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A Multi-Functional Polymeric Nanoparticle Strategy for Modulation of Drug Resistance in Cancer

by Lilian E. van Vlerken and Mansoor M. Amiji

This article describes an investigation on the use of a combination therapy administered within polymeric nanoparticles in order to overcome Multiple Drug Resistance (MDR), one of the most challenging threats to survival in the battle against cancer.

Introduction

In the battle against cancer, the development of Multiple Drug Resistance (MDR) poses one of the most challenging threats to survival, and is commonly found to be the reason for tumor persistence despite invasive chemotherapy. MDR refers to a cross-resistance to structurally and functionally unrelated drugs, thereby rendering the tumor unresponsive to most chemotherapeutic options. Chemo-resistance can generally result from either of two means, by a physical impairment to drug delivery to the tumor,[1] such as poor absorption, increased metabolism/excretion, or poor diffusion of systemically-administered drugs into the tumor mass, or more challengingly, through intracellular mechanisms in the cancer cell itself.[2] Alterations in the intracellular machinery of cancer cells is commonly implicated in the development of MDR, and often more than one mechanism, either simultaneous or sequential, may be responsible for development of the resistant cell phenotype.[3] Initially, the ATP-dependent drug efflux transporters, which included P-glycoprotein, were identified as the sole basis for MDR,[4] leading to tremendous therapeutic development efforts aimed at blocking the efflux transporters. Unfortunately, the preclinical and clinical results from this strategy have not been encouraging. This strengthened the idea that MDR in cancer is in fact due to other mecha-

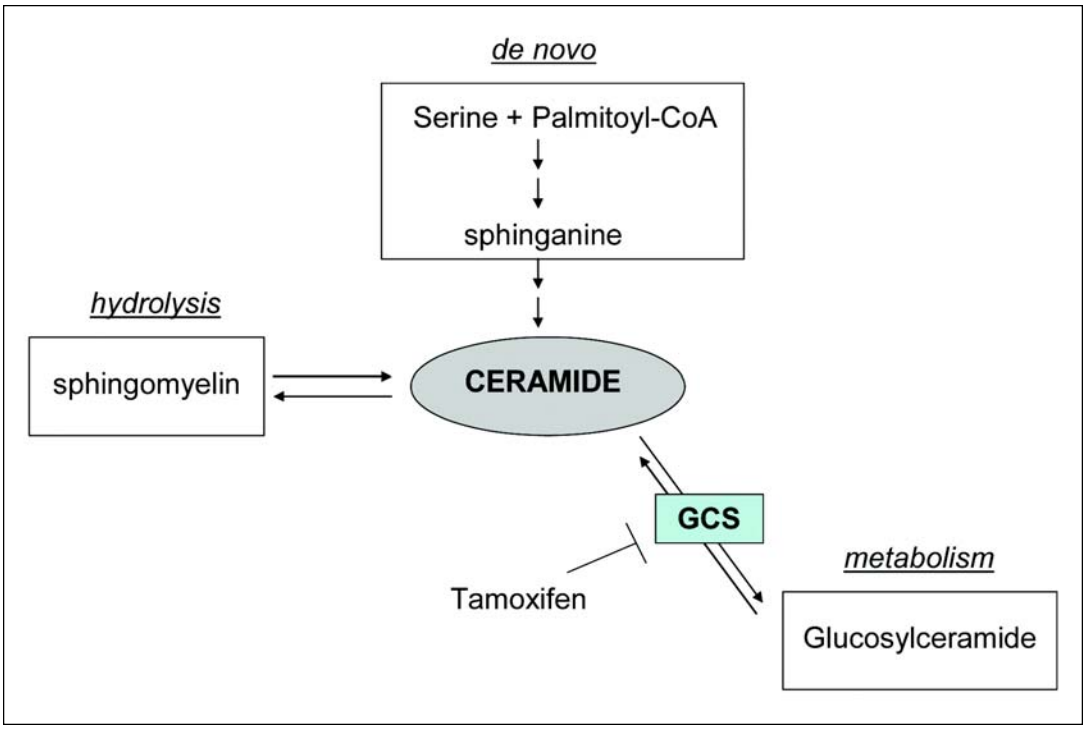

Figure 1. Schematic illustration of ceramide synthesis and metabolism.

nisms besides drug efflux, and so in recent years, studies are being performed to establish and potentially exploit other mechanisms by which the MDR phenotype develops. Of this, the role of DNA repair following damage through topoisomerase I and II activity and neutralization of electrophilic drugs by glutathione-s-transferase have been reported as mechanisms whereby the cancer cells also develop chemoresistance.[3] In addition, modulation of programmed cell death (*apoptosis*) following chemotherapeutic stress has emerged with clear importance as a strategy whereby cancers become chemoresistant. Deregulation of several key apoptosis modulating factors has been described in various experimental cases of MDR,[5] including functional up-regulation or overexpression of anti-apoptotic mediators such as p21, Bcl-2, and Bcl-XL, and/or down-regulation of the classic oncogenic mediator, p53. As a result, MDR modulation strategies are increasingly looking away from the ABC-transporter paradigm and toward modulation of cellular apoptotic signaling. Several apoptosis modulating strategies (e.g., protein tyrosine kinases PKI166 and ST1571, Bcl-2 antisense such as G-3139, and retinoids 9-cis-RA and AM-580) are currently in clinical trials, and their efficacy in MDR modulation is largely under preclinical and clinical investigation.

Ceramide (CER), a naturally occurring sphingolipid, is derived intracellularly by hydrolysis of the lipid sphingomyelin, or by *de-novo* synthesis through N-acylation of sphinganine[6] - *Figure 1*. Accumulation of endogenous CER, produced either by hydrolysis or *de novo* formation, is known to result in response to several stimuli, including stress, regulating apoptosis and cell cycle arrest, where CER functions as a second messenger in the signaling cascade that initiates these responses.[6,7] In fact, studies have shown that administration of exogenous CER analogs, particularly C2- and C6-ceramide, encourages cell death by apoptosis and inhibition of tumor growth in several tumor models.[8] In the cell, CER can subsequently be further metabolized by the enzyme Glucosylceramide Synthase (GCS) to yield glucosylceramide (gluCER), a glycosylated form of CER that does not have pro-apoptotic activity.[9] Several MDR tumor cell lines have exhibited elevated levels of non-cytotoxic gluCER and corresponding elevated levels of GCS, and clinical studies have noted elevation of gluCER levels in tumor specimens of breast cancer and melanomas that were poorly responsive to chemotherapy.[9] These findings not only suggest the importance of CER in the mediation of the cytotoxic response to anti-tumor chemotherapeutics, but also they suggest that inhibition of apoptotic signaling may be an important mechanism whereby tumors develop MDR.

While the development of MDR poses a great threat to survival of cancer patients, drug delivery to solid tumors in and of itself is a significant challenge that also determines survival outcome. A major barrier to successful anti-cancer therapy is the challenge of delivering the required therapeutic concentration to the tumor site while minimizing undesirable side effects resulting from systemic administration. Site-specific drug delivery systems increase the therapeutic benefit by delivering a greater fraction of the dose at the target site, which minimizes the amount of therapeutic that accumulates at non-specific targets. Drug delivery throughout the tumor mass is crucial for the treatment to be effective since residual cancer cell survival can promote re-growth and often becomes the cause for drug resistance.[10] Physical hurdles posed by solid tumors greatly hinder chemotherapeutic drugs from entering and/or traversing throughout the tumor mass, thereby resulting in an ineffective treatment. Nanoscale drug carriers, such as liposomes, micelles, dendrimers, and polymeric nanoparticles, can bypass these hurdles by taking advantage of unique physiologic parameters of the tumor mass, termed the enhanced permeability and retention (EPR) effect,[11] to greatly improve drug delivery to and throughout the tumor mass.

Biodegradable polymers such as poly(epsilon-caprolactone) (PCL) are useful materials to formulate drug delivery carriers for tumor targeted delivery. Biocompatibility and degradation methods of these polymers have been widely studied,[12] and found to be non-toxic, leading to the US FDA approval and acceptance for medical applications. Additionally, these polymers offer an advantage for drug delivery, whereby they efficiently encapsulate hydrophobic compounds, and slow degradation of the particle allows for extended release of the drug.[13] Surface modification of the nanoparticles with a poly(ethylene oxide)-poly(propylene oxide) triblock copolymer (PEO-PPO-PEO, Pluronic®) improves the stability of the nanoparticle in the aqueous environment of the body, while decreasing immune activation, repelling plasma proteins and decreasing reticulo-endothelial uptake leading to an increase in circulation time and passive tumor targeting by the enhanced permeability and retention effect. Previous studies from our group have shown that paclitaxel (PTX)-containing PEO-PCL nanoparticles remain stable *in-vivo*, and retain their Pluronic® surface layer to increase the circulating half-life of PTX from a fraction of an hour to 25.3 hours, alongside an 8.7-fold higher tumor drug concentration.[14]

The purpose of this work was to overcome MDR in a model of human ovarian cancer through a combination therapy administered within long-circulating polymeric nanoparticles. The combination therapy consists of either C_6-ceramide (CER) or the GCS inhibitor tamoxifen (TAM), aimed to restore the defaults in apoptotic signaling, along with a pro-apoptotic chemotherapeutic drug paclitaxel. The aspect of this therapy is to overcome MDR through a multi-pronged approach that includes: (1) restoration in the defects in apoptotic signaling, (2) enhancement of drug delivery to the tumor site, and (3) by delivering the drugs intracellularly, thereby potentially avoiding P-glycoprotein-mediated drug efflux. Few groups have investigated the use of nanoparticles in the treatment of MDR, and those that have focused on facilitating the delivery of chemotherapeutic drugs past the P-glycoprotein pump, thereby evading drug efflux and leading to enhanced chemosensitivity. However, to date, the use of nanoparticles has not been investigated as a therapeutic approach to overcome alternate, or simultaneously multiple mechanisms of MDR, supporting the novelty of the described therapeutic approach.

Materials and Methods

Nanoparticle Fabrication and Characterization

Poly(ethylene oxide)-modified poly(epsilon-caprolactone) (PEO-PCL) nanoparticles were prepared by controlled solvent displacement in an acetone-water system with a 20% (w/w) surface modification with a poly(ethylene oxide)-poly(propylene oxide) triblock copolymer, Pluronic® F- 108 NF grade Nanoparticles were loaded individually at 10% (w/w) PTX, 20% (w/w) C_6-CER, or 20% (w/w) TAM. For intracellular trafficking studies, PTX-loaded nanoparticles were supplemented with 0.1% w/w rhodamine-paclitaxel. Nanoparticles were analyzed for size on a Brookhaven ZetaPlus particle analyzer and visualized by Scanning Electron Microscopy (SEM) on a at 5,000x magnification under an accelerating voltage of 3kV.

Cell Culture and Treatment

Human ovarian carcinoma cells, SKOV3, and their MDR phenotype, $SKOV3_{TR}$., were kindly provided by Dr. Michael Seiden (Massachusetts General Hospital, Boston, MA). The $SKOV3_{TR}$ culture was developed by prolonged exposure of increasing concentrations of paclitaxel, and maintained in 0.2 µM paclitaxel to uphold the MDR phenotype. Cells were subjected to dose-response treatments of the individual drugs and drug combinations in serum-supplemented medium either as free drugs (solution) or encapsulated within PEO-PCL nanoparticles. Culture medium was used as a negative control (0% cell death) and 50 µg/mL poly(ethyleneimine) in medium was used as a positive control (100% cell death). Treatment proceeded for six days undisturbed at 37°C in a humidified chamber at 5% CO_2, after which remaining cell viability was measured by the MTS assay.

Intracellular Drug Trafficking and Quantitation of Intracellular Drug Levels

To quantitatively determine the amount of intracellular PTX accumulation resulting with or without the nanoparticle delivery system, PTX loaded PEO-PCL nanoparticles were manufactured as previously described with the addition of ^{3}H-PTX at 1.5 µCi/mg unlabeled drug. SKOV3 and $SKOV3_{TR}$ cells were allowed to adhere in six well plates at 1 x 10^5 cells/well, and treated with a 0.1 µM dose of PTX for six hours at 37°C in a humidified cell culture incubator. Following the treatment period, cells were washed three times, lysed with 1 mL of lysis buffer, and collected into scintillation vials. Each sample received 10 mL Scintisafe® scintillation fluid per 1 mL lysis buffer, and was left to quench for two hours in the dark.

Following this, counts per minute of the ^{3}H were collected on a a/b scintillation counter. To determine the total amount of protein in 1 x 10^5 cells for each cell type, cells were lysed in parallel for extraction and quantitation of total protein. The results are expressed as % of dose accumulated intracellularly per mg of total protein.

Measurement of Apoptotic Activity

To measure the degree of apoptosis in $SKOV3_{TR}$ cells following treatment with PTX alone and PTX + CER, apoptosis was measured using a commercial apoptosis assay kit that stained apoptotic cells using Yo-Pro-1® and propidium iodide (PI). SKOV3 and $SKOV3_{TR}$ cells were allowed to adhere into 96-well optical quality plates at a density of 2x10^4 cells/well, and subjected to treatments with PTX, CER, or PTX + CER at varying doses for 12 hours. Following the treatment period, cells were stained for apoptotic activity and measured by *in-situ* cytometric analysis of live cells by simultaneous Laser Scanning Cytometry (LSC) and epifluorescent microscopy. Yo-Pro and PI were excited at 488 nm by an argon laser and absorbed at 515 to 545 nm and 600 to 635 nm respectively. Each sample scan was repeated four times, all treatments were run in triplicate, and the entire set up and analysis was repeated once more at a later date.

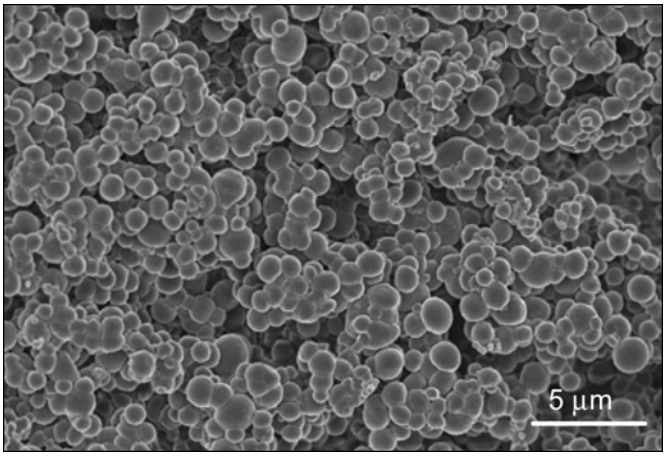

Figure 2. Scanning electron micrograph of poly(ethylene oxide)-modified poly(epsilon-caprolactone) (PEO-PCL) nanoparticles. (Scale bar represents 5 μm).

Results and Discussion

Using the solvent displacement method, optimized in our lab, PEO-PCL nanoparticles were formed in a reproducible manner with a uniform spherical appearance and a mean diameter of around 210 nm - *Figure 2*. The encapsulation efficiency of PTX, CER, and TAM was found to be more than 95% at the added concentrations in PEO-PCL nanoparticles. Dose-response studies on the SKOV3 and $SKOV3_{TR}$ lines against PTX verified the highly drug-resistant nature of the MDR line, where PTX IC_{50} was more than 100-fold higher at 1.08 µM (versus 0.008 µM for the SKOV3 cells), as demonstrated by the far right-shifted dose response curve - *Figure 3*. In addition, the MDR phenotype of this cell line was further characterized by the presence of both P-glycoprotein and GCS, which were not expressed by the SKOV3 cells (data not shown). Modulation of the MDR nature will result in chemosensitization against PTX, causing the far-right shifted dose-response curve to shift back toward that of the drug-sensitive SKOV3 cells. Figure 3a shows that the co-therapy of PTX with CER (at a consistent dose of 10 µM) on the $SKOV3_{TR}$ cells in fact shifts the dose-response curve slightly to the left. Chemosensitization with this combination treatment is seen, for example, whereby a 1 µM dose of PTX kills merely one-third of the MDR population (65.6 ± 2.2% survival), but the

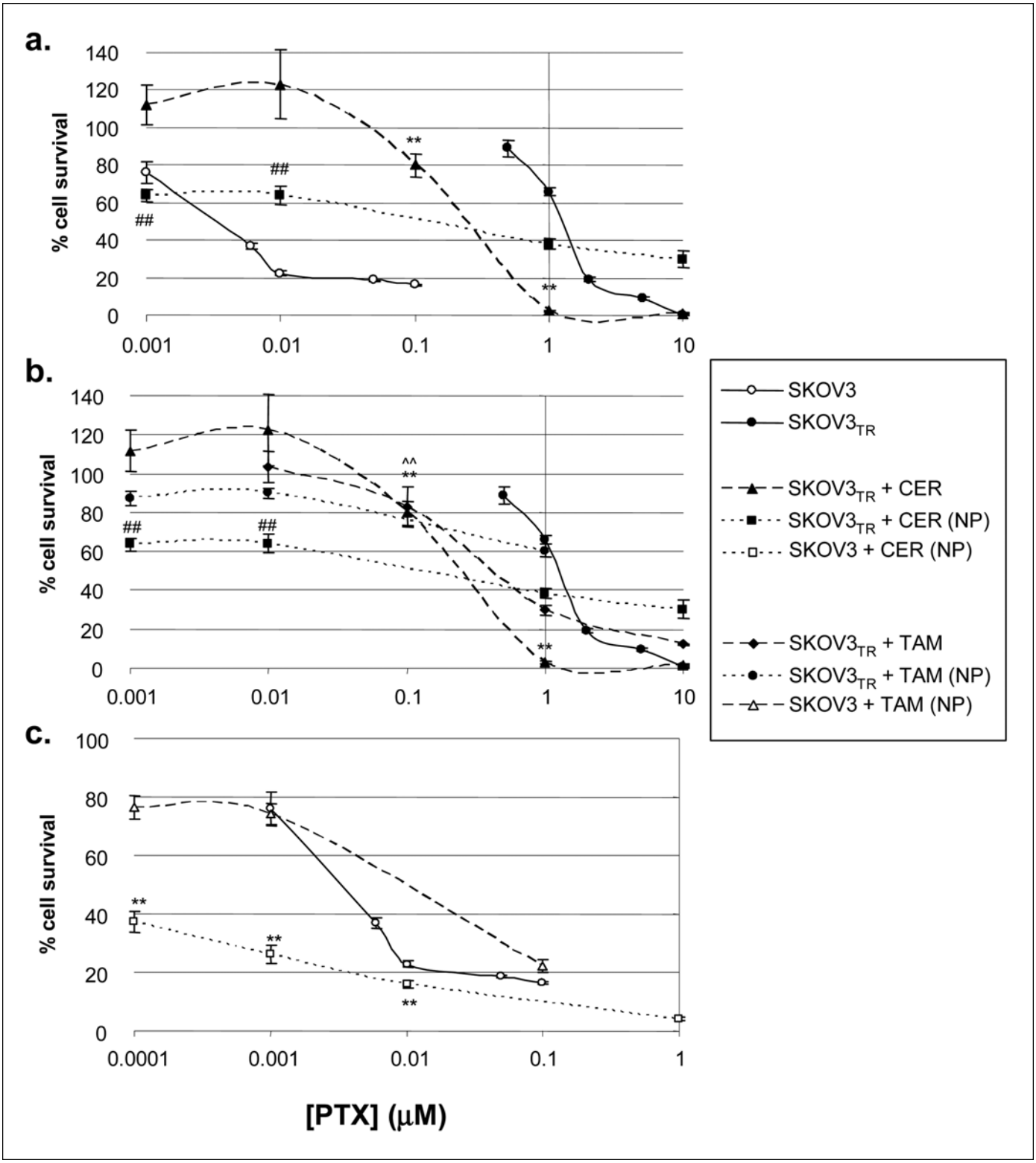

Figure 3. PTX dose response of SKOV3 and $SKOV3_{TR}$ cells with or without a co-therapy as free drug or encapsulated within PEO-PCL nanoparticles (NP). a) comparison of the PTX dose response on SKOV3 and $SKOV3_{TR}$ and the effect of the PTX + CER therapy in solution and in nanoparticles, b) comparison of the PTX dose response in $SKOV3_{TR}$ cells to the PTX + CER therapy and the PTX + TAM therapy, and c) comparison of the PTX dose response in SKOV3 cells and the effect of the PTX + CER and the PTX + TAM therapies; ** indicates a statistically significant difference ($p<0.001$) between treatment with PTX alone and PTX + CER within the same cell type, ^^ indicates a statistically significant difference ($p<0.001$) between treatment with PTX alone and PTX + TAM within the same cell type, and ## indicates a statistically significant difference ($p<0.001$) between treatment with a co-therapy in solution and in nanoparticles ($n = 8$ samples/group).

same 1 µM dose of PTX alongside 10 µM CER eradicates nearly the entire population (2.7 ± 0.5% survival). It is important to note that this dose of CER in itself is not cytotoxic, purposefully chosen to investigate whether this co-therapy acts synergistically rather than additive. However, the combination therapy did not possess the power to revert the MDR chemosensitivity back to the drug-sensitive nature - e.g., a 0.01 µM dose of PTX alongside CER did not result in any cell death - while that same dose of PTX on the SKOV3 cells resulted in a mere 22.7 ± 1.1% survival. This is likely due to the remains of other mechanisms of MDR in the cells. Since it is ?known that the $SKOV3_{TR}$ cells over-express P-glycoprotein in addition to GCS, and since it is well known that PTX is a substrate for P-glycoprotein efflux, it was of interest to examine whether the former mechanism of MDR could be overcome by this therapy as well. Although nanoparticle encapsulation is mainly for the *in-vivo* benefit of enhanced tumor drug-delivery, it was of interest to see whether nanoparticle drug delivery could lead to intracellular drug delivery, thereby evading the P-glycoprotein efflux machinery, a phenomenon that has been described by several groups.[15-17]

Dose-response studies on the $SKOV3_{TR}$ cells interestingly revealed that the combination of CER modulation and nanoparticle delivery did in fact revert chemoresistance even further, as predicted, as seen in Figure 3a. Hereby the 0.01 µM dose of PTX alongside CER that did not revert chemoresistance when delivered as free drugs (solution), resulted in an eradication of nearly half the MDR population (64.0 ± 5.0% survival) when delivered to the cells encapsulated within nanoparticles. To verify that this phenomenon indeed occurred due to enhanced intracellular retention of the P-glycoprotein substrate PTX, intracellular levels of drug following solution or nanoparticle delivery were quantitated through the presence of a ^3H label on the PTX.

Figure 4 reveals precisely what was expected, mainly that intracellular retention of PTX in the $SKOV3_{TR}$ cells following administration of the un-encapsulated drug was only about half of the amount that retained in the drug sensitive SKOV3 cells, likely explained by the presence of P-glycoprotein-mediated drug efflux in the $SKOV3_{TR}$ cells. However, when the same dose was delivered to the $SKOV3_{TR}$ cells encapsulated in nanoparticles, a significantly greater amount of the dose retained intracellularly. Since this phenomenon was not present in the drug-sensitive SKOV3 cells, which lack P-glycoprotein, the data indeed suggests that the enhanced chemosensitization seen with the nanoparticle-mediated PTX + CER treatment could be due to a modulation of both apoptotic signaling as well as P-glycoprotein drug efflux. However, nanoparticle therapy lacked this profile at higher doses of PTX, and in fact resulted in less chemosensitization at these doses than the solution co-therapy. This is likely explained by the fact that the internalization of nanoparticles into cells is a saturable process, whereby the cell saturation limit of these particles had been reached at these higher doses of PTX. Nonetheless, it is the objective to obtain cell-kill at lower therapeutic doses of PTX in the MDR phenotype, thus

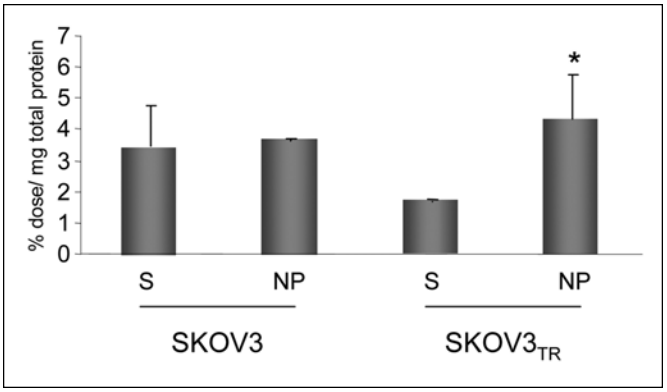

Figure 4. Intracellular paclitaxel (PTX) accumulation in SKOV3 and $SKOV3_{TR}$ cells treated with 0.1 μM PTX containing a ^3H-PTX label (1.5 μCi/mg drug) in solution (S) or in PEO-PCL nanoparticles (NP) after a six hour treatment period; * indicates a statistically significant difference ($p < 0.05$) between S and NP drug accumulation ($n = 3$ samples/group).

the effect of this therapy at lower doses of PTX is of greater importance.

Since the CER co-therapy aimed to re-instate the defects in apoptotic signaling, it was of importance to verify that chemo-sensitization of MDR by this combination approach is indeed due to a restoration of apoptotic signaling. To verify this, the $SKOV3_{TR}$ cells were stained for apoptotic activity at 12 hours after treatment initiation, by staining with green-fluorescent YO-PRO-1™ and red-fluorescent Propidium Iodide (PI). Blue-fluorescent Hoechst staining was included as an internal control for cell count. Apoptotic activity was measured by laser scanning cytometry with simultaneous fluorescence microscopy. Data supports the notion that the PTX and CER combination therapy indeed restores apoptotic signaling to overcome MDR, as seen by the 2-fold increase in apoptotic activity in cells treated with the combination therapy compared with treatment with PTX alone - *Figure 5*.

Modulating MDR through a feedback of exogenous CER to reinstatement the CER signal has been shown to be successful. However, it was of interest to see if the same phenomenon occurs when GCS is blocked in the MDR cell line, therein preventing endogenous CER from undergoing metabolism to glucosylceramide. The drug tamoxifen (TAM) has been reported to inhibit GCS;[18] therefore, it was speculated that a combination therapy of PTX with TAM would produce the same chemosensitization profile as the PTX + CER therapy. Figure 3b shows that this combination of PTX + TAM indeed also chemosensitized the MDR cell type, to a similar degree as the PTX + CER co-treatment. And like the PTX + CER treatment, the PTX + TAM treatment was similarly enhanced by nanoparticle delivery, e.g., while the co-therapy in solution at a 0.001 µM PTX dose did not produce any cell kill, the co-therapy delivered in nanoparticles at this dose resulted in slight cell kill (87.2 ± 3.8% viability). However, like the PTX + CER nanoparticle therapy, the PTX + TAM nanoparticle therapy also exhibited saturation of cell internalization at the higher doses of PTX.

Unlike prior generations of MDR modulation strategies,

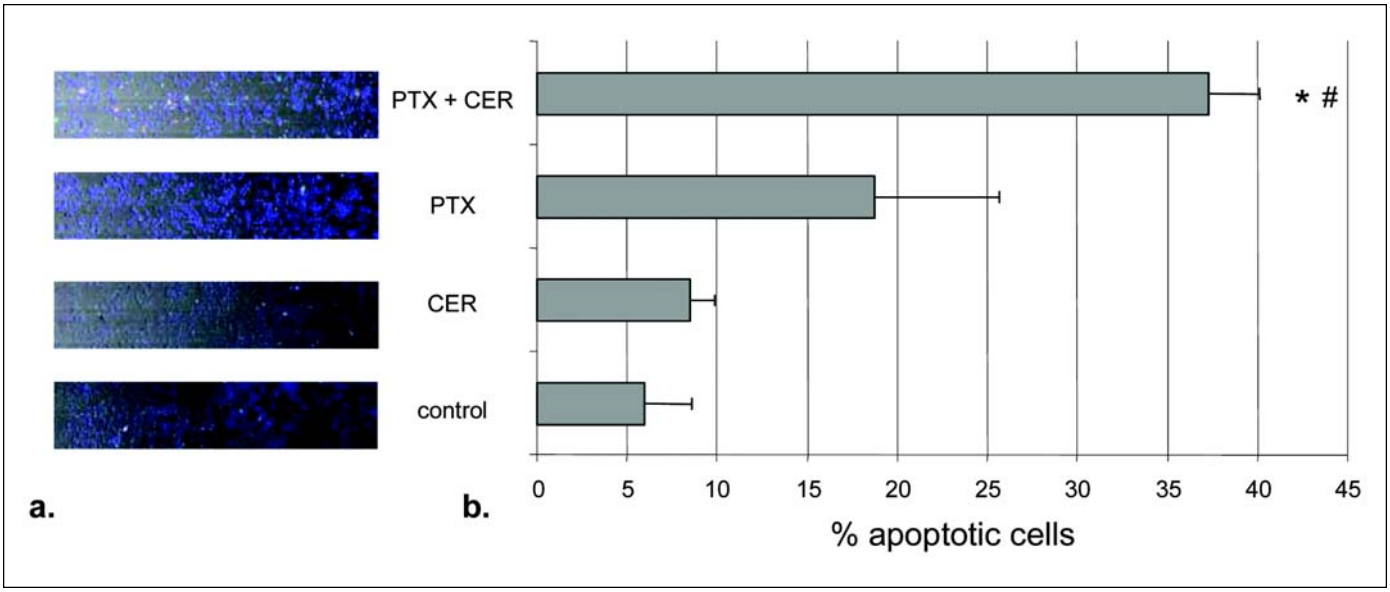

Figure 5. Apoptosis in $SKOV3_{TR}$ at 12 hours following treatment with C_6-ceramide (CER), paclitaxel (PTX), and combination of PTX + CER. Control refers to cells that did not receive any treatment. a) Fluorescence microscopy images of $SKOV3_{TR}$ cells a 12 hour treatment, stained positive for apoptosis with green-fluorescence YO-PRO-1™ and red-fluorescence PI, along a blue-fluorescent Hoechst counter-stain for cell count. b) Percent apoptotic cells per treatment. * indicates a statistically significant difference ($p < 0.05$) from control, # indicates a statistically significant difference ($p < 0.05$) from PTX and CER ($n = 3$ samples/group).

therapeutically aimed at mechanisms particular to the MDR phenotype, modulation of the apoptotic signal also could enhance chemosensitization of drug sensitive cells. Figure 3c illustrates how the PTX + CER nanoparticle therapy greatly improves chemosensitization of the SKOV3 cells, as seen by a left-shift of the dose-response curve. Although the SKOV3 cells benefit from the addition of exogenous CER to induce cytotoxicity, it was not expected that they would respond to the PTX + TAM co-therapy since the drug-sensitive cells do not suffer from an overexpression of GCS. And indeed, the results verify that the PTX + TAM nanoparticle therapy did not enhance chemosensitivity in the SKOV3 cells. These results indicate not only the importance of GCS- mediated CER metabolism and apoptotic modulation as an important contributor to the MDR phenotype, but moreover, they reveal the success of an apoptosis modulation strategy to not only revert MDR in cancer, but also chemosensitize non-MDR cancer types.

Conclusions

Since the development of MDR in cancer greatly hinders success of chemotherapeutic approaches, thereby limiting patient prognosis and survival, therapeutic strategies to circumvent MDR are greatly needed. Although prior MDR modulation attempts seemed promising, clinical success of these therapies remains inconclusive, fueling the drive toward alternate approaches to overcome MDR.

The modulation of apoptotic signaling has emerged as an important mechanism in the MDR phenotype, offering promising potential as a therapeutic target to overcome MDR. However, since MDR is most likely due to multiple mechanisms within the cancer cell, a multifunctional therapeutic strategy that simultaneously overcomes multiple mechanisms of MDR would be beneficial. In this work, we have developed a therapeutic strategy that would deliver a combination therapy of PTX and CER packaged within polymeric nanoparticles to overcome MDR by a multifunctional approach. While exogenous CER administration aimed to restore the defects in apoptotic signaling, nanoparticle delivery of the combination therapy aimed to not only improve systemic drug delivery to the tumor site, but also deliver the drugs intracellularly, thereby evading P-glycoprotein mediated drug efflux. The data support the ability of this novel therapeutic to chemosensitize MDR cancer by this multiprong approach. And unlike prior MDR modulation strategies, this novel therapeutic has been shown to enhance chemosensitization of non-MDR (drug sensitive) cancer cells as well. Together, these results support the promising clinical potential for this therapy to overcome MDR in cancer.

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About the Authors

Lilian E. van Vlerken is currently a Doctoral Candidate in pharmaceutical sciences at Northeastern University, and additionally the recipient of an IGERT fellowship in Nanomedical Science and Technology, co-sponsored by the NSF and NCI. Van Vlerken participated in ISPE's annual poster competition at the 2006 ISPE Annual Meeting in Orlando, FL as the ISPE Boston Area Chapter graduate winner. She can be contacted by e-mail at: Vanvlerken.l@neu.edu.

Mansoor M. Amiji, RPh, PhD, is a Professor and Associate Department Chairman of the Pharmaceutical Sciences Department in the School of Pharmacy, Bouve College of Health Sciences at Northeastern University in Boston, MA. He can be contacted by e-mail at: m.amiji@neu.edu.

Northeastern University, Pharmaceutical Science, 360 Huntington Avenue, 312 Mugar Building, Boston, Massachusetts, 02116.

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Risk-Based Equipment Qualification: A User/Supplier Cooperative Approach

by GAMP Italia - Equipment Validation Workgroup:
Sandro De Caris, Marco Bellentani, Beny Fricano, Carlo Bestetti, Marco Silvestri, and Barbara Testoni

This article presents an efficient cooperative approach to Commissioning and Qualification (C&Q) for manufacturing equipment and covers the entire life cycle for the specification, design, manufacture, installation, commissioning, qualification, operation, and maintenance of the equipment in a risk-based approach. This article reflects the current status of the work in progress conducted by the GAMP Italia Equipment Validation Workgroup. The main topics covered in the article are:

- **holistic risk-based approach covering business, safety, and quality risks**
- **involvement of the supplier in the risk management process and risk analysis**
- **support from the supplier in the C&Q activities (risk-based)**
- **team building**
- **time savings**
- **trends**
- **good engineering practice**

GAMP Italia and Equipment Validation Group

GAMP Italia is a local Community of Practice that was introduced to the ISPE community in December 2005, during the ISPE Milan Conference.

The mission of GAMP Italia is to improve the communication among users, suppliers, consultants, regulatory authorities, and academia, helping life sciences companies streamline their validation processes through a more consistent application of good practices and the GAMP guidance on both the supplier's and user's side.

GAMP Italia operates in accordance with the general objectives of the International GAMP Forum and reports to the GAMP Europe Steering Committee, like other regional groups (GAMP Nordic, GAMP D-A-CH, and GAMP Francophone).

The Equipment Validation Group is the first working group started within GAMP Italia and is composed of members coming from equipment manufacturers, consultants, end users (pharmaceutical companies), and academia.

The group is currently preparing document templates useful for supporting qualification of different standard and non-standard equipment.

Background

Most equipment currently available on the market is the result of a very long and uninterrupted improvement process that started many years ago and brought to the current design.

There is a significant difference between the purchase of a **standard system**, as opposed to the development of a **bespoke or custom made** equipment. Pharmaceutical users in most cases are just buying and installing standard pieces of equipment. The design of new parts or new functionality is often negligible, or limited to a small part of the process. Nonetheless, users are currently spending significant human efforts and financial resources in commissioning and qualification activities that are sometimes excessive and redundant, quite often including a mere repetition of verifications already performed by the manufacturer.

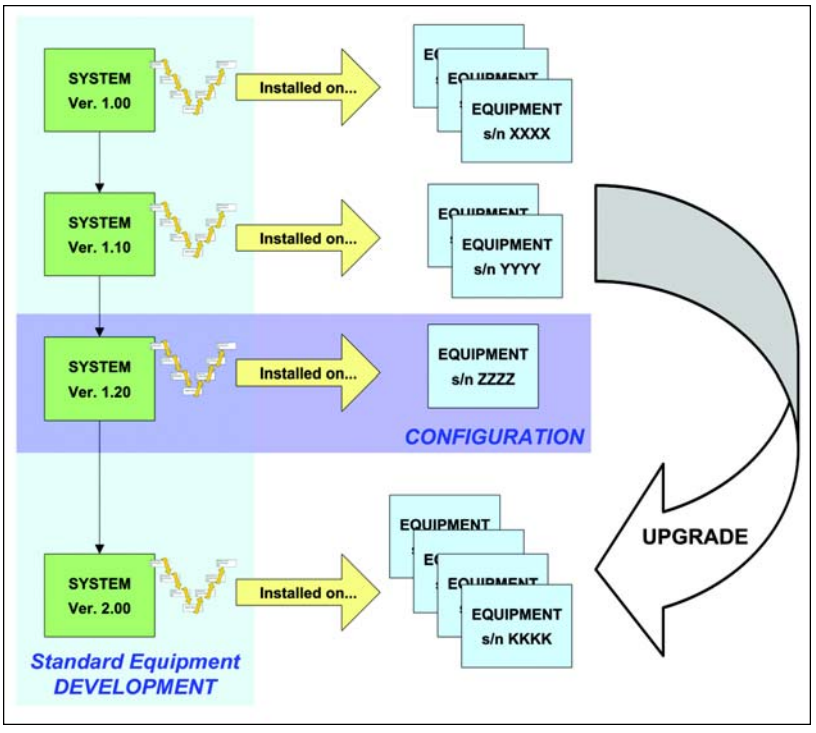

Figure 1. Standard equipment development Life Cycle.

Inefficiencies also arise from the variable formulation of different requirements (from different users) for the manufacture of the same standard equipment (from the same supplier). This may easily lead to different validation approaches and sometimes to very different set of documents on behalf of the supplier. A more uniform approach and a risk-based definition of the requirements can result in a significant savings in time and effort spent for both parties.

Risk-based qualification can improve quality and reduce validation efforts. ISPE is actively suggesting this approach, which is now being used more and more extensively.[8,9]

Risk management can be significantly enhanced with the supplier support, because they have a deep knowledge of the systems they produce. This approach can ensure faster, cheaper, more complete, and reliable results.

Indeed, **C&Q activities can be significantly abbreviated when the supplier is involved since the early stages of the process** and the efforts done during the product development and subsequent manufacturing are taken into account.

The main objective of the Equipment Validation Working Group operating within GAMP Italia is to suggest a more profitable role of the supplier during the entire equipment life cycle from specification and purchase, through manufacture and delivery, commissioning and qualification, use, maintenance, and even retirement.

Considering the current high level of automation in the industry, it is important to look at **computerized systems** and **process control software**, either embedded or standalone related with the equipment. The importance of computer control systems is emphasized because in some cases, the equipment is completely dependent on the proper behavior of the software. Computer systems may include PLC or microcontrollers and Human-Machine Interface (HMI), supervisory PC (e.g., SCADA systems, statistical process control), as well as interfaces with other remote systems like Manufacturing Execution System (MES).

Therefore, the discussion includes both computer validation and equipment qualification in an integrated approach.

More complex and potentially GxP critical scenarios are on the horizon due to the emerging **Process Analytical Technology (PAT)** applications that may bring new computer systems operating in strict connection with the equipment to ensure product quality. The proper identification and management of Critical to Quality Attributes and the relevant Critical Process Parameters may significantly help develop a PAT-ready equipment and extend the ICH Q8 Design Space concept into the equipment process variables.[10]

Basic Concepts

Good practices help ensure high quality products. Properly designed and manufactured products are safe, robust and reliable, well documented; therefore, they should be easy to qualify and/or validate.

This is true for both pharmaceutical products and the equipment used to manufacture the products.

Commissioning, qualification, and validation activities are only the final stage of a long process, and can be more easily and successfully performed if the entire development life cycle of the equipment is considered, supporting best practice and the concept of "Quality by Design" (QbD) when these are pursued by the manufacturer of the equipment. This approach closely relates to good engineering practice, which is endorsed by the ISPE Baseline® Guide on Commissioning and Qualification.[8]

There is a strict similarity between GEP and GMP: in both cases, quality should be achieved by design, and not just tested at the end of the process. Embedding quality into an equipment design is mostly a supplier's responsibility in a cooperative and trustworthy relationship with the user.

A **risk-based approach** requires the identification of critical items, distinguishing them from "ordinary" items, and dealing with them in a differentiated manner. Criticality may refer to different aspects of the product or process: quality, safety, and business being the most common areas of interest.

Critical items and key documents should be identified from the beginning of the project (i.e., explicitly documented in the User Requirements Specification), properly traced to standard offerings of the supplier and managed during the design and manufacture of the equipment, and then carefully verified during C&Q in a conscious and efficient manner. C&Q should concentrate on critical items, according to a sound risk evaluation methodology, and following a structured risk management process.

Standard, non-critical parts (e.g., non contact parts, functionality with no or little impact on product quality) can be implicitly qualified during manufacturing if the supplier is capable of demonstrating suitable **maturity** in the design and manufacturing. Verifications performed during FAT and SAT can be used as a proof of the good design and good manufacture, without the need of repeating the same tests over and over.

The expertise and knowledge of the supplier and the activities performed during manufacturing should be used to avoid redundancy.

Development Life Cycle

A practical risk-based approach should consider the **"real" life cycle of the product development** (as opposed to the life cycle in the delivery of a single instance of the standard equipment). Most manufacturers today have very standard equipment, designed for a large market and highly modular. This is quite common for instance with automatic machines like capsule fillers and tablet presses, and packaging lines, etc. The "design" of the equipment for a single customer is largely a matter of choosing the right model and assembling together the appropriate optional parts. Practicing good engineering practice is largely sufficient to qualify many elements of standard equipment.

Equipment Categories

To simplify the management of equipment qualification/

validation, it may be useful to distinguish the following main classes of equipment:

- standard equipment with no configurable parts or functions
- standard configurable equipment, having two possible levels of configuration:
  - definition of which standard parts are to be included
  - setting of parameters for the parts included
- custom or bespoke apparatus (prototypes of new equipment, custom built) specifically developed by the supplier to meet a set of specified user requirements

Standard configurable equipment may contain some custom parts that should be identified and treated as bespoke apparatus.

Development vs. Configuration

The development of new products (standard equipment) follows a complex life cycle, normally defined in the supplier's Quality Management System. A good reference is the V model included in GAMP Guide.[2]

The product is released on the market following an incremental life cycle with many different releases during the product life span. The entire process, limited to software portion for simplicity, may be summarized in Figure 1.

The large variety of customer requirements results in a very high level of modularity within the same equipment. Different models, different optional units, and a large amount of variable parameters are normally available in a standard equipment.

A new version of the equipment and/or its relevant control software is delivered to the Customer only when the development process has been completed. This includes the management of functional and technical specifications, and the execution of all defined test cases. New custom (bespoke) functions may become part of the evolving standard.

Therefore, the standard product development line is **orthogonal** to the configuration process, needed to tailor the general product to the customer specific requirements.

Software for a single piece of equipment is quite often upgraded during the operation period, even long after the start-up, for instance when new products are to be manufactured. The life cycle for the delivery of a single system from a combined user and supplier viewpoint can be seen in Figure 2.

The knowledge of the actual product life cycle and the differentiation between the management of standard parts vs. bespoke parts is fundamental for an appropriate risk management.

A Holistic Risk Management Approach

Risks may arise in different areas:

- Quality

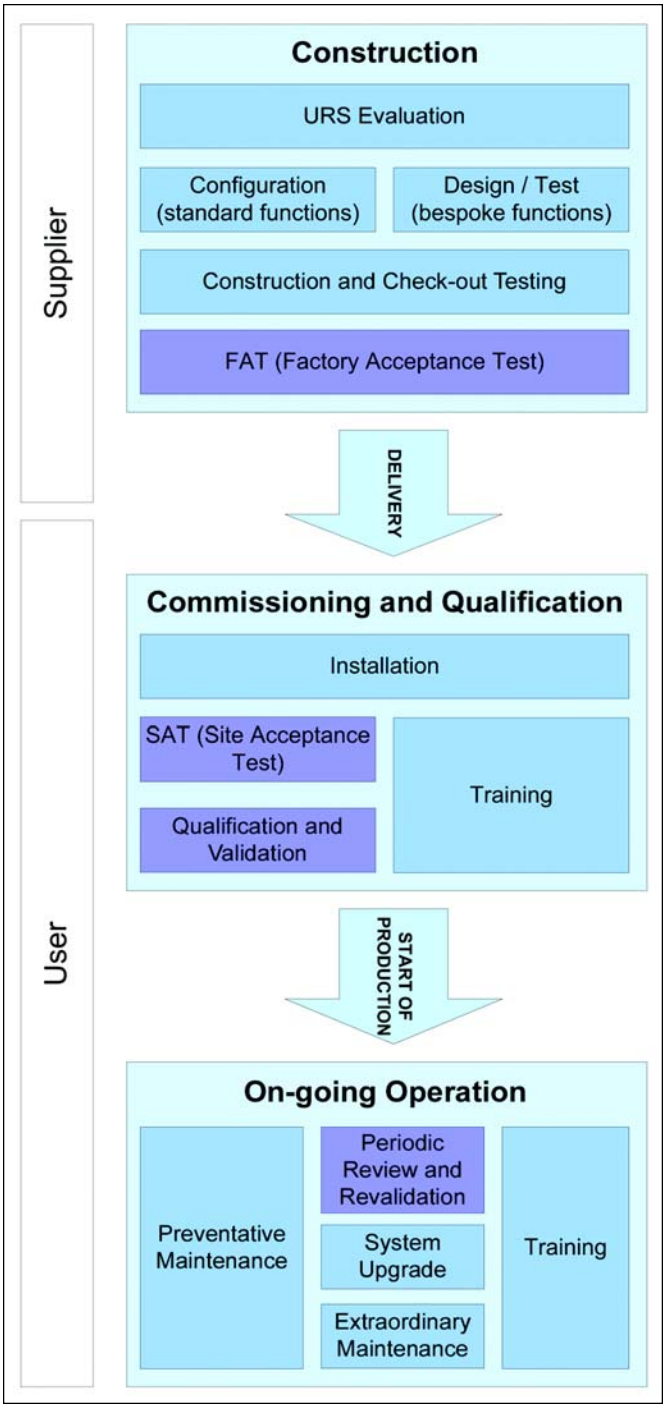

Figure 2. Delivery life cycle for a specific user.

- Safety
- Business

Product Quality Aspects (GxP)

In this case, what matters in the pharmaceutical industry is the quality of the final product delivered to the patient. In this area, all GxP requirements are included. The quality hazard impact can be evaluated according to:

- damage to patient (illness, temporary or permanent side effects, death)

- compliance issues with the authorities

Typically, quality aspects are identified by Critical to Quality Attributes (CQAs) for the product.

Safety Aspects (Operator and Environment)

In this case, what matters is the evaluation of the potential damage to the personnel operating the equipment and/or the impact on the environment caused by system malfunctions. The safety hazard impact can be evaluated according to:

- damage to personnel (temporary or permanent injury, death)
- damage to the environment (damage to people who live outside the factory)

Business Aspects

In this case, what matters is the evaluation of the potential damage for the business caused by system malfunctions or lack of availability. The business hazard impact can be evaluated according to:

- cost of components to be replaced and workmanship (direct damage)
- production loss (indirect damage)

Business continuity, line efficiency, down time, size change over, and line set-up are important items in this perspective.

A description of an overall risk management process is shown in Figure 3.

Risk Analysis

The results of the analysis depends largely on the impact that the customer assigns to each identified source of risk. The same function could be potentially critical in a specific application and non-critical in a different one. Cooperation between customer and supplier is essential to properly manage risks.

User - Supplier Cooperation

The supplier can provide a large number of support activities and services during the life cycle of a product, under all the different perspectives, offering a significant contribution in the risk management process.

A general risk management flow can be adopted. ICH Q9 established a standard approach for "Quality Risk Management" that is quite general and can be easily adopted for all three areas.

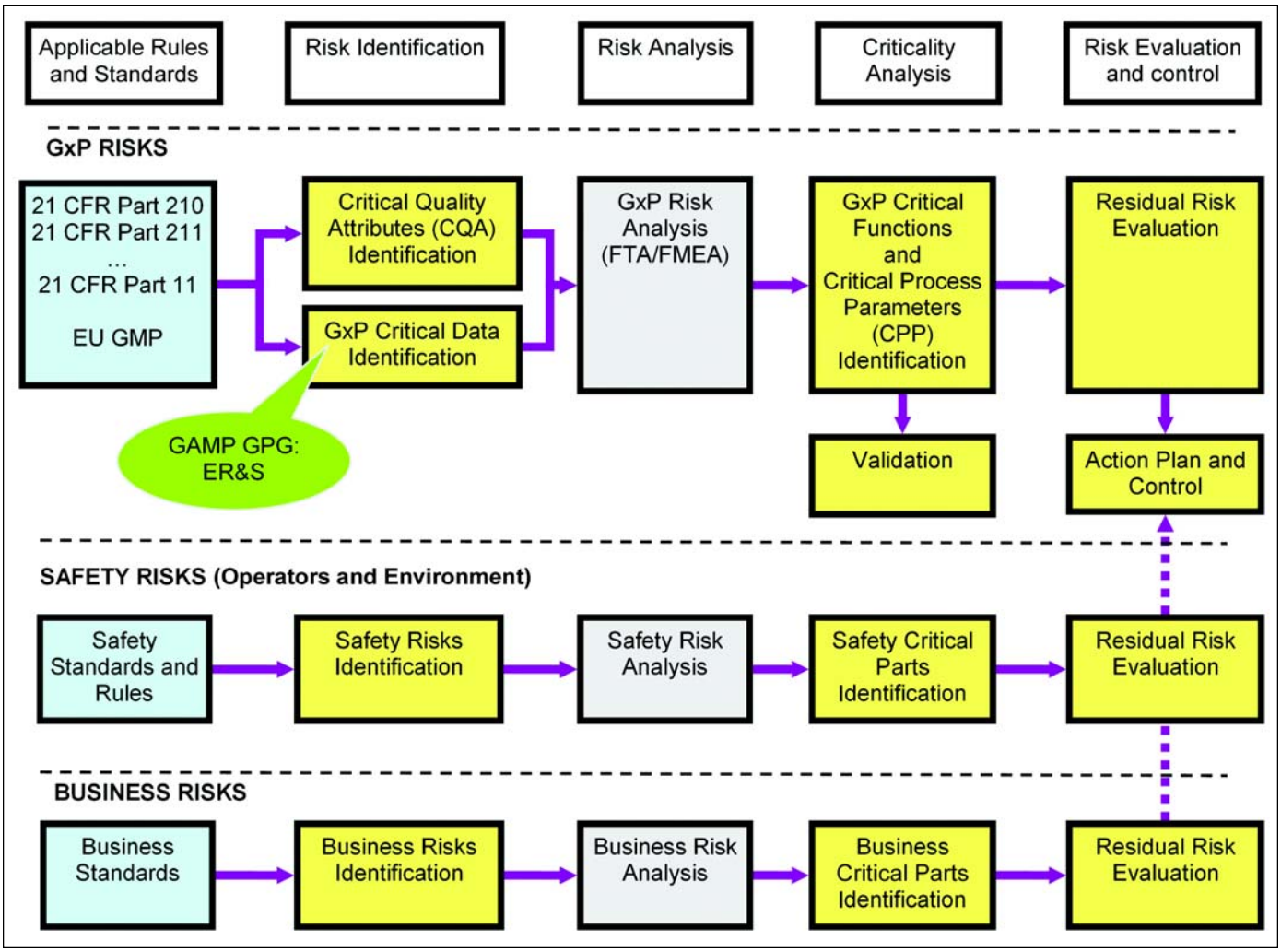

Figure 3. Overall risk management flow chart.

Involvement of the supplier in the process can include a large part of the risk analysis, provided it is based on the information supplied by the user.

In more detail, the sequence of operations can be seen in Figure 4.

The flow of operation also illustrates the embedded Risk Communication process between user and supplier along the entire life cycle, and their different role and responsibility in the risk management process. The following three main phases can be distinguished:

1. **Specification Phase**. It's the responsibility of the user to communicate potential risks and the relevant impact to the supplier so that important items are properly managed during design and manufacturing of the equipment. The supplier should be made aware of unwanted issues impacting the quality of the product, the safety of the operators and the business, and the relevant impact level.

2. **Design and Manufacture Phase**. It's the responsibility of the supplier to identify critical parts (such as mechanical units, components, software functionality, or parameters) and communicate these to the user. The user can then wisely evaluate the risks and provide additional controls or countermeasures where necessary, and finally accept the system design when residual risks are below an acceptable threshold.

3. **Operation Phase**. The operation and maintenance of the equipment should be performed in cooperation with the supplier to maintain constant performances over the time and/or improve the system when necessary.

It should be noted that **while the technical part of the risk analysis can be performed by the supplier, it's a responsibility of the user to evaluate the risks, to provide any required additional controls, and finally to accept the residual risks**. This possible separation of roles has been clarified in ICH Q9.[16]

It's important to distinguish between **elements criticality** and **process (residual) risk**: an element (system component or function) may be critical because it guarantees the product quality, nonetheless, the residual risk for the process can be low due to the high reliability of the element.
However, irrespective of the residual risks, critical parts should be identified because they need qualification/validation.

Standard parts exhibit less risks than custom parts and functions. Under a risk perspective, the explanation is in their improved reliability and lower probability of failure (while the impact remains unchanged).

When the risk analysis is conducted purely for compliance purposes (e.g., to define qualification/validation activities), it can be performed at a high level, without entering into system details such as analysis at component level.

When the risk analysis is required to investigate on specific quality hazards or to cover safety and business risks (e.g., reliability of the equipment), additional difficulties arise on the user's side: the user doesn't have sufficient information and knowledge about the system and the analysis can be very labor intensive and time consuming. One of the difficult items to characterize the system is the probability of occurrence for adverse events since these are quite often related to system components reliability. The manufacturer on the other hand has the necessary knowledge, can guarantee an investigation with sufficient level of detail, and can afford an investment of time and resources on a product that is intended for a wide market and not only for a single user.

It's worth observing that risk analysis performed by the supplier should be somewhat "parametric." The results should in fact be tailored to the specific list of hazards and their impact level, as communicated by the user during the specification phase.

Validation Life Cycle

Based on the Equipment Validation Group experience, the following are preliminary recommendations on the entire life cycle of a generic piece of equipment. Further and more specific suggestions will be included directly in the dedicated documents the group will produce in the future for each equipment type.

The Equipment Validation Group is preparing document templates useful for reducing the time and efforts in the entire delivery process, including C&Q. Templates are produced in an industry wide perspective and include suggestions for tailoring the document to the specific application case.

The group realizes that producing standard documents is not always possible considering the variety of different mechanical, electrical, and software solutions available on the market. Where a general template can't be produced, the group will prepare a guide for the preparation of the document.

User Requirements

To properly implement a holistic risk-based approach, it is necessary to start defining critical items from the beginning of the process. The user should provide the supplier with the identification of different hazards (quality, safety, and business) and the relevant impact evaluation.
The following are some specific suggestions:

- The User Requirements Specification (URS) should be treated as a contractual document, avoiding conflicts with other technical specification documents. The URS should not be considered a mere part of the validation documentation, but rather the main - and possibly only - specification document for the equipment.

- Ideally, the requirements should be independent from the supplier's product and express customer needs without addressing specific design solutions.

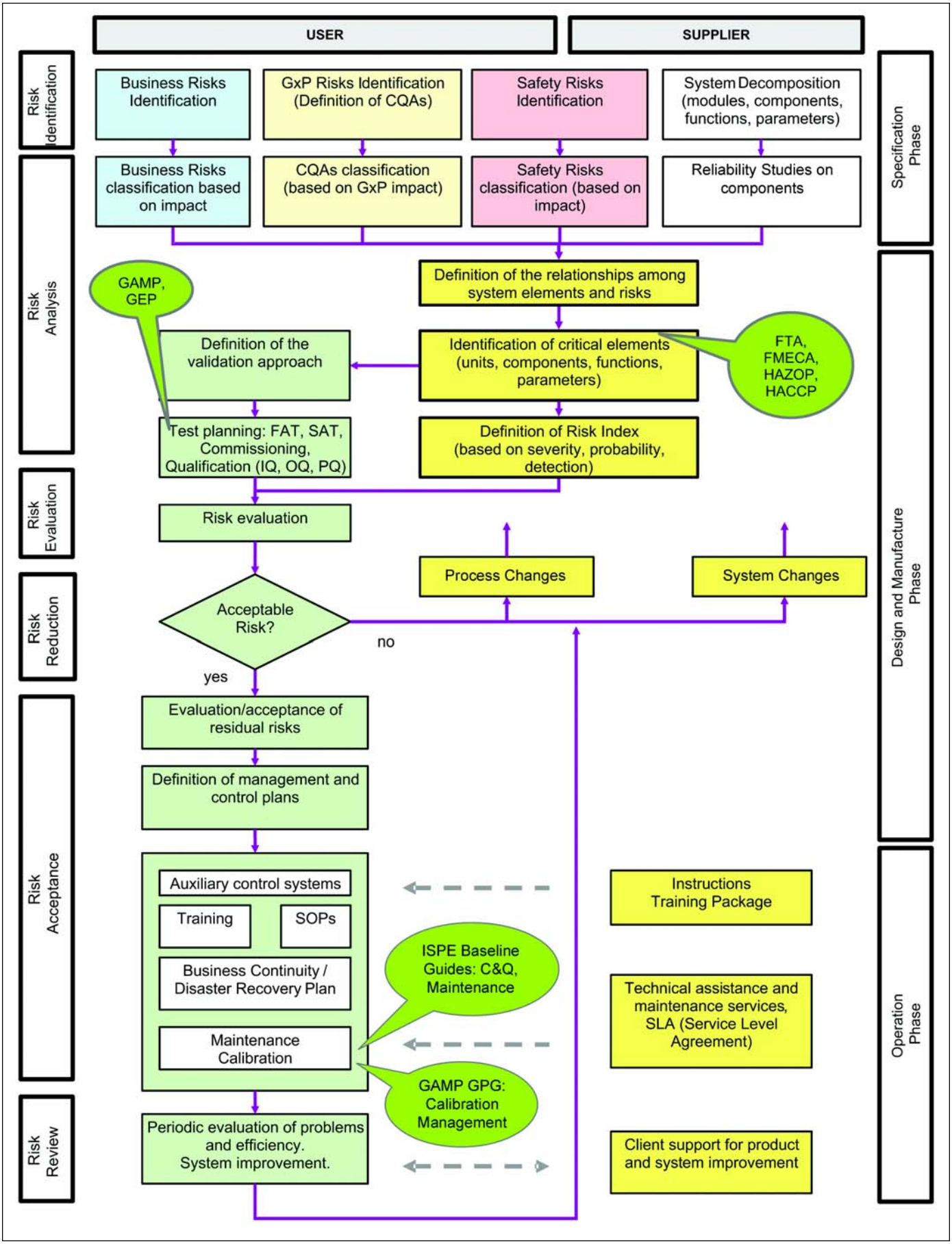

Figure 4. User-supplier cooperation scheme.

- The URS should, as a minimum, cover all mandatory parts, including those necessary to guarantee the final product quality and achieve compliance with the rules. One often neglected part is the definition of the expected quality of the product and the level of allowance for unwanted defects.
- Requirements on equipment safety and business performances also should be included.

- Detailed technical requirements which are typically produced by the user may be included if appropriate in an annex of the URS, as this document usually specifies design solutions rather than equipment performances.

- Ideally, all requirements should be identified with a unique code for easy and unambiguous traceability and classified according to the impact. If possible, impact should be defined in more than one level (e.g., high/medium/low). Business requirements should be classified according to their priority (e.g., mandatory or "nice to have.")

- Generic requirements like "the software shall be 21 CFR Part 11 compliant" should be avoided. High level identification of GxP critical data which are expected to be handled by the system should be done at this stage of the process.

The main issue for the customer during the requirement phase is to identify the most appropriate supplier and the most appropriate equipment model that can satisfy all the requirements.

Validation Plan

The Validation Plan should be developed by the user considering the actual life cycle of the manufacturer that changes significantly depending on the amount of design activities

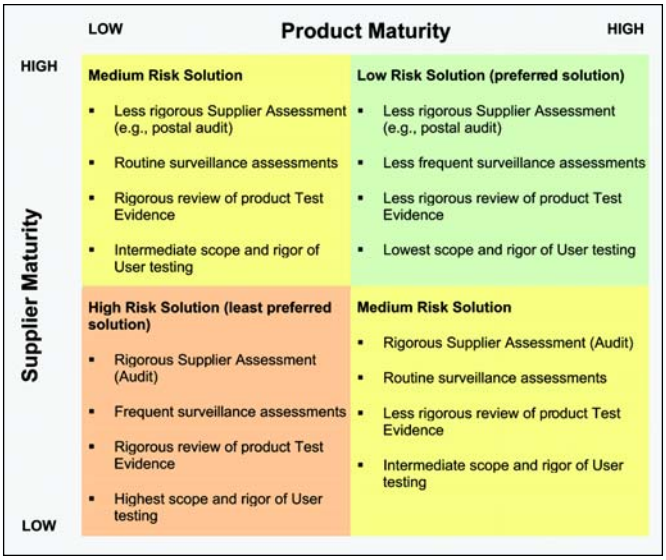

Figure 5. GAMP GPG: Testing of GxP Systems (Figure C1.1: Supplier and Product Maturity Model - Chapter. 1: Minimizing User Testing).

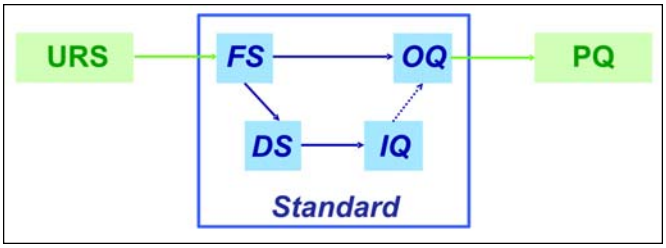

Figure 6. Standard vs. specific documentation.

required to deliver the equipment. Efforts should be based on the overall risk scenario, thus, considering on a global level, aspects related to standard components, supplier, and product maturity.

Overall Risk Scenario

Product and supplier maturity should be evaluated. A good guide is provided in the GAMP Good Practice Guide: Testing of GxP Systems;[6] - *Figure 5*.

Supplier Maturity

The supplier maturity should be evaluated with a detailed analysis of the design, manufacturing, and support processes of the supplier. The supplier audit is the best tool to achieve this goal and it's an important part of the process. To facilitate sharing and comparison of information, the use of standard checklists is highly recommended, such as the one proposed in the Appendix M2 of the GAMP Guide.[3]

Re-use of previously performed supplier audits is encouraged, especially within large organizations, thus, avoiding repetitions and redundancy. A secrecy agreement with the supplier may be necessary.

Product Maturity

Product maturity should be carefully evaluated, considering the level of standardization achieved for the specific equipment. This may require an investigation with the supplier, and a standard survey may prove useful when selecting among different suppliers. Standard and robust products should be preferred to custom solutions, unless strictly necessary. Custom (bespoke) systems normally exhibit much higher risks and should be handled with extra care.

Functional Specifications

Functional Specifications (FS) are documents commonly produced by the manufacturer. FS for a standard equipment can be structured in a standardized "validation package" that often includes Design Specification (DS), plus Installation Qualification (IQ) and Operational Qualification (OQ) protocols - *Figure 6*.

The main issue here is to map variable User Requirements with standard elements (components or functionalities) of the equipment. This is normally done by the supplier during the User Requirements evaluation phase. Different situations may arise when analyzing each User Requirement:

1. The requirement can be satisfied with a standard basic element.
2. The requirement can be satisfied with an optional element.
3. The requirements involves the re-design of an existing element.
4. The requirement involves the design of a new element.

Cases 1 and 2 are very similar: the main difference is generally only at the commercial level, and both can be considered as standard equipment.

Case 3: The re-design should be managed by the supplier under strict change control and the decision should be made to include the change in the standard product or consider this as a customer specific (bespoke) difference. Bespoke components are highly discouraged in the development of standard equipment, but this may be the only way forward.

Case 4: New parts can be designed on demand and still be included in the standard product life cycle, but the risk may be higher for the first installations. Software is normally managed as a standard product, typically highly configurable with many parameters.

To ensure traceability with the User Requirements, each single Functional Specification should be identified with a unique code.

Traceability Matrix

Producing a Traceability Matrix (TM) is very important for C&Q activities. It can help to trace all user requirements, thus, ensuring both complete coverage of URS and test coverage of the critical functions.

Following the GAMP suggestions, TM should report the criticality level of each function. This can help the quick identification of critical functions. Safety and/or business critical functions also should be properly identified in the TM to achieve a holistic system criticality understanding.

In addition to the recommendations from the GAMP Guide,[4] additional information should be included in the TM regarding the level of standardization of the function. Higher risk non-standard functionality can be quickly located in this way.

Design Specifications

Design specifications for standard equipment should describe the equipment, rather than fit specific User Requirements. The main purpose of the documentation is to provide the user with useful information for the operation and maintenance of the equipment. Normally, the supplier is able to demonstrate traceability between standard DS and the relevant standard FS. This traceability also may be included in the standard Qualification/Validation Package.

However, design solutions that are arranged specifically for the user should be identified. Non-standard solutions should be managed with additional care and specific details, especially when they cover critical aspects of the system.

The supplier should provide all the required documents for the parts included in the final equipment. As-built documentation (such as electrical, lubrication, and pneumatic diagrams) is commonly available from the supplier.

Additional documents may be contractually agreed between the user and the supplier in the technical annex of the URS.

Risk Analysis (and/or Risk Management Plan)

The supplier may play a very important role in the risk management process. This has already been covered in the discussion "A Holistic Risk Management Approach."

Under the modern approach of ICH Q9, the risk management concepts along the entire life cycle should replace the pure risk analysis performed in a single phase. Therefore, it is recommended to prepare and follow a Risk Management Plan, rather than a single Risk Analysis document.

It should be remembered that according to the spirit of ICH Q9, risks should be carefully evaluated by the user and residual risks formally accepted.

Before starting the risk analysis process, it is essential to establish the scope: to either evaluate only the quality aspects and define the validation approach, or also to cover safety and business aspects.

In the first case, the risk analysis can be efficiently performed by the user, adopting a top-down technique like Fault Tree Analysis (FTA) to cover specific product quality related risks.

In the latter case, risk analysis should be more detailed and cover system components. This is in general a complex and time consuming exercise that can be effectively performed by the supplier using a bottom-up technique like Failure Mode and Effects Analysis (FMEA). This approach also helps with preparing the list of critical items (GxP, safety, business). Making this information available to the user is an important part of the risk communication process.

Equipment Construction, Commissioning and Qualification

Significant savings can be achieved if efforts are focused on critical items of the equipment and the results of previous testing phases - *Figure 7*.

Check-Out Testing

Consolidated software versions installed on each equipment are tested by the manufacturer according to the development life cycle.

The check-out internal testing phase at the supplier's premises has the purpose to ensure that the equipment is properly built and functioning in all of its components (mechanical, electrical, electronic, and software) and that it satisfies the specific user requirements provided by the customer. The focus of testing activities before the delivery of a standard equipment to a specific user is the proper configuration (selection of items and parameters that satisfy the user requirements), and proper integration in the equipment. These testing activities can be optimized. For instance, if a software algorithm has already been tested during the development process, it is not always necessary to include it

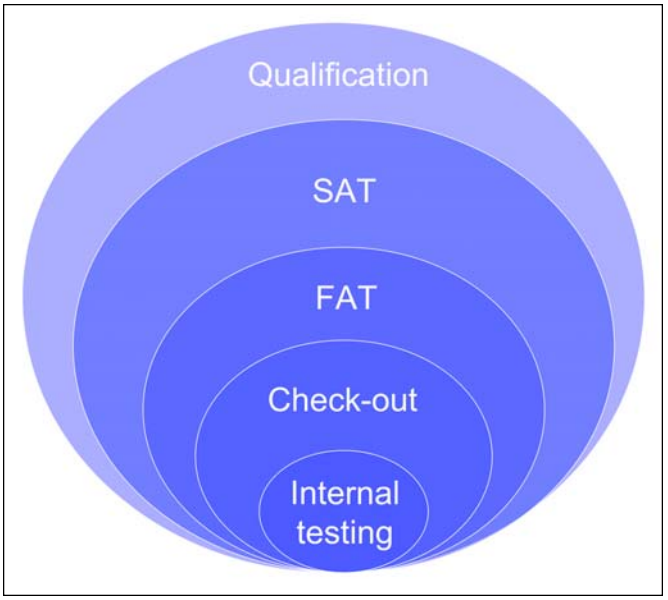

Figure 7. Testing activities.

in the check-out.

Quite often the equipment check-out is ignored during the subsequent steps of the commissioning and qualification, while the evidence of these tests could provide sufficient information and avoid test redundancy.

FAT

A Factory Acceptance Testing (FAT) phase can be executed to check congruence of the system to the purchase order and its proper functioning with the actual customer products. FATs are mainly intended to allow the customer to verify proper construction and operation of the equipment at the supplier's premises; therefore, authorizing delivery to the user's plant. The documentation produced during the FAT may be in part re-used during the subsequent Site Acceptance Test (SAT).

When the supplier has been properly qualified, a significant reduction in testing activities can be done. FAT should concentrate on critical items identified in the previous steps of the process. Testing of standard parts can be evidenced by the internal test results of the supplier, including the final check-out documents.

The execution of FAT may be skipped for standard equipment produced by well-known suppliers, while the user may require the testing documentation (e.g., final checkout results) before authorizing delivery.

Commissioning and SAT

The supplier normally supports the customer during the installation of the equipment, connecting utilities, and performing initial installation tests. The usage of standard check-lists is highly recommended in this stage.

When the installation has been completed, a Site Acceptance Testing (SAT) phase can be executed to verify proper operation of the equipment at the user's premises, including local interfaces with other systems. SAT efforts may efficiently be reduced re-using the experience and documents already produced during the FAT, focusing on parts and functions that may be compromised by the disassembling, transport, and reassembling process. The supplier may help with indicating which tests are to be repeated at the final destination. Testing of non critical parts or functionality may adequately be covered by the SAT, without any need for a formal qualification. Additional suggestions about the management of commissioning activities can be found in the ISPE Baseline Guide on Commissioning and Qualification.[8]

The supplier supports the customer with plenty of documentation that can be used to develop the specific preventative maintenance plan and the calibration plan. Additional suggestions can be found in the GAMP Good Practice Guide: Calibration Management.[7]

Information from the supplier may be useful to prepare:

- training
- SOPs
- business continuity/disaster recovery planning
- maintenance planning and action procedures

Qualification: IQ, OQ, and PQ

IQ, OQ, and PQ activities should be limited to systems and components with Direct Impact on the product quality. All of the rest of the system may be simply commissioned and managed according to good engineering practice. The identification of critical parts is an outcome of the Risk Analysis.

IQ and OQ may be easily conducted using the standard Qualification/Validation Package normally available from the supplier, covering the majority of physical and functional features of the equipment. This documentation should be produced in accordance with a sound risk-based approach. The execution of IQ and OQ tests may be accelerated with the support of the supplier, especially when using its document set. However, specific URS and relevant Critical Process Parameters also should be addressed by IQ and OQ with additional tests to be integrated into or enclosed to the supplier standard package. The responsibility of the qualification testing is still with the user who should review and approve the documents and witness the execution of the tests. Repetition of tests already performed during equipment check-out, FAT or SAT is normally redundant and should be performed only when the previous tests can be compromised by other activities.

PQ is more specific for the customer application and some level of tailoring from a standard template is quite often necessary. The supplier may optionally contribute in the preparation of this document as well as support the execution of the relevant tests.

Training

Training is another important part of the commissioning and qualification phases. Specific sessions for the different roles involved in the usage of the equipment should be designed by the supplier in order to explain the right things to the right people. The supplier should prepare a suitable risk-based training package with specific instructions about the man-

agement of GxP and safety risks.

On-Going System Operation

Once the equipment is in production, there are still several opportunities for the customer and supplier to keep on the positive cooperative relationship created during the start-up.

The supplier may support the user to perform most critical and complex maintenance checks and operations with specific frequencies.

In addition to these maintenance interventions, the user should periodically review and evaluate the system performances.

As a result of this analysis, the user may decide to perform a periodic revalidation repeating a subset of IQ/OQ tests covering the components and features with higher criticality level in order to demonstrate that the system maintains its validated state. The supplier can still support the customer to identify appropriate tests and execute them more rapidly.

Other services that the supplier can provide during the life-time of the equipment cover the following aspects:

- specific training sessions to new people involved in the equipment operation
- software and/or hardware upgrade and relevant qualification activities (typically performed to comply with updated regulations, to renew obsolete components, or to adopt improvements applied to the product installed on different equipments)
- warranty services
- extraordinary maintenance interventions
- support for equipment relocation from one site to another

Decommissioning

The supplier may support the user even in the final stage of the equipment's life. At system retirement, it may be necessary to safeguard important information that is kept in the system, because the mere backup or recovery procedures could not fit for data migration to a new, different, equipment. The supplier role, in the case, may be helpful in many aspects, including managing obsolete mass storage devices or coding specific software filters.

Quality Audits

The customer may increase his confidence in the supplier during the life cycle: by means of quality audits performed on the development process, periodically inspecting the supplier during the construction phases, controlling check-out results during FAT, and finally during the installation and qualification phases.

The mature supplier uses the results of audits, verifications, and inspections in a pro-active philosophy as drivers for continuous improvement.

Developing standard products, both the supplier and the equipment progressively increase their maturity level, going toward the preferred solution where customer verifications may be reduced in terms of frequency and rigour - *Figure 5*.

Trust is based on the confidence on the supplier quality system and the overall design and manufacturing processes that bring to the final equipment.

Conclusions

To save time and money in the commissioning and qualification activities still guaranteeing the final proper quality level of the equipment and the relevant production, it is basilar to use a risk-based approach that focuses on critical items of the equipment and critical activities of the life-cycle.

The knowledge of the actual manufacturing life cycle may aid in the identification of critical steps in the process, distinguishing the production and assembling of standard parts from the design of custom parts.

Supplier involvement from the early stages of the process can further improve savings. Building a trustworthy relationship between the user and supplier can reduce redundancies and provide significant advantages for both parties.

C&Q efforts can be significantly reduced using mature products and mature suppliers. Using best practices in the design and manufacturing bring the mature supplier closer to the sphere of Quality by Design, improving their products and services.

Glossary

C&Q	Commissioning and Qualification
CQA	Critical to Quality Attribute
DS	Design Specification
FAT	Factory Acceptance Test
FMEA	Failure Mode and Effects Analysis
FS	Functional Specifications
FTA	Fault Tree Analysis
GAMP	Good Automated Manufacturing Practice
GEP	Good Engineering Practice
GMP	Good Manufacturing Practice
GPG	Good Practice Guide
HMI	Human Machine Interface
IQ	Installation Qualification
MES	Manufacturing Execution System
OQ	Operational Qualification
PAT	Process Analytical Technology
PLC	Programmable Logic Controller
PQ	Performance Qualification
QbD	Quality by Design
SAT	Site Acceptance Test
SCADA	Supervisory, Control, and Data Acquisition
SOP	Standard Operating Procedure
TM	Traceability Matrix
URS	User Requirements Specification

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About the Authors

GAMP Italia – Equipment Validation Workgroup

The working group has a Steering Committee, active members, and associate members. *The following list includes only the members of the group who authored the article.*

Sandro De Caris is an IT Compliance Consultant for the life sciences industry, supporting both manufacturers and suppliers. His expertise covers computer systems validation, GxP compliance, risk management, and PAT. He graduated in electronics engineering and has more than 20 years of experience in the pharmaceutical industry at the international level, operating in hardware and software design, software quality assurance, computer validation, project management, and company management. Before moving into a freelance profession, his last role was managing director of a leading Italian company specialized in compliance and validation; a subsidiary of an international IT company based in the UK. De Caris is currently chairman of GAMP Italia and coordinates the Equipment Validation Workgroup. He can be contacted by telephone at: +39 051 6516945 or by e-mail at: sandro@decaris.it.

IT Compliance and Validation Consultant, Via Giardino, 60, 40065 Pianoro, Bologna, Italy.

Marco Bellentani graduated in computer science at the University of Bologna, joined MG2 in 1993 as a software engineer, and for 11 years has held a position of Software Projects Leader and Product Manager with particular focus on quality assurance, validation, standards, and methodologies definition. GAMP, GxP, risk management, electronic records and signatures have been some of the quality and regulatory aspects experienced during these years. In 2005, Bellentani joined the Quality Assurance Department as Validation Manager and Software Quality Assurance Manager. In this role, he defines validation, training and documentation policies and software development standards, conducts Supplier quality audits required by customers, and follows internal projects for process optimization. He also is the coordinator and project quality assurance of MG2 PAT Team, a group of experts supporting customers in the implementation of practical PAT solutions, and in this role, he attends to pharmaceutical meetings both as a speaker and as an attendee. Since the beginning of 2006, he has been a member of MG2 Executive Board involved in the definition and supervision of MG2 strategies for the future. He can be contacted by telephone at: +39 051 4694 111 or by e-mail at: mbellentani@mg2.it.

MG2 S.r.l., via del Savena, 18, I-40065 Pian di Macina di Pianoro, Bologna, Italy.

Beny Fricano graduated in electronics engineering at the University of Ferrara. Since 2001, he has been involved in software quality assurance and qualification and computer system validation at I.M.A., a company engaged in the design and manufacture of packaging machinery and Systems for both pharmaceutical and alimentary products. Fricano has been an ISPE member since 2005. He is involved as active member of the Gamp Italia (Equipment Validation Workgroup). He can be contacted by telephone at: +39 051 6514999 or by e-mail at: FricanoB@bo.ima.it.

IMA SpA, I.M.A. Industria Macchine Automatiche, Via Emilia 428/442, 40064 Ozzano dell'Emilia, Bologna, Italy.

Carlo Bestetti is a consultant in computer system validation and compliance. With an educational background in classical studies and a degree in mechanical engineering c/o Politecnico di Milano, his working life has been spent in application fields such as mechanics, electronics, petrochemistry, energy in engineering companies, production companies, plant maintenance, and validation services touching every aspect of automation engineering. Bestetti shares his experience by tutoring on the job, publishing articles, presenting papers at international congresses, and has obtained patents. He is an active member of Gruppo Imprese Strumentazione Italia (GISI) and Associazione Italiana per l'Automazione (Anipla). He joined ISPE in 1995 as member of the Italian Affiliate Steering Committee, and in 1996, he received an ISPE special Award. Bestetti is now active in the GAMP COP. He can be contacted by telephone at: (+39) 039 24 96 855 or by e-mail at: carlo.bestetti@convalida.net.

Compliance and Automation Validation Consultant, Via Ramazzotti, 11, I-20052 Monza, Milano, Italy.

Marco Silvestri received the Laurea Degree in mechanical engineering from the University of Parma, Italy in 1999. After collaborating with the Industrial Engineering Department of the same university, he was employed as researcher by Computes s.r.l. (Niviano di Rivergaro, PC), a software house that produces CAD/CAM for mechanical industry. During 2001-2002, he was head of research and development of Tecnomec s.r.l. (Vignola, MO), a manufacturer of machines and plants for the meat industry. In this role, he developed innovative solutions for plants of Campofrio (Burgos, Spain) and Rovagnati (Biassono, Italia). Silvestri also was involved in vision system projects for industrial automation, collaborating with Vicivision s.r.l. (Fidenza, PR) on developing automated control machines for pharmaceutical (GlaxoSmithKline) and medical device (B.Braun) industries. Since October 2002, he has held the position of Assistant Professor at University of Parma, lecturing on actuators mechanics at the mechanical engineering laurea degree, on mechatronics at the mechanical engineering laurea magistrale degree, and Packaging mechanics at Food Industry Mechanical Engineering laurea magistrale degree. He can be contacted by telephone at: +39 0521 90 5700 or by e-mail at: silve@ied.eng.unipr.it.

Universita' degli Studi di Parma, Dipartimento di Ingegneria Industriale Pal., 8 Viale G.P. Usberti 181/A 43100, Parma, Italy.

Guerrina Barbara Testoni is a Project Manager and Executive Consultant with Adeodata, Italy. She has a degree in math. Prior to join Adeodata, she was the R&D IT Development Area Manager with Chiesi Farmaceutici. Testoni has more than 16 years of experience in the pharmaceutical industry specializing in computer system validation, information system implementation and management, system integration, and business process reengineering of various systems such as: LIMS, EDMS, eSubmission, CDMS, Drug Safety, Clinical Database, ERP. She can be contacted by telephone at: +39-338-8426687 or by e-mail at: barbara.testoni@adeodata.it.

Adeodata, Via Grigne, 5, I-20020 Lazzate, Milano, Italy.

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Variable Frequency Drives Role in Control System Strategy

by Irina Kurjatko

This article gives an overview of Variable Frequency Drive (VFD) technology and its various applications to a control system strategy.

Introduction

A Variable Frequency Drive (VFD) is a system controlling the rotational speed of an Alternating Current (AC) electric motor by varying the frequency of the electrical power supplied to the motor.

At present time, VFD technology shows improved reliability and performance and has ramification in many disciplines, including electrical and control systems. The proper application of VFDs in Control System Strategy should be considered to obtain the valid technical solution in project multidisciplinary environment.

VFD can act as a final control element providing safe and economical solutions in many applications where control valves applications raises cost too high (sanitary requirements in biopharmaceutical industry for example).

The use of VFD as a Proportional Integral Derivative (PID) controller simplifies the wiring and provides economical alternative to single loop controller.

VFD Network capability allows multiple data to be transferred from VFD to remotely located Control System for data acquisition, alarms, and report generation.

VFD Controller

General

Variable frequency drive controllers are solid state electronic power conversion devices. The usual design first converts AC input power to DC intermediate power using a rectifier bridge. The DC intermediate power is then converted to quasi-sinusoidal AC power using an inverter switching circuit. The rectifier is usually a three-phase diode bridge, but controlled rectifier circuits also are used. Since incoming power is converted to DC, many units will accept single-phase as well as three-phase input power (acting as a phase converter as well as a speed controller). Figure 1 depicts a VFD Diagram.

AC motor characteristics require the applied voltage to be proportionally adjusted whenever the frequency is changed. For example, if a motor is designed to operate at 460 volts at 60 Hz, the applied voltage must be

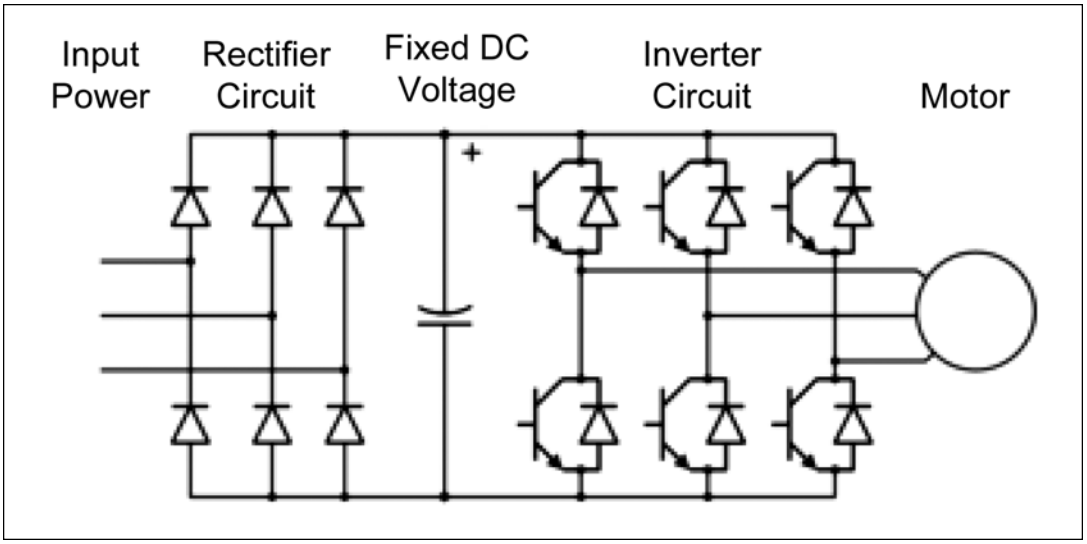

Figure 1. VFD diagram.

reduced to 230 volts when the frequency is reduced to 30 Hz. Thus, the ratio of volts per hertz must be regulated to a constant value (460/60 = 7.67 in this case).

An embedded microprocessor governs the overall operation of the VFD controller. The main microprocessor programming is in firmware that is inaccessible to the VFD user. However, some degree of configuration programming and parameter adjustment is usually provided so that the user can customize the VFD controller to suit specific motor and driven equipment requirements.

VFD Operator Interface

The operator interface provides a means for an operator to start and stop the motor and adjust the operating speed. Additional operator control functions might include reversing and switching between manual speed adjustment and automatic control from an external process control signal.

The operator interface often includes an alphanumeric display and/or indication lights and meters to provide information about the operation of the drive. An operator interface keypad and display unit is often provided on the front of the VFD controller. The keypad display can often be cable-connected and mounted a short distance from the VFD controller. Most also are provided with Input and Output (I/O) terminals for connecting pushbuttons, switches, and other operator interface devices or control signals. A network communication port also is often available to allow the VFD to be configured, adjusted, monitored, and controlled using a computer.

VFD Operation

When a VFD starts a motor, it initially applies a low frequency and voltage to the motor. The starting frequency is typically 2 Hz or less. Starting at such a low frequency avoids the high inrush current that occurs when a motor is started by simply applying the utility (mains) voltage by turning on a switch. When a VFD starts, the applied frequency and voltage are increased at a controlled rate or ramped up to accelerate the load without drawing excessive current. This starting method typically allows a motor to develop 150% of its rated torque, while drawing only 150% of its rated current. When a motor is simply switched on at full voltage, it initially draws at least 300% of its rated current, while producing less than 150% of its rated torque. As the load accelerates, the available torque usually drops a little and then rises to a peak, while the current remains very high until the motor approaches full speed.

A VFD can be adjusted to produce a steady 150% starting torque from standstill right up to full speed, while drawing only 150% current.

VFD Communications

Many VFDs utilize open network architecture. This provides the common set of features and services for DeviceNet™ ControlNet™ EtherNet/IP, and RS-485 networks.

VFD Flexible Installation

The multi-lingual LCD Human Interface Module (HIM) features a start-up utility that quickly and easily provides users with a set of the most commonly programmed parameters, permitting simple drive set-up without in-depth knowledge of the parameter structure. Optimized global voltage settings designed to worldwide standards. PC tools assist with programming, monitoring, and troubleshooting.

VFD Flexible Packaging Options

VFDs can be programmed to cover a wide range of applications, including standard transistor and available drive-mounted (or separately mounted) braking resistor.

A process PID function provides process control. Slip compensation for speed regulation and I/O flexibility cover many applications by offering a choice of 115V AC or 24V DC.

VFD Flexible Application Solutions

The Configuration Drives Programs simplify installation and start-up by allowing users to order drive packages that combine operator interface, control, communications, and power options in pre-configured assemblies.

Communication Interface Configuration

VFDs can be networked using protocols such as Profibus, Modbus, DeviceNet, and LonWorks over wiring based on standards such as Ethernet and RS232/RS485. The advantage of this approach is that after the drive is connected to the network, connections such as start/stop and motor speed can be performed in software over the network. This approach simplifies wiring complexity and reduces cost by eliminating the need to hardwire each of these functions.

The drives have parameters that activate/deactivate network communication. When using this feature, the drive can communicate with a personal computer, Programmable Logic Controller (PLC), or other external device that utilizes compatible communication protocol for control. The network interface may be used to read present parameters setting, write new parameters settings, monitor present parameters settings, and control drive activity.

Control System Principles

General

The ultimate goal of applying instrumentation and associated controls to a process is to achieve stable and economical plant operation.

Control system model consists of the process parameter to be controlled, controller that compares the desired value of the parameter with the measurement of this parameter, and final control device which modifies process operation.

Controller can be implemented individually as a single loop controller, embedded in VFD, or as part of a larger control system.

Final control devices are those that regulate position (control valves, dampers) or speed (VFDs). The energy efficiency of the final control element can be an important factor in the economic operation of the process.

PID Controller Embedded in VFD

Most of the drives have parameters that can be configured to allow VFD to act as a PID controller. Process parameter measured is sent to VFD via hardwired connection or digitally via Network. VFD filters the measured process variable to reduce the effect of electrical noise that may be present in analog input signals. It should be set to the lowest value that yields acceptable performance, as setting it too high may cause the drive to react too slowly to signal changes. PID algorithm is embedded in a VFD microprocessor. The drive can be programmed for inverse operation so that the speed reference increases, the drive speed will decrease, and as the speed reference decreases, the drive speed will increase.

Duct Flow Control Embedded in VFD (Example)

The supply fan is supplying air flow to the duct. The supply fan motor is VFD driven. A flow transducer measures duct flow, providing a 4-20 ma DC signal proportional to the measured flow. Transducer is wired to the VFD. The VFD minimum frequency parameter is set to 20Hz, and the max to 60Hz. As the duct flow rises, the output signal from the transducer will increase, and PID Controller embedded in VFD causes the speed of the drive to decrease. The decrease in motor speed results in a decrease in duct flow and a decreasing transducer signal. The drive responds to the decreasing signal by increasing speed, which again raises the duct flow. This way, the average duct flow can be maintained at a certain level. However, if acceleration and deceleration rates are set too fast, the drive will react quickly to signal changes, which will cause the drive speed to "hunt" up and down excessively. The PID parameters (proportional, integral, derivative) imbedded in VFD are tuned to achieve process response of the quarter amplitude decay. The instrumentation wiring is limited to connecting flow transducer to VFD. All control is performed within VFD.

VFD Economical Advantage in Pump Pressure Control (Example)

Figure 2 represents existing cooling tower circulating system controlled manually. Plant operators adjust the pump discharge valve to provide necessary flow to the system based on the number of users. In this application, the energy dissipated across the discharge valve. The pump is designed for 1800 GPM at the discharge pressure of 150 feet. The pump is driven by a 100 HP motor and has a dead pressure of 77/1 psig.

Electrical energy costs associated with the motor operation show that a 22% percent of flow reduction from 1800 GPM to 1400 GPM results in only 8% reduction of power consumption.

Figure 3 represents a pump discharge pressure control loop where pump speed is controlled by VFD. It is estimated that due to the better pressure control provided by VFD, the total water flow can be reduced by 10% by throttling the discharge valves associated with users without affecting production. From the field data, it is estimated that the operating discharge pressure will be controlled at 40 PSIG.

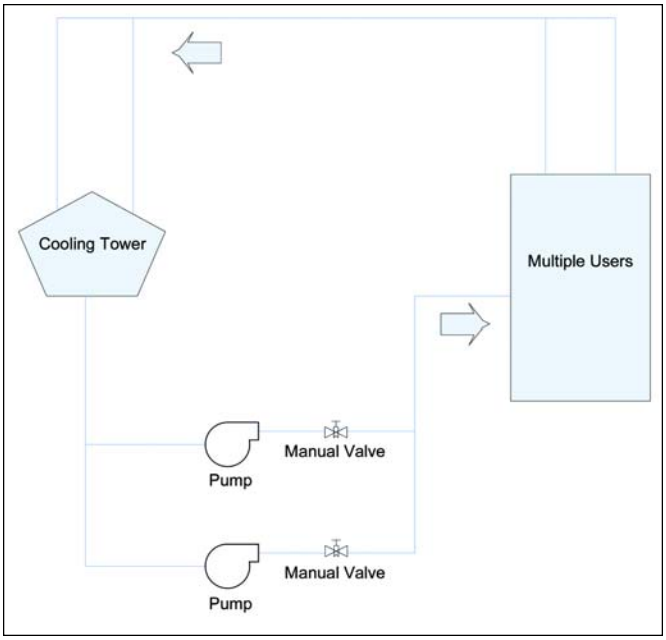

Figure 2. Existing cooling tower circulating system - controlled manually.

Control system cost: VFD = $15,000
Pressure Transmitter = $1,000
Controller = 0 (Part of VFD)

- The installed cost of VFD and pressure transmitter is around $16,000.
- One year operating cost of automated system using VFD speed control is $18,000.
- One year operating cost of the system with manual control is $34,000.

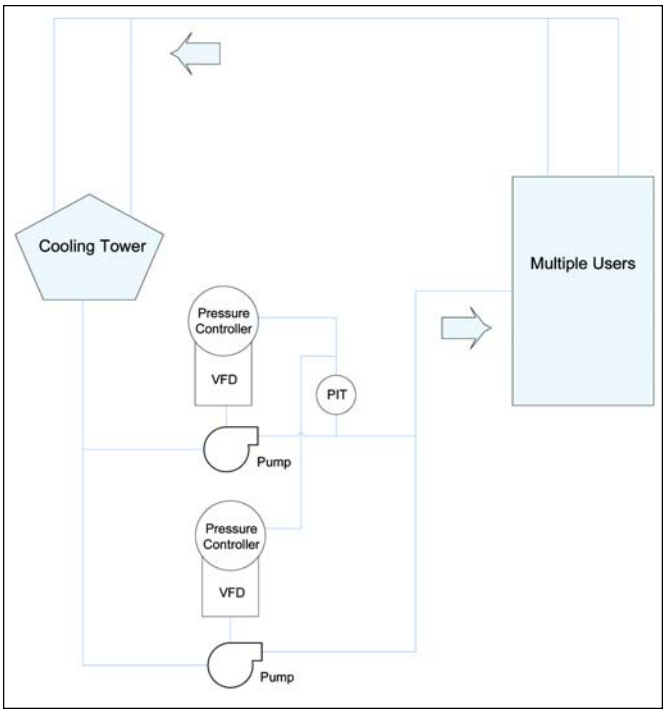

Figure 3. A pump discharge pressure control loop where pump speed is controlled by VFD.

These numbers illustrate that payback is one year if controls shown in Figure 3 are used.

From the above analysis, it can be seen that VFD application represents significant economic advantage due to the substantial reduction in power consumption of electrical energy of a large motor.

Alarm Management

Alarm management is one of the assets of process automation. In a hardwired system, a single alarm could cost $1,000 to implement so there is limited number of alarms activated. Many alarms might be configured in VFDs and sent to the main control system via network. But more is not necessarily better. The most important characteristic of a good alarm system design is a requirement of operator response. If the alarm condition does not require the operator to take an action, then there should be no alarm provided for this condition. The following recommendation should be followed:

- Focus operator attention on the most important alarms.
- Provide information on the recommended corrective action.

To follow this recommendation, some alarms can be suppressed (locked) in VFD during parameters configuration.

Final Control Device

Control Valve

Control valves are used as final control elements by varying a restriction in a flowing fluid and throttling fluid flow. The control valve is a device that dissipates hydraulic energy in a controlled manner. The energy dissipated by control valves used for liquids is:

KW= Q*"P*SG/6116, where KW represents Kilowatts, Q is calculated in LPM (liters/minute), "P is calculated in PSI, and SG is specific gravity of the liquid (unitless).

Damper

Dampers were used in the centrifugal fan applications to throttle flow. The damper would be located upstream or downstream of the fan. The damper located at the fan inlet would reduce power consumption of the fan by five to 25% in comparison to the damper located at the fan outlet.

Whenever the dampers are replaced by VFDs that throttle flow by controlling centrifugal fan speed, the power consumption is reduced by 20 to 30% in comparison to the damper located at the fan inlet.

VFD

Many centrifugal fans and constant torque loads are oper-

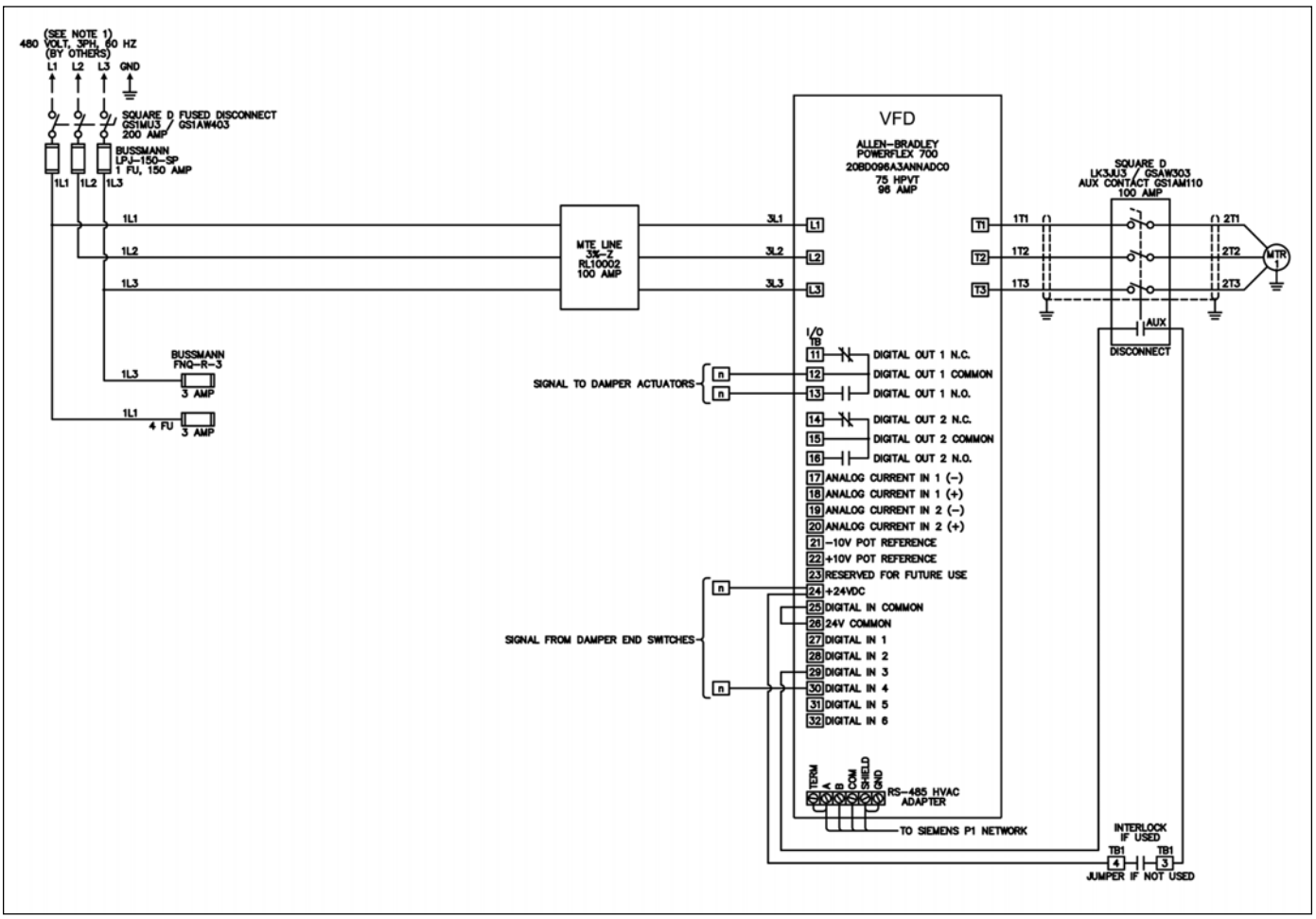

Figure 4. VFD wiring.

Qualification	Control Valve/Damper	AC VFD
Motor Efficiency	Does not have any impact on motor efficiency	Improves motor efficiency
Power factor	Does not have any impact on power factor	Improves motor power factor
Equipment Efficiency	Does not have any impact on equipment efficiency	Improves equipment efficiency
Flexibility of operation	Available	Flexibility of VFD is better then flexibility of Control Valve or Damper
Exposure to Process	Exists	None
Shut-off capability	Shut-off capacity of Control Valve or Damper is better then the shut-off capability of VFD	-----
Potential for leaks	Exists	Potential for leaks when VFD is used is less then Control Valve's or Damper's
Installed cost for small drives	-----	Installed price for small drives is less then installed price of Control Valve or Damper
Installed cost for large drives	Installed price for Control Valve or Damper is less then installed price for the large drives	-----
Overall Maintenance	-----	Overall maintenance of the VFDs is less then maintenance of the Control Valve or Damper

Table A. Summarizes the comparison between control valve/damper and VFD application as a final control device.

ated by VFDs. Most variable frequency drives contain power correction and operate at a power factor of 95% percent of full load, but is significantly lower at lower loads. Power factor correction represents the advantage by reducing the current required to operate the drive at the reduced speeds.

Final Control Devices Application Comparison

Table A summarizes the comparison between control valve/damper and VFD application as a final control device.

Use of VFD as an Interlocking Device (Example)

An Air Handler (AH) Supply Fan is supplying air flow to the duct. The supply fan motor is VFD driven.

The drive controls the duct pressure. The AH is provided with an inlet damper. The damper is open/closed automatically by electric actuator based on the hard-wired signal coming from the VFD output. The signal to start the damper is sent through the network interface from the Building Automation System (BAS) to the VFD. The damper "open" position is provided by the switch located on the damper and is hard-wired to the VFD. The Duct Pressure Controller is residing within BAS. Output from the BAS Pressure Controller controls the VFD speed only if damper is open. There are limited hard-wired connections between VFD and BAS since the majority of information is sent through the network interface between BAS and VFD.

To allow the information between BAS and VFD to be sent through the network, the VFD is configured as follows:

- When the VFD parameter indicates auto mode and the start command from BAS is issued via serial interface, the drive will enter the run mode and will change the state of the VFD digital output (hardwired to damper) to 1, commanding the damper to open. At this point, the preset reference speed parameter within VFD is set to 0 HZ.
- When the damper opens, the position switch located on the damper closes, indicating that the damper opened. The signal from the position switch is hardwired to VFD's digital input terminals. Once this signal is detected, the speed reference parameter within VFD is set for the speed reference coming from the BAS Pressure Controller via serial interface.

In this example, VFD acts not only as a network interface, but performs interlocking functions as well.

The use of VFD in this capacity reduces wiring and maintenance cost and increases reliability of the control system.

Conclusion

Variable Frequency Drives technology entered the world of programmable automation controllers.

PID controllers within VFDs simplify the wiring and provide an economical alternative to single loop controllers.

VFD can act as a final control element providing safe and economical solutions in many applications where control valve applications increases cost.

VFD Network capability allows pharmaceutical companies to switch to wireless technology, which helps to meet safety requirements and comply with federal regulations.

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About the Author

Irina Kurjatko is the Control Systems Department Manager for the San Francisco office of Fluor Enterprises. Kurjatko has 29 years of industry experience with a primary focus on control systems. Working throughout the world has provided her with the rare opportunity to participate in and successfully complete a wide range of engineering projects for which she gained international recognition. In the last decade, she has directed her technical energies in the area of biopharmaceuticals. Kurjatko is actively involved in multiple aspects of control system design implementation and start-up of the plants, including instrument specifications, P&ID, and AFR development, software programming, and validation. She can be contacted by telephone at: 650-742-4320 or by e-mail at: Irina.Kurjatko@fluor.com.

Fluor Enterprises Inc., 395 Oyster Point Blvd. Suite 321, South San Francisco, California, 94080-1931.

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Effective Commissioning Strategy

by Chris Ward, Stephen Anisko, Jenny Oberlag, and Matthew B. Davis

This article examines a combined commissioning and qualification approach and provides some general definitions of the commissioning and qualification process.

Introduction

The development and execution of an effective commissioning strategy is currently a source of great interest and discussion. Historically, commissioning has existed almost as a separate engineering effort; that had minimal input or communication with the subsequent quality and process driven functions. In recent years, there has been a move to integrate the commissioning of systems and equipment into a larger approach that has it strongly linked with qualification activities. This article will discuss some of the considerations that should be thoroughly examined prior to the initiation of a combined commissioning and qualification approach as well as provide some general definitions of the commissioning and qualification process. It also will set out to define some of the important roles and responsibilities that the commissioning group fulfills, as well as discuss what steps are critical to putting a successful team in place. Finally, an analysis of how these activities will interact with other groups within the project team is discussed.

Effective Commissioning Strategy

Experience has shown that there exists a gray area between the installation of a new piece of equipment or system and its subsequent qualification. What are the necessary steps that should take place between mechanical completion and initiation of validation activities? The terms often used for this important phase of a project include Start-up, Turnover, Site Acceptance Testing (SAT), and Commissioning. These terms are sometimes used interchangeably with no distinct difference between them.

A natural conclusion to reach here is that all these activities will result in the same outcome, a qualified piece of equipment, so the term used is irrelevant. This conclusion could not be further from the truth. Start-up, Turnover, and SAT activities generally describe an engineering and onsite vendor collaboration. This collaboration often provides a concise overview and functional check of the acquired system.

Start-up varies based on the equipment or system under examination. In general, this activity will provide a listing of acceptable utility connections and provides verification of equipment controls, alarm features, and expected operation. Vendor provided turnover documentation provides a key piece of the foundation that subsequent commissioning and qualification documentation are tested against. This documentation may include material certifications, cleaning and passivation documentation, software functionality documentation, as well component cut sheets for any supporting items found in the equipment. The SAT is often a vendor supported activity that ensures that the equipment is installed and operates as expected after being delivered to the site.

In comparison, commissioning is a more detailed and in-depth examination of the system. Although commissioning is more labor intensive, if executed properly, the results are significant. Poor planning and execution of this phase can completely derail a project; often leading to numerous groups duplicating efforts with little value added or worse yet, schedule compressions that may affect the outcome of quality initiatives. This is why it is important to take proper steps at an early stage of a project to define the critical commissioning functions and systems that will be implemented. By defining the functional responsibilities and putting in place coherent systems and procedures, the commissioning team can have a significant overall contribution to a project. This often overlooked and underappreciated effort will ultimately lead to a facility whose installation and operation has been verified and proven to be adequately installed and functional prior to the commencement of validation.

What is Commissioning – What are its Important Functions?

Commissioning is an engineering function that ensures that the start-up and turnover of facilities, systems, and equipment to the end-user meets the design requirements. The ISPE Baseline Guide defines commissioning as "a well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user that results in a safe and function environment that meets established design requirements and stakeholders' expectations."[1] Its ultimate goal is to provide assurance that a mechanically complete facility, piece of equipment, or utility system is properly installed with its system boundaries and utilities clearly defined, as well as having its operational range and functionality verified against the design documentation and specifications. The specific duties of this function can be wide reaching and vary greatly depending on the scope of the project.

In general, the commissioning group's responsibilities include working closely with the construction team, equipment vendors, and internal operational groups. Their activities also include involvement with the vendor bid process, factory and site acceptance testing, equipment startup, controls testing and occasionally, engineering support during validation.

It is this wide range of activity that often leads to confusion over the definition of the specific roles of the commissioning group. In fact, there often exist significant differences between organizations in how commissioning is implemented. The picture gets more complicated when one attempts to define the interaction between commissioning and validation. Obviously, from both a business and quality standpoint, duplication of work is to be avoided. So the question now becomes – where should one draw the line between construction, commissioning, and validation?

While commissioning is generally regarded as an engineering activity, validation challenges the system from a quality perspective. It is a highly specific approach that documents that the installed system is appropriate for its intended use and meets the initial design intent. Validation provides the end user with assurance in the form of documentation that their system properly functions, the process requirements are met, and the performance meets or exceeds regulatory standards.

This brief comparison of commissioning and validation highlights a key difference between the two roles. Commissioning should focus on the system's installation and operation. It will verify ranges of functionality, software compatibility, alarming features, utility requirements, as well as issues such as proper permitting and certification in accordance with federal, state, and local code requirements for construction and installation. Validation will take the project from this point, and will focus on quality aspects of the system. It will look at issues such as critical instrumentation, standard operating procedures, data backup, and collection as operational tests that support the quality assessment of the component. Validation focuses on the key product and process characteristics that may affect the quality of the final product.

Structuring a Successful Commissioning Team

As specific roles and responsibilities are being shaped at the beginning of a project, management should start thinking about how their commissioning team will be structured. In defining a successful commissioning team, it is important to remember that the team does not exist in a vacuum. The success of the team will be dependent on a variety of factors, including the team's fundamental understanding of the design intent as well as cohesion between all groups involved with the system.

When putting together a team, management must understand the scope of their project. Whether it is a new large scale facility or a renovation project; the ultimate deliverables must be defined. As an example, consider a facility that will have several utility systems, multiple pieces of processing equipment, and also be used for the manufacturing of at least two different products. From just this point, staffing will be an issue. Personnel will be needed who have working knowledge of utilities and the various pieces of equipment. In addition, there is the complication of multiple products. Therefore, expect variations within the process itself. From this, personnel also will be required to communicate with manufacturing and laboratory departments to obtain information such as process ranges and tolerances, instrumentation critical to the process, and any equipment configuration issues.

Once skilled lead personnel have been identified, issues such as support personnel can be addressed. Often the project will require bringing outside support in to meet the work load and keep to project schedules. Careful thought and consideration should be put into who is brought on site for these roles, especially if contractor personnel are to be brought on board to supplement in house staff. You first want to identify the roles these personnel will fill within your project. Being able to clearly state what their functions will be, will help keep your total costs down by avoiding a situation where they sit idle, or fill redundant positions. Timing is an important factor in deciding when to bring relevant personnel into the project. This step will require an examination of the project schedules as well as your documentation requirements.

Regulatory requirements also may impact your personnel and staffing needs. Considerations such as materials of construction, proper vendor documentation, level of acceptance testing performed, process piping, and pressure vessel verification are all dictated in part by regulatory requirements. This is one example of how the commissioning process is highly linked to other functions. Anticipating what validation requires, or on the other end, what documentation will be expected from vendors, is one of the more important roles commissioning can play. The ability of the commissioning group to recognize these requirements will aid in identifying any potential documentation or installation shortcomings at an early stage. It is important to identify these issues at an

early stage in the project, rather than at a point where significant rework or additional documentation will be required.

Defining a Commissioning Master Plan

A complete commissioning strategy should be developed and implemented as personnel and project scope decisions are being made. This overall strategy may come under many different titles and may even be found in multiple documents. A common name that is given to this document is the Commissioning Master Plan (CMP). This document is similar to that of the Validation Master Plan, in that it is an approved document that will lay out the framework that provides the direction that staff will follow while performing their duties. At a minimum, the CMP should define which systems fall under the scope of the commissioning program, the level of testing required for specific pieces of equipment or systems and responsibilities for each member or group that makes up the team.

System Impact Assessments

All systems will undergo some level of commissioning; however, not all systems will undergo subsequent validation activities. An essential aspect of developing a Commissioning Master Plan is the identification as to what level the systems will be qualified if at all. This approach is referred to as a system impact assessment. A system impact assessment is the process by which the effects of operating, controlling, alarming, and failure conditions of a system on the quality of a product are evaluated. A system can be defined as having "direct," "indirect," or "no impact" on product quality.[1] This process is found in the form of an approved document that clearly states the considerations and rationale behind the ultimate criticality decision. The rationale applied here should be consistent for all systems included in the scope of the project and include substantial input for the Quality Assurance and Validation Groups.

This is an important stage of the integrated commissioning and qualification process because this process will determine which system or equipment is deemed necessary of having validation performed. Ultimately, this determination will define the level of Quality Assurance or Validation oversight applied to this system. Therefore, these groups will play an important role in performing these assessments. Their review and approval in making this determination is to be based primarily on the process under consideration and applicable regulatory guidance that the facility falls under.

Systems which are classified as having "direct impact" on product quality require both commissioning and qualification activities. This class includes utilities such as Water for Injection or HVAC systems. Failures observed with these systems have the potential to detrimentally impact product quality. These systems will undergo a thorough validation exercise that typically includes an Installation, Operational, and Performance Qualification. Systems that are classified as "indirect impact" on product quality may only require commissioning and "no impact" systems will need a minimal level of commissioning. "Indirect impact" systems include heating hot water used for HVAC unit coils or the chilled water system used for temperature control of process tanks. A boiler plant steam or low voltage electrical distribution system would be considered as "no impact."

Performing impact assessments, allows the various commissioning and qualification team efforts to be focused on product quality related systems. This eliminates any unnecessary efforts on "no impact" systems, as well as providing for the reduction in time, costs, and workload on limited resources. At the same time this process assures that product quality needs are achieved. For "direct" or "indirect" systems quality and validation considerations must be considered as their subsequent activities will require a thorough commissioning package.

Component Impact Assessments

Many companies are faced with the inevitable and crucial question of which components or instruments should be deemed critical or non-critical. Component criticality should be assessed to determine whether or not that component is related to product quality. By answering a few questions such as "will the normal operation or even failure of this component have a direct affect on product quality" or "does this component come into direct contact with product," the evaluation of criticality is fairly straight forward.[1]

It is important to note that while System Impact Assessments are made in the initial stages of the project, Component Impact Assessments should be made after the detailed design is far enough along to do so.

The intent of this component level assessment is to determine which components within the system are deemed critical. Because of this, the Component Impact Assessment will only be performed on "direct impact" systems. "Indirect impact" systems and "no impact" systems will not have a Component Impact Assessments performed because, by definition, there are no critical components found within these systems.

Commissioning Master Plans

The CMP will drive a host of other procedures and guidance that will govern commissioning throughout the process from start to finish. Approved procedures or work instructions

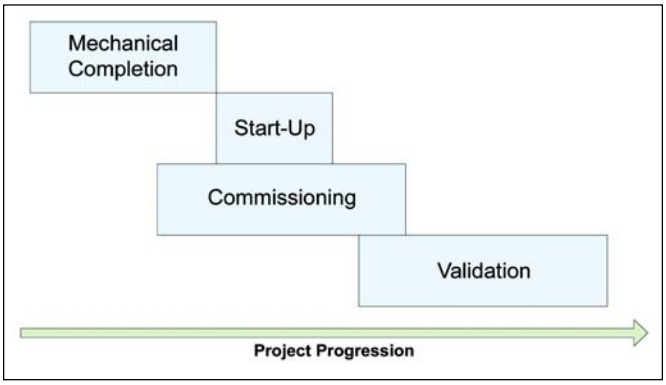

Figure 1. Timeline of required activities of a "direct impact" system.

Installation Verification (IV)	Operational Verification (OV)
• Design Verification (Bid Package and Purchase Order review) • FAT Review (Punch List Items) • User Requirement Specification (URS) • Equipment Specifications • Receipt Verification • Component List • Weld Documentation • Materials of Construction • Cleaning/Passivation Certifications • Pressure Test Reports • Drawing Verifications • Control System Documentation • Utility Verification • O & M Manuals • Spare Parts List	• SAT Execution and Review (Punch List Items) • Functional Specifications (Final Version) • Functional/Operational Testing • Alarm and Interlock Testing • Power Loss and Recovery Testing • Operational Set Points and Ranges • Software Specifications (Final Version) • Control System Testing

Table A. Tasks typically encountered in a Commissioning Protocol.

should be generated by the commissioning engineering group that defines any supporting documentation requirements. Supporting documentation includes project submittals, bid packages, drawings, good documentation practices, or vendor turnover packages that fall within the scope of the project.

Therefore, the depth and strength of this documentation will be very important in defining the overall qualification approach. The implications of this documentation go beyond just the engineering function, in that when there exists a vigorous commissioning approach, validation will have the confidence to reference significant portions of their execution on the work generated at this stage. If the CMP is not equipped with a well defined approach that spells out traceable procedures, it would be of little use to validation or quality functions.

Another important function of the CMP is that it defines the requirements for the individual Commissioning Protocols or plans. These plans are often divided into different sections although they often contain separate Installation Verification (IV) and Operational Verification (OV) stages. Although many of the tasks are similar to validation functions, their objectives are often different, and thus, they often approach the task differently. It also is important to realize that this overlap with validation does not necessarily have to be redundant in execution.

A relevant example of this is Alarm Testing. As part of their functional testing, both commissioning and validation should test for proper alarm functionality and notification. As a general rule, commissioning should test 100% of the alarming from an equipment operational standpoint; confirming any audible/visual or remote alarming as applicable, properly functions at their established set points. Validation will then have the confidence to verify only the functionality of quality based critical alarms. The determination of critical alarms can be traced back to the component assessment discussed earlier. It is not necessary for validation to verify the functionality of all equipment alarms again. Their efforts should be focused on those alarms whose functionality quality decisions are based.

It is important to ensure that the testing plan implemented in the Commissioning Protocol is consistent with the documentation currently in place. Documentation that should be consulted includes the User Requirement Specification (URS), the Functional Requirement Specification (FRS), the Factory Acceptance Test (FAT), and the SAT. The Commissioning Protocol will summarize the findings of these tasks, and provide assurance that states that the equipment or facility is ready for subsequent validation and operation. Table A lists tasks that are typically encountered in Commissioning Protocols. This is a partial listing, and each system or equipment will have its own unique bill of testing depending on its intended use and operation.

Importance of Design Documentation

One thing that has been observed during this approach is the importance of developing thorough and concise design documentation. It is imperative that the vendors are supplied with documentation that informs them what is needed from the onset of the project. Equipment and User Specifications, Good Documentation Practice (GDP), and Good Manufacturing Practice (GMP) requirements should be communicated to vendors during the initial phases, not during construction or after installation has commenced.

Performing quality system audits of anticipated vendors and suppliers prior to awarding work is a good way to avoid this. This way, they are aware of any specific concerns or requirements that your particular corporation requires. Also it provides you with assurance that their final deliverable will be acceptable. If these specific expectations are not adequately communicated, you may end up with a generic product, supported with a weak documentation package that may not meet your specific requirements. In addition, the end product may not operate in a way that meets with the end user's original design intent.

Equipment Specifications are documentation that defines how the system or equipment will operate, be constructed, and function. They should define the engineering aspects such as performance, materials of construction, required support documentation, available utilities, and instrumentation. Equipment Specifications also serve to clarify non-engineering issues such as warranties and preferred vendors as well referencing other relevant specifications.

The User Requirement Specification (URS) also known as Requirements Deliverable, lays the foundation and defines functionality for the system or equipment. It outlines precisely what the user and customer are expecting, eliminating any ambiguity with regard to vendor interpretation. Ill-defined user requirements ultimately will result in a sub-standard system. Properly defining user requirements will help streamline the commissioning and qualification process.

A Test Matrix is often used to ensure that all requirements of the URS are challenged or captured within commissioning and qualification. This matrix serves to identify that the User Requirements are challenged or documented during testing. Another important use of a test matrix is to manage change

by linking, or tracing back, what documents are affected by any modifications so that these documents can be revised to reflect the most up to date system. In addition, a test matrix provides a tool by which the regression of testing of a system can be tailored to the tests relating to the affected functions rather than retesting everything.

Taking this design documentation as the starting point, it can be assumed that changes will often be implemented in the system during the course of the project. Following approval of design documentation, it is important for the commissioning group to document all changes and modifications that are implemented to the system or equipment through a defined change control program that is governed by the quality group. The quality group is responsible for creating a system that ensures that any changes that are made are documented and captured using a tracking system. It is the responsibility of any group making a modification to capture the change under this procedure. Groups that are included under this program may include commissioning, validation, or the end user group. There is a lower level of change control formality observed during the commissioning phase that allows for flexibility in refining the system prior to qualification activities.

Good Documentation Practices

Having a well defined URS and equipment specification is a vital step to communications with the vendor, but equally important are the documentation practices used to support this effort. The vendors should be informed in the Equipment Specification that Good Documentation Practices are a requirement for their testing.

In the Commissioning and Qualification approach proposed in this article, the proper documentation of work can often be the deciding factor between the success or failure of the project. The importance of this cannot be stressed enough, especially when one is looking to shift responsibilities from a validation function to engineering. If validation is going to rely on any of this testing, it must have been done with work that is held to the same standards of documentation. Without proper documentation, the value added from commissioning is significantly reduced, in that a large portion of it will be repeated at additional time and expense.

Just as is typical for a validation or any GMP related function, the commissioning engineer should be aware of documentation practices used in the support of GMP operations. This training takes on additional importance due to the fact that often times, engineering groups are not exposed to the same level of documentation audit and may not be aware what is required. Therefore, a formalized training program should be implemented of the overall commissioning program. With this approach, the project team will be able to show good documentation throughout with no gaps.

Another group that often gets left out of this training is outside vendors or general contractors who may be on site to develop documentation in support of startup activities or the installation of facility infrastructure. The documentation generated at time of their work may be used to support work during the commissioning and qualification phase of the project. Being provided clean, traceable documents makes the subsequent steps of the process easier, in that all documentation used is traceable as to who performed the work, when the work was performed, as well provide an accurate history of the component. Whenever a new group is brought on site, the documentation requirements should be made clear to their supervisors upon their arrival. The time to discuss what is expected from them from a good documentation stand point is not six weeks after their arrival. You do not want to pay these groups to regenerate their work or delay current efforts because they were unaware of this. Records also should be kept of their training just as it would be for any in house employee.[2]

Commissioning Document Integration with Validation Installation and Operational Qualifications

Through analysis of Table A, it becomes evident that there exists a certain level of overlap between validation and commissioning activities. A thoroughly commissioned system will result in more efficient validation activities in that commissioning documentation can be referenced in validation protocols with a greater degree of assurance. The ability to leverage commissioning for validation purposes will save time and money; however, there may be several prerequisites prior to the integration of commissioning into validation.

As discussed, the Commissioning Master Plan is the document that lays out a set of procedures, guidelines, and establishes personnel roles and responsibilities that drive the entire program. When properly instituted, it is a tool which establishes the level of integration that can be obtained. For this reason, careful review of its contents should be performed by the Validation and Quality Assurance Groups.

In general, the following are prerequisites to using data generated by other groups for validation purposes:

- Good Documentation Practices
- Defined Commissioning Master Plan
- System and Component Impact Assessments
- Approved Commissioning Procedures
- Quality Assurance Involvement

As a result of the system impact assessment, decisions were made as to what level systems and equipment will be qualified. Since commissioning is primarily an engineering function, many of its activities are not necessarily quality reviewed to the same degree that validation activities are. They instead adhere to Good Engineering Practices. It can be stated that audit of these commissioning packages will most likely be held to a much different standard by the user group and Quality Assurance than one would expect in a typical engineering document.

The objective in this integrated commissioning and qualification approach is to streamline the process so that activities are not duplicated or unnecessary work performed. "Direct impact" systems have been determined by the quality,

validation and user group as requiring a higher level of qualification. Clearly, test procedures which directly challenge product or process quality in some way should be more thoroughly reviewed than those that do not. Commissioning packages for these systems will go through a pre-approval and post-execution Quality Assurance review. However, if the intention is to replace qualification activities with Commissioning Protocol testing, then it should be understood that there will be active quality involvement throughout the process, equivalent to that observed during validation testing.

Conclusions

The development of a rigorous commissioning program can be a cost effective way to ensure that a project is completed with fewer delays and greater value added results. When this function is properly implemented, it can serve as a bridge between the start up and installation to the subsequent qualification and validation activities. Developing an overall strategy that takes into account the myriad of activities and support functions that make up the project is vital to the success of this approach. Not identifying the key engineering and regulatory constraints at the outset of the project can doom the effort to multiple delays, duplicated work, and cost over runs that will void any of the potential benefits desired.

The integration of the engineering functions of commissioning with the quality and regulatory perspective of validation activities will enable the team to streamline the commissioning and qualification approach. This will ensure that all participants are on the same page throughout the project and communication issues are kept to a minimum. This allows the various functions to focus on their strengths, and not get bogged down in unnecessary duplicated tasks.

In order to achieve this high level of confidence in your commissioning and qualification approach, several prerequisites should be met. Defining your commissioning approach in a Commissioning Master Plan as well defining supporting procedures will lay the foundation for all activities subsequently performed by your group. It also will define your expectations to vendors, outside contractors, and your support staff. Training procedures, a change control program, and good documentation practices should be well defined. Additionally, detailed and accurate Engineering Specifications, User Requirement Specifications, and System Impact Assessments define what it is to be commissioned, and to what degree. Finally, if you are planning on replacing your qualification activities with those performed by commissioning, ensure that quality involvement is maintained throughout the process.

Through the implementing and adherence of a well defined commissioning strategy that is integrated into the qualification approach, you will avoid any unnecessary pitfalls, complete your project, and achieve operational status with fewer cost and personnel overruns.

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About the Authors

Chris Ward has more than ten years of experience in the commissioning and validation of facilities, equipment, and utilities within the pharmaceutical, biotechnology, and medical device industries. He is a Project Manager with Barry-Wehmiller Design Group, a provider of manufacturing automation and engineering consulting services to the world's leading consumer products, pharmaceutical, and biotech companies. His most recent project involved the commissioning and validation of a new clinical vaccine manufacturing facility in Frederick, Maryland. Ward received his BS in nuclear engineering from North Carolina State University and his MS in organizational change and leadership from Pfeiffer University. He can be contacted by telephone at: +1-919-418-7071 or by e-mail at: Chris.Ward @BWDesignGroup.com.

Stephen Anisko is a Validation Engineer with ProPharma Group, a consulting company that provides validation, compliance, and technical services to the pharmaceutical, biotechnology, and medical device industries. His work in the pharmaceutical and biotechnology industries has focused on the validation of facilities, equipment, and utility systems. Anisko also has worked with multiple start-up and commissioning teams in support of new manufacturing and laboratory facilities. He received his BS in chemical engineering from the University of Maryland. He can be contacted by telephone at: +1-888-242-0559 or by e-mail at: Stephen.Anisko@propharmagroup.com.

Jenny Oberlag is a Senior Quality Engineer with Boston Scientific and is currently involved in daily quality operations as well as new product development. Prior to joining Boston Scientific, Oberlag worked as a consultant where she was involved in the commissioning and qualification efforts for multiple pharmaceutical and biotech facilities throughout the Midwest and East Coast. She holds a BS in chemical engineering from the University of Oklahoma. She can be contacted by telephone at +1-763-494-2642 or by e-mail at Jenny.Oberlag@bsci.com.

Matthew B. Davis is a Validation Engineer for ProPharma Group recently assigned to assist in the commissioning and validation of a new clinical manufacturing vaccine facility in Frederick, Maryland. Prior to joining ProPharma Group, he worked at Centocor Biologics in St. Louis, Missouri as a validation intern. Davis received his BS in biology from the University of Southern Illinois at Edwardsville. He can be contacted by telephone at: +1-888-242-0559 or by e-mail at: Matthew.Davis@propharmagroup.com.

ProPharma Group, 5235 Westview Dr., Suite 105, Frederick, Maryland 21703.

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Testing, Commissioning, Qualification, and Acceptance of Biopharmaceutical Skids

by Roy F. Greenwald and Thys Smit

This article describes the tremendous variability in requirements for testing and final acceptance of process skids and suggests specific steps to standardize that process.

Overview

In an industry that is dominated by standard operating procedures and protocols, the lack of a single prevailing standard for the detailed testing, commissioning, qualification, and acceptance of skids in the biopharmaceutical industry often leads to confusion and costly execution. These skids may be any packaged assembly of equipment, piping, controls, and instrumentation designed to complete one step or unit operation in a process. Although the ISPE Good Automated Manufacturing Practice (GAMP) Guide contains some standard process flowsheets, predecessor or intermediate steps typically taken for skids are not fully covered.[1] Once a skid project has been initiated, and as it approaches final acceptance by an owner, it typically passes through at least four steps: Factory Acceptance Testing (FAT), Site Acceptance Testing (SAT), start-up/commissioning, and Installation Qualification (IQ) - although even these terms are not universal or exclusive throughout the industry. During these and other steps, an owner and/or its representative usually require that certain procedures be taken to ensure timely and efficient acceptance of the equipment.

In some cases, critical parameters need to be assessed to allow for efficient remediation of deficiencies; in other cases, the costs of a project can be needlessly driven up by requiring redundant or even unnecessary steps. Finally, the desire or ability to incorporate validation data within prior steps can create additional constraints and/or requirements. This article, written from the perspectives of both an owner and a supplier, attempts to bring some clarity and consistency to the process. Some of the major skidded systems, including bioreactors, filtration skids, chromatography, clean-in-place systems, and others have been addressed. By defining an Equipment Acceptance Chain, it is possible to develop standardized matrices on what testing could or should be necessary at each of the acceptance steps. Using these as a baseline, an approach for most other skids can be easily extrapolated.

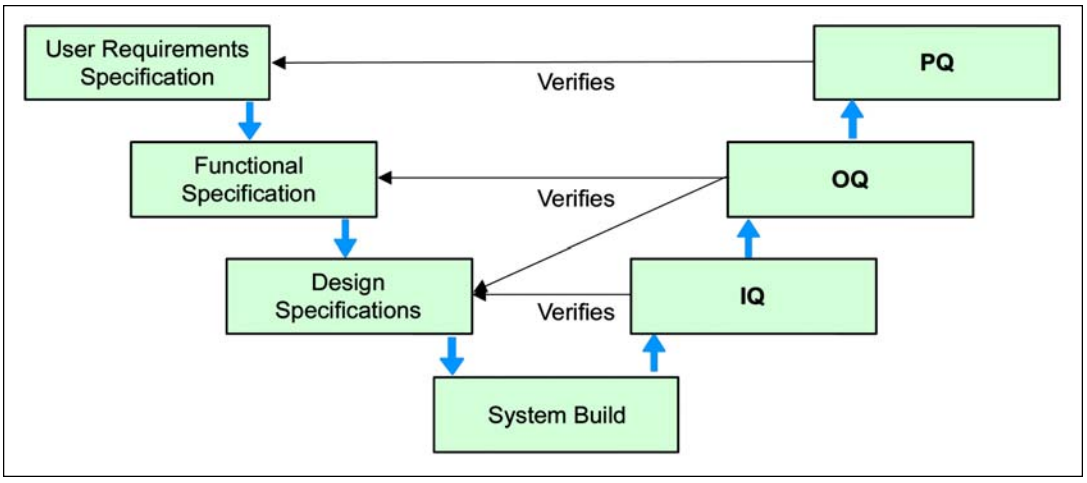

Figure 1. GAMP® 4 basic framework for specification and qualification.

Introduction

One of the authors acts as both a purchaser and a user of most skidded systems within the biopharmaceutical industry. He therefore not only sees, but reaps the benefits of well thought-out purchase, testing, and acceptance specifications. The other author is a designer and supplier of such systems and witnesses firsthand the significant variability in purchase and testing specifications produced by various owners' and engineering organizations. Often these documents address one, two, or even three elements within what the authors refer to as an Equipment Acceptance Chain (EAC); rarely do they address the entire chain. Such a chain can be unique to each project, but it is critical that each step of the EAC be addressed within a single, holistic continuum. The goal is to address both (1) the needs of the owner and (2) the cost of meeting those needs. Both objectives are best met by focusing on the entire chain before the equipment is purchased. Although validation will be addressed as it relates to the EAC, the actual details related to validation of equipment will not. In addition, the details related to validation of the process control system itself (e.g., computer or logic-controller) are not covered within this article.

It is important to note that despite GAMP guidance, there is no commonly accepted EAC within the industry. Figure 1 is reproduced from the GAMP 4 Guide for Validation of Automated Systems.[1] It clearly shows the evolution of the "System Build" through each of the specification stages. Furthermore, it shows how each step of Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) are typically correlated with each specification step. However, as is implied, they must all eventually tie back into the User Requirement Specification (URS). The URS is produced early in the project cycle by the owner, either alone or in collaboration with an engineer or supplier, and serves as the baseline document. The Joint Equipment Transition Team (JETT), working under GAMP, also has produced many useful URS guidelines and actual documents that can be accessed via their Web site.[2] Another excellent reference is the ISPE Baseline® Guide on Commissioning and Qualification.[3]

Most of the variability in equipment acceptance occurs upstream of the IQ, and is in fact, evolving more rapidly now than in the past several years. A description of each of the steps in the EAC and its value to the owner is discussed under the heading "The Equipment Acceptance Chain." One reason that there is presently no common approach within the industry is because some of the steps in the EAC are now being included as part of the qualification processes. GAMP 4, within its Life Cycle Model for Process Control Systems "V" model,[4] does reference the FAT and SAT, showing them as preceding IQ and OQ, not as an element of them. They are independent predecessors. This has been the customary approach in the past. However, not all owners or purchasers are following this model, which is creating some of the lack of conformity and confusion within the industry. Although the GAMP Good Practice Guide: Validation of Process Control Systems[5] provides valuable additional detail beyond the Process Control System Validation section of GAMP 4, it does not totally clarify the acceptance process for skidded equipment mechanical systems. It is equally important to remember that once a skid itself has finally been qualified, the system of which this skid is a part, must still go through its own qualification and validation steps.

The section on the EAC is followed by more detailed information on each of the individual acceptance steps. The OQ and PQ steps shown in Figure 1 are not specifically discussed within this article as they typically are undertaken by the owner or engineer after the equipment has been accepted on site. Although there was a concerted attempt in years past to integrate the testing documentation with documents needed for validation, it has been recognized that this is not always a desirable approach. Problems arise because of the inherent conflict between how the testing and validation processes exercise control over changes. This is discussed in more detail in the next section.

Commissioning versus Validation

No discussion on equipment testing and commissioning can begin without at least recognizing the requirement to eventually qualify the equipment and validate the process. At its simplest, the qualification step is required to conclusively verify and document that the equipment performs the functions initially defined by the user. For this reason, the most important document to most engineers, suppliers, owners, and validation experts is typically the URS. When engineering firms perform the detailed design of skids, they often purchase them from suppliers based on the engineer's specifications. Assurance that the final equipment aligns with the URS then becomes totally dependent upon the thoroughness of the engineering purchase specifications. To allow the validation team to trace conformance of the equipment back to the URS, a rigid change control process must be in place to record any design changes from that document. This assures that both the ability to make changes is controlled, and that once a change is made, it is properly documented. The validation step is almost always completed by either the owner or its direct-hire subcontractor.

Commissioning, on the other hand, precedes validation as a separate and distinct process. It is best defined as a well-planned, documented, and engineered approach to start-up and turnover of equipment to the end user. Commissioning is typically performed by the engineer or construction manager with assistance from others within the project team. However, it usually precedes Installation Qualification, and is not strictly the same as the Operational Qualification in Figure 1, which GAMP defines as "Documented verification that a system operates according to written and pre-approved specifications throughout all specified operating ranges." But, if performed properly, much of the documentation produced during commissioning can be used for the OQ. For commissioning the most basic objective is to demonstrate that the equipment is manufactured and performs to its specified requirements.

To try to fully combine commissioning with the IQ or OQ

is not necessarily a judicious approach. Many projects are undertaken with the understanding that changes can be made easily during the commissioning step, outside the stringent change-control environment of validation. A simple example might be an improperly sloped drain line. If discovered during the FAT or commissioning, it can simply be changed as long as the IQ document trail is maintained. If discovered within a fully documented validation framework, a change control process must be followed, often requiring multiple reviews and sign-offs before this simple change can be made.

The Equipment Acceptance Chain

Figure 2 shows what the authors have seen evolving within what we refer to as the Equipment Acceptance Chain. As noted previously, there is no commonly recognized standard despite the GAMP Guide, but a few steps do seem to be endemic to all projects. These include the FAT, the SAT, Commissioning, and IQ. Strictly speaking, the first three actually fall between the "System Build" and the IQ shown in Figure 1. Each step is reviewed briefly within this section. Following this are several sections that detail the execution of each individual step of the EAC.

The FAT takes place within the supplier's facility. The primary goal of this test is to identify deficiencies, variances, or changes that require correction before the unit leaves the supplier. The benefit of this is obvious: at least the purchaser knows that the equipment is constructed and/or functions as intended within the factory-environment. Changes or corrections can be undertaken at the supplier's facility, where they can be done expeditiously and cost-effectively. A great deal of variability exists in engineer and owner requirements for the FAT.

The SAT is conducted at various levels of detail. Its value is in assuring the product performs essentially the same as during the FAT, but at site conditions. It is not unusual for the SAT to be more extensive than the FAT, often containing many redundancies between the two. There are valid reasons for this. Some are simple: different sign-offs may be required by the owner's project team - or slopes and alignments might be checked to assure nothing changed during shipping or installation.

In some instances, due to the size and complexity of the equipment, the FAT may only cover a fraction of the desired tests. Some firms elect to limit the FAT to "dry tests," leaving the "wet tests" to be performed during the SAT. In these cases, the SAT assumes greater importance than the FAT as it relates to the supplier's performance obligations. In fact, as skids become larger, engineers and owners are finding that many of these operational tests must be moved to the site, due solely to logistical concerns. This lessens FAT requirements and increases SAT requirements. The reasons are numerous and might include:

- a mismatch or insufficient utilities between the supplier and the site
- site-located motor drives or starters
- centralized controls systems
- lack of chemicals, feeds or buffers
- lack of access/platforms
- incomplete insulation of skidded support systems
- limited time constraints
- shipping break-down requirements, necessitating some degree of retesting anyway upon reassembly

Commissioning is the final step before equipment is turned over to an owner. Ten years ago this step was common for plant HVAC and utility systems, but process equipment commissioning was not so formalized. Now it is rare to find any project wherein process equipment does not go through a formalized commissioning step.

In Figure 2, it can be seen that both SAT and commissioning have been included within a common box labeled "Construction Qualification (CQ)." This term, although it does not appear in any of the referenced ISPE Guides, is being applied more and more by construction managers. It may, but need not, include elements of both the SAT and/or commissioning. CQ would fall on Figure 1 between "System Build" and IQ. Many of the activities undertaken during the SAT are repeated during commissioning. However, commissioning is often completed and documented via GMP documents; the SAT is not. Nonetheless, because a single construction manager or the original engineer along with the owner often oversees both of these steps, some of them blend the lines between the two. It is still important to recognize that there are slightly differing objectives and "ownership interests" for the two steps. For instance, the intent of the SAT is to prove the equipment performs as specified, while continuing to hold the supplier responsible for corrections to and through this step. As such, the supplier "owns" assuring that the equip-

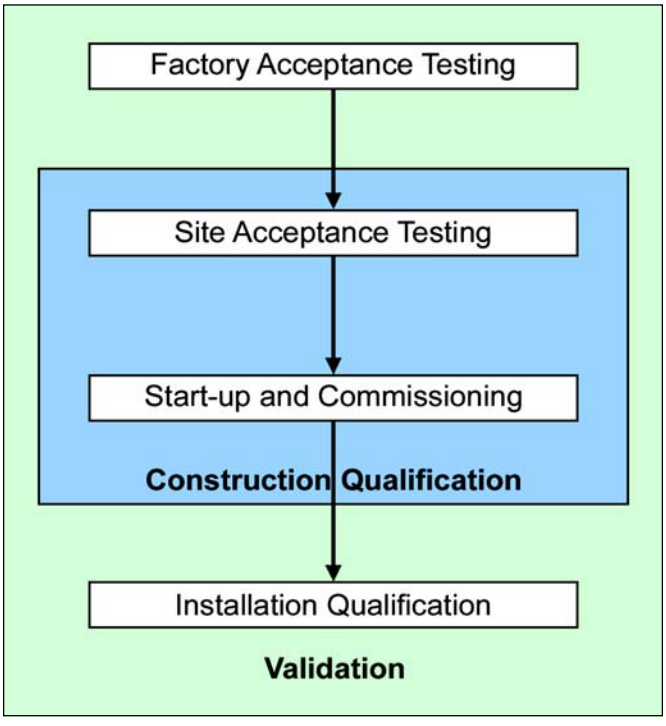

Figure 2. Equipment acceptance chain.

Figure 3. CIP skids configured for testing.

ment performs to specification during the SAT. One wants the simple mechanical changes made during SAT to be outside of the validated change control process. Because the SAT takes place immediately prior to commissioning, and because its results are dependent upon other plant-wide systems, the engineer/owner start-up team will usually be working with the supplier. Together they bring the equipment on-line the first time and complete the testing required of the SAT. The owner's team can clearly benefit by taking part in the SAT. As an example, if a member of the owner's validation team is involved in checking tags, these need not necessarily be checked again if properly documented initially. The owners' protocols will govern this aspect of the SAT.

As shown graphically in the Equipment Acceptance Chain of Figure 2, validation can and should be involved at all stages. This is often beneficial since the testing can be designed to demonstrate compliance with the original URS. Individuals from the validation team need not be specifically involved in the tests themselves, but projects usually flow more smoothly when they are. For instance, it is common for the IQ step to be conducted by the owner's validation team after the commissioning is complete. But by making a visit to the supplier's facility during FAT, a quick check of the supplier's Turnover Package can be conducted. Any shortcomings can be corrected then, early in the process. Eventually, during IQ all of these problems must be corrected, so sooner is better.

Discussions of the EAC early in a project are often general and vague. By determining what steps will be conducted early in the project, and who will own these steps, the information flow will be more complete and timely throughout. It is also more likely to be correct as it passes from one EAC step to the next. Each of the major EAC steps is discussed in the sections that follow.

The Factory Acceptance Test (FAT)

The FAT is conducted at the supplier's facility with representatives of both the engineer and the owner typically present. When the supplier has worked to detailed, engineered specifications, the testing usually relates to assuring compliance to these specifications. When the supplier has taken on both engineering and fabrication responsibilities, the testing usually relates to assuring compliance with the owner's URS. Fortunately, the testing is very similar in both cases. Prior to the test, it is important to produce a detailed FAT Plan (FATP). This is usually done by the supplier and reviewed by the purchaser. It must allow adequate time for review and acceptance by all parties. A good FATP lists all of the tests that will be performed, what will be measured, and what the acceptance criteria will be. In addition, it outlines what the supplier will have tested before the engineer and owner visit the supplier's facility. Agreeing on pre-FAT tests saves those parties who may have to travel from spending non-productive time at the FAT location.

Not all factory tests need to be conducted as "wet tests;" this is one of the first determinations the team should make before purchasing the equipment. For instance, most Clean-in-Place (CIP) skids will undergo a wet test, but many filter skids will not. Figure 3 shows an example of three CIP skids set up for FAT testing at the supplier's facility. These particular skids went through full wet tests to assure that common chemical feed and control systems could manage all three systems together.

Some larger skids are now being shipped without a full wet-test for reasons as noted previously. Larger equipment imposes constraints on project construction schedules, so savings in FAT time results is a quicker ship date. In addition, because a detailed SAT and biological challenge on-site may be required for equipment such as a bioreactor, many purchasers have decided to forego the need for the wet tests. Finally, strictly physical constraints may require breakdowns and reassembly that for various reasons will render the FAT of minimal value. Figures 4 and 5 show a Buffer Prep Skid that underwent dry testing due to both physical size limitations and interconnectivity requirements with the balance-of-plant design. The testing did include low pressure gas integrity testing and full functional testing of the control system although it did not include agitator or pump rotations. Power checks to such equipment were included in the FAT.

Figure 4. Buffer prep skid in supplier's facility.

Good planning through use of the FATP can ensure that almost all functional checks are done in the shop without the need for the wet testing.

Table A contains a matrix that shows typical acceptance criteria that may be evaluated during FAT for nine different types of skids or equipment. For the most part, these items can be evaluated with a dry test. If a wet test is anticipated, the specific test parameters should be added to this list and included in the test plan. The items within the table are expanded below, separated by sub-section. The bullet points can be aligned with the items in Table A.

A. Mechanical

- A pressure test should be completed prior to the FAT by the supplier. FAT cannot begin without it. Proper documentation of the testing is important.
- P&ID conformity implies a full walk-down to assure compliance with the approved Piping and Instrumentation Drawings and that they are in compliance with the FRS.
- Layout conformity is a simple dimensional and tie-in check to assure equipment conforms to the previously approved design to allow full functionality and accessibility at site. All information on the drawings also is checked for completeness and accuracy.

Sample Equipment Acceptance Matrix												
		Description	Typical Equipment – Systems									
			Bioreactor Systems	Centrifuge System	Depth Filtration Skid	UF/MF Skid	Filtration Skids	Chromatography Skid	CIP Skids	Autoclaves	Glass Washers
FAT at Vendor Shop												
a	**Mechanical**	Pressure Test (by Vendor prior to FAT)	X	X	X	X	X	X	X	X	
		P&ID Conformity	X	X	X	X	X	X	X		
		Layout Conformity	X	X	X	X	X	X	X	X	X
		Drawing Conformity	X	X	X	X	X	X	X	X	X
		Component Verification Tests (Drawing List, Instrumentation/ Vessels, etc.)	X	X	X	X	X	X	X	X	X
		Structural Steel Weld/Finish Conformity Check	X		X	X	X	X	X		
		Piping Visual Weld Inspection	X	X	X	X	X	X	X	X	X
		Tagging and Labeling	X	X	X	X	X	X	X	X	X
		Line Slopes/Drainability	X	X	X	X	X	X	X		
		Valve Orientation/Drainability Check	X		X	X	X	X	X		X
		Connection Fitup Verification	X	X	X	X	X	X	X	X	X
		System Drainability	X	X	X	X	X	X	X	X	X
		Mechanical Instrument Functionality	X	X	X	X	X	X	X	X	X
		System Hydraulics Test		X					X		
		Sprayball Riboflavin Cover Test (Tanks)	X		X				X		
b	**Electrical**	Electrical Panel Conformity	X	X	X	X	X	X	X	X	X
		Electrical Wiring Conformity	X	X	X	X	X	X	X	X	X
		Disconnects Conformity	X	X	X	X	X	X	X	X	X
		Specifications Conformity	X	X	X	X	X	X	X	X	X
c	**Controls**	Control Panel Layout	X	X	X	X	X	X	X	X	X
		Control Panel Components Conformity	X	X	X	X	X	X	X	X	X
		Instrumentation Loop Checks	X	X	X	X	X	X	X	X	X
		On-Off Valve Functionality Test with Solenoids located in Panel	X	X	X	X	X	X	X	X	X
		Control System Operation	X	X	X	X	X	X	X	X	X
d	**Documentation (Turn Over Package)**	Verify content as per approved Index	X	X	X	X	X	X	X	X	X
		Turnover Package Review	X	X	X	X	X	X	X	X	X

Table A. Typical FAT acceptance criteria.

- Drawing conformity assures all sub-components have been properly integrated into the completed skid. Often the sub-components have been selected, submitted, and reviewed individually.
- Component verification tests assure that required documentation for each item exists and specified components have been incorporated. This should include confirmation of alignment with engineering and procurement data.
- The skid frame and structural components are reviewed for conformance with fit, finish, and weld compliance.
- Piping is visually inspected for proper support, materials, and examinations. Material certifications for product contact materials, welding certifications, weld logs, and other inspection reports are reviewed. ASME's Bioprocessing Equipment standard part DT-14 can be helpful.[6]
- Tagging and labeling are checked for conformance with the specifications, both physically and on the project documentation.
- Line slopes and drainability tests can be conducted. If wet tests are not performed, a decision can be made of whether slope checks will suffice.
- Valve orientations are reviewed for conformance to specifications, accessibility, and for proper orientation to assure drainability.
- The connection fit-up verification usually includes random checks at mechanical connections to assure that piping systems align and connect without stress.
- System drainability checks may go beyond the line slope checks to include heat exchangers, tanks, and other equipment. Some of these tests may have been performed at the component vendor's facility and others can be tested individually without a full system wet test.
- Mechanical instrument functionality may be limited in a dry test and should be a focal point of the FATP. Instruments should at least be checked through the calibration documentation. Those with electronic output may be checked via the control system. Intended operational range of the instrument is not normally covered in a wet test and requires follow-up work on-site during OQ.
- System hydraulics tests are included in most wet tests and usually cover confirmation of flow paths along with performance characteristics of pumps. As control loop tuning is not usually part of the FAT, the extent of the hydraulic test also should be included in the FATP.
- Sprayball coverage of tank and large filter housings is almost always included in the FAT. Often this may be done remotely, if there are third-party purchases of equipment components. Modifications and corrections for improper

Sample Equipment Acceptance Matrix												
		Description	Typical Equipment – Systems									
			Bioreactor Systems	Centrifuge System	Depth Filtration Skid	UF/MF Skid	Filtration Skids	Chromatography Skid	CIP Skids	Autoclaves	Glass Washers
SAT – On Site (Perform the same as FAT with additional requirements)												
a	**Mechanical**	Installation Conformity	X	X	X	X	X				
		Mechanical Assembly Checks	X	X	X	X	X				
		Execute P&ID/Drawing Walkdown	X	X	X	X	X				
		Mechanical Instrument Functionality	X	X	X	X	X				
		Line Slopes/Drainability	X	X	X	X	X				
		Verify Labelling	X	X	X	X	X				
		Verify Bowl and all internal components installed		X							
		Verify Equipment levelness	X	X	X			X	X	X	X
		Verify that holding down bolts installed	X	X	X						
		Verify Agitator installed and secured	X								
		Verify that structural platforms correctly installed	X		X						
b	**Electrical**	Electrical Wiring Conformity	X	X	X	X	X	X	X	X	X
		Electrical Conduit Conformity	X	X	X			X	X		
		Electrical Motors Installed	X	X		X	X	X	X	X	X
c	**Controls**	Control System Operation	X	X		X	X	X	X	X	X
		Instrument Loop Checks	X	X	X	X	X	X	X	X	X

Table B. Typical SAT acceptance criteria.

coverage are most easily performed in the shop environment.

B. Electrical

- Electrical panels are checked for conformity to specifications and the URS. Both physically and functionally, the system can be used to at least power up various elements of the skid.
- Electrical wiring is checked for compliance with project requirements. Proper routing should be confirmed. Point-to-point checks can be performed during FAT.
- Electrical disconnects must be reviewed for both project and code conformance. Special attention needs to be given to accessibility once the equipment will be in place.
- Specifications conformity refers to individual elements that form part of the system itself and the panel internals. Each should be reviewed to assure proper sub-components have been supplied and appropriate documentation exists.

C. Controls

- The controls panels and Human-Machine Interfaces (HMIs) are checked for physical conformance to documentation. Both location and panel layout are checked.
- Control panel component conformity is checked for items such as solenoid blocks, screen parameters, and internal wiring.
- Instrument loop checks are often an important element of the FAT.
- On-off tests or stroking of valves should be checked. Individual control modules, with required valve positions, can usually be confirmed during the FAT.
- Control system operation is often limited during the FAT, but simulations can frequently be used to test software. At a minimum, screens should be reviewed and control modules confirmed.

D. Documentation

- The purchase specification normally designates the required documentation to be provided by the equipment vendor as part of the Turnover Package. It is helpful if an index is approved during the submittal phase. During FAT, samples of each individual element can be reviewed for completeness and conformance. All data defined during the engineering and procurement stages are confirmed. If this step has been taken previously, the Turnover Package itself may be as much as 80 to 90 percent complete and can be reviewed.

The Site Acceptance Test (SAT)

The SAT is very similar to the FAT, but relies upon the fluids, utilities, and interconnections that exist at the end-user's facility. Many of the steps are the same as those described for the FAT. Table B contains a sample matrix checklist for the SAT, and those unique to the SAT are covered below:

Figure 5. End-user supervision of the FAT.

A. Mechanical

- Installation conformity must take into account not only the skid, but that it is properly incorporated in the proper location with proper connections.
- Mechanical assembly checks assure that any items removed or installed for shipping have been returned to their proper state for operation.
- The P&ID and drawing walkdown must assure that all connections have been properly made to new supporting inlets, utilities, and outlets.
- Unique equipment hardware, such as the centrifuge bowl, bioreactor agitator, and pumps must be checked to assure proper installation and assembly.
- At the site, equipment must be properly held in place with appropriately sized anchors.
- Structural platforms should be inspected both for completeness and proper clearances.

B. Electrical

Once the equipment is located at the user's site several new electrical components are introduced. Motor starters and variable frequency drives that were not part of the skid are now connected. In addition, power wiring and breakers are now connected to the permanent plant system. Some specifics follow:

- Field wiring point-to-point checks are completed.
- Motor and their connections are checked for conformance to specifications.
- Starters and drives must be checked for conformity to project requirements.

C. Controls

A full performance check must be conducted on the control system. This is usually performed in a somewhat redundant fashion to the FAT, beginning with point-to-point checks followed by loop checks. Each control element must be tested for functionality. Control module checks are performed followed by operation of the equipment. The exact details are skid-specific and driven by the original URS. Whatever data

Sample Equipment Acceptance Matrix												
		Description	Typical Equipment – Systems									
			Bioreactor Systems	Centrifuge System	Depth Filtration Skid	UF/MF Skid	Filtration Skids	Chromatography Skid	CIP Skids	Autoclaves	Glass Washers
Start-Up and/or Commissioning (CQ) – Performed by mechanical contractor under the CM directions												
a	**Mechanical/Controls/ Instrumentation**	Drawing verification	X	X	X	X	X	X	X	X	X
		P&ID Walkdown	X	X	X	X	X	X	X	X	X
		Inspection of equipment system: Documentation, Material and Construction Verification, Component Installation	X	X	X	X	X	X	X	X	X
		Point-to-Point Continuity	X	X	X	X	X	X	X	X	X
		Electrical Instrument Function	X	X	X	X	X	X	X	X	X
		Control Module Confirmations	X	X	X	X	X	X	X	X	X
		Electrical Assembly Checks	X	X	X	X	X	X	X	X	X
b	**Operational**	Pump Rotations	X			X	X	X	X	X	X
		Instrument and Sensor Calibration	X	X	X	X	X	X	X	X	X
		Service and Utility Connections and availability	X	X	X	X	X	X	X	X	X
		Final Walkdown of equipment system	X	X	X	X	X	X	X	X	X

Table C. Commissioning equipment acceptance matrix.

are specified in the URS - temperature, rpms, flow rates, pressure levels, or others - are confirmed during the SAT

Commissioning/Start-Up

Commissioning and start-up are the primary elements of the CQ. The first step in commissioning is often a review of the design, usually referred to as the Design Qualification or DQ; it is also possible that a prior design qualification could have been performed during the skid design stage. The DQ verifies that the system meets the needs of the end user. It is a final opportunity to make engineering changes to the system before steps are taken to put it into operation. The DQ may be completed either through field verification of installed conditions or via an engineering document review. Whichever approach is adopted, the design qualification must be completed and approved by the system owner and engineering before any final installation qualification is undertaken.

Table C, the Commissioning Equipment Acceptance Matrix, shows that almost all of the steps undertaken during commissioning have been addressed in whole or in part previously. The primary difference is that this is typically done and recorded as GMP documents. Therefore, rather than addressing each bulleted item, details are provided below for three key areas addressed as part of commissioning:

1. Inspections are conducted to verify that equipment and system documentation, materials, construction, and installation are in accordance with design specifications.

Inspection can be sub-divided into the following:

- documentation verification to ensure compliance to design specifications
- material/construction tests to ensure compliance to design specifications
- component installation verification to ensure compliance to design specifications

Details of each of these follow:

Documentation – Verify that all documentation reflects installed equipment by tying into procurement and engineering elements. This must include data from purchase orders, drawings, P&IDs, change orders, and receipt inspection documents

Material/Construction Tests – Verify that materials and construction of all equipment and system components reflect installed equipment and design specifications.

- *Material Verification* – Copies of all material documentation must be collected and compiled into the Turnover Package. If, at this point, all documentation is not provided by the supplier, it must be supplemented to create a complete package. (Material test reports, certificates of compliance, and lab reports are key for material contact products).
- *Construction Verification* – Copies of all construction documentation must be collected and compiled into the Turnover Package. (Details of piping, valves, instruments, and all subcomponents incorporated in the work as well as

welding specifications, certifications, welder qualifications, weld logs, argon certifications, and weld inspection records).
- *Testing Verification* – Confirm proper certification of both inspector's and equipment calibrations.

Component Installation – Verify that the physically installed equipment, instruments, piping, and controls reflect design specifications.
- *Component Equipment* – For items such as pumps, agitators, panels, and vessels, verify all information related to materials of construction, finish, and performance.

2. Preparation for Operation ensures that all components of equipment or system are prepared for performance testing. At a minimum, procedures for preparation of operation include:
   - verification of all instrumentation and sensor calibrations
   - verification of service and utility connections, ratings, and availability
   - complete and final walk-down of equipment-system as a check for completeness, safety

3. Performance Testing verifies that equipment or system delivers the required capacity and performs according to specified design function. Reference to the URS is important at this stage.

Installation Qualification (IQ)

After the equipment has been proven to meet the specified requirements, the installation goes through a final qualification step. This is usually performed by the owner's validation team with outside assistance as warranted. Table D provides a matrix for the IQ step. The level of detail at this step needs to be the most complete and covers the full expected range of operation. Therefore, what follows is intended to provide some additional detail related to the steps in Table D:

1. The Drawing Verification step has the following focal points:
   A. Pre-requisites to the IQ being performed are that the DQ and CQ be completed.
   B. Execute the walk-down and verify the following:
      - line sizes
      - connection types
      - instruments are in-line
      - reducers – types and locations
      - completeness of tagging
      - equipment data
      - general notes from drawings
      - accessibility for operations
   C. When completed, sign off the drawings "As-Built" and initial and date them for record.
   D. Generate an Engineering Drawing Change (EDC) for any required changes.

2. Piping Walk-down: Use isometric drawings and P&IDs to verify the following:
   - slope verification
   - weld visual checks
   - piping support check
   - diaphragm valves installed; angle verification
   - weld log verification
   - material marking
   - proper fit-up

Sample Equipment Acceptance Matrix											
		Description	Typical Equipment – Systems								
			Bioreactor Systems	Centrifuge System	Depth Filtration Skid	UF/MF Skid	Filtration Skids	Chromatography Skid	CIP Skids	Autoclaves	Glass Washers
IQ – Installation Qualification – By Owner											
	Owner/Client Signed Protocol to be used and all information and data to be recorded	Verify that the CQ and DQ completed prior to start IQ	X	X	X	X	X	X	X	X	X
		Execute System Walkdown	X	X	X	X	X	X	X	X	X
		Drawing Verification (P&ID)	X	X	X	X	X	X	X	X	X
		Piping Walkdown	X	X	X	X	X	X	X	X	X
		Name Plate Verification	X	X	X	X	X	X	X	X	X
		Component Installation	X	X	X	X	X	X	X	X	X
		MOPC Verification	X	X	X	X	X	X	X	X	X
		Passivation Verification	X	X	X	X	X	X	X	X	X
		Insulation Verification	X	X	X	X	X	X	X	X	X
		Component Labelling Verification	X	X	X	X	X	X	X	X	X

Table D. Installation qualification criteria.

3. Nameplate Verification
   - Confirm and document nameplate information through field verification and vendor documentation.
   - Document Materials of Construction.
   - Document Turnover Package inclusion for all Materials of Product Contact (MOPC).

4. Procedures regarding component verification
   A. Field-verify that typed text (tag, description, service, size, specification) in component tables (valve, instrument, static components) are correct.
   B. Field-verify and document manufacturer, model number, and serial number for each component within the system boundary.
   C. Review supporting documentation for MOPC of each component.
   D. Instrumentation calibration ID and due date is field-verified and recorded from calibration sticker.
   E. Non-fieldbus instrumentation requires configuration records to be verified as being on file.
   F. Components used in oxygen service are required to be cleaned and degreased. Review and document these.

5. Procedures regarding MOPC Verification
   A. Acceptable MOPC verification methods include the following:
      - certified Mill Test Reports to verify material heat number
      - Certificates of Compliance (C of Cs) stating material and surface finish comply with specifications
      - certified vendor drawings with a Bill of Material
      - approved vendor submittals
      - Material of Construction stamped on component
      - direct testing as a last resort
   B. Other MOPC Verification Notes:
      - Elastomers require Certificates of Compliance that state the material meets 21.CRF177.2600 or USP Class VI.
      - MOPC for sprayballs may be verified through weld logs or vendor drawings.
      - MOPC for vessel thermowells are verified through heat number or vendor prints.

6. The procedure regarding system lubrication verification simply requires Certificates of Compliance.

7. The procedure for passivation verification requires a back-check of the passivation report and highlighted passivation P&IDs to the system boundary drawings.

8. Procedure for insulation and labeling requires the following:
   - Field verify that each line within the system boundary has been labeled and insulated.
   - Confirm and document these in the engineering table.

By following this set of procedures, a complete IQ package can be developed. The skids and systems should now be ready for manufacturing to assume their role.

Conclusion

Although the Guides[1,3] contain recommended approaches for qualifying systems, they do not clearly apply to every step that the industry seems to be taking toward acceptance of manufactured skids. Some precede the GAMP steps and some are woven between them. Steps to properly place skidded equipment into operation in a biopharmaceutical facility have been shown schematically in an Equipment Acceptance Chain (EAC). This does not replace the GAMP Guide, but supplements it. The goal has been to develop an approach for consistent and timely testing and document production that applies to most biopharmaceutical skids.

By focusing on the EAC early in the purchase cycle, project requirements and expectations can be defined in a way that will tie back to the owner's User Requirement Specification. By assigning responsibilities for each step of the EAC to engineering, design, fabrication, installation, or end-user personnel, clear ownership of the steps can be established. Testing and document production can then be governed by making use of sample equipment acceptance matrices. This has the potential to streamline testing, avoid redundant test steps, and allow for the downstream use of a prior step's efforts. By simply adopting this approach early in the project cycle, savings to the owner in time and money can be substantial.

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About the Authors

Roy F. Greenwald, PhD is the President of DECCO, Inc. and President/CEO of DENS Partners, Inc., of Brookline, New Hampshire. DENS Partners is the parent company of a family of firms specializing in services to the biotechnology and pharmaceutical industries that range from skid manufacturing to field construction and full facility management.

Prior to joining DECCO, Dr. Greenwald was the executive vice president of a process engineering firm. Under Greenwald, the companies have won numerous national awards for their client satisfaction, project performance, and safety records. Greenwald earned BS degrees in both chemical and mechanical engineering from the Massachusetts Institute of Technology and a Masters and Doctorate from the University of California at Berkeley. He holds multiple professional engineering licenses and master contracting licenses and also has served as the chairman for several technical committees within ASME and Associated Builders and Contractors. He can be contacted by telephone at: +1-603-249-7409 or by e-mail at: roy_greenwald@decco.com.

DECCO, Inc., Brookline, Hew Hampshire.

Thys Smit has nearly 32 years of engineering and construction experience from conceptual design through start-up/commissioning on nuclear, fine chemical, chemical hydrocarbons, and biopharmaceutical production plants. He went to school in Pretoria, South Africa were he finished his mechanical engineering degree. Smit has worked on various projects in South Africa and the US for Fluor, Phoenix Imperative (AMEC) Lifetek Solutions, Parsons, and Lonza. Projects completed in the US to date include: a new biotech contracts facility for Lonza (LSBO), Portsmouth, New Hampshire; a new biotech facility for Human Genome Science (HGS), Rockville, Maryland (conceptual to detail design); a biotech contracts facility for Covance, Research Triangle Park, North Carolina (from inception to completion); conceptual studies for various projects in house with Fluor Daniel. Projects completed outside the US to date include: a conceptual design for a citric acid facility for Roche, Shanghai, China; a conceptual design for a vitamin B2 facility in Shanghai, China; various projects from petrochemical/oil refineries to nuclear projects with Fluor Daniel, South Africa. Smit is a member of the South African Draughting Institute, the Engineering Council of South Africa, and the American Society of Mechanical Engineers. He can be contacted by e-mail at: thys.smit@lonza.com.

Lonza Biologics, Inc., 101 International Dr., Portsmouth, New Hampshire 03801.

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A Risk-Based Approach to Packaging Machinery Validation

by Jonathan Davey

This article describes a method of validating both the hardware and the software in conversion and packaging machinery, using a risk-based approach.

Over the years, confusion has reigned about how much software and hardware validation should be performed when validating process and packaging machinery, especially when the equipment may not be brand new. There is clear guidance on prospective validation of control systems in GAMP 4 and the GAMP Good Practice Guide: Validation of Process Control Systems (VPCS) so this article will not go over old ground. One area that often needs addressing is that of older machinery, which may have been modified or upgraded a number of times to handle different products. This is very common in the medical device industry, particularly around two-dimensionally packaged products such as gloves and wound care dressings.

It is important to note that the validation of the printing system for producing lot number and expiration date will not be covered in this article as a risk-based approach is not appropriate for validating these types of systems.

The requirement to validate process and packaging machinery is often triggered when the equipment is relocated – perhaps due to new acquisitions or sub-contract manufacturer, product rationalization, or a number of other reasons. The key problem may be that when this work is carried out, the existing documentation set may not be up to the standards expected within industry. The task of bringing it up to date can seem daunting, especially where software is concerned – but using a risk-based approach and with the appropriate personnel, it's possible to quickly generate the documentation and determine the appropriate controls to prove the system operates as intended.

During this process, it must be understood that not all software functionality will necessarily be tested; nor will it generate as comprehensive a validation package as would be expected with a new system – but it will identify and test what is deemed critical and will test the identified functionality. Using this method, the machine is subject to 'black box' testing of the software using the principle of testing the functionality rather than testing down to code level. If this is combined with a risk-based approach to determine criticality and impact, testing can be targeted at where it will be most effective. This will reduce the time and cost associated with this validation exercise.

Taking a typical validation V model as shown in Figure 1, on the left there is the User Requirement Specification (URS), Functional Specification (FS), Design Specification (DS); and on the right the Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). Often there may be no software-related documentation available, or at best the information will be sketchy. By using this approach we can quickly generate the Functional Specification and the

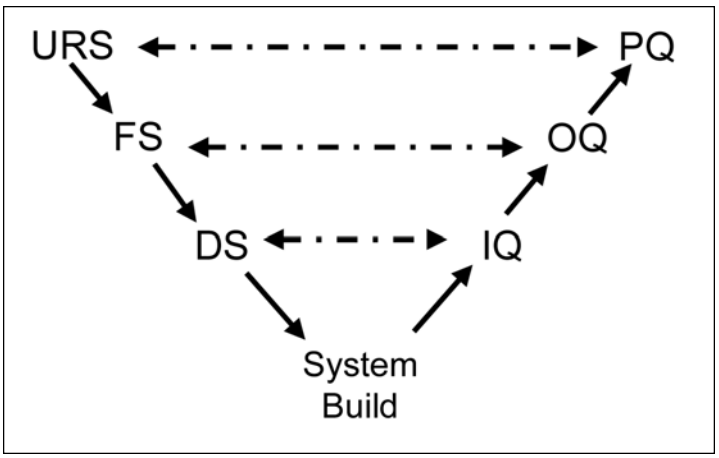

Figure 1. A typical validation V model.

Test Documentation that is both appropriate and prioritized.

Prior to starting the risk-based approach, it is essential that the key User Requirements are identified and documented, and would typically include the following; pad placement, splice detection (and failure mode), run out detection (and failure mode), web tensions, speed control, temperature of sealing system (including pre-heat), pressure of sealing system, registration system, seal strength, reject on start-up, reject on selection, reject on splice detection, reject on empty pack, and reject on machine inch or slow speed. This is not intended to be an all inclusive list and as such, additional user requirements should be added as appropriate to the process. Figure 2 shows a typical machine layout which is a good reference point to ensure that all of the key user requirements have been identified. This also can be used later in the process to ensure that all functional elements of the machine have been assessed.

The key to this method is to reverse engineer the documentation using the machine as the starting point. This can only be achieved by using personnel who have the knowledge and experience of the machine. By dividing the machine into small sub-assemblies or components and assessing each one, it is possible to gather enough information to determine the level of risk, and the level of validation work required - *Figure 2*. This method of reverse engineering is a four-step process.

Step 1

Divide the machine into small parts or assemblies with a clear description and its interface with the control system and the rest of the machine. It is then possible to assign a GAMP category to the hardware. GAMP 4 provides clear guidance on the level of qualification recommended for all categories of hardware and software.

Step 2

Describe the function of this part of the machine and determine its impact on the finished product using the user requirements as the starting point. This is best achieved using a team of people who are used to working with the machine – typically an engineer, an operator, and a representative from the quality department. As the description is documented, the impact that this element of the machine has on the finished product can be established.

Step 3

Determine the failure mode of this part of the machine and the impact this failure would have on the finished product based on the user requirements. This knowledge is essential in determining the controls needed to ensure that the quality and efficacy of the finished product can be maintained.

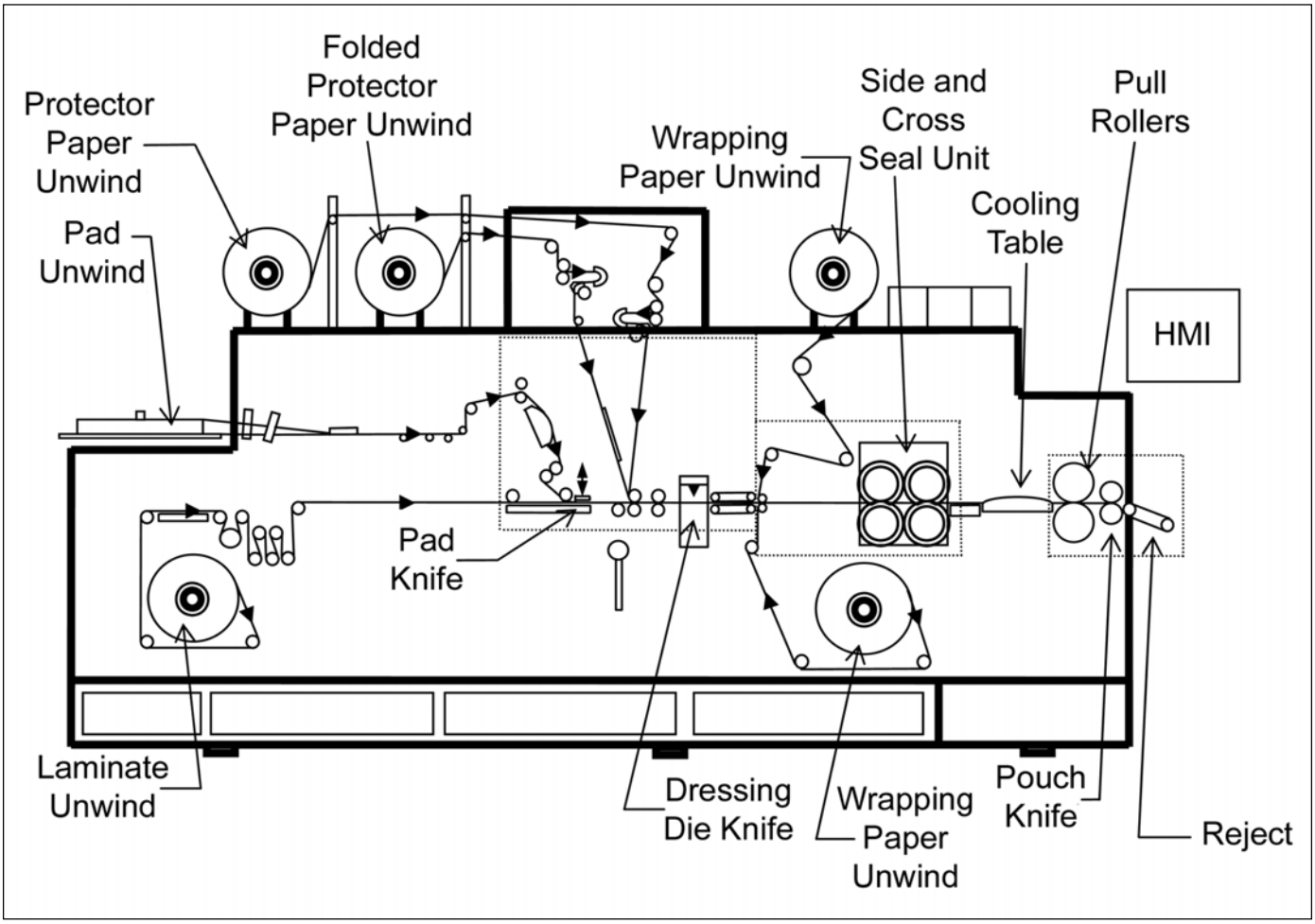

Figure 2. A typical machine layout.

Figure 3. Device used to reject a faulty product – identified during the manufacturing process.

Step 4

Determine the appropriate control methods for this part of the machine. These can vary from functional testing through to operational instructions and will be determined by the impact and likelihood of detection. Older packaging machinery may not have the high level of automated inspection and self diagnosis available on its modern equivalent so a high level of operator intervention will normally be required.

Figure 4 shows a simple form to capture the information generated through this reverse engineering process. In this example, the equipment categories (the impact that the particular component could have on the finished product) and the control methods (the actions needed to validate the equipment) have been pre-determined as follows:

Equipment Categories

1. ***Product critical – sterility.*** This category covers any machine components likely to impact the product sterility – for example, the sealing system, machine speed, and packaging quality.

2. ***Product efficacy.*** This covers machine components impacting the product quality – for example, those that place the product in the final packaging, such as infeed and product positioning.

3. ***Product appearance.*** This category is used for any machine components impacting the product appearance – for example, those that would typically revolve around cutting, shaping, or handling the product.

4. ***Operational efficiency.*** This covers any number of components impacting the operational efficiency of the process – for example, salvage haul-off (where waste from a cutting operation is cleared away) may not impact on product *quality,* but may result in poor efficiency if not operated correctly.

5. ***No criticality.*** This category covers components that have no criticality at all.

Control Methods

1. ***Process variable – validation required.*** In this instance, full validation is required for the process variable. Such items as the sealing system, where we would typically see temperature, speed, and pressure as variables, would be challenged across a range of settings to generate an operating window where acceptable seals are achieved.

2. ***Functional testing.*** In this instance, the component will require some form of functional testing or qualification – for example, splice detectors used to detect joints in materials and reject gates used to remove a faulty product from the process.

3. ***Calibration.*** In this instance, the component will require some form of calibration – for example, sealing systems. Typically, temperature, pressure, and speed are three attributes where the control devices require calibrating.

4. ***Operational instruction.*** In this instance, the component will require some manual intervention by the machine operator so it will need to be included in the machine operating instruction – for example, line clearance after a stoppage (not all machines will do this automatically).

5. ***Maintenance activity.*** In this instance, the component will require some maintenance activity to keep the desired operating conditions. This can range from mechanical settings that generate the correct sealing pressure through to routine checks on the temperature distribution of the sealing systems.

Item	Description	Functionality	Categorization	Control Method	Cross Reference
1	Reject gate to good product or reject following fail criteria. Controlled by the PLC.	The unit comprises one pneumatic cylinder and one product sensor. When triggered by the PLC, the reject gate opens to direct the faulty product into the reject bin. The PLC does not verify that the product has gone into the bin or that the gate has opened and as such is not failsafe. PLC programmed to reject product on Inch speed selection, machine start-up, splice detection, and operator manual reject selection.	1/2/3	2 – Functional testing of operation during operational qualification.	
				4 – Operator instructions required for routine testing of operation and operational modes.	
				5 – Maintenance procedures required for the reject gate.	

Table A. Traceability matrix.

Section 1. The Machine/Process Information		
Brief System/Module/Component Description		
Reject gate to pass good product or reject following fail criteria. Controlled by the PLC.		
List Device/System Interfaces		
Sensors for splice detection, registration fail, manual reject selection, reject on Inch speed, reject on start-up.		
Reject on start-up (first five products) and reject override selected by the operator.		
	GAMP Category	HW 1 SW 5

Section 2. Functional Description							
The unit comprises one pneumatic cylinder and one product sensor. When triggered by the PLC, the reject gate opens to direct the faulty product into the reject bin. The PLC does not verify that the product has gone into the bin or that the gate has opened so is not failsafe. PLC programmed to reject product on Inch speed selection, machine start-up, splice detection, and operator manual reject selection.							
Equipment Category				3	Product Appearance	✓	Comment
1	Product Critical – Sterility	✓		4	Operational Efficiency		Cat 1 for outer pack only.
2	Product Efficacy	✓		5	No Criticality		

Section 3. Failure Mode	
Failure Description	Fail when closed, fail when open, fail in mid position, and intermittent operation.
Impact	If fail when closed, faulty product will be packed. If fail when open, all product will be rejected. If failure in mid position, product will jam the out-feed and no product will be packed. Intermittent failure could have any of the above outcomes.

Section 4. Control Method	
1 Process Variable – validation required, 2 Functional Testing, 3 Calibration, 4 Operational Instruction, 5 Maintenance Activity, 6 Spares Information, 7 Parameter Recording, 8 None	
The hardware record form has been completed and the appropriate control method has been identified:	2/4/5
2 – Functional testing of operation during operational qualification.	
4 – Operator instructions required for routine testing of operation and operational modes.	
5 – Maintenance procedures required for the reject gate.	

Figure 4. Specimen form.

6. ***Spares information.*** In this instance, the component may be critical to the process so the spares need to be correctly identified and sourced.

7. ***Parameter recording.*** In this instance, the component will have either electronic or mechanical configuration that will impact the product quality so it will need to be recorded. Inverters, temperature controllers, and complex sensors fall into this category.

8. ***None.*** It's unlikely that none of the control methods above would be required, but in that event, this category is available.

These categories and control methods should of course be modified to suit the terminology of the individual organization or the requirements of the particular machine.

Completing the Form

Figure 4 is a specimen form completed for an assessment of the reject gate mechanism. This device is used to reject a faulty product identified during the manufacturing process and a picture of this is shown in Figure 3.

Section 1 contains a description of the component being assessed, along with the interfaces – in this example, splice detection sensors, a manual reject selection, and a series of reject functions generated by the PLC. Due to the nature of the hardware, both a Programmable Logic Controller (PLC) and electronic sensors for the splice detection, there is a hardware Category of 1 and a software Category of 5 for the PLC.

Section 2 contains a functional description of the action of the reject gate detailing the action of the PLC, the operator, and the sensors. In this case, the equipment category for this component impacts the finished product in three areas:

"Once all the assessments have been completed, the data should be transferred to a traceability matrix, which provides a clear method of tracking all actions identified for the given component."

1. ***Product critical – sterility.*** If the product is not rejected on machine start-up, the final packaging seals may not be integral and will not maintain sterility.

2. ***Product efficacy.*** If the reject operation has been overridden by the operator, the faulty product would not be rejected and may continue through the manufacturing process, and possibly, on to the customer.

3. ***Product appearance.*** If the reject gate does not operate correctly, the actuator may damage the product during its operation and impact on the product appearance.

Section 3 describes the failure modes – in this case, the reject gate which can fail when it is closed (remain closed), fail when open (remain open), fail in mid-position (neither open nor closed), and suffer from intermittent operation where the gate may operate slowly or sporadically. The section also describes the impact of the failure modes as follows:

- If it fails when it is closed, the faulty product could be packed.

- If it fails when open, all products will be rejected, creating an efficiency issue.

- If it fails in mid-position, the product would jam the mechanism so no faulty product would be passed on from the machine.

- Intermittent failure could result in any of the above conditions.

Section 4 describes the control methods, which in this case has identified: 2 – functional testing; 4 – operational instructions; and 5 - maintenance procedures. The correct operation of the gate, sensors, and operator selections would be proved as part of the Operational Qualification. Clear operator instructions would be required to periodically check the correct operation of the gate and use of the machine. Maintenance instructions may be needed to maintain the reject gate at its optimum.

By completing this assessment, we have been able to identify the component, its function, a functional description, its category and risk, the failure mode and impact, and the action needed to validate it. An assessment sheet would be completed for every part of the machine and the total number of assessments would depend on the number of parts into which the machine had been divided (the more numerous the divisions, the more information would be gathered).

The machine shown in Figure 2 was divided up into 28 separate parts or assemblies for the assessment process, and in this instance, the lowest level of categorization was Category 4 and no items were deemed as having *No criticality*. Examples of parts that were deemed Category 4 were, safety guard functionality, cooling station after the sealing system that allows the sealed dressing to be handled, and the inputs to the PLC from devices such as overload protection on the electrical supply. None of these have an impact on product quality, but could affect the machine efficiency.

Traceability Matrix

Once all the assessments have been completed, the data should be transferred to a traceability matrix, which provides a clear method of tracking all actions identified for the given component. This is not only essential to ensure that nothing is missed, but it also provides a means of sorting or arranging the actions in order of risk. On this basis, it's possible to quickly generate a list of the highest risks and the required actions which would form the basis of the validation strategy.

Table A shows a simple traceability matrix where the information from Figure 4 has been transposed. The description, functionality, categorization, and control methods (actions) have been completed. The last column records the document references where the actions have been completed.

Of course, some dangers exist with this process: the machine may not contain all the automated functionality required and by simply looking at the machine, these may be missed. Therefore, it is essential to continually refer back to the user requirements at each stage of the assessment process. Once the assessments have been completed, a review must be undertaken to ensure that nothing has been missed. This review should be conducted by a team comprising representatives from all relevant departments to ensure a high level of confidence.

Software Validation

Once all the assessments have been completed, it's a relatively simple task to extract all functional descriptions and failure modes relating to the control system and to generate a functional specification. This is by no means a substitute for not conducting prospective validation, but it does provide a means of compiling information where little or none is currently available.

Other Benefits

A number of other benefits can be derived from this process. First, a full list of parts requiring calibration can be generated based on how the machine operates. Second, a list of critical spares (or at least the components that have been

declared critical) can be identified, thereby, helping identify which spares should be held in stock. Third, the assessment sheets provide basic information on machine operation to assist the maintenance staff with fault-finding, even though it may not be as comprehensive as desired. And the final benefit is associated with change control. Once a traceability matrix has been generated and risk or criticality identified, there is a means of quickly assessing whether a proposed change in parts would impact on the product quality. The traceability matrix would clearly identify both high- and low-risk components.

Conclusion

There is no substitute for following a proper validation lifecycle as detailed in GAMP 4. This is the best way to ensure that any control system or process has been designed, developed, and tested so that it functions as required. However, there is a great deal of older packaging machinery around where the documentation set would not meet the current industry expectations; this is where this process could help.

Validation is often viewed as time-consuming, onerous, and non-value adding. But if simple processes such as these outlined here are used, it is possible to quickly identify where the risks are, the actions to be taken, and aspects such as which equipment needs calibrating. This keeps the workload to a minimum while still identifying the critical elements where the validation effort needs to be targeted.

About the Author

Jon Davey is Managing Director of Provalidus Ltd. He graduated in 1984, specializing in electrical and electronic engineering, and spent two years with the Civil Aviation Authority as an air traffic engineer. He then became a project engineer working for a number of companies before moving into the medical device and pharmaceutical industries where he had various roles ranging from project engineer, engineering manager, production manager, validation manager through to quality assurance manager. Davey was a member of the Process Control Special Interest Group (SIG) that produced Section 9 of GAMP® 4 and the GAMP® Good Practice Guide: Validation of Process Control Systems, and he now runs his own consultancy business. Davey can be contacted by telephone at: +44-1482-650514 or he can be contacted by e-mail at jond@provalidus.com.

Provalidus Ltd., 46 West Ella Road, Kirk Ella, Hull, East Riding of Yorkshire HU10 7QN, United Kingdom.

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Integration of Commissioning and Qualification (C&Q) with Other Phases of the Project Lifecycle

by John Devlin

This article considers the integration of the C&Q process with engineering, procurement, construction, as well as other sustaining operations activities, including production, quality, and maintenance.

Introduction

The complexity and capital value of projects in the pharmaceutical/biotech industry has increased significantly in recent years. The number of investments exceeding a billion dollars has increased and projects costing hundreds of millions of dollars have become more common. The demand for quality and regulatory compliance in these projects remains high, consequently the risk of cost and schedule overruns exists and the extent of these overruns can be significant. In order to minimize these risks, it is important to examine ways of executing key phases of each project in a manner which will facilitate a right first time approach later in Commissioning and Qualification (C&Q).

Commissioning is often the phase which poses the greatest risk to project success and very often can be the point at which project budget or schedule problems first become visible. Deficiencies in the engineering, procurement, and construction phases are frequently not identified until the testing of individual or combined system components in the field. The cost and time delays associated with resolving such issues are considerably higher during commissioning than during the earlier phases in which the deficiency first originated.

In order to reduce the risk of such cost and schedule overruns, it is crucial to plan the C&Q process from an early stage in the project. Decisions that are made during the engineering, procurement, and construction phases can significantly affect the C&Q process. If these decisions are made using an integrated approach with a view to facilitating the C&Q process, then the benefits can be great and the risk of cost and schedule overruns can be much reduced.

Similar benefits can be achieved by integrating the client's sustaining operations into the C&Q process.

Previous project experience both by the author and associates has shown a clear relationship between the timing of the start of the C&Q planning process and the likelihood of a successful C&Q execution phase. In order to maximize success and minimize the risk of overruns, it is strongly recommended that the C&Q planning phase starts no later than the beginning of detailed design.

This article does not examine the integration of commissioning with validation. Instead, it considers the integration of the C&Q process with the other project phases, i.e., engineering,

Table A. Reference project list.

Project ID	Project Description	Facility Location	Location of Detailed Engineering	Timing of C&Q Input	Total Investment Capital
1	Bulk / API Facility	Europe	USA	At start of Detailed Engineering	$200 million
2	Purification	Europe	Europe		$15 million
3	Purification	Europe	USA		$20 million
4	Bulk Biotech	Europe	USA	At Various Points During Construction	$500 million
5	Fill Finish	Europe	USA		$250 million
6	Bio Process Purification	Europe	Europe		$150 million
7	QC Laboratory	Europe	USA		$80 million

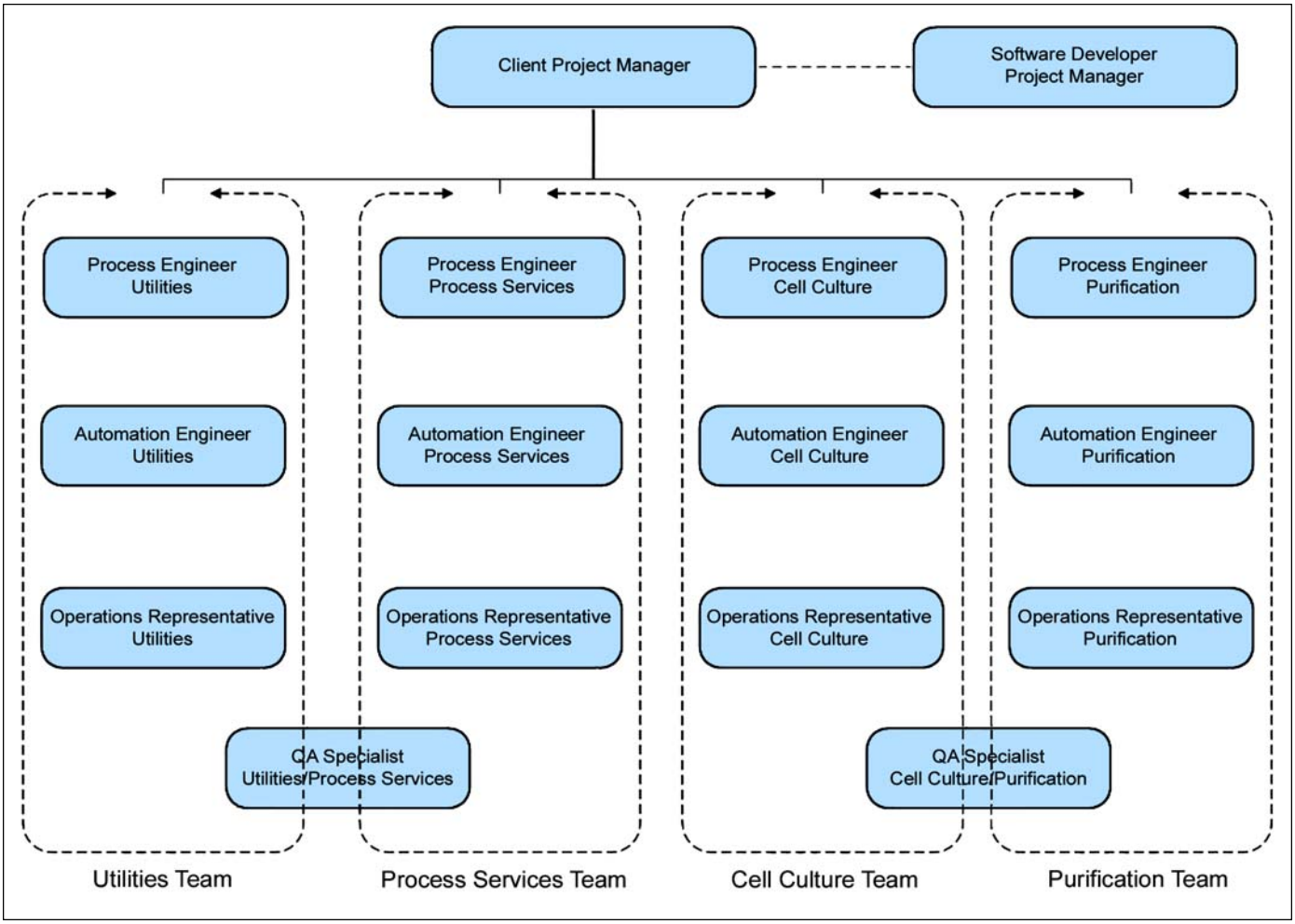

Figure 1. Sample client organization for the development phase of process control software on a large scale bulk biotech facility.

procurement, construction and also sustaining operations activities such as production, quality, and maintenance. The development of control system software, although an inherent part of engineering, can independently pose a significant risk to the success of the C&Q phase of the project. It is for this reason that the topic of control system software development has been considered separately to engineering in this article. Throughout the article, reference is made to some problems that have arisen during the C&Q of previous projects by way of examples. These problems, and the resulting cost/schedule impact, could have been avoided with early involvement of C&Q.

Table A lists the key projects on which this article is based. In projects with ID 1 to 3, dedicated C&Q personnel were appointed at the start of the engineering phase. Each subsequent phase of the project was progressed with a view to efficient C&Q execution and in all cases, projects were completed within budget and on schedule. On the other hand, on Projects ID 4 to 7, the planning of C&Q did not occur until later in the construction phase, resulting in schedule and budget overruns. Client sensitivity on lessons learned precludes the provision of further detail on the project specifics in this article.

Engineering

A general expectation of the engineering phase of a project is for completion on schedule and within budget. This is largely because architectural/engineering firms, through years of experience, have strong benchmarking capabilities, streamlined engineering procedures, and knowledgeable teams of people who move from one project to another. However, the quality or effectiveness and hence the real success of the engineering phase cannot be determined until during the commissioning phase when it is observed how well each system works in relation to the specifications. This is often the first real test of success for the engineering phase.

Some of the main C&Q activities which should take place during engineering are as follows:

Develop C&Q Master Plan and Execution Strategy

Producing these documents at the start of design will align all parties toward the ultimate goal of successful C&Q. The preparation of master documentation is a process which should ensure the 'thinking through' of the steps in the plan as well as implications or impacts for other project elements. These documents should clearly state the responsibilities of all participants and define their accountabilities (refer to

Table B for example of a matrix which identifies such responsibilities). Making these documents available to other project groups can contribute toward a greater awareness of the impact of engineering decisions on C&Q.

Define System Boundaries

System boundaries should be developed at an early stage of the project and must be consistently applied to all aspects of the project from engineering onward. Failure to do this can lead to confusion as in the case of one project where system boundaries were not properly defined until mid way through construction - *Table A, Project ID 5*. Out of necessity, the team with responsibility for developing the Distributed Control System (DCS) software had defined their own set of system boundaries which were different to those eventually defined by C&Q. For time saving purposes, the software was delivered to site on a phased basis in groups of systems. However, due to the differences in system boundary definition, the software to drive some devices, which was part of a C&Q defined system, was not delivered when required.

While this may seem like a minor inconvenience, it can have very serious consequences and cause unnecessary delays to already overburdened C&Q schedules. It is an indication of what can go wrong when system boundaries are not clearly defined and applied at an early stage of the project.

Define Sequence in which Systems will be Commissioned

Although this should form part of the C&Q execution strategy, it warrants independent attention because of the considerable benefits to be gained by achieving 'construction complete' status of each system in the same sequence that is required for start up purposes. In cases where engineering and construction are not fully aligned with the sequential requirements for commissioning, the result can often be that systems are lying idle for periods of time. An example is a project where a CIP skid and distribution loop was construction complete a number of months ahead of the utilities that fed into the skid - *Table A, Project ID 4*. Although an amount of pre-commissioning and dry testing could be undertaken, the bulk of the commissioning had to be delayed until the utility systems were themselves construction complete and partly commissioned.

Had the construction team been more aware of and aligned with the C&Q requirements, they could have focused their energies on completing the upstream utility systems earlier so that the C&Q team could complete their work earlier.

Consider Impact of Value Engineering Exercises on C&Q Activities

A 'value engineering' exercise can pose a significant threat to C&Q if careful consideration is not given to the activities required to take place within C&Q. Some examples of resulting problems are as follows:

A project supposedly saved millions of dollars in removing permanent access platforms which were to be used for accessing high level devices on HVAC ductwork and other utility systems - *Table A, Project ID 5*. The basis for the decision was that a mobile platform would be purchased by the maintenance group at a later stage and this would suffice for ongoing maintenance requirements. However, the extent, duration, and frequency of access required for commissioning purposes was not considered and ultimately the project spent 50% more than the original expected saving on temporary scaffolding. A further knock on effect of the scaffolding was that the final room and corridor completion had to be delayed until the scaffolding was removed.

#	Description	Engineering	Commissioning Manager	Commissioning Steering Team	Commissioning Authority	Commissioning Engineer(s)	Project Manager	Plant Engineering	Manufacturing Department	Quality Systems, QA	Quality Systems, QC	Manufacturer	Supplier	Construction Manager	Elec. Contractor	Mech. Contractor	Controls Commtractor	Process Automation Contractor	Administrative Disapline
1	Commissioning Plan		R&A	R&A	W&R		A	A	A	A				A					F
2	Commissioning Schedule		R&A	R&A	W&R									R&A	R&E	R&E	R&E	R&E	F
3	URS	W	R		R	R	A & R	A & R	A & R	A & R				R			R&E	R&E	F
5	DS	W & A	R	R	R	R	A & R	A & R	A & R	A & R		W	R	R&E	R&E	R&E	R&E	R&E	F
6	FS - Seq. of Ops	A	R	R	R	R	R	A & R	R	R		W	R						F
7	Design Drawings	W	R	R	R	R	R	R	R	R		W	R	R&E	R&E	R&S&E	R&S&E	R&S&E	F
8	HAZOP/FMEA Review		P	P	P	P		O&P	P	P		P							F
9	GMP Review	W	P	P	P			O&P		A & P	P								F
10	PDI	W & E	P & R		R	R		A & P				R	W				W	W	F
11	FAT	A	P & R		R	R		A & P	A & P			S&E	W&E				W&E	W&E	F
12	SAT		R		R	R		A & P	A & P			S&E	W&E				W&E	W&E	F
13	Commissioning Documents	R & A	R & A	R & A	O&R&A	W&E		R & P	R & A			R&E	R&E	R&E	R&E	R&E	R&E	R&E	F
14	As-Built Drawings	A	R		R	R	R	R				S	S	R&E	S	S	S	S	F
15	Training and Documents	W	P&R		R	R&P		E&R	E&R	E&R&A		S&E	S&E	S&E	S&E	S&E	S&E	S&E	F
16	SOPs		R		R	R		R	W&E	R	R								F
17	Summary Reports		R&A	R	R	W		R	R	R	R								F
18	ETOP		R&A	R	W	S&O		R											F

Abbreviations Used:

URS	User Requirement Specification	PDI	Pre-Delivery Inspection
DS	Design Specificatoin	FAT	Factory Acceptance Test
FRS	Functional Requirement Specification	SAT	Site Acceptance Test
HAZOP	Hazardous Operations	SOPs	Standard Operating Procedures
FMEA	Failure Mode Effect Analysis	ETOP	Equipment Turn-Over Package
GMP	Good Manufacturing Practices		

Legend:

W= Write and Maintain	S= Supply
R= Review	F= Route/File/Archive
A= Approve	P= Participate
E= Execute	O= Organize

Table B. Responsibility matrix.

On another project a decision was made to replace DCS activated control valves on WFI systems and replace them with self actuating control valves - *Table A, Project ID 6*. The WFI systems themselves were complex and were required to feed a large number of users with wide varying pressure and flow requirements. After months of trying to get these valves working in line with the complete system requirements, the commissioning team decided to replace the installed valves with DCS controlled valves. New valves were ordered at 12 week delivery and the software was modified to accommodate the revised strategy.

In effect, the items removed in the value engineering exercise were eventually reinstated, but at a considerably higher cost and schedule penalties.

Conduct Commission-Ability Review

A timely commission-ability review can contribute significantly toward a cost effective and right first time commissioning exercise. The review should be led by senior C&Q personnel and conducted on a system-by-system basis. The following are some of the items which should be addressed:

- What are the system boundary limits of the system in question?
- What other systems are needed to fully commission the system in question and at what stage are they required?
- Define a list of tests to be conducted during each phase of the commissioning process and provide a brief description of what each test will be required to prove. Table C contains a sample list of tests for a Reaction Vessel and demonstrates the level of detail that should be assembled at this stage of the project.
- Identify any prerequisites required for the execution of the tests; consider what commissioning tests can be integrated with tests for construction completion.
- Consider what level of stress testing will be needed for utility systems such as Water for Injection.
- Identify any risks that exist and how they could affect C&Q cost and schedule.
- Who will carry out activities such as initial start-up and pre-commissioning preparations, pressure testing, leak testing, cleaning, passivation, testing, and balancing, and when will these activities be executed?
- Who has responsibility for safety factors during testing, e.g., area clearance and electrical lock out, particularly when access is required by construction and commissioning personnel?

Such reviews should be chaired and driven by C&Q personnel. If conducted carefully and with the full support and cooperation of non C&Q personnel (such as engineering, construction, and operations), the output of the review could be invaluable. On one specific project where C&Q personnel were not involved in the engineering phase, it was decided that construction would carry out a ***partial*** leak test of ductwork on HVAC systems - *Table A, Project ID 6*. The leak tests were completed as required and the systems were insulated and handed over for commissioning. During C&Q, it was discovered that the rate of leakage throughout each system was far greater than specified in design and as a result, extensive amounts of insulation had to be removed and leak tests repeated so that the systems could be brought into specification. This waste of resources and time could have been avoided by earlier involvement of C&Q personnel and the potential risks resulting from partial leak tests could have been identified.

Procurement

Procurement activities can be divided into two sections - pre order and post order. It can be of great benefit to the C&Q activities if C&Q personnel are involved in the pre order phase so that risks to the C&Q process can be identified and mitigation plans put in place before orders are placed. The following includes some of the areas that should be addressed:

Documentation

Problems can frequently arise due to poor advance definition of what type and quantity of documentation is required. Vendors should receive an order with the clear expectation of what documentation will be required and when. The C&Q personnel who will be responsible for the start-up of the system should be given the opportunity of specifying the documentation required from vendors. This should substantially reduce the risk of discrepancies between documentation required and documentation provided. It is strongly recommended that the documentation delivery is linked to the payment schedule.

Vendor Involvement During C&Q

The full extent of vendor involvement with C&Q should be decided before an order is placed and most importantly vendor attendance rates and timings also should be agreed. Through the development of their execution strategy, C&Q personnel should have a solid understanding of what is required from each vendor on site and the best time to obtain agreement concerning this is before an order is placed. This is also the best time to agree on the cost of vendor attendance on site.

On a particular project where there were a small number of TOC meters, the procurement personnel placed the orders on schedule, the meters were delivered and installed on schedule, and the vendor was fully paid - *Table A, Project ID 5*. However, the commissioning personnel did not have the in-house capability to calibrate the meters and thus, it was necessary to employ the local agent for the vendor to carry out the calibration and train project personnel in the calibration and operation of the meters. Some components of the meters had been damaged either in shipping, storage, or installation and thus, had to be reordered and replaced. Also, the availability of the local service agent was poor due to a high workload and other priorities. It took more than five months to successfully bring the meters into operation. Such delays and associated effects on costs could have been reduced if the

original scope of the vendor was expanded to include commissioning of the meters.

One of the main discrepancies between the purchaser and vendor expectations can arise during Site Acceptance Test (SAT) execution. It is not unusual for vendors to arrive on site having allocated a period of time in which to execute their standard pre-commissioning and commissioning tests only to be presented with a more complex client driven set of tests.

It is important for C&Q involvement when agreeing on the timing for vendor site involvement. In order to optimize the usage of vendor resources, any prerequisites such as utilities and client resources should be clearly defined. C&Q personnel should be able to assist with agreeing the framework around which vendor commitments are being made.

Control System Software Development

Complex software systems are commonplace in most modern pharmaceutical projects. This article examines C&Q involvement in the design, development, and testing of large bespoke systems such as Distributed Control Systems (DCS) or Building Management Systems (BMS).

Control system software often poses significant risks to the success of C&Q activities. In cases where delivered software undergoes major modifications on site, cost and schedule overruns can be expected.

There are a number of factors when implemented correctly can contribute toward a successful implementation of the control system on site. These include:

- Adhere to User Requirements without unnecessary over elaboration.
- Maximize FAT to the extent that confidence is high that significant changes will not be required on site.
- Link the timing of software delivery with system availability on site.
- Establish an organization structure to ensure continuity of knowledge from software design phase through to C&Q testing on site. Such continuity is important in order to differentiate between essential and non essential changes.
- Ensure that software changes or modifications are communicated to others beyond the software engineers so potential issues can be evaluated.

A model which has proved successful on previous projects is shown in Figure1 where a bulk biotech project is used as an example. At the software design stage, the plant is divided into areas and teams are assigned to each area. Each team consists of between three and four people, including a Process Engineer, Automation Engineer, Operations Representative, and a QA representative who can be assigned to multiple teams. The teams should be located at the same place as the software developers to ensure good communication and prompt response to implementation queries thus, minimizing delays in software development. The following presents a brief description of roles:

Client Project Manager

The main functions of the Client Project Manager are to manage the budget and schedule aspects of the software development and to provide technical coordination across the area teams as shown in Figure 1.

Process Engineer

Functions as the team leader, ensures adherence to URS, keeps schedule on track by responding to process related queries from implementation team, participates in Factory Acceptance Test (FAT) document development and execution, and has the autonomy to approve changes which are necessary to ensure that software is effective when it is delivered to site. When on site, this person can move into an area manager role and armed with the detailed knowledge gained in the design phase, should be able to guide the C&Q team efficiently through the start up phase.

Automation Engineer

Responds to automation related queries from the implementation team, participates in FAT document development and execution, liaises with automation engineers on other teams

COMMISSIONING TEST	TEST DESCRIPTION
Commissioning System Checklist	A high level check list will be completed to ensure that minimum safety, quality and logistical requirements for system commissioning have been addressed prior to start of field commissioning.
Hardwired Alarm and Interlock Test	All hardwired alarms and interlocks in the system will be verified against design requirements and specifications.
Safety Device Verification Test	Verification will be undertaken of all pressure relief valves and bursting discs on the system.
Utility Introduction and Verification Test	All utilities required for operation of the system will be verified against design requirements and specifications.
In Service Leak Test	The pressure in the vessel will be raised and held at a predefined set-point to determine the vessel leak rate prior to starting commissioning.
Agitator Pre-Commissioning Check Test	Mechanical checks of all agitators will be carried out initially and followed by a full performance test.
Coverage and Drainability Verification Test	Coverage of vessel internal surfaces from the fixed spray balls will be verified by means of a Riboflavin test. Vessel drainability will also be verified.
Steam In Place (SIP) Test /Cold Spot Test	To test that a set temperature can be reached and maintained at the temperature elements above each of the steam traps at the SOP station. This test will also check that there are no cold spots in the system.
Product Sample Verification	Verify that a sample can be taken at the product sample point on the Reaction Vessel

Table C. Commissioning sequence for reaction vessel.

to ensure consistency application of standards, and approves automation related changes which are necessary to ensure that software is effective when it is delivered to site. When on site, the Automation Engineer owns all aspects of the software for the area from initial download to version control to change control.

Plant Operator

Attendance of a Plant Operator is not essential and is not always possible due to cost and availability restrictions. In cases where it is possible, the benefits can be significant. Participation in software development, FAT, and the subsequent site testing of the control system during C&Q all provide an excellent training ground for the person who will be expected to operate the plant long into the future. Also, it provides an opportunity for the development of any SOPs that may be required to manual intervention in the plant operation.

QA Specialist

The QA Specialist is responsible for ensuring compliance of all aspects of the software development lifecycle with corporate and regulatory requirements. It is usually practical to have one QA representative working across a number of teams. In Figure 1, each QA representative is assigned to two teams.

Interface with C&Q

One of the benefits of following the model as depicted in Figure 1 is that the full team can follow the software to site for the C&Q phase, bringing the detailed knowledge gained during the development process. These personnel can integrate into C&Q teams across the project, contributing toward a more efficient start-up. It also is essential for these team members to be accountable for the quality and functionality of the software.

Construction

Relationship between Construction and C&Q

One of the most important relationships on the project is between the Construction Manager and the C&Q Manager. While both have their own set of priorities and targets concerning budget, schedule, and quality, it is essential that they find common ground and align their efforts toward the common good of the overall project.

The best way of doing this is to have early involvement of the C&Q Manager on the project so that the expectations of what marks the end of construction and the start of commissioning can be clearly defined. In some cases, there can be a period of overlap toward the end of a system completion where construction and commissioning can combine forces to avoid duplication of effort and combine some tests for construction completion with early commissioning tests, e.g., instrument loop testing.

In any event, once early involvement of C&Q is achieved, the Construction Manager can develop the construction plan and issue contracts with the knowledge that the end results are defined and agreed in a detailed and clear manner. This includes the areas of pre-commissioning where, through proper coordination, maximum efficiency can be achieved.

Sequence of System Handover

Early C&Q involvement in the project will facilitate advance agreement of the sequence in which systems will be commissioned and consequently the sequence in which systems will need to reach construction complete status. A carefully planned sequential start-up strategy is an important factor which contributes to the optimum use of C&Q resources on site. The size of C&Q project teams can be reduced and the rollover of C&Q resources from earlier systems to later systems can be facilitated.

There are obvious examples of areas where sequential handover of systems can be beneficial, such as the making available of utility systems in advance of process systems. However, some relationships are not as straightforward and need careful planning. Consider the project where bio burden and endotoxin level testing forms part of the C&Q scope of a WFI system. Prior to this phase of testing, it is necessary for the WFI system to be in an operational mode where it is continuously running under operating conditions and also being sanitized in accordance with procedures. Facilities and procedures for sanitizing and sterilizing sampling components such as sample valves and flexible hoses should be in place. This in turn means that qualified laboratories, analytical methods, autoclaves, and washers need to be available. The alternative is to outsource some of these activities. However, this can be costly and may not provide the prompt and flexible response needed during the C&Q phase of a project.

The timing and sequence of handover of complex utility systems, such as HVAC, needs careful consideration and planning. The commissioning of complex individual systems, such as air handling units, ductwork, control systems, and room envelopes, ultimately are required to converge in order to meet stringent requirements laid out in environmental monitoring programs. This is usually complicated by the fact that access to these areas should be limited during such testing and that it can conflict with access required by the personnel testing the process and utility systems within the rooms.

Accountability

Even with detailed planning, it is inevitable that some difficulties will be encountered and delays in some areas will occur. It is important to cultivate a culture of cooperation and one of accountability so that when things go wrong, the emphasis is on prompt remediation focused on the specific objective of a completed project rather than allocating blame.

A straightforward example is in the testing of instrument loops from DCS Operator Interface through to the field. On a project where there is a high initial failure rate, the allocation of blame is a wasteful exercise and the focus should rather be on how engineering, construction, and commissioning can combine forces to rectify the situation and get the schedule

back on track.

This culture of cooperation can be achieved by early involvement of the C&Q Manager on the project as long as the manager clearly identifies the criteria for success and obtains agreement from senior engineering and construction personnel. This culture should not be mistaken for one in which accountability can be avoided but rather where the priority, i.e., a team-based approach to early problem resolution and thereafter, a secondary focus on lessons learned.

Sustaining Operations

The C&Q phase of a project is perhaps the best training ground for people who will operate, maintain, and support the plant long after the project is over. There are many opportunities to incorporate sustaining operations personnel into the planning and execution of C&Q activities, some of which have been mentioned earlier.

The benefits include, but are not limited to, 'on the job' training, and possible C&Q cost reduction by utilizing 'in house' personnel, possible schedule acceleration by having greater access to varied resource pools, early and more accurate Standard Operating Procedure (SOP) development. The main challenges of integrating operations personnel into the project teams is where Sustaining Operations personnel have more varied job descriptions than their C&Q focused counterparts and may have other priorities, particularly on a Greenfield site where a new organization is being set up. This can be a major barrier to full and unconditional involvement of these personnel in C&Q.

There may be other challenges to overcome such as cultural issues (project verses sustaining operations) and contract related issues. However, it is well worth the effort to overcome these barriers and to integrate operations personnel into the C&Q teams.

A good example of integration of sustaining operations personnel into the C&Q team is where WFI quality testing is part of C&Q scope. System operation and maintenance, sample taking, sample analysis, SOP development and training, valve and hose sanitization and sterilization are all activities where sustaining operations personnel are required.

Conclusion

The success of each phase of the capital investment project can often be judged on separate success criteria. The success of engineering can often be judged on the cost and timing of issuing design documentation for procurement and construction. The success of construction can often be judged on the time and cost involved in building the plant to the specifications provided by engineering.

In reality, the success of these phases of the project lifecycle should, to a great extent, depend on the success of the C&Q phase. There is a greater chance of success when system components are designed, purchased, and built with the C&Q challenges in mind.

There are many project organizations which operate in such an integrated manner as suggested in this article; however, there are many who don't and consequently run a higher risk of cost and schedule overruns. Some project organizations see the early involvement of C&Q as an extra cost which is unnecessary. For these organizations, it is important to note that if financial justification of an early and full time involvement of C&Q is difficult, then part time involvement should be considered. Experienced C&Q personnel can participate in document and strategy reviews on a periodic basis and in line with key project milestones.

Similarly, there are benefits to be gained from integration of the C&Q activities with those of sustaining operations personnel. Ultimately, this can make the operation and maintenance of the plant easier, can provide cost and schedule savings, as well as having significant training benefits.

Acronyms

BMS	Building Management System
C&Q	Commissioning and Qualification
CIP	Clean in Place
DCS	Distributed Control System
FAT	Factory Acceptance Test
HVAC	Heating Ventilation and Air Conditioning
SAT	Site Acceptance Test
SOP	Standard Operating Procedure
TOC	Total Organic Carbon
URS	User Requirements Specification
WFI	Water for Injection

About the Author

John Devlin is the Founder of and a Senior Consultant with Kinetics Process Consulting Ltd, leading their commissioning and qualification consulting services globally. He has 22 years of pharmaceutical project execution experience in areas such as project management, engineering, commissioning and qualification, and has worked on projects in USA, Africa, and Europe. Devlin has worked on high capital projects in a senior capacity, including being a member of the commissioning and qualification leadership team on a project which exceeded $1 billion in total investment capital. Since 2001, he has focused his efforts on providing commissioning and qualification consulting services with the particular emphasis on development and execution of "Right First Time" strategies. Devlin holds a bachelor's degree in chemical engineering from University College Dublin (Ireland) and can be contacted by telephone at: +353-21-2307087 or by e-mail at: john.devlin@kineticspc. com.

Kinetics Process Consulting Ltd., NSC-Campus, Mahon, Cork, Ireland.

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Using AIMS Tools to Automate the Qualification and Validation Lifecycle

by Fursey Duggan and Nick Giuffrida

This article presents a number of examples of software tools which provide an integrated approach to qualification and the validation lifecycle.

Introduction

There is currently a great effort within the regulated life science industries to re-evaluate and improve the efficiency of the compliance processes by which they are obliged to conduct their business. The drive for more efficient compliance is being encouraged by the regulators to the industry, as best exemplified by the US FDA's risk based approach initiative.[1] There has never been a better time for the industry to examine its traditional approaches to compliance and explore more innovative options.

In the past few years, a number of software tools and solutions supporting part of the validation and compliance process have emerged within the industry. These solutions are generally referred to as Automated Information Management System (AIMS) Tools. This article describes a number of examples of the application of these new tools, which offer a complete and integrated approach. This has significant advantages for the efficiency of the processes involved, especially qualification and validation. This article also examines the wider issue of information management in the compliance process with Web-based AIMS tools.

Automated Information Management Systems

Perhaps the most powerful feature of AIMS tools is their ability to establish *dynamic* links between statements within a single document or even across multiple documents of different types. This linking is achieved not just at the document level, but also between the actual statements themselves.

AIMS tool statement linking is dynamic in nature allowing the user to quickly navigate between two or more linked statements (effectively jumping from a section in one document to a linked section in the other document) or to manipulate the documents so that linked statements can be readily shown in useful views of the source documents. This linkage can be performed upon documents that are created within the AIMS application itself; this is typically the same as creating a document in a word processor environment, or documents that are imported into the AIMS application from external programs such as Microsoft Word and Excel, likewise, documents and document views generated within the AIMS environment can be readily exported to such external applications.

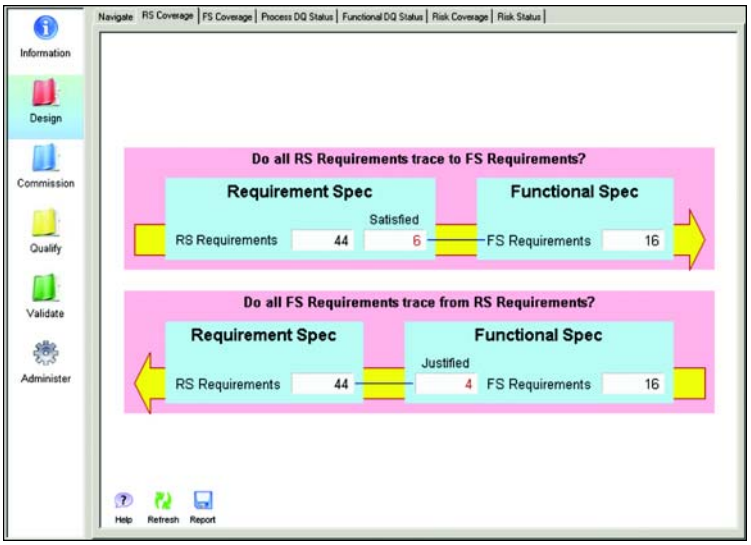

Figure 1. AIMS Tool coverage statistics.

An obvious advantage of linking functionality is the ability to establish links between any statements, e.g., of requirements held in one document to a statement of how that requirement is

to be met in one or more other documents. Other typical life science examples of where such linkage could be applied would be between a clause in a regulation and the section of a standard operating procedure that has been written to comply with that clause or a clause in a regulatory standard and the section of a specification document that specifies the necessary compliance.

In a further example, links can be readily established between the statements contained in a supplier's proposal and the relevant requirement statements contained in the original tender or Request For Proposal (RFP) document. The ability to make links between statements within multiple documents is the key to the functionality features of AIMS solutions that hold particular compliance benefits for life science industry users. These features are further explored below:

Coverage Analysis - The Basic AIMS Compliance Tool

Once links have been established between documents, coverage analysis is an *immediately available* AIMS output. Coverage analysis can be used, for example, to ensure that every compliance statement in the source document is matched by one or more compliance statements in one or more other documents. Typically, an AIMS tools coverage analysis will report coverage statistics that show the proportion of requirements that have been addressed, as well as allowing the user to open a view of the source document that shows only those requirements that have not been addressed - *Figure 1*.

This type of coverage analysis could be applied, for example, to ensure that every clause in a regulation or standard has been addressed by the company's procedural documents. In a design context, it can be used to ensure that every clause in a regulatory standard has been captured in the design requirements documentation or to ensure that every requirement in a tender document has been addressed in the supplier's proposal. While such coverage analysis can be achieved by manual means, it is typically time consuming and gets proportionately more difficult with the size and complexity of the source and responding documents. With AIMS tools, coverage analysis can be performed instantaneously and is a by-product of linkage requiring little extra effort in itself.

Coverage analysis should be considered the initial step of compliance verification. Every compliance professional knows it is not enough to merely have specification statements

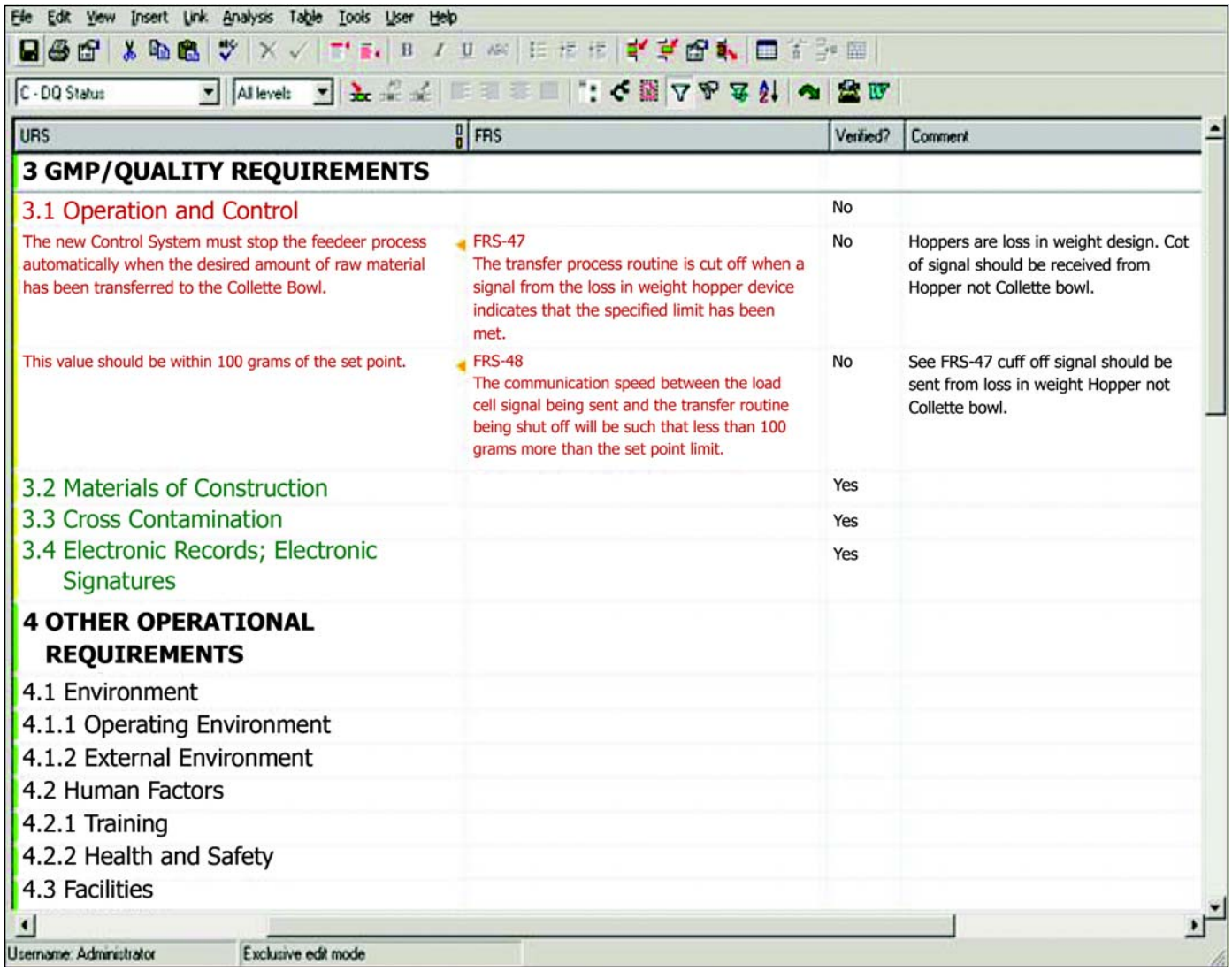

Figure 2. AIMS tool Design Qualification view generated from specification documents.

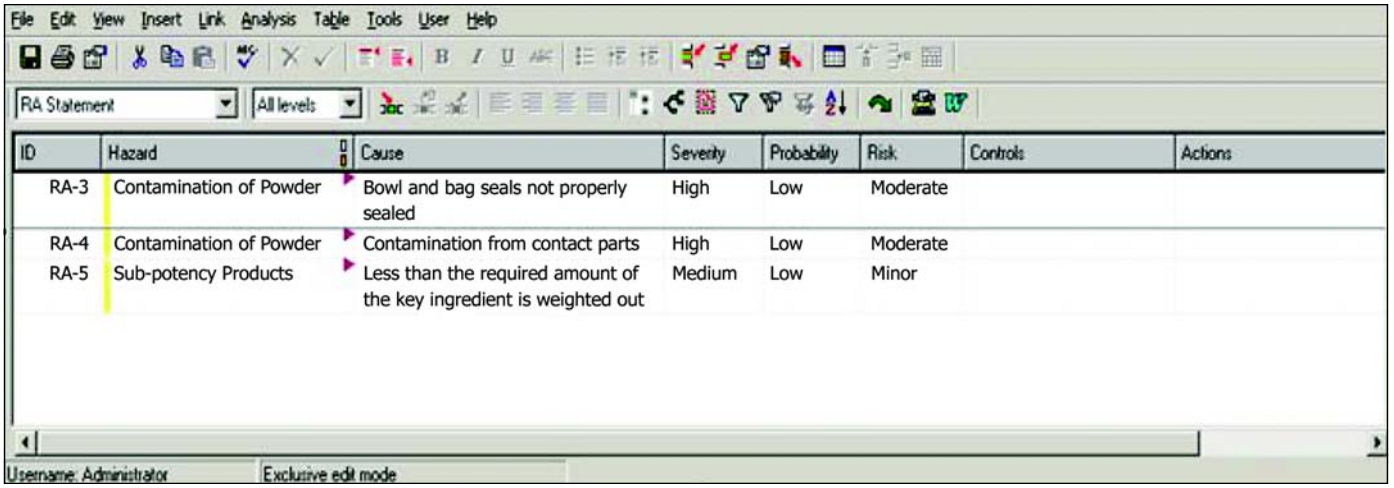

Figure 3.An AIMS risk analysis module with linkage to design specification documents. Colored arrows are active dynamic links to these other documents.

matched by compliance statements but true compliance can only be achieved when the compliance statement fully captures the intent and meaning of the requirement. The verification of compliance can be greatly assisted by using AIMS tools, which like coverage analysis is another by-product of the dynamic linking discussed above.

Once documents have been linked, the AIMS tool can quickly generate views that place the linked statements side by side. For example, this means that a clause in a regulation or standard can be quickly viewed *right next* to the very section or sections of the document or documents that were written to implement its compliance. This makes compliance verification so much easier than working at the document level in the traditional way, where such compliance verification would involve searching through multiple documents to find the compliance statements and then having to compare them back to the relevant clause, while flipping between two or more documents.

Using AIMS Tools for Risk Management and Design Qualification

An area where the viewing functionality of AIMS tools has huge potential benefit is Design Qualification (DQ). DQ entails the verification that the design of a facility, system, or equipment is suitable for its intended purpose.[2] By using AIMS tools to establish links between the design requirement documents (e.g., Requirement Specification) and the design specification documents (Functional Specification, design specification documents, specification drawings, etc.), design qualification views can be generated that match each of the individual requirement statements with their corresponding design specification, thereby facilitating the verification that the design intention is appropriately captured - *Figure 2*. This not only facilitates compliance, but also ensures that the implementation of the design is controlled from the start to meet the design requirements, the key to successful design.

There are associated benefits of these generated DQ views for the design review process, whereby the design stage documentation is reviewed to ensure that the design intention is being met. The fact that all parties participating in the design review can be given access to the DQ view (as discussed later some AIMS tools are Web based) means that the reviewers have early access to the pertinent sections of the design documentation that specify how the relevant design requirements are to be fulfilled. This would allow the design review process to be performed in a continuous proactive manner, allowing the reviewer's feedback to be incorporated into the design specification documentation as it develops. This is much more efficient than the typical end of stage one off design review meeting, which invariably leads to much duplication of effort as the reviewed documents go through multiple revisions to satisfy the various review comments.

It also is worth noting that currently available AIMS tools feature automated risk analysis modules. These tools can be readily adapted to analyze the hazards associated with life-science design activities - *Figure 3*. The AIMS tool can automatically calculate the risk of the safety hazards associated with a particular design feature based upon their severity and probability of occurrence and then dynamically link the identified risk mitigation controls to the specification document that specifies their implementation.

Using AIMS Tools to Track the Validation Life Cycle (Traceability)

The use of AIMS tools is not just restricted to one-stage activities that involve establishing compliance between statements contained in one or more documents as in the previous examples. The power of AIMS tools could be applied with great effect to the more complex multi-stage projects that are performed by the life science industries.

The validation life cycle involved in the design, commissioning and qualification, and validation of facilities, equipment, and systems is an example of such a project and an area where both regulators and the industry[3] are focusing on for potential compliance efficiencies. It has already been discussed in this article how AIMS tools can be applied to the design process, but what is their potential use in the remaining steps of the validation life cycle? Once links have been

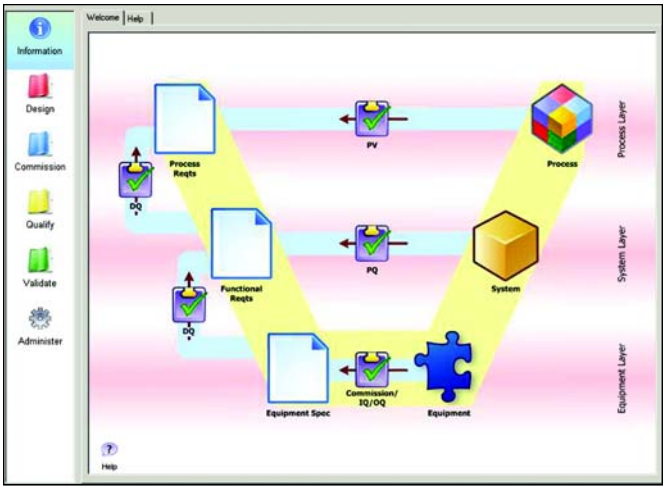

Figure 4. Use of an AIMS Tool to track the overall Process Validation Life Cycle.

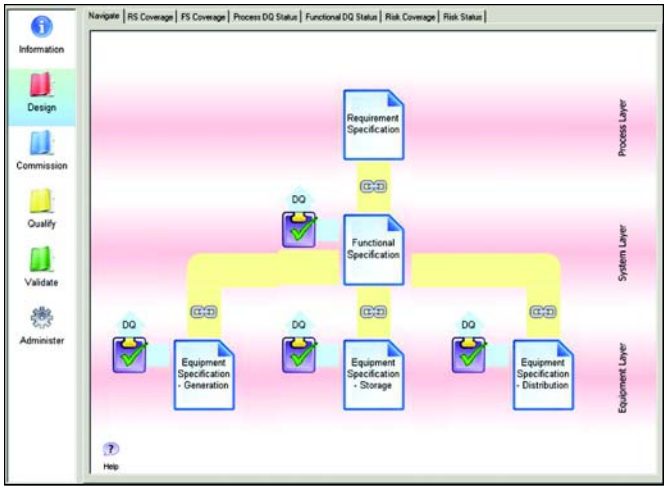

Figure 5. Use of an AIMS Tool to drill into the Process Validation Life Cycle.

established between the design requirements, risk analysis, and the design specification documents, the AIMS tools can link these in turn to the test documentation that is generated to plan and report both commissioning and qualification activities - *Figures 4 and 5*.

The ability to link statements within documents that occupy different levels of a multi-document hierarchy generated at different stages of a project provide AIMS tools with perhaps their most powerful compliance feature - traceability. Traceability can be used, for example, to track a design specification that has been defined as critical by risk analysis through its implementation in the relevant equipment specifications through to the very sections of the commissioning and qualification document that verifies it has been appropriately implemented.

Once such traceability has been established, the coverage analysis and verification viewing functionality of AIMS tools can then be used to analyze and view the implementation and testing of the feature at any stage of the project. This means that its criticality is recognized at all stages of the project, thereby ensuring it is not neglected during the project and that its implementation throughout the project can be quickly traced by any interested party, including those responsible for Quality Assurance.

This ability to verify the implementation of critical features at any stage of the project should then give the Quality unit the confidence to entrust more of the testing activities to the engineering disciplines, allowing them to focus on the true purpose of the Quality role, the verification of compliance. For example, the verification of a critical installation feature, such as material of construction of product contact parts, can be planned as part of the commissioning performed by the engineering disciplines. The AIMS tool would be used to link the test planning documentation for this verification to the risk assessment documentation that determined that material of construction of product contact parts is a critical feature. The Quality unit can then use the AIMS tool's traceability to identify and see all instances where this and other critical features are planned for verification in the commissioning test planning documentation. This allows them to ensure that the test planning documentation is set up to appropriately document the verification. Once commissioning has been completed, the documented results of the testing of the critical features can then be quickly located in the commissioning documentation to assure it has been appropriately tested and documented. The Quality unit does not now have to repeat the testing during qualification, but instead can use Installation Qualification (IQ) and Operational Qualification (OQ) as an audit activity that verifies the outcome of the commissioning. This means that commissioning and qualification can be considered two parts of the one activity rather than two separate activities with consequent savings in terms of the time and costs that are avoided by not having to replicate commission testing during qualification.

Additional Features of AIMS Tools

In addition, AIMS tools allow the user to add additional attributes to any piece of data. So for example, it is possible to add the attribute "Critical" to a specification statement within the equipment specification which is automatically inherited in the commissioning and qualification test documentation, which means that the user will be instantly alerted to its importance no matter what stage of the validation life cycle it is encountered. In fact, there is no limit to the attributes that can be added to a piece of data using an AIMS tool. For example, a component specification could be supplemented with useful maintenance and regulatory compliance attributes such as cost, supplier, quantity on hand, calibration due dates, applicable regulations, etc.

AIMS tools can mark individual specifications no matter how numerous and ensure that they are addressed at the predefined project stage. The advantage of using Web-based AIMS tools for this type of test planning is that it can be agreed at early stages in the project in a collaborative environment that can involve all interested stake-holders, including those not working at the actual site undergoing commissioning and qualification. The latest generation of AIMS tools are now available in a hosted Web-based environment that

particularly facilitates this kind of multi-site collaboration in a secure and cost effective manner.

A hosted service means that the data entry, viewing, and other functionality of the AIMS tool takes place on the provider's server not on the users own network. This means that all stakeholders can quickly be provided access to the project data without the large infrastructure efforts and at very much reduced cost than is usually associated with similar multi-site software based applications.

Test Planning

The test planning benefits of Web-based collaboration made possible with AIMS tools goes beyond merely deciding when an attribute is to be tested. Web based collaboration makes it possible to present the individual test cases next to the specification that they are designed to test in verification views that are accessible to all project stake-holders.

As these attributes, target values, and test cases are the most meaningful parts of the test planning (protocol) documents that are used to plan and document the execution of commissioning and qualification exercises, the collaborative use of the AIMS tool means that the individual test cases can be agreed in advance of the commissioning or qualification document being prepared. This advance agreement would significantly reduce document review and approval cycles, which is frequently one of the biggest causes of delays in validation projects. As discussed earlier, the verification views can be directly exported into external applications such as Microsoft Word or Excel meaning that the commissioning and qualification worksheets can be generated directly from the AIMS tool itself. Therefore, AIMS tools have the potential to not only reduce the commissioning and qualification documentation review cycle, but also the time taken to generate the vast number of documents that are typically required.

In addition to the reduced project time advantage of online collaborative review, there also are significant compliance advantages to capturing the commissioning and qualification attributes and test cases within an AIMS tool. By dynamically linking these test cases to the specifications that they are devised to verify, it can be assured that all specifications have been covered by appropriate test cases. This includes the facility, equipment, and system attributes assessed as critical that must be verified during qualification.

The primary source of regulatory body dissatisfaction with the qualification process is where the qualification protocol either does not test all of the critical specifications of the item being qualified or the test cases it defines are considered inadequate for their verification. The risk of this type of non-conformance increases with the complexity of the item being qualified. The coverage analysis and verification viewing functionality of AIMS tools discussed previously can greatly reduce the risk of inadequate protocols. Coverage analysis ensures that each specification is covered by a test case. Verification viewing means that each test case can be compared side by side with the specification that they are there to verify enabling the reviewer to ensure that the specification is appropriately verified by the test case. In other words, the use of AIMS tools would significantly reduce the risk of inadequate qualification protocols and consequent adverse observations from regulatory reviewers.

The tracking of criticality through the project documentation also should provide Quality Assurance with the confidence to entrust more of the test activities to the engineering disciplines knowing that the AIMS tool is tracking compliance upon their behalf.

Once verification views of the commissioning and qualification stages of the project have been established, it is then a relatively easy task to populate them with the results of each of the individual test cases - *Figure 6*. If this is performed as the project progresses, the Web-based accessibility of these views means that all project stakeholders can keep track of the project's progress. For example, coverage analysis can quickly show the proportion of qualification activities that have been completed with the potential for providing project metrics, filtered verification views that can quickly focus on items that have not yet been completed or have failed particular qualification tests. The ability to highlight test failures (deviations) is of particular note.

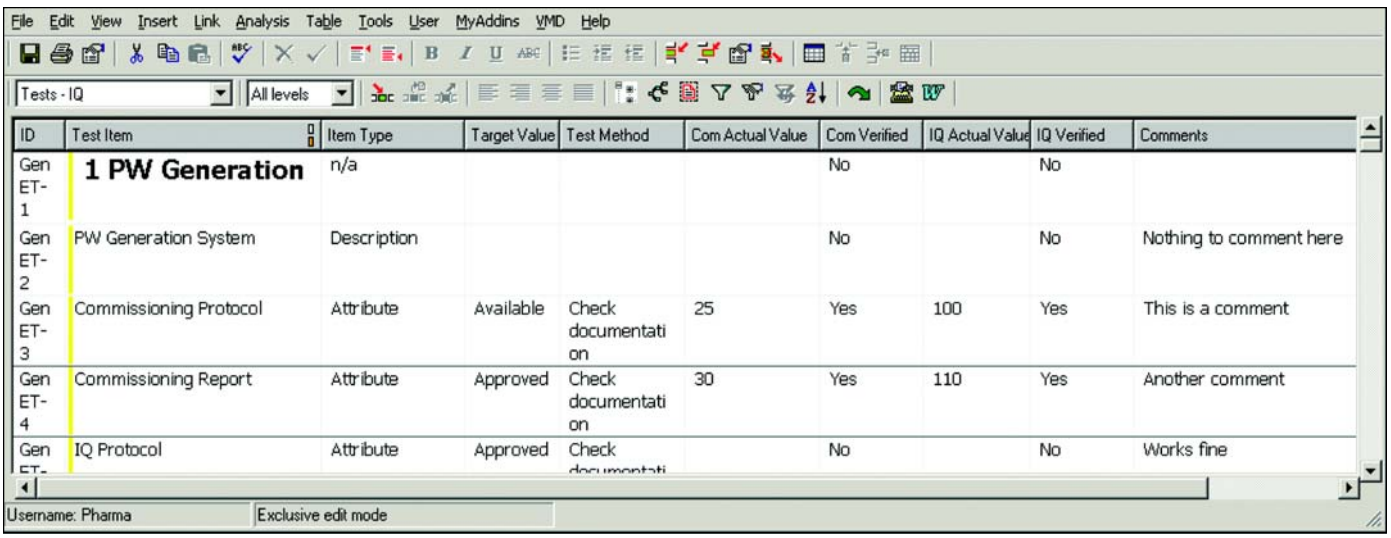

Figure 6. IQ data captured using an AIMS Tool.

The populated verification view also would be of tremendous benefit during regulatory and other third party inspections. The populated view would in effect provide a traceability matrix showing the traceability between the specifications, test cases, and implementation documentation with dynamic linking to the design specifications and risk analysis documentation. For example, in a regulatory inspection scenario, the AIMS tool would quickly locate the objective evidence that a specification marked critical by risk analysis has been tested and implemented, thereby ensuring expeditious delivery of this evidence to the inspector.

Impact Analysis and Change Control

Another significant benefit of a populated verification view held in an AIMS tool is in terms of impact analysis and change control. The verification view and other traceability features of an AIMS tool mean that the impact of changes can be quickly analyzed across the whole project, using the information already documented. For example, a proposed change to a piping specification can be quickly analyzed in terms of the test cases that would have to be re-verified in the related commissioning and qualification documentation.

In fact, there is no reason why the use of the verification view for impact analysis has to end with the project in which it was generated. Because the verification view holds the individual specifications in the same location as the compliance documentation, it would provide an effective compliance register of the completed facility or system at the end of the project. Therefore, the populated verification view could be used in conjunction with routine change control to quickly analyze the validation impact of any proposed change.

Using AIMS Tools for Secure Readily Retrievable Data Storage

It also should be noted that some commercial AIMS tools are linked to secure data storage environments. In this context, the populated verification view can be considered a portal to these secure environments from which the data can be readily retrieved in the same structure that it was entered. By providing access to a secure, easily retrievable data storage environment, AIMS tools also have the potential to solve the electronic data compliance challenges that face the life science industries.

Summary

AIMS tools have tremendous potential to improve the efficiency of activities associated with demonstrating compliance in the life science industries. This arises from their ability to link statements across multiple documents that are generated at different project stages. These links mean that it can be quickly verified that all specification requirements, risk information, and even the details of test plans or scripts have been addressed and verified and to trace their implementation throughout the project. These advantages are further leveraged when subsequent changes are made to validated processes, equipment, and systems. Web-based AIMS tools provide a cost-effective collaborative environment that facilitates project planning to better leverage good engineering practices in qualification activities. AIMS tools also provide an opportunity to exploit secure, readily retrievable storage environments for compliance data.

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About the Authors

Fursey Duggan is a regulatory compliance consultant to the life sciences industries. He has worked for almost 15 years within these industries and has supported pharmaceutical, biotechnology, and medical device companies through all stages of the regulatory approval cycle. Duggan graduated from Dublin City University (DCU) in 1990 with an honors degree in biotechnology and worked in various quality assurance roles within the regulated life science industries before becoming founder of First Solutions Ltd. where he has worked as Managing Director and Senior Consultant since 1998. He can be contacted by telephone at: +353-1-8859339 or by e-mail at: fursey@firstsolutions.ie.

First Solutions Ltd., 17 Hollystown Park, Hollystown, Dublin 15, Ireland.

Nick Giuffrida is one of the founders of Comply-Serve UK Ltd. Comply-Serve provides companies with an easy and efficient way of navigating and managing the regulatory and standards compliance world, through an internet-based managed service. Over the years, Giuffrida has moved from a senior technical role to a more strategic and commercial role. Giuffrida was previously Sector Manager responsible for the Life Sciences Industry for Telelogic, a Swedish software company. He can be contacted by telephone at: +44-7824486177 or by e-mail at: nick.giuffrida@complyserve.com.

Comply-Serve Limited, Townsend House, 79 Station Road, Leicester, LE9 6PU, United Kingdom.

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PHARMACEUTICAL ENGINEERING Interviews Frederick Sexton, Senior Vice President, Technical Operations, Purdue Pharma

by Gloria Hall, Editor, *Pharmaceutical Engineering*

A key member of ISPE's International Leadership Forum discusses why Purdue is focusing on expanding its product portfolio through internal development and licensing; how cost pressures can be a driver for innovation in R&D, as well as manufacturing; the importance of forging strategic alliances; and the extreme measures the company is taking to prevent counterfeiting.

Fred Sexton began his career with Ayerst Laboratories in Rouse's Point, New York, and worked for Boehringer Ingelheim Pharmaceuticals, Inc. from 1984 to 1995, progressing through a series of managerial positions, domestically and abroad, in production, engineering, and quality assurance. He joined Purdue in 2003 after seven years with Kos Pharmaceuticals, Inc., in Miami, Florida. His most recent position at Kos was Senior Vice President, Technical Operations and Product Development, where he had direct responsibility for production, engineering, materials management, quality control, intellectual property, non-clinical R&D, and real estate management. A member of the ISPE International Leadership Forum (ILF), Sexton managed the development and publication of ISPE's Good Practice Guide on Technology Transfer. He holds a BS, with concentrations in biology and chemical engineering, from Clarkson College of Technology in Potsdam, New York.

Q What are your key responsibilities at Purdue Pharma?

A My responsibilities include leadership and oversight of Discovery Research, Non-Clinical Development – including Toxicology, Bioanalytics, Pharmaceutics, Analytical Chemistry; Technical Services – including Process and Package Engineering, Scale-Up, Technology Transfer, and Validation; Manufacturing – including Bulk and Dosage Forms, Supply Chain Management, Engineering, and Corporate Quality. This organizational design is non-traditional. We structured ourselves in this manner in an effort to facilitate knowledge and technology transfer. If you look at the functions in my organization, they are all closely related. Our expectation is that this type of structure will make us more efficient and at the same time improve our compliance in all matters of drug development and commercialization.

Q Purdue is a privately held company with a revenue exceeding $1.5 billion in 2005. What has been managements' strategy to fuel such growth over the years?

A Unfortunately, the growth we experienced early on has recently been reversed by generic competition. After a federal District Court in New York ruled in January 2004 that certain Purdue patents for OxyContin® Tablets were unenforceable, generic versions of OxyContin® came on the market before the last of our patents were set to expire in 2013. Purdue is a relatively small pharmaceutical company and the subsequent loss of revenue forced the company to reduce its workforce by more than 50 percent and scale back on research and development projects. However, in February 2006, a Federal Circuit panel of judges, which had previously upheld the District Court's judgment,

"I view the "industry" as a composite of pharmaceutical companies, technology companies, and regulatory agencies. I think it is important to recognize this as we can't exist in isolation."

withdrew its earlier decision and vacated the District Court's findings, enabling us to resolve our patent disputes with some manufacturers of infringing products and to move steadily in the direction of restoring our patent rights under US law. In the meantime, we are working to expand our product portfolio through internal development and licensing promising products from the outside. We have a number of late-, mid-, and early-stage development projects that will support and sustain our growth well into the future. As long as we continue to develop and provide important medicines for healthcare professionals to use in the care of their patients, I'm confident that we will resume our strong growth trajectory.

Q How will Purdue address escalating cost pressures and generic competition in the future?

A First let me say that cost pressures should not be viewed as a negative. Competition on cost, particularly from generics as patents expire, is really a driver for us to innovate not only in our R&D organization, but also in our manufacturing and supply chain groups. As a company, we are focusing on finding and leveraging value all through the drug development lifecycle. Our researchers are focused on effectively leveraging academics and off-shore collaborations to increase the depth and speed of R&D, while at the same time, reducing our costs. Obviously, this is not a novel concept; however, we are seeking to differentiate ourselves through focused execution. We are following a similar approach in our manufacturing and supply chain groups. We will focus on keeping core intellectual property in-house; for everything else, we focus on identifying the highest quality, lowest cost solution and then effectively integrating the solution into our business. If the solution comes from within, we are all the happier.

Q How will healthcare reform affect your business and/or your industry?

A I think that everyone agrees that people who need medical care and medicines should not be denied access due to cost. We continue to negotiate with managed care companies and other healthcare payors to make sure our products are available and affordable. Like the rest of the industry, we will do our very best to adapt as needed to changes in the healthcare sector.

Q What does the pharmaceutical company of the future look like to you?

A My short answer is: an entity forged on strategic relationships based on intellectual property and/or specialized competencies linked through a highly integrated international supply chain. If we expand on that thought and look simply at our business, we seek to find and develop new products from:

- internal discovery
- internal drug delivery system development
- focused in-licensing of compounds and drug delivery technology
- acquisition

This is pretty basic. In my view, the most successful companies in the future will be those that can efficiently stay connected to the emerging science, envision how the new science can add significant patient and/or healthcare value, effectively integrate all of the key elements, and finally, produce and distribute product for the lowest possible cost. I see this happening with companies engaging regulators earlier and more frequently to ensure that the regulator, as a key stakeholder, is involved and proactively kept abreast of the development activities. Finally, I see successful pharmaceutical companies, independent of whether they are innovator or generic, as expert in effective communication and knowledge transfer. With all of the strategic alliances being forged, there is no other way.

Q What changes do you see the industry needing to make and what do you see as the biggest obstacle to change in our industry?

A I view the "industry" as a composite of pharmaceutical companies, technology companies, and regulatory agencies. I think it is important to recognize this as we can't exist in isolation. It would be nice to see substantial improvement in the process of bringing new molecules and technologies to market. I view the current industry/regulator new product review process as being more incremental and serial in nature than it perhaps could be. Because of this, in my view, it takes longer to reach a decision to either proceed with or terminate development of a drug candidate, which in turn adds cost and ultimately delays efforts to discover and develop a drug that will ultimately help improve healthcare. I am not suggesting for a minute that we do anything to compromise efforts to ensure patient safety. However, I think that if industry and regulators can work together on a continuous basis rather than on an incremental level, we will be able to provide effective and innovative healthcare at an affordable price. I also see the marketplace, through effective competition between innovator companies, and between innovator and generic companies, keep-

ing the value proposition in balance and focused on the cost/benefit to the patient. This is important and healthy.

In my view, the biggest obstacles here are current industry/regulator mode of interfacing, resources, and a fear of change. As for the first, I am happy to say that I see the regulatory community as actively trying to engage earlier and be involved along the way. In fact, they are quickly becoming more proactive and progressive in this area than some pharmaceutical companies. By example, the US FDA has been piloting a continuous review process, they are working toward a Regulatory Agreement concept, and have just recently published draft guidance on developing Target Product Profiles; all of which drive at improved and continuous interaction with industry. However, this is a fine balance for regulators, as they must maintain objectivity at all times. The second obstacle is resources. To effectively accelerate the development of new innovative medicines, resources from both the companies and the regulators need to be applied differently. Notice I didn't say we need more. I think, at a macro level, that a more integrated review would actually require in aggregate less total resources, but that is perhaps for another discussion. Lastly, fear is an obstacle. I think there is a fear of, or resistance to, change from the "old" way of doing things and despite some very heroic efforts by many people in the pharmaceutical industry and in the regulatory agencies, I think resistance to change is impeding our ability to move to the next level of effectiveness in the industry. That said, I am quite confident that the champions of effective change will eventually succeed; we will just need to remain diligent and patient.

Q What are your views on managing a successful pharmaceutical company?

A In my view, managing a successful pharmaceutical company in the 21st century will require a global outlook. The successful leader will have a deep understanding of customer and key stakeholder (I include regulatory agencies in this group) needs in the region and markets they choose to enter. He or she will also have a keen ability to identify talent and acquire it, either through employment or strategic partnerships. Finally, a successful leader will be able to rapidly develop differentiated products with broad intellectual property protection at low cost and effectively and efficiently commercialize those products. Sounds easy . . . but the real key, in my opinion, is having the right people. With the right people, you can do just about anything.

Purdue Pharma's Fight Against Pain

Purdue Pharma L.P. has long been known for its pioneering research on persistent pain and addressing inadequate treatment of it by developing sustained-release medications to manage pain. Purdue also has applied its expertise to other therapeutic areas such as respiratory diseases, oncology, and bacterial infections, and to a growing line of non-prescription products including laxatives, microbicides, and nutraceuticals. Purdue also has assumed a leading role in addressing the serious public health problem of prescription drug abuse. The company has implemented a comprehensive program designed to assist in detection of the illegal trafficking and abuse of prescription drugs without compromising patient access to proper pain control. Purdue scientists are discovering new weapons against pain and developing innovative formulations and delivery systems to improve patient compliance and safety while at the same time reduce the risk of unwarranted product tampering.

Q What skills should pharmaceutical managers and professionals develop in order to contribute to the pharmaceutical and biotech companies of the future?

A I think that pharmaceutical managers and professionals should have a balance between scientific/technical skills and business skills. It is very important to be technically grounded; we work in a science-based industry, but I also believe our managers/professionals, our future leaders, need to have a good business sense. They need to know how what they do today fits into the big picture. Personally, I prefer members of my team to have international experience. I believe that the ability to understand and work in different business and multi-cultural environments is a real plus.

Q What is Purdue doing to address any potential counterfeiting or product diversion?

A We have done quite a lot in these areas. While the shipping and handling of controlled substances is conducted under secure conditions, every step along the pharmaceutical supply chain presents an opportunity for the introduction of counterfeit medicines or diversion of authentic product by criminals. It is important to realize that counterfeiters and diverters are often both clever and persistent and always work to find a way around existing countermeasures. Everyone along the supply chain has to continually assess and improve their security to prevent and deter attacks. Purdue Pharma has gone to great lengths to protect the pharmaceutical supply chain by introducing innovative security measures in its manufacturing facilities as well as throughout the drug distribution channels.

In 2004, Purdue Pharma began a pilot program to tag individual bottles of OxyContin® Tablets with small electromagnetic chips known as radio frequency identification (RFID) tags. RFID allows pharmaceutical manufacturers and wholesale distributors

to closely track products as they move throughout the distribution chain. We are in the process of expanding this program to tag bottles, cases, and pallets of OxyContin® Tablets. The company also employs Global Positioning Satellites (GPS) and ground-based surveillance to track shipments of pharmaceutical products once they leave the manufacturing site.

Additionally, the company has developed and implemented a number of programs to help deter and prevent diversion, including:

- Supporting non-promotional educational programs to teach healthcare professionals how to properly recognize and deter drug seeking behavior
- Providing tamper-resistant prescription pads to prescribers, at no charge, to help protect against prescription fraud
- Maintaining RxPATROL®, an online information clearinghouse designed to collect, analyze, and share information on pharmacy robberies, burglaries, and theft. RxPATROL® is intended to help pharmacists guard against pharmacy theft, and assist law enforcement efforts in apprehending and prosecuting pharmacy robbers. We have partnered with the CrimeStoppers network to offer rewards for information that can help law enforcement investigate and solve pharmacy crimes. To date, this effort has led to the arrest of 28 pharmacy robbery suspects.
- Supporting the development of state prescription monitoring programs (PMPs) to help prescribers, pharmacists, and law enforcement detect and prevent diversion of prescription medicines in numerous states. To date, 31 states have enacted legislation to implement a prescription monitoring program and 12 additional states are considering such legislation.
- Partnering with community coalitions to raise awareness and educate parents, teachers, and students about the dangers of abusing prescription medicines. The company developed Painfully Obvious® to specifically address the abuse of prescription medicines among teens and pre-teens.
- Establishing a law enforcement liaison and education program that is helping state, county, and municipal law enforcement groups enhance their drug diversion investigations
- Changing the indicia on OxyContin® Tablets distributed in Latin America and Canada. This assists law enforcement in determining the country of origin in medication seized within the United States
- Establishing the RADARS® System in 2001 to study the prevalence and nature of abuse and diversion of commonly prescribed prescription pain medicines. This research-based initiative is designed to obtain valuable information on the relative rates of abuse, addiction, and diversion of commonly prescribed opioid medications. In 2006, Purdue transferred ownership of the RADARS System to the Rocky Mountain Poison and Drug Center to encourage other pharmaceutical companies and government agencies to gain access to these valuable data.
- Developing new formulations that have abuse deterrent properties is one of Purdue's top research priorities. To date, we have spent more than $275 million to test and develop novel products and new forms of pain relievers that will hopefully be more resistant to abuse or less attractive to drug abusers, while still providing safe and effective pain control to patients with pain. All medications are susceptible to abuse in one manner or another, and it may not be possible to develop a product that completely deters determined abusers. Drug research and development takes years to complete, and results cannot be guaranteed. Therefore, we cannot at this time give a timeline for the introduction of an opioid analgesic that may deter or reduce abuse.

Q Why did Purdue partner with Wal-Mart on RFID and how is it currently being used?

A Initially, Wal-Mart requested that Purdue and numerous other suppliers employ RFID tags on their products to enhance supply chain security and assist the retailer with inventory control. During our initial RFID pilot, we shipped RFID tagged bottles to Wal-Mart and wholesaler HD Smith. Purdue is now working to incorporate new generation (GEN2) ultra high frequency RFID chips onto bottles, cases, and pallets of OxyContin® Tablets. Over the past several years, we have expanded pilot projects to other distributors and buyers and are now in the process of implementing RFID tagging on all of our manufacturing lines for OxyContin® Tablets.

Q How will industry adapt to state regulations requiring e-pedigrees? What should the US FDA do on the national level to harmonize requirements?

A I can't speak for the rest of the industry, and it's not my place to tell the US FDA what to do, but our plan is to be ready to either make adjustments as needed or move forward with our current approach. We have worked on an e-pedigree solution that we think will help us meet any federal and state guidelines and standards.

Q In 2001, Purdue established the RADARS® System. What is the purpose of this program?

A We realized that in order to more effectively combat illegal trafficking and abuse of OxyContin® Tablets, we needed to place these activities into context and so we were seek-

"Purdue has partnered with CrimeStoppers, a network of municipal anti-crime organizations, to offer cash rewards for information that can help law enforcement investigate and solve pharmacy crimes."

ing more information on how and where the product was being diverted and abused. We needed more timely and more geographically-specific data than what is currently available from the various federal surveys. The RADARS® System (www.radars.org) comprises four studies designed to provide this information: a study of diversion cases reported by various law enforcement and regulatory agencies, an analysis of abuse calls to a network of Poison Control Centers covering about 70% of the US populace, a study of abuse patterns of persons seeking methadone treatment for addiction to opioids, and regular surveys of people who are involved in studying and treating substance abuse around the nation. The System provides rates of abuse of several opioids, including buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and tramadol at the 3-digit ZIP code level by calendar quarter. In January 2006, the RADARS® System was transferred to the not-for-profit Denver Health and Hospital Authority, which operates the program and provides data to pharmaceutical companies and government agencies on a subscription basis.

Q In 2005, Purdue provided grant money to 13 crime prevention agencies, specifically offering rewards that led to an arrest in pharmacy theft cases. How successful has this program been, and has it expanded?

A Purdue has partnered with CrimeStoppers, a network of municipal anti-crime organizations, to offer cash rewards for information that can help law enforcement investigate and solve pharmacy crimes. Originally focused on theft of controlled substances from retail pharmacies, the program has been expanded to cover the theft of both prescription and over the counter medications. More than 2,500 drug diversion investigators are receiving RxPATROL® pharmacy crime alerts daily. To date, this effort has led to the arrest of 28 pharmacy robbery suspects, 12 arrests were made in 2006, and 16 arrests have been made in the first quarter of 2007 alone.

Q As a leader in the ISPE organization and a member of the International Leadership Forum, what do you see as future opportunities for ISPE to serve the industry?

A I think ISPE should continue what it is doing to serve the international community. In terms of future opportunities, I can envision the Society getting more involved in the development related aspects of our business. The products of the future will be more complex and many will involve use of non-traditional delivery systems. That means our understanding of the requisite materials, methods, manufacturing unit operations, and people skills will need to evolve. If ISPE wants to remain as the premier source of information and training in Chemistry Manufacturing and Controls (CM&C) related matters, we will need to engage our new product development colleagues earlier to ensure success – theirs and ours.

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Containment Considerations for Toxic and Potent Aseptic Liquid Filling

This article presents containment requirements for liquid handling operations.

by Lee Francis

Overview

Over the last 15 years, the sterile filling of highly potent compounds, cytotoxic, genotoxic, and other hazardous materials has moved from what was essentially an academic curiosity to a real-world issue that affects the majority of parenteral facilities around the world. Manufacturing and compliance issues that used to focus on protection of the product from the world have been expanded to include protecting the world from the product. Unfortunately, these two goals are in conflict, resulting in significant debate and disagreement between Environmental Health and Safety (EHS), which is watching out for the safety of the employee, and manufacturing and other compliance disciplines that are tasked with producing a product and ensuring product integrity. In order to properly develop answers, it is necessary to look at containment requirements, capital and operating cost impact, industry trends, regulatory input, and competitive comparisons.

Due to the nature of the products to be handled, it is necessary to consider both operator protection as well as proper aseptic conditions. These two requirements are frequently at cross purposes and the facilities and processes must be carefully designed to achieve both goals concurrently. Current industry trends, regulations, and corporate containment guidelines, both internal and external, indicate that material handling of these toxic products must involve proper containment. Toward that end, the use of isolators, rapid transfer ports, split butterfly valves, and comparable engineering controls for both powder and liquid handling of these materials is indicated for both aseptic and containment considerations.

This article will focus on containment requirements for liquid handling operations. Additionally, room classifications in this article are based on United States "only in operation" definitions versus European and Japanese "at rest and in operation" classifications. The significant need for proper containment for powder handling operations may be addressed in another article.

Three primary technology options are available for sterile liquid filling operations: traditional cleanroom style aseptic processing, which may incorporate the use of flexible or rigid wall barrier/curtain systems; Restricted Access Barrier Systems (RABS), utilizing openable rigid walls with glove ports and transfer systems; and full isolation (isolator), fully enclosing the filling operation and requiring interface through glove ports and closed-system transfer. The traditional aseptic cleanroom provides the lowest capital cost, least containment consideration, and highest operating cost, while the fully isolated system represents the highest capital cost, highest containment level, and least expensive operating cost. The RABS version provides no containment, high operating cost, and an intermediate capital cost.

It must be noted that as more and more aseptic filling operations within the industry are becoming involved with hazardous products, new facilities are being built utilizing isolator technology to protect both operators and product. The reasoning behind this industry trend includes the recognition of potential risk from operator exposure, control of cross-contamination, and increased product quality due to advanced aseptic capability. Additionally, the current cGMP guidelines from the US FDA, as well as comments from FDA personnel, indicate an increasing regulatory preference for advanced aseptic processing, specifically isolators, for future facilities. As a result, standard cleanroom technology may not be considered viable for new facilities in the near future. This, coupled with a strong industry

trend toward extending internal corporate containment guidelines for hazardous products to contract manufacturers, may place a company's market segment for the Highly Potent Compound (HPC) or toxic products at risk if conducted in traditional cleanrooms. The use of isolators would provide both the advanced aseptic controls and the necessary containment controls, while significantly decreasing the operating costs for the facilities. Their use would result in a state-of-the-art facility that will attract customers and provide the highest possible level of product quality and manufacturing efficiency.

Issues Handling HPC Material

Highly Potent Compounds (HPC) products present numerous material handling concerns. In order to mitigate these concerns, most companies working with these materials will assign Occupational Exposure Limits (OELs). These products are frequently then placed into categories or bands of OELs that define a range of hazard.

Categorization and Exposure Limits

Most pharmaceutical companies currently handling toxic and/or hazardous materials have established internal guidelines for the safe handling of these materials. These guidelines include industrial hygiene exposure guidance and categorization that may be applied to all products and processes within the company. The basis of this guidance is a categorization scheme that establishes an OEL for each Active Pharmaceutical Ingredient (API) handled by the company. An OEL is defined as an airborne concentration of a substance that represents conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse health effects. They are generally a time weighted average concentration for a normal eight hour workday and a 40 hour workweek, e.g., 10 µg/m^3 or a Short Term Exposure Limit (STEL) or ceiling limit. The OEL indicates theoretically safe limits of exposure for a given compound or product over an eight hour time frame corresponding to a typical work shift. These products are frequently then placed into categories or bands of OELs that define a range of hazard, thus facilitating the application of a basket of controls designed to control exposure limits defined by that category or band. While there is no industry standard, most categorization schemes have three, four, or five bands. Category 5 materials almost universally are within the nanogram range and Categories 3 and 4 tend to be in the low microgram to high nanogram range. Category 1 materials are at the other end of the range, toward the milligram level.

For any given project, it is necessary to determine what specific products or categories of products will be handled within that facility. The project team, with significant input from the Environmental Health and Safety department, must set a Design Exposure Limit (DEL) for the project. The DEL is usually some fraction of the lowest OEL or category considered for the facility. For instance, a facility designed to handle products down to 1 µg/m^3 might set a DEL of 0.5 µg or even 0.1 µg. All containment controls utilized for the project must be capable of achieving or exceeding that DEL for the project.

These highly potent or toxic products are generally classified as Category 3, 4, or 5 materials (depending upon an individual company's scheme) in both powder and liquid form requiring significant engineering controls to prevent exposure risk to the operators. For the purpose of this article, the final forms considered are sterile parenteral liquids, requiring aseptic conditions during manufacture.

Powders and Liquids

Current industry standards generally do not differentiate between liquid and powder handling processes when considering containment controls. However, this has not always been the case. Traditionally, there has been very little disagreement in the pharmaceutical industry that powder form API requires containment controls in order to protect operators and prevent cross-contamination. These controls may vary from process modifications to the implementation of engineering controls such as isolators and split butterfly valves, and the application of certain administrative controls.

However, for liquid handling there has been much debate as to the requirements for safe handling practices. The disagreement was a result of several influences. First, liquids are significantly easier to handle and control than are powders. Second, liquids are generally a fairly diluted form of the API. Third, most industrial hygiene monitoring is for airborne concentrations, and liquids generally only become airborne through aerosolization, which is limited during normal manufacturing operations. Fourth, powders are more easily visible when airborne, making it more difficult to see the liquid hazard. Fifth, HPC, cytotoxic, genotoxic, and other hazardous materials have, until recently, represented a small percentage of products for sterile fill. Additionally, the regulatory requirements of aseptic processing make modifications to existing processes costly and difficult. **The net result is an industry comprised primarily of grandfathered aseptic filling operations that were never designed with containment in mind.**

The reality of material handling, both powder and liquid, for the pharmaceutical industry in the 21st century involves both a high number and a high percentage of hazardous APIs. An increasingly high number of products coming out of research and development involve hazardous API materials. As a result of this, companies throughout the industry are faced with the task of either modifying existing processes or building new capability designed for the proper and safe handling of these materials.

Airborne Versus Surface Exposure Risk

When considering exposure risk in pharmaceutical operations, there is a significant difference between surface and airborne exposure. Traditionally, Occupational Exposure Levels (OEL) are based on a time weighted airborne concentration over an eight hour average. However, surface con-

tamination is generally not a part of these calculations. As a result, it is quite possible for airborne concentrations to be at zero when the operator is standing next to a puddle of liquid hazardous product. As long as this liquid does not come in contact with the operator via aerosolization, disturbance of dried product, active contact by the operator, or other such event, the risk of airborne exposure is unlikely. In reality, this surface exposure represents a significant risk of exposure to the operators and cross-contamination with other products.

Frequently, when EHS departments conduct Industrial Hygiene (IH) air monitoring during filling operations in existing facilities, the data will, more often than not, indicate acceptable (within the guidelines for the given products) or no detectable exposure to the operators within the breathing zone. This is contrasted by the fact that it is very normal during filling operations for some quantity of liquid material to escape the system and puddle or collect at various places on the equipment or the floor. Assuming that such typical spillage occurred during those IH monitoring activities, it may be deduced that this surface contamination does not tend to become airborne at the breathing zone level and is not picked-up by the testing. That does not mean there is not contamination, only that it is not reaching the breathing zone during manufacturing operations. Additionally, it is clear that operators will come in contact with the materials during post-filling vial handling and cleaning operations (both spillage during operations as well as post-campaign cleanup). It also must be considered that aerosolization during filling will tend to fall onto the outer surface of the container. This will then dry, returning to a powder form and increasing its ability to be transferred to the operators, equipment, and surrounding surfaces, including other product containers. The risk here is not only exposure of the operators, but cross contamination as well.

The risk to the operators also carries beyond the manufacturing area. Operators will primarily tend to come in contact with liquid or powder on their hands and lower extremities, including their feet. This is a result of the manual handling of containers and equipment, stepping on spilled material, parting of the curtains (which are extremely difficult to clean), and the downflow caused by the laminar flow in the room. This will increase risk of exposure through skin absorption and inadvertent ingestion. Any material left on the operator after degowning will tend to be dragged along. This could have a huge impact as that "drag along" is carried through-out the facility and home. The risk may be multiplied at home where small children tend to hug feet and legs and then put their hands in their mouths. This risk may only be effectively mitigated by eliminating the risk of exposure during filling operations.

Regulatory Environment

Several regulatory agencies oversee pharmaceutical operations around the world. Probably the most visible, certainly in the United States, is the FDA. It is the responsibility of this and similar agencies around the world, to assure product integrity and the safety of the products for use by the population. These agencies are generally not specifically tasked with a focus on protecting the workforce involved in manufacturing these products. As a result, information and guidance from these agencies is focused on product quality and not operator protection. Thus, their interest in alternate technologies is essentially only in their ability to further protect the product.

On the other hand, the Occupational Safety and Health Administration (OSHA) is focused on the protection of personnel and not on protection of the product. As a result, their attention is on how a given product may impact the safety and health of the operators of the facility and not how those operators may impact the integrity of the product.

FDA

The FDA has been conspicuously aggressive in its communication with vendors and industry as a whole concerning the use of advanced aseptic technologies, specifically isolators. Their most recent guidance, issued in September of 2004, mentions isolators 55 times. While this is not binding and should not be construed to mean that the FDA is requiring isolators, they are obviously very interested in them and their verbiage indicates that they see the potential for improved aseptic conditions. The guidance states: *A well-designed positive pressure isolator, supported by adequate procedures for its maintenance, monitoring, and control, offers tangible advantages over traditional aseptic processing, including fewer opportunities for microbial contamination during processing.*[1]

Additionally, the FDA recognizes that removing the operators from the critical zone has the potential to increase aseptic conditions. As a result, the FDA is indicating a lower requirement for media fills during validation and qualification. The guidance continues: *In contrast, a process conducted in an isolator… can have a low risk of contamination because of the lack of direct human intervention and can be simulated with a lower number of units as a proportion of the overall operation.*[2]

Recently, at the 2006 ISPE Tampa Conference, Rick Friedman of the FDA specifically stated that were he to build a new facility today, he would not utilize cleanrooms. His reasoning was that he anticipates such facilities may not be acceptable in the next two to five years. Additionally, he specifically stated that he would recommend the use of isolators when handling highly potent or otherwise toxic materials during filling operations. He further expressed concern on the ability of Restricted Access Barrier Systems (RABS) to provide advanced aseptic conditions. Based on these comments, serious consideration must be given to the use of isolators for both aseptic and containment considerations.

EMEA

While the FDA has been surprisingly open in its dialogue with industry concerning the use of isolators, the European regulators have been significantly less so. The FDA September 2004 *Guidance for Industry* is the first regulatory pronouncement concerning the use of isolators, but has not been

directly reflected by the European regulators. Although significantly more fill lines have been enclosed in isolators in Europe than in the US, the European regulators have been much less forthcoming in official guidance than the FDA.

When considering the European position, this lack of official guidance forces us to review their actions. As mentioned above, the large number of isolated fill lines that have been approved and continue to be approved in Europe would indicate that the European regulators also view the isolator technology favorably.

OSHA

The Occupational Safety and Health Administration is involved in this discussion as it pertains to containment considerations. Although their charter does not include product safety, they are focused on operator protection in general and hazard control in particular. The OSHA regulations establish a hierarchy of control that begins with engineering controls, e.g., isolators, split butterfly valves, local exhaust ventilation; then administrative controls, e.g., work practices; and finally the use of personal protective equipment. OSHA has stated that, *Employers must use engineering or administrative controls to bring employee exposure to airborne contaminants within the levels permitted under 29 CFR 1910.1000. You may use Personal Protective Equipment (PPE) to supplement engineering and administrative controls only when these controls cannot be feasibly implemented to reduce employee exposure to permissible levels.*[3] Additionally, they have published, *Respirators have their limitations and are not a substitute for effective engineering at work practice controls*.[4] The bottom line is that OSHA regulations first require the implementation of engineering and administration controls to limit employee exposure risk before the use of PPE is allowed as primary operator protection. Facilities utilizing PPE as primary operator protection may be in violation of these OSHA regulations, placing operators at risk and increasing corporate liability.

Industry Standards and Trends

As noted above, virtually all pharmaceutical companies today recognize the inherent risk in handling powder form API and the need to implement proper controls for new or existing processes. Many facilities have already, or are planning for, the upgrading of existing processing to provide containment capabilities for the safe handling of these materials. New facilities designed to handle hazardous powder materials are almost exclusively being designed with containment capability.

However, liquid handling facilities have not been as clear-cut. Based on the considerations noted in section *Powders and Liquids* above, most current handling of liquid hazardous materials has been conducted in traditional cleanroom facilities. These facilities, for both internal and contract manufacturing, have been the only available capacity for handling these hazardous products. As the industry in general, and the individual companies and regulators in particular, have recognized the risk in open handling of the hazardous products and the significant aseptic benefits to advanced aseptic manufacturing, there is a definite trend toward isolators for these processes.

Interestingly, most of these companies have internal containment guidelines that do not differentiate between liquid and powder form API and may currently be in violation of their own guidelines. Many of these companies, when confronted with the cost of building a new facility or upgrading existing capabilities, decide to place these products with a contract manufacturer. Traditionally, very few of these client companies have extended their internal containment guidelines to a contract manufacturer; however, this is changing as more companies, e.g., Johnson & Johnson, Bristol-Myers Squibb, Eli Lilly, and others, are extending those guidelines to their suppliers. There has been a misconception in the industry that legal responsibility passes exclusively to the contract manufacturer when handling these materials. In point of fact, legal remedies will likely be sought from both the owner of the NDA and the contract manufacturer. The attorneys and the courts will seek the deepest pockets, with potentially disastrous effects on both the owner and the contractor. This potential liability is resulting in much greater scrutiny of contract manufacturers by their potential clients.

More and more frequently, a full-scale containment review is becoming a critical part of the due diligence conducted by the client companies. Contract manufacturers not capable of providing proper containment controls will not be awarded contracts. The net result for these companies is that this entire market segment (contract manufacturing of highly potent or toxic products) is put at risk when handling toxic materials in a traditional cleanroom facility or without the use of full isolation for powder handling.

Deliveries for isolators for sterile filling applications have increased significantly over the last several years. The most recent data available[5] indicates global delivery of 84 units by 1998, 174 systems delivered by 2000, an additional 27 units delivered by 2002, and 57 more in 2004 for a total of 256. Deliveries to Europe have, over time, far outstripped those to North America, Asia, and other regions. However, that trend appears to be changing. Whereas Europe represented two thirds of the deliveries through 1998, deliveries to North America actually exceeded those to Europe in the 2003/2004 time period.

Recently, anecdotal evidence indicates a sharp upturn in the use of isolators for sterile fill operations. Glaxo SmithKline is reported to have made the corporate decision to order upward of a dozen high-speed isolated filling systems for syringes and vials. Sanofi Aventis in France, already utilizing two high-speed isolated filling systems, has just ordered an additional three. Abbott in Germany and others in the US have determined that all filling of aseptic/toxic products will be conducted in isolators. Bristol-Myers Squibb has recently installed two filling systems in isolators, one for high-speed lyophilized vials and one for pilot speed filling of cytotoxic and highly potent products. Johnson & Johnson, Eli Lilly, Pierre Fabre, Apotex, and numerous other companies are currently using isolators with many more, including companies such as

Amgen, with isolator projects currently under way. There is a very clear trend toward the use of isolators for aseptic filling operations, particularly those involving hazardous products.

Material Handling Options

Overview

The engineering control technologies for sterile filling operations break down into three primary categories: traditional ISO 5 (Class 100) cleanroom style aseptic processing (traditional), which may incorporate the use of flexible or rigid wall barrier/curtain systems; Restricted Access Barrier Systems (RABS), utilizing rigid walls with glove ports and transfer systems; and isolators that fully enclose the filling operation and require interface through closed-system transfer and glove ports. The RABS and isolator systems are designed to enhance aseptic processing capabilities over traditional cleanroom processing. Additionally, the isolators are capable of total separation of the filling environment from the background area and the operators, resulting in true containment and advanced aseptic capabilities. Needless to say, the RABS and isolator systems employ progressively restrictive access and may impact turnaround times and may restrict equipment choices for the filling equipment (e.g., time pressure versus pumps, material compatibility, etc.) if not properly designed.

There is a significant improvement in advanced aseptic capabilities provided by isolators and the greatly decreased background classification required for the filling area. This may be seen on the following table that compares Decontamination Assurance Levels (DAL) achievable versus the background Cleanroom Classification for the three technologies.

It should be noted that the term "Sterility Assurance Level" (SAL) is frequently used in the industry to quantify the degree of "sterility" of the area enclosing the process area. The application of this term when discussing process envelopes such as isolators or RABS is inappropriate as it implies a degree of sterility; there are no degrees. From a microbiological perspective, we define a sterile condition based on the theoretical extrapolation of exponential decay of a reference organism population log reduction of at least 10^{-6}. Further, we properly look at single units as either sterile or not. An isolator or RABS is a single unit that will never be truly sterile, while a product is a single unit that either is or is not sterile. The word "decontamination" is then more appropriate for quantifying the surrounding area as it better describes the condition being evaluated. Furthermore, while the log reduction of the product itself and all contact surfaces must be at least six, the area surrounding it may be less and will vary depending upon a number of factors such as materials of construction and their exposure to disinfectants.

Figure 2 provides an overview of the industry standard containment controls for liquid handling applications. The red hatched area indicates the product categories that cause the greatest concern for occupational safety. As can be seen, isolators are generally considered the only effective control for containing these toxic materials.

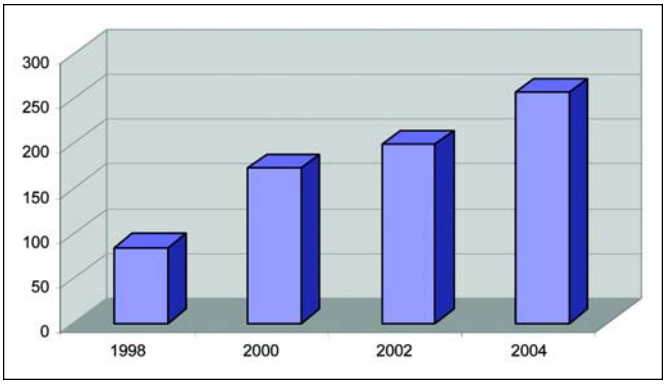

Figure 1. Barrier isolator deliveries.

Traditional Cleanroom Style Aseptic Processing

Traditional ISO 5 (Class 100) cleanroom style aseptic processing is employed at facilities around the world and has a long history of successful operation. These facilities place the filling equipment in open ISO 5 (Class 100) space with the operators sharing the environment. Frequently, cleanroom style processing is enhanced by the use of simple flexible or rigid barrier systems. The systems are hung from the ceiling and channel the laminar airflow generated from the room ceiling panels and discharge the air out the bottom of the barrier. These barriers do not provide any containment capability, but are provided purely to enhance aseptic conditions. In fact, the discharge of process air out the bottom will tend to increase the exposure risk by spreading potentially contaminated air through a larger area of the room. Since this discharge is at a low height, contamination will tend to occur on operators' feet and lower room surfaces rather than reaching the breathing zone where it would be picked up by standard air monitoring. The result is a high risk for product cross-contamination as well as operator exposure during degown and other gown contact procedures.

The flexible barriers are usually plastic strips hung together to form a curtain that allows operators to easily pass through to manipulate the filling operations. This version offers the greatest amount of flexibility and access, while providing the least amount of control of the environment for both aseptic or containment requirements.

The rigid version utilizes Lexan or other polycarbonate panels mounted in frames and hung in a similar fashion as the flexible curtains. The system offers a theoretically higher aseptic capability than the flexible because it further limits operator access to the filling equipment, limiting the greatest source of contamination in the cleanroom (the operator). However, when manipulation of the filling equipment is required, the operator must open the panels, which are interlocked with the filling line, causing the line to stop until the door is re-closed. This stopping of the fill line reduces throughput and also increases the likelihood of an upset condition, due to the mishandling of the vials during the start and stop operation. This mishandling may contribute to increased release of liquid product, resulting in a significant exposure risk. Additionally, the operator must enter the

	Traditional	RABS	Isolator
Decontamination Assurance Level	3	Up to 6*	6+
Background Classification	ISO 5	ISO 7	ISO 8
*Note: the wide variation is due to the ability of an operator to open the door during processing. This would compromise the decontaminated zone by exposing it to the surrounding area and reducing, at best, the DAL to that of the surrounding room. The net effect is that virtually all RABS are in the three to four range, unless a strict protocol prohibiting opening the doors is followed.			

Table A. DAL vs. background cleanroom classification for the three technologies.

critical filling zone, placing product at risk for contamination and the operator at risk for exposure from the product.

Cleaning and disinfection of the cleanroom and the barrier systems is a manual process that will include spraying and wiping of all surfaces with decontaminants, sporicidal agents such as alcohol or aldehyde, or other materials. These cleaning processes place the operators in direct contact with the hazardous materials, both in liquid and potentially dried powder form on the room, equipment, and barrier surfaces.

Restricted Access Barrier Systems (RABS)

Restricted Access Barrier Systems (RABS) are a variation on the rigid panel barrier system discussed in the Cleanroom section above. RABS are designed to further control operator access to the equipment by providing glove ports to allow operator manipulation of the fill operations without actually entering the space defined by the RABS.

Currently, within the industry, considerable discussion is being held as to the definition of a RABS and how performance levels are defined. There is an active effort by the FDA, ISPE, and others to study and generate definitions and performance guidelines for RABS.

Decontamination (disinfection) of a RABS is a process similar to that conducted in a traditional environment where operators spray and hand wipe all surfaces to disinfect. The use of the much more efficient gaseous sporicidal agents such as Vaporized Hydrogen Peroxide (VHP) is generally not possible in a RABS environment.

In its basic (passive) design, the RABS consists of a framework system and polycarbonate panels with glove ports and transfer ports mounted in pre-selected locations to provide the most efficient access from the exterior to the filling process inside. Air enters the RABS from the top via the existing ceiling panel hood system in the cleanroom. The air is pushed vertically (laminar) downward until it exits below the bottom of the framework, forcing the air mostly horizontally into the room.

The standard (active) RABS carries on-board HVAC including filtration. This version also may be designed to provide cooling and dehumidification of the air inside the RABS. Background room classifications are Class 1000 (ISO 6).

The advanced cRABS ("closed" RABS) provides a higher level of separation between the filling section and supporting processes such as infeed from the sterilizing tunnel and

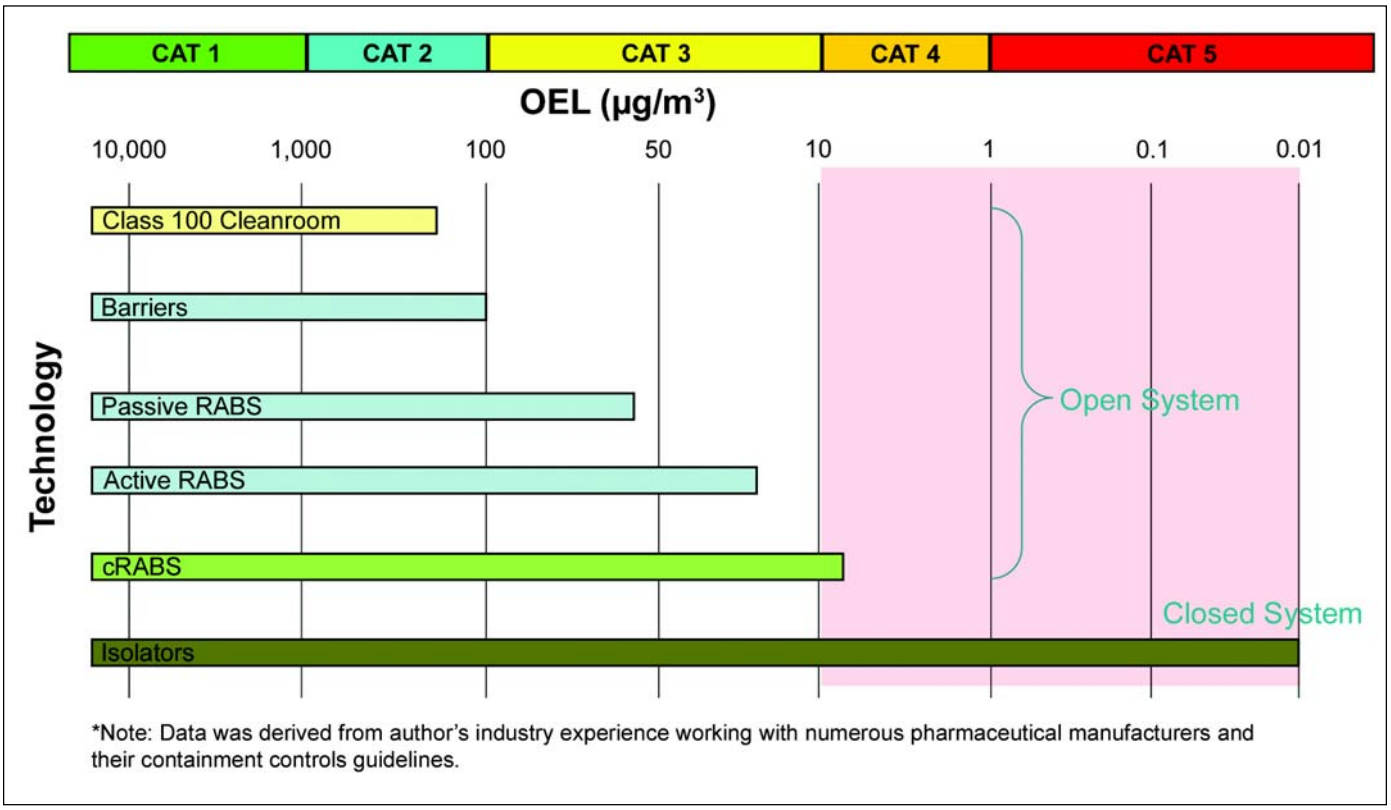

Figure 2. Typical industry standard liquid containment controls.*

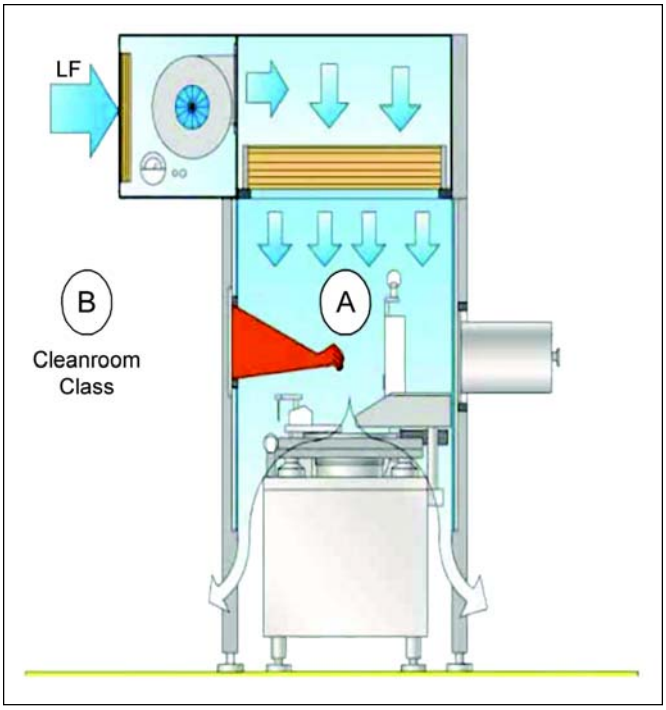

Figure 3. Typical RABS airflow scheme. *Courtesy of Bosch Packaging.*

outfeed to traying or lyophilization. Most importantly, the system adds an additional level of environmental control by capturing and recirculating the discharged air. This air can be captured from the bottom or drawn across the back and recirculated to the top, drawing the air away from the operators. As with the active RABS, the cRABS allows the option for cooling and the dehumidification of the internal air. However, the system does not allow the use of a gaseous sporicidal agent such as Vaporized Hydrogen Peroxide (VHP) or CIP technologies, thus requiring the more traditional cleaning and disinfecting of a nontraditional system.

During cleaning operations, the equipment and the surrounding room are manually sprayed and wiped. As with traditional cleanroom operations, the operators are in contact with the hazardous materials during these operations. Sterility Assurance Levels of approximately four to five may be possible with the RABS if the doors remain closed.

When considering the RABS, it must be remembered that the systems are not designed to provide total containment of the processes or the materials inside. They are designed to enhance aseptic conditions only. A few companies are experimenting with the use of cRABS for highly potent or toxic products. However, in order to be truly successful at this the systems would need to be totally isolated from the surrounding area and allow for manual and/or CIP decontamination without opening the system to the room. Additionally, it will be necessary to disinfect the equipment via the use of a gaseous sporicidal agent such as VHP as not all internal surfaces will be accessible from the outside when the system is closed.

Recent comments by Rick Friedman of the FDA at the 2006 ISPE Tampa Conference indicate that the FDA has great concerns about the ability of an operator to open a RABS located in less than ISO 5 (Class 100) space for intervention during operation. At a minimum, he stated, should an operator open the system during operation, all vials exposed in the RABS must be cleared and considered contaminated. Additionally, the gloves and internal surfaces of the doors must be wiped clean prior to re-closing the RABS.

Considering that the RABS is not designed for hazardous material handling, that they carry regulatory concern and suspicion, that they must be closed to the surrounding room, that disinfection with a gaseous sporicidal agent is not possible, and that there are relatively few in operation, the question must be asked as to the benefit of the systems versus the more widely accepted isolator for both containment and advanced aseptic requirements.

Isolators

Isolators represent the highest level of control, the highest level of aseptic assurance, the highest level of containment and operator protection, while at the same time involve the highest level of interference between the operators of the process equipment, the highest level of validation, and the highest level of equipment cost of the three technologies discussed in this article. This technology is not new, but the industry has not been as quick to implement it for sterile filling operations as it has for solid dosage, particularly in the US.

What is clear is a trend within the industry to utilize isolators for both advanced aseptic considerations as well as containment. As indicated in the *Regulatory Environment* section above, the FDA appears to strongly support the use of isolators to provide advanced aseptic environments as well as for containment of toxic materials. Additionally, based on current industry trends and Figure 1 of section *Industry Standards and Trends,* the use of isolators for both aseptic and containment considerations is significantly on the rise within the industry.

Isolators are totally enclosed systems providing ISO 5 (Class 100) conditions internally, while being located in an ISO 7 (Class 10,000) or ISO 8 (Class 100,000) room. The

Figure 4. Isolated fill line, Aventis, UK. *Photo courtesy SKAN AG.*

systems are most frequently integrated with specially designed filling equipment to maximize efficiency in operations and cleaning. Interface with the equipment during filling operations is through glove ports and closed system transfer ports. The isolators are designed to prevent opening during processing.

The background requirements are the most lenient of all the technologies discussed. The FDA has stated in its most recent guideline: *The interior of the isolator should meet Class 100 (ISO 5) standards. The classification of the environment surrounding the isolator should be based on the design of its interfaces (e.g., transfer ports), as well as the number of transfers into and out of the isolator. A Class 100,000 (ISO 8) background is commonly used based on consideration of isolator design and manufacturing situations. An aseptic processing isolator should not be located in an unclassified room.*[6]

Cleaning operations for these systems may be manual through glove ports, via a Clean-in-Place (CIP) system and spray balls, or a combination of the two. The equipment is designed to allow reach through glove ports of all internal surfaces (exclusive of ductwork) to facilitate cleaning operations prior to opening the equipment. This is the only system allowing cleaning of the equipment and surrounding barrier that does not place the operator in direct contact with the product.

Set up of the equipment is accomplished through large open doors that provide easy access to all internal areas and equipment. Anecdotal evidence from current users of the technology such as CILAG (J&J) in Schaffhausen Switzerland and Sanofi-Aventis in Dagenham UK, indicates that change-over set-up should require no more time in an isolator than in an open cleanroom. With the doors opened, all of the internal equipment is virtually as accessible as in a traditional cleanroom.

After set up, the system is closed and a decontamination (disinfection) cycle is run with a gaseous sporicidal agent, most frequently Vaporized Hydrogen Peroxide (VHP). During the cycle, Sterilization-in-Place (SIP) is run on the filling equipment product contact parts. Current VHP technologies require approximately three and a half to four hours for a complete cycle, including aeration to 1 ppm H_2O_2. New technologies are under development, with commercial release expected in the near future, which will run a complete cycle in approximately one and a half to two hours. Properly designed isolator systems are generally capable of sterility assurance level log reduction of approximately six or greater.

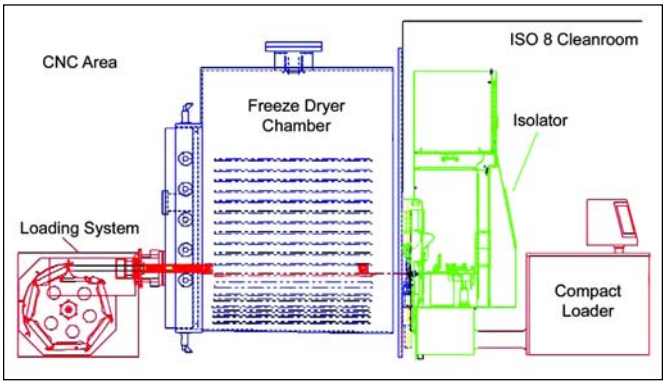

Figure 5. Auto load/unload scheme. *Courtesy of BOC Edwards.*

In addition to the advanced aseptic capabilities of the isolators, they remain the only true solution for the safe handling of HPC materials. The isolators provide a rigid barrier between the room and the critical zone where the materials are exposed. Operators are able to interface with the process without compromising the integrity of the critical zone. Parts and materials are transferred in via closed system transfer systems such as Rapid Transfer Ports. Conveyor systems can be enclosed in isolators and allow transfer of filled vials to isolated external vial washers or enclosed loading systems for freeze dryers. Additionally, unloading systems for the freeze dryers will be enclosed in isolators and provide contained transfer to the isolated external vial washers.

An added benefit to the use of isolators is seen when dealing with certain products that may be solvent based or are otherwise flammable. The isolator can be designed to provide an inert environment that will have no effect on the surrounding areas or the operating team. This capability is simply not possible with open technologies such as cleanrooms or RABS.

Freeze Dryer Operations

Many products require lyophilization, returning the API to a powder form, increasing the risk of exposure and cross-contamination. Containment controls are required for safe material handling.

Frequently, lyophilization operations will involve the manual traying of vials, placement in a portable Class 100 cart, transfer to the lyophilizer, and then manual loading of the freeze dryer shelves. Due to the eventuality of spillage within the filling operations, it is very likely that many of these vials will have product on the outside surfaces. Operators coming in contact with these vials may very well transfer liquid or dried product from the vials to the operator's gloves or other gowning. This product may then be transferred to other areas within the sterile suite, potentially serving as a source of cross-contamination and risk to other operators. Additionally, the operators may come in dermal or inhalation contact with the product during degowning activities. It may even be possible for the transfer carts to pick up hazardous product on their wheels or other surfaces. Product could then be transferred out of the room to other areas within the suite, posing a risk to operators or other products.

The loading of the vials into the dryer chambers involves manually removing the trays from the transfer carts and unloading the trays onto the dryer shelves. The containment risk during this operation is primarily from surface contamination on the vials due to spillage or aerosolization in the filling and transport operations. This contamination may be liquid or, more likely, dried powder that presents a risk of exposure to the operators.

Unloading operations present a significantly higher prob-

ability for operator exposure due to the frequent incidence of vial rupture during the lyophilization cycle. Some manufacturers have reported experience indicating a high exposure to ruptured vials during unloading operations as up to 5% of a chamber load may be crushed or ruptured during a cycle for certain products. Since the lyophilization process returns the API to a powder form, these ruptured vials will contaminate the interior of the chamber and surrounding spaces and equipment, greatly increasing the risk of operator exposure and cross-contamination. The best prevention for this is the installation of an isolator for loading and unloading operations.

While manual loading and unloading operations for the freeze dryers are possible, the ergonomic impact on the operators negates the effectiveness of the method. The most efficient method involves the use of an automatic loading system. These systems are capable of operation in a traditional cleanroom, but are most frequently integrated with an isolator. As is shown in Figure 5, this isolator mates to the front of the freeze dryer with access to the shelves provided through a vertically opening small profile "pizza door" with indexing shelves inside the chamber. A conveyor system brings the vials to the door and a pusher/actuator system loads and unloads the vials. Recent comments from the FDA indicate a preference for the systems, because they reduce human interface with the vials and their surrounding environment. This controlled human interface also provides a significant containment benefit by eliminating the direct human contact with the vials. Additionally, the cross-contamination risk is eliminated, because the environment containing the vials is isolated from the rest of the facility.

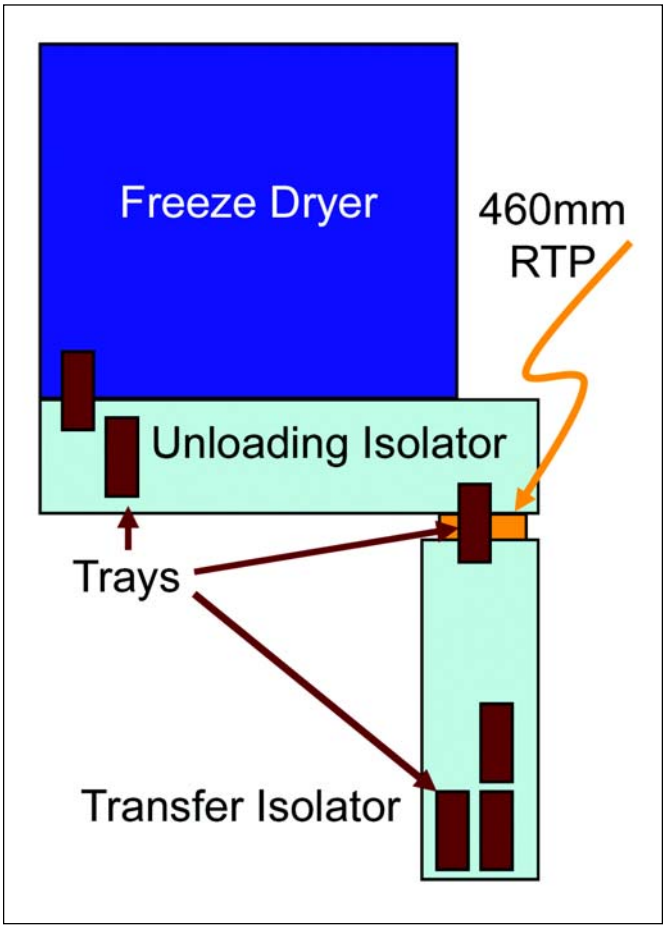

Figure 6. Freeze dryer unloading isolator scheme.

Cleaning of the chamber is by CIP, while the isolator utilizes either CIP with spray balls, manual spraying, and wiping through glove ports, or a combination of the two. Once cleaned, the isolator doors may be opened to allow easy access to the component parts and chamber inside. Decontamination of the freeze dryer and isolator after set up is achieved through the use of a gaseous sporicidal agent such as VHP.

The Hybrid: Traditional Cleanroom with Partial Isolation

As previously mentioned, there continues to be disagreement in the industry concerning safe handling practices for liquid form highly potent or toxic materials. The result for some companies is to allow liquid handling operations with more traditional technology. For these processes, liquid filling would be conducted in a traditional cleanroom with lyophilizers either in the same room or an adjacent hallway or room. Freeze drying operations, of course, return the hazardous material to powder form; thus, in order to comply with corporate powder handling guidelines, freeze dryer unloading would need to be conducted in containment, requiring an isolator. Some companies are experimenting with a hybrid layout that would utilize traditional cleanrooms for sterile filling, but loading and unloading of the freeze dryer would be via an isolator. The dryer might still be located in an ISO 5 (Class 100) room or corridor, but would be capable of accepting attachment of an unloading isolator. The purpose of this isolator would primarily be to provide containment for the handling of potentially contaminated vials and their surrounding environment during unloading operations.

To save costs for facilities with multiple freeze dryers, the isolator could be portable with wheels to facilitate ease of handling and docking to the face of the freeze dryers by means of an inflatable seal and a flange on the freeze dryer face. The isolator would be attached to the freeze dryer prior to opening the freeze dryer door for transferring the vials. The freeze dryer would be loaded or unloaded through a "pizza door" low-profile vertically opening door and would be assisted by a pushing system in the freeze dryer that would push the trays forward and out the door into the isolator. A transfer isolator would dock to the unloading isolator through a 460 mm rapid transfer port connection to allow transfer of the vials from the freeze dryer. A "roller skate" manual conveyor would be provided in the isolator to assist in moving the trays from the freeze dryer through the rapid transfer port into the transfer isolator. The RTP would allow aseptic connection of the transfer isolator to the unloading isolator, allowing the sequential aseptic docking of multiple transfer isolators in order to handle a full chamber load of vials.

The isolator would have an integrated air handling system, including HEPA filters and would be designed to run at

a negative differential pressure to provide maximum containment during handling and cleaning operations. Access to the interior will be through window mounted gloves. Cleaning could be accomplished by the use of an internal spray wand and drain.

From the containment perspective, this alternative would tend to suffer from the same lack of containment during liquid handling as in standard cleanrooms. There would continue to be significant manual handling of vials, placing operators at risk for exposure. The primary advantage to this hybrid system is the containment of freeze dryer unloading where the product has been returned to a powder form. This isolator system would provide containment during unloading operations and would technically provide sufficient containment during all powder handling operations. However, the liquid handling operations would essentially remain without containment and be susceptible to the same risk as with a traditional cleanroom.

From the regulatory perspective, this alternative also is susceptible to the same regulatory concerns as discussed in the traditional alternative. While this alternative provides a higher level of containment, the FDA and other regulators are focused on product quality and not operator protection. As such, this alternative does not address their concerns of product quality and advanced aseptic capability.

From the cost perspective, this alternative would provide a lower capital cost than a fully isolated system. The cost would be similar to a traditional cleanroom plus the addition of the unloading and transfer isolators and a simple automatic unloading system on the dryer. There are no operating cost reductions presented by this alternative since all manufacturing operations will still be conducted in ISO 5 (Class 100) space.

External Vial Wash

Unlike manufacturing operations for non-hazardous products, the filled and capped product container for a hazardous material will quite likely be contaminated on the outside and present a risk to operators during downstream handling. As a result of this, it is necessary to wash the external surfaces of the product container. This external washer will take hold of the container and spray the outside surfaces with water to remove any residual product. The problem with the system is where the handling equipment holds on to the product container. The vials are held around the neck to allow the water jets to hit the shoulder and body of the vials as they pass through the washer. However, the caps will remain unwashed and may still present some level of risk during packaging and pharmacy operations downstream. No system is currently available to mitigate this risk, so proper industrial hygiene planning must be provided downstream.

Costing for Containment Controls

Capital Cost Considerations

The capital costs involved with implementing an isolator system for sterile fill operations is frequently seen as the limiting factor in the decision. There is no question the capital cost for the equipment will be higher with isolators than for a traditional cleanroom. The roughly $2 million cost for the isolator for the filling equipment is not a factor in a traditional ISO 5 (Class 100) cleanroom. The trade-off for a new facility is the reduced cost of construction required for the isolators. An isolated filling system should be designed to include all of the process equipment, from the glass washer infeed through capping and external container wash, in the same room. This large room should be run as ISO 7 (Class 10,000) for products overseen by EMEA or Class 100,000 for those controlled by the FDA (see Isolators section above).

The net result of implementing isolators in a new facility will likely be a somewhat higher capital cost (building and equipment) than for a traditional cleanroom. For retrofitting an existing facility, capital costs will likely be that much higher for an isolated system since the trade-off in building construction costs will be less since the ISO 5 (Class 100) systems and layout will already be in place. However, for both the new and retrofit scenarios it is critical to look at both capital cost considerations and life cycle cost considerations to determine the true bottom-line impact for the company.

Life Cycle Costs: Traditional vs. Isolator for Liquid Handling

Due to the reduced environmental and support requirements of the isolator facility, the operating or "life" costs will, over the life of the facility, be significantly less than for the Class 100 design.

As an example, the Sanofi-Aventis facility in France has traditionally conducted filling operations in Class 100 facilities. In 1995, they installed their first fill line in an isolator. Their second line was installed in 2000, and they have recently placed an order for three additional isolated lines. In order to determine the proper technology for their filling operations, they have, since 1995, been able to compare life cycle costs for Class 100 cleanroom operations versus isolated.

Sanofi-Aventis[7] has experienced significantly lower operating costs for the isolated systems as well as dramatically increased sterility assurance levels. In fact, their isolated filling systems have not had a contamination positive since 12 October, 1998, while their conventional sterile area has seen, on average, just more than 1% positive tests for that same period of time. Furthermore, they indicate operational costs for the sterile facility that are approximately three times those of the isolator facilities. These costs include more than $100,000 per year in increased gowning for the sterile facility for one fill line running one shift per day. Additional savings are possible due to support staff reductions inside the sterile room and supporting spaces. Where an aseptic facility requires upward of 12 or more people per line per shift, an isolated facility may require as few as six to nine people due to the increased automation and reduced personnel flow restrictions required by a Class 100 facility.

Further life cycle cost savings were experienced due to

reduced microbiological testing, reduced square footage of HEPA filtration and laminar flow volume requirements, personnel reductions in both process and laboratory areas, reduced costs for maintenance and intervention due to less restrictive access requirements afforded by the isolators and their ISO 7 (Class 10,000) background, and significantly reduced energy costs.

For Sanofi-Aventis, these significant life cycle cost savings, when coupled with the reduced capital cost for building a facility with no ISO 5 (Class 100) spaces, have been more than sufficient to support their recent decision to install three new high-speed fill lines in isolators rather than traditional cleanroom space. For any company considering toxic sterile fill solutions, these cost considerations must be seriously considered, particularly when handling toxic materials that require containment. Existing ISO 5 (Class 100) space will be able to be operated as ISO 7 (Class 10,000) space when utilizing isolators. New construction will be built as ISO 7 (Class 10,000) space initially. Both of these scenarios will recognize significant life cycle cost savings over traditional cleanroom operations.

Summary

When considering containment technologies, manufacturers are faced with whether to utilize open or closed system technologies. For the liquid handling, three alternatives are available, traditional cleanroom, Restricted Access Barrier System, and fully isolated. The traditional provides the lowest capital cost, least containment consideration, and highest operating cost. The RABS design is identical to the traditional design for facility requirements and operating costs, but utilizes the barrier systems to control operator access and enhance aseptic conditions. As such, its capital cost is somewhat higher than the true traditional design with comparable operating costs. The containment considerations are improved, but still leave all liquid handling operations without containment. The fully isolated system provides total containment for all material handling with the highest capital costs offset by the lowest operating costs.

All companies conducting sterile fill operations of highly potent or toxic materials are faced with containment decisions that will have a huge impact on the business for years to come. There is no question that manufacturing in the pharmaceutical industry is becoming more and more dominated by hazardous APIs. As such, a significantly higher number and percentage of products presented to these companies for filling, both from development or on a contract basis, will be hazardous and require containment. For contract fillers, the question of proper containment may be even more critical. As more and more clients seek to extend their internal containment guidelines to their contract filling suppliers, contract manufacturers, in order to maintain this product segment, must be able to meet these internal guidelines. For all companies, though, the bottom-line impact on margins is a huge consideration. It is critical, when making these decisions, to consider not only capital cost, but the life cycle cost impact that will result from that decision. Additionally, this decision must be balanced with personnel safety, product quality, process requirements, as well as regulatory and industry trends in order to provide a system that will meet the current and anticipated future needs for the facility. It is clear that isolators will be a major part of the containment solution for these facilities.

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7. Sanofi-Aventis, Quantified and Comparative Study: Sterile Area and Filling Isolator, undated.

About the Author

Lee Francis, President of Containment Consultants, Inc., is a graduate of the University of Colorado. He is an expert in the field of containment for pharmaceutical and biotech processing, both powder and liquid. Since the late 1980s, he has successfully designed and implemented hundreds of contained pharmaceutical processes for highly potent/toxic and aseptic/sterile product applications. Francis has been a frequent containment course leader for ISPE, PDA, INTERPHEX, and other societies and was a visiting lecturer at the University of Tennessee, School of Pharmacy. He can be contacted by telephone at: +1-704- 655-8408 or by e-mail at: lee.francis@containment-consultants.com.

Containment Consultants, Inc., 19033 Double Eagle Dr., Cornelius, North Carolina 28031.

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Clive Mullins, Chairman of the 2007 FOYA Committee, Discusses Enhancements to the Competition

Now in its third year, the Facility of the Year Awards (FOYA) competition, sponsored by ISPE, INTERPHEX, and *Pharmaceutical Processing* magazine, provides a platform for the pharmaceutical manufacturing industry to showcase its new products and accomplishments in facility design, construction, and operation, while sharing the development of new applications of technology and cutting-edge approaches that are being adopted by the industry.

In an effort to properly acknowledge projects worthy of recognition, the sponsors made significant enhancements to the 2007 awards program. Awards are now given to leaders in specific categories, as well as the presentation of the overall Facility of the Year.

The following is an interview with Clive Mullins, VP, Global Pharmaceutical Business, Foster Wheeler, and Chairman of the 2007 FOYA Committee. He is the leader of Foster Wheeler's global pharmaceutical, biotechnology, and healthcare business line. A graduate of Exeter University in the UK, with a degree in chemical engineering, he has worked in the engineering and construction industry for 36 years. For the last 26 years he has focused exclusively on the pharmaceutical, biotechnology, and healthcare segment, accumulating extensive experience in design, construction management, sales, marketing, and team leadership.

Mullins discusses the enhancements made to the competition, why the program benefits companies, and how future FOYA applicants need to be aware that the competition is not one based on beauty and size, but on innovation, creativity, and the learning benefits their project provides.

Q The FOYA program for previous years was based on a format comprising finalists and an overall winner chosen from that group. This year's program has been enhanced, with the addition of categories (Process Innovation, Project Execution, Equipment Innovation, Facility Integration, Energy Efficiency, Operational Excellence). What were the reasons behind this change?

A Although presented as an awards program, from the outset the prime consideration of all the sponsors has been to use this as a vehicle to identify and disseminate innovation and excellence in the industry. The changes are aimed at enhancing our ability to do this. The categories you mention reflect the selection criteria that the judges have used in selecting the finalists and they have always had it within their discretion to make special awards as they did last year. This year we decided to make this change to make clearer the types of projects we were seeking to identify, to reinforce the fact that this is not a 'big is beautiful' contest, and to give a tangible award to all the finalists.

We hope that this change will also help people understand why a particular project has been chosen and what knowledge will be gained from reading and listening to presentations about the particular facilities.

Q Also different this year is the time and place for the announcement of the FOYA winner, who is chosen among the Category Winners. Usually the big announcement is made in the spring at INTERPHEX*2007*. But this year, the announcement will be made in November at ISPE 2007 Annual Meeting in Las Vegas. Why was the competition schedule altered?

A All those selected are winners in our eyes - indeed being selected as the project your company wishes to submit out of all its projects in the applicable timeframe, makes that project and the people that were associated with it, special.

We felt that announcing the overall winner of the Facility of the Year Award at the same time as the finalists, took some of the gloss off the achievement of being selected as a finalist. By making this change we create a space (around 6 months) where the category winners can be promoted and the lessons they provide for the industry disseminated (for example at the Facility Summit being held at ISPE's Washington Conference in June). It also creates more of a build up to the announcement of the overall winner since people will have learned more about the candidates, will have their own ideas, and thereby generates interest and excitement prior to the announcement at the ISPE Annual Meeting.

Q How have these program enhancements been received by the industry?

A Initial feedback has been very positive, but you touch on an important point. This awards program is for the benefit of the industry and it's vital that it remains relevant and becomes increasingly regarded as the leading accolade within our industry. I'm fortunate to lead a team of people representing a true cross section: owners representing a range of types and scale of operation, service providers and equipment manufacturers. Between us and with the wealth of experience that we represent, we have been able to create a valuable development that recognizes excellence and shares lessons learned.

However, we realize that although we have ideas we don't have all the answers. Having run the program for three years we've asked for some market research to guide our future planning. We'll be gathering this information at events, such as INTERPHEX, during the course of this year and us-

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Clive Mullins... Discusses Enhancements to the Competition

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ing the results to influence the shape of the program in 2008 and subsequent years. As part of this process I'd be only too pleased to receive any feedback your readers may want to give.

Q Why is it beneficial for companies with eligible facilities to submit an entry?

A Firstly, recognition. This varies from organization to organization. Clearly for a contract manufacturer the accolade provides a marketing edge. For a large pharma company, where there is always inter-site competition for new investment, it can be an internal marketing edge. For a smaller company it might provide an opportunity to create positive PR in its local community. These days recruitment and retention of personnel is a key issue and the award can be used as a differentiator. The process also creates an opportunity to recognize and reward the many people who participated in delivering a successful project.

Secondly, learning. As I mentioned earlier, this was a prime motivator in establishing the program. Everyone can benefit from learning about the (non-proprietary) innovations of others, but this only works if people participate. Therefore, there has to be some give as well as take.

"The important point to make here is that the submission needs to get across, as clearly as possible, the key features that make it a candidate for selection with quantifiable evidence of the claims."

Q Is the submission process too onerous for all but the larger organizations?

A This hasn't been the case so far, as we have received submissions from across the spectrum of the industry. However, this does allow me to address some points that we discussed in the organizing committee earlier this year and have implemented for the 2008 program.

We have done the best we can to define the minimum requirements for entry while giving the judges the information they need to make an informed decision. The important point to make here is that the submission needs to get across, as clearly as possible, the key features that make it a candidate for selection with quantifiable evidence of the claims. That, together with the required information about the submitter, the facility and the project participants can be presented concisely – I know because I've prepared one on behalf of one of my clients. As I said, this is not a beauty contest and in the same sense it's not dependent on the size, nature, and quality of the submission, although if you want to make an impressive presentation you can do so.

Each year we've been fortunate to have assembled an excellent judging panel comprising some of the leading figures in the industry. They are more than capable of looking beyond the gloss to determine the real merits of a submission and their conclusions stand up well to scrutiny. The size and nature of the project is secondary to the innovation, creativity, and learning benefits that it provides.

I would encourage as many people as possible to enter and I would encourage equipment manufacturers and service providers to persuade their customers to do so. Each year the judges have found merit in virtually every submission and the more participants, the more we can stimulate discussion and critique of the facilities that we are building; leading to benefits for all.

Q This year's five Category Winners come from four different countries. What does this say about the competition and the industry?

A A lot! Since its inception, we have received submissions from 19 different countries, 65% of submissions have been from outside the US, only 29% have been from 'big pharma' and the submissions have represented all the continents except Africa (so far!). The Facility of the Year Awards program has clearly quickly gained widespread recognition and acceptance as the industry-leading program that we aspire to.

My task in the coming years is to increase awareness and participation, to demonstrate the learning benefits and make the results as eagerly awaited within our industry as the leading awards in other industries – I'll see you on the red carpet!

2007 Facility of the Year Awards Winners Featured in *Pharmaceutical Engineering* Special Editions

Accompanying this issue of *Pharmaceutical Engineering* (PE) is the Facility of the Year Awards Special Edition, featuring case studies for each Category Winner.

An upcoming edition, to be mailed with your copy of PE's November/December issue, will take you behind the construction and competition curtains. Articles will focus on the making of each facility, featuring exclusive interviews with the overall Facility of the Year Awards Winner and Category Winners. The issue also will include a candid interview with Andy Skibo, Chair of the FOYA Judging Panel, who will provide valuable insight into why the winners were chosen and the importance of this prestigious competition to the global pharmaceutical manufacturing industry.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

ISPE Helps Shape the Industry's Future with "PQLI"

In its role as a "catalyst for change," ISPE has partnered with regulatory agencies in the United States, Europe, and Asia-Pacific to help industry and regulators find solutions to the challenges in implementing ICH guidances.

One of these critical initiatives is a series of workshops entitled Product Quality Lifecycle Implementation (PQLI), which focuses on the 21st century perspective on the product quality lifecycle. The goal of PQLI is to garner input from industry to help develop a pragmatic approach to implementing Q8, Q9, and ultimately Q10. Output from PQLI will include guidances produced by ISPE for the industry.

Three upcoming opportunities to get involved with PQLI include:

- ISPE Washington Conference, 4-7 June
- ISPE Berlin Conference, 17-20 September
- 2007 ISPE Annual Meeting, Las Vegas, Nevada, 4-7 November

PQLI Begins at Washington Conference – A Cooperative Effort

This summer, ISPE will pair with the US Food and Drug Administration (FDA) to bring sessions on Q8, Q9, and eventually Q10. On 6-7 June, ISPE will co-sponsor practical, industry-impacting sessions with the FDA on Product Quality Lifecycle Implementation (PQLI), and real life workshop sessions that will turn theory into reality, during the Washington Conference (4-7 June 2007) at the Crystal Gateway Marriott in Arlington, Virginia, USA.

Both regulators and industry leaders have determined a need for this cooperative effort. It is timely, global, and a critical step for the industry.

The sessions in Washington are the first in a series of meetings that will ultimately result in guidances produced by ISPE for the industry. Leaders from science, manufacturing, quality, and engineering will be able to engage with the FDA and other regulatory agencies to turn Q8 and Q9 into a cross-functional and practical reality.

"This initiative will have a significant impact for companies interested in FDA's offer to provide regulatory flexibility by providing new ways to file drug applications, supplements, and implement modern quality systems," said Paul D'Eramo, Johnson & Johnson's Executive Director for Quality and Compliance Worldwide and Chair of ISPE's Regulatory Affairs Committee. "We strongly encourage all professionals working in these areas to attend the workshop and provide their input."

"The PQLI session is at the forefront of the industry, finally giving credible answers and showing how to really implement Q8, Q9, and Q10 while helping shape the future thinking of the industry," said Bruce Davis, a session leader, and Global Capital Director at AstraZeneca.

The goal of these sessions is to begin to define areas where industry will be able to provide the technical framework for the implementation of Quality by Design (QbD) in regulatory submissions. The interactive seminars also will allow delegates to impact their own futures by participating in the development of how the Q8, Q9, and ultimately Q10 guidelines will be implemented. This ground-breaking event will comprise six break-out sessions for working groups to comment on and capture industry input.

The interactive workshops will cover API Design Space, Drug Product (DP) Design Space, API Critical versus Non-Critical, DP Critical versus Non-Critical, API Control Strategy versus Quality by Design, and DP Control Strategy Traditional versus QbD.

Presenters and planning committee include:

- Robert Baum, PhD, Executive Director, Pfizer, Inc.
- John Berridge, PhD, Senior Regulatory Consultant, Pfizer Ltd.
- Bruce Davis, Global Capital Director, AstraZeneca
- Joseph C. Famulare, Deputy Director of Office of Compliance, CDER, FDA (keynote)
- Charles Hoiberg, Executive Director, Pfizer, Inc.
- Yatindra Joshi, Vice President of Technical Research and Development, Novartis (keynote)
- George Millili, PhD, Senior Director of Tech Development, Ortho McNeil GPSG
- Moheb Nasr, PhD, Director, ONDQA, CDER, US FDA (keynote)
- Richard Saunders, PhD, Vice President of Pharma Development, Wyeth Research
- Thomas Schultz, PhD, Director, Global Regulatory Affairs, Johnson & Johnson
- Russ Somma, PhD, SommaTech, LLC
- James Spavins, Vice Preside0nt, Regulatory CMC/QA, Pfizer, Inc.

PQLI Continues at Berlin Conference – Imperative to Success of Industry

The ISPE Berlin Conference, to be held 17-20 September, will build on the work begun in June. This session will include speakers from the EMEA and other European regulatory agencies and industry leaders for follow up on PQLI, imperative to the success of the industry. This half-day event updates attendees and continues the next phase of ISPE's unique leadership in the facilitation of global solutions for a globally based industry.

It is a vital opportunity for attendees, regulatory, and industry leaders to continue to define practical solutions to implementing Q8 and Q9. Leaders from development, manufacturing, quality, and engineering will be able to engage with regulatory agencies to turn Q8 and Q9 into a cross-functional and practical reality.

The goal of these sessions is to further define areas where

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ISPE Helps Shape the Industry's Future with "PQLI"

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industry will be able to provide the technical framework for the implementation of QbD in regulatory submissions.

Subsequent sessions will follow as concepts are developed and input received worldwide, the conclusions from which will result in technical implementation documents produced by ISPE for industry's use worldwide.

Professionals from the pharmaceutical manufacturing industry can learn about issues from pilot studies to dossier submissions; listen to and share with colleagues practical solutions on how QbD affects your job today; contribute insight and discuss critical components of the ICH guidelines to help shape implementation and documents and position which will transform the industry; learn from selected case studies and provide your views on the key questions to be discussed that will provide understanding and direction for QbD; drill into areas of Design Space, Control Strategies and Critical versus Non-Critical, and help refine the practical encyclopedia which will become a major "go to" resource for the industry.

PQLI Continues at 2007 ISPE Annual Meeting – Transforming Tomorrow

ISPE 2007 Annual Meeting – Delivering Today, Transforming Tomorrow – will be held 4-7 November at Caesars Palace in Las Vegas, Nevada, USA.

On 5 November, Product Quality Lifecycle Implementation (PQLI) Design Qualification and Design Review will continue as the next generation of PQLI will continue what was discussed at the Berlin and Washington Conferences. This will be a rich panel of industry leaders and regulatory leaders from around the world. It will again include the opportunity for you to have your say in submissions and development of the guidances.

The process and tools used to conduct these activities vary greatly. As we move to a new Quality by Design paradigm with its focus on design space and risk-based approaches to qualification, Design Qualification and Design Review (DQ/DR) will be critical elements of facility delivery.

Successful case studies of DQ/DR implementation will be presented. These will focus on general project philosophy, methodologies, and tools used to document the activity, and the benefits gained. Participants can take part in an open forum to examine best practices across the industry, learn from others, share knowledge, and gain practical knowledge that will help you do your job more effectively.

More information will be available in the weeks and months to come at www.ISPE.org/annualmeeting.

Other Highlights at ISPE Washington Conference

ISPE Facility Summit 2007: Innovative Ideas for Accelerating Performance

As the international expert on pharmaceutical facilities, ISPE will offer presentations and innovative case studies from leaders in the field at the ISPE Facility Summit 2007: Innovative Ideas for Accelerating Performance. This multi-day, multi-track program will develop content in three key areas of project delivery, regulatory, and manufacturing

Background on ICH

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan, and the United States along with experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

ICH's purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.

ICH objectives are a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.

ISPE's Involvement

ISPE has partnered with several organizations to facilitate the implementation of the new quality guidelines (Q8 and Q9) developed by the ICH.

At the 2006 ISPE Annual Meeting, Moheb Nasr, PhD, of FDA's Center for Drug Evaluation and Research (CDER), announced the Agency's interest and willingness to work with ISPE to facilitate the implementation of the ICH Q8 and Q9 Guidelines.

Also during that meeting, Dr. Nasr, Joe Famulare of FDA CDER/Compliance, and representatives from ISPE's Regulatory Affairs Committee (RAC) met, and a vision and roadmap for implementation was discussed. The FDA said they were willing to provide advice on these plans.

ISPE partnered with PDA to sponsor conferences in December 2006 in Washington, DC, and in February 2007 in Brussels, Belgium. With a focus on ICH Q8 and Q9, these two sessions featured presenters from the committees that develop the guidelines in each of the three participating regions, the US, Europe, and Japan Then in February and March, ISPE partnered with the FDA and AAPS to sponsor a conference in Bethesda, Maryland, US — a follow-up to the PQRI/FDA workshop, "Drug Quality Systems for the 21st Century," held in April 2003.

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ISPE Communities of Practice Enable Virtual Collaboration with Enhanced Features

For 26 years, ISPE has served pharmaceutical manufacturing professionals, focusing on innovative ways to share relevant, timely information and make it easily accessible to the ISPE community.

In support of ISPE's commitment providing opportunities for addressing emerging industry trends and increasing operational efficiency through networking and online collaboration, ISPE Communities of Practice (COPs) continue to evolve and increase in number. Currently, there are 14 COPs including:

- Active Pharmaceutical Ingredients (API)
- Biotechnology (BIO)
- Commissioning and Qualification (C&Q)
- Process Analytical Technology (PAT)
- Process/Product Development (PPD)
- Containment (CON)
- Critical Utilities (CU)
- Disposables
- Heating, Ventilation and Air Conditioning (HVAC)
- Investigational Products (IP)
- GAMP
- Packaging
- Project Management (PM)
- Sterile Products Processing (SPP)

These Communities of Practice are now an inherent component of ISPE, enabling COP members around the world to connect and share ideas, while collecting valuable information relevant to the job they are doing. Membership in ISPE COPs is critical to inducing technological innovation across the industry and allows COP members to:

- learn and work together to address regional, domestic, and global issues in an open and efficient manner
- develop personal and collaborative relationships while offering the advantages of access to a wider global network
- enhance technical excellence across multiple business units, geographical regions, and project teams
- generate and disseminate valuable technical knowledge within the community through active participation of community members

Beginning in June, ISPE's Communities of Practice (COPs) will provide enhanced connectivity through an interactive online community offering global networking opportunities and access to a community-specific Body of Knowledge.

By accessing ISPE's enhanced global Communities of Practice, COP members will be able to:

- engage in electronic discussions on topics of interest
- search for other ISPE or COP members
- schedule electronic chats to discuss a particular issue or challenge
- collaborate on documents, important resources, and content relevant to the discipline of the community
- keep a calendar of important dates and meetings
- obtain current news and learn about upcoming community activities

Most importantly, ISPE Communities of Practice provide instant access to others facing the same challenges as well as to the "experts" offering advice on how to resolve those challenges.

To take advantage of the numerous enhanced benefits soon to be offered by ISPE Communities of Practice, you first have to become a COP member. Once you become a member, you simply need to log in to your individual community on a regular basis and make the commitment to becoming active.

For additional information about ISPE COPs or to join, please visit www.ispe.org/cops.

ISPE Helps Shape the Industry's Future with "PQLI"

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technology/operations, using breakouts, panel discussions and armchair case study presentations, as well as lectures. These breakouts will target both advanced and beginning levels, focusing on challenges, what the hottest trends are now, and what is ahead for the future.

Panel discussions will include Facility of the Year 2007 Category Winners with virtual facility tours. Participants can learn how they solved everyday problems, and can participate in interactive discussions on practical solutions to facility design (new or renovated), construction, building green, and qualification for operational excellence.

Gold Standard in Barrier Isolation

ISPE will host the 16th Annual Barrier Isolation Technology Forum – Innovation Updates and New Case Studies – the longest running Barrier Isolation Technology Forum in the world. ISPE's Barrier Isolation Technology Forum, which will be held 4-5 June, is the standard by which all others are measured, and continuously builds upon the foundation of knowledge and best practices set in place during previous years, providing a vital opportunity to gain updates and examine new case studies.

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ISPE Helps Shape the Industry's Future with "PQLI"

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Seminars to Feature Technical Documents

The Conference will offer seminars examining three ISPE technical documents. Delegates will discuss techniques and solutions from the teams that developed ISPE's pharmaceutical industry-impacting technical guides. These include:

- ISPE Good Practice Guide: Commissioning and Qualification of Water and Steam Systems, 4-5 June
- ISPE Baseline® Guide: Active Pharmaceutical Ingredients, formerly Bulk, Review by Developers and Application Implications, 4-5 June
- GAMP® Validation of Automation and Computerized Systems Related to Manufacturing Systems, and Roundtable Discussions, 5 June

Containment Technology Forum

Risk MaPP and Applying ICH Q9 Principles, 6-7 June

Hear the latest on Risk MaPP and regulation on dedicated facilities. You can help make history by participating in this interactive session that will show industry, and more importantly, regulators, how science-based risk assessments can be used to determine when multi-product facilities can safely be employed.

CPIP™ Workshop

Learn more about the new Certified Pharmaceutical Industry Professional (CPIP) – a new international credential for pharmaceutical industry professionals, at workshops held Monday, Tuesday, and Wednesday from 8 to 9 am. For more information, please visit www.ispe-pcc.org.

For more information about the Washington Conference, or to register, please visit www.ispe.org/washingtonconference.

Special thanks to our current Washington Conference sponsors:

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Sponsorship and table top exhibition opportunities are still available. Please contact Dave Hall, ISPE Director of Sales, by tel: +1-813-960-2105, Ext. 208, or e-mail: dhall@ispe.org for details.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

Mark Your Calendar with these ISPE Events

June 2007

4 - 7	**2007 Washington Conference, Crystal Gateway Marriott, Arlington, Virginia, USA**
7	Central Canada Chapter (Montreal), Annual Golf Tournament, Atlantide Golf Club, Ile-Perrot, Quebec, Canada
7	France Affiliate, Conference: Flexibility in Design and Operation, Huningue, France
7	San Diego Chapter, Baseball Game: Padres vs. Los Angeles Dodgers, Petco Park, San Diego, California, USA
7	South Central Chapter, Golf Outing, Doral Tesoro Hotel and Golf Club, Fort Worth, Texas, USA
9	Carolina-South Atlantic Chapter, Race for the Cure, Meredith College, Raleigh, North Carolina, USA
10 - 12	**2007 ISPE Singapore Conference in association with INTERPHEX, Suntec, Singapore**
12 - 14	Italy Affiliate, Conference with Pharmintech 2007 Exhibition, Bologna, Italy
13	New Jersey Chapter, Chapter Day, Holiday Inn, Somerset, New Jersey, USA
14	Chesapeake Bay Area Chapter, Summer Social, Baltimore Inner Harbor Cruise, Baltimore, Maryland, USA
14	San Diego Chapter, Extended Education Course (full-day): HVAC Systems, Design and Specification, Installation, Start-up and Commissioning, Calibration, Validation, Environmental Monitoring, California, USA
19	Boston Area Chapter, Seminar: Control Systems in Parallel Industries, Massachusetts ,USA
19	San Francisco/Bay Area Chapter, Commuter Conference: Sustainability-LEED and Project Methane Regeneration, ALZA, Vacaville, California, USA
20	Greater Los Angeles Area Chapter, Golf Tournament followed by Awards Banquet, Rio Honodo Golf Club, Downey, California, USA
21	Midwest Chapter, Annual Golf Outing, Quarry Oaks Golf Course, Omaha, Nebraska, USA
21	Puerto Rico Chapter, Biotechnology Track, Puerto Rico, USA
22	Czech/Slovakia Affiliate, Filtration Workshop, Holiday Inn, Brno, Czech Republic

July 2007

4 - 6	India Affiliate, Conference, Hyatt Regency, Mumbai, India
5	Italy Affiliate, ISPE Night, Polytechnic Auditorium, Milan, Italy
7	Puerto Rico Chapter, Summer Activity, Puerto Rico, USA
10	San Diego Chapter, New Member Breakfast, San Diego, California, USA
12	Puerto Rico Chapter, Project Management Track, Puerto Rico, USA
12	San Diego Chapter, Facility Tour, San Diego, California, USA
17	New England Chapter, Golf Tournament and Networking, Sterling Country Club, Sterling, Massachusetts, USA
19	Greater Los Angeles Area Chapter, Joint Meeting with PDA, Technical Training at B. Braun, California, USA
26	San Francisco/Bay Area Chapter, Golf Tournament and Winery Tour, USA
31	Boston Area Chapter, Annual Golf Tournament "Duffers Only," Massachusetts, USA

August 2007

9	San Diego Chapter, Vendor Night, Theme: Football Tailgate Party, Hilton La Jolla Torrey Pines, La Jolla, California, USA
10	San Diego Chapter, Annual Golf Tournament, Twin Oaks Golf Course, San Marcos, California, USA
21	San Francisco/Bay Area Chapter, Commuter Conference: Maintenance Panel-Predictive vs. Preventative, Best Practices, Nektar, San Carlos, California, USA
23	Puerto Rico Chapter, BioPharm/Medical Device/Tech Convention, Puerto Rico, USA
29	Nordic Affiliate, Event: Science Based Manufacturing - Packaging, Stockholm, Sweden
30	Puerto Rico Chapter, Member's Night, Puerto Rico, USA

Dates and Topics are subject to change

ISPE Student Chapter Profiles: Featured Universities of the Carolina-South Atlantic Chapter (CASA)

Editor's Note: This article is part of an ongoing series profiling ISPE Student Chapters and the people, education, research, and activities of tomorrow's pharmaceutical professionals.

Five Clemson students attended the 2007 East Coast Leadership Forum in NC.

The ISPE Carolina-South Atlantic Chapter (CASA) provides support to ISPE Student Chapters at the following universities: Campbell University (profiled in the March/April issue of PE), Clemson University, James Madison University, North Carolina A&T State University, North Carolina Central University (NCCU), North Carolina State University (NCSU), and University of North Carolina-Chapel Hill (UNC-CH). The following are profiles provided by four of the most active Student Chapters.

Clemson University Student Chapter

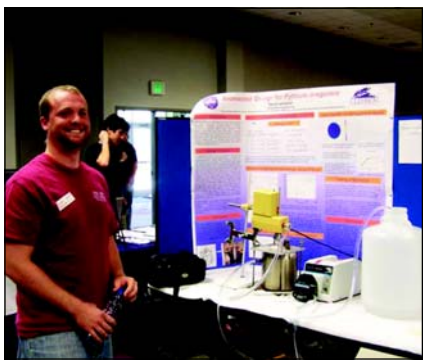
The Clemson University Student Chapter of ISPE was formed in the spring of 2006 and was recognized by the university for funding during the spring of 2007. The Clemson Student Chapter was started by Dr. Caye Drapcho from Clemson University, Bruce Craven of BE & K, and a few Clemson students who later became the Student Chapter's first officers. The major goal of the Student Chapter was to link industry with academia to allow students to get industry experience before they entered the work force.

The Student Chapter began with approximately ten students and later grew to 22 in the first year of operation. The Student Chapter gains new members by advertising for events, tours, and guest lecturers from industry that the Student Chapter sponsors. The Student Chapter is composed of Clemson biosystems and chemical engineering majors. During the first year of operation, Nicole Litton was the President. Brian Corbett was the Vice President and Darryl Jones was the Treasurer. During the recent meeting in March 2007, new officers were elected. Justin Montanti was elected President for the upcoming year. Jessica Easterling was elected Vice President, Lindsey Sanders was elected Treasurer, and Nylen Simmons was elected Secretary.

During the 2006 year, the Student Chapter toured many companies in the biotechnology industry. These companies included IRIX Pharmaceuticals in Green-ville, SC, Martek in Kings-tree, SC, Roche in Florence, SC, and Bausch and Lomb in Greenville, SC. In addition to company tours, the Student Chapter sent four members to attend the ISPE Annual Meeting in Orlando, Florida. David Johnson, an ISPE Student Member at Clemson University, won the undergraduate poster competition in the South East and won an all-expenses paid trip to present at the International Student Poster Competition in Orlando.

Members of the Clemson University Student Chapter also attended ISPE training workships during the 2006 academic year. Five students attended the ISPE East Coast Student Leadership Forum in Raleigh and networked with employers as well as other ISPE Student Chapters. Four students attended the BE & K Fill Finish Facility of the Future seminar and learned about validation and construction of future facilities in the biotechnology industry. The ISPE Student Career

Clemson field trip and tour to IRIX Pharmaceuticals.



Participating in Clemson's Engineering and Science Week.

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ISPE Student Chapter Profile: The Universities of the CASA Chapter

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Fair in Raleigh was attended by two students from the Chapter in February of 2007.

As our Student Chapter enters our second year at Clemson we hope to be further involved in community activities. In February 2007 we hosted a table at the Engineering and Science Expo again and reached out to the local youth. More than 300 middle school students came to Clemson for the day and participated in various activities to get them interested in science, math, and engineering. Industry Advisor Bruce Craven participates in many activities and is always available to help.

North Carolina Central University Student Chapter

The North Carolina Central University (NCCU) Student Chapter of ISPE recently became an official Student Chapter. The NCCU Faculty Advisor is Dr. Weifan Zheng and the Industry Advisor is Charles Wright, an alumnus of NCCU, who is currently employed at Tyco Healthcare. NCCU currently has 13 Student Members and hopes to steadily increase their membership over the coming years. Some of the students have already benefited from a tour organized at Biogen Idec. Below is a description of a unique program which allows for the perfect environment for an ISPE Student Chapter.

NCCU has established the Biomanufacturing Research Institute and Technology Enterprise (BRITE) Center of Excellence. BRITE will provide the biomanufacturing industry with skilled workers who are prepared to pursue careers in biopharmaceutical science and management. The 52,000 square foot state-of-art facility is currently under construction and scheduled to be completed by Fall 2007. The Golden Leaf Foundation Inc. has provided a grant of $17.8 million for the construction of the BRITE facility. In 2005, the Golden Leaf Foundation Inc. awarded BRITE $1.5 million for additional laboratory equipment.

As a component of the North Carolina Biomanufacturing and Pharmaceutical Training Consortium, BRITE will offer education and training in biotechnology and biomanufacturing for students at the Bachelors, Masters, and Doctoral levels.

Biomanufacturing related programs would initially focus on bioprocess improvement, bioanalytical, and formulation sciences. The University is developing its curriculum to train students to become competitive in working in a biomanufacturing or a biotechnology related company. Coursework will include microbiology, cell and molecular biology, biochemistry, instrumentation, and analytical chemistry for the first three years. New courses focusing on biomanufacturing topics will be added throughout the four-year curriculum. In the senior year, students will participate in specific projects in laboratory modules that will simulate the work environment of the biomanufacturing industry. This model will build upon NCCU's successful investment in the Julius L. Chambers Biotechnology/Biomedical Research Institute. In the five years since this state-of-the-art facility opened, it has attracted top scientists who are training students in cardiovascular biology, neuroscience, cancer, and genomics in an environment that replicates the laboratories found in industry.

Interdisciplinary biology and chemistry concentrations will provide a solid foundation in the sciences and specialized education in biomanufacturing competencies. Students from community colleges will enter into the BRITE program at the junior level. Many summer courses will be offered to students as a flexible entry into the BRITE programs. Students will also be able to take courses in the schools of business and law for intellectual property and business ethics that will augment the small and medium-sized biotechnology company.

The BRITE program will provide students with fellowship and internship opportunities depending on their academic performance and merits on a competitive basis. BRITE's academic program will provide collaborations and logistical support for biomanufacturing and biotechnology industries.

The BRITE program will deliver educational programs that provide essential hands-on training and high-quality students to meet and exceed the current needs of the biomanufacturing, pharmaceutical, and agribiotechnology industries in North Carolina. Professional science Masters degrees and Doctorates in bioprocess and biopharmaceutical sciences will produce future technical and business leaders, a development that will ensure this industry cluster remains vital and innovative well into the future.

Initially, NCCU students with a science major in biology or chemistry (or other scientific major, such as environmental science, physics and mathematics) and students from community colleges with an interest in biotechnology will benefit from such training experience. It is projected that 40 students per year will graduate from the BRITE program; eventually the number of students will increase. Incumbent workers currently employed in the operational sector of biomanufacturing can also be trained in the BRITE program to prepare them for moving up to the other sectors of their company.

North Carolina State University Student Chapter

The North Carolina State University Student Chapter of ISPE was founded in 1995 by Jane Brown, Dan Dunbar, and Dr. Peter Kilpatrick. They felt that students were an untapped resource and knew that ISPE had a lot to offer these future professionals. Students at North Carolina State University (NCSU) recognize that ISPE is a gateway into the pharmaceutical and biotech industry as well as a resource for industry information, networking, and career development.

The NCSU Student Chapter currently has 20 members. The majors

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NCSU participation in the 2007 East Coast Student Leadership Forum.

NCSU alumni.

represented in this Chapter include chemical and biomolecular engineering, microbiology, and food science. The NCSU Student Chapter has monthly dinner meetings providing free food and industry speakers. The marketing for student involvement includes word of mouth, e-mail, and flyers across campus. The Student Chapter also utilizes the student-focused Carolina-South Atlantic Chapter events to promote the benefits of membership. Student Chapter activities include monthly meetings and CASA Chapter sponsored events. Recently, the Student Chapter held a joint meeting with the CASA Chapter and the NCSU American Institute of Chemical Engineers (AICHE) in which 80 industry professionals (NCSU and Campbell University faculty) and students attended.

The NCSU Student Chapter hosted the 2007 ISPE East Coast Student Leadership Forum on its campus and had the privilege of working with industry professionals who offered support to students and organized the event. Within the community, the Student Chapter holds an annual toy drive outside of a local Toys "R" Us and has collected hundreds of toys to support the local CASA Chapter Toys for Tots toy drive. Members of the Student Chapter also participated as volunteers at the local Walk for Life event in 2006 and plan to volunteer again this year.

NCSU students collect toys for the CASA Chapter Toys for Tots drive.

The NCSU Student Chapter has many outstanding accomplishments. There are several ISPE International Student Poster Competition winners from the Chapter, including Ryan Hill and Kristen Jones. NCSU student Jeffrey Stowe won the 2007 CASA Chapter regional poster competition in the undergraduate category. Young alumni, including Jennifer Brown-Chin, Jennifer Lauria Clark, Kari Lauria Delahunty, Sherry Nelson, and Ryan Hill have stayed highly involved in student development for ISPE since their graduation. The continued involvement of these former students is proof that the goal for founding the Student Chapters has been realized.

Current officers are Shannon Manning, President; Stephen Gregory and Chad Thompson, Vice Presidents; Lisa Saxon, Treasurer (and former President); Christine Virgilio, Secretary; and Kimberly Shearer, Publicity Chair. Advisors include Industry Advisors Joel Youngblood, (Talecris - Planning and Production Scheduling, Supply Chain) and Ryan Hill, (Talecris - PAT Engineer), and Faculty Advisor Marcello Tellez, Assistant Director for Student Coordination of the Golden LEAF Biomanufacturing Training and Education Center (BTEC).

The BTEC is an exciting new facility being built on NCSU's Centennial Campus. This facility will provide students the opportunity to learn about biomanufacturing at the pilot scale in a cGMP modeled environment. For more information on BTEC please visit http://www.engr.ncsu.edu/btec/index.php. With this new facility and the support of its faculty, the NCSU Student Chapter expects to see accelerated growth within the next five years.

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ISPE Student Chapter Profile: The Universities of the CASA Chapter

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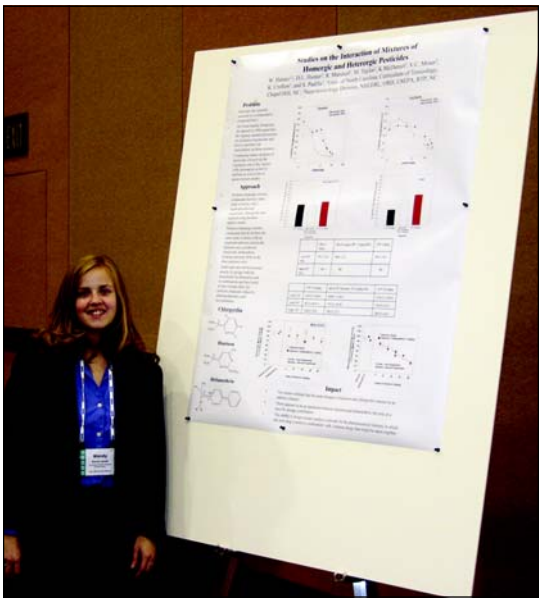
University of North Carolina-Chapel Hill Student Chapter

The University of North Carolina-Chapel Hill (UNC-CH) Student Chapter of ISPE had a unique start. One of the founding members of the Campbell University Student Chapter helped to start the UNC-CH Student Chapter. Along with the help of Jane Brown, currently the ISPE Chairman, Wendy Haines started a Student Chapter at the University where she was pursuing her graduate degree. Haines enlisted her toxicology classmates: Anicka Bissahoya, Elmarie Bodes, Sharon Oxendine, and Checo Rorie to make up the first five members and officers of the UNC-CH Student Chapter in 1999. These students helped to find the first Faculty Advisor, Dr. Catherine Hammett-Stabler. Dr. Hammett-Stabler was a new faculty member of the Pathology Department and thought that ISPE would be a good way to introduce students and herself to the pharmaceutical/biotechnology industry. With the help of ISPE Headquarters, the students were also able to ask an eager UNC-CH alumna, Jennifer Williams, to be their Industry Advisor. Williams was then employed at Bayer and pursuing a Masters degree at North Carolina State University. After UNC had interested Student Members and advisors, they were on their way to having a successful ISPE Student Chapter.



2001 Student Poster Competition Graduate Winner: Wendy Haines, University of North Carolina.

There is another component that makes the UNC-CH Student Chapter of ISPE unique – graduate students. The UNC-CH Student Chapter was first made up predominately of graduate students pursuing a wide-variety of scientific Doctorate degrees. Most of these students were interested in obtaining jobs in the pharmaceutical industry and being involved in ISPE was a step in the right direction. Not many student organizations can help scientific graduate students learn more about industry, go on plant tours, and network with professionals working in industry. ISPE Student Chapters provide all of these things and more.

Since the UNC-CH Student Chapter is made up of mostly PhD candidates, this Student Chapter has had some very interesting meetings. Chief Toxicologist for the Medical Examiner, Dr. Ruth Winecker, took students through crime-scene photos and toxicological results to determine cause of death. UNC-CH has had a former FBI agent, Cecil Yates, discuss espionage cases and describe what it is like to work for the FBI. There have been other discussions with published authors on how to give scientific presentations. HR managers have given tips on resume writing and interviewing skills. Former students come back to talk about their jobs in industry.

In 2000, ISPE unveiled the first ever Student Poster Competition. The competition was for a current full-time undergraduate or graduate student. The Carolina-South Atlantic (CASA) Chapter had about 20 students compete at the local level. Susan Bielmeier, graduate student in Toxicology at UNC-CH, won the CASA Chapter competition and went on to win the International Student Poster Competition. Since then, the UNC-CH has had three other graduate students win at the International Student Poster Competition. UNC-CH has had a total of four International Student Poster winners.

2004 Student Poster Competition Graduate Winner: Gillian S. Backus, University of North Carolina Chapel Hill.

Today, UNC-CH is trying to focus on recruiting undergraduate students to be involved in ISPE. The Student Chapter feels that more undergraduate students would make the decision to pursue jobs in industry if only someone told and showed them this great opportunity. Due to the current Faculty Advisor pursing a career opportunity elsewhere, UNC-CH is looking for a new Faculty Advisor. Patrick Buckner, of NNE, is an alumnus of UNC-CH and the current Industry Advisor for the UNC-CH Student Chapter.

The CASA Chapter recently had a local student poster competition and a UNC-CH graduate student, Stacey Foti, won in the graduate category. The UNC-CH Student Chapter wishes her luck at the International Student Poster Competition at the 2007 ISPE Annual Meeting in Las Vegas, Nevada. Student Chapter Members are the future of ISPE and ISPE leadership. The UNC-CH Student Chapter would like to thank all who have supported ISPE students and encourages continued support.

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International

The International Conference on Harmonisation (ICH) has indicated on their Web site[1] that a new tripartite guideline under topic Q10 Pharmaceutical Quality Systems should be available for release for consultation by the Spring of 2007. It is designed to augment existing quality systems.

Australia/ New Zealand

No information of significance was added to the **Therapeutic Goods Administration (TGA)** Web site[2] in February /March 2007:

In February 2007 the Australia New Zealand Therapeutic Goods Authority (ANZTPA)[3] published on its Web site a 'Questions & Answers' page on the proposed regulation of blood, including blood products for therapeutic use.

Europe

Reported on the Web site for the **European Medicines Agency (EMEA)**[4] in February/March 2007 were:

- Effective 1 February 2007, the EMEA has adopted the guideline on dossier structure and content on marketing Authorisation Applications for influenza vaccines derived from strains with a pandemic potential for use outside of the core dossier context (EMEA/CHMP/VWP/263499/2006).

The **CHMP** (Committee for Medicinal Products for Human Use) have published their monthly report[5] from the February Plenary meeting held 19-22 February 2007.

Only one relevant guideline was prepared, reviewed or adopted by the various CHMP working parties during this review period. Document prepared by the Safety Working Party:

- Re-released draft Guideline on Specification Limits for Residues of Metal Catalysts (EMEA/CPMP/SWP/QWP/4446/00). Deadline for comments is 23 May 2007.

The **HMPC** (Committee on Herbal Medicinal Products) have published their monthly meeting report[6] for the meeting held 11 January 2007.

The CVMP (Committee for Veterinary Medicinal Products) report on their website[7] that the VICH steering committee has recommended for adoption by January 2008, the following guidelines:

- Revised VICH Topic GL3 – Guideline on Stability - Stability Testing of New Veterinary Substances and Medicinal Products

- Revised VICH Topic GL10 – Guideline on Impurities in New Veterinary Drug Substances

- Revised VICH Topic GL11 – Guideline on Impurities in New Veterinary Medicinal Products

The **European Directorate for the Quality of Medicines (EDQM)**[8] have published a Top Ten summary of the main deficiencies found in Applications for a Certificate of Suitability (CEP) for chemical purity. It is based upon first evaluation of 87 Applications up to July 2006.

No new information of significance has been published during this period by The European Council and Parliament, the Heads of Agencies or The European Commission DG Enterprise.

United Kingdom

MHRA have announced on their Web site[9] the publication of the 2007 Edition of Rules and Guidance for Pharmaceutical Manufacturers and Distributors (Orange Guide).

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This information was provided by Peter Hagger, Pharmaceutical Research Associates (UK).