Developing an understanding of the needs of our customers (you – the ISPE membership) was fundamental in developing the scope of the Guide. We relied on each member of our extended team to consider why content should or should not be included and continually challenged the benefit it would bring.

Risk

The Guide was managed using a risk-based approach. All areas of uncertainty were identified and managed. A good example is the way that *chapter content* and *schedule adherence* was reviewed:

Each chapter was given a Red, Amber, Green (RAG Rating) dependent on these two factors enabling the core steering team to predict likely success (development of a value add guide able to be launched at the 2011 ISPE Annual Meeting – 18 months from start to finish!!).

Team Ways of Working

Control of the project schedule and risk profile was managed through regular virtual meetings allowing a "one-team" approach no matter where in the world a team member was located.

Most of us would attribute our success to having working sessions via a Webex platform:

- Action logs were generated "live" with no need to write lengthy minutes after the fact.
- Chapters were written and reviewed "live" avoiding the need for team members to have extended writing sessions outside of the virtual environment.
- Work was available on a shared area thus avoiding revision issues and emailing large documents.

Success

The Guide will be released at this year's Annual Meeting as a part of the PM COP Track and I hope to shake the hand of everyone who has contributed to this success. A ***real*** team effort born out of a combined desire to:

- share knowledge
- provide good practices to improve project outcomes
- demonstrate the value of project management

I look forward to seeing you all in Texas!

Trish

A Message from Chairman, Keith Gibbs, PM COP Chair

State of the Project Management (PM) Community of Practice (COP)

I write to you today to communicate that as we look forward to meeting in Texas, our industry and our society are experiencing many challenges. Yet, the state of our COP has never been stronger. Over the last 12 months, we have seen a steady growth in our membership, a staggering abundance of new source volunteerism, an astronomical effort to prepare a Good Practice Guide, delivery of multiple successful education events, and a rapid alignment with new challenges facing ISPE. These achievements are the result of the hard work of our membership, and for this effort, I thank you.

This last year has seen a true globalization of the PM COP. In an effort to align the COP with Chapters and Affiliates, local liaisons have been identified in all except seven of the established regions globally, including a virtual affiliate to accommodate membership without an accessible local group. Every North American Chapter/Affiliate has an active local lead, with Europe, Asia-Pacific, and South America missing only a few representatives. Over the next 12 months, these liaisons will be tasked with developing local groups of active like-minded PM Professionals to determine what is needed most in each Chapter or Affiliate. We are excited about the future growth that will happen at the local level.

We have also made an effort to align with and support other COPs. Liaisons have been identified to increase the level of communication between the PM COP and most others, in an effort to align the efforts we are all making to increase the value ISPE brings to its membership. This cross-communication is leading to tangible results, especially in the area of educational programming and curriculum development. Again, over the next 12 months, we as a COP will see dramatic increase in the output from these partnerships already established. Project Managers cross into many other topic areas, and it is only natural that we work in tandem with other Communities of Practice to promote program development and knowledge sharing.

This year's Annual Meeting in Texas will see the launch of the ISPE Good Practice Guide (GPG): Project Management for the Pharmaceutical Industry. This volume was created in record time and is a testament to the successful application of Project Management practices that are both generic across industries and specific to our own. This Guide was developed by leaders within ISPE, and will form the basis for programming and skill based training for many years to come. It is both current and forward thinking, and will be beneficial to anyone who wears the hat of a Project Manager.

And speaking of hats, this year at the Annual Meeting the PM COP presents the "Real World of Project Management VII: Applying Project Management Good Practices across your Organization." In 2010, the PM COP took you into the future, and introduced you to the "Science of Project Management." Annual Meeting delegates participated in a series of five interactive workshops to explore how a Project Manager assesses risk, mitigates against change and crisis, controls project knowledge and promotes project culture, establishes communication methods and defines reporting channels, and works to assure a collaborative partnership approach to project execution.

Now one year into that future, the track turns in the other direction, and explores how Project Management is like the Wild, Wild West; a period in American history where expansion was eminent, resources were undiscovered, and the rate of innovation was on a sharp rise. However, lawlessness prevailed, as those outside the direct oversight of authority lived life in any way deemed fit. Cattle were rustled, stakes were claimed, jumped and reclaimed, and whoever had the biggest gun and fastest horse was usually the one who made the rules.

That is, until the Sheriff came to town. Larger than life stories of these "enforcers" are commonplace in the American legend, and their counterparts exist in examples from other cultures throughout the world. They maintained order. They enforced the law. They were leaders in their community. They were tasked with a scope to end the chaos and lawlessness, given a schedule to meet that goal and a budget of men, horses, weapons and tools to do it. They wanted to keep the law abiding citizens safe, and do it all without bringing the US Marshalls or other "regulators" into the matter. In short, the Sheriff was the Project Manager of the Wild, Wild West.

This year, the PM COP provides you with another opportunity to wear a different hat and explore your own role as a Project Manager. These five sessions will include information from the ISPE GPG and role playing exercises to promote understanding of methods that will help enforce PM Good Practices. These will be sessions as wild as the Frontier West. We look forward to your participation in these highly interactive sessions.

In conclusion, the state of the COP is strong, but it could be stronger. Volunteers are always welcome and always valued. Please consider helping us make the next year even better than the past, and give back to the society that gives to you. Help us grow. Make us better by sharing your own skills and knowledge. Make us the best.

ISPE Meets Industry Demands for Training in Asia Pacific

by Rochelle Runas, ISPE Technical Writer

ISPE Training completed a successful 19-day tour (27 June through 15 July) of the Asia Pacific, delivering training on a variety of topics to hundreds of participants in Shanghai, Jakarta, Manila, Singapore, Beijing, and Bangkok.

In collaboration with ISPE Affiliates and associated conferences in China, Indonesia, Philippines, Singapore, and Thailand, trainers Gordon Farquharson and Rob Walker, both of the UK, taught courses in:

- Sterile Drug Manufacturing (Shanghai, Jakarta)
- Drug Manufacturing Facility Design and Development (Shanghai)
- Cleaning Validation (Jakarta, Singapore, Beijing)
- Life Science/Pharmaceutical Water Systems (Manila)
- A Practical Approach to Assessment and Control of Cross Contamination in Multi-Product OSD Plants (Bangkok)
- Oral Solid Dosage Forms (Beijing)

"After coordinating Asia Pacific training for several years, I feel that 2011 is turning into our most active year," said Ali Montes, ISPE Director of Training. The success and popularity of ISPE Training in this region has prompted plans for additional Asia-Pacific training events through December, said Montes.

"The Asia Pacific region is rapidly implementing GMPs that are closely aligned with EU and WHO models," said Farquharson. "This is generally being achieved through the PIC/S accreditation route for many nations such as Indonesia, Philippines, Hong Kong, and Thailand. In China, the process is a little different. The China state FDA has just introduced new GMP regulations based on the WHO GMP with a target of three years for implementation. The profound effect of this is that now the indigenous manufacturers, supplying medicines to the region, need to understand and meet these new GMP requirements. Previously, it was mainly the multi-nationals that brought these western derived GMPs into the market. To meet this demand, ISPE has been able to respond with practical education and training based on thorough experience of the GMP guidance."

From left: Mr. Rob Walker (ISPE Trainer), Ms. Dhahirah Jawahar (ISPE Singapore Affiliate C&Q Chair), Mr. Taj Rana (ISPE Singapore Affiliate Vice President), Mr. Nicholas Kong (Singapore Workforce Development Authority), and Ms. Thong Hui Min (Singapore Workforce Development Authority).

Walker said the Asia Pacific training courses this year have shown a wide range of knowledge and understanding from the delegates. "As in all training sessions, there is always going to be a range in both the knowledge of the delegates and their expectations in respect to the training course they are attending," said Walker.

"From my experience, in the region where the GMP regulations are changing, such as China or where specific companies require information about different regulatory standards, there is an increasing demand for information about how to implement these new GMP regulations in a cost effective and GMP compliant manner. The globalization of GMPs, with their adoption by many countries of the PIC/S GMPs as well as the supply of medicinal products from Asia to the Western markets, has resulted in this demand for knowledge about GMP standards. ISPE has, by the range of training course and subject matter, provided significant support to meet this demand for training."

As a membership-based organization, ISPE draws from the expertise of its Members to develop training courses that address current needs to meet industry demands. ISPE instructors work in the industry and face the same daily challenges as its Members. ISPE Training provides solutions to a company's immediate goals to lower production costs, improve process efficiency, increase production quality, and meet regulatory requirements.

In addition, ISPE offers On-site Training, featuring customized on-site training programs to help meet specific employee productivity and knowledge requirements. The program will cost less than sending groups to off-site training and can work to fit employee work schedules. Most courses are two days and can accommodate up to 30 participants.

For details and photos from Asia-Pacific training events, please view the August 2011 Asia Pacific Affiliate News, at www.ISPE.org.

For further information on ISPE Training, please visit the Training section at www.ISPE.org.

ISPE Supports Biotech Industry through Partnership with University of Florida

Unique Translational Research Master's Program Trains in Science and Business

by Rochelle Runas, ISPE Technical Writer

The partnership between the International Society for Pharmaceutical Engineering (ISPE) and the University of Florida (UF) to train workers for Florida's growing biotechnology industry continues with the creation of a new Science Master's Program in Translational Biotechnology.

Added to the UF College of Medicine's catalog in 2010, the NSF-funded program is a collaboration between the UF College of Medicine and the UF Warrington College of Business Administration. The interdisciplinary program provides curricular and practical training in biomedical and laboratory science and includes intensive training in business administration. Graduates earn a Master of Science degree in medical science, with a graduate minor in business administration.

As part of its agreement with UF's Center for Excellence for Regenerative Health Biotechnology (CERHB) Education and Training Center, ISPE supports the curriculum development of the master's program by serving on the program's curriculum advisory board and facilitating relationships between the program and ISPE's student and young professional constituencies.

"ISPE's worldwide membership includes a large and thriving biotech community," said Bob Best, president and CEO of ISPE. "The Society's body of knowledge in biotechnology and related expertise in pharmaceutical science and manufacturing enable us to affect education, training, and career development and prepare strong candidates to enter the biotech workforce. ISPE is honored to continue collaborating with University of Florida on the shared effort to grow Florida's biotech industry."

According to Richard Snyder, Ph.D., the program director and director of Biotherapeutic Programs in the UF Office of Research, Florida's biotechnology industry is poised to change from a primarily research base to high-growth product development and manufacturing. In preparation for this change, the master's program offers students the opportunity to "really understand the science fundamentals, how products are developed, how business functions, what the main drivers of project management are, how projects and resources are budgeted, the types of timelines involved and the different kinds of expertise needed to develop new therapeutic products."

Traditionally, such skill combinations are found in industry settings, but more and more they are being nurtured in academic institutions, as clinical and translational science programs thrive and researchers develop and evaluate novel therapies for various diseases.

"The Society's body of knowledge in biotechnology and related expertise in pharmaceutical science and manufacturing enable us to affect education, training, and career development and prepare strong candidates to enter the biotech workforce. ISPE is honored to continue collaborating with University of Florida on the shared effort to grow Florida's biotech industry."

The two-year program is research-intensive and includes a formal internship at a Florida biotechnology company. Industry leaders serve on the program's advisory board.

In addition to ISPE, the program's industry partners include BioFlorida, RTI Biologics Inc., Banyan Biomarkers Inc., Exactech Inc., Pasteuria Bioscience Inc., Scripps Florida, Nanotherapeutics Inc., Workforce Florida, and the Florida Research Consortium.

Since 2006, ISPE has supported UF's CERHB Education and Training Center by providing industry input/feedback, which led to the development of a high school level program in Industrial Biotechnology taken by more than 900 students since 2007; teacher training; a Biotechnician Assistant credential; and industry/workforce training courses.

For information about enrolling in UF's translational biotechnology master's program, contact the graduate coordinator at +1-352-273-6380 or kminkoff@ufl.edu.

For further information on the CERHB Education and Training Center, visit www.cerhb.ufl.edu/education-center, or contact Tamara Mandell, Assistant Director, Education and Training, at +1-386-462-6397 or tmandell@cerhb.ufl.edu.

Reference

Reid, C. (2010). *University of Florida launches unique translational biotechnology master's program*. Available: http://news.health.ufl.edu/2010/14319/colleges/college-of-medicine/university-of-florida-launches-unique-translational-biotechnology-master%e2%80%99s-program/. Last accessed 2 August 2011.

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International

WHO Expert Committee Specifications Available for Pharma Preparations[1]

WHO's report includes information on evaluation of certain food additives and contaminants in food and specifications for pharmaceutical preparations. It can be found at http://apps.who.int/gb/ebwha/pdf_files/EB129/B129_10-en.pdf.

WHO Publishes "The World Medicines Situation Report 2011"[2]

The third edition of the World Medicines Situation Report brings together new data on 24 key topics relating to pharmaceutical production and consumption, innovation, regulation, and safety – in one place. Topics include selection, procurement, supply management, rational use, financing, and pricing. Cross-cutting chapters cover household medicines use, access and human rights, good governance, human resources, and national medicines policies. Each chapter of this report is written by a different author. Chapters are being published electronically, in batches, between April and December 2011. The new report updates the 1988 and 2004 reports.

Margaret Hamburg, US Commissioner of Food and Drugs, Commemorates the 40th Anniversary of PIC/S with Speech: The Importance of PIC/S in Our Globalized World[3]

To commemorate the 40th Anniversary of PIC/S, Margaret Hamburg gave a speech detailing the efforts undergone by the US FDA to join PIC/S, and the benefits it has received from membership. She also addressed why PIC/S is critical to helping ensure the safety of products with a globalized supply chain.

European Medicines Agency and US Food and Drug Administration Receive First Parallel Quality-by-Design Application[4]

The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) have agreed to accept the first application under their pilot program for the parallel evaluation of marketing-authorization applications involving Quality by Design (QbD). The application, from Pfizer, will allow the two agencies to assess the parts of the application related to QbD in parallel. The agencies will communicate with and consult each other regularly during the evaluation process, resulting, if possible, in a common list of questions to the applicant and harmonized evaluation of the applicant's responses.

European Medicines Agency and US Food and Drug Administration Set Up Biosimilar "Cluster" and Publish First Report on Interactions[5]

The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) have set up a new "cluster" on biosimilar medicines. Clusters are topic areas of mutual interest for the two agencies, which they have identified as benefiting from the regular exchange of information and collaborative meetings. Biosimilar medicines is the latest addition to the existing list of topics, which already includes medicines to treat cancer, orphan medicines, medicines for children, and blood-based products.

The new cluster will allow the two agencies to increase their degree of interaction and will begin with a kick-off meeting to discuss the group's activities. The group will follow this with discussions by teleconference around three times a year.

USP Publishes Freely Available Standards to Help Ensure Quality of Medicines throughout the World[6]

To help ensure that medicines and their ingredients used around the world are of good quality, the United States Pharmacopeial Convention (USP) has a free, online collection of voluntary public standards to allow testing of a medicine and its ingredients. These standards appear in the new USP Medicines Compendium (MC).

The MC will support good quality medicines through tests, procedures, and acceptance criteria for critical quality attributes. Published by USP and available at www.usp-mc.org, the MC will include standards for medicines legally marketed in various countries. Initially, the MC will include 10 standards proposed for public comment, and another 11 standards proposed for development.

Q&As with Regulators from Regulatory Affairs Forum in Frankfurt[7]

International regulators answered questions at ISPE's Regulatory Affairs Forum in Frankfurt. This document can be viewed at http://www.ispe.org/index.php/ci_id/28015/la_id/1.htm.

Swedish Medical Products Agency Cooperation Finalized Agreement with Brazil's Medical Products Agency ANVISA[8]

The Swedish Medical Products Agency has signed a cooperation agreement with its Brazilian counterpart ANVISA. The aim of the agreement is to increase the exchange of information and experience within the areas of the improved use of medical products, sustainable development, resistance to antibiotics, medical technology, electronic submissions, and pharmacopoeia and pharmacovigilance activities.

Asia/Pacific

Australia/New Zealand

Australia New Zealand Therapeutic Products Agency (ANZTPA) Moves Forward[9]

The Australian and New Zealand Governments have agreed to proceed with a joint scheme for regulation of therapeutic goods (i.e. medicines, medical devices, etc). The creation of a joint regulatory scheme across both countries will safeguard public health and safety, while encouraging economic integration and benefitting industry in both countries. Over time, the joint arrangements will be administered by a single regulatory agency, the Australia New Zealand Therapeutic Products Agency, which will absorb the current regulators – Australia's Therapeutic Goods Administration and New Zealand's Medsafe.

Australian TGA Publishes Update to Regulatory Framework for Biologicals[10]

The framework was established based on a recommendation endorsed by all Australian State and Territory Health Ministers and will result in improved regulation of human tissues and cellular therapies. The new framework will provide improved clarity by applying different levels of pre-market regulation to biological products based on the risks associated with the use of each product. In addition, the framework has been designed to be flexible to accommodate emerging technologies.

Australian TGA Transparency Review Released[11]

The Australian Government released the report of the Therapeutic Goods Administration (TGA) Transparency Review panel, chaired by Professor Dennis Pearce. The purpose of the review was to improve public knowledge of regulatory decision-making and to enhance public understanding of the benefits and risks of therapeutic goods so that the Australian community can understand how the TGA operates and the reasons for its key decisions.

Europe

European Union

European Medicines Agency Establishes Geriatric Expert Group[12]

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has established a Geriatric Expert Group to provide scientific advice on issues related to the elderly. The group's mandate, objectives, and rules of procedure explain that the group will contribute to the work of the CHMP and the Agency secretariat by:

- giving input on guidelines under consultation
- giving advice on geriatric aspects of the development, assessment, or safety monitoring of medicines
- taking part in meetings where expertise on geriatrics is needed
- contributing to the geriatric implementation plan

European Medicines Agency's Management Board Nominates Guido Rasi as New Executive Director[13]

The European Medicines Agency's Management Board nominated Guido Rasi on 8 June 2011 as new Executive Director of the Agency. The Executive Director-designate was invited to a hearing in front of the European Parliament Committee on Environment, Public Health and Food Safety on 13 July 2011. The Board will officially appoint the new Executive Director following his hearing and a positive response from the European Parliament. Rasi has been Director-General of the Italian Medicines Agency and a member of the European Medicines Agency's Management Board since 2008.

European Medicines Agency Management Board Elects Kent Woods as New Chair[14]

At its 9 June 2011 meeting in London, the European Medicines Agency's Management Board unanimously elected Kent Woods, Chief Executive of the Medicines and Healthcare products Regulatory Agency of the United Kingdom, as Chair for a three-year mandate. Accepting his election, Professor Woods told the Board that, "it is my ambition to provide strategic leadership in helping the EMA to continue to protect public and animal health and maintain public trust."

European Medicines Agency Publishes Format for Submission of Information on Medicines[15]

The European Medicines Agency reached the first milestone in the implementation of the new pharmacovigilance legislation, by publishing the format in which pharmaceutical companies need to submit information on all of the medicines authorized or registered in the European Union (EU).

The format shows the types of information that companies will need to submit to the Agency by the legal deadline of 2 July 2012. This information will help the Agency to:

- create a list of all medicines authorized and registered in the EU, including medicines authorized centrally via the Agency and medicines authorized by regulatory authorities in EU Member States
- identify medicines accurately, especially medicines included in reports of suspected adverse reactions
- coordinate the regulation and safety-monitoring of medicines across the EU

European Medicines Agency Welcomes New Rules on Falsified Medicines[16]

The European Medicines Agency has welcomed the new Directive on falsified medicines, published in the Official Journal of the European Union on Friday 1 July. The new laws aim to prevent falsified medicines entering the legal supply chain and reaching patients. They will do this by introducing harmonized safety and strengthened control measures across Europe, including:

- obligatory features on the outer packaging of medicines to demonstrate that they are authentic
- strengthened requirements for the inspection of the manufacturers of pharmaceutical ingredients
- the obligation for manufacturers and distributors to report any suspicion of falsified medicines
- an obligatory logo that must be placed on the Web sites of legally operating online pharmacies with a link to official national registers

European Medicines Agency Plans Public Access to Information on Side Effects[17]

The European Medicines Agency published its plans for granting public access to the information held in its databases of the potential side effects of human and veterinary medicines. The two policies explain the Agency's plans to release information held in its EudraVigilance and EudraVigilance Veterinary databases. These are the central repositories for reports of suspected adverse reactions related to medicines authorized in the European Economic Area and medicines being studied in clinical trials.

European Medicines Agency Improves Package Leaflets[18]

The European Medicines Agency updated the template for package leaflets for human medicines to make the information easier for patients to understand and to include new sections on medicines' benefits and their uses in children.

The Agency introduced these changes to contribute toward the safe and effective use of medicines. They address the feedback from five years of user testing and from a range of stakeholders, including patient and consumer groups, national medicines regulatory agencies, the pharmaceutical industry, and academics.

Iceland

Icelandic Medicines Agency Publishes Annual Report 2010[19]

In the introduction of the report Ranveig Gunnarsdottir, the Executive Director of IMA, writes:

"The year 2010 has been challenging in many respects, with financial restrictions of the budget on spending and a heavy workload. To save resources the two units, Inspection and Licencing, were temporarily merged into one unit. The financial restrictions had consequences regarding workload and finishing tasks. With hard work, IMA's staff still managed to improve output compared to 2009 in spite of budget restrictions. Still we need to do better."

Sweden

Swedish Initiative for Green Medicine Production[20]

The Swedish Medical Products Agency (MPA) published a report on how environmental standards in pharmaceutical production can be sharpened within the EU. The proposal is unique and forces all manufacturers to follow the GMP rules on pharmaceuticals sold on the EU markets. In recent years, manufacturing of pharmaceuticals in low cost countries like India and China has drawn attention because of the environmental impact.

United Kingdom

Britain's MHRA Publishes "Annual Report and Accounts 2010-2011"[21]

The MHRA Annual Report and Accounts 2010-2011 were laid in Parliament on 14 July 2011. The Annual Report and Accounts give a selective overview of the events that have had most impact on the Agency during the past year, highlighting the landmark events and the safety issues the Agency has had to deal with. These included taking part in international enforcement action targeting the online sale of counterfeit and illegal medicines, and publication of the final report of the Expert Advisory Group on soft tissue reactions associated with metal-on-metal hip replacement devices.

North/South America

United States

US FDA Takes "First Step" Toward Greater Regulatory Certainty Around Nanotechnology[22]

The US Food and Drug Administration released draft guidance to provide regulated industries with greater certainty about the use of nanotechnology, which generally involves materials made up of particles that are one billionth of a meter in size. The guidance outlines the agency's view on whether regulated products contain nanomaterials or involve the application of nanotechnology. Nanotechnology, the science involving manipulation of materials on an atomic or molecular scale, is an emerging technology with a broad range of potential applications, such as increasing bioavailability of a drug, improving food packaging and in cosmetics. The draft guidance, "Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology," is available online and open for public comment. It represents the first step toward providing regulatory clarity on the FDA's approach to nanotechnology. Specifically, the agency named certain characteristics – such as the size of nanomaterials used and the exhibited properties of those materials – that may be considered when attempting to identify applications of nanotechnology in regulated products.

FDA Examines Ways to Improve Consumer Understanding of Prescription Drug Ads[23]

Findings from three studies conducted by the US Food and Drug Administration confirm that the way information is conveyed and displayed in printed drug advertising affects consumer understanding of prescription medications. The studies, designed by experts in FDA's Division of Drug, Marketing, Advertising and Communications (DDMAC) in the Center for Drug Evaluation and Research, examined ways to improve understanding of how consumers use the "brief summary" section of printed prescription drug ads.

US FDA Unveils New Global Strategy to Help Ensure Safety and Quality of Imported Products[24]

The US Food and Drug Administration unveiled a new strategy to meet the challenges posed by rapidly rising imports of FDA-regulated products and a complex global supply chain in a report called the "Pathway to Global Product Safety and Quality." The FDA report calls for the agency to transform the way it conducts business and to act globally in order to promote and protect the health of US consumers. Highlights of the report include four key elements needed to make the change:

1. The FDA will partner with its counterparts worldwide to create global coalitions of regulators focused on ensuring and improving global product safety and quality.
2. The coalitions of regulators will develop international data information systems and networks and increase the regular and proactive sharing of data and regulatory resources across world markets.
3. The FDA will build in additional information gathering and analysis capabilities with an increased focus on risk analytics and information technology.
4. The FDA increasingly will leverage the efforts of public and private third parties and industry and allocate FDA resources based on risk.

US Top Court Rejects Generic Drug Labeling Suits[25]

The U.S. Supreme Court ruled that generic drug companies cannot be sued under state law over allegations that they failed to provide adequate label warnings about potential side effects.

US FDA Outlines Oversight of Mobile Medical Applications[26]

The US Food and Drug Administration is seeking input on its proposed oversight approach for certain mobile applications specific to medicine or healthcare called mobile medical applications ("apps") that are designed for use on smartphones and other mobile computing devices. This approach encourages the development of new apps, focuses only on a select group of applications, and will not regulate the sale or general consumer use of smartphones or tablets.

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