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Biopharmaceutical Process Characterization: Defining the Design Space

by Anthony Newcombe, Keith Watson, and Claire Newcombe

This article presents an overview of the current regulatory guidelines for pharmaceutical development and evaluates the application of Process Analytical Technology (PAT) and experimental design as tools to expedite biopharmaceutical process characterization.

Introduction

Biopharmaceutical process characterization is typically defined using data generated from scaled down (proven equivalent) equipment that is representative of the anticipated commercial unit operations. Establishing process robustness at laboratory scale to support process validation of biopharmaceutical production is essential, particularly when the characteristics of the desired biopharmaceutical product may share a closer analogy to molecules purified from dairy products than small molecule chemical therapeutics.

As mentioned above, hidden sources of variability may exist within a manufacturing process and an assessment of the multidimensional effect of such variables and process parameters during biopharmaceutical development is often phrased as understanding the 'Design Space.' The Design Space may be defined as an established range of process parameters that have been demonstrated to provide an assurance of product quality. Operating within the design space produces a product that meets the defined product attributes. Design of Experiments (DOE) has been used for many years within the chemical industries, and the biopharmaceutical industry is beginning to grasp the concept of how to define the so called 'Design Space' for bioprocess development.[4] DOE has been successfully used at small scale to define optimized conditions for both upstream and downstream bioprocess steps including fermentation,[5] chromatography,[6,7] and digestion of antibodies for the production of therapeutic antibody fragments.[8] Methods to define the Design Space using factorial and response surface designs are useful for bioprocess development and validation allowing critical process attributes and process variables to be identified, permitting the ability to predict product quality, process performance, and detect and prevent process deviations.

Figure 1. Chromatography columns of 100 cm diameter are routinely used for biopharmaceutical production. Technology transfer and process scale-up may present a number of additional technical challenges (Used with permission from Process Development (Scale-Up) Group, Protherics UK Ltd.)

Defining critical process steps and controls early in the development stages has a number of advantages. Although generic biopharmaceutical processes are desirable[9] and companies utilizing platform technologies typically have an understanding of critical process parameters, similar classes of biopharmaceuti-cals (such as monoclonal antibodies) may show distinct biochemical characteristics (charge, hydrophobicity, solubility, stability) that may impact the performance of a critical process step.[10] Process characterization addresses such inherent variability during the development stage and ensures that a proposed manufacturing process for

Background

More than a third of all drugs now under development by pharmaceutical and biotechnology companies are biopharmaceuticals. Biopharmaceuticals include relatively simple proteins like insulin, as well as more complex molecules like monoclonal antibodies, blood products, and vaccines.

In 2005, there were approximately 300 biopharmaceuticals licensed on the worldwide market generating around $85 billion in revenue and the number of licensed biopharmaceuticals has been growing at around 20% per annum since that time. In addition to the currently licensed biopharmaceuticals, there are hundreds of biological medicines in clinical trials worldwide and it is clear that the health and economic value of biological products will become increasingly more important in future years.

However, biological products are large and complex molecules which require, in most cases, sophisticated manufacturing methods which themselves may have hidden sources of variability, including critical assay components, buffers, raw materials, stains, dyes, standards, filters and membranes, and other bioprocess and analytical reagents or components.[1]

This article presents an overview of the current regulatory guidelines for pharmaceutical development (ICH Q8) [2] and evaluation of the application of Process Analytical Technology (PAT) and experimental design[3] as tools to expedite process characterization strategies appropriate for the manufacture of biopharmaceuticals is presented using a real case study. The approaches described may be applicable to multivariate analysis of upstream or downstream processing parameters and analytical techniques and technologies used to support biopharmaceutical production.

a defined biologic will be capable of meeting predetermined specifications. Technology transfer and scale up of a manufacturing process from pilot to commercial scale often presents a number of technical challenges such as buffer preparation and solution handling, the scalability of equipment and the impact of large scale manual operations (such as column packing) that may differ in methodology from laboratory scale experiments[11] - *Figure 1.* Therefore, it is critical that process robustness is understood and critical parameters clearly defined. The term 'Process Analytical Technology' has been defined as a mechanism to design, analyze, and control pharmaceutical manufacturing processes through the measurement of critical process parameters and quality attributes and encompasses a variety of techniques such as DOE.[12,13]

Review of Regulatory Guidelines

The term Process Analytical Technology (PAT) has been used to describe a system for designing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes for raw and in-process materials and also processes with the goal of ensuring final product quality. Two PAT tools are: (a) multivariate data acquisition and analysis and (b) modern process analyzers or process analytical chemistry tools. The introduction of the PAT system can bring a number of advantages:

1. possibilities to introduce 'real time release'
2. reduction of cycle times
3. improved product quality
4. possibility for more efficient and effective control of some process changes

The pharmaceutical development guideline ICH Q8[2] was finalized in November 2005 and provides current regulatory guidelines for pharmaceutical development. The ICH Q8 (Pharmaceutical Development) introduces the notion of Design Space. The Design Space is proposed by the applicant as part of the Marketing Authorization Application and is subject to assessment. The establishment of a robust Design Space is in line with new approaches on quality which focus on building quality into the medicinal product by design (the Quality by Design or QbD concept). QbD (Quality by Design) as a concept is well recognized in Europe; even before the introduction of the Common Technical Document (CTD) the regulatory systems required information on the pharmaceutical development of the medicinal product. This part of the dossier focused on a comprehensive analysis of the active substance, the choice of the composition, the manufacturing method, as well as the identification of the critical process parameters and the development of suitable analytical methods. One of the goals is to ensure that all sources of variability affecting a process are identified, explained, and managed by appropriate process measurements so that the finished product consistently meets its predefined characteristics from the start ("right first time"). This is in accordance with the fundamental principle that quality cannot be tested, but is instead built into the medicinal product by design. In addition, ICH Q9 (Quality Risk Management) provides an approach and a selection of tools which can be used to manage risks associated with these processes.[14]

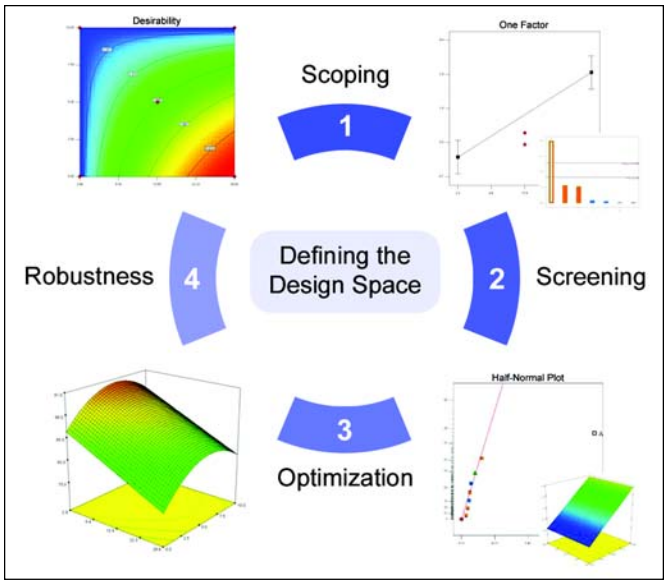

Figure 2. Defining the Design Space using design of experiments (DOE).

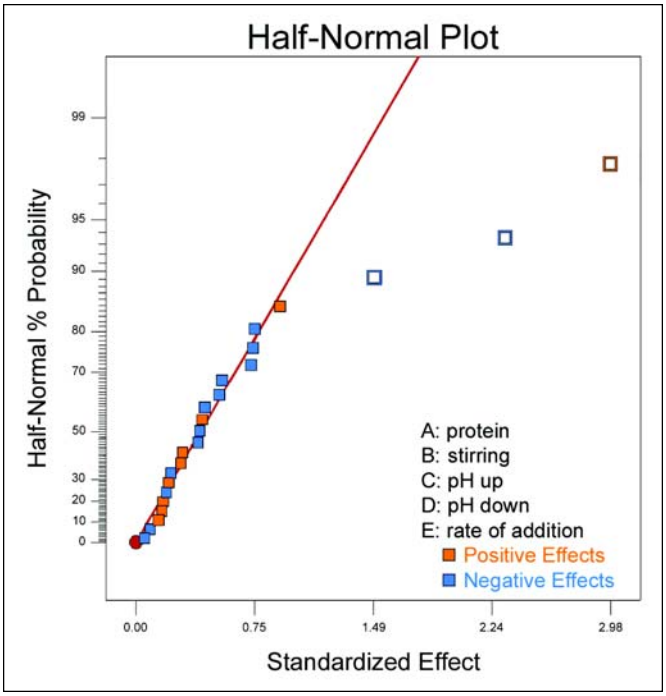

Figure 3. A half normal probability plot of the factors impacting the pH stability of an antibody derived biotherapeutic (figures shown were generated using Design-Expert 7.0.3).

In order to support the PAT activities in European Union, a European Agency for the Evaluation of Medicinal Products (EMEA – www.emea.europa.eu) PAT team was created in November 2003. It is a forum for dialogue and understanding between the Quality Working Party and the Ad Hoc Group of Good Manufacturing Practice (GMP) Inspection Services with the aim to review the implications of PAT and to ensure that the European regulatory framework and the authorities are prepared and adequately equipped to conduct thorough and effective evaluations of PAT-based submissions.

Design of Experiments (DOE): Approaches and Applications

DOE may be used to rapidly screen a large number of process parameters to define critical process parameters and quality attributes.[15] Although traditional 'one factor at a time' (OFAT) experimentation (varying each process parameter individually) provides a simple development approach, multivariate DOE allows the investigator to change multiple parameters simultaneously to evaluate how a combination of changes affects the key attributes (such as purity, recovery, processing time) under investigation. There are a number of well-known and proven software packages to undertake DOE analysis. A typical application of DOE for biopharmaceutical development would involve an initial set of preliminary scoping experiments with the subsequent results used at laboratory scale to evaluate the assay range and reproducibility. Additional screening experiments are then added to the factorial design to utilize linear model fitting and identify critical process parameters (and eliminate less critical factors) prior to optimization of a process step. The experimental design may be subsequently augmented with additional experiments to model curvature and evaluate proposed operating parameters and outer limits. Finally, process robustness may be assessed to define proven acceptable ranges for the process step - *Figure 2*. Modeled results are usually verified experimentally at small scale to test both the optimum modeled conditions, define outer limits, and verify the edges of failure prior to performance qualification and commercial scale manufacture.

Multivariate Data Analysis – A Case Study

A major advantage of DOE for biopharmaceutical development is that the experimental design and subsequent analysis may be readily understood by the development scientists conducting the experiments as well as those to whom the results are reported, such as quality control and validation groups. Here we present a case study describing the application of DOE to simultaneously consider a number of factors that have the potential to impact the stability of an antibody derived biotherapeutic (data discussed is based on laboratory data).

In this example, the factors impacting solution turbidity (measured by absorbance at 600 nm) during the pH adjustment of a purified antibody therapeutic has been described. Here the purified biotherapeutic has been pH adjusted to 10.0 - 12.0 prior to pH neutralization (6.0 - 8.0). The affects of five factors on final solution turbidity have been assessed: protein concentration (mg/mL), rate of stirring, the final alkaline pH (defined as pH up), the final neutralized pH (defined as pH down, pH 6.0-8.0), and the rate of solution addition during pH adjustment. An initial set of screening experiments were undertaken and analyzed using Design Expert 7.0.3 (Stat-Ease, Inc). The half normal plot (Figure 3) is a graphical tool that uses ordered estimated effects to help assess which factors are important and which are unimportant. Unimpor-

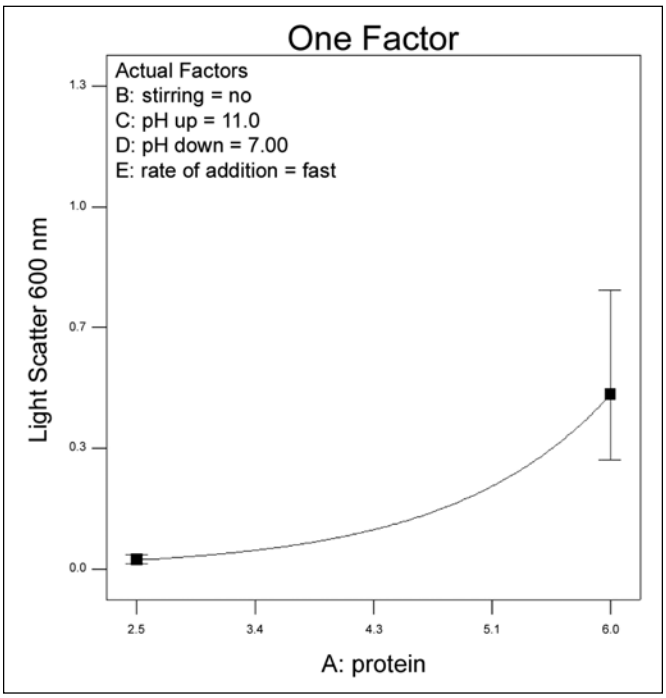

Figure 4. A one factor plot showing the relationship between protein concentration (mg/mL) and light scattering.

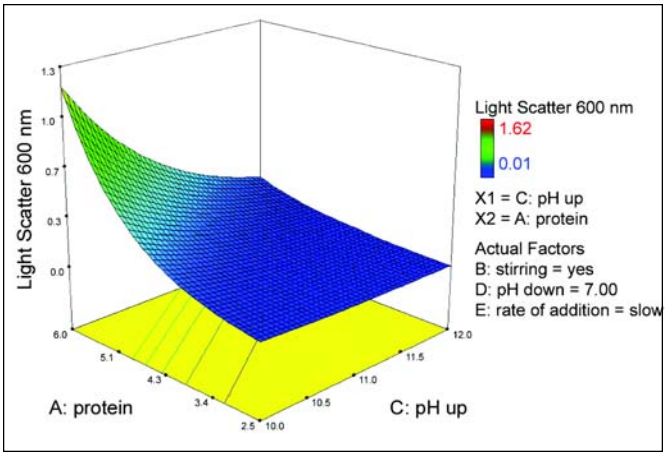

Figure 5. A three-dimensional plot showing the relationship between protein concentration (mg/mL), final pH (pH up) and light scattering (absorbance at 600nm).

tant effects tend to have a normal distribution centered near zero, while important effects tend to have a normal distribution centered at their respective true large (but unknown) effect values. If the normal probability plot of the estimated effects is linear, this implies that all of the true (unknown) effects are zero or near-zero. That is, no factor is important. Figure 3 shows a half normal plot of screening experiments and indicates that factors A (protein concentration), C (final alkaline pH or pH up), and D (final neutralized pH or pH down) are the critical factors with D (final neutralized pH) having a lesser effect on solution turbidity following pH adjustment. The half normal plot has discounted factors B (stirring) and E (rate of solution addition) as critical factors. Further analysis of the experimental data using a one factor plot shows the relationship between the main factor A (protein concentration) and light scattering - *Figure 4*. The analysis indicates that at low protein concentration (2.5 mg/mL), minimal turbidity is observed following the pH adjustment steps described. Analysis of the three dimensional (3D) response curve (typically obtained after augmenting the original factorial design with further experiments) shows the relationship between protein concentration (mg/mL), final alkaline pH (pH up), and light scattering - *Figure 5*. The 3D analysis clearly shows that at low protein concentration (2.5 mg/mL), the alkaline pH has little effect on turbidity. As protein concentration increases, the modeled effect of pH on solution turbidity becomes apparent. The information presented in this theoretical example would be technically challenging and time consuming to evaluate using the traditional approach of separately testing each process parameter and individually evaluating the impact of the selected factor on product quality.

Current and Future Challenges

Biopharmaceutical process characterization at small scale requires a significant commitment of time and resources, but the potential advantages make this a worthwhile investment. Due to the commercial pressures of development and technology transfer within the industry, limited time and resources for biopharmaceutical characterization and validation at small scale may not permit sufficient time to gain the requisite understanding of a process step. Attempts to expedite development studies by implementing accelerated timelines (with the hope of reducing time and costs to prior to conformance runs at manufacturing scale) can backfire, and as a result, over the long term, result in false economy; inadequate manufacturing process characterization and validation (particularly for late stage products in development) may result in inconsistent manufacturing processes and in the worst case scenario could result in batch failures. Statistical experimental design and multivariate analysis identifies the critical process parameters and permits relatively rapid and efficient assessment of the Design Space.[17] Recent presentations and scientific publications from both the biopharmaceutical industry[18] and regulatory authorities indicate an increasing emphasis on DOE approaches for modern biopharmaceutical development.

A well defined Design Space for biopharmaceutical production is also advantageous as it could permit a company to (potentially) make changes to an approved manufacturing process without lengthy prior approval times. Such process modifications may permit improved product quality, increased efficiency, throughput or yield, and the cost savings at commercial scale would outweigh the additional investment in research and development to define the Design Space.

However, on a note of caution, it is worth remembering that no PAT-based submissions for a biological submission has yet to be received by the assessors in Europe. Should such a submission arrive on the regulators desk, it will be interesting to see how robust and valid PAT is when attempting to control the complex beast that is a biopharmaceutical. For although the application of PAT in pharmaceutical manufacturing is well established, the jury is still out regarding the application of PAT to biologics manufacturing.

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Innovation Diffusion within the Pharmaceutical Manufacturing Industry: A Study on the Adoption of Modular Facility Technology

by Gordon Leichter and Tao Gao

This article reports summary findings of an empirical study on the factors that influence people's decision to adopt a complex innovation within the pharmaceutical manufacturing industry, namely modular facility technology.

Introduction

This article discusses summary findings of a study conducted on factors influencing pharmaceutical companies' decisions to adopt a complex innovation modular facility technology in building new pharmaceutical manufacturing facilities. The study examined how both technical (non-relational) factors and social (relational) factors influence the intention to adopt an innovation. An online survey was utilized to gather data from senior level decision makers from pharmaceutical manufacturing companies, using a mailing list extracted from the ISPE membership database. The data was analyzed using advanced statistical methods to assess the validity of the study variables and test several hypotheses.[1]

The results indicated that value is a stronger influence over risk avoidance on intention to adopt, and non-relational factors (tangible aspects) have more influence on an adopter's perceived value and perceived risk than relational factors. The remainder of the article will present the conceptual model on factors influencing the intention to adopt a modular facility innovation, describe the survey and sample, report the key findings, and discuss their implications for practical application. The study results should provide insights for marketers and adopters alike.

Modular Technology Innovation

The innovation of modular facility technology examined in this study is a relatively new and complex phenomenon occurring in the pharmaceutical industry. The technology was introduced globally in 1986, originating in Stockholm, Sweden. At the time of this study, only a small fraction of the pharmaceutical manufacturing companies has utilized this technology. However, the number is increasing annually as the innovation diffuses.[2] The concept of modular technology is neither new nor unique and has been utilized in the construction industry for a long time. The Statue of Liberty was one of the most notable modularly constructed structures in the United States history.[3] Furthermore, modular equipment skids as well as modular homes are very commonplace and widely accepted.

The innovation of modular facility technology goes a few steps beyond the conventions of what has previously been accomplished within the construction industry. The study conducted by the Construction Industry Institute (CII[4]) recognizes modular facility technology as a construction/project execution model innovation in the early adopter phase.

Expanding upon the simple example of modular homes, modular facility technology employs an extensive application of resources and techniques. The technology involves manufactur-

Figure 1. Innovation of focus: modular facility technology. a. Facility modules fabricated in a factory; b. An entire facility assembled and pre-tested in a factory; and c. Facility modules rapidly assembled at site.

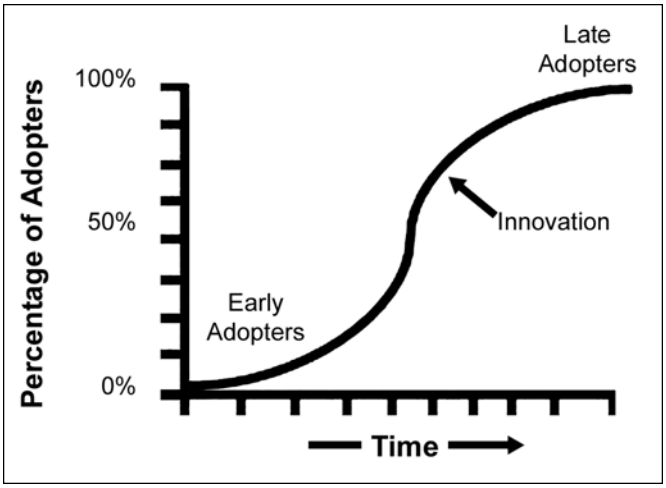

Figure 2. Innovation Diffusion S-Curve.[5]

ing the facility within a factory, inclusive of structural aspects and internal finishes of the facility, complete with processing equipment, and then transporting the disassembled facility in modules to the final location, and reassembling - *Figure 1*. The size of facilities produced utilizing this concept has reached more than 200,000 square feet with costs in the hundreds of million dollars range. To give a comparison of scale, the factories where these facilities are produced used to be utilized for building ocean tankers.

Innovation Diffusion

Innovation is stressed as one of the cornerstones of the ISPE mission. While innovation may mean many things to many people, there is an entire field of study associated with innovation theories. Referred to as *innovation diffusion literature*, this body of research examines how innovations are adopted in a society. Simply, an innovation can be considered as an improvement to a product or process that provides advantages over the existing entity.[5] An innovation has no value to society unless it is adopted (e.g., RCA's Video Disk, Apple's Newton, Sony's Betamax, Dvorak Keyboard, etc.).[5,6]

Aspects of innovation diffusion contend with innovation types and characteristics, as well as adoption stages and adopter types. There are different types of innovations, e.g., product, process, business model, marketing, organizational, service, supply chain, etc. Innovation characteristics vary in terms of their relative advantage, compatibility, complexity, observability, and trialability.[5] Furthermore, theoretical discussions about innovations examine how innovations are adopted (stages) and by the different types of adopters. Innovation adoption occurs through the respective stages of knowledge, persuasion, decision, implementation, and confirmation,[5] as well as by different types of respective adopters: innovators (technical enthusiasts); early adopters (visionaries), early majority (pragmatists), late majority (conservatives), and laggards (skeptics).[5] The adoption of an

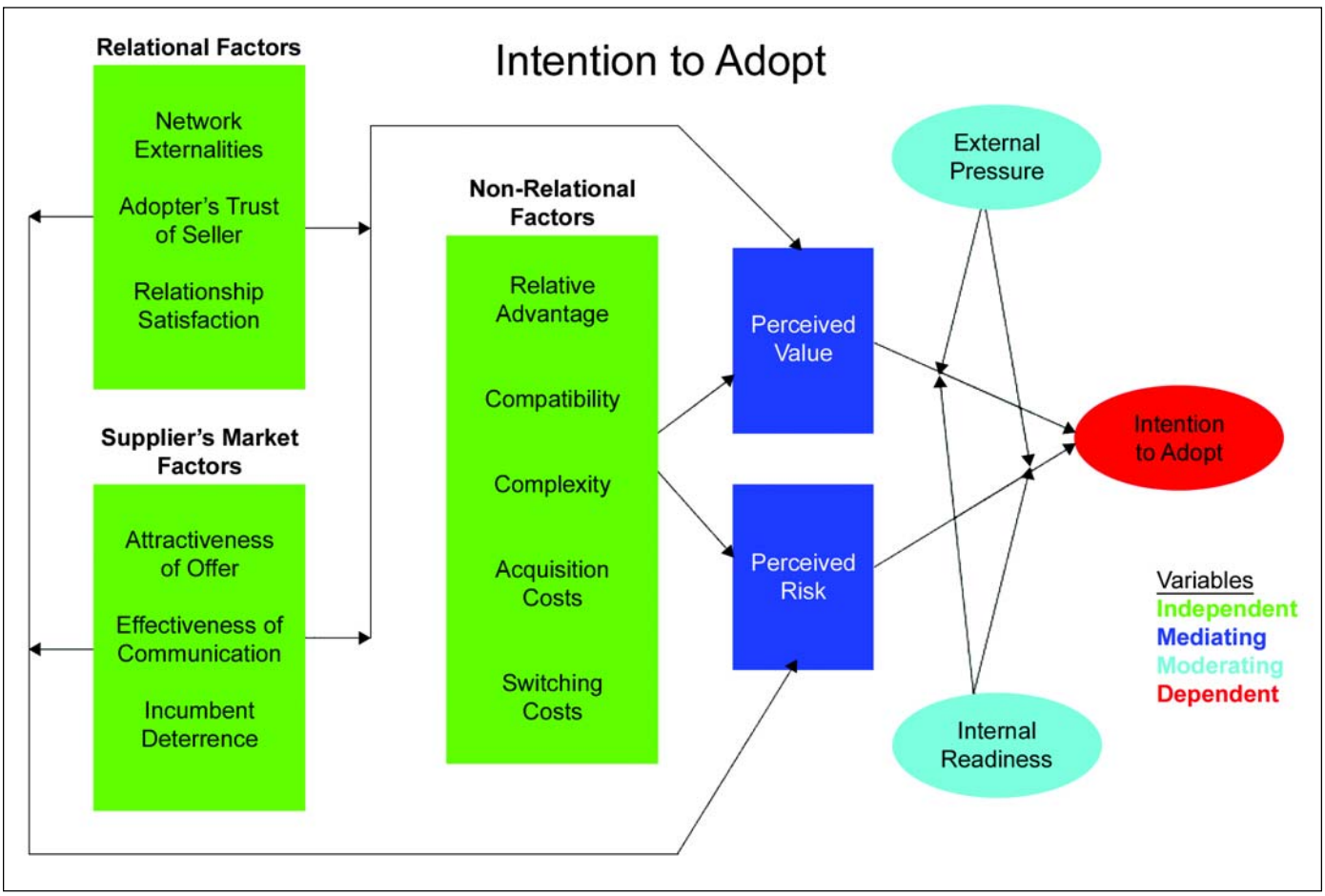

Figure 3. The Conceptual Model.[8]

Name of Construct	Definition*
Intention To Adopt	The likelihood that a user would actually purchase the innovation.
Perceived Value	The potential adopter's overall assessment of worth or utility of an innovation.
Perceived Risk	Risk is based upon the uncertainty and adverse consequences of adopting the innovation.
External Pressure	The level of current competitive and industry conditions that influence participants to pay close attention to each other's competitive moves.
Internal Readiness	The level of technical sophistication and financial resources within an organization to undertake the adoption of an innovation.
Relative Advantage	The adopter's belief in the likelihood that the technology can improve the economic benefits for the individual, the organization, or both (Disadvantages were added for objectivity).
Compatibility	The degree to which an innovation is perceived as being consistent with exiting values, past experiences, and needs of the potential adopter.
Complexity	The degree to which an innovation is perceived as relatively difficult to understand and use.
Acquisition Costs	The potential adopter's level of perceived sacrifice in the expenses to be incurred in acquiring an innovation.
Switching Costs	The level of perceived costs that make it difficult to change to a superior alternative.
Network Externalities	The level and influences of users of an innovation within a social system.
Trust of Seller	The degree of one party's confidence in the credibility, integrity, and benevolence of a supplier.
Relationship Satisfaction	The level of belief that an adoption experience will be positive with a provider because the level of past performance has been consistently satisfactory.
Attractiveness of Offer	The degree that the provider's incentives and product trialability are positively viewed.
Effectiveness of Communications	The level of quality and availability of information about the innovation.
Incumbent Deterrence	The degree of influence that existing suppliers of opposing technologies have against adopting an innovation.
*All definitions are referenced through an extensive literature review conducted as part of the study,[8] respective authors/references are not indicated for simplicity.	

Table A. Variable definitions.

innovation goes through an S-curve growth comparable to the amount of users associated by the type of user - *Figure 2*.

The actual process of innovation adoption is the main premise of this study. Innovation diffusion is theorized as a four component process "… by which (a) an innovation (b) is communicated through certain channels (c) over time (d) among members of a social system."[5] Specifically, this study provides an estimation of the influence of critical factors involved in determining the intention to adopt an innovation. The intention to adopt stage of the adoption process is felt to be a critical stage in the process, which occurs between persuasion and decision.[7]

Modular facility technology provided an excellent opportunity to form a better understanding of the behavioral aspects associated with the phenomenon of adoption intention under an applied circumstance, while an innovation is still in a relatively 'early adopter' phase of the adoption curve.[5] The perceived value and risk associated with adoption of this innovation is not diminished by a larger number of adopters. Therefore, the particular innovation provided an outstanding opportunity to conduct research on the influence of technical and social factors on the decision to adopt an innovation.

Conceptual Model

To best assess and understand the above influences, a conceptual model or a flow diagram of constructs (concepts) and their inter-relationships was developed. A simplified version of the model is shown in Figure 3, which depicts a relational network of constructs positioned as variables to measure an *Intention to Adopt*. These relationships are stated as hypotheses and were estimated by using survey data.

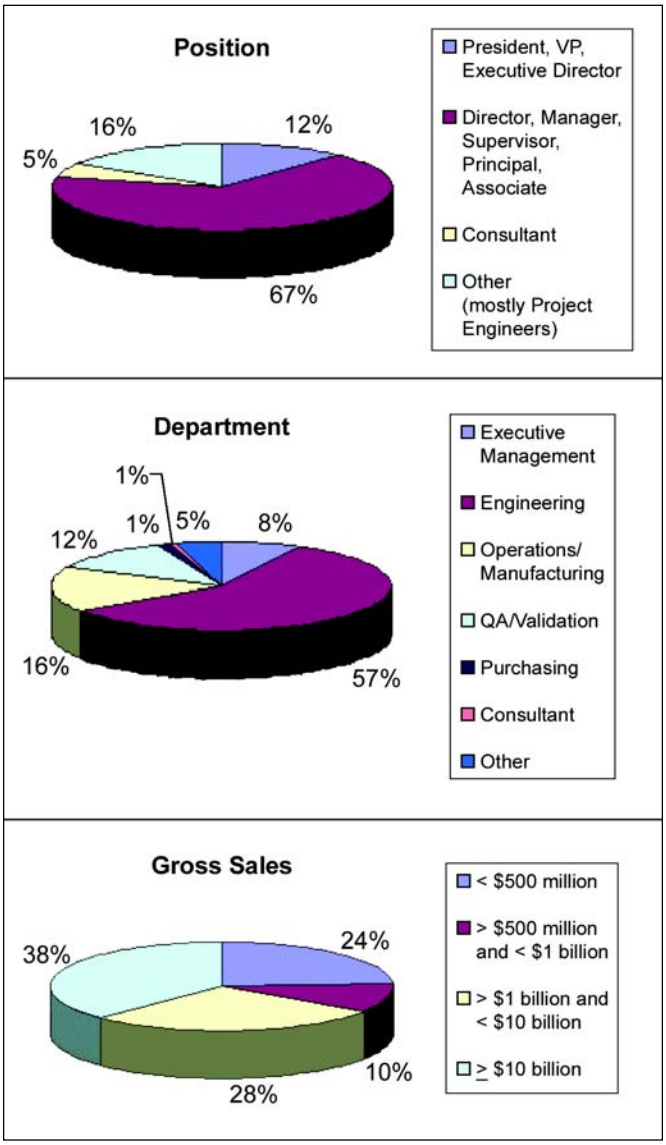

Figure 4. Distribution of the sample of pharmaceutical manufacturing executives.

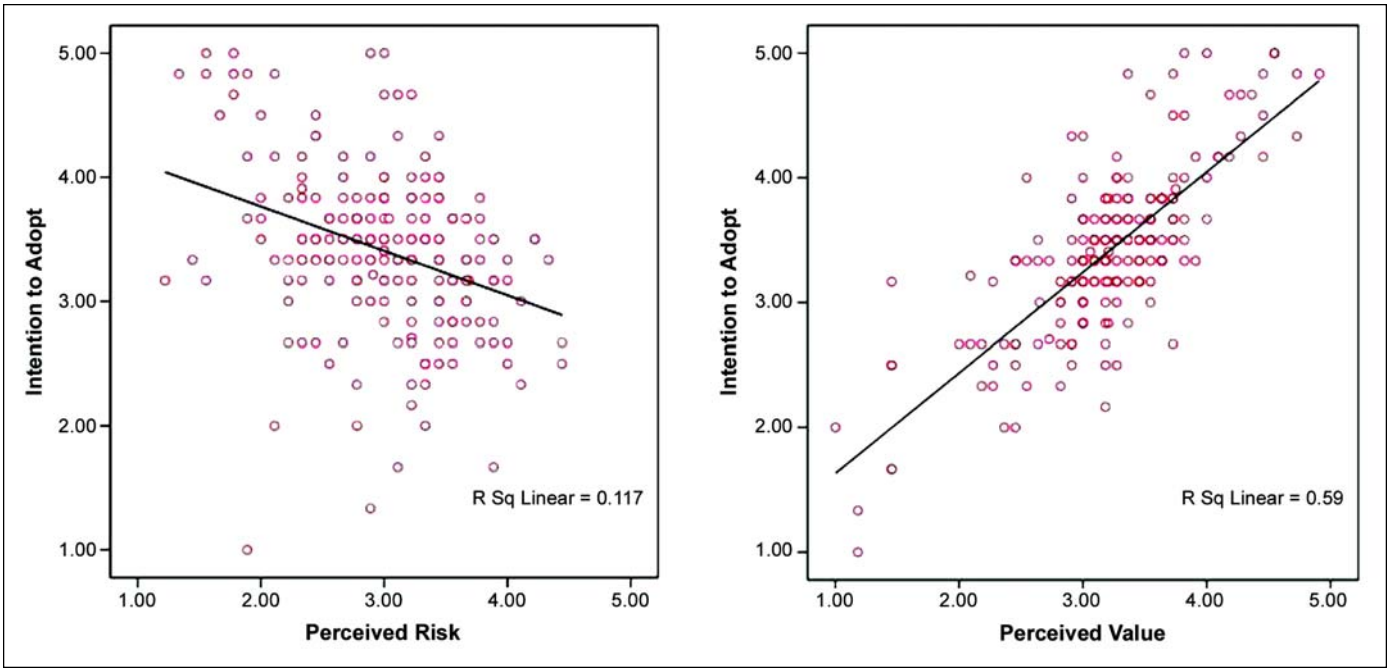

Figure 5. Simple Regressions - Intention to Adopt vs. Perceived Risk and Perceived Value.

The model is represented by 16 variables, which are defined in Table A. With the conceptual model being viewed from right to left, the dependent variable (the variable that will change in relationship to the other variables) is positioned to the extreme right as the focus of the research, i.e., the Intention to Adopt.

Influences of *External Pressure* and *Internal Readiness* are considered to have a moderating relationship toward the specificity of context and place in properly understanding the relevance of a potential adopter's attitude. Since intentions and situations can change over time, a respondent's situation will be influenced by changes in their market environments, and their need of an innovation will influence their perspective.

The remaining 11 variables in the model are positioned as direct influences of Perceived Value and Perceived Risk, which are grouped into three categories of *Non-Relational*, *Relational*, and *Supplier's Market Factors*. These variables are considered mutually exclusive, but not exhaustive. There are a number of other variables (e.g., organizational culture, adopter characteristics, etc.) that were excluded for simplicity, but worthy of consideration in future studies.

Sample and Survey

The survey sample was drawn from a targeted group of key decision-making individuals associated with pharmaceutical manufacturing. Access to these individuals was based upon a manual search of the ISPE membership directory, which resulted in 4,698 names from 95 pharmaceutical manufacturing companies. A pre-study survey was conducted among some industry experts to test the validity of the research instruments. Data for both the pre- and final studies were collected utilizing an online Web-based survey service.

The survey contained 142 questions, which represented measures of all the variables. The survey was initially launched on 20 December 2005 and was closed on 1 February 2006. The survey invitation e-mail was sent out to the 4,698 e-mail addresses a total of five times (one initial e-mail and four follow-up messages), roughly a week apart. Respondents were offered two incentives to participate in the survey. The first was the opportunity to receive the survey results as a reward for their participation. The second was that their participation would result in a collective contribution to the ISPE Foundation in their name. The donation subsequently was used to help fund a West Coast Student Forum in February 2006. A personalized acknowledgement letter from Susan Humphreys Klein, former Secretary-Treasurer of the ISPE Foundation, was sent to each participant who selected the option to receive the letter.

In total, there were 421 visits to the survey Web site as the result of the five e-mailings. Two hundred and ten (210) people completed the survey, of which 200 surveys were deemed usable in the analyses. This resulted in an overall useable response rate of 4.25%, which is rather low compared to the population, but comparable to other innovation studies. Figure 4 indicates the distribution of respondents.

The online survey service can be considered a double-edge sword. Its benefits range from quick and cost effective distribution with fast results that easily transfer into analytical software eliminating transcription errors. Its disadvantages range from erroneous e-mail addresses to spam filters and firewalls, as well as being deluded among numerous other e-mails.

All survey items were scored on a 5-point scale from 1 = strongly disagree to 5 = strongly agree, unless otherwise noted. When appropriate, an option for "not sure" or "hard to assess" was added to allow for an alternate response, as well as an assessment of the level of early stage adoption for particular variables.

Findings

The more significant results and sample survey questions are shown in Table B. These findings provide valuable insights into the influences of various factors on the adoption intention. Perceived Value proved to be a stronger factor than Perceived Risk in influencing the intention to adopt the focal

Variable	Result					
The top percentage indicates total respondent ratio; the bottom number represents actual number of respondents selecting the option.*						
Perceived Value	Strongly increases an Adopter's Intention to Adopt more than the opposing influence of Perceived Risk.					
	1 Strongly Disagree	2 Somewhat Disagree	3 Neither Agree nor Disagree	4 Somewhat Agree	5 Strongly Agree	
I believe that modular facility technology offers my organization increased value compared to the conventional process of building a facility.	4% 8	14% 27	39% 77	37% 72	6% 11	
Perceived Risk	Moderately reduces an Adopter's Intention to Adopt.					
	1 Strongly Disagree	2 Somewhat Disagree	3 Neither Agree nor Disagree	4 Somewhat Agree	5 Strongly Agree	6 Hard to Assess
I believe that there is a high probability that the proposed benefits of modular facility technology may not materialize if we were to utilize the technology.	3% 6	23% 45	29% 57	27% 53	10% 20	7% 13
The level of overall risk in utilizing modular facility technology for my organization is very high compared to conventional construction.	9% 17	23% 44	26% 49	29% 55	8% 16	6% 11
External Pressure	Strongly increases the Perceived Value of adopting the innovation.					
	1 Strongly Disagree	2 Somewhat Disagree	3 Neither Agree nor Disagree	4 Somewhat Agree	5 Strongly Agree	6 Hard to Assess
Modular facility technology would allow my organization to get our product to market sooner or before our competitors.	4% 8	11% 21	31% 60	35% 67	8% 16	11% 21
Relative Advantage	Strongly increases the Perceived Value of adopting the innovation.					
	1 A clear disadvantage for modular technology	2 Somewhat of a disadvantage	3 Neither an advantage nor disadvanage	4 Somewhat of an advantage	5 A clear advantage for modular technology	6 Hard to Assess
Getting a product to market sooner than conventionally built facilities.	1% 3	1% 3	16% 32	39% 79	34% 68	8% 16
Predictable and controllable project costs.	1% 3	3% 7	13% 26	42% 85	36% 73	3% 7
Switching Costs	Strongly increases the Perceived Risk of adopting the innovation.					
	1 Strongly Disagree	2 Somewhat Disagree	3 Neither Agree nor Disagree	4 Somewhat Agree	5 Strongly Agree	
By utilizing modular facility technology, there will be additional costs involved with switching from one or more of the engineering/consulting firms we normally use to build new manufacturing facilities.	17% 34	25% 50	29% 57	25% 50	3% 6	
Compatibility	Strongly increases the Perceived Value of adopting the innovation, and moderately reduces the Perceived Risk.					
	1 Strongly Disagree	2 Somewhat Disagree	3 Neither Agree nor Disagree	4 Somewhat Agree	5 Strongly Agree	
My organization can adjust to the different project execution model involved with modular technology.	2% 3	14% 27	26% 51	45% 90	14% 28	
*Percentages and distributions are not considered indicators of influence. More advanced statistical evaluations, i.e., regression analysis, correlations, and structural equation modeling, where used to determine influential relationships.[1]						

Table B. Significant results. (continued on page 25)

Variable	Result					
The top percentage indicates total respondent ratio; the bottom number represents actual number of respondents selecting the option.*						
Acquisition Cost	Moderately reduces the Perceived Value of adopting the innovation.					
	1 Modular facility costs are more than 10% more relative to costs of conventional construction	2 Less than 10% more	3 About the same	4 Less than 10% less	5 Modular facility costs are more than 10% less relative to costs of conventional construction	6 Hard to Assess
I think the overall project cost difference is:	17% 34	20% 39	15% 30	24% 47	12% 24	11% 21
Network Externalities	Strongly increases the Perceived Value of adopting the innovation, while not impacting the Perceived Risk.					
	1 Of No Importance	2 Below Average Importance	3 Average Importance	4 Above Average Importance	5 Very Important	
Case studies presented at industry association meetings.	3% 5	11% 21	37% 73	33% 65	17% 33	
Published articles in industry/association publications.	4% 7	12% 24	47% 93	26% 52	11% 21	
Experiences of other users.	1% 1	1% 2	7% 13	35% 69	57% 112	
Incumbent Deterrence	Strongly increased the Perceived Risk of adopting the innovation.**					
	1 Strongly Disagree	2 Somewhat Disagree	3 Neither Agree nor Disagree	4 Somewhat Agree	5 Strongly Agree	N/A
Utilizing modular facility technology would be a departure from how we currently conduct projects with an A&E firm.	2% 4	8% 16	11% 21	37% 73	31% 61	11% 21
Based upon information provided to me by an engineering or third party consultant, I am uncertain about the benefits of modular facility technology.	16% 32	18% 35	26% 51	12% 24	4% 7	23% 45
Overall Intention to Adopt	Strong indication of adoption intention.					
	1 Strongly Disagree	2 Somewhat Disagree	3 Neither Agree nor Disagree	4 Somewhat Agree	5 Strongly Agree	
I would be willing to use modular facility technology for my next manufacturing facility project.	3% 6	9% 17	35% 68	42% 82	11% 22	
I believe that utilizing modular facility technology is a good idea.	2% 3	4% 8	31% 61	48% 95	15% 29	
**This variable had some validity constraints in the study; however the strength of influence warrants discussion in this article.						

Table B. Significant results.

innovation. The distribution of intention to adopt responses indicated a very strong intention to adopt the innovation as well, further supporting the evidenced strength of perceived value in the results. While estimates of both effects were considered significant, the influence of Perceived Risk, $t = -2.57$, was weaker than that of Perceived Value, $t = 7.9$. Figure 5 provides simple regression comparisons.

It was interesting to find that Perceived Value had a relatively larger role than Perceived Risk in affecting the Intention to Adopt. This may be related to the capital-intensive nature of the purchase and the perception of realizing large rewards being more relevant to adoption as compensation verses the potential risk involved with adopting the innovation. This result was surprising due to the risk adverse nature of pharmaceutical manufactures, but it was understandable.

Based upon the many dimensions of uncertainty, combined with human nature having a preference for negative information, and to be doubtful of how good something can truly be without trying it,[9] risk would appear to be a more dominant influence. These uncertainties are an inherent aspect of an innovation, especially in the magnitude of the large capital investment associated with a new pharmaceutical manufacturing facility. However, there was a low level of agreement regarding the measures of uncertainty, as a component of risk, indicating that there is a high level of

perceived predictability with the particular innovation. Predictability, which is characteristic to the specific innovation, is further evidenced in the strong influence of Relative Advantage on Perceived Value. Furthermore, the process of building a pharmaceutical manufacturing facility is in itself a risky undertaking and the strength of perceived value indicates that the attributes reduce the potential risks.

External Pressure provided a strong increase in the Perceived Value toward the intention to adopt. However, there was a large discrepancy of shared knowledge about the innovation in the industry with 66 or 33% of respondents not being aware if their competitors were using the innovation to get their products to market faster.

Finally, there were mixed testing results from the groupings of Non-Relational, Relational, and Supplier's Market factors. Non-Relational factors, or the tangible attributes of the innovation, had the most significant influences on Perceived Value and Perceived Risk. The Relational factors, or the intangible attributes, had a weaker influence on Perceived Value, but did not have a significant influence on Perceived Risk. Comparatively, only Incumbent deterrence had an influence on Perceived Risk as part of the Supplier's Market factors.

Initially, it was anticipated that Relational factors would have the most influence on the intention to adopt. Furthermore, Perceived Value was anticipated to be strongly influenced by attitude formation based upon the strength of social norms in a complex decision making situation where there is a high level of uncertainty, e.g., *theory of reasoned action.*[9] However, the results were not as significant as expected. Only Network Externalities proved to be significantly influential toward Perceived Value.

Conclusions and Managerial Implications

With the influences of Perceived Value prominently standing apart from the influences of Perceived Risk, there is a clearer picture of the drivers toward the development of adoption intention. Comparatively, the measures of high value predisposed risk aversion in the rather risky undertaking of building pharmaceutical manufacturing facilities. However, in other situations where the incumbent alternative may not be as risky, risk drivers may become more prominent.

Pharmaceutical manufacturing managers looking to introduce an innovation of magnitude to their organization must think similarly as marketers trying to affect commercialization. Everyone has a customer, and the managerial aspect of internal marketing is very relevant in organizational adoption. All decision makers have to contend with some form of customer, whether a superior, subordinate, end-user, or facility owner. Understanding the complexity of these behavioral tendencies cannot be avoided. The conceptual model developed in this study can provide similar guidance for those trying to introduce an innovation into their organization. Perceptions of value and risk, moderated by their own readiness and external pressures, will be internal drivers as much as externally. The measures and relationships provided will likely be of similar use and value.

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Enterprise Knowledge Management for Operational Excellence

Real-Time Integration and Modularization of Business and Production Data Extends Closed Loop Control to the Enterprise Level

This article presents how important it is to be able to easily integrate applications, information, and systems in pharmaceutical facilities globally.

by Janice Abel

Introduction

To meet growing data integration and knowledge management requirements in the pharmaceutical and biotechnology industry, an Enterprise Control System (ECS) is becoming a key to competitiveness. Not to be confused with a Distributed Control System (DCS) or Programmable Logic Controller (PLC) – based plant control solution, an enterprise control system is a fairly new type of system that should be considered in the automation strategy. An ECS does integrate production and business systems, but is much more than just an integrator. It extends plant and loop control to the entire enterprise and enables integration of disparate systems, workflow, and vast quantities of information and data. Business, assets, and profitability can be controlled and managed in real-time. An enterprise control system consists of an open integration platform which supports modularization and templatization of business processes to ease both implementation and validation and simplifies integration of both proprietary and open, best of breed applications. Implementing an enterprise control system enables true knowledge management that can lead to true Operational Excellence (OE).

Driven by increasing global pressures in both branded and generic products, manufacturers are looking for new and better ways to decrease time to market, optimize asset availability and utilization, and cut production costs. All companies are seeking new ways to improve business performance, but where the strategic focus has been almost exclusively on discovery, for many companies today, productivity improvement is as important.

This is becoming increasingly apparent as executives describe what they see as the barriers to operational excellence. In one recent forum, pharmaceutical and biotechnology executives described the following business challenges they face in today's markets:

- tightening margins with more pressure to reduce cost of goods sold; greater need to justify capital investments
- building production systems at new and renovated facilities to help get products to market faster
- integrating disparate database and systems, including laboratory, production, and business systems for the entire supply chain
- managing and making sense of data (knowledge management)
- compliance with increasingly more stringent government regulations
- transitioning to systems that comply fully with global standards – from equipment to software and software templates

And these same executives felt they needed the following solutions to achieve true operational excellence:

- ability to collaborate and share best practices globally
- assistance in reconciling disparate systems resulting from mergers and acquisitions; and integrating with business systems within the plant
- help in transitioning single-product production facilities to multiple-product production facilities
- greater transparency of data, management of information, and documentation

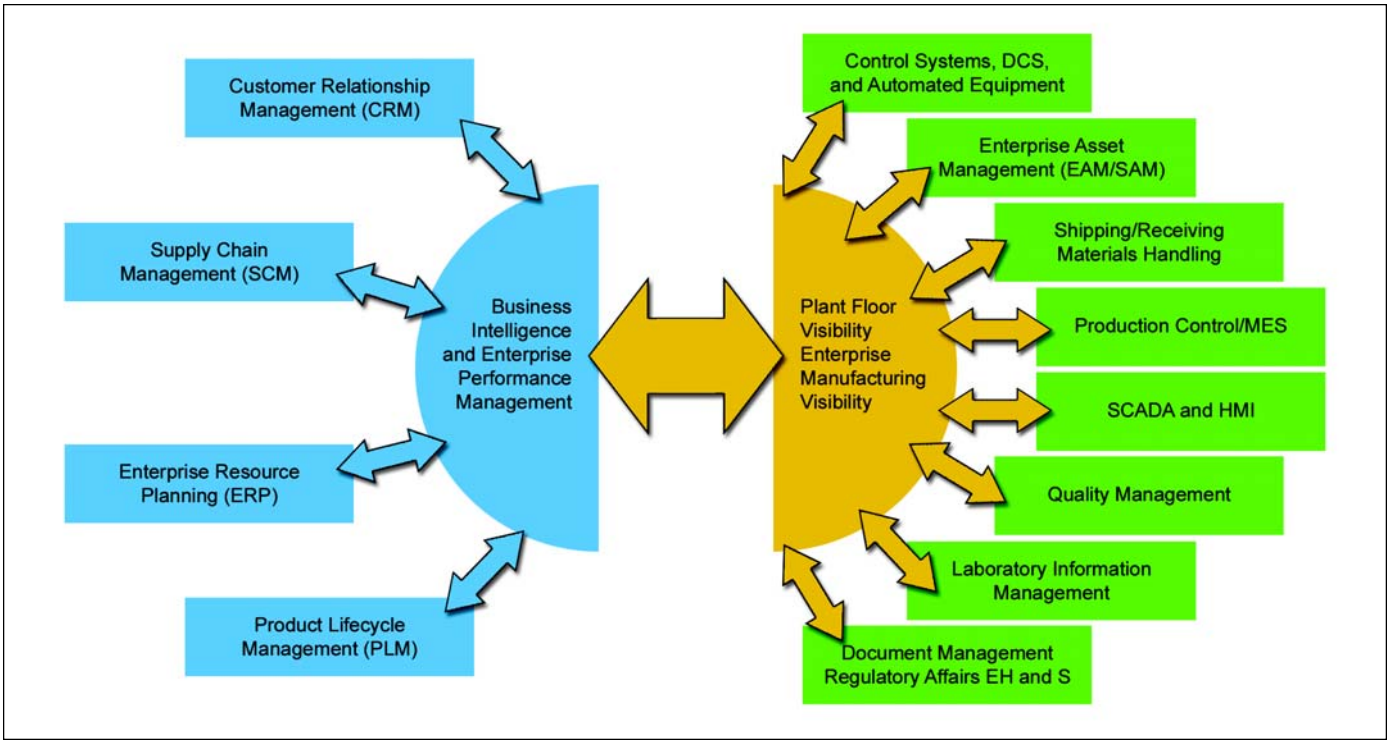

Figure 1. Effective enterprise control requires seamless integration of plant operating information with all plant operating loops, including inventory, processes, orders, resources, status, downtime, products, lab results, and exceptions.

Attaining the collaboration, data integration, and transparency that these executives desire requires a common strategic, enterprise-level vision for starters, but it must be supported by the types of enterprise-wide information and automation platforms which are already emerging in other industries.

Describing one such integration platform for the chemical industry, for example, John Snodgrass, Advanced Process Control Leader at global specialty chemical company Chemtura Corporation commented recently to a process industry analyst, "*Finally, a system that will connect all my control systems and all my business systems without requiring the prohibitive investment to build a bridge. This is something I have been hoping to see for a very long time.*"[1]

Commenting to that same analyst, Greg Gorbach, Vice President of Collaborative Manufacturing Research at ARC Advisory Group, said "*Maximizing the performance of your manufacturing assets requires a two-pronged strategy: utilize real-time information from every area and plant to inform people and your business systems; and provide a dynamic feedback mechanism to allow you to swiftly respond to changes to optimize business performance throughout the enterprise… The ultimate goal is to provide closed loop control for your business processes…we believe that this is exactly what manufacturers are looking for.*"[1]

Achieving True Enterprise-Wide Integration

In a system which can truly enable control across the entire enterprise, the business, plant floor, supply, and customer organizations must be on the same page with the business strategy and all must have easy, real-time access to the same base of data necessary to execute that strategy. Enterprise control extends the concept of plant floor control loop to the enterprise, resulting in a true business control loop. An enterprise control system is not a single box or software application, but an open integration platform which enables collection of and access to an evolving congeries of modules, templates, programming objects, and best of breed applications that companies need to reduce costs, increase speed to market, maintain quality, and pursue whatever additional strategies they need to be competitive.

Steps Toward Enterprise Control

One pharmaceutical company well on its way to implementing an enterprise-wide control system is Pfizer International. The Catalyst system trial now under way there provides an excellent example of integrating functionality that spans the API manufacturing process, including design, production planning, and analysis. Recipes are highly structured models that are stored in a central database so that they can be shared by other applications and users. This model takes into consideration all information about materials, reactions, and available plant equipment, and calculates a production recipe in a matter of seconds. It also validates the model. If there was an error made in the assumptions or input, it can re-compute in seconds.[2]

Eventually, the system will adapt recipes for other plants and their unique capabilities automatically for help with production planning. Production supervisors will be able to assess current production status at plants around the world, identify what equipment is available, and rank each piece of equipment based on its ability. The system can determine whether a vessel is in use or fallow and note special characteristics – for example, if a vessel or tank is in use, clean, dirty,

or glass or stainless steel.

The system also helps comply with pharmaceutical industry regulations, including environmental, safety, and US FDA validation requirements, providing centralized, real-time access to all production data, reducing out of spec investigation time from weeks to days or even less. The system also helps pharmaceutical manufacturers prove that they followed validated procedures, generating an electronic record of the process for FDA verification.

The system is based on a multi-tier, distributed .NET architecture using Web Services, and will incorporate a rich graphical user interface. When the system is fully-deployed, engineers will collaborate on projects with ready access to Pfizer resources around the world to split up production between plants, while maintaining quality and consistency. This unique enterprise framework gives Pfizer, which operates a dozen API plants around the world, an unprecedented and highly efficient means of scheduling production and optimizing capacity on a global scale. That capability can greatly reduce the time it takes to get a drug to market once it is approved. Pfizer officials estimate that savings in time, effort, and inventory will deliver a full return on its investment in six to 12 months.[2]

Achieving such enterprise-wide alignment of business and operations is a challenge given the islands of organization that exist in most pharmaceutical plants today. This isolation is very apparent on the plant floor, where many plants and companies are burdened with several different Distributed Control Systems (DCS), Programmable Logic Controllers (PLC), Laboratory Information Management Systems (LIMS), and other digital systems that do not integrate easily. Many are still running their businesses on isolated spreadsheets and working with structures that may be 50 data tables deep just to integrate historical data with real-time batch data. Those who are using more sophisticated data integration tools are using homegrown systems, which are cumbersome, aging, and require labor intensive maintenance programming. These may be achieving some success today, but stand a high probability of degradation over time.

What To Do

Achieving enterprise level integration requires pulling information together from multiple applications. However, the plant has historically been somewhat of a black hole for information. On one side of the enterprise you have the customer relationship, supply chain, and enterprise resource management applications that the business uses and on the other, you have all the real time systems that drive the plant - *Figure 1.* Traditionally, these two groups have had little dialog.

"The IT people chose the business systems, and engineering chose the plant systems, and neither group really understood how the other software worked. As a result, the systems do not share data easily. What baseline integration has

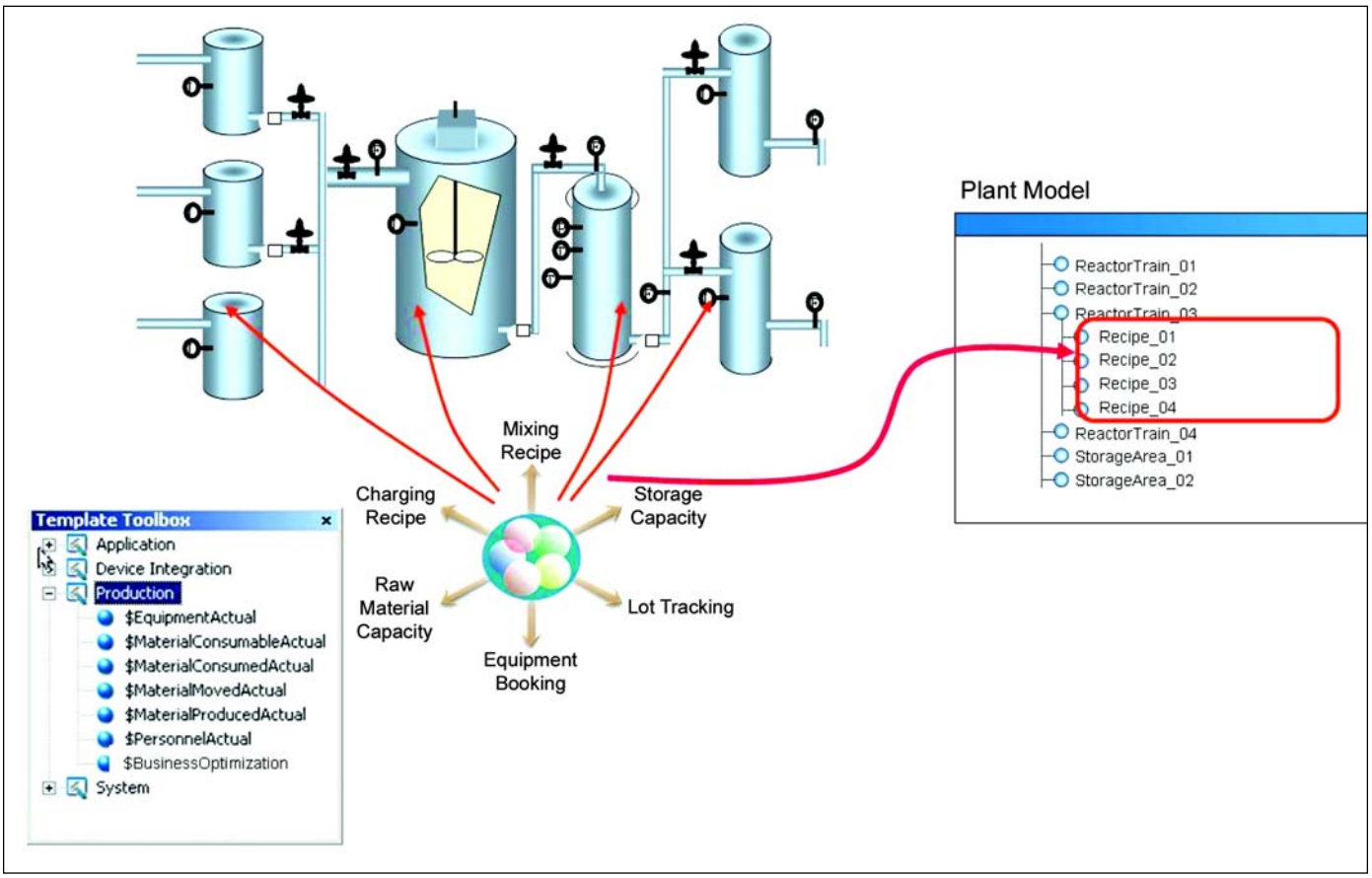

Figure 2. S95-influenced object model in which standard templates are configured for specific equipment or company parameters and contextualized for enterprise integration.

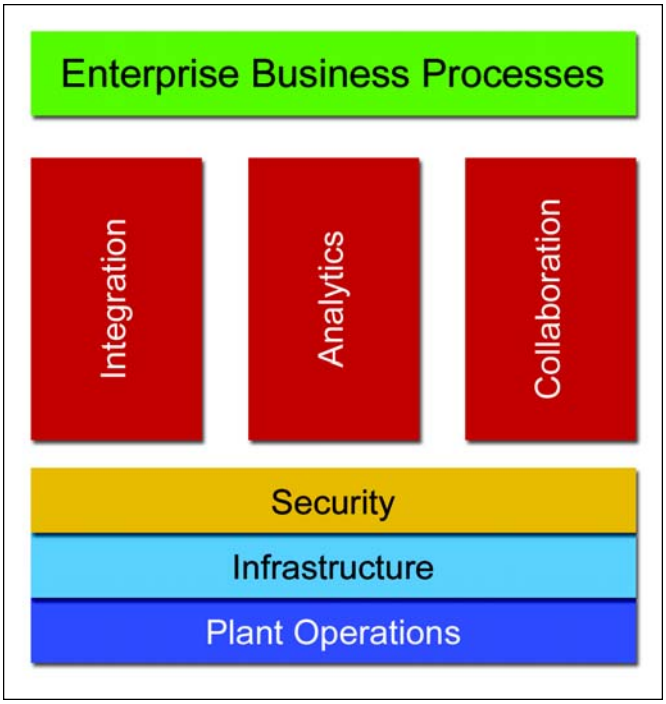

Figure 3. Enterprise control systems integrate traditional architectural functions.

occurred resulted in costly exchange of data, but not much information to support strategic decisions. You might, for example, feed manufacturing production data to month-end financial reporting, but it would not be timely enough to drive dynamic production changes that could actually impact those numbers. Breaking down that wall between the business and plant systems requires true visibility, from the business systems into the manufacturing systems, and visa versa," said Rüediger Dorn, Managing Director Pharmaceutical Industry, Microsoft Corporation.

The ISA recognized the need for integrated plant floor and business control many years ago, when it began work on the S95 standard.[3] S95 is about production management and the information that needs to flow between business and production systems. It consists of an abstract object model, similar to that depicted in Figure 2, with associated attributes and transactions that define the points of integration. This model calls for development of standard templates that address basic application, device integration, production, and system functionality, configuring these to match company specific parameters for recipe, storage, tracking and material management, and eventually extending these to a broader plant model which adds context and additional services automatically.

The standard also called for "a method of assuring the overall reliability and availability of the total control system through fault detection, fault tolerance, redundancy, uninterruptible power supplies, maintenance planning, and other applicable techniques built into the system's specification and operation."

Although the use of the word "total control system" is often misconstrued to mean plant floor control systems, there is actually nothing in the standard that restricts the "total control system" to the plant floor. In fact, the "total control system" must include all plant information loops. Availability and utilization are in fact system parameters measured in real time.

To achieve total enterprise control, the ISA S95 standard recommends a common model and data structure for information exchange between enterprise business systems and the process systems. But even data content structured according to common industry and enterprise specifications, while necessary, is not sufficient for successful integration. These documents must be compatible between systems, which mean that data delivery must be standardized.

Traditional control systems impose a significant limitation on information transfer because transferred information has very simple content and is often hardwired point-to-point. Manufacturers typically utilize proprietary data transfer technology for encoding and delivering information between enterprise and manufacturing systems - *Figure 3*.

More recently, standardized models and protocols are emerging and most leading pharmaceutical manufacturers are planning on achieving enterprise integration at this level.

An Integration Platform for Global Standards

Building modularized templates or otherwise standardizing operations, there must be platforms that enable collection of these objects and distribution across the enterprise. Whichever enterprise integration platform is selected, the key is to work with standard data structures which will enable sharing of data with any platform.

The path to a true enterprise control system is not a single box or software package, DCS, or LIMS system that one buys from a single vendor. It is a platform that simplifies open integration not only of best of breed solutions from multiple vendors, but integrates disparate functions within the same enterprise so that process control, maintenance, finance, purchasing, and scheduling are all working together.

For example, a company might standardize a specific bioreactor for all of its processes throughout the world. They could configure temperature control exactly the same and build a module around that. They would then validate that standard module, and encapsulate all of the information that goes with it. Another example might be the configuration of a specific report as a module that can easily be reused.

The Benefits of Enterprise Integration and Control

Effectively meeting the growing need for data integration and information management requires an expansion of the concept of plant floor automation to the entire enterprise. The key is an open integration platform across which a company can store its unique operating modules, templates, and programming objects to streamline and make consistent its operations anywhere in the world. This essentially converts the vast amounts of data that are now being collected in disparate operations across the company, including the busi-

ness office, supply chain, and distribution channels as well as the production floor and puts it into commonly formatted information groups, making the company knowledge truly manageable and visible.

The technology to implement an enterprise control system, one that enables sharing information across enterprise functional units, is available today with integration costs at about 10 percent of earlier methods. Progressive companies such as Pfizer are already benefiting from enterprise control implementations. Those who implement similar enterprise control solutions can expect the following benefits:

Production Improvements and Reduced Costs

A common enterprise platform integrates shop floor manufacturing systems and applications (MES) to ERP Systems. Leveraging this integration, manufacturers can manage the complete cycle from the laboratory to product delivery with state-of-the-art tracking and documentation. Managing data in real-time improves the accuracy of business decisions, agility, and production yields.

Improved Quality and Consistency

Up-to-the-minute information and the flexibility to respond to frequent changes in the market and adapt operations at a moment's notice are integral to having consistent platforms and ultimately OE success. This is especially relevant as companies expand global operations or outsource processes to the secondary market.

Greater Regulatory Compliance, Tracking, and Security

Having a standard platform can reduce the time-to-compliance by supporting compliance with global standards or templates of information, which can include standards for records, security, audits, etc.

Faster Time to Market

A flexible platform enables the manufacturer to design systems that respond better to their unique operations.

Pharmaceutical manufacturers can start with packaged and disparate applications and systems for the specific functionality they need. As their needs grow, they may eventually want to implement an enterprise platform that the applications can easily plug into for enterprise sharing. Where developing such applications in the past would have taken many months and thousands of dollars, the technology and the market has advanced to the point that cost and implementation have been reduced to about 10 percent of what it previously was. The business need and enterprise control technology are converging to bring pharmaceutical manufacturers promising new and affordable opportunities to achieve new levels of operational excellence.

Definition of Terminology

Service Oriented Architecture (SOA)

SOA refers to a portfolio of loosely-coupled, network addressable business Services. These Services are programs that 1) communicate by exchanging well-understood messages and 2) are composed of a set of components which can be invoked and whose interface descriptions can be published and discovered.

ISA-95 (ANSI/ISA-95) is an international standard for developing an automated interface between enterprise and control systems. It applies to all industries, but it is particularly relevant to pharmaceutical processes, like batch manufacturing, which are continuous and repetitive. The objective is to provide consistent terminology which is a foundation for supplier and manufacturer communications, provide consistent information models, and to provide consistent operations models which are a foundation for clarifying application functionality and how information is to be used.

Manufacturing Execution System (MES)

A MES is a system for measurement and control of critical production activities. Its benefits include increased traceability, productivity, and quality; also may provide equipment tracking, product geneaology, labor tracking, inventory management, costing, electronic signature capture, defect and resolution monitoring, alarming, real-time performance monitoring dashboards and other reporting. MES systems can scale, from simple tracking of work in progress to complex integration with Enterprise Resource and Planning Systems (ERPs), Product Lifecycle Management (PLMs), Supervisory, Control and Data Acquisition (SCADA)solutions, Scheduling and Planning Systems.

Enterprise Resource Planning (ERP) Systems

ERP systems strive to unify all data and processes of an enterprise, but most systems have focused on integrating enterprise financial and human resource information systems. However, in recent years ERP systems have been expanding scope to integrate other enterprise applications, including manufacturing asset management, supply chain, Customer Relationship Management (CRM), and warehouse management. The term Enterprise Control System (ECS) has emerged to cover this broader level of enterprise integration.

Enterprise Control System (ECS)

An ECS enables manufacturers to develop solutions that span manufacturing business enterprises without concern for constraints traditionally imposed by crossing the boundaries of the different classes of systems. The following four characteristics define an ECS: full plant floor interoperation; open communication access across the business enterprise; support for Asset Performance Management (APM) tools which enable unified maintenance and operations management; and a unified engineering environment across all plant floor domains.

Extensible Markup Language (XML)

XML is an open-standard mark-up language for sharing of data across different information systems, particularly sys-

tems connected via the Internet. XML provides a standardized structure that enables anyone to create a markup language suitable for their applications. As such, it is the basis for numerous mark-up languages in use today, including RSS, MathML, GraphML, XHTML, and Scalable Vector Graphics.

Distributed Control System (DCS)

A DCS is a manufacturing automation system in which the controller elements are distributed across multiple process points with each component sub-system under the control of one or more controllers. The entire system may be networked for communication and monitoring.

Programmable Logic Controller (PLC)*

A PLC is an electronic device used for automating industrial processes. Unlike general-purpose computers, the PLC is designed for extended temperature ranges, dirty or dusty conditions, immunity to electrical noise, and resistance to vibration and impact. PLCs differ from DSCs in that they have traditionally been used to control closed-loop, isolated manufacturing processes although advances in technology are enabling increasing integration of PLCs to provide distributed functionality in limited applications.

*Programmable Logic Controller is a registered trademark of the Allen-Bradley Company,

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Stage Gated Approval Processes – A Practical Way to Develop and Filter Capital Investment Ideas

by Gordon R. Lawrence

This article presents reasons how and why a stage gated approach to capital project approval is efficient in terms of both time and money. It also dispels some of the common misconceptions about such an approach.

Introduction

A key step in deciding to proceed with any new capital investment project is the development of the cost estimate. Typical questions include how much will it cost? Can we justify the cost of the project against the business case? How much time and effort are we willing to spend to find out whether the project cost can be justified?

In the pharmaceutical industry, there is often pressure to provide accurate cost estimates at short notice and there is confusion over the amount of effort required in order to develop a certain level of estimate accuracy. This can lead to unreasonable expectations of what is possible when preparing a cost estimate.

Ultimately, it can lead to inefficient expenditures in one of three ways: (1) expenditure of large quantities of funds on a project idea that ultimately proves to be unjustifiable; (2) a project being approved on the basis of an optimistically inaccurate estimate that would not have been approved, if the true costs been known; (3) a project being approved on the basis of a very rough estimate, leading to lack of strong budgetary control and ultimately a project that is built for an uncompetitive (and possibly unpredictable) cost and schedule.

This article will examine how much effort is required to produce an estimate of a given level of accuracy. It will then go on to examine a stage gated approach as the best way to balance the two conflicting concerns of (a) spending money to get a better estimate against (b) avoiding wasting money on estimating a non-viable project. Next, it will look at the situation where the business idea is of such value that the project capital cost is only a small proportion of the business case, and the key issue is getting the product to market quickly. It will examine how a balanced, structured, stage gated approach to project scope and estimate development is of benefit even in such extreme "schedule driven" situations. Finally, the article will examine the negative effects of two common actions taken by business management: (1) the desire to "force" an estimate to be more accurate than the scope development can justify and (2) an overly optimistic view of early estimates.

The article is intended for senior managers whose role includes making decisions on whether to proceed with a project idea, but who may have not previously received any engineering or cost estimating training. By the end of the article, readers should have a better appreciation of the amount of effort required to

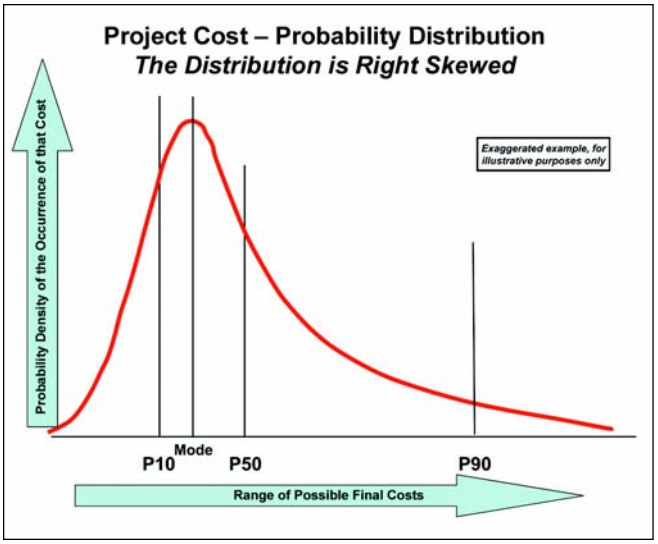

Figure 1. Probability distribution of possible cost outcomes.

achieve a certain level of estimate accuracy and an appreciation of how to balance the desire for greater estimate accuracy before making a final decision against a desire not to "throw good money after bad" on a project idea that won't come to fruition. They also should have a better appreciation of the need for a structured approach to project scope development and estimating, even for a schedule driven project with a solid business case.

How Much Effort is Required?

Problem Number One – I need a number!

Someone has come up with an idea for a project. The business case says that if it could be built for an investment of less than X, then it would meet the company payback criteria.
But can it be built for less than X?

You call the Project Engineering Department and ask them to quickly tell you how much it would cost to build this facility. They ask a few questions and hang up. They call you back the next day with the answer that the 50/50 cost is X with a range of 0.8X to 1.5X, or -20% and +50% at the 80% confidence level.
Should you go ahead?

Your immediate questions to the Project Engineering Department are:

a. Why can't you just give me one number? Why are you giving me a range and what does this range mean?
b. How do I narrow the estimate range to find out if the true project cost is closer to 1.5X or closer to 0.8X? (This is important since the answer will decide whether the project is viable or not).
c. How do I narrow that range without wasting a lot of time and money?

Estimates are Ranges, not Points

Any cost estimate for a capital investment project is exactly what it says: an estimate. It is a prediction of what the final cost will be at some time in the future. Since no one has yet invented a foolproof crystal ball, no-one can predict the future

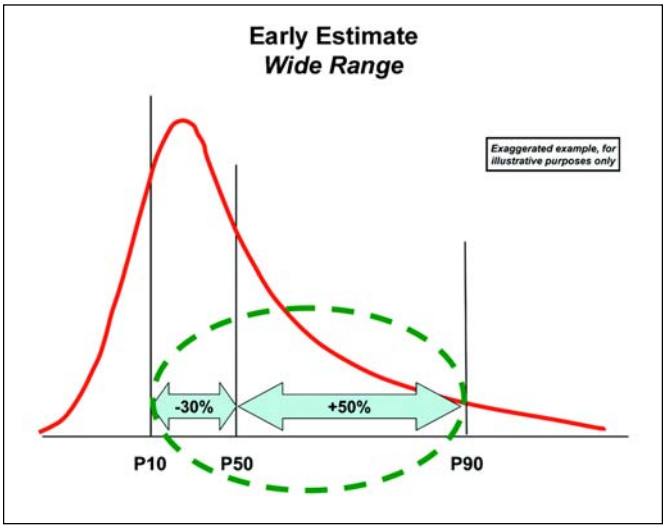

Figure 2. An early estimate with the correct, wide range.

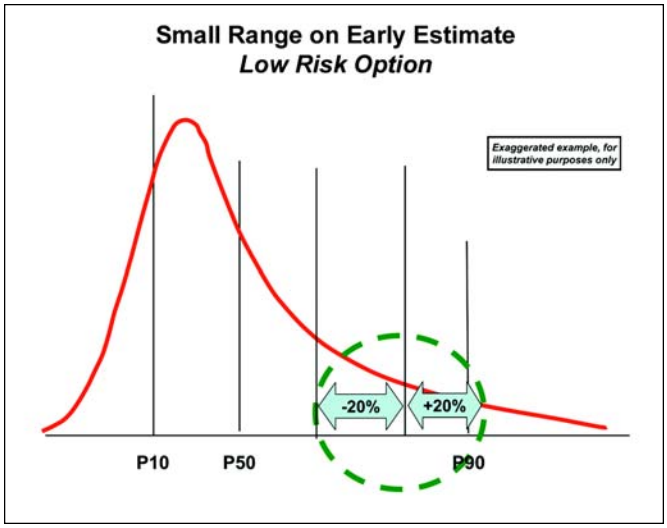

Figure 3. An early estimate with a low risk attempt at a narrow range.

with absolute certainty. Consequently, any estimate will have a range of possible outcomes. That range of outcomes can be expressed as a probability distribution. Because the minimum cost is fairly certain, but the maximum is less certain, the probability distribution curve is generally not normally distributed, but is right skewed, as shown in Figure 1.

A cost estimate is usually quoted as a point number with a range around it. For example, "the cost is $X million, ±50%." The fact that the ± percentage is even (the same on the plus and the minus side) is a reflection of the common tendency to simplify and assume that the distribution curve is normal. A more accurate percentage might be something like -20%, +50%. The percentage range is usually quoted as a confidence range (typically the 80% confidence range). So, if we return to our probability distribution in Figure 1 we can see that:

- The base cost calculated by the estimator (without contingency) is the **mode** (i.e., the "most likely" outcome – but note that the final cost has a less than 50% probability of being this value or less – that point is denoted by the median). This discussion of mode, median, and range is taken from Lawrence.[1]
- The point number for the estimate (i.e., base cost plus contingency) is the **P50** (i.e., the median or the point at which there is a 50/50 likelihood of the actual cost being greater or smaller than this value).
- The percentage range limits are (assuming we used an 80% confidence interval) the **P10** and **P90** values. (That is, there is a 10% probability of achieving a lower cost than the bottom percentage value and a 10% probability of achieving a higher cost than the top percentage value. Note that this means the percentage range cost is NOT a guarantee of being within that range, it merely expresses an 80% probability of being within that range.)

So, now that we know why estimates are quoted as ranges and what those ranges signify, how do we go about reducing the

range and hence improving the estimate accuracy?

Narrowing the Range – Developing Increasingly Accurate Estimates

It is clear that the less risk and uncertainty there is around a project, the more the range of possible outcomes can be reduced. Ultimately, when the project is built, all final costs are known; therefore, there is no more risk and uncertainty about the cost and hence no range is needed at all.

Therefore, greater estimate accuracy is achieved by reducing the level of risk and uncertainty surrounding the project. As discussed in numerous studies, such as Merrow,[2] the sources of project risk and uncertainty can be broadly characterized as:

- The **project type** – for example, a project that is using new technology carries greater design and execution risks than a project to build a facility that contains no new process technology and that uses processes and equipment that are tried and tested.
- The level of completeness of **project front-end definition** – a cost estimator prepares an estimate based on the scope of work documents supplied to him/her. Therefore, any items omitted from that scope of work will not be picked up by the estimator and will remain as potential risks to the project cost outcome. Similarly, any ill-defined items will carry greater risk than clearly defined items.
- Risks arising from the **project environment** – for example, risks from extreme weather or from labor shortages in a remote environment.

Of these three, project type is out of the control of the project team, but the other two are within the control of the project team and are relevant to our current discussion. We shall focus on front-end definition since by doing this correctly, risks arising from the project environment also should be mitigated.

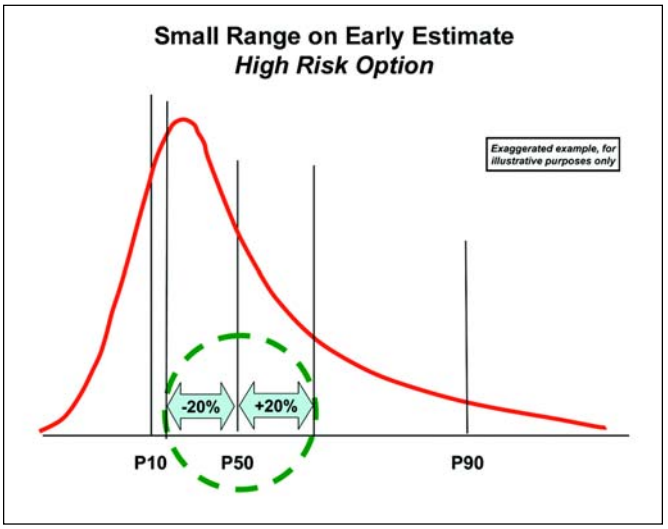

Figure 4. An early estimate with a high risk attempt at a narrow range.

Cost Estimate Classification

If completing more front-end definition can mitigate risk and uncertainty, how much front-end definition is required in order to achieve a cost estimate of a particular accuracy?

The Three Main Estimate Categories

The following will focus on three key estimate accuracy levels:

- Rough, Order of Magnitude (ROM) Estimate
- ±30% Accuracy Estimate
- Control Estimate

Sources of Scope Definition Classification

Several organizations, including the Association for the Advancement of Cost Engineering-International (AACE-I), have produced documents classifying estimate types, and describing in a **qualitative** way, the approximate estimate accuracy level to expect, based on the amount of front-end development of the design package that has been done.[3]

Two **quantitative** methods of measuring the level of front-end definition achieved that are becoming industry standards include the Construction Industry Institute (CII) Project Definition Rating Index (PDRI)[4] and the Independent Project Analysis (IPA) Front-End Loading (FEL) Index.[5] All three sources generally give a similar description of what level of front-end definition is required in order to achieve a cost estimate of a particular level of accuracy.

Level of Front-End Definition Required for a Particular Estimate Accuracy Level

Stochastic or Deterministic?

As a general rule, project estimates develop from very rough estimates that use a "Stochastic" method of calculation (i.e., they are "top-down" estimates, based on rough cost capacity benchmarks – cost per m^2 for a laboratory or cost per ton of production for a bulk chemical plant, etc.) to get an estimate when very little is known about the detail of the project to a "Deterministic" method of calculation when the scope is defined in more detail (i.e., a "bottom-up" estimate, based on material take-offs of estimated material quantities). A useful overview of stochastic versus deterministic estimates is given in Dysert.[6]

Rough Order of Magnitude Estimate

This is a stochastic estimate, typically used when very little is known about the project scope. (Table A provides an example of the level of deliverables required). This Table is adapted from the AACE-I[7a] and Griffith and Yarossi.[7b] Such an estimate uses simple benchmarks, based on historical data. For a (highly simplified) example, "*The last five facilities built had an average cost of $X per 1000 tablets/day of production capacity. Therefore, since our facility will produce 5,000 tablets/day, it will cost in the region of five times $X.*"[8]

Assuming a database of benchmarks is available,[9] this type of estimate can be produced very quickly, and with very little expenditure, typically less than 0.5%[10] of the Total Installed Cost (TIC) of the project.[11] However, one can only

expect an accuracy of -50 to -100% up to + 50 to +100% with a typical range being in the order of -20 to +50%.

30% Accuracy Estimate

At this stage, one begins to move between the stochastic and the deterministic approach. Such an estimate is very often developed using factors based on one key element of the scope. For example, in a bulk API plant, if the major equipment list is known, one can factor the cost of the entire facility from the equipment cost (a Lang factor approach[12]).

This type of estimate requires more work and would typically cost around 1.5% of the TIC of the project to produce. The level of front-end definition required is reflected in the example deliverables shown in Table A. By the time this amount of scope definition is completed, the project estimate accuracy should be in the region of -20% to + 30% (with the proviso that some projects, with unusual characteristics, may have a wider estimate range).

Control Estimate

For an estimate of this accuracy, one moves to a detailed level of scope definition and a deterministic approach.

At this stage, the major equipment (and possibly the building in a laboratory project or pharmaceutical finishing project) and possibly the detailed engineering office work will be based on firm quotations. Other equipment may be based on budget quotations. Material costs will be based on material take-offs either priced using historical data or via budget quotations.

This type of estimate requires the expenditure of a further 3-5% of TIC, over and above that spent to develop the 30% estimate. As shown in Table A, the level of definition required is quite detailed, but the accuracy achieved can be expected to be in the range of -5% to +15% or better.

How to Balance Effort Against Results

It is now clear that developing greater definition of the project scope during the front-end phase of a project takes time and money. It takes very little effort to produce a rough estimate, but it takes a cumulative expenditure of upward of 4 to 7% of TIC to produce an estimate with an accuracy in the region of -5 to +15% or better.

Problem Number Two – I need a number, but I don't want to waste time and money!

It is clear that we have two opposing concerns:

- On the one hand, management would like as accurate an estimate as possible of what a project idea will cost and how long it will take so that they can decide whether the project is worth pursuing.
- On the other hand, management does not want to waste money on projects that will prove to be not worth pursuing, once the true costs are known.

Management needs a system that balances the advantages of having a more accurate estimate of costs against the disadvantages of having to expend time and effort to achieve that better accuracy on an idea that might then be dropped as being uneconomic.

A Parallel with Drug Discovery

The issue can be viewed in some ways as a parallel with the research function in the pharmaceutical industry. Manage-

	ROM Estimate	30% Estimate	Control Estimate
General Project Data			
Project Scope Description	General	Defined	Defined
Facility Capacity	Assumed	Defined	Defined
Facility Location	General	Specific	Specific
Ground Surveys	None	Defined	Defined
Project Execution Plan	None	Defined	Defined
Contract Strategy	Assumed	Preliminary	Defined
Project Schedule	Rough milestone benchmark	Preliminary	Detailed, resource loaded schedule
Cost Estimating Plan(Code of accounts, escalation philosophy, work breakdown structure)	None	Defined	Defined
Engineering Deliverables			
Block Flow Diagrams	Outline	Complete	Complete
Plot Plans	None	Preliminary	Complete
Process Flow Diagrams	None	Complete	Complete
Utility Flow Diagrams	None	Preliminary	Complete
Piping and Instrumentation Diagrams	None	Preliminary	Complete
Heat and Material Balances	None	Preliminary	Complete
Process Equipment List	None	Preliminary	Complete
Utility Equipment List	None	Preliminary	Complete
Electrical Single Line Diagram	None	Preliminary	Complete
Process Engineers Equipment Datasheets and specifications	None	Preliminary	Complete
Mechanical Engineers equipment datasheets	None	Preliminary	Complete
Equipment General Arrangement	None	Preliminary	Complete

Table A. Outline of deliverables required for a given level of estimate accuracy.

ment receives thousands of "promising" drug ideas. It then wants to know which ones will be successful, but it can't know that without spending at least some money to develop each idea. The trick is to spend the minimum on each idea to get a sufficiently accurate idea of whether it should be abandoned or not.

The Solution

The system that has been worked out over the years across the process industries is a "stage gated approval" system, whereby an investment idea is developed from a ROM estimate through a ±30% estimate to a control estimate. At each stage, the idea goes through a "gate" where it can be challenged and a decision made on whether to proceed further. This system has now been adopted across most of the pharmaceutical, chemical, oil and gas, metallurgical, and many other industries as being "best practice."

The advantages of this system are that not only does it provide the best compromise between expenditure and estimate accuracy that has been found to date; but it also provides a controlling framework to ensure that project teams develop the design in the most cost and schedule efficient way. As discussed earlier in this article, developing a "rough order of magnitude" estimate requires very little capital expenditure; developing a ±30% estimate requires a little more expenditure; and developing a control estimate a little more.

The stage gate process requires a project team to develop the project estimate through each of those three estimate stages, but it also requires the team to pass through an approval gate after each estimate at which management reviews the project and decides whether it is worth expending the next portion of funds to develop the project further. The gates are intended to provide a set of information to allow decisions to be made in alignment with business needs. The objective of the process is to spend the minimum to provide the right level of information to allow a decision to be made on whether to proceed. The process also provides a structured framework for developing a good front-end design package.

The Three Gates

So what are these three phases with gates at the end of them, and what are the criteria for passing the gate and moving to the next phase?

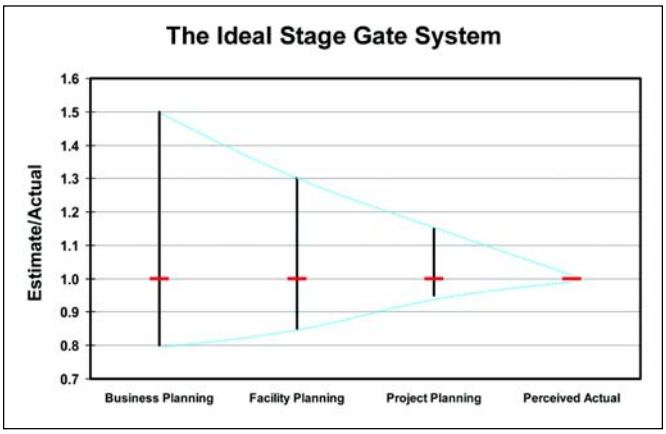

Figure 5. Estimate progression in an idealized stage gate system.

Business Planning – Initiation Phase

- **Focus**
  This phase focuses on the development of the idea for the investment. (i.e., is this an idea worth pursuing?)
- **Cost Estimate Accuracy**
  Estimates are developed only to the "rough order of magnitude" level. (±50-100%)
- **Object**
  The object of this phase is to invest the minimum amount necessary to decide whether the business opportunity is a viable idea.
- **Leadership**
  Business representatives usually lead this phase, not project engineering staff (although project engineering staff may provide support).
- **Deliverables**
  The key deliverables of this phase are a clear description of the "business opportunity" and business objectives and a clear list of possible alternatives that will be examined in the next phase.
- **Decision**
  The decision to be made in the gate at the end of this phase is "Is this business idea viable? Do I want to spend money costing it out?"

Facility Planning – Conceptual Design Phase

- **Focus**
  This phase focuses on evaluating the possible alternative project solutions to meet the business objectives. (e.g., do I want process A, process B, or outsourcing? – Do I want to build in the USA, Europe, India, or China? – Do I want to expand plant X or build a new plant at site Y? – etc.)
- **Cost Estimate Accuracy**
  Estimates are developed to the ±20 or 30% level.
- **Object**
  The object of this phase is to invest the minimum amount necessary to decide which SINGLE option gives the best fit with the business objectives and then whether the business opportunity is still a viable idea.
- **Leadership**
  In this phase, project engineering staff typically take over control from the business representatives, as the work to develop conceptual design studies becomes more technical.
- **Deliverables**
  The key deliverables of this phase are a clear differentiation between options in order that one option can be chosen, and a ±30% estimate of that option.
- **Decision**
  The decision to be made in the gate at the end of this phase is three-fold "Are we agreed on a single option? – Does this option still meet the business objectives – Is the business idea still sufficiently viable that I want to spend money to go to the next stage?"

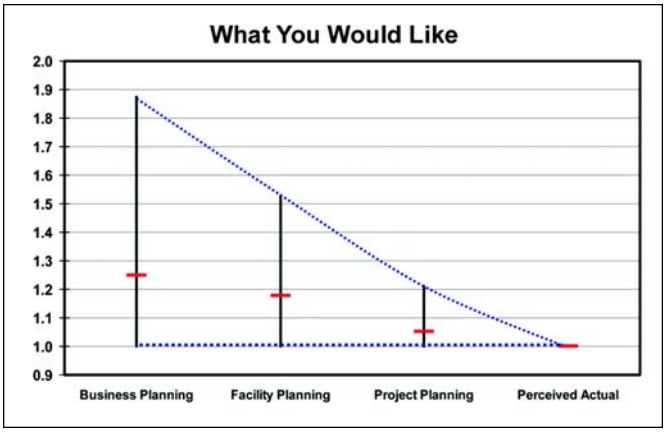

Figure 6. An optimistic view of estimate progression.

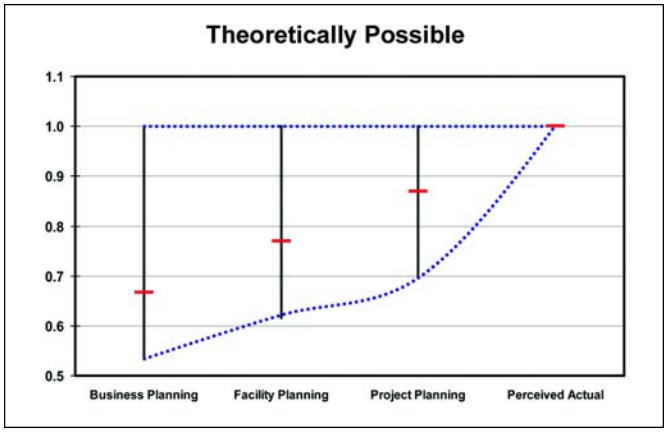

Figure 7. A pessimistic view of estimate progression.

Project Planning – Basic Design Phase

- **Focus**
  This phase focuses on developing a control estimate of the chosen option.
- **Cost Estimate Accuracy**
  Estimates are developed to the ±5 to 15% level.
- **Object**
  The object of this phase is to invest the minimum amount necessary to develop a control estimate of the chosen option and to check that the business opportunity is still a viable idea.
- **Leadership**
  In this phase, project engineering staff control the development of the basic design.
- **Deliverables**
  The key deliverables of this phase are a control budget, coupled with an estimate of an accuracy in the region of -5+15% or better.
- **Decision**
  The decision to be made in the gate at the end of this phase is "Do we want to build this?" (i.e., does the business case still make sense?)

The Advantages of a Stage Gated Approach

The advantages of this system are that it allows controlled expenditure of funds up to a maximum of only around 4-7% of TIC, while gradually improving the level of knowledge about the likely final cost; and within the system, management receives three clear opportunities to review whether it wishes to proceed or not.

The Role of the Gatekeeper

For such a gate system to work, it is vital that no project is allowed to pass through a gate until it has fulfilled all the necessary criteria. Therefore, a gatekeeper either needs a good knowledge of the scope definition criteria for a ROM estimate, a ±30% estimate and a control estimate; or he/she needs a proxy way of measuring the scope definition.[13]

In addition, it is important to recognize that as well as not allowing a project to pass through a gate until it is ready, the gatekeeper has a duty to stop any project that no longer meets the business criteria. This "stop" decision should not be viewed as a failure. Rather it should be viewed as the gate process doing its job – that is, encouraging business ideas, but canceling those that prove not to be viable.

Fast Track Projects and the Use of Stage Gates

A common complaint about stage gated systems is that they appear to be just extra bureaucracy; therefore, hindering the achievement of fast projects. However, this assertion can be challenged.

Several studies have shown that a pharmaceutical industry project using best practices (i.e., following a rigorous stage gate process to develop a good front-end package) compared to a pharmaceutical industry project using poor practices (i.e., bypassing the rigorous process) achieves an execution schedule[14] advantage. Two examples drawn on for this discussion are Merrow[15a] and Lawrence.[15b]

The question then becomes: Does that advantage during execution outweigh any perceived additional time needed during the front-end phase?

The studies show that projects performing with very good front-end definition by following a rigorous stage gated process achieve an execution schedule advantage of anything up to 32% over the industry typical project and up to 43% over those projects that do not achieve a good level of front-end definition.

Therefore, a strong case can be made that any extra time spent in developing a good front-end package would be more than recovered during execution ("more haste, less speed"). In addition, an argument can be made that if proper planning is performed there is no reason why preparing a good front-end package should take much longer than inefficiently preparing a weak front-end package.

High Risk Methods of Fast Tracking Projects

There are other methods that can be used to fast track projects. However, since they carry risks and costs, they should only be considered if after implementing a strong stage gate process and achieving best practical front-end definition, further acceleration is seen to be required. If they

are used, it should be on the understanding that they come with risks and costs attached. Examples of such methods are discussed below.

Early Ordering of Long Lead Items

Many firms order long lead equipment during Basic Design with the proviso that if the project does not go ahead, the equipment will be cancelled. This carries some risks, depending on how early in Basic Design one orders the equipment – the wrong equipment specification may be given or even the wrong item may be ordered. The risk is slightly less for a Bulk API facility than for a pharmaceutical facility or for a facility in other process industries because much of the large equipment is of very standard designs.

Starting Construction Early

Starting construction early carries a risk of inefficient working. The construction team may outstrip the supply of engineering drawings or the supply of material, or they may have built an item that then undergoes a late change. All of these risks will have a cost effect and also may have a schedule effect, thus negating the very purpose of starting construction early.

Use of Overtime and Shift Work

The use of overtime and shift work is a highly expensive and generally inefficient way to try to accelerate a project. If used too early in construction, these methods can result in the same problems as starting construction early. Overtime work is paid at a premium rate. In addition, several studies have shown that although paid at a higher rate, the productivity of the workers is less, their susceptibility to accidents increases, and if it continues for more than a couple of months, overtime can actually cause a project to take more time, not less. The most famous study is probably the 1974 Business Round Table Report.[16a] Other examples include Hanna[16b] and also CII Report SD-98.[16c]

Some Points to Ponder

The previous sections have explained why the project department will quote an estimate as a range, how the range can be reduced, and how to develop a good, control estimate in a controlled manner.

However, what if you insist on a greater level of accuracy than the level of front-end development can justify, and/or you take an overly optimistic or aggressive view of early estimates. These points are discussed below.

Asking for Greater Accuracy than the Scope Can Justify

One situation that may arise is when a team is asked to provide a cost estimate to a high degree of accuracy, but is not given the time or resources to develop an estimate to that level of accuracy. Thus, we have an estimate range that may look like that in Figure 2. But the team is asked to present the estimate as being of greater accuracy. The team has effectively two choices if it is to comply. It can take the lower risk option, as shown in Figure 3. But in doing this, the team is offering a price that is above the 50/50 point and hence is headed toward achieving predictability at the expense of competitiveness. Alternatively, it can take a high-risk option, as shown in Figure 4. In that case, the probability of having an unpredictable, cost overrun outcome is greatly increased.

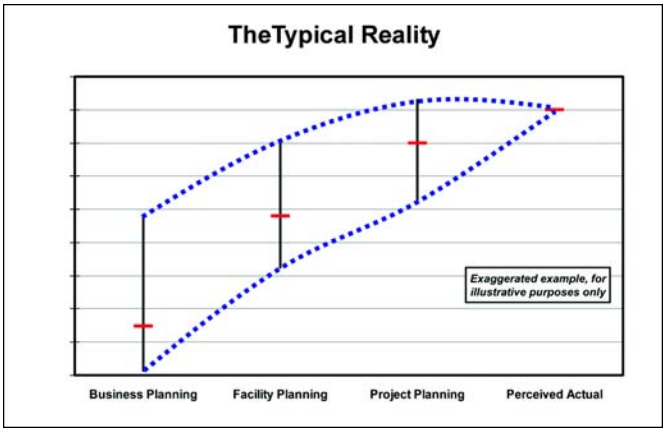

Figure 8. The reality of estimate progression.

Optimism Skews Cost Estimate Progression

In developing a gradually improving level of accuracy of a project cost, the ideal and the common perception is that the 50/50 point will stay the same, as the accuracy improves, as shown in Figure 5. Many people may even take an optimistic outlook and choose to perceive the likely outcome as being gradually converging on the bottom end of the estimate range, as shown in Figure 6. People also tend to forget that theoretically, the cost could converge on the top end of the range, as shown in Figure 7.

In fact, numerous studies have shown that, human nature being what it is, what typically happens is that projects are underestimated in the early stages and reality looks like the example in Figure 8. Some of those studies, such as Merrow,[17] attribute this to wishful thinking on the part of the project sponsors in the early phases, or to weak front-end development, thus failing to recognize the full potential costs. Others have studied the phenomenon and see it as a deliberate political act by the business sponsors and project champions, designed to increase the probability that a project is approved.[18]

Conclusions

This article has shown why estimates are quoted as ranges and how to reduce those ranges, improving estimate accuracy. The article also has shown that the level of accuracy achieved is a function of the time and effort spent on developing the front-end package. Furthermore, the article outlined a stage-gated process, giving an efficient way to balance the need for greater estimate accuracy against the desire not to waste money on projects that may not get authorized. The discussion also demonstrated that following a stage gated approach can help, not hinder a fast track project. Finally, an indication has been given that taking an optimistic view of

early estimates is usually a mistake.

In summary, the advice for finance managers, business sponsors, project champions, and end users is:

- understand what level of front-end development is required for a given accuracy level
- expect to have to spend in the region of 6% of TIC if you want a good control estimate of what the project will cost
- follow a rigorous stage gated process, even if you're in a hurry; it will give you a faster project in the end
- Remember that historical evidence shows that optimism about the final cost, based on early estimates, is usually misplaced.

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4. The Project Definition Rating Index (PDRI) is a weighted checklist of project scope definition elements developed by the Construction Industry Institute (CII). It is a self-assessment tool, designed to facilitate assessment of a project during pre-project planning. Two different versions of the tool exist - one for industrial (process) facilities and one for building facilities. See the Web site http://www.construction-institute.org/pdri/pdri-is.cfm for more information.
5. The Front-End Loading (FEL) Index is a weighted checklist of project scope definition and project planning elements developed by Independent Project Analysis (IPA). It is an independent assessment tool, designed to facilitate assessment of a project during pre-project planning. Several different versions of the tool exist – including versions for different types of industrial (process) facilities, offshore oil and gas exploration, and production facilities, buildings and laboratories, pipeline projects, and Information Technology (IT) projects. See the Web site http://www.ipaglobal.com/index.asp for more information.
6. Dysert, Larry R.; Sharpen Your Cost Estimating Skills, *Chemical Engineering*, Vol. 108, No. 11, Oct 2001 – reprinted in *Cost Engineering*, Vol. 45, No. 6, June 2003.

7a. *AACE-I Recommended Practice No. 18R-97* (2005) Cost Estimate Classification System – As Applied in Engineering, Procurement, and Construction for the Process Industries (estimate classifications 5, 3, and 2).

7b. Griffith, Andrew F. and Yarossi, Mary-Ellen; Stage Gated Process for Project Definition of Capital Projects; *19th IPMA World Congress*, New Delhi, India 13-16 November 2005.

8. This example is highly simplified. In fact, the relationship is rarely linear, a fact first discussed by Williams and particularly Chilton in the late 1940s and early 1950s. The relationship of cost to capacity usually has a capacity ratio exponent in the range of 0.5 to 0.85 and the methodology is often referred to as the "six tenths rule" in recognition of the fact that 0.6 is the typical exponent value. An example would be (cost of new facility/cost of old facility)=(capacity of new facility/capacity of old facility)$^{0.6}$.
9. Sources of cost benchmarks and cost ratios include the CII (through their pharmaceutical benchmarking forum), IPA (through the pharmaceutical section of their cost engineering committee), Compass directories, Richardsons Means publications, and many others.
10. This and the percentage expenditures given for the other two estimate types are taken from - Griffith, Andrew F. and Yarossi, Mary-Ellen; Stage Gated Process for Project Definition of Capital Projects; *19th IPMA World Congress*, New Delhi, India 13-16 November 2005 – However, similar benchmark values are very common and can be found in numerous other publications.
11. Total Installed Cost (TIC) includes Conceptual Design, Basic Design, Detailed Engineering, Procurement, and Construction up to mechanical completion. It does not include Initiation, Commissioning, IQ, OQ, or PQ.
12. Lang factors (ratios of total project cost to the cost of the major equipment) were first proposed by H.J. Lang in 1947. They have subsequently been updated by others, such as Chilton in the 1950's and Guthrie in the late 1960s and early 1970s. They have since been widely adopted as a common stochastic estimating method across the process industries.
13. One solution used by some process industry firms is to use the PDRI or FEL quantitative measures as a proxy check on whether a project is sufficiently well defined.
14. Execution phase – the phase from end of Basic Design up to mechanical completion.

15. a.Merrow, E.W., It's time for Capital Excellence in Pharma Projects, presented at *The Pharma Summit on Aseptic Technologies*, June 1-3 2005, Cork, Ireland.

15. b.Lawrence, G.R., Achieving Faster Project Delivery – More Haste, Less Speed. *Pharmaceutical Engineering*, May/June 2006, Vol. 26 No. 3.

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tion Industry Institute.
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18. Flyvbjerg, Bent, and Bruzelius, Nils and Rothengatter, Werner; Megaprojects and Risk: An Anatomy of Ambition*; Cambridge University Press*, 2003.

About the Author

Gordon Lawrence has more than 20 years of experience in project management, having worked for several pharmaceutical owner firms, as well as Jacobs Engineering, the international contractor, and Independent Project Analysis, one of the leading management consultancies in the field of project management best practice. He currently works as a Senior Project Manager for a major pharmaceutical firm and is based in Basel, Switzerland. Lawrence has a degree in chemical engineering and advanced degrees in biochemical engineering and business administration. He is a chartered engineer, registered in the United Kingdom and Europe. He is a fellow of the UK Institution of Chemical Engineers, a member of the American Institute of Chemical Engineers, a member of the Project Management Institute, and a member of the Association for the Advancement of Cost Engineering – International. He is a member of the ISPE French Affiliate, a member of the Project Management Community of Practice, and is Vice-Chair of the ISPE Membership Services Committee. He can be contacted by telephone at +41-79-618-7391 or by e-mail at gordon_r_lawrence@hotmail.com.

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In this interview, Rick Lawless discusses in detail the making and the mission of BTEC in North Carolina, USA, the only center of its kind in the nation that provides hands-on biomanufacturing training and education on state-of-the-art equipment, techniques and methods.

PHARMACEUTICAL ENGINEERING Interviews

Rick Lawless, Associate Director, Strategic Support, Golden LEAF Biomanufacturing Training and Education Center (BTEC)

by Cathy Middelberg, Co-Chair, *ISPE Pharmaceutical Engineering Committee*

Rick Lawless has more than 22 years of experience in biomanufacturing, including two years as an administrator and instructor at BTEC. While working for global companies like Eastman Kodak, Johnson & Johnson, and Wyeth, he completed assignments in R&D, process engineering, compliance, and cGMP production management while manufacturing industrial enzymes, diagnostics, and vaccines. His current interests include developing training methods using simulated production experiences and designing upstream bioprocesses to optimize business goals, regulatory compliance, training, and safety. He obtained a BSE in Chemical Engineering and a BS in Microbiology from the University of Michigan and a MBA from SUNY at Buffalo.

Background

Q Can you tell us about your career in the biotechnology industry?

A My career in the industry started 22 years ago when biotechnology was just getting started. My first assignment involved developing fermentation processes for industrial chemicals like amino acids, enzymes, and even an ice nucleation protein that helped make better snow. The pace of development was a bit too slow for me so I transferred to a division that manufactured diagnostic devices. Over time, I transferred into operations management and I thrived on the daily chaos of hitting production targets, maintaining cGMP compliance, and keeping costs within budget. After 12 years of long winters, I loaded up the truck and moved to North Carolina, where I managed the start-up of a new production facility to make the active ingredient for Prevnar®, the pediatric vaccine launched in 2000. After a successful start-up and a brief stint in corporate quality operations, I became the Manufacturing Director at Wyeth's vaccine facility in Sanford, North Carolina. It was about that time when I also became involved with the conceptual design for BTEC and represented Wyeth on the BTEC Advisory Board. I wanted to ensure that BTEC offered courses that industry employees could attend without having to spend all of our travel money. In 2005, I realized that I really wanted a job that allowed me to teach others about biomanufacturing so I left corporate life and took a job at BTEC. In addition to teaching our large-scale fermentation course, I lead support groups that are responsible for student coordination, process operations, instructional design, administration, and industry relations.

Biomanufacturing Training and Education Center Facility

Q Could you tell us about the new Golden LEAF Biomanufacturing Training and Education Center (BTEC) that opened last year? What is the mission of BTEC? What are the academic programs at BTEC and who are your students?

A The mission of BTEC is quite straightforward: 1) educate and train prospective and current employees for the commercial biotechnology industries on state-of-the-art equipment, techniques, and methods; 2) help the industry create its own future by developing new technologies for new and improved methods for biomolecule production; and 3) attract new biomanufacturing companies to North Carolina.

North Carolina State faculty are offering hands-on laboratory courses in biomanufacturing to undergraduates majoring in life sciences and engineering. The North Carolina Community College System (NCCCS) offers bioprocessing and aseptic processing courses to industry incumbents and community college students in the BioNetwork Capstone Center housed in the Golden LEAF BTEC.

Q How many students will the Golden LEAF Biomanufacturing and Education Training Center train per year? How long is the training program?

A In our first year, we estimate that up to 500 community college, university, and industry incumbents will receive training in BTEC. At full capacity, we'll be able to train up to 2000 students per year. There is no set training program – students can take one or all the courses offered in BTEC.

Q Is the concept to study unit operations or biological processes?

A Several departments at North Carolina State University already provide education in the fundamentals of biological processes. Our introductory courses bridge the gaps between those courses and what's needed in the biomanufacturing industry. Our intermediate-scale courses focus on unit operations, while our capstone courses take place in pilot-scale laboratories that simulate a cGMP production suite.

Students learn how to remove a clean sample from the seed bioreactor.

Q What type of degree can a student earn and what kinds of careers will they be prepared for?

A BTEC courses are an integral part of the new Bioprocessing Science (BBS) degree and the Biomanufacturing Sciences concentration in the Chemical Engineering major. Students also can obtain a Biomanufacturing minor by completing 16 credit hours of BTEC courses. These students can pursue careers in engineering, operations, validation, quality, or development.

Q Have classes begun?

A Last fall, one month after receiving occupancy of our facility, BTEC started offering half of its core courses, including courses in introductory biomanufacturing, bench-scale bioreactors, fermentation unit operations, and large-scale fermentation and purification. The rest of the courses were added in spring of 2008. Courses for FDA field personnel and short courses for industry incumbents will launch in summer of 2008.

Q Are you considering any on-line versions of your biotechnology training?

A Our strategy is to offer the lecture components of all of our courses via Web-based instruction by summer of 2009. Some courses already offer online lecture content. Courses that offer theoretical background and have no laboratories also will be offered online.

Q Do you believe that the training facility will help create new jobs in North Carolina?

Student checks contents of 300L bioreactor during transfer to harvest tank.

BTEC Bioprocessing Training Associate explains cGMP documentation to a student.

A BTEC training will not only help students and employees fill open jobs, but will create a larger trained workforce that will attract companies with new jobs to North Carolina.

Q How does the facility compare to other training programs and facilities globally?

A The Golden LEAF BTEC facility is the largest of its kind in the world. Very few states or countries would invest the money required to open and operate a training facility of this size. The Golden LEAF Foundation provided funding for the facility and the state of North Carolina is committed to biomanufacturing and provides all the on-going support we need.

BTEC Background

Q Where did the idea for a state training and education center for biomanufacturing originate?

A The North Carolina Biotechnology Center started exploring the concept of a training center in 1996. North Carolina has traditionally been very forward-thinking.

Q How was BTEC funded?

A When some of the funds from the national tobacco settlement became available through the Golden LEAF Foundation, North Carolina State and its partners, the North Carolina Community College System and North Carolina Central University, applied for a grant in July 2003 to initiate the Biomanufacturing and Pharmaceutical Training Consortium (BPTC) capable of providing world-class training and education in biomanufacturing to North Carolinians in every part of the state. The proposal included construction of the BTEC facility, which was eventually re-named the Golden LEAF BTEC. Over the past few years, BTEC received almost $38 million from Golden LEAF to build the facility and another $6 to 7 million from the state of North Carolina to equip and start-up the facility.

Q How was the North Carolina legislature involved?

A The North Carolina legislature has approved recurring funds to support faculty salaries and operational expenses. It believes BTEC is a good investment when it comes to economic development and attracting new employers to the state.

Q How will BTEC engage and support the Biotech Industry?

A BTEC has an active Advisory Board with members from 15 different biomanufacturing companies. The board has provided input throughout construction and curriculum development. BTEC also works with human resource officials and hiring managers to help match graduates to open positions. Lastly, BTEC can provide custom training experiences to individual companies.

Production/ Manufacturing Process

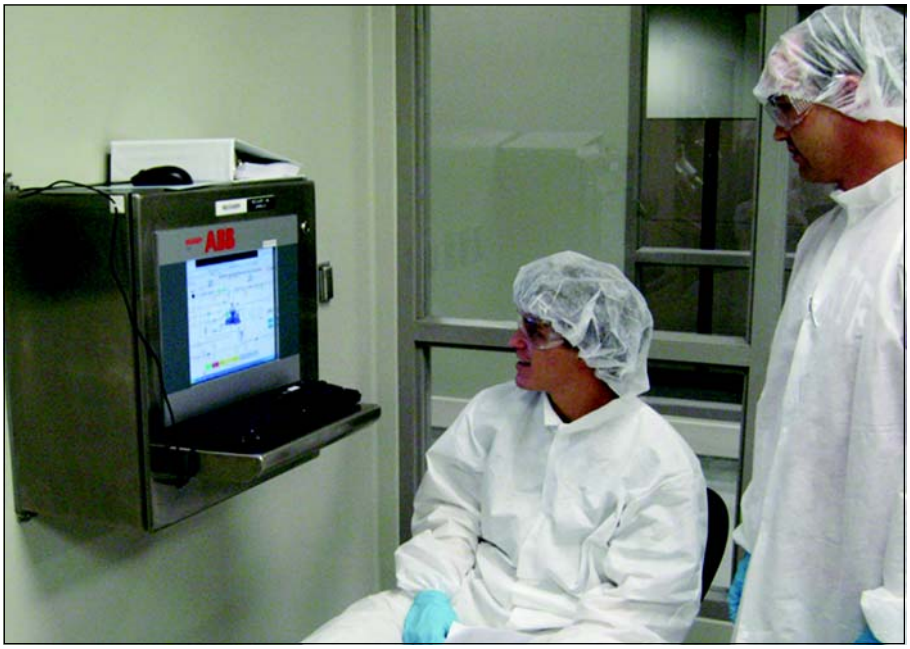
Q How large is the BTEC facility and how is it laid out? What proportion of BTEC is manufacturing area, laboratory, and classroom?

A The Golden LEAF BTEC has just more than 82,000 gross square feet. About 75% of the space is bench, intermediate, and pilot-scale training space. The rest is evenly distributed between classrooms and office space.

Q What types of equipment does BTEC have?

A North Carolina State's pilot-scale bioprocessing area has two large-scale bioreactor trains that terminate in a bioreactor with 300L working volume. All vessels in the trains are piped for CIP and SIP. One train is fully automated with capabilities for monitoring and process control, S88 compliant batch control, Electronic Batch Records, Manufacturing Execution Systems, and PAT.

Recovery operations include equipment for centrifugation, microfiltration, and homogenization. Purification



Two students monitor the automated centrifuge operation.

includes equipment for ultrafiltration/diafiltration, chromatography, viral inactivation, and filtration. The pilot-scale bioprocessing area also has an equipment cleaning area and enough vessels to support media and buffer preparation. Analytical instrumentation is available in all laboratories and in a central analytical testing laboratory for testing all process streams. The NCCCS BioNetwork Capstone Center's aseptic processing suite is capable of providing training on equipment cleaning, depyrogenation, sterilization, filling, lyophilization, and capping.

Q Will you manufacture in this facility? Is the facility designed to be a multi-product facility? If so, will this facility be licensed for product production?

A BTEC is a training facility. Manufacturing clinical or commercial product would not allow us to conduct the hands-on training we want to provide and allow students to learn from their mistakes.

Q If research is being conducted at this facility, what types of research are you envisioning?

A BTEC is a training facility. We will conduct technology development projects at BTEC, as this is a great way to train students to think analytically and solve problems. These development projects may result in some marketable intellectual property.

Q Will the facility follow cGMPs? Was the FDA or other regulatory body involved in the planning process for BTEC? Will the FDA participate in any of the training?

A Courses conducted in the large-scale bioprocessing laboratories will require students to adhere to cleanroom practices, follow SOPs, document their work in batch records, conduct failure investigations, and implement process improvements. Students that take the large-scale courses will be ready to work in the cGMP-regulated industry after they complete the courses.

Our facility and curriculum design teams obtained expert advice on cGMP from industry consultants and staff hired out of industry. As part of a contract to train FDA investigators, the FDA will provide curriculum review and lectures on regulatory topics.

Q Are there any plans for process improvements for this facility?

A Our short-term plan is to purchase equipment at a rate that matches student demand for our courses. As far as process improvements, we will upgrade our equipment contemporaneously with industry. Implementation of disposable technologies is a good example.

Project Management

Q What project management concepts or techniques have you consistently utilized in the construction and expansion projects? In managing this project, what was your biggest challenge?

A A project manager from the North Carolina State Facilities organization worked closely with Skanska, the construction management firm. To accelerate the schedule, the team was able to manage concurrent equipment installation/start-up and facility construction.

The biggest challenge was communication and getting everyone to talk with each other (as in all other projects I've ever been on.)

Future Plans

Q Are there any future plans at North Carolina State for other types of biotechnology facility or training centers?

A BTEC has some unfinished space for future expansion. We are already looking at adding a process development laboratory and a solid dosage/formulation suite.

Q What has ISPE done to support BTEC and other programs in North Carolina?

A ISPE is a partner in the Validation Academy, which teaches its courses in the Golden LEAF BTEC.

Q Are you working with ISPE to help train biotech professionals? Could you tell us about this training?

A We are currently working with ISPE to offer a conference called, "Comprehensive/Hands-on Biotechnology Courses in a Simulated cGMP Pilot Plant Facility," on 12 to 14 May 2008.

Q What do you see as the future of biotechnology in the North Carolina and the US? Do you believe the US biotech manufacturing industry can compete with international or third world companies?

A Unlike computer components and other widgets, the production of drugs, vaccines, and biologics requires a trained workforce. Neglecting tax incentives, cost-of-living, and other macroeconomic criteria, prospective companies prefer locating to an area that already has a large number of experienced employees and can readily produce graduates that can perform on Day 1.

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PAT Study of a Drug Manufacturing Design Space: Effect of Blend Flow Rate and API Level on Homogeneity and NIR Measurements

by Dr. Nicolas Abatzoglou, Jean-Sébastien Simard, and Carlo Benedetti

This article presents the results of a study on two critical process parameters – flow velocity and initial blend API level – through designed experiments in an effort to map part of the process design space for a commercial formulation from a Process Analytical Technology/ Quality by Design perspective.

Introduction

Spending on prescription drugs rose at an average rate of 14.5% in the United States between 1997 and 2002,[1] and while it is expected to slow in the near future, Gross Domestic Product (GDP) or average salary increases will definitely contribute to keeping the growth positive.[2] As prescription drug spending growth slows,[2] drug manufacturers are interested in improving their understanding of processes to enhance efficiency and reduce costs for equal or superior product quality.[3] As the mission of the US Food and Drug Administration (FDA) includes not only ensuring pure, safe, and effective, but also affordable and available medicines, the FDA shares this interest, indicated by some of its publications devoted to increasing production efficiency.[4, 5]

Many techniques and processes can reduce production costs, while augmenting quality through process understanding. The first major push to move from empirical to science-based manufacturing was described by Taylor in 1911 in "*The Principles of Scientific Management.*"[6] Then, in the 1980s, Deming[7] developed his "14 Points of Management," to "create a constancy of purpose toward improvement of products and services with a plan to: a) become competitive, b) create jobs, and c) stay in business." More recently, six sigma (6σ) initiatives employing "define, measure, analyze, improve, control" methodology and statistical techniques, such as Design of Experiments (DoE), have led to considerable progress in many hi-tech industries, such as semiconductors, automobiles, and avionics. This 6σ initiative is similar to quality by design[4, 8] imperatively advanced by the FDA as it emphasizes scientific knowledge and in-process measurements, as opposed to empirical knowledge and end-process measurements to ensure quality.

The present work focuses on the characterization of granular flow process space. It undertakes to identify and understand relationships between critical process parameters by Near Infra-Red (NIR) analyses and chemometric models.

Two different NIR applications (combination of NIR analyzers/sampling optics/PLS models for a specific process) have been used to monitor the NIR spectra of an ibuprofen-based, flowing, non-aerated, cohesive, commercial pharmaceutical powder formulation of 13 components in separate, replicate experimental series. Two different chemometric models have been employed to predict the API level of flowing powders and are presented to show that acceptable and statistically equivalent results can be achieved with different modelling techniques, independently of process analyzers. This is illustrated for the pharmaceutical industry by Fearn's[9] observation that "most NIR problems fall into one of two classes: NIR will work and any one of a dozen calibration methods will give good results, or it will not and no amount of chemometric sophistication will rescue it." There will be no discussion on the "best" model-building approach or on the best process analyzer/sampling optics in our article as both model/analyzer combinations have met their objectives, even though different chemometric techniques and equipments were deployed.

The following steps have been completed and reported in this article:

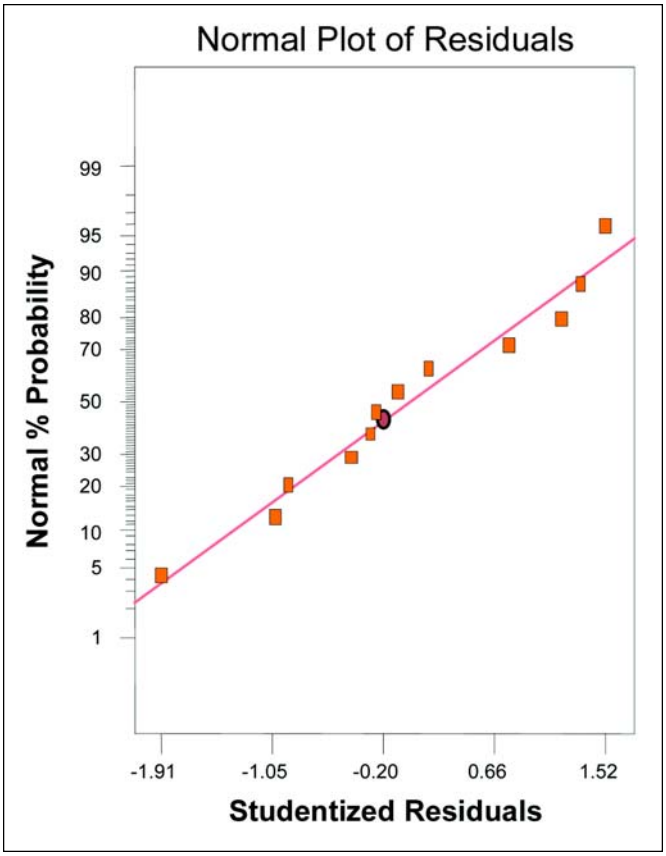

Figure 1. Global design – normal plot of residuals – average model-predicted API response.

- design of two different NIR applications, combining a NIR analyzer, sampling optics, and PLS model for dense, flowing powder API quantification
- monitoring and prediction of flowing powder API level in a cohesive, dense, multi-component pharmaceutical powder blend with the two NIR applications
- process design space mapping with experimental designs

The results from two series of experiments were studied to:

- evaluate the effect of initial blend API level and powder flow rate on average API level predictions
- appraise the influence of initial blend API level and powder flow rate on the Relative Standard Deviation (RSD) of API predictions
- assess the effect of initial blend API level and powder flow rate on the RSD of API predictions averaged to represent one Unit Dose (UD) of product
- gauge the potential of different NIR applications on process responses
- map the average API level predicted design space according to powder flow speed and initial blend API level
- plot the design space of the RSD of predicted API level averaged to represent one UD of product according to powder flow speed and initial blend API level

Theory

The Targeted Pharmaceutical Process

Non-aerated powder flows are frequently encountered in downstream pharmaceutical processes. Perhaps the most universal process operation where such flows occur is at the entrance of a compression unit, which also is the last point where powder inhomogeneity may be detected before blend composition is fixed in a tablet.

In this specific case of pharmaceutical powder flow processes, API level and blend homogeneity are the main variables that must be controlled by solids-processing units. While this may seem simple, it is not an easy task, as shown by the current state of the pharmaceutical industry, where the complexity of segregation phenomena combined with a lack of in-process control are important factors explaining, among others, its relative process inefficiency[10] compared to other industries.

Segregation, by definition, is the biggest challenge to blend homogeneity and quality. Williams[11] defined segregation as "the preference of particles, possessing a similar property, for being at some part of the system." In a blend, segregation may be caused by differences in chemical nature, chemical properties, relative particle sizes, density, and shape. It occurs through the same principal mechanisms as mixing, which also are present during powder flow: diffusion, shear, and convective movements among powders.[12] The forces driving the segregation can be as diverse as gravity, air diffusion, electrostatic, capillary, intra-molecular (Van der

Run	C: NIR application	A: API Level %	B: Flow Rate kg/min / lb/min	Average Model-predicted %	SD intra-dose	RSD intra-dose	SD 1 UD	RSD 1 UD 1 UD
1	Application 1	75.00	1.50 / 3.30	65.94	5.50	0.08	3.17	0.05
2	Application 1	75.00	2.80 / 6.16	69.47	5.10	0.07	2.90	0.04
3	Application 1	100.00	2.00 / 4.40	92.81	6.00	0.07	1.49	0.02
4	Application 1	100.00	2.00 / 4.40	95.44	5.80	0.06	2.16	0.02
5	Application 1	125.00	1.50 / 3.30	123.87	6.60	0.05	2.56	0.02
6	Application 1	125.00	2.80 / 6.16	127.62	5.80	0.04	3.09	0.02
7	Application 2	75.00	1.50 / 3.30	77.71	4.78	0.06	1.22	0.02
8	Application 2	75.00	2.80 / 6.16	78.39	2.51	0.03	1.65	0.02
9	Application 2	100.00	2.00 / 4.40	100.85	5.61	0.06	2.46	0.02
10	Application 2	100.00	2.00 / 4.40	97.09	3.69	0.04	1.62	0.02
11	Application 2	125.00	1.50 / 3.30	123.18	4.09	0.03	1.20	0.01
12	Application 2	125.00	2.80 / 6.16	124.48	4.76	0.04	4.26	0.03

API – Active Pharmaceutical Ingredient
NIR – Near Infra-Red
RSD – Relative Standard Deviation
SD – Standard Deviation
UD – Unit Dose

Table A. Global experimental design.

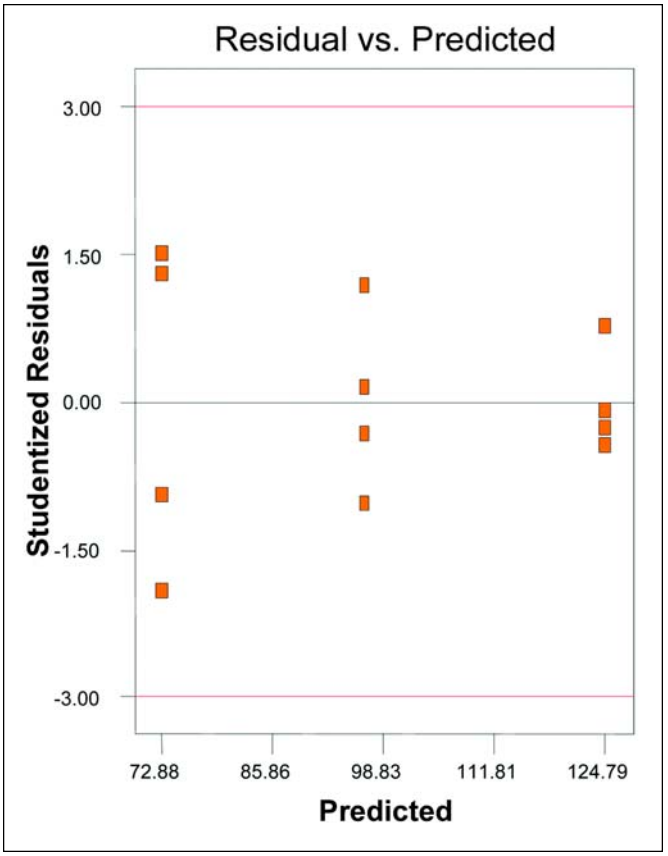

Figure 2. Global design – residuals vs. predicted – average model-predicted API response.

Waals), and friction.[13, 14] The fact that such forces can develop spontaneously, and their extent depends on process conditions, such as humidity and temperature, or through mechanisms present in powder flow of pharmaceutical formulations composed of heterogeneous components, makes a certain degree of segregation inevitable during powder processing.

Even so, there are means to ensure consistent blend homogeneity. In current processes, this is often achieved through the use of cohesive granular blends or powders. While such powders are more difficult to blend and they are less subject to segregation,[14] their behavior is more difficult to predict than that of free-flowing powders. Nevertheless, such particulate systems are frequently implemented in the pharmaceutical industry.

While in-line powder flow process monitoring could help to acquire insights into segregation phenomena to increase productivity and achieve better Quality Control (QC) and Quality Assurance (QA), hinted by FDA stratified sampling guidance,[5] it is rarely performed in the industry. Some reasons are related to the lack of quick, non-invasive, and proper sampling methods, and the fact that flowing powder blends can be extremely complex and are generally not well-understood.[15, 16] For example, the rheological properties of granular systems cannot be fully predicted, as attested by the in-process occurrence of stable arches, convection under vibration, and cluster formation during fluidization.[17]

Many researchers have tried to develop an understanding of factors affecting the performance of solids-processing units. Hutter and Rajagopal[18] found that many flow complexities come from the effect of various boundary conditions, the influence of local structure formation, and the role of interstitial fluid. Wibowo[19] published a detailed review on the performance of solids-processing units as a function of bulk mechanical properties and forces acting on the blend, these two factors being a function of granular material characteristics (i.e., Young modulus, dielectric constant, Hamaker constant), particle attributes (i.e., shape, shape distribution, composition, porosity), equipment design (i.e., geometry, constituent parts, material properties), and operating conditions (i.e., speed, temperature, humidity).

As the performance of a powder flow process is a function of both its chemical and physical properties, the introduction of a tool capable of simultaneously measuring such parameters could lead to significant and appropriate knowledge of process behavior.

NIR Technology

NIR technology is fast, often non-invasive, non-destructive, stable, reliable, precise, accurate, clean, and in general, a suitable analytical method for plant environments. Broad and Moffat[20, 21] have shown that chemometrics can yield important information on the suitability and applicability of NIR in analyzing particulate material. Indeed, the NIR signal is affected by both the chemical composition (all C-H, O-H, N-H, C=C, C=O bonds) and physical characteristics of samples, namely, size, aeration/porosity/density, humidity,

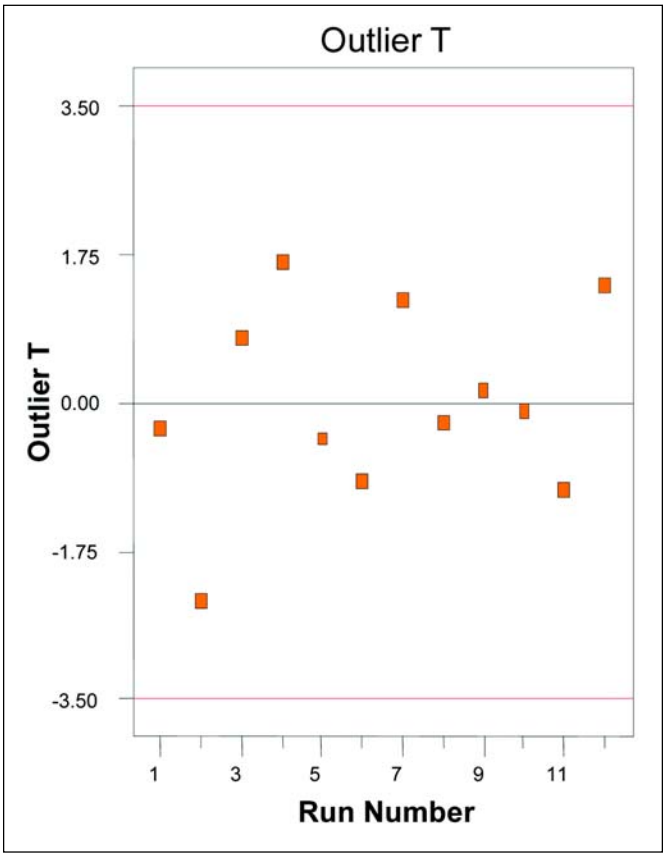

Figure 3. Global design – outlier vs. run – average model-predicted API response.

Response: Average Model-Predicted API level						
Source	**Sum of Squares**	**DF**	**Mean Square**	**F Value**	**Prob > F**	
Model	5,403.23	2	2,701.62	152.86	< 0.0001	significant
A (blend API level)	5,403.23	2	2,701.62	152.86	< 0.0001	
Residual	159.06	9	17.67			
Lack of Fit	152.01	8	19.00	2.70	0.4407	not significant
Pure Error	7.05	1	7.05			
Corresponding Total	5,562.29	11				
Response: RSD of Individual Non-Averaged API Predictions						
Source	**Sum of Squares**	**DF**	**Mean Square**	**F Value**	**Prob > F**	
Model	2.084E-03	3	6.945E-04	6.18	0.0177	significant
A (blend API level)	8.364E-04	2	4.182E-04	3.72	0.0721	
C (NIR application)	1.247E-03	1	1.247E-03	11.09	0.0104	
Residual	8.996E-04	8	1.125E-04			
Lack of Fit	7.445E-04	7	1.064E-04	0.69	0.7337	not significant
Pure Error	1.552E-04	1	1.552E-04			
Corresponding Total	2.983E-03	11				
Response: RSD of API Predictions Averaged to Represent 1 UD						
Source	**Sum of Squares**	**DF**	**Mean Square**	**F Value**	**Prob > F**	
Model	9.013E-04	5	1.803E-04	2.12	0.1939	not significant
A (blend API level)	2.648E-04	2	1.324E-04	1.55	0.2857	
B (powder flow rate)	3.686E-04	2	1.843E-04	2.16	0.1960	
C (NIR application)	2.236E-04	1	2.236E-04	2.63	0.1562	
Residual	5.108E-04	6	8.514E-05			
Lack of Fit	4.815E-04	6	9.630E-04	3.28	0.3952	not significant
Pure Error	2.933E-05	2	2.933E-05			
Corresponding Total	1.412E-03	11				

ANOVA – Analysis of Variance; DF – Degree of Freedom; NIR – Near Infra-Red; UD – Unit Dose
API – Active Pharmaceutical Ingredient; Prob > F, F-test result; RSD – Relative Standard Deviation

Table B. ANOVA case #1 (global DoE).

and morphology.[22, 23] This renders NIR of particular interest to monitor solids-processing units. The technology was shown to be applicable in predicting the API level of flowing powder blends at varying flow speeds.[24] However, the cohesive flowing powder process design space was not mapped to estimate the effect of powder flow speed and initial blend API level on the process.

Moreover, from a Process Analytical Technology (PAT) perspective, the number of possible combinations of chemometric models/NIR analyzers/sampling optics, which may be applied to map the design space of pharmaceutical processes, may become a crucial hurdle in the endeavor to implement the technique in pharmaceutical production environments. While Madan et al.[25] established that, for in-line liquids API-monitoring, different predictive models applied to spectroscopic data gave statistically similar results, the effect of PLS model/sampling optics/NIR analyzer on process design space mapping for dense, flowing powder processes has not been investigated.

DoE and Chemometrics

Analysis of Variance (ANOVA)

Our protocol optimized the number of experiments required to map design space. ANOVA was performed to evaluate if the effects of the studied parameters and their interactions on process responses were statistically significant.

Experimental

Materials

The Active Pharmaceutical Ingredient (API) was ibuprofen (Eurand, Vandalia, OH), representing roughly 15% w/w of a proprietary formulation. Mannitol (SPI Pharma, New Castle, DE) was chosen to balance the active ingredient mass change during model building and runs since it was the main excipient and accounted for roughly 70% w/w of the standard formulation. Eleven other excipients were added and blended according to a scale down of the official manufacturing batch record.

Experimental Design

A fully-replicated, full factorial experimental design (Table A) was chosen as it provided the highest resolution to separate statistical effects calculated by ANOVA.

The studied parameters were:

- initial blend API level (A)
- powder flow rate (B)
- NIR application (C)

The monitored responses were:

- average API level predicted
- RSD of API predictions
- RSD of API predictions averaged to represent approximately one UD

ANOVA was undertaken with Design Expert, version 6.0.9 (Stat-Ease, Minneapolis, MN).

Batch Preparation for Experimental Series

The blends were prepared according to the test design plan shown in Table A. Each experimental series is reported there

Response: Average Model-Predicted API level						
Source	**Sum of Squares**	**DF**	**Mean Square**	**F Value**	**Prob > F**	
Model	3,368.64	1	3,368.64	523.62	< 0.0001	significant
A (blend API level)	3,368.64	1	3,368.64	523.62	< 0.0001	
Residual	25.73	4	6.43			
Lack of Fit	22.28	3	7.43	2.15	0.4561	not significant
Pure Error	3.46	1	3.46			
Corresponding Total	3,394.38	5				
Response: RSD of Individual Non-Averaged API Predictions						
Source	**Sum of Squares**	**DF**	**Mean Square**	**F Value**	**Prob > F**	
Model	9.568E-04	2	4.784E-04	97.53	0.0019	significant
A (blend API level)	8.703E-04	1	8.703E-04	177.42	0.0009	
B (powder flow rate)	8.653E-05	1	8.653E-05	17.64	0.0246	
Residual	1.472E-05	3	4.905E-06			
Lack of Fit	6.715E-06	2	3.358E-06	0.42	0.7373	not significant
Pure Error	8.000E-06	1	8.000E-06			
Corresponding Total	9.715E-04	5				
Response: RSD of API Predictions Averaged to Represent 1 UD						
Source	**Sum of Squares**	**DF**	**Mean Square**	**F Value**	**Prob > F**	
Model	5.071E-04	1	5.071E-04	6.24	0.0669	not significant
A (blend API level)	5.071E-04	1	5.071E-04	6.24	0.0669	
Residual	3.251E-04	4	8.128E-05			
Lack of Fit	3.037E-04	3	1.012E-04	4.73	0.3232	not significant
Pure Error	2.142E-05	1	2.142E-05			
Corresponding Total	8.322E-04	5				

ANOVA – Analysis of Variance; DF – Degree of Freedom; NIR – Near Infra-Red; UD – Unit Dose
API – Active Pharmaceutical Ingredient; Prob > F, F-test result; RSD – Relative Standard Deviation

Table C. ANOVA case #2-1 (first application).

as a factor. For each factor, three 16kg batches of an ibuprofen-based, 13 component, direct-compression, commercial formulation were prepared. Each of the three batches possessed a different theoretical active ingredient level (75, 100, or 125% w/w of the nominal active ingredient concentration in the commercial formulation) and was split in two 8kg (17.6 lb) batches. Each 8kg batch was used for one run and discarded.

Instrumentation

The experiments were conducted in a stainless steel bench-scale tablet press hopper, which was modified for in-line powder measurements.[24]

The NIR analyzers were:

1. an Axsun IntegraSpec XLP 410 NIR analyzer (Axsun Technologies, Billerica, MA) fitted with a 13mm (0.5 inch) diameter effective measurement Axsun NIR diffuse reflectance probe

2. an ABB-Bomem FTPA2000-260 NIR analyzer (ABB-Bomem Inc., Quebec City, Quebec, Canada) fitted with a 2mm (0.08 inch) diameter effective measurement ABB-Bomem NIR diffuse reflectance probe

Uniform NIR powder penetration of 1 mm (0.04 inch) over the spectral range was considered as following the manufacturer's recommendations.

PLS Models

Two separate models were built for each of the experimental series, using a different procedure:

1. Spectra were pretreated by standard normal variate correction[26] and a Savitsky-Golay first derivative smoothing filter[27] with 31 data points to remove baseline offsets before applying the PLS algorithm (Matlab v7.04 with PLS Toolbox): Model R^2 of 0.991 (Model #1).

2. Spectra were pretreated by a Savitsky-Golay second derivative smoothing filter with 15 data points to remove baseline offsets. Multiplicative scatter correction was then applied to remove optical path differences before the PLS algorithm (Grams/AI PLSIQ, version 7.0): Model R^2 of 0.984 (Model #2).

Both models were designed for the same seven laboratory-prepared samples of API levels: 50%, 75%, 90%, 100%, 110%, 125%, and 150%. The samples were processed according to the methodology described previously.[24]

In addition, three other samples of 75%, 100%, and 125% API levels were included during development of the second model. The objective was not to determine which analyzer and/or model was the most efficient, but to demonstrate that similar results could be obtained with different combinations of NIR analyzers, sampling optics, and chemometrics.

Procedure

Flowing powder tests were conducted under the following experimental protocol:

1. The NIR system was started and sufficient time allowed for source stabilization.
2. The butterfly valve was closed.
3. The powder batch was loaded into the hopper by pouring it from a bag, while maintaining a light vacuum near the bag outlet.

4. Powder compaction homogeneity was checked visually through the viewport (by the same technician to avoid the bias of visual inspection).
5. NIR data collection was started and static powder spectra were stored in the computer.
6. A light vacuum was maintained near the powder collection bag to ensure negative pressure during powder flow.
7. The butterfly valve was opened to the desired setting: gravity powder flow was started and the collection of NIR spectra continued.
8. NIR data collection was stopped when the hopper was empty.

Results

The influence and interaction of the three chosen parameters on the process responses were evaluated by ANOVA of the designed experiments. The experimental series were first considered as part of the same experimental design since they were conducted with the same formulation and under identical flow dynamics. Their variance was analyzed as such. Then, the experimental series were studied as separate, full factorial experimental designs where the NIR application parameter was not considered.

In both cases, three process responses were monitored:

- Response #1: Average model-predicted API level
- Response #2: RSD of individual API predictions
- Response #3: RSD of API predictions averaged to represent one UD of product

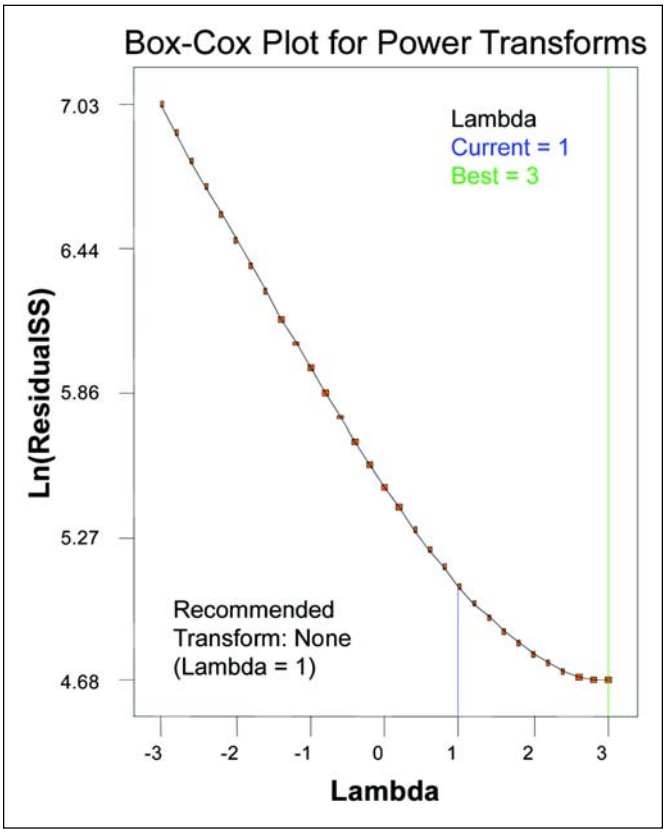

Figure 4. Global design – Box-Cox plot – average model-predicted API response.

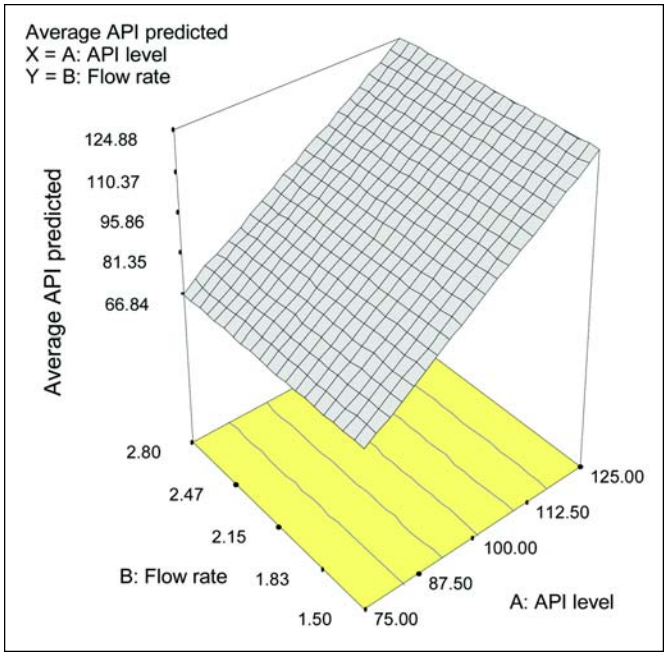

Figure 5. Case 2-1 – design space surface plot – average model-predicted API response.

Average model-predicted API was selected to verify API level predicted at the sampling point, while RSD was studied as an indicator of blend homogeneity variation at the sampling point. RSD is often used in the pharmaceutical industry as performance metrics, especially for UD and blend uniformity measurements.

RSD was calculated from process data as:

$$RSD = \frac{Std.\ Deviation}{Average} \times 100\%$$

RSD was averaged to give an indicator of blend homogeneity at the sampling point for one UD of product as this performance metric is commonly employed in QA assessments. NIR spectra were averaged according to flow rate and powder density to represent one UD of product according to the method described by Benedetti et al.[24]

Table E presents a summary of significant parameters for each case.

Case #1: Both Experimental Series as Factors of the Same Experimental Design

The data reported in Table B show that the ANOVA model was significant for the average (PLS) model-predicted API level response and the RSD of individual non-averaged API prediction responses. The ANOVA model was not significant for the RSD of API predictions averaged to represent one UD of product. Figures 1 through 4 demonstrate that this ANOVA model satisfies the assumptions of variance analysis.

In the case of RSD of individual non-averaged API predictions, NIR application was the only significant parameter. Diagnostic plots (not shown for brevity) revealed that the ANOVA model satisfied the assumptions of variance analysis.

Response: Average Model-Predicted API level						
Source	**Sum of Squares**	**DF**	**Mean Square**	**F Value**	**Prob > F**	
Model	2,095.82	1	2,095.82	629.80	< 0.0001	significant
A (blend API level)	2,095.82	1	2,095.82	629.80	< 0.0001	
Residual	13.31	4	3.33			
Lack of Fit	6.26	3	2.09	0.30	0.8366	not significant
Pure Error	7.05	1	7.05			
Corresponding Total	2,109.13	5				
Response: RSD of Individual Non-Averaged API Predictions						
Source	**Sum of Squares**	**DF**	**Mean Square**	**F Value**	**Prob > F**	
Model	2.884E-04	2	1.442E-04	0.91	0.4919	not significant
A (blend API level)	1.212E-04	1	1.212E-04	0.76	0.4464	
B (powder flow rate)	1.672E-04	1	1.672E-04	1.05	0.3802	
Residual	4.761E-04	3	1.587E-04			
Lack of Fit	3.210E-04	2	1.605E-04	1.03	0.5709	not significant
Pure Error	1.552E-04	1	1.552E-04			
Corresponding Total	7.646E-04	5				
Response: RSD of API Predictions Averaged to Represent 1 UD						
Source	**Sum of Squares**	**DF**	**Mean Square**	**F Value**	**Prob > F**	
Model	2.167E-04	1	2.167E-04	6.21	0.0673	not significant
B (powder flow rate)	2.167E-04	1	2.167E-04	6.21	0.0673	
Residual	1.396E-04	4	3.490E-05			
Lack of Fit	1.103E-04	3	3.675E-05	1.25	0.5625	not significant
Pure Error	2.933E-05	1	2.933E-05			
Corresponding Total	3.563E-04	5				

ANOVA – Analysis of Variance; DF – Degree of Freedom; NIR – Near Infra-Red; UD – Unit Dose
API – Active Pharmaceutical Ingredient; Prob > F, F-test result; RSD – Relative Standard Deviation

Table D. ANOVA case #2-2 (second application).

Finally, the data reported in Table B indicate that there were no significant ANOVA model terms for the RSD of API predictions averaged to represent one UD of product. Diagnostic plots (not included for brevity) demonstrated that the ANOVA model satisfied the assumptions of variance analysis.

Case #2-1: DoE Applied Only on the First Experimental Series

Average Model-Predicted API Level

The data reported in Table C and Figure 5 show that the ANOVA model was significant for the average (PLS) model-predicted API level response and the RSD of non-averaged API prediction responses. The ANOVA model was not significant for the RSD of API predictions averaged to represent one UD of product.

In the case of the model-predicted API level response, initial API level in the blend was the only significant parameter. Diagnostic plots (not included for brevity) demonstrated that the ANOVA model satisfied the assumptions of variance analysis.

In the case of RSD of individual non-averaged API predictions, NIR application was the only significant parameter. Diagnostic plots (not presented for brevity) established that the ANOVA model satisfied the assumptions of variance analysis.

Finally, the data reported in Table C show that there were no significant ANOVA model terms for the RSD of API predictions averaged to represent one UD of product. The diagnostic plots (not included for brevity) indicated that the ANOVA model satisfied the assumptions of variance analysis.

Case #2-2: DoE Applied Only on the Second Experimental Series

The data reported in Table D and Figure 6 show that the ANOVA model was significant for the average (PLS) model-predicted API level response. The ANOVA model was not significant for the RSD of non-averaged API prediction responses and the RSD of API predictions averaged to represent one UD of product.

In the case of model-predicted API level, the initial API level in the blend was the only significant parameter. Diagnostic plots (not presented for brevity) demonstrated that the ANOVA model satisfied the assumptions of variance analysis with the exception of the outlier T plot where one outlier was identified (run #10). No special cause was found to explain the outlier, and the point was kept in the dataset for analysis.

Finally, the data reported in Table D reveal that there were no significant ANOVA model terms for the RSD of non-averaged API prediction responses and the RSD of API predictions averaged to represent one UD of product. Diagnostic plots (not shown) substantiated that the ANOVA model satisfied the assumptions of variance analysis.

Discussion

Case #1: Both Experimental Series as Factors of the Same Experimental Design

Preliminary Evaluation

Table B, Table C, and Table A illustrate that the average model-predicted response of the first experimental series was slightly less accurate – when theoretical batch composition was considered – than that of the second series. Moreover, rough comparison of the RSD for individual spectrum showed that the latter was slightly higher in the first than in the

Significant Factors, by response and case	Case #1 (Applications #1 and #2 in same DoE)	Case #2-1 (Application #1 DoE)	Case #2-2 (Application #2 DoE)
Average prediction	A	A	A
RSD of independent predictions	C	A, B	---
RSD of predictions averaged to represent 1 UD	---	---	---

Table E. Summary of significant factors for each response.

second experimental series. There does not seem to be any difference between the two series for RSD averaged to represent one UD of product (referred to as the one averaged RSD). However, these qualitative observations may be caused by random error, and their variance must be analyzed for confirmation. An F-test on the design revealed no significant differences between the average model-predicted and averaged RSD for each experimental series. However, a significant difference was apparent between the RSD of individual spectrum for each NIR application.

These seemingly contradictory results can be explained by the different sampling time and optics of the two applications. They indicate that the average of the predictions - and their RSD – over the length of the batch does not differ, whereas the RSD of individual predictions does differ since individual predictions by the different applications do not necessarily measure the same sample mass for reasons mainly related to flow uniformity over a short time period, such as the duration of each NIR measurement.

Significant Factors

Variance analysis revealed that the average API level predicted and the RSD of individual predictions were both affected by initial API level in the blend, while the RSD averaged for one UD was not affected by any DoE factor. These results were satisfactory, as we expected the average model-predicted API level to have a linear relationship with initial API level in the blend and would prefer the method error to be independent of API level.

Case #2: Comparison of the Experimental Series Analyzed as Separate DoE

Significant Factors

The two independent DoEs confirmed that initial blend API level was the only factor affecting the average model-predicted API level. Both initial API level and flow rate affected the non-averaged RSD of application #1, whereas they did not affect the non-averaged RSD of application #2. This is the source of the significant effect of the "NIR application" factor on the response detected in case #1. Moreover, initial API level may have affected the averaged RSD in Application #1. This could not be demonstrated statistically, but the "Prob > F" of 0.067 was very close to the acceptance criteria of 0.050.

However, when the good Model R^2 was considered because of the high statistical resolution of the experimental design and the fact that this factor was not significant by the joint

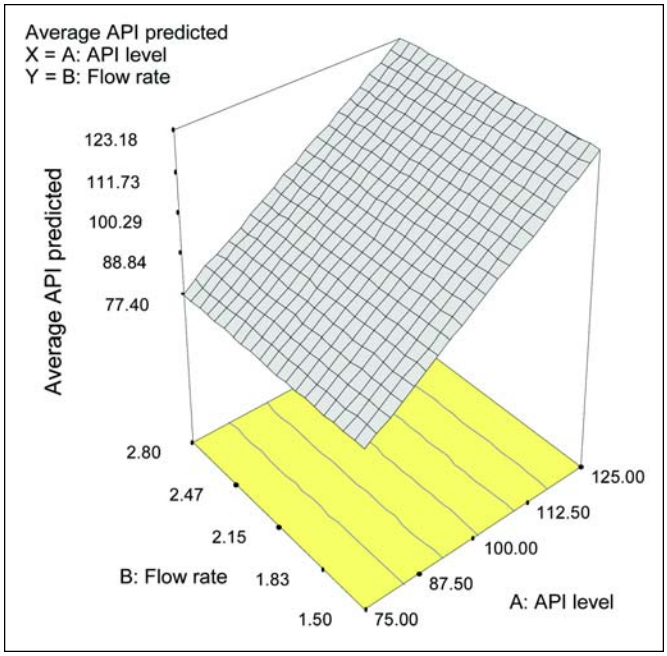

Figure 6. Case 2-2 – design space surface plot – average model-predicted API response.

experimental design, it was still deemed non-significant.

Model Differences

Application #1 had a larger sample size and required less spectral averaging than Application #2. This was linked to a higher RSD on individual spectrum, which indicated that it was more sensitive to powder changes than Application #2, and its RSD was affected by more factors. Model #1 R^2 was also better than that of Model #2, but was not supposed to have any statistically significant effect on the average prediction. A statistical outlier was detected when the second experimental series was analyzed independently, but no special cause was attributable to this effect.

Conclusion

Understanding the critical parameters affecting pharmaceutical processes is essential to justify the changes aimed at their optimization. In this research, part of the flowing ibuprofen formulation process design space was mapped, using NIR analyzers, different sampling optics and chemometric models allowing fast and efficient in-line data collection during granular cohesive flow. In all studied cases, initial blend API level was the only significant factor affecting the average model-predicted API level. The RSD of spectra averaged to represent one UD of product was not affected by either the initial blend API level or flow rate. However, the RSD of individual, unaveraged spectrum was found to be affected by sampling optics/chemometrics, and care should be taken when analyzing these metrics as an application performance indicator. No segregation was observed during the flow of different API level blends.

The two PLS models yielded comparable results, confirming that there is often more than one way to properly translate NIR spectra into meaningful and statistically significant

information through chemometrics. Both NIR analyzers were able to monitor flowing powders, and more importantly, the methods were found to be statistically similar in regard to the average API level predicted during each run.

The short-term application of these results for the pharmaceutical industry would be as a tool to streamline process development or in-line real time quality assessment during routine manufacturing. The experimental data on segregation and flow patterns of powders under controlled conditions collected by the analyzer could eventually complement data acquired by Jenike shear cells or other granular system characterization methods (i.e., powder rheology measurement equipments) to validate theoretical models and/or computer simulations of granular flow phenomena. Finally, designed experiments studying the impact of other parameters on flow behavior could be used to further map this process design space.

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Good Design Practices for Pharmaceutical Manufacturing Facilities: Chapter 21 Support Laboratories

by Terry Jacobs

Introduction

Research and Development Laboratories are the engines for the pharmaceutical industry; they are where basic research is conducted, compounds are developed, and initial chemical supplies are produced for testing. In a pharmaceutical manufacturing facility, support laboratories are required for testing of the product, and are typical referred to as Quality Control (QC) laboratories or Quality Assurance (QA) laboratories. These support the manufacturing operations. Both types have similarities and differences.

The laboratory environment is a place where creative and practical work is conducted. Functional and safety concerns of importance to both the employee and the product. The design of the laboratory environment must take into account the specific needs of this environment, anticipate what changes must occur in the future, and in the end, create a work environment that is conducive to supporting the facility's mission.

Laboratories are high-energy users, and expensive to build. The energy costs of a typical laboratory with 100% outside air can be five times that of a normal laboratory. QA laboratories may have recirculated air, or may be 100% exhausted.

The laboratory is a strategic tool for the pharmaceutical company, and it is an expensive environment to create. This chapter discusses how to program and design a pharmaceutical support laboratory and to identify the key issues in this process for both new facilities and the renovation of existing facilities.

Key Concepts and Principles

Key Concepts and principles in designing a laboratory are:

- establishing a laboratory module
- understand the equipment used in a (QC) Laboratory
- creating a "lab" card
- understanding linear feet of bench required
- determining whether to use 100% outside air or recirculated air
- lab flexibility
- open versus discrete laboratories
- compliance issues
- location of office/write-up space

Programming the Laboratory Facility

This is the program seeking phase where the criteria for the design is identified. In the design process it is critical to differentiate between problem seeking (programming) and problem solving (design).

The reason this is important is that there is a natural tendency to begin to solve problems

Figure 1. Design process.

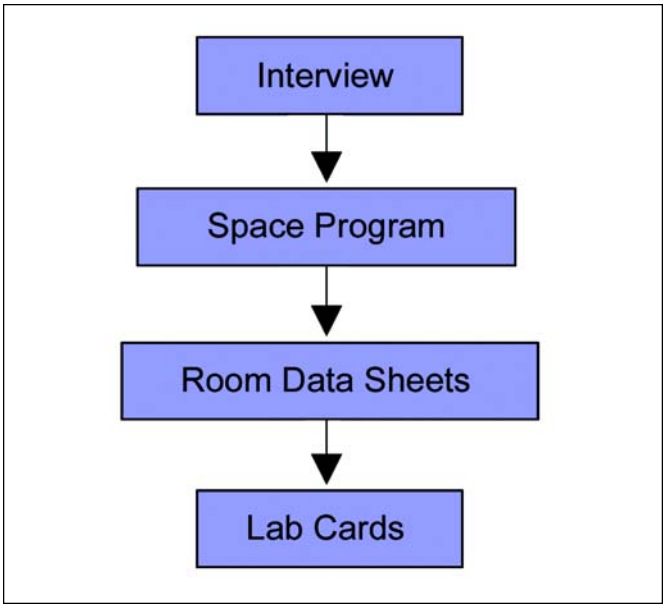

Figure 2. Steps involved in the development of a typical program document.

(design) before the design problem (criteria) is defined. The programming phase is where the "problem solving" should be identified.

The programming of the facility starts with the mission statement for the project. The mission statement will identify the need for the project, and will help you understand what the business and functional drivers are for the project. Examples would include how much flexibility are you trying to design into your facility or upgrading of existing facilities.

Information Gathering: Defining the Users' Needs

The key to information gathering is communication and documentation. The programmer will interview the user to define their needs, to identify what functions are occurring in their laboratory, and to understand the inter-relationship between their laboratory and other spaces. A "user survey form" is a useful tool to initiate this process.

Figure 2 indicates the steps involved in the development of a typical program document.

The following discussion describes and gives examples of the steps presented in Figure 2.

Interview Phase

The interview phase is where the key users are interviewed to define their needs. Issuing questionnaires before interviews to fill out is an effective methodology for obtaining information. The scientists and technicians are typically busy and you have to be the editor for the information and assist them in completing this information. The user should provide an equipment list of all the present and anticipate equipment to be utilized.

Typically the following is an example of a typical equipment list for a quality control laboratory. Remember: It is important to gather an equipment list early in the design process.

Space Program

The space program is a matrix of the required spaces, sizes, and adjacencies, and their projected growth. It is the first step in the programming phase and will establish the first indication of the size of the facility. The space program can be expanded to contain information of lab services, adjacencies, fume hoods, and so forth.

A typical QC Laboratory will be comprised of the primary laboratory space and support spaces, which include office space, stability rooms, chemical storage rooms, glass wash, and amenities such as a break room.

In establishing a space program for a laboratory, a laboratory-planning module must be established which will become the planning basis for the facility.

Laboratory Planning Module

The laboratory planning module is the space allocated for each scientist and technician in a facility and should provide a standard amount of space for a typical user. To understand how to generate a laboratory module, it is important to understand how laboratory casework is designed and functions. Casework may be *fixed* or *flexible*. The following diagram is a section cut through a typical fired laboratory bench.

The standard distance between centerline of benches ranges from 10 foot to 11 foot. This space is set by the amount of space needed for two people to work back to back. The standard fume hood is deeper (i.e., 36 inches) and in a 10 foot module will be tight if placed back to back.

Key Concept: Allow for door widths greater than 36 inches wide in rooms that contain fume hoods; otherwise, the fume hood will not fit through the door!

Based on the selection of a planning module of 10 feet to 11 feet, we next will develop a plan for a generic lab module, which will have bench space and office space for the users.

Figure 3. High Pressure Liquid Chromatography (HPLC). This is used for testing and required bench top space or racking.

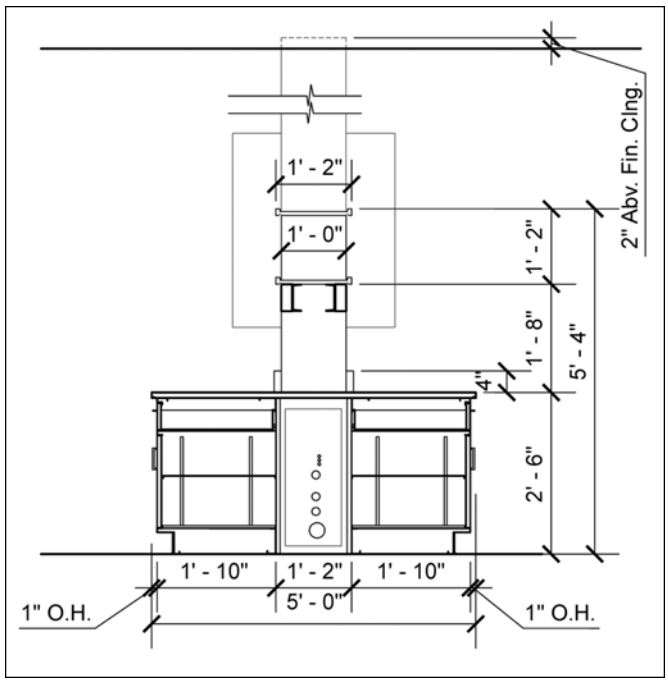

Figure 4. Cross-section of a fixed laboratory bench.

The users will define the Equivalent Linear Feet (ELF) of bench required for each person, and the size and relationship of the office space required.

Rules of thumb indicate that a bench should be no longer than approximately 16 feet. A module is for planning purposes only; the decision to have an "open lab" vs. enclosed rooms may be made at a later date. The result of this exercise is a selection of a planning module for programming.

In addition to the required bench and fume hood spaces, space for equipment and services are required, which can be programmed into the module on a separate space.

Summary of Space Program

The space program will summarize the total personnel and the total Net Square Feet (NSF) for instance:

Total Personnel:	235
Total NSF:	47,000 SF
Total NSF per person:	200 SF

Based on the NSF, a grossing factor which includes walls and circulation can be utilized to determine the range of sizes of this facility. For a laboratory this factor ranges from 50% to 65%. The calculation is as follows:

$$GSF = \frac{47{,}000}{.5} = 94{,}000 \text{ GSF}$$

Where GSF is gross square feet. For example, for a facility that is 50% efficient, the total gross square feet of the facility would be:

$$GSF = \frac{NSF}{\text{Efficiency Factor}}$$

Key Concept: From the GSF we can apply a range of construction costs to determine an initial construction cost. The gross square footage is the actual size of the building or renovated area when complete. A common mistake is not to use the correct grossing factor. If the space is 30% efficient, I will just add 30% to the net square feet. This is wrong!

Compliance Analysis

As part of the initial programming or Basis of Design Phase (BOD), a compliance analysis of the local and national codes needs to be conducted. Laboratories are potentially hazardous workplaces, that use varies solvents and other flammable materials. There also is an increasing trend to use potent compounds, and this will impact the facility design.

An outline of the relevant codes are as follows:

- International Building Code
- Boca Code
- Local Code Supplements
- The National Codes incorporate by reference other codes such as: National Fire Protection Agency (NFPA) 45 and NFPA 30
- Good Laboratory Practices (GLPs)

Refer to Chapter 15 for complete code information.

Key Concept: In designing labs to meet the code, remember:

- Understand the quantity of solvents/hazardous materials being used. The Code allows for control zones, which govern the amounts of hazardous materials writing an area. This is a critical key concept.
- Understand if 100% outside air versus recirculated air is a requirement. The code will make recommendations for this. Most research and development laboratories are 100% outside air. Many quality control laboratories allow for recirculated air. This needs to be discussed with your safety personnel and laboratory director, as well as the design firm.
- Most laboratories are designed as "B" business use.
- Pressure requirements for containment must be taken into consideration. Most laboratories of their nature are designed for negative pressure.

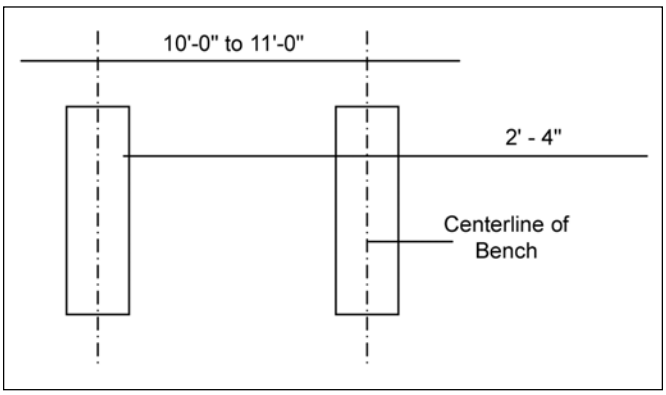

Figure 5. Planning module.

Details/Implications for Performance

Designing the Laboratory Creating a "Lab Module" for Planning Purposes

From the programming phase, a laboratory planning module has been established. From the laboratory module, you can begin to organize the laboratory and the concept; i.e., the concept discrete laboratories or open laboratories. There is a trend (actually, in some companies it is a requirement) to have the office space or write-up space for the technicians and the supervisors located elsewhere not in the laboratory space.

A discrete lab module is typically a 20 x 30 foot dimensions that has walls on all sides. In *open laboratories,* walls are eliminated to allow for flexibility and interaction and for sharing of equipment. Except for code issues, there is no limitation on the size of control zones or for the size of open laboratories. The number of control zones is regulated by floor. The control zone determines the quantities of solvents and hazardous materials that may be present.

No.	Equipment Name	Services Required	Electrical Requirements	UPS Power
001	HPLC	He		
002	HPLC Computer			•
003	HPLC Printer			•
004	Atomic Absorption	CA, Acetylene, N_2O	110v	
005	Dissolution Baths			•
006	FTIR	N_2, Jug Dour, Liquid N_2	110v	•
007	TOC Analyzers			•
008	Milli-Q	DI		
009	UV VIS			•
010	UV VIS Computer			•
011	UV VIS Printer			•
012	Multi-Dose			•
013	Culter Counter		110v	•
014	Light Cabinet			
015	Gas Chromotographs	N_2 Compressed Air	220v	•
016	Gas Chromotographs Computers			•
017	Centrifuge			
018	TPW Table		220v	•
019	Moisture Analyzer			•
020	Nitrogen Generator			•
021	Refrigerator/Freezer		110v	
022	Ovens			
023	Balance Tables			
024	Solvent Storage Cabinets			
025	Book Shelves			
026	Bio-Safety Cabinet			
027	Fume Hood, 12'-0"			
028	Fume Hood, 10'-0"			
029	Fume Hood, 8'-0"			
030	Sink	HCW, DI, EW	480v, 60Hz, 3Ø, 30A	
031	Glassware Washer	HCW, DI, CA	480v, 60Hz, 3Ø, 30A	
032	Glassware Washer	HCW, DI, CA	208v, 60Hz, 3Ø, 22A	
033	Glassware Dryer			
034	Balance Slab			

Table A. A typical equipment list for a quality control laboratory. An Equipment list is a basic first step.

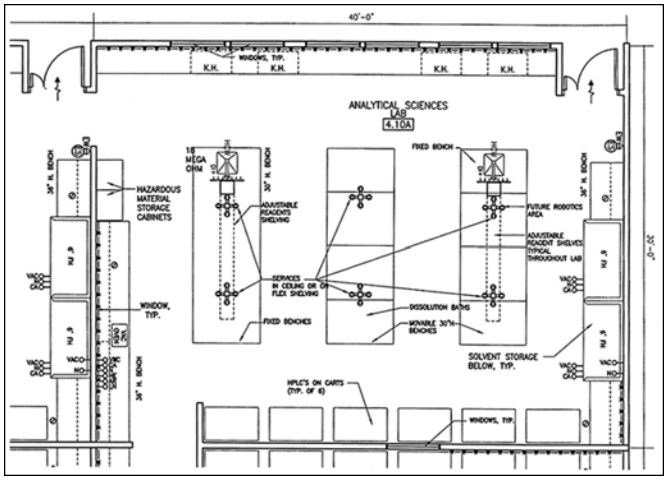

Figure 6. Discrete lab concept.

Key Concept: Consider what degree of flexibility is desired in the laboratory. This effects the selection of casework and design. For complete flexibility, all the services may be located in the ceiling, with casework on wheels. This is the latest trend in laboratory design.

Movable casework may not be required in QC laboratories where the functions are set up for a period of time which meet the user's needs. There is a range of casework choices that can meet the user's needs and budget.

Casework Options

Casework options can vary from fixed benches, to systems that are moderately flexible, to completely flexible systems, as Figure 8 illustrates.

Many QC laboratories utilize HPLC's, which require bench space and can be stacked. A "low tech" design option is to create a "split bench" that may be lowered to 30 inches instead of the standard 36 inches height. The following is an illustration of a "split bench."

Providing Space for the Employee

The trend in the design of QC laboratories is to have the employee's workspace located outside the laboratory. This is for both health and safety reasons both, as well as practical consideration – the employee can now drink coffee at his/her desk! Figure 9 is a sample of a floor plan illustration. Key concepts: Provide glass between the labs, office space and exterior (outside) views.

Classification	Bio-Safety Level	Application
Class I	1, 2, 3	Low to moderate risk biological agent
Class II	1, 2, 3	Low to moderate risk biological agent
Class III	4	High risk biological agent

Table B. Types of biosafety cabinets.

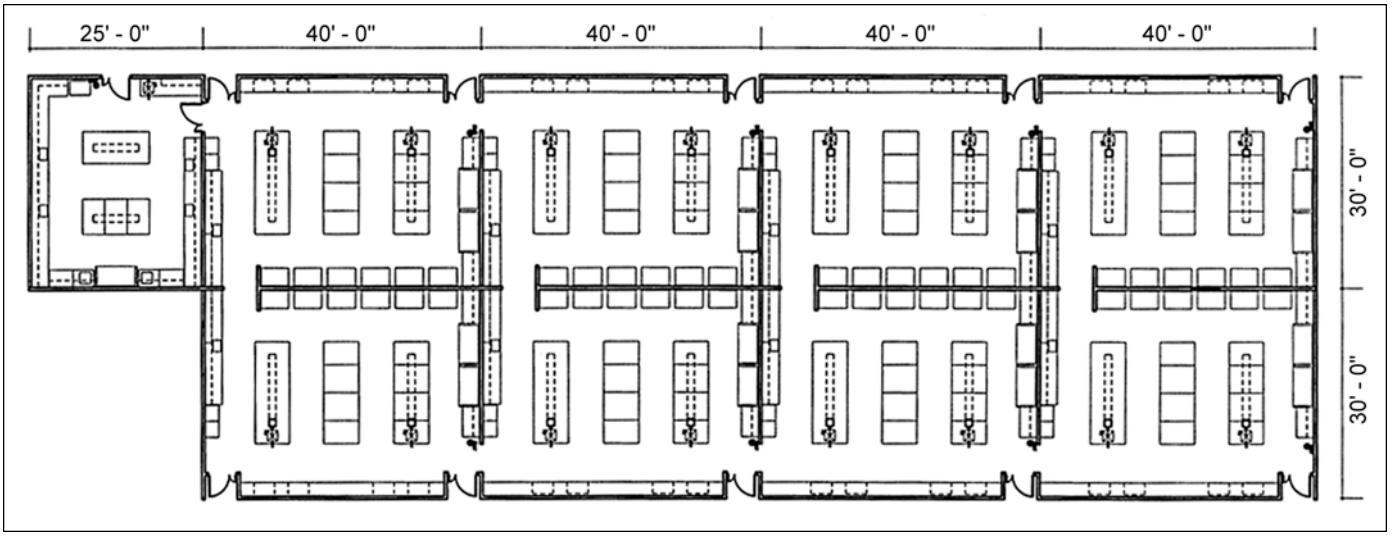

Figure 7. Open lab concept.

Some laboratories test biologicals. The following is a summary of biosafety levels.

Biosafety Levels

Biosafety Level 1: Lowest Level of Hazard

- typical laboratories with work done on benchtops or in chemical fume hoods
- minimum of 3 to 4 AC/H of outside air
- negative pressure to adjacent spaces

Biosafety Level 2: Moderate Level of Hazard

- limited access to lab
- biossafety cabinets Class I and II are used
- 100% outside air systems
- minimum of 6 to 15 AC/H of outside air
- negative pressure to adjacent spaces
- high equipment loading

Biosafety Level 3: High Level of Hazard

- serious or potential lethal hazard as a result of exposure by inhalation
- work conducted in Classes I, II, and III biosafety cabinets
- separate HVAC system
- negative pressure to adjacent spaces and must be monitored
- all exhaust must be HEPA filtered

Biosafety Level 4: Highest Level of Hazard

- all work is conducted in Class III cabinet or pressure suit

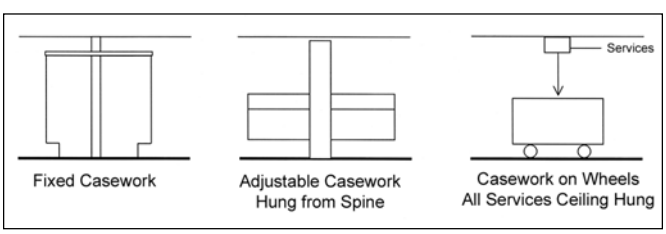

Figure 8. Casework options.

- all vent lines are HEPA filtered
- separate HVAC system with monitoring and control of pressurization. Supply fans are interlocked to exhaust system so that in case of exhaust failure, the space shall not become positively pressured
- both supply and exhaust air from space is HEPA filtered with exhaust being bag in/bag out

Egress

Labs should have two exits from each space where possible with doors swinging out. Fixed elements such as fume hood and bio-safety cabinets should be located away from doors and traffic. National Fire Protection Association (NFPA) has recommendations on door swings depending on the lab classification.

Lab Services

Typical services to benches may include compressed air, vacuum, di-ionized water hot and cold water, and lab gases, such as nitrogen, helium, and so forth. These gases may be centralized and piped to the bench, or be located at the bench.

MEP Issues for Laboratories

Heating, Ventilation and Air Conditioning (HVAC)

The key issue in designing QA/QC laboratories in terms of HVAC is to determine if air can be recirculated with possible terminal HEPA filter on the return air, or if it must use 100% outside air. The typical air change of a 100% outside air system is 8 to 10 air changes/hour. Temperature and humidity are typically 68°F to 75°F with 50% relative humidity. Generally, the laboratory should be negative with regard to air flow from the corridors. For clean areas such as microbiology, the lab air flow will be positive to the corridor. Point exhausts may need to be provided for specific pieces of equipment.

Fume hood and bio-safety cabinets are typical of QC laboratories. Fume hoods typically have face velocities of 60-

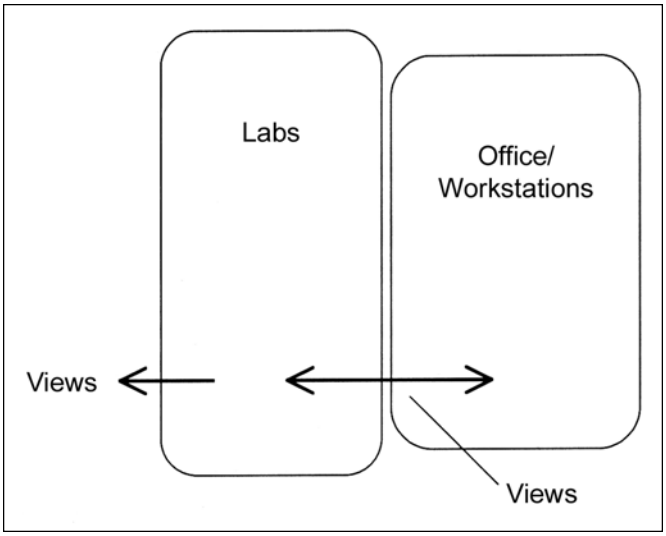

Figure 9. Floor plan.

100 CFM of hood opened at 18 inches, and may have vertical or horizontal siding; the exhaust duct velocity is from 1000-3500 FPM.

Biosafety cabinets are designed in three types depending on the user needs - *Table B*.

There are three basic elements of containment in laboratories. These are:

1. Laboratory practices and procedures
2. Safety equipment
3. Facility design

Electrical Issues

During the design phase, equipment requiring special electrical needs should be identified from the equipment list and located on the "lab" cards. Equipment requiring emergency power or Uninterrupted Power Supply (UPS) should be identified.

Materials and Finishes

Materials used for a typical QC laboratory may follow the following matrix - *Table C*.

Project Management Issues and Costs

The costs for the average renovation or new construction of QC and QA laboratories fall within a range of $200.00 to $400.00 per square foot. Higher and lower costs are possible. Many QC laboratory projects involve renovation within existing facilities, which requires staging and phasing, to keep the facilities operational, which will increase costs.

	Floors	Base	Ceiling	Walls	Comments
Typical labs	VCTV	VBEP	ACT	GWB EP	
Microbiology	V	V	ACT cleanable	GWB EB	May have drywall ceilings
Legend: VCT, Vinyl Composition Tile; V, Sheet Vinyl; EPF, Epoxy; VB, Vinyl Base; ACT, Acoustical Tile, Cleanable or Non-Cleanable; GWB, Gypsum Drywall; EP, Epoxy Paint.					

Table C. Materials used for a typical QC laboratory.

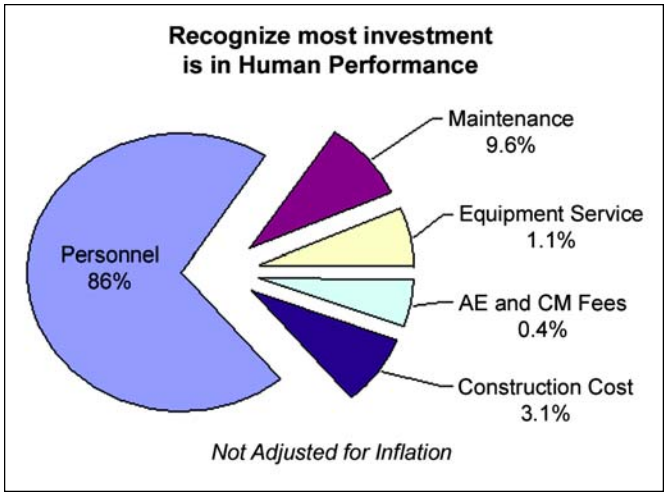

Figure 10. Lifetime science facility cost.

Another consideration is to look at the life cycle cost of the facility, as the following chart illustrates. The facility cost is small, compared to the personnel cost!

Trends and Future Developments

There is an increasing trend to utilize automated equipment and robotic laboratories. The issues to consider now are to allow space for bench or floor mounted equipment in the future, so that the laboratory may be modified with robotics and more automation in the future.

The design of the workplace outside of the laboratory also is key because increasing time is spent not at the actual bench. The introduction of natural light and expansive use of glass between the laboratories and office/work space will create a positive working environment for the employee.

A summary of trends in the design of QC/QA laboratories are as follows:

- separate lab space from employee work up space
- use of flexible laboratory casework
- use of split bench
- use of laboratories versus metal casework
- Sustainable Design or Leadership in Energy and Environmental Design (LEED)
- introduction of natural light and glass between laboratories and offices
- use of robotics for laboratories

References

1. ANSI/AIHA Z9.5, 1992, Laboratory Ventilation.
2. ANSI/ASHRAE 110, 1885, Methods of Testing Performance of Laboratory Fume Hoods.
3. ANSI/NFPA. 1991, Fire Protection for Laboratories Using Chemicals.
4. ASHRAE, 1991 Applications, Chapter 14, Laboratories.
5. BOCA and International Building Codes.
6. NIH/CDC, Biosafety in Microbiological and Biomedical labs.

7. ISPE Delaware Valley Chapter, lecture, Bernie Friel, Introduction R&D, June 2003.

About the Author

Terry Jacobs, AIA, is a Principal with Jacobs/Wyper Architects, LLP, an architectural, planning and interior design firm founded in 1981 in Philadelphia, PA. The firm's practice focuses in part on large and more complex projects for corporate and educational clients including research laboratories, manufacturing facilities, and data centers for the biotech, pharmaceutical and electronic industries and research universities – many delivered using design-build. Jacobs has substantial experience managing the design aspects of complex design-build projects. Jacobs was an adjunct professor at both Temple University and Drexel University and a visiting critic at the University of Pennsylvania. He has won design awards from the American Institute of Architects and the Pennsylvania Society of Architects. Jacobs earned his BA from Dartmouth College and his masters in architecture from the University of Pennsylvania. Mr. Jacobs co-edited a new book entitled, "Good Design Practices for GMP Pharmaceutical Facilities." The book is a single source reference for professionals involved in the planning, construction, validation and maintenance of modern pharmaceutical facilities. He is chairman of ISPE's Continuous Advancement Sub-committee and was president of the Delaware Valley Chapter of ISPE. He has been a course leader and speaker at numerous ISPE courses, and a member of ISPE since 1981.

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EPDM Diaphragms

GEMÜ has developed a new EPDM diaphragm for use at high temperatures and steam for the pharmaceutical and biotechnological industries. The diaphragms feature a greatly improved thermal load capacity. Steam tests at GEMÜ and with customers in production have revealed potentially up to three times longer service life in comparison with other diaphragms of the same design.

GEMÜ Gebr. Müller Apparatebau GmbH & Co. KG, www.gemue.de.

In-Line Sterilization Tunnel

An in-line sterilization tunnel has been developed by Linac Technologies for complete sterilization of products entering a Class A environment and/or final sterilization of pre-packed medical devices or pharmaceutical products. The SterBox stand-alone unit is designed to house a medium energy electron beam accelerator with up to 5 MeV energy, a customized handling system, and all associated ancillary equipment within a compact area. Visit Linac Technologies at PharmaMed Device (booth 4721) and PDA Annual Meeting 2008 (booth 114).

Linac Technologies, www.linac technologies.com.

Dust Collector

Farr Air Pollution Control's new "FDC Controller" provides user-friendly and reliable pulse cleaning control for all types of cartridge and baghouse dust collection systems. Using factory-programmed or customer-selected settings, the unit monitors pressure differential across the filters to ensure more efficient pulse cleaning, reducing compressed air energy usage, and extending filter life.

Farr Air Pollution Control, www.farrapc.com.

Cleanroom Ergonomic Equipment

Svenema AB, a Swedish designer and builder of custom, high quality lift trolleys for clean room applications, is introducing its full product range to the US market. Svenema's lift trolleys are of all stainless steel construction and are built commensurate with cGMP's. For more than 12 years, major pharmaceutical companies throughout Europe have relied on Svenema when applications call for portable, clean, compact, and customized lift trolleys for a broad range of lifting tasks such as drum lifting/tilting, tray handling, packaging material handling, etc. MLA Associates, Inc., Philadelphia, is the exclusive distributor/sales agency for Svenema's cleanroom lifting equipment in North America.

Svenema AB, www.svenema.se.

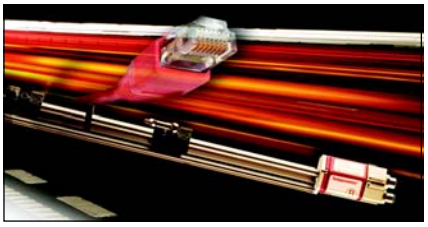
MLA Associates, Inc., mike@mlaassociates.com.

Ion Trap

Thermo Fisher Scientific Inc.'s Thermo Scientific ITQ Series of gas chromatography/mass spectrometry (GC/MS) ion trap instruments feature external ionization. The ITQ 700, ITQ 900 and ITQ 1100 ion trap systems feature fully upgradeable systems designed to provide high performance and high specificity. Developed for a wide range of applications, from routine GC/MS to research-grade ion trap MS, these new systems address the analytical needs of the environmental, food safety, pharmaceutical QA/QC, forensics and toxicology industries, as well as academic laboratories.

Thermo Fisher Scientific Inc., www.thermofisher.com.

Sensor



MTS Systems Corp., Sensors Division's Temposonics® R-Series EtherCAT® sensor, a high-speed networking solution based on industrial Ethernet technology, is providing the fastest rates of data transmission and communication

in industrial settings where high-speeds are necessary for complete factory automation. The sensor is being used in environments as varied as injection molding machines, high speed presses, woodworking, and packaging, and has allowed machine builders to overcome bandwidth and node limitations found with other commercially available industrial networks.

MTS Systems Corp., www.mtssensors.com.

*To submit material for publication in **Pharmaceutical Engineering**'s New Products and Literature department, e-mail press releases with photos to **pharmeng@ispe.org** for consideration.*

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Hoiberg Receives Humanitarian Award

Dr. Charles P. Hoiberg, Vice Chair the ISPE International Board of Directors and Executive Director in Pfizer's Reg CMC – Policy and Regulatory Environment group, has been selected as the 2008 recipient of the Pennsylvania State University Graduate School Alumni Society Humanitarian Award. The Award recognizes Alumni who have made a substantial contribution to society.

Hoiberg received a BS in chemistry from the College of William and Mary and a PhD in biochemistry (chemistry minor) from Pennsylvania State University. He worked for more than eight years at Sterling Drug Inc. in R&D before joining the FDA. Dr. Hoiberg had a leadership role and held numerous positions in the Agency and was involved in numerous global initiatives. When he retired from the Agency, he was the Deputy Director of the Office of New Drug Chemistry and the Associate Director for International Activities. He was the CDER ICH Quality Coordinator. He represented the Agency in negotiations of many ICH topics and has had close contacts with many worldwide regulators and industry leaders. While at the Agency, he was very involved in working with ISPE on developing the SUPAC Equipment Addendum.

Dr. Hoiberg has been a frequent lecturer for ISPE at its domestic and international programs in Europe and Asia. In addition to his position as Vice Chair for the ISPE International Board of Directors, he is a member of various ISPE Committees, such as RAC, PQLI, and the Science and Technology Task Team.

Dr. Hoiberg will be honored with an award presentation at a special event at his alma mater in March.

Capalbo Retires from Boehringer Ingelheim

Lou Capalbo has retired from his position as Director of the Global Clinical Supply Unit at Boehringer Ingelheim (BI) Pharmaceuticals in Ridgefield, Connecticut, USA. Prior to joining BI in 2003, he was Director of Clinical Supply Operations at GlaxoSmithKline, Research Triangle Park, North Carolina. He also developed and managed the Clinical Supply Unit at Pfizer Inc., Groton, Connecticut. In addition, as a consultant, he worked with clients on all phases of drug development from discovery to NDA approval. Capalbo has wide international knowledge and possesses multi-disciplinary experience in medical study design, regulatory affairs, pharmaceutical development, manufacturing, drug safety evaluation, analytical chemistry, and a thorough understanding of all drug development phases.

Capalbo is a registered pharmacist and received a BS in Pharmacy from the University of Rhode Island and has more than 30 years experience in the pharmaceutical industry. He was a founder of PhRMA Clinical Materials Group and was past Chair. He was also past Chair of Investigational Materials Discussion Group, and founder of Equal Partners in Clinical Supplies. He has made presentations on various aspects of clinical supplies and was a workshop coordinator and leader at major meetings. He has been an active contributor on a number of ISPE committees, inclusive of ISPE Professional Certification Committee, leader and Chair of ISPE Clinical Materials Committee, and served four years on the ISPE International Board of Directors.

Now a resident of North Carolina, Capalbo said he does not plan to retire and is currently seeking new opportunities in the pharmaceutical industry.

Packaging Technologies Acquires MAP Systems

Packaging Technologies today announces the acquisition of MAP Systems, a division of Clear Lam Packaging. The combination of Packaging Technologies and MAP Systems creates a primary packaging solutions provider specializing in packaging line integration.

The patented MAP Systems technology is based on the delivery of very specific, non-abusive streams of inert or active gasses into the product and its primary package; cans, jars, bottles, vials, pouches, bags, trays, etc. Packaging Technologies is a worldwide leader in the design, engineering, manufacturing and delivery of packaging, processing and filling machinery.

Packaging Technologies, www.oystar.packt.com.

MAP Systems, www.clearlam.com.

Extract Technology Downflow Booths to be Manufactured in US

Extract Technology downflow booths and products for North America and Puerto Rico will be manufactured at Walker Barrier Systems New Lisbon Wisconsin facility. Walker Barrier Systems has been producing high quality stainless steel isolators for both containment and aseptic applications for more than 20 years. The New Lisbon facility has been expanded to produce the same high quality Extract Technology products to provide North American customers with local manufacturing and service.

Extract Technology, www.extract-technology.com.

Walker Barrier Systems, www.walkerbarrier.com.

Foster Wheeler Acquires Biokinetics

Foster Wheeler has completed the acquisition of Biokinetics, a recognized industry leader in process systems design for the biopharmaceutical industry. According to Foster Wheeler, the transaction enables them to expand its global presence in biopharmaceutical sector and further enhance its existing biopharmaceutical skills base. Foster

Wheeler gives Biokinetics the best opportunity to internationalize its business and grow as part of an organization that offers a comprehensive set of consultancy, design, construction, qualification, and project management services to the industry.

Foster Wheeler, www.fwc.com.

Biokinetics, www.biokinc.com.

Bay-Tec Engineering Opens New Office in Pacific Northwest

Bay-Tec Engineering has recently opened a new office in the Pacific Northwest and is hoping to quickly fill some open positions with qualified candidates. Bay-Tec has built its business providing control system engineering, integration, and construction services to clients in pharmaceuticals, biotechnology, semiconductors, petrochemicals, and the food and beverage industry. With more than 25 years of experience, Bay-Tec has developed a complete set of Standard Operating Procedures for every phase of a control system project. Bay-Tec is currently looking for qualified staffing engineers and technicians in the automation engineering field as well as calibration technicians.

Bay-Tec Engineering, www.bay-tec.com.

*To submit material for publication in **Pharmaceutical Engineering**'s Industry and People department, e-mail press releases with photos to **pharmeng@ispe.org** for consideration.*

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New Venue for INTERPHEX*2008*

For the first time in many years, INTERPHEX will not take place at the Jacob Javits Center in New York. Instead, the industry's largest trade show will be held at the Pennsylvania Convention Center in Philadelphia, USA, from 26 to 28 March.

Also new for INTERPHEX*2008* is the debut of BIOTECHNICA AMERICA, the result of a partnership with BIOTECHNICA, the leading biotechnology show in Europe. INTERPHEX*2008* again will feature the co-location of PharmaMedDevice.

Sponsored by ISPE and presented by Reed Life Sciences, a part of Reed Exhibitions, INTERPHEX is the world's largest and most comprehensive pharmaceutical conference and exhibition. Last year, approximately 1,000 leading global companies serving the pharmaceutical and biotechnical industries showcased the latest lines of equipment, technologies, and services in the areas of pharmaceutical manufacturing, outsourcing and services, IT, and facilities.

For ISPE Members, here are some important highlights for this year's event:

- Visit the **ISPE Booth #1301**. There will be a raffle for a GPS Navigation System. The prize drawing will be announced Friday, 28 March, before the close of the show.

- Meet the **2008 Facility of the Year Award Category Winners** and learn first-hand about the facilities at Booth #4441 in Hall D. For detailed information on each Category Winner's project, pick up *Pharmaceutical Engineering*'s Facility of the Year Special Edition available at ISPE Booth #1301, the Facility of the Year Booth #4441, or the ISPE Member Lounge.

- The **Life Sciences Job Fair**, produced by ISPE and AAPS, in collaboration with INTERPHEX, will be held 26 to 27 March from 10.00 to 18.00 on Wednesday and 10.00 to 15.00 on Thursday.

Concludes on page 4.

European Congress on Innovation to Feature GAMP 5, PQLI, and EMEA Keynote

In addition to the European launch of **GAMP 5** (see article on page 102), the ISPE European Congress on Innovation, to be held 7 to 11 April in Copenhagen, Denmark, will feature highly interactive workshops on PQLI and a Keynote session by an official from the European Medicines Agency (EMEA).

The **Product Quality Lifecycle Implementation (PQLI)** initiative is an industry-driven effort encouraged by the US FDA and led by ISPE, to find practical, global approaches to implementing the high level ICH Guidelines Q8, Q9, and Q10.

At the Congress, there will be interactive workshops with more than 20 regulators from the EU community and discussions on Design Space, Criticality, Control Strategy, and Legacy Products, plus Submission vs. Inspection Data, Real-time Release, and Release Specifications. There will be opportunities to input into the future development of White Papers for industry consideration.

Thomas Lönngren, Executive Director of the EMEA, will deliver the **Keynote**, "Facing the Economic Challenges in Processing and Operations." His address will cover the new regulatory frameworks, which offer opportunities for more flexible approaches to change, particularly when it comes to restructuring organizations. Increasing environmental regulations and other challenges that present new imperatives to re-engineer traditional approaches to business also will be discussed.

As part of the Keynote Session, regulators from Europe, USA, and Japan will speak on key regulatory issues and considerations.

The Congress also will feature seminar sessions on:

- Technology Transfer
- New Drug Delivery Systems
- Plant Tours
- Innovation in Process Technology for Manufacture of APIs and BCPs

For more detailed information on the full Congress program, visit www.ISPE.org/copenhagen.

Mark Your Calendar with these ISPE Events

April 2008

14 – 17	Great Lakes Chapter, Spring Program held in conjunction with ISPE Chicago Classroom Training Series, Oakbrook Terrace, Illinois, USA
14 – 17	**ISPE Chicago Classroom Training, Holiday Inn Oakbrook, Oakbrook Terrace, Illinois, USA**
17	Boston Area Chapter, Seminar on S88 in Parallel Industries, The Royal Sonesta Cambridge, Cambridge, Massachusetts, USA
17	New Jersey Chapter, Presentation on ASTM 2500, Bristol-Myers Squibb, New Brunswick, New Jersey, USA
17	Pacific Northwest Chapter, Program and ISPE Career Information, Seattle, Washington, USA
17 – 18	Japan Affiliate, Annual General Meeting held concurrently with the 7th Japan Affiliate Annual Conference, Tower Hall, Funabori, Tokyo, Japan
23 – 24	Spain Affiliate, Conference on Risk Assessment, TBD, Spain
24	Midwest Chapter, Education and Vendor's Day, Omaha, Nebraska, USA
26	**ISPE Student Leadership Forum, Interamerican University of Puerto Rico, Bayamon, Puerto Rico, USA**
28	Argentina Affiliate, Workshop Topic: Quality Systems – Six Sigma Methodology and Application, Laboratorios Rontag Auditorium, Buenos Aires, Argentina

May 2008

2	San Diego Chapter, Spring Golf Tournament, South Course, La Costa Resort and Spa, Carlsbad, California, USA
5	Carolina-South Atlantic Chapter, Golf Tournament, Chapel Ridge Golf Club, Pittsboro, North Carolina, USA
8	Greater Los Angeles Area Chapter, Vendor Night, The Queen Mary, Long Beach, California, USA
8	Italy Affiliate, Event on Manufacturing and Control Systems Security by GAMP Italian Forum, Parma, Italy
8	Puerto Rico Chapter, Program on Utilities (Critical and Non-Critical) WFI, Gases, Process Water, Clean Steam, Plant Steam, and Plant Utilities, Guaynabo, Puerto Rico, USA
12 – 14	**ISPE and the Golden LEAF Biomanufacturing Training and Education Center (BTEC), North Carolina State University, Centennial Campus, Raleigh, North Carolina, USA**
13	Boston Area Chapter, Site Tour and Presentation, Topic: Establishing a Project Team for World Scale Bio Facility, BMS-Devens, Massachusetts, USA
14	New Jersey Chapter, Golf Outing, Farmstead Country Club, Lafayette, New Jersey, USA
15	Pacific Northwest Chapter, Program on Bio-Similars, Seattle, Washington, USA
19 – 20	Argentina Affiliate, Course I on Design, Construction, Qualification, and Validation of Cleanrooms, Laboratorios Rontag Auditorium, Buenos Aires, Argentina
19 – 22	**ISPE Brussels Classroom Training, Radisson SAS Royal Hotel, Brussels, Belgium**
20	Boston Area Chapter, Water Seminar, The Royal Sonesta Cambridge, Cambridge, Massachusetts, USA
20	Central Canada Chapter, Toronto Breakfast Seminar, Pharmaceutical Session, Toronto, Ontario, Canada
20	New Jersey Chapter, Dual Track Program, Topics on "The Continuing Evolution of the Pharmaceutical Industry" and "Energy Master Planning and Environmental Impact for Pharmaceutical Campuses," Holiday Inn, Somerset, New Jersey, USA
20	Nordic Affiliate, PIC/S Conference, Copenhagen, Denmark
21	Central Canada Chapter, Montreal Breakfast Seminar, Pharmaceutical Session, Montreal, Quebec, Canada
22	Belgium Affiliate, RABS and Isolator Technology Event, Salons Waerboom, Groot Bijgaarden, Belgium
22	Carolina-South Atlantic Chapter, Program, Angus Barn, Durham, North Carolina, USA
22	Central Canada Chapter, Quebec City Breakfast Seminar, Pharmaceutical Session, Quebec City, Quebec, Canada
29	Central Canada Chapter, Annual Golf Tournament, Glen Eagle Golf Club, Caledon, Ontario, Canada
29	DACH Affiliate, Workshop and Site Visit at SWISS CAP: Technologies and New Developments for Production of Soft Gelatine Capsules, Kirchberg, Switzerland
29	Midwest Chapter, Golf Outing, Minneapolis, Minnesota, USA
30	DACH Affiliate, Workshop and Site Visit at Excelvision: Aseptic Fill and Finish of Eyedrops and GMP Upgrade and Modular Extension of Production Facility, Hettlingen, Switzerland

Dates and Topics are subject to change.

Japan Affiliate Combines Annual General Meeting and Conference

The ISPE Japan Affiliate will be holding their Annual General Meeting concurrently with the 7th Japan Affiliate Annual Conference, 17 to 18 April. Approximately 350 delegates are expected to attend the event, entitled, "Pharmaceutical Innovation! – Challenging New Steps," at Tower Hall, Funabori, Tokyo.

On 17 April, Touichi Takenaka, Chairman of Astellas Pharma Co. will give a special address. Presentations by ISPE President Bob Best and representatives from the US FDA are expected. Fumi Yamamoto, a representative from the MHLW, also will be in attendance. Six workshops are scheduled for 18 April, three of which will offer simultaneous translation in English, including:

- WS1: Containment: "The Latest Information about Risk-MaPP"
- WS3: Regulatory: "Global Trends of Regulation (tentative title)" by FDA (tentative)
- WS6: Solid Dosage: "General Introduction to New Solidification Baseline® Guide"

There also will be a PQLI Meeting, chaired by Bruce Davis, ISPE Chairman and Global Capital Director of Astra Zeneca. Topic areas to be discussed are Design Space, Critical vs. Non-Critical, and Control Strategy.

For more information, contact Natsumi Sahara, Office Manager, at +81-3-3818-6737 or by e-mail at ispejapan@iris.ocn.ne.jp, or e-mail Tsutomu Samura at Tsutomu.Samura@sanofi-aventis.com.

Japanese Translations of ISPE Publications

ISPE Baseline® Guides:

- Commissioning and Qualification
- Biopharmaceutical Manufacturing Facilities
- Active Pharmaceutical Ingredients - *coming soon!*

ISPE Good Practice Guides:

- Technology Transfer
- Assessing the Particulate Containment Performance of Pharmaceutical Equipment
- C&Q of Pharmaceutical Water and Steam Systems - *coming soon!*

ISPE/GAMP® Good Practice Guides:

- Electronic Records and Signatures
- Validation of Laboratory Computerized Systems
- IT Infrastructure Control and Compliance
- Testing of GxP Systems - *coming soon!*

To purchase, visit www.ispe.gr.jp

ISPE and BTEC to Offer First-of-its-Kind Hands-On Biotech Training

ISPE is partnering with a major American university for the first time to provide comprehensive, hands-on biotechnology training 12 to 14 May at North Carolina State University's Golden LEAF Biomanufacturing Training and Education Center (BTEC) in Raleigh, North Carolina, USA.

The training program will offer four three-day courses that include lectures, problem-solving workshops, and hands-on activities at BTEC's state-of-the-art cGMP pilot plant facility. Participants will learn how to implement new concepts, improve process efficiency, address manufacturing challenges, and much more.

The BTEC facility simulates a biomanufacturing pilot plant capable of producing biopharmaceutical products and packaging them in a sterile environment using commercial-scale equipment. It is currently the only facility in the US that can do this from inoculation to filling, and the partnership between ISPE and North Carolina State University is one of the few opportunities for professionals to receive this hands-on, industry-specific training.

Developed for professionals in the pharmaceutical manufacturing and biotechnology industries to help increase knowledge in their respective fields, the training will focus on current issues, including:

- Process Validation for Biotechnology Manufacturing
- Biopharmaceutical Manufacturing Facilities
- Getting the Most from Your Bioreactor
- Disposables in Biomanufacturing: An Objective Assessment

Recognized industry experts will present relevant curriculum to give professionals the tools they need to be successful in their careers while earning Continuing Education credits. In addition, several of the courses contain information related to competencies for the Certified Pharmaceutical Industry Professional℠ (CPIP℠).

Read more about the BTEC in an interview with Rick Lawless, Associate Director, Strategic Planning, in this issue of *Pharmaceutical Engineering*.

For more information on specific courses and instructors, please visit www.ISPE.org/BTECtraining.

ISPE and US FDA Join Forces at Washington Conference

The ISPE Engineering Regulatory Compliance Conference, 2-5 June in Washington, D.C., USA, will feature the FDA co-sponsored event: Regulatory Perspectives on Hot Topics, Regulatory Trends, and Observations. This town-hall type of event provides an interactive opportunity for companies and regulators to discuss regulatory requirements.

The Conference also will include the Facilities Summit, which will explore non-traditional approaches to facility design and challenges and solutions to setting capital budgets. The 17th Annual Barrier Isolation Technology Forum will provide updates on innovations and review recent case studies.

In addition, there will be seminars on C7Q; containment, design and validation, HVAC; critical utilities; cleaning; and application of the new *Risk-MaPP ISPE Baseline® Guide*.

More detailed Conference program information will soon be available at www.ISPE.org.

New Venue for INTERPHEX*2008*

Continued from page 1.

- The **ISPE Member Lounge**, an exclusive benefit for ISPE Members, is in Room 204 A/B. The Lounge, sponsored by Burkert Fluid Control Systems, Commissioning Agents, Hecht Containment/KMPT USA, and Pharmadule, will have complimentary breakfast, beverages, Internet access, and small meeting rooms.

- The first **Young Professionals Networking Event** will take place at Lucky Strike Lanes on Thursday, 27 March, 17.30 – 10.30. This information networking event is free to pre-registered ISPE Members age 35 and younger. Download a registration form at www.ISPE.org/interphex.

- **New Members joining ISPE at the show save $40**; download the special application at www.ISPE.org/interphex.

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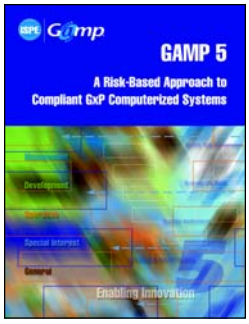
North American Launch of GAMP 5 a Success

European Debut in April



Nearly 200 people attended the much anticipated North American launch of GAMP 5 at the ISPE Conference on Manufacturing Excellence, held February in Tampa, Florida, USA.

A major upgrade to GAMP 4, *GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems*, focuses on the principles, concepts, and approaches to computer systems compliance. While the previous edition covers aspects of risk management, GAMP 5 embeds the process and takes it to a new level.

GAMP 5 addresses the entire lifecycle of an automated system in detail and is applicable to a wide range of information systems, lab equipment, integrated manufacturing systems, and IT infrastructures.

The new Guide recognizes the reality that most businesses no longer build their own software systems, but buy configurable software. The Guide examines leveraging supplier capabilities in order to build trust with suppliers and use of their documentation.

The interactive seminar, "GAMP 5: Enabling Innovation and Technological Advance," held in Tampa, helped participants learn how to apply GAMP 5 principles and explained how the Guide will enhance effectiveness and efficiency on the job.

Conference participants heard the latest GAMP thinking on interpreting and understanding current regulatory trends, as GAMP 5 points to the future of computer systems compliance by centering on principles behind major industry developments such as PQLI, ICH Q8, Q9, Q10, and ASTM E2500.

Additional discussion topics included outsourcing, electronic batch recording, end user applications (such as spreadsheets and small database applications), and patch management.

Conference participants received both a complimentary copy of the Guide and a CD of checklists, templates, diagrams, and other useful resources.

A similar program is planned for the European launch of GAMP 5, which will take place 7-8 April at the ISPE European Congress on Innovation in Copenhagen, Denmark. For detailed information, visit www.ISPE.org/copenhagencongress.

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March/April 2008, Vol. 28 No. 2

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International

The International Conference on Harmonisation (ICH) Steering Committee and its expert working groups met in Yokohama, Japan, from 29 October to 1 November 2007. An important milestone was reached with the adoption for public consultation of a new annex on "Pharmaceutical Development" (Q8). The annex focuses on quality by design and design space throughout the life-cycle of a pharmaceutical product.

ICH has also announced on their Web site[1] the adoption of the following new finalized Step 4 Guidelines:

- Q4B: Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions
- Q4B Annex 1: Residue on Ignition/ Sulphated Ash General Chapter EMEA/CHMP/ICH/222063/2006

The following new Step 2 Guidelines also have been released for public consultation:

- Q4B Annex 2: Test for Extractable Volume of Parenteral Preparations General Chapter (EMEA/CHMP/ ICH/559409/2007)
- Q4B Annex 3: Test for Particulate Contamination: Sub-Visible Particles General Chapter (EMEA/ CHMP/ICH/561176/2007)
- Annex to Q8: Pharmaceutical Development (EMEA/CHMP/ICH/ 518819/2007)

Australia

The Australian Therapeutic Goods Administration (TGA) has issued via their Web site revised guidance[2] on the standards of manufacture, and quality control of therapeutic goods manufactured outside Australia. A sponsor applying to the TGA for registration or listing of a therapeutic good manufactured outside Australia, must provide an acceptable form of evidence to show that the manufacture of the goods is of an acceptable standard. This is referred to as Good Manufacturing Practice (GMP) clearance of overseas manufacturers. The purpose of this guidance document is to provide information to sponsors and manufacturers on the acceptable form of evidence of GMP compliance for overseas manufacturers, and, to outline how to submit such evidence to the TGA for assessment.

The TGA has also invited submissions[3] from interested parties in relation to the development of a best practice guideline on non-reclosable packaging. The guideline is intended to assist sponsors of therapeutic goods improve the effectiveness of blister or foil strip packaging as a barrier to children and thereby reduce the potential for accidental childhood poisoning from medicines packaged in this way.

China

The Chinese Food and Drug Administration has introduced strengthened GMP requirements[4] with the intention of improving the quality and safety of drugs manufactured in China. Requirements as to quality control, production, process validation and personnel qualifications are strengthened to improve supervision and quality management. It is reported that falsification of documents will, for the first time, be classified as a severe defect.

Israel

As of December 2007,[4] Israeli Pharmaceutical companies will be expected to include the name and address of active raw material suppliers, finished product shelf life changes and primary packaging changes on application forms for quality control certificates. The new requirements were announced by the Israeli Ministry of Health in October 2007.

The Pharmaceutical Administration of Ministry of Health has also updated the guidance on medical product recalls to clarify the procedures for reporting of quality defects. The updates are essentially procedural.

Jordan

The Jordanian Food and Drug Administration has asked all pharmaceutical companies to submit a stability report summary sheet for each product registration or re registration.[5] The mandated form applies to accelerated and real-time studies for pharmaceutical and nutritional products that are registered in Jordan. The following information is required: Name of drug product and dosage form, manufacturer's and packager's name and address, batch number, size, date of manufacture, expiry date and type of batch (e.g. experimental, pilot, production), proposed shelf-life, number of samples tested per batch and packaging material, storage conditions (temperature, humidity, etc.), test methodology used for each test, finished product specification, brief summary of results (chemical results, physical findings, microbiological and biological findings, data evaluation and conclusion). These requirements came into effect in November 2007.

Europe

In January 2008, DG Enterprise and Industry released via their Web site[6] an updated guideline[7] on the packaging information of veterinary medicinal products (Veterinary Notice to Applicants, Volume 6C). The annex to the guideline provides updates required by Bulgaria, Portugal, Romania and the United Kingdom.

The Committee for Medicinal Products for Human Use (CHMP)[8] has published reports from its December and January plenary meetings held on 10-13 December 2007 and 21-24 January 2008

The following relevant guidelines[9] have been prepared or adopted for consultation by the Biologics Working Party:

- Note For Guidance On Plasma Derived Medicinal Products (CPMP/ BWP/269/05 REV. 3) adopted for 6-month public consultation EMEA/ CHMP/BWP/ 99698/2007
- Addendum to the Note for Guidance on Plasma Derived medicinal products (CPMP/BWP/269/05 rev. 3) on the replacement of rabbit pyrogen testing by an alternative test for plasma derived medicinal products

adopted for 6-month public consultation (EMEA/CHMP/BWP/452081/2007)

The Committee on Herbal Medicinal Products (HMPC)[10] has published their monthly meeting report[11] for the meeting held on 9-10 January 2008.

A final version of the Guideline on quality of combination herbal medicinal products/ traditional herbal medicinal products (EMEA/HMPC/CHMP/CVMP/214869/2006) together with the overview of comments received during the consultation period (EMEA/HMPC/559281/2007) was adopted and transmitted to the Quality Working Party (QWP) for agreement.

Further, the HMPC adopted a draft reflection paper on markers (marker substances) used for quantitative and qualitative analysis of herbal medicinal products and traditional herbal medicinal products (EMEA/HMPC/253629/2007) for public consultation until 15 April 2008. This reflection paper describes issues related to markers, which are intended for quantitative and qualitative analytical control of herbal medicinal products, and provides possible criteria to be taken for selection of markers.

The Paediatric Committee (PDCO)[12] has published their monthly meeting reports for the meetings held on 18-20 December 2007 and 16-18 January 2008. No new relevant information was noted.

The Committee for Orphan Medicinal Products (COMP)[13] has published their monthly meeting reports for the meetings held on 10-13 December 2007 and 9-10 January 2008. No new relevant information was noted.

The Committee for Veterinary Medicinal Products (CVMP)[14] has published their Monthly Reports of Application Procedures, Guidelines and Related Documents for November 2007, December 2007 and January 2008. Each includes an accumulative summary of the opinions issued by the CVMP in the current year and a list of adopted Guidelines and other public documents.

Noteworthy, the following relevant guidelines were adopted for public consultation at their December meeting:[15]

- Revised Guideline on Stability Testing: Stability testing of existing active substances and related finished products (EMEA/CVMP/QWP/846/99-Rev.1) for a 6-month period of public consultation. The aim of this revision is to update provisions in line with the recently updated VICH guideline on stability (GL3).

- Guideline on the quality aspects of single-dose veterinary spot-on products (EMEA/CVMP/QWP/544461/2007) for a 6-month period of public consultation. This guideline provides recommendations on certain quality-related issues for single dose spot-on products.

- Revised Guideline on the declaration of storage condition (EMEA/CVMP/422/99-Rev.3). This revision is only made for clarity in line with Human guidelines

Further, a reflection paper on consideration of adjuvants and preservatives (EMEA/CVMP/IWP/339116/2007) was adopted for 3-month period of public consultation.

Denmark

In January 2008, the Danish Health Agency issued on their website[16] guidance on national implementation of the "sunset clause" according to article 23a of the directive on medicinal products for human use (2001/83/EC) and article 27a of the directive on veterinary medicinal products (2001/82/EC). Under section 22(1) of the Danish Medicines Act, the holder of a marketing authorization is required to notify the Agency if the product ceases to be placed on the market, either temporarily or permanently. It is possible to use the form "Notification about initiation or cessation of marketing of medicinal products," which is now available at their website.

Under the sunset clause, a marketing authorization or registration shall cease to be valid if the authorized or registered product has not been placed on the market within three years of the granting of the registration or authorization or if an authorized or registered product has been absent from the market for a period of three consecutive years. The enabling Danish Medicines Act entered into force on 17 December 2005, and the earliest date when a marketing authorization can cease to be valid under the "sunset clause" is therefore 17 December 2008.

Finland

Similarly, the Finnish National Agency for Medicines has also issued on their Web site[17] guidance on national implementation of the "sunset clause" according to article 23a of the directive on medicinal products for human use (2001/83/EC) and article 27a of the directive on veterinary medicinal products (2001/82/EC).

The Finnish agency further states they will publish on its website on 15 August 2008 a list of those marketing authorizations and registrations that will cease to be valid pursuant to section 29(1)(3) and for which no waiver has been sought by the deadline. If the holder wishes to retain the marketing authorization or registration of a product appearing on this list, the product must be placed on the market by 7 November 2008. If the holder of a marketing authorization or registration has not applied for a waiver to extend validity by that date, the marketing authorization or registration will ceased to be valid and a list of marketing authorizations that have so ceased to be valid will be published on 15 November 2008.

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4. RAJ Pharma December 2007
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6. http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm
7. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-6/c/vol6c_packaging-guideline_bluebox2008.pdf

8. http://www.emea.europa.eu/Press%20Office/chmp.htm
9. http://www.emea.europa.eu/pdfs/human/press/pr/58563707en.pdf
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15. http://www.emea.europa.eu/pdfs/vet/press/pr/60509307en.pdf
16. http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=746
17. http://www.nam.fi/english/

This information was provided by Ian Morland, MRPharmS, PhD, Pharmaceutical Research Associates (UK).

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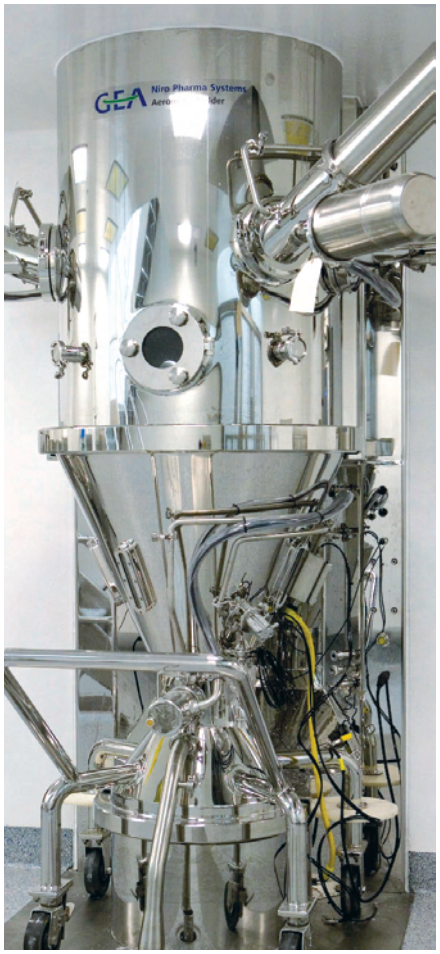

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ISPE
ENGINEERING PHARMACEUTICAL INNOVATION

The 2008 Facility of the Year Awards

The Facility of the Year Awards (FOYA) program, sponsored by ISPE, INTERPHEX, and *Pharmaceutical Processing* magazine, recognizes state-of-the-art pharmaceutical manufacturing projects that utilize new and innovative technologies to enhance the delivery of a quality project, as well as reduce the cost of producing high-quality medicines.

Now in its fourth year, the Awards program effectively spotlights the accomplishments, shared commitment, and dedication of individuals in companies worldwide to innovate and advance pharmaceutical manufacturing technology for the benefit of all global consumers.

"It's amazing to see the consistency in quality of projects submitted year after year," said Scott Ludlum, ISPE's Director of Business Initiatives. "It was not an easy choice for the judges to choose the five winners with so many outstanding projects being submitted. I believe this indicates the commitment of the industry to build truly innovative facilities that reduce costs and improve operational efficiency," said Ludlum.

Each of the submissions was reviewed by an independent, blue-ribbon judging panel of global representatives from the pharmaceutical design, construction, and manufacturing sectors:

- **Andy Skibo, Judging Panel Chair** – Senior VP, Global Engineering and Facilities, MedImmune
- **Geoff Monk** – VP Global Engineering Services, Schering Plough
- **Jim Breen** – VP Project Management, Johnson and Johnson
- **Jon Reed** – VP Corporate Engineering, Genentech
- **Brian Lange** - Director of Engineering, Merck & Co.
- **Christian Ilsøe** – VP Quality & Validation Assurance, NNE
- **Ron Trudeau** – VP Facilities Engineering, Baxter Healthcare
- **Shinichi Osada** – General Manager, Hitachi Plant Technologies Ltd.
- **Chaz Calitri** – Senior Director Global Engineering, Pfizer
- **Andrew Ellis** – VP Engineering & Technology of Consumer Healthcare, GSK

2008 Facility of the Year Award Winners

Five pharmaceutical manufacturing facilities located in Germany and the United States were selected as Category Winners. The companies and respective award categories include:

- **Boehringer Ingelheim Pharma GmbH & Co.KG**, located in Biberach, Germany, winner of the Facility of the Year Award for Facility Integration for its **Pharmaceutical R&D Building** project
- **Bristol-Myers Squibb**, located in New Brunswick, New Jersey, US, winner of the Facility of the Year Award for Equipment Innovation for its **Clinical Supplies Manfacturing and Drug Product Technology Center Expansion** project
- **IDT Biologika GmbH**, located in Dessau-Rosslau, Germany, winner of the Facility of the Year Award for Operational Excellence for its **Facility for Production of Live Human Viral Vaccines IDT 201** project
- **Pfizer**, located in Illertissen, Germany, winner of the Facility of the Year Award for Process Innovation for its **NEWCON (New Containment Facility for Oral Solid Dosage)** project
- **F. Hoffman La Roche AG**, located in Basel, Switzerland, winner of the Facility of the Year Award for Project Execution for its **Biologics IV** project

The announcement of the coveted Facility of the Year Award Winner, which will be chosen among the five category winners, will take place at ISPE's 2008 Annual Meeting in October in Boca Raton, Florida, US. For more information, visit www.ispe.org or www.facilityoftheyear.org.

In addition to ISPE's Annual Meeting, opportunities to meet the 2008 Facility of the Year Award Winners and learn firsthand about the facilities will be made available at INTERPHEX*2008* in March in Philadelphia, Pennsylvania, US. The Category Award Winners will be at Booth Number 4441 in Hall D of the Pennsylvania Convention Center. For more information, visit www.interphex.com.

Pharmaceutical Processing Features FOYA Winners

Pharmaceutical Processing magazine is featuring each of the FOYA Winners in upcoming editions of the magazine. To learn more and read about these award-winning facilities visit www.pharmpro.com.

Pharmaceutical Engineering Focuses on Winners

This supplement was developed specifically to highlight the remarkable features and technologies of each individual project. The following pages provide detailed case studies for each Category Winner project.

In addition to this supplement, *Pharmaceutical Engineering* (PE) magazine will release another supplement to be distributed at the 2008 ISPE Annual Meeting in October and will be mailed with your copy of PE's November/December issue. This upcoming supplement will take you behind the construction and competition curtains and feature exclusive interviews with the Overall Facility of the Year Award Winner, Category Winners, and the FOYA Judging Panel. The issue will provide valuable insight into current industry trends affecting facility design and what specific features designated these projects as award-winning projects.

2008
Facility of the Year Awards
CATEGORY WINNER
Project Execution • Supplier

VOGELBUSCH congratulates

F. Hoffmann La ROCHE

Winner of the Facility of the Year Award for Project Execution

VOGELBUSCH BIOPHARMA

Project Biologics IV

The detailed planning and preparation really paid off. Early commissioning was a tribute to the professionalism of a highly motivated team, where engineers and the operator's staff collaborated closely.

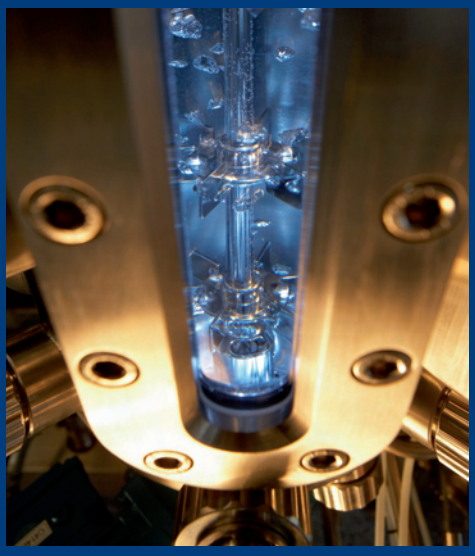
C. Herrmann, Biologics IV project manager at Roche

Meeting the tight installation deadlines required a detail prefabrication plan combined with just-in-time delivery.

H.G. Sabata, project manager VB Biopharma

Breathing life into sophisticated hardware calls for complex and mature software. The fully automated control system guarantees both user-friendly operation and top product quality.

M. Feistmantel, bioprocess engineer at VB Biopharma



Services provided by VB Biopharma during the Biologics IV project:

- Review Basic Engineering
- Detail Engineering
- Procurement and Delivery
- Commissioning
- Qualification Support

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Boehringer Ingelheim

Form and Functional Excellence Under One Roof

To accommodate a growing number of development projects and to promote the application of new technologies, Boehringer Ingelheim (BI) decided to erect a state-of-the-art facility encompassing all relevant stages of pharmaceutical development: formulation, process development/scale-up, clinical supplies manufacture, and packaging/labeling.

Their vision materialized with the construction of the new Pharmaceutical R&D Building in Biberach, Germany – winner of the 2008 Facility of the Year Award (FOYA) for Facility Integration. The facility integrates all major functions of pharmaceutical development in one building, promoting synergies, optimal communication, and seamless cooperation across the relevant disciplines.

A Space for Synergy

BI's key goal is to bring value to patients by researching and developing innovative pharmaceutical medicines. The Biberach site represents not only the largest of BI's R&D centers within the global network of interlinked R&D facilities, it is also their global center for research in the areas of central nervous diseases, metabolic diseases, respiratory diseases, and a key global skill center for development.

The existing premises for pharmaceutical development at the Biberach site required more laboratory space, which had been distributed in several buildings and needed substantial upgrading.

In 2002, this planning process resulted in the decision to create a new building that should house all relevant disciplines of pharmaceutical development, providing a basis for the optimal exploitation of synergies between all functions.

Pharmaceutical development of drug products encompasses several disciplines, which are functionally related, but require different prerequisites that needed to be reflected in the facility design:

- *Formulation development* uses laboratories for small-scale experiments to develop preliminary formulations with new compounds for first clinical trials and subsequently design formulations for the market use.
- *Process development / scale- up* requires pilot plant facilities equipped with all machinery necessary to develop and optimize manufacturing processes ready for transfer to commercial production.
- The manufacture of *clinical trial supplies* requires adequate space and equipment in full compliance with all international GMP requirements.
- To support international clinical trial programs, a globally organized unit for the coordination of all BI clinical trials, including GMP packaging/labeling operations is to be integrated.

Main entrance of the pharmaceutical R&D building.

The plan also called for a facility with maximum flexibility to enable handling of a broad diversity of product types, batch sizes, potencies, and dosage forms. With a growing number of highly potent active compounds emerging from research, suitable areas were necessary for safe handling without compromising flexibility.

To meet this variety of requirements, BI constructed a building that accommodates formulation laboratories, pilot plants for solids and parenterals, GMP facilities, and offices. Both building layout and the concept for technical support systems allow easy adaption to future needs and the implementation of new technologies.

Boehringer Ingelheim

Category Winner – Facility Integration

Project: Pharmaceutical R&D Building Biberach
Location: Biberach, Germany
Project Management: Boehringer Ingelheim Pharma GmbH & Co. KG
Architect: Henn Architekten
Domestic Engineering: Ingenieurbüro Mayer
General Contractor: Axima GmbH
Size: 95,357 sq. ft. (8,859 sq. m.)
Cost: US $64.7 million (44.6 million Euros)

State-of-the-Art GMP Facilities

One of the major goals of the project was the creation of state-of-the-art GMP facilities for the manufacture of solid, liquid, and parenteral clinical trial supplies. All relevant international GMP standards had to be met. Since all clinical trial phases from I to IV had to be supported, multi-purpose facilities and equipment were made available for manufacturing operations with batch sizes from 1 up to approximately 200 kg, depending both on the availability of drug substance and the trial size.

All major equipment and systems used for process development or manufacture of clinical supplies were fully validated, which allows a fast production of high-quality clinical trial supplies without additional ramp-up time.

As the solids and sterile pilot plants are designed as GMP areas and are equally suitable for GMP manufacture and process development, the need for internal technology transfer was minimized with the benefit of saving time and resources.

Important features of the applied GMP concept within the facilities are:

- zoning concepts for all three GMP facilities (solids manufacture, sterile area, packaging/labeling) with airlocks providing a clear separation from the non-GMP area, supporting by building design and technical control systems

Technical maintenance area adjacent to production rooms.

- processing rooms with adjacent technical areas and accessible cleanroom ceilings for technical installation above, allowing maintenance without disturbing the process flow
- corridors function as a buffer area, guaranteeing ideal room conditions within the processing rooms

Fostering Flexibility and Communication

Another important factor for a fast and successful development process is the optimal communication between the different

Concludes on page 8.

Isolator suite for highly potent compounds/small scale operations.

"Throughout the project, there was a clear focus on promoting synergies, communication, and seamless cooperation across the relevant disciplines to execute effective product and process development work."

disciplines within the facility. Flexibility and easy communication were two key elements of the user requirements and consistently translated into the building design.

The following goals were obtained by typical construction features and facility layout, which allows maximum flexibility to accommodate the installation of new manufacturing technologies from lab scale-up to full scale (300 kg) and foster communication among the disciplines:

- In the sterile facility, a widely column-free core area supports flexible use of rooms and equipment, including future technologies.
- Use of modular cleanroom wall and ceiling systems which are easy to rearrange
- Since pilot plant areas are operated under GMP conditions, subsequent manufacture of clinical trial supplies can occur on the same premises using the same equipment, without additional technology transfers.
- Because of the broad variety of processes and batch sizes in a pilot plant the use of classical isolator technology is limited. However, maximum flexibility could be achieved by the installation of HVAC systems, leading to a significant reduction of dust exposure by technical means and providing the option to handle highly potent compounds down to OELs of approximately 10¼g/m³ ('SMP area').
- The clear separation of dust generating processes and testing/documentation work in the formulation area allows optimal protection for laboratory personnel.
- Due to the sensitive GMP environment, major technical maintenance operations are performed in dedicated technical areas outside the GMP zone. The building concept with vertical and horizontal support 'backbones' contributes to an efficient and undisturbed workflow in the GMP processing areas and to personnel safety. Thus, each processing room can, in addition to the technical floor above, be serviced from at least one adjacent technical area.
- The redundancy concept for HVAC systems allows easy repair and maintenance and reduces down-time in the GMP-facilities.
- The architectural layout provides a pleasant environment and supports the exploitation of synergies between different development functions.

Handling Highly Active Compounds

A challenging task for the project team was the creation of areas for safe handling of highly potent actives without compromising the flexibility necessary in a development environment. The solution derived from a longer planning and testing phase and resulted in a two-way approach for the new building:

- For larger scale operations, special HVAC systems were developed, which lead to a significant reduction of dust exposure by technical means in the pilot plant, providing the option to handle highly potent compounds down to OELs of approx. 10¼g/m³ ('SMP area').
- Two separate isolator suites for handling highly potent compounds (OEL > 0.1 ¼g/m³) were installed, capable of GMP manufacture and development work in small scale.

Isolators and equipment are operated under GMP conditions and are suitable for formulation development and manufacturing of small-scale clinical trial supplies.

The introduction of downflow booth technology combined with a sophisticated HVAC system in the pilot plants extends the range of workable compounds down to OELs of approx. 10¼g/m³, without compromising safety at work or process flexibility. Filter units are designed for dust-free maintenance and exchange; all processing rooms are monitored with pressure and overflow controls.

Facility Integration at its Finest

This renovation project impressively achieved the integration of all major pharmaceutical development functions – formulation, process development/scale-up, clinical supplies manufacture, and packaging/labelling – in one building.

Throughout the project, there was a clear focus on promoting synergies, communication, and seamless cooperation across the relevant disciplines to execute effective product and process development work.

SKAN

CONGRATULATIONS BRISTOL-MYERS SQUIBB, CATEGORY WINNER, EQUIPEMENT INNOVATION, 2008 FACILITY OF THE YEAR AWARD.

2008
Facility of the Year Awards
CATEGORY WINNER
Equipment Innovation

WE ARE HONORED TO HAVE BEEN THE MAJOR SUPPLIER OF THE ISOLATORS FOR THE FILL-FINISH AND OSD OPERATIONS FOR YOUR FACILITY

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Bristol-Myers Squibb

Advancing Clinical Manufacturing and Drug Product Development

Forecasting a 20-year business plan, Bristol-Myers Squibb (BMS) developed and implemented a new strategy to discover and develop innovative medicines to address significant areas of unmet medical needs. These areas include affective (psychiatric) disorders, Alzheimer's/dementia, atherosclerosis/thrombosis, diabetes, hepatitis, HIV/AIDS, obesity, oncology, rheumatoid arthritis, and related diseases as well as solid organ transplant.

To further develop its product pipeline, to foster collaboration among numerous functions and facilities, and to sustain on-time delivery of future clinical supplies, BMS designated its New Brunswick, New Jersey, US campus as a Pharmaceutical Development Center of Excellence. To create this Center, BMS embarked on its Clinical Supplies Manufacturing and Drug Product Technology Expansion Project – winner of the 2008 Facility of the Year Award (FOYA) for Equipment Innovation.

Creating a Pharmaceutical Development Center of Excellence

The project brought early and late phase cGMP clinical manufacturing and development scale-up together within a single facility to create a Pharmaceutical Development Center of Excellence. Construction of the project was phased to allow full implementation of lessons learned in containment and process automation technology was integrated into already existing operations.

Phase One implemented a state-of-the-art Clinical Supply Operations (CSO) expansion facility, including full containment for expanded Oral Solid Dose (OSD) operations, and according to a BMS spokesperson, the most flexible clinical-scale continuous barrier line in the US for sterile products. This facility was designated for manufacturing OSD batches up to 400 Kg and parenteral liquid fill batches up to 250L. The goal was to create a flexible facility capable of performing multi-product clinical scale manufacturing and processing solvent-based and potent compound operations. The first phase consists of processing, manufacturing, support, and mechanical space.

BMS CSO/DPTC facility.

Phase Two built upon the technologies in Phase One and added additional processing space to the OSD clinical operation and a new stand-alone Product Technology Center (PTC) for development scale-up activities. The addition to OSD operations allows the manufacture of long term stability batches within the CSO facility in at least one-tenth commercial scale.

Compressing the Critical Path

The CSO facility, according to BMS, is the first operational clinical facility to utilize continuous process sterile isolators. The PTC represents significant advancement and usage of cutting edge technology in drug development in the United States. The extensive use of containment technology coupled with the flexibility to manufacture throughout development from First-in-Human through the end of Phase III for both sterile and

Bristol-Myers Squibb

Category Winner – Equipment Innovation

Project: Clinical Supplies Manufacturing and Drug Product Technology Center Expansion
Location: New Brunswick, New Jersey, US
Engineering/Design: IPS, Inc.
Construction Manager: Torcon, Inc.
Size: Phase One 93,110 sq. ft. (8,650 sq. m.); Phase Two 39,300 sq. ft. (3,651 sq. m.)
Cost: Phase One US $53,719,000 (34 million Euros); Phase Two US $36,968,000 (24 million Euros)
Product: Solid and liquid dosage forms, including sterile products

solid dose products makes this facility the most complete GMP development facility currently in use in the United States, according to a BMS spokesperson.

The production of clinical supplies involves added complexity in comparison to marketed products by virtue of the lack of fixed routines, variety of clinical trial designs, complex packaging designs, and the increased risk of cross-contamination. The complexity of the project was increased with the integration of innovative isolation technology, thereby offering an improved compliance profile and the highest level of environmental control and protection for both the product and personnel.

The Phase One expansion was segregated into three manufacturing zones: Parenteral, OSD Band 1 through 4, and OSD Band 5. The CSO Parenteral area is equipped with an isolated vial filling line to satisfy both sterility and containment requirements. Features of the filling line include:

- manufacture in a full nitrogen environment for safe solvent processing
- manufacture a full range of vial sizes
- filling technology that utilizes peristaltic or rotary piston pumps
- automatic loading of the freeze-dryer with no trays or rings that can alter heat transfer between the shelf and the vials
- standard and cold-shelf loading of the freeze dryer
- use of product thermocouples within the isolated environment
- capping under full Grade A/Class 100 conditions

Formulation isolator.

- automated differential pressure control scheme to maintain containment of potent compounds
- automated ductwork CIP for potent compound cleaning
- exterior vial wash capability to remove any product residues

All formulations processed in the isolated filling line are produced in a formulation isolator located in an adjacent room that includes the same solvent and potent handling features. Both isolators have multiple rapid transfer ports for transporting materials, consumables, and equipment in and out of the isolator in a contained and aseptic manner.

Concludes on page 12.

The OSD Band 4 Manufacturing Area includes processing rooms focused on the production of oral solid dosage clinical materials. The area was designed for operations handling Active Pharmaceutical Ingredients (APIs) categorized as Band 4 and below. The OSD Band 4 area was expanded in Phase II to include the Long Term Stability (LTS) area. The LTS area includes processing rooms focusing on the production of oral solid dosage clinical materials and handling API categorized as Band 4 and below and also includes one room capable of handling solvent coating of up to Band 5 compounds. The manufacturing of LTS batches aids product scale-up and technical transfer into commercial manufacturing sites with batch sizes at least one-tenth commercial scale.

The OSD Band 5 area is used for OSD operations handling APIs categorized as Band 5 and includes two processing suites. Primary equipment containment utilizes several isolation/containment technologies, including closed system processing equipment, contained material transfer systems, and isolated equipment and operations. The two OSD processing suites support a variety of contained OSD operations, such as wet and dry granulation, bin tumble blending, compression, encapsulation, tray drying, and dry milling.

Phase Two of the project was designed to build upon the innovation in Phase One and add supplemental processing space and scale to the oral solid dose clinical operation. Additionally, a new Product Technology Center focuses on R&D and scale-up for future CSO technologies.

The PTC area is designated to perform both process development and scale-up. Batch sizes for the PTC range from 20Kg to 100Kg and are manufactured using different unit operations and processes. Although the operations performed within the PTC area are characterized as non-GMP activities, the qualification, maintenance, and operation strategies provide sufficient support for future changeover to cGMP operations. In addition, the area is designed for operations handling API categorized as Band 1 through 4. The following rooms are designated to carry out processing capabilities for a variety of OSD operations: new technologies (hot melt extrusion, pelletizing, nanomilling), capsule filling, roller compaction, tablet compression, weighing and wash operations, high shear wet processing, blending, tablet coating, and an in-process laboratory. The PTC area includes design features, such as high ceiling height in the tablet press room to mimic material drops in commercial facilities, yellow lighting for light sensitive compounds, and low humidity capabilities.

Commitment to Safety

Environmental, health, and safety concerns were centered on providing ultimate flexibility through overall facility design, utility availability, and developing processes and procedures to safely handle Band 1 through 5 formulations.

Isolation technology reduced reliance on personal protective equipment in OSD and scale-up operations. In sterile manufacturing, the same technology eliminated the need for Class A support space and gowning rooms, and reduced overall expected operating costs.

Personnel, material, and process flows were optimized to minimize and limit the duration of exposure to sterile product elements. For example, access to the PTC space is controlled through airlocks, maintaining cGMP zone integrity. All raw and finished materials flow in and out through a designated material airlock and all approved personnel also enter/exit through a designated personnel airlock. Appropriately gowned personnel, sealed materials, and clean and/or wrapped equipment are able to move freely through the manufacturing corridors. Process room airlocks were designed to provide secondary process containment control, and also serve as an area in which to gown/de-gown and transition portable equipment and in-process materials. Primary containment is achieved through Local Exhaust Ventilation (LEV), used for Bands 1, 2, and 3, and through isolation technologies for Band 4. In the event of a breach in primary containment, operators use airlocks to assist in personnel decontamination.

Continuous process isolated fill line.

Throughout the project, BMS was recognized for numerous government and state health and safety awards, most notably as an OSHA Voluntary Protection Program Star Demonstration Site for voluntarily achieving outstanding safety and health management.

Collaboration is Key

Another significant advantage for this project was the ability to coordinate and manage all involved disciplines. For the project, IPS provided schematic design, design development, construction documentation, construction administration services, and validation master plan development and validation. Torcon, Inc. provided construction management services (including commissioning and start-up) with a hands-on approach through project completion. Flexible, adaptable design, and tight budget control were imperative to introducing and integrating isolation technology into each phase in the most cost-effective manner.

Increasing Speed to Market with Equipment Innovation

The project implemented innovative isolator technology, multiple filling technologies, and unique automation techniques.

This kind of equipment innovation provides BMS with the increased capacity to meet clinical demand and deliver compliance, productivity, and technical innovation to meet present and future drug development pipeline needs – ultimately helping speed products to market.

Congratulations Bristol-Myers Squibb,

Category Winner, Equipment Innovation, 2008 Facility of the Year Award.

2008
Facility of the Year Awards
CATEGORY WINNER
Equipment Innovation

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Knowledge Delivered

Cover Image: Amy Shutt, PE, LEED® AP, Senior Mechanical Engineer, IPS

IDT Biologika GmbH

Operational Expertise in Biologics Drives Facility Design

Recent scientific findings in molecular biology, pathogenesis, and immunology of infectious diseases are opening up new approaches to vaccination for disease control. Emerging pathogens and evolving scientific understanding of immunopathology regarding some chronic diseases are prompting new needs for vaccination. New technologies are being developed and optimized for innovative and promising vaccines.

It is against this backdrop that IDT Biologika GmbH started contract development and manufacturing activities for newly developed human viral vaccines. Using the latest technologies in sterile production and operational expertise gained from more than 10 years of contract manufacturing experience, IDT designed the new Facility for Production of Live Human Viral Vaccines, IDT 201 – winner of the 2008 Facility of the Year Award (FOYA) for Operational Excellence.

Tradition Continues to Thrive

Located in Dessau-Rosslau, Germany, IDT has its origin in the Bacteriological Institute of the Anhaltian Administrative Areas and was founded for the Free State of Anhalt in 1921. This institute was the starting point for veterinary and human medical research and drug manufacture in Dessau. Vaccine manufacture for commercial use started in 1925 and extended to become the Anhalt Serum Institute until 1945.

IDT developed from this institute and in 1993 was integrated as an independent concern into the Klocke Group. IDT started contract development and manufacturing activities for newly developed human viral vaccines and since 1997 has been producing vaccines in one building at the Dessau site.

Exterior view on the east side of the building with visitors gallery.

The Category-winning project – Facility for Production of Live Human Viral Vaccines, IDT 201 – expands IDT's Dessau site from one to two buildings for vaccine production.
The new building includes two different aseptic production lines for egg-based and cell culture production and implements Restricted Access Barrier Systems (RABS) and robotic systems to maximize flexibility and improve production efficiency.

Constructed within 19 months and operating since the end of 2007, the addition expands IDT's capacities to produce viral vectors from process development through Phase 1 and 2 clinical trials and up to manufacture of batches for Phase 3 testing, and subsequent commercial production. IDT's new facility is one of a few in Germany and worldwide that has the capacity for large-scale, campaign manufacture of batches of different vaccine products.

The project's use of unique transparent building features, manufacturing area adjacencies, material handling, and equipment technologies is anticipated to result in a four-fold increase in production capacity.

New Ways of Designing Sterile Production

The building's transparency and color, state-of-the-art equipment, and flexibility, demonstrate technological progress

IDT Biologika GmbH

Category Winner – Operational Excellence

Project: Facility for Production of Live Human Viral Vaccines, IDT 201
Location: Dessau-Rosslau, Germany
Architect/Designer: Heene + Proebst GmbH
Process Engineering: BIDECO GmbH
General Contractor: Technik-Energie-Wasser Servicegesellschaft mbH
Size: 50,568 sq. ft. (4,698 sq. m.)
Cost: US $37,470,000 (23 million Euros)
Products: Live recombinant and non recombinant viral vaccines for human use

and developments gained over 10 years of production. "Sterility does not have to be lifeless," said IDT representatives.

All-glass material locks and glassed-in passageways allow views of the entire building. Excessive light contributes to a pleasant work environment and different colors designate the building's various functional units.

The multi-purpose facility consists of strict horizontal division of service areas and the serviced areas into four levels. A strategy was devised to guarantee the shortest supply and disposal routes: the production area is located at the building's center with maintenance level and air conditioning systems located above and the media supply for the production area below. All operations are as much as possible contained in cleanrooms and contained technical systems.

Roller culture used for virus production has been fully automated in Class A (100) cleanrooms using robots.

Two production lines were created for different aseptic manufacturing technologies with a fumigation lock, automated laser technique for opening eggs, and Restricted Access Barrier System (RABS) for processing eggs on one line. The other line has robots for cell culturing and virus propagation. The production area also includes a second cooling system for -80ºC storage, fully automated CIP/SIP, and continual wastewater inactivation.

Large cleanrooms classified B (10,000) and C (100,000) allow long-term space for climate chambers of every temperature range making virus production on various cell substrates and different technologies possible.

Since the vaccines currently being manufactured are live virus vaccines which cannot be sterile filtered, the use of optimal aseptic production technologies was critical. These technologies include an automatic disinfection hose for eggs, a laser for opening the eggs, a RABS for extracting the embryos, and the use of a hose-sealing system for creating all hose connections during production. The use of these technologies achieves a closed process for the entire chain of production steps.

Increasing Efficiency with Automation

With the ability to fumigate all production rooms with formalin, it is possible to change production campaigns on each production line within 12 hours. Since the separate production rooms are fully independent from one another, it is also possible to facilitate a campaign switch step by step, room by room (from USP to DSP).

Through the use of robots to process roller bottles, the personnel required for this step was reduced by half and at the same time a higher production safety could be guaranteed through improved aseptic production conditions.

Equipping the rooms with standard media panels supplying all available media and mobile hanging media panels capable of being adjusted into nearly every position in each of the cleanrooms,

Continued on page 16.

Transparent clean rooms in Class 100 allow complete visibility.

"IDT used their experience gained over 10 years of production of viral vaccines for human use as a design tool to build an award-winning facility."

makes it possible to introduce new equipment at any time and significantly increase production capacity.

Highest Level of Containment

Access to the building, various production areas, and cleanrooms is controlled by an electronic access system. Only persons possessing appropriate approval and training are permitted in the production area. Personnel locks are designed as three-chambered airlocks; the material locks are double-chambered. Entry and exit occurs through separate locks. Production rooms where infectious material is handled have sub-pressure conditions. Deviations from target values are signaled on internal

Fully automated roller culture for virus production using robots.

and external monitors.

Ventilation occurs through two HEPA filter steps. All HEPA filters are fitted in fluid seals. During campaign switches, the production rooms and internal locks are fumigated with formaldehyde.

Protecting the Environment and Saving Energy

To facilitate room sterilization, the concept of contained fumigation with formaldehyde was implemented. The system operates automatically in hermetically sealed rooms. Exhaust air containing formaldehyde is conducted through an exhaust gas washer (formalin washer) and residual formaldehyde is removed by complete oxidation. Within the building, the fumigation zones are sealed off from the rest of the building during the process by doors with inflatable seals. Strict control and release procedures for residual formaldehyde assure safety for the employees.

Wastewater is drained separately according to its microbiological pollution at the site where it is created. The biological wastewater from production is collected and inactivated at 135ºC in a continual process.

Energy is saved through night-mode operation for air-conditioning systems. Through the space between cleanroom inner walls and façade (room-in-a-room principle), the outlet air is used for conditioning the intermediate area and for thermotechnical separation. Automatic blinds on glass surfaces offer optimal protection against heat and cold. Efficient energy use is attained through connecting all media to the site's central utilities supply network. Energy is saved through changing over from wastewater inactivation for each batch to a constant operating mode and through use of condensate for sanitary water production.

Operational Excellence Based on Experience

IDT used their experience gained over 10 years of production of viral vaccines for human use as a design tool to build an award-winning facility. The project's use of unique transparent building features, manufacturing area adjacencies, material handling, and equipment technologies maximizes flexibility and improves production efficiency.

Pfizer Manufacturing Deutschland GmbH

Safety and Efficiency through Containment Manufacturing

Rapidly growing demands for the smoking cessation product Chantix and future capacity for highly potent compounds led Pfizer Global Manufacturing to expand the existing capacity at Pfizer Manufacturing Deutschland GmbH in Illertissen, Germany.

Combining existing site expertise, Pfizer built the New Containment (NEWCON) Facility for Oral Solid Dosage, a fully automated oral solid dosage facility. Winner of the 2008 Facility of the Year Award (FOYA) for Process Innovation, the NEWCON facility features the highest degree of process automation within the production plant with numerous online process analytical technologies to ensure not only greater safety, but also manufacturing efficiency.

A Treatment in Demand

According to the World Health Organization (WHO), every year approximately five million deaths worldwide are attributable to diseases associated with nicotine use. Smoking is the trigger for more than 40 diseases, 20 of which can have a fatal outcome. The burden on the economy due to smoking is also serious. The WHO estimates the worldwide costs of treating diseases caused by tobacco consumption will be approximately US $635 (407 billion Euros) a year by 2010. Many smokers try to quit, but according to the WHO, only 0.5 to 5 percent are successful over the long term.

In 2006, Pfizer introduced a new drug to help adults to quit smoking. The active pharmaceutical ingredient, varenicline (Chantix/Champix – European product name), reduces smoking cessation withdrawal symptoms and reduces the craving for cigarettes. In clinical trials, it has been demonstrated that after treatment, almost half of the users successfully stopped smoking.

NEWCON exterior view.

Pfizer globally manufactures the active pharmaceutical ingredient of this highly effective drug in Little Island, Ireland and conducts the secondary production (tablets) by Pfizer Manufacturing Deutschland GmbH in Illertissen, Germany. Pfizer Illertissen ranks among the world's most modern pharmaceutical secondary production plants, and within the Pfizer Global Manufacturing Division, specializes in the oral solid dosage form production of highly potent compounds involving complex containment requirements for production staff and environment protection.

Pfizer Manufacturing Deutschland GmbH

Category Winner – Process Innovation

Project: New Containment Facility for Oral Solid Dosage (NEWCON)
Location: Illertissen, Germany
Architect: PhC PharmaConsult, Heidelberg
Consultant: PhC PharmaConsult, Heidelberg
Construction Manager/Project Manager: Hans Sägmüller, Pfizer Illertissen
Size: 83,958 sq. ft. (7,800 sq. m.)
Cost: US $55 million (35 million Euros)
Product: Chantix®/Champix®

New Directions for the Pharmaceutical Industry

The history of the NEWCON facility began in 2001. With the first planning phase of the new production facility for the smoking cessation drug, the project team from Pfizer Illertissen was faced with a challenge that is increasing in frequency in the pharmaceutical industry. That is, many newly discovered pharmaceutical actives from research are highly potent, requiring extraordinary measures to protect the production staff and the environment.

Since the conventional exposure protection using protective suits with external air supply is effective, but physically demand-

ing for staff, the planning team in the Pfizer works at Illertissen opted for an innovative solution. To ensure that no dust of highly potent substance varenicline can escape from the manufacturing area, the entire production equipment was located in a dedicated processing module and was largely automated.

This containment concept was completed and put into operation in 2003 in an existing building complex, as a prototype for further plant development. This pilot production plant Illertissen Containment (ICON) made possible, for the first time, dust-free production and fully automated production of film-coated tablets, and contributed significant features of the innovative plant design to its "big brother" NEWCON.

Manufacture in the Containment Module

The central idea behind ICON was of an impressive logic, even if that meant overturning all conventional concepts of pharmaceutical manufacturing plants. Instead of the usual spatial isolation of individual process stages in order to avoid cross-contamination, the designers achieved a single-room concept, in which the various oral solid dosage process unit operations are virtually separated by the use of isolator technologies.

Furthermore, the entire production area is encased by a hermetically sealed "high containment" module. The safe inward and outward transportation of the substances and products are ensured by vacuum systems and split-valve containment technologies. Inside the production area, laser-controlled, driverless transporter vehicles move the containers with the materials to the weighing and granulation area, to the tablet press, and to the coaters.

All the process stages are controlled and monitored from a separate control room so that the employees do not come into contact with any dust that might be generated during the tablet production run.

AGV transport system for bins in manufacturing cell.

This extent of automation has not previously existed in containment production anywhere in the world; nevertheless, ICON was only the start of an even more comprehensive innovation campaign.

Full Speed Toward a New Era of Manufacturing

Building on the plant design for the ICON project with the new

Concludes on page 20.

manufacturing facility, the batch sizes were to be multiplied and the production efficiency was to be optimized.

Particularly challenging was the ambitious aim of completing the facility in a very short time. This time pressure was further intensified a few months after the start of construction in 2006 by the extremely successful market launch of Chantix in the USA. Nevertheless, the building was completed in October 2007 after a construction period of just 25 months, six months earlier than originally planned.

This remarkable achievement was made possible by the high motivation and skill of the project team at Pfizer Illertissen and the many technical and functional experts from across Pfizer, as well as by excellent project organization.

In spite of the short time span, those responsible had succeeded in further developing significant features of the containment technology from the ICON project even during the hectic construction phase, and in further increasing the degree of automation.

Precision for the Highest Level of Safety

NEWCON is a milestone on the road to the future of the pharmaceutical industry. The elegant, futuristic company building houses one of the most modern and intelligent pharmaceuticals production plants in the current pharmaceutical industry.

The plant concept follows the through-the-wall design: all those parts of the machines, tailor-made for NEWCON, which come into contact with the product, are screened off by a transparent containment module, while all machine driving parts are located outside the containment unit and are readily accessible for maintenance and repair work.

The highest level of precision also applies to the isolator technology, as demonstrated not only by the standards that can be met within the plant in regard to dust measurement. The active substance for varenicline is categorized in Pfizer's internal upper exposure safety range, permitting a maximum workplace concentration of between 1 and 10 µg per cubic meter. NEWCON's containment system also will safely process active substances whose exposure limit level lies well below 0.1 µg per cubic meter.

Thus, the safety concept of NEWCON reaches the limits of what is technically possible today. Theoretically, employees could remain within the containment area even without protective measures and still be unharmed.

A Farewell to Time-Consuming Analysis Procedures

A comprehensive implementation of PAT technologies follows the vision of an adaptive, automated quality control system, which is intended to entirely replace the classical analysis procedures such as HPLC analysis in the future. PAT applications are used in all key areas of the NEWCON production process. For example, in the mixing and granulation process, Near Infra-Red (NIR) spectroscopy is used to check whether the mixture is homogeneous and the active substance is present in equal doses in all the tablets.

Additional PAT applications determine whether the weight, hardness, and diameter of the tablets conform to the specified standards. In contrast to the time-consuming HPLC analysis using manual samples, the continuous online analysis enables staff to respond swiftly in the event of faults and irregularities. PAT components were already in the predecessor ICON production plant in order to optimize the quality and stability of product manufacture.

Control center.

However, it is only in combination with process control systems that process analytical technologies can reach their full potential, and thus make a significant contribution to increasing the quality, safety, and efficiency of the manufacturing process.

Lean Manufacture without Frictional Losses

As early as the planning phase of NEWCON, the planning team placed great importance on implementing the concepts of lean manufacturing. With model simulation software in the run-up to production, all the future production processes were illustrated virtually, and optimized. The NEWCON team of experts was able to synchronize all the process stages so far that the plant is running at full capacity after just a brief running-in period and downtime can be avoided. As soon as the first process stage within the containment plant is completed, the next batch is brought in so that up to three batches can be produced in parallel. Through this semi-continuous production sequence, it has been possible to achieve a significant increase in output compared with the predecessor project ICON. NEWCON has a capacity of a billion tablets per year in three-shift operation round the clock and five days a week.

Innovation Yields Safe and Efficient Manufacturing

Initially, the introduction of containment production at Pfizer Illertissen was largely aimed at improved health and safety at work. However, this innovative method of production not only ensures safety, but is also capable of releasing unanticipated efficiency potential.

The intelligent linking of the production stages within the fully automated containment production leads to greatly reduced personnel costs and much lower frictional losses over the overall production process.

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F. Hoffmann La Roche AG

The Ultra Fast Track to Innovative Cancer Drugs

To make their innovative cancer drugs available as quickly as possible to an increasing number of patients, Roche made plans to "ultra fast track" their Biologics IV project in Penzberg, Germany for target completion in three years.

Not only was the project delivered four months ahead of schedule. It was executed below budget and resulted in high satisfaction ratings from the owner. For these reasons and more, Biologics IV is the winner of the 2008 Facility of the Year Award (FOYA) for Project Execution.

Paving the Way for More Innovation

Headquartered in Basel, Switzerland, Roche is one of the world's leading research-focused healthcare groups in the fields of pharmaceuticals and diagnostics. The company is a world leader in in-vitro diagnostics and drugs for cancer and transplantation, a market leader in virology, and active in other major therapeutic areas such as autoimmune diseases, inflammation, metabolic disorders, and diseases of the central nervous system.

To increase production capacity for Trastuzumab, the Active Pharmaceutical Ingredient (API) for the anti-breast cancer drug Herceptin, and eventually production for other monoclonal antibodies, Roche initiated expansion of its Penzberg site, already one of the world's largest biotechnology centers. The expansion, called "Biologics IV," was designed, built, and put into operation in under three years.

Four stories high, the expansion consists of two highly automated production lines each containing three 12,500 Liter fermenters and downstream processing. The project also included associated laboratory and office space.

Biologics IV, Penzberg, Germany.

Teamwork at Its Best

A team of experienced, high quality, and team-orientated Roche engineers who previously worked together on projects all over the world, was assembled. Under the guidance of Horst Hohler, Head of Roche Pharma Global Engineering, the team provided continuity and stability to Biologics IV.

The Users, led by Dr. Juergen Wahl, head of Biotech Production Penzberg, were also key team members. The Users were fully integrated into the project team from day one and took part in every aspect of the project, resulting in the Users receiving a facility in which they were fully trained, leaving them free to focus on production.

Most of the major contractors selected also previously worked with Roche. The project team invested a great deal of time and effort to ensure the contractors were fully integrated into the spirit of the project. Team building workshops and social events to celebrate success were a welcome feature of the project. Challenges were openly discussed with the contractors in a "no blame" culture, with suggestions welcomed, evaluated, and acted upon.

The complete Penzberg team developed a close cooperative relationship with their Roche colleagues who were simultaneously constructing a new biotech production facility in Basel, Switzerland. The exchange of knowledge and experience was highly valued by both teams. This led directly to cost and time savings when solutions to common problems were implemented on both projects.

"We were facing a lot of challenges in this

F. Hoffmann La Roche AG

Category Winner – Project Execution

Project: Biologics IV
Location: Penzberg, Germany
Architect: Koppenhöfer & Partner GmbH
Engineer: Roche Pharma Global Engineering
Engineering Contractor: LSMW GmbH – Total Life Science Solutions
Construction Manager: SIBC GmbH – A Turner & Townsend Co.
Size: 355,209 sq. ft. (33,000 sq. m.)
Cost: US $290 million (186 million Euros)
Product: Trastuzumab (API for Herceptin®)

"There are many reasons why Bio IV was so successful. Most importantly, however, has been the excellent cooperation and communication within the integrated, highly motivated project team, said Horst Hohler, Head of Roche Pharma Global Engineering."

Down stream processing.

project but one was very specific: Running two investments of this size and complexity in parallel," said Hohler. "There are many reasons why Bio IV was so successful. Most importantly, however, has been the excellent cooperation and communication within the integrated, highly motivated project team."

The elevated level of performance in project execution would not have been possible without the drive and focus of the project team, led by Project Manager Claus Herrmann.

Starting in project initiation and continuing through qualification, Herrmann organized a series of workshops where the challenges, risks, and solutions were systematically identified, analyzed, and resolved. The critical series of workshops developed the highly successful and innovative execution strategies for design, procurement, construction, and commissioning.

Concludes on page 24.

"This project was teamwork at its best," said Herrmann. "Everybody was so passionate and committed to the project and proud to be part of it."

Time-Saving Strategies

A schedule analysis showed that the equipment and piping installation and automation software development drove the critical path during construction. Building on experience of past projects, the team realized that skid mounted equipment reduced process equipment installation time from weeks to days.

A major review of the process and utility equipment was organized with the aim of using skid mounting as much as possible. This brought three immediate benefits: 1) The skids could be completed while the building construction was still in process, 2) The quality of the process equipment installation could be guaranteed as it was carried out under factory conditions, and 3) The field installation time for the process equipment was reduced from months to days.

The skids were installed very quickly. It took only six weeks for the hook-ups and the first skid was commissioned before the last skid was installed.

The project team also focused its attention on automation. Borrowing software techniques from the telecom industry, the huge volume of process automation software was broken down into small modules and additional programming resource was applied to compress the writing and testing time.

The natural extension of this was to use "copy/paste" as much as possible in the process design and the automation software production. To ensure the timely delivery of fit-for-purpose software, a large quality and progress control regime was set up. This delivered the software fully tested and ahead of schedule.

The final compression of the schedule was achieved by analyzing the commissioning and qualification steps required. Everything possible was commissioned and qualified in the factory. The actual field commissioning and qualification was managed using "Petrochem Shut Down" techniques. The work was subdivided into small tasks and two seven-day week shifts were employed to reduce the commissioning/qualification time to a minimum. An added benefit was that the skid mounted equipment allowed field commissioning to take place in close integration with the construction work. In practice, this meant field commissioning a skid while the building contractor was still working in the area. This called for careful co-ordination of the average 400 trade operatives and commissioning teams.

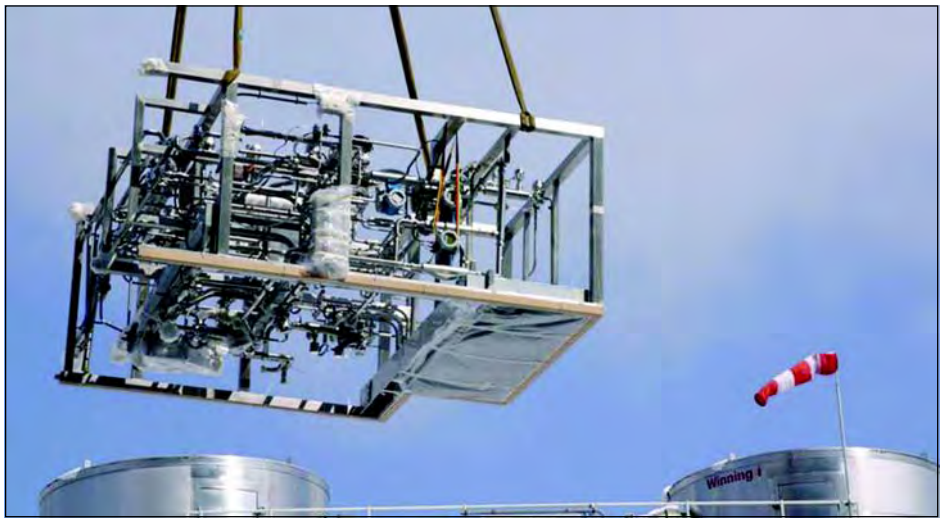
Customized for the Users

By involving the User's management and operatives from the start of the design, the final plant reflected their working practices. They were involved in the equipment layouts and advised on instrument positions and access stairs. The modular software was developed to their requirements which eliminated a lot of changes, training, and familiarization time required with a normal plant.

For the Cleaning and Sterilization in Place, which was critical to the success of the facility, the operatives brought the practical knowledge from every day experience and the design engineers developed the system around the operative requirements. The resulting systems run efficiently.

The facility's Manufacturing Execution System (MES), including Electronic Batch Recording, was developed in a similar manner. The MES delivered a reduction of labor cost and an increase of production process quality with the following built-in functionality:

- batch planning board for optimal sequencing of batches increasing equipment utilization
- sample and filter management to enforce correct equipment and batch status in real-time assuring highest GMP standards
- complete tracking of material movements allowing a full genealogy of use of raw materials vs. finished goods batches traceable from both ends
- shuttle management tracks inventory and location of containers and controls transport orders to shuttle system leading to optimized use of transport and storage capacity



Arrival of prefabricated skids on site.

Excellence in Project Execution

With teamwork and innovation, Roche's ultra fast track project execution achieved its first production batch 36 months after the start of conceptual design. Once running at full capacity, Biologics IV will enable the supply for 100,000 additional Herceptin patients per year.

"The challenging project was terminated well in time and within budget," said Wahl, head of Biotech Production Penzberg. "This could only have been achieved by excellent project teams and perfect coordination by the project management."

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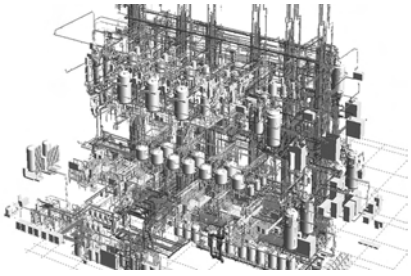

CLIENT: Roche Diagnostics
LOCATION: Penzberg, Germany
PERIOD: 2004 - 2007
PROJECT: BIOLOGICS IV
New Biotechnological Production Facility with 2 Multi-Product Lines for the Production of Monoclonal Antibodies

“2008 Facility of the Year Category Winner”

CLIENT: GSK Biologicals
LOCATION: Dresden, Germany
PERIOD: 2005 - 2007
PROJECT: New Facility for the Production of Flu Vaccine

CLIENT: Hermes Pharma
LOCATION: Wolfsberg, Austria
PERIOD: 2007 - 2008
PROJECT: New Production Facility for Solid Dosage Forms

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Why Our Project Should Win the 2008 Facility of the Year Award

The following are excerpts from the Category Winners' submissions stating, in their own words, the top reasons why their project should win the 2008 Facility of the Year Award:

Boehringer Ingelheim

- The **integration of all major functions** for pharmaceutical development in one building promotes synergies, optimal communication, and seamless cooperation across the relevant disciplines (formulation development, process development, clinical trial supplies manufacture, and packaging/labeling).
- The creation of **state-of-the-art GMP facilities** for internationally acceptable manufacture of solids, liquids, and parenteral clinical trial supplies from small scale Phase I supplies up to large Phase III batch sizes provides a unique multipurpose GMP environment for the development of new drug products.
- **Flexibility** provided by the building layout and zoning concept is essential for a R&D multipurpose facility where a broad diversity of product types, batch sizes, potencies, and dosage forms are typically handled … future needs for new technologies must be accommodated without major renovation.
- Creation of **areas for safe handling of highly potent actives** without compromising flexibility necessary in a development environment
- **Technical concept** for HVAC systems allows cost effective and sustainable operation of the building. This is realized by heat recovery systems, energy saving by light and sunblind control, variable air changes dependent on the specification and processes, separate technical areas for repair and maintenance, and permanent monitoring of the HVAC systems.

Bristol-Myers Squibb

- First **GMP operational** clinical sterile continuous process isolation facility in the US.
- **Innovative integration** of overall manufacturing strategy with scalable design for sterile and oral solid dosage products.
- Incorporates **innovative technologies** into existing facility for solvent-based and potent compound to promote safety, quality, and compliance.
- **Wireless technology** and electronic batch records allow development data to be automatically gathered during GMP manufacture.
- Increased GMP development capabilities allow **Quality by Design (QbD)** throughout the clinical program.
- **Increases overall capacity** and productivity for the pipeline
- **Minimal** site and **environmental disruption**
- Simultaneous **multi-product processing**
- **Technology** lessons learned could be implemented for the later phase development and transfer.
- Facilitates **technology transfer** to commercial sites.
- Accommodates new **US FDA Vision** for QbD and Process Analytical Technology (PAT)
- **Cutting edge**, wireless Delta V Data Gathering.

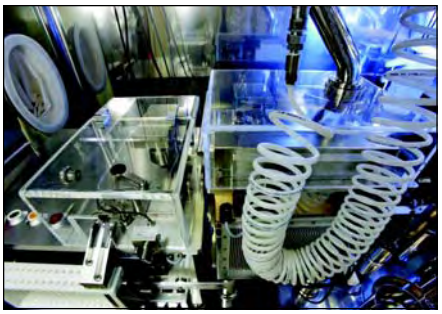
IDT Biologika GmbH

- **Trend Setting –** The building's transparency and color, state-of-the-art equipment, and flexibility demonstrate technological progress and developments over 10 years of production. All-glass material locks and glassed-in passageways allow views of the entire building.
- **Building Concept –** The concept of the multipurpose facility consists of strict horizontal division of the service areas and the serviced areas into four levels. A strategy was devised to guarantee the shortest supply and disposal routes. All operations are as much as possible contained in cleanrooms and contained technical systems.
- **Equipment Innovation –** Two production lines were created for different aseptic manufacturing technologies with a fumigation lock, automated laser technique for opening eggs, and Restricted Access Barrier System for processing eggs on one line. The other line has robots for cell culturing and virus propagation.
- **Flexibility –** Climate chambers for every temperature range allow pro-

duction of viruses on various cell substrates using different technologies. Standard and mobile hanging media panels capable of being adjusted into nearly every position make use of the new equipment possible, as well as significant increases in capacity.

- **Effective Project Management –** Project Management achieved consistent application of established on-site standards during design of piping materials, MSR and automated technologies, integration of electronic planning into a network of all planning partners, implementation of a change control system during the entire project, and ongoing fitting of a prototype room with relevant equipment.

Pfizer



- **Facility Design –** A new facility was built under an extremely aggressive timeline to support market demand. Equipment installations utilize the so-called containment technology. All such contained equipments are combined in a single High Containment Module with a high degree of automation and without manual operator intervention.
- **Systems –** The degree of automation is completely novel. MES layer system triggers all process sequences from dispensing to coating in the automation layer. Transporting of goods and materials is carried out automatically by Automated (laser-) Guided Vehicles without any operator control. The processing is executed at equipment level. The batch data are collected automatically into the MES. Raw data are archived in data historian.
- **Operational Excellence –** From design of robust process (as part of US FDA's pilot program), from facility concept to ramp up of production, the project comprises all elements of modern manufacturing. Process robustness, facility design, and throughput simulation for lean manufacturing was applied to accommodate synchronized operations to maximize capacity with "semi continuous flow."
- **PAT –** PAT applications are installed across the manufacturing process to support the vision of continuous quality verification. Raws NIR identification and evaluation, online NIR blend monitoring, online NIR core testing, and NIR testing of film coated tablets are in place to support the vision of adaptive process control and/or to replace conventional release testing. NIR water content is filed; filling of online NIR core testing is foreseen.
- **Safety –** No operator attendance is required, substantially enhancing health and safety aspects for the employees.

F. Hoffmann La Roche AG

- **Ensuring supply of innovative oncology drug to patients.**
- **Excellence in execution of an ultra fast track project:**
  - Delivering a high quality facility four months ahead of a fast track schedule.
  - 36 months from start of concept design to successful production of performance lots is a record for Roche and for the industry in general we believe.
  - 100% tested functionality (process, building, automation) and qualification reports approved at the time of hand over.
  - Project within cost budget.
  - Outstanding safety record.
- **Excellence in project procurement, expediting, and quality control.**
  - Close coordination of procurement with another major biotech project in Switzerland running in parallel.
  - All trade contractors and vendor's packages, except proprietary equipment, were bid competitively.
  - Sophisticated expediting including extensive progress and quality control at the suppliers workshops (including the automation package) to ensure timely delivery of high quality packages to site.
- **Exemplary project management and leadership**
  - Established excellent project cultural behavior.
  - Team-spirit and outstanding focus on ultimate project goal.
  - Implementation of innovative design and execution strategies to achieve ambitious project goals.
- **Innovative, economic, and lean technical solutions implemented and/or developed within the project**

ISPE would like to thank the following Facility of the Year Category Winners' key project participants for their generous advertising support which made this Supplement possible.

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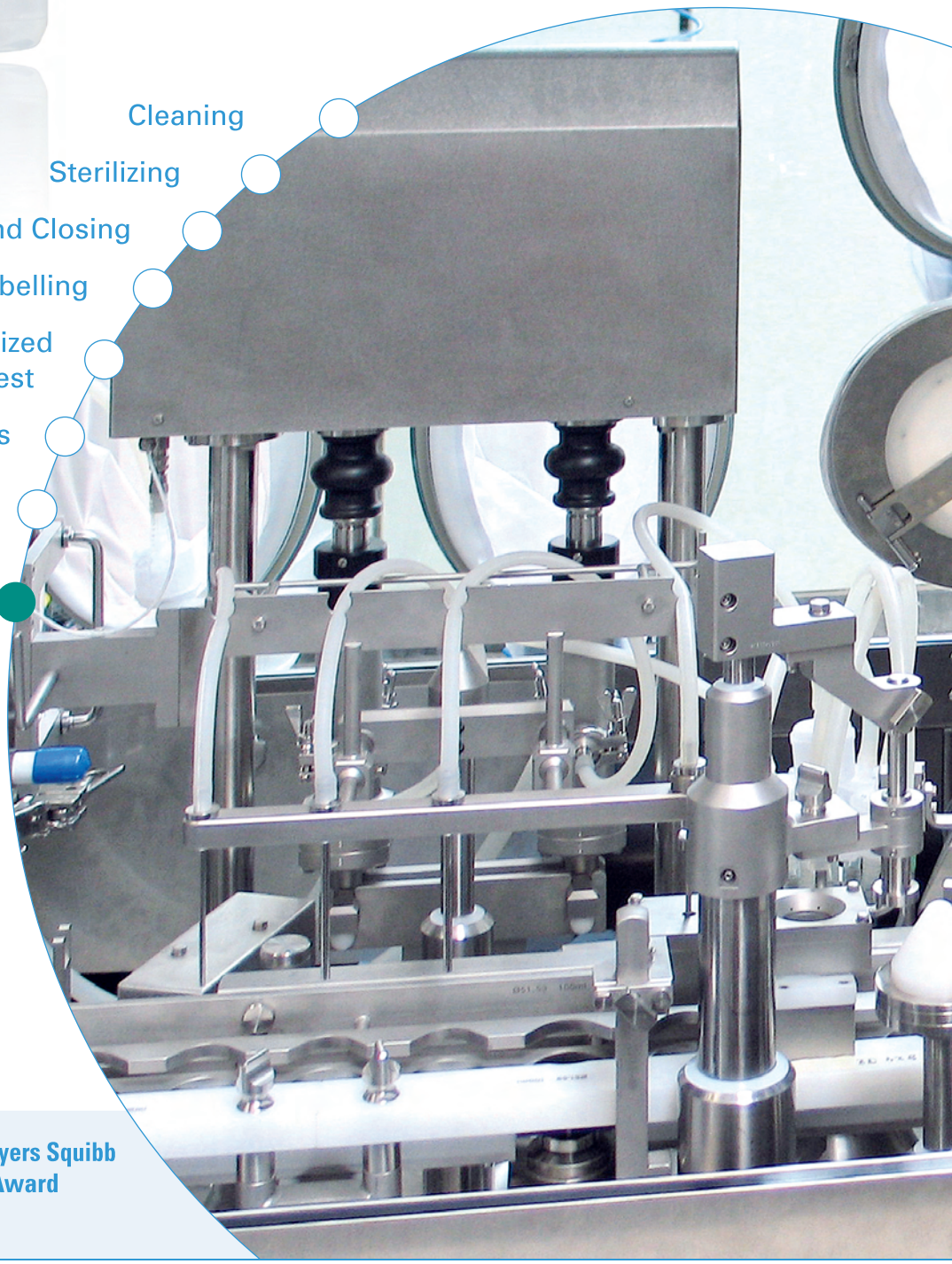

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