This article reviews the complex chemical management challenges facing pharmaceutical manufacturers and offers guidelines and recommendations for choosing a software or Internet-based management system and its potential for integration across the production environment.

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A Prescription for Chemical Management: Beyond Compliance in 2002

by Mark Wysong

Introduction

These days, profits are hard to come by, no matter what the industry. Given the mounting regulations and complex issues affecting pharmaceutical companies, it's no surprise that many are seeking innovative ways to make themselves more profitable.[1] One profit strategy pharmaceutical companies should consider is a renewed focus on safety because the last thing most can afford right now is costly and avoidable OSHA fines - *Figure 1*.

In an industry that deals with so many chemicals in the development and manufacture of drugs, chemical management has become a key safety issue from both the employee health and government compliance perspectives.

Many elements factor into a comprehensive chemical management plan. Companies must have a way to comply with Superfund Amendments and Reauthorization Act (SARA) Title reporting requirements and state laws for chemical use. They must ensure that all employees are properly trained in the hazards and use of chemicals encountered on the job. This training needs to cover everything from proper storage information to personal protective equipment to be worn. In addition, companies should have an effective chemical emergency response plan. Sophisticated chemical management also encompasses integration of chemical tracking with purchasing, inventory control, and overall safety management practices.

One way some companies have chosen to address many of these chemical management issues is to adopt an electronic chemical management system that tracks Material Data Safety Sheets (MSDS) and organizes a company's chemical information.

Compliance for Profitability

The Hazard Communication Standard (HCS), also known as the "Right to Know Law," requires employers to provide chemical information and training about chemical hazards to all employees who may be exposed to hazardous chemicals on the job.[2] The law covers more than 35 million workers at more than 3.5 million sites across the country.

The primary way a company complies with the HCS is by carefully maintaining MSDS. These sheets list the physical and health hazards of a particular chemical, control measures such as ventilation requirements, and personal protective equipment required during use. An MSDS also contains vital emergency information, such as first aid measures and spill mitigation procedures. The trouble is, the companies that manufacture chemicals are not required to follow any specific format for the MSDS they provide to their customers. So MSDS formats, and the information contained therein, can and do vary widely. Furthermore, while MSDS information is not subject to any federal or state regulations, manufacturers who use or store hazardous chemicals are required, as previously mentioned, by federal law to have the MSDS documents on site.

Not surprisingly, it's a common complaint that the information contained on some MSDS is sometimes too technical (and therefore incomprehensible to most users) or too basic (filled with obvious or scant warnings). There also are concerns that the MSDS are too long - sometimes as long as 20 pages which makes finding the right information difficult in any situation and potentially fatal in an emergency.

Managing Chemicals through MSDS

Keeping track of chemicals in the workplace is clearly an important task facing pharmaceutical companies. Although maintaining MSDS information became a US regulatory requirement in 1983, some companies may not yet be in full compliance. A company that has an organized, accurate, and efficient MSDS distribution system is in a better position to ensure compliance with the law, as well as the highest degree of safety for its employees.

For companies that use only a small quantity of MSDS, an amount easily housed in one or two binders, a manual system may be more than satisfactory for their needs and would not re-

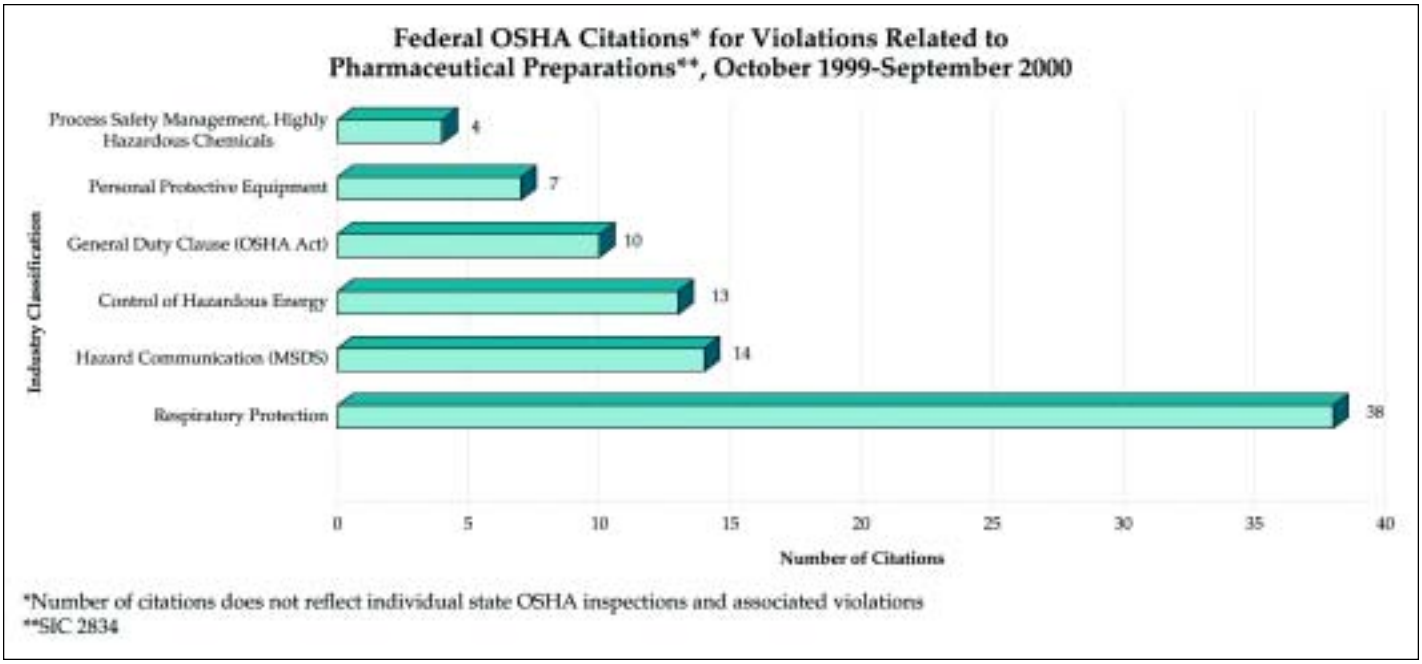

Figure 1. Federal level OSHA citations for violations in pharmaceutical preparation manufacturing, October 1999 to September 2000.

quire an investment in new software or hardware. For larger companies that deal with many chemicals; however, a manual system is at best, inconvenient. MSDS binders are often cumbersome volumes stuffed with hard copy documents. They're difficult to store, worse, they're even more difficult to keep current. Old MSDS must be replaced by hand, which is labor intensive, leaves room for error, and makes searchability a time-consuming chore. And, because they take up so much room, MSDS binders are usually stored away from work areas, so they're typically not close at hand in an emergency. Employees needing information including first aid procedures associated with a certain chemical must wade through pages, many of which may be out of date, incomplete or simply missing. The process could take hours, or in extreme cases, days. In addition, the reality of globalized manufacturing means with facilities sited worldwide, organizations routinely face communication challenges across languages and regulatory demands across countries.

For these larger pharmaceutical companies, a software or Internet-based MSDS management system can offer many benefits. It does typically take anywhere from two to six months to implement and will require an investment in equipment and training. But, once up and running, such a system allows MSDS information to be accessed from virtually any computer in the workplace. And, unlike hard-copy binders, storage isn't a problem. Searchability is another advantage. When using a subscriber-based system, users can log on to the database and search by worksite to determine which chemicals exist at each site. Or, they can search by chemical to find out which sites contain a certain chemical. Since many employees probably aren't familiar with the exact name of the chemical they're using, databases are often indexed by many key fields. This permits searching by chemical or generic names, or even the name of the manufacturer. Indeed, it's entirely possible for emergency response times to be reduced to two minutes.

Beth Donnerberg at Dolphin Software, a supplier of software and Internet-based MSDS systems, has seen the difference such a system can make for manufacturers, both in terms of streamlined processes and elimination of potential OSHA violations.

"I've worked with a number of pharmaceutical companies that had systems in place that were extremely antiquated and ineffective," said Donnerberg. "Dozens of three-ring binders sitting on shelves with MSDS that contained lots of duplication and outdated information. It was scary. And the companies themselves realized, as pressures mount to get products to market, the last thing they need is for a critical timeline to be thwarted because they can't retrieve an MSDS or worse yet are cited by OSHA for a safety violation."

Donnerberg cited other examples of how an electronically based system has saved companies time and money.

"One of the most dramatic results I've seen is in the time savings, not just for administrators, but employees," she explained. "With the hard copy system, it could take hours to look through the binders full of sheets, especially if the employee only knew the common name or a generic category. And, sometimes the sheets disappeared altogether."

According to Donnerberg, companies typically find that by changing to an electronic system, tasks that previously took a week's worth of data input can now be accomplished in 15 minutes.

"Time and again, companies expressed amazement at how the indexed computer system reduces the search to a matter of minutes," she said. "Where they had several employees managing their MSDS system, they now get the job done with one administrator, shifting the employees to other areas of the company. At that point, it's easy to do the math about how the system benefits the corporate bottom-line. A reduction in hours spent by one or more employees searching for MSDS can be added directly to savings in terms of both productivity and costs."

A customized software or Internet-based chemical management system also solves the problem of giving employees access to this pertinent information whether a company operates from single or multiple sites. Through centralized workstations, the Internet or an Intranet, employees have immediate access to vital MSDS information. Sophisticated systems

also will have advanced features including full MSDS administration, indexing and retrieval of key information, reports, labels, MSDS collections, attachments, location assignments, user-defined fields and more.

Choosing a Chemical Management Application

Moving from a manual MSDS system to a software or Internet-based system requires some homework. In the long run, it pays to know what to look for when choosing an MSDS management system provider. In fact, there are a number of providers on the Internet that offer "free" MSDS search services. However, these programs have significant limitations. Many have a very limited number of MSDS available or represent only a small number of chemical manufacturers. Free sites are slow to download information and may actually ask the user to provide them with updates, making the credibility of site data questionable. There is typically no training available and no opportunities for customization for your particular organizational needs.

A critical component to look for when choosing an MSDS software application or Internet-based system is its ability to access the most up-to-date chemical information. One of the main problems companies encounter is staying abreast of required and updated MSDS. Currently, there are more than two million MSDS available from more than 27,000 worldwide manufacturers. Because MSDS are constantly being revised by all those manufacturers, the system your company chooses should offer comprehensive updates. And a credible MSDS data services company should provide revision management including contacting chemical manufacturers on a regular basis to ensure the integrity of your data.

There are also a few data services companies that specialize in MSDS text conversion, in other words, translating hard-copy MSDS to electronic text and filing it in a database. On the one hand, this service can be a great relief to safety managers who don't have the time to convert hard-copy MSDS themselves. But some service companies attempt to cut costs by simply using a scanned image which shows a 30 percent failure rate when it comes to legibility instead of the higher quality text conversion which is 100 percent legible.

Look for a company with high standards for ensuring the accuracy of text conversion, such as verifying each text file character-by-character against the original document. And you will want to choose an MSDS system that permits searching by chemical or generic names. It also is helpful if MSDS can be retrieved through a text search for words or phrases anywhere within the body of the document.

In addition to these basic services, some companies can offer specialized services, such as customized secondary labeling of containers (the labels include manufacturer information and also the user's choice of key MSDS information), and emergency MSDS faxing to provide urgent care information on demand and translated in languages germane to the needs of multinational companies. Data services companies also can create completely customized software packages that assist with regulatory reporting activities such as those required under SARA. And, some companies offer modules that use data typically found on MSDS, such as ingredient names, and integrate them with inventory records.

Guidelines for Selection and Usability of a Chemical Management Application

- Web-based product - An MSDS system is supposed to enable employees to easily access information on chemicals in the workplace. A sophisticated software product will certainly do the trick, but easier still is the convenience of a Web-based system with the ability to limit program access to the appropriate personnel.
- A consistent procurement process - All chemicals, regardless of how they are purchased, should be cataloged through a consistent purchasing system. A method should be established to track purchased chemicals as part of the procurement process.
- Selective central management - A limited number of representatives within an organization should have access to the system for the purposes of changing the data. Updating should occur using secret passwords.
- Enterprise level of chemical detail - The MSDS system should be available at all of a company's locations and reflect consistency in data formatting, part numbers, measures of product and container tracking mechanisms.
- Comprehensive chemical tracking - The MSDS system should track all chemicals including those categorized as extremely hazardous substances (EHS), hazardous air pollutants (HAP) and SARA 313 regulated substances such as persistent bioaccumulative toxins (PBT). Additional regulatory concerns should be addressable according to the region and business practices of the company.
- Easy cataloging procedure - The system should provide a method for assigning a chemical container with a barcode that includes unique container identification, the part number of the substance, its MSDS data and the expiration date, as well as other important cataloging features. Technology exists that enables the barcodes to be scanned by a device that is similar in appearance and function to the Palm Pilot.™

Inventory Integration

Such integration is crucial in this industry where the task of keeping track of inventory has become daunting due to the increased number of materials that must be managed.[3] Given that there are anywhere from 10,000 to 40,000 chemical substances onsite at some workplaces, software or Internet-based MSDS systems solve the challenge of keeping employees informed about where a particular chemical is stored, its quantity, and when it was last used.

Without an integrated system, there exists great potential for data gaps in chemical inventory management. Purchase cards (or P-cards) contribute to one of the most common data gaps. These accounting tickets, which can be approved for use by virtually anyone in a company, are used to purchase a variety of items including chemicals. The procedures for using P-cards often do not provide a mechanism to track the details of a purchase, such as the chemical information of the product purchased. That level of information is often considered incon-

sequential, unnecessary, or too cumbersome to incorporate into P-card procedures.

Another concern surrounding chemical management is the standardization of purchasing information across all divisions of a company. Ideally, the goal of the company is to refer to the same product using the same internal identification (item or part number) whenever and wherever that product is purchased. But consider a company with offices on the East Coast and the West Coast of the United States. Both divisions of the company might use the same chemicals, yet different people can be purchasing these chemicals from different vendors. The individuals involved may refer to the same chemical using different product names, resulting in different part numbers for the same product. The scope of the problem becomes nearly insurmountable when compounded across an enterprise in which thousands of chemicals are being purchased by dozens of purchasing personnel.

The methods used for measuring amounts of chemicals purchased represent another data gap associated with chemical management. Where ambiguous measures such as "each," "box," and "tote" are used to account for amounts of chemicals purchased, methods to convert to a scientific measure such as "gallon," "pound," or "liter" are often not enforced.

In some environments, the challenges posed by P-cards and units of measure are compounded by the necessity to track individual containers or lots. An efficient tracking system would allow every chemical substance that is purchased by a company to be tracked from the time it enters a facility until the time it is used. Due to the time requirements for setting up a tracking system, most of the world is not ready to implement this type of mechanism. However, some laboratories have taken it upon themselves to implement systems for container tracking. Laboratories regulated by the US Food and Drug Administration (FDA) are likely candidates for the use of a container tracking system.

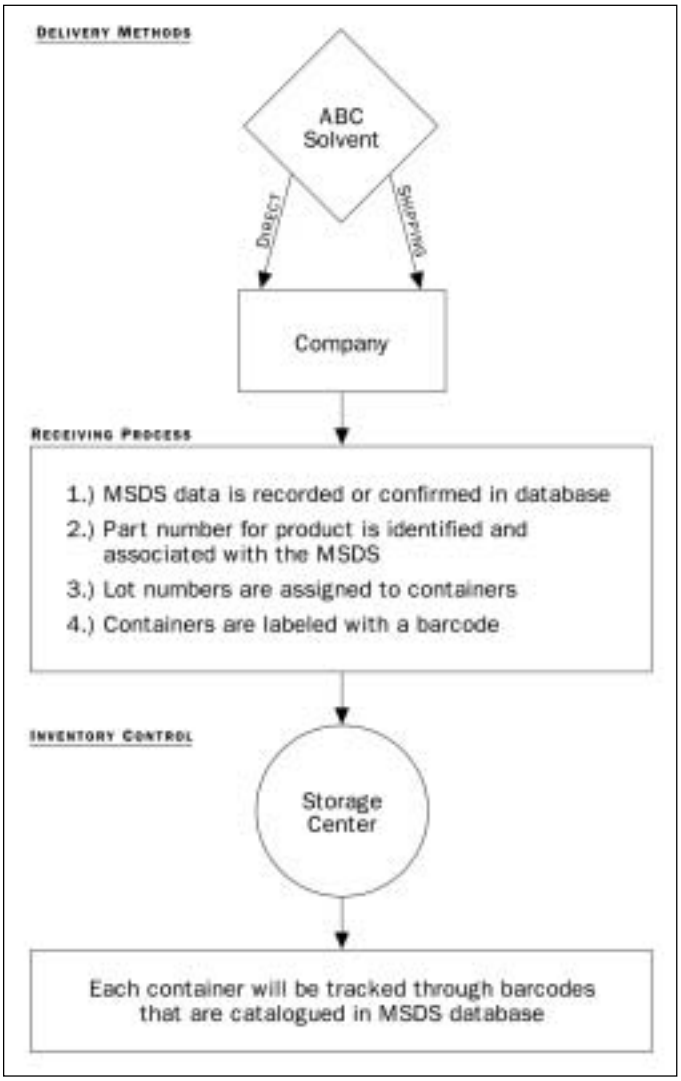

Figure 2. Flowchart of the integrated ERP approach with a computerized MSDS system.

Enterprise Resource Planning and Chemical Management

For the past six or seven years, some of our country's largest companies have been using an Enterprise Resource Planning (ERP) approach to materials management that combines container (or lot) tracking with a parts center. Under this type of management, containers are assigned lot numbers and cataloged according to their composition and expiration dates. This addresses the needs of the purchasing and hazardous materials (hazmat) departments of a company, and facilitates the ability to respond to specific regulatory concerns.

Tracking chemicals by using a standardized part number is an obvious approach to ERP. This calls for assigning the same part number to substances with identical chemical compositions and separating them from products that differ chemically by using other part numbers. Under this system, part numbers are consistent throughout a company. When a chemical is purchased, the appropriate part number is used to identify the product and a lot number is assigned to each container. A quantity, expiration date (as applicable) and the storage location define every lot. The part number and container tracking occurs on an enterprise or company wide level. This means every branch of a company has current information on the quantity and whereabouts of chemicals and containers within its facilities.

Incorporating a software or Internet-based MSDS system with an ERP process can be a highly effective method for chemical management under these conditions – *Figure 2*. As previously mentioned, some companies offer products to help simplify the part numbering and container tracking process by using barcoding.[4] The inventory barcode system works much like the scanners at a department or grocery store. Using either a stationary or hand-held scanner, scanned data and inventory levels can be uploaded at once from centralized docking stations. Data to be scanned can be as simple as container size and content measurements or include all the chemical ingredients in a product. User identified fields also can be customized for internal requirements such as electronic signatures, computer validation, and so on.

However, if a company's MSDS and procurement systems are currently incompatible, a lot of legwork will need to occur before an effective system can be installed. Of course, once the work is done, the time saved in the future will far outweigh the time invested in the implementation of the solution.

Consider this example of a chemical substance and how an ERP process combined with a software or Internet-based MSDS system has the potential to benefit a company.

- ABC Solvent is delivered to a company in one of three ways: a P-card used by an employee at a store; a direct delivery

from a vendor; or a regular delivery through shipping and receiving.

- Upon receipt of the product, the MSDS data is recorded or confirmed.
- The part number for the product is identified and associated with the MSDS.
- Lot numbers are assigned to the containers; their expiration dates and quantities are noted.
- Each container is labeled with a barcode that reflects its lot number, chemical composition, expiration date, and hazardous information according to the company's labeling standard.

The solvent is then transferred to a storage center, a manufacturing area, or a lab. From that point forward, each container will be tracked (using the barcodes) until the product is used or until the expiration date has been exceeded and the product has been discarded.

Implementation and Training

Once a system is selected, implementation, data conversion, application set up, and training can take up to two months. While training can typically begin immediately, there are variables such as number of sites, quantity of MSDS and how data is provided (hard copy or CD ROM files) that have an impact on the length of time to convert a system.

Take note that even if you select a comprehensive MSDS application that allows inventory integration and other process streamlining features, if it isn't easy to use, it's as useless as cumbersome notebooks or outmoded software. For this reason, many data services companies offer ongoing personnel training and support. MSDS training sessions can be regularly incorporated into safety meetings. Several data services companies offer a software module that allows administrators to monitor personnel training. And, the software can be used to create a database of important information about the company's safety training classes, including the schedule of classes and employees' test scores.

Conclusion

Because computerized MSDS systems are easy to access, employees who formerly might not have bothered to look up MSDS information now tend to keep themselves informed. Using software or a Web-based system also makes the MSDS more versatile, allowing other useful information, such as state-specific or local regulations, to be attached to the electronic MSDS file.

However, the real test comes when an employee faces a contamination situation. At the moment when chemicals may have compromised the environment and an employee's safety, the ability to quickly retrieve MSDS information allows an immediate determination about the level of hazard and appropriate first aid and clean up measures.

Experts believe that for pharmaceutical companies all across the nation, MSDS retrieval online has become the best method to ensure employee safety and regulatory compliance. Moreover, it allows pharmaceutical manufacturers to manage chemicals, not just data sheets. Most importantly, companies who adopt such systems are those who will maximize their ability to be front-runners in productivity and competitiveness now and for the future.

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About the Author

Mark Wysong is the Founder and CEO of Dolphin Software, a leader in hazardous chemical information management. When Wysong started the company in 1991, automating hazard communication was in its infancy. Dolphin's influence on the industry has resulted in chemical management programs across the world in such varied industries as pharmaceuticals, aerospace, engineering, healthcare, forest products, and government. Wysong received a BS from Wayland Baptist College and a MS in limnology, or fresh water ecology, from Baylor University. He is a seasoned speaker and media personality on chemical safety issues, and he has authored numerous articles on worker safety and MSDS topics for many national publications.

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Perm-Selective Chitosan-Alginate Hybrid Microcapsules for Enzyme Immobilization Technology

by Ehab Taqieddin, Carolyn Lee, and Mansoor Amiji

Hybrid double-layered microcapsules composed of calcium-cross-linked alginate core coated with chitosan were made. Enzyme loading and activity studies were performed. The enzyme was shown to retain activity after loading into the final microcapsule system.

This article was the winning poster in the 2001 ISPE Boston Chapter Student Poster Contest. It was presented at the poster contest at the 2001 ISPE Annual Meeting held in Las Vegas.

Introduction

Enzymes are biological catalysts that serve different functions in the body and are also useful in different industrial processes.[1] Being protein in nature, enzymes are generally not very stable in aqueous environments and cannot withstand changes in temperature, pH, ionic strength, and other perturbing conditions. Enzyme immobilization, therefore, has emerged as a promising solution to enhance the stability of enzymes and improve the separation from complex reaction systems.[2,3] The basic idea behind enzyme immobilization is either to covalently attach or entrap the protein in a support material, which prevents the enzyme from leaving while allowing substrates, products, and co-factors to permeate through.[4] When an immobilized enzyme is used *in vivo*, the support material must be biocompatible and the encapsulated system must be able to prevent immune recognition of the protein. For *in vitro* applications, the enzyme immobilization system must be mild as not to damage the fragile protein.

Since immobilized enzymes are generally more stable, there are many potential applications that range from chemical synthesis to biotechnology and medicine.[3, 5-7] For instance, immobilized enzyme systems have been used for the conversion of starch into glucose, manufacturing of various pharmaceuticals, biosensors, and treatment of enzyme deficiencies.[8] Advances in protein isolation, chemical analysis, and polymer science have extended the applications of the immobilized systems. Enzyme immobilized microcapsules are common design systems that provide a large surface area for diffusion of substrate and product. The inner core where the enzyme is present could be either liquid or solid, depending on the polymer used and the method of preparation. Liquid core systems are preferred for cellular immobilization since they furnish more space for the cells to grow. In addition, the liquid core is better in terms of mass transfer of nutrients and products. Solid core microcapsules have the advantage of having better mechanical strength and durability as compared to liquid core capsules.

Based on the intended application, there are many different types of polymers used for enzyme immobilization - *Table 1*. When the enzyme is covalently bound to the polymer matrix, the material should have functional groups for reaction. In case of physical immobilization, the polymer system is usually a hydrogel with enzyme entrapped in the swollen matrix.[3,9] Calcium alginate is commonly used for enzyme immobilization since the hydrogel formation occurs under very mild conditions. In addition, calcium alginate gel is biocompatible and has good mechanical strength for many different applications. However, the disintegration of a cross-linked calcium-alginate system in physiological media by phosphate ions has hampered its large-scale application.[10] Chitosan is another promising candidate for enzyme immobilization. It is obtained from alkaline hydrolysis of chitin, and thus, abundantly available from renewable resource. Chitosan is biocompatible and has been used in many applications includ-

*Table A. Examples of polymers used for preparation of microcapsules.**

Inner Polymer	External Polymer	Gelling Agent (Cross-linker)
Alginate	Polyvinylamine	Calcium
Chitosan	Alginate	Calcium
Carboxymethylcellulose	Chiosan	---
Alginate	Protamine	---
Chondroitin Sulfate A	Spermine	---

*Adapted from reference 12.

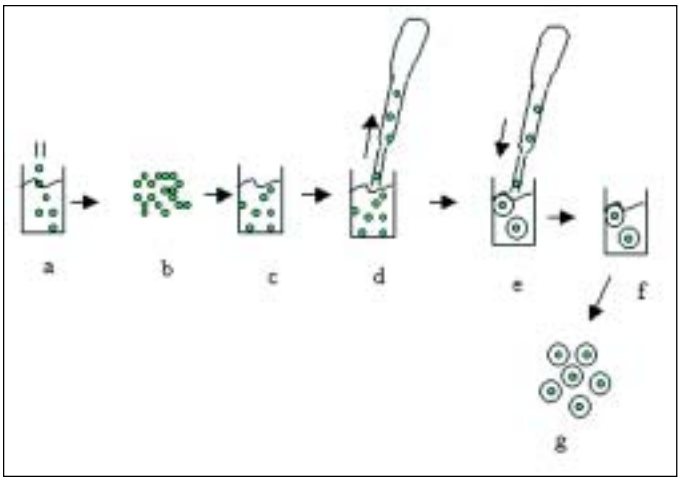

Figure 1. Schematic diagram illustrating the method of preparation of chitosan-alginate hybrid microcapsules.

ing drug delivery systems.[11] One disadvantage of chitosan is its limited solubility in water. Chitosan requires dilute acidic solutions for dissolution. The low pH of chitosan solution tends to denature most proteins and cells, and as such, is not a suitable material for immobilization.

In order to develop an immobilization system that can entrap the enzyme under mild conditions, improve the stability of the enzyme, and control the permeability, we have designed chitosan-alginate, double-layered hybrid microcapsules.

Materials and Methods

Materials

Chitosan, with an average molecular weight of 760kDa and a degree of deacetylation of 87% as well as sodium alginate (Protanal® LF 20/200), were obtained from Pronova Biopolymers (Raymond, WA). Calcium chloride and sodium tripolyphosphate were purchased from Sigma Chemical Company (St. Louis, MO). Horseradish peroxidase, o-phenylenediamine, and hydrogen peroxide were purchased from ICN Biomedicals Inc. (Aurora, OH). Amplex Red® was purchased from Molecular Probes (Eugene, OR).

Preparation of Chitosan-Alginate Hybrid Microcapsules

Chitosan solution was prepared by dissolving the polymer in 0.1 M acetic acid to make 1.0% (w/v) concentration. Two grams of sodium alginate was dissolved in 100-ml distilled water and mixed for approximately four hours. The hybrid microcapsules were prepared according to the scheme in Figure 1. First, calcium alginate beads were prepared by dropping the alginate solution through a needle into a 0.34 M calcium chloride solution (a). After five minutes of cross-linking, the beads were taken out and washed (b). The beads were then suspended in the chitosan solution (c), the hybrid microcapsules were formed by taking the beads into a specially modified plastic pipette with a slight suction (d), and dropping it into 3% w/v sodium tripolyphosphate solution (e). The negatively charged tripolyphosphate reacts with the positively charged amine residues of chitosan to form ionic cross-links. In addition, the tripolyphosphate also diffuses into the calcium alginate and chelates the calcium ion to liquify the core. The microcapsules were kept in the cross-linking solution for 90 minutes (f) and washed with distilled water (g).

Equilibrium Water Uptake

The extent of Equilibrium Water Uptake (EWU) by hydrogels is inversely proportional to the mechanical strength.[13] For EWU studies, the control and hybrid double-layered microcapsules were incubated in deionized distilled water and allowed to hydrate for 1 hour at room temperature. EWU was determined according to the following equation:

$$EWU\ (\%) = [(W_s - W_d)/W_s] \times 100$$

where W_d is the weight of the dry microcapsules and W_s is the weight of the swollen microcapsules.

Enzyme Immobilization and Activity Studies

Horseradish Peroxidase (HRP) was mixed with sodium alginate solution by continuous stirring and the cross-linked beads were formed as previously described. Enzyme-containing calcium alginate beads were further treated with chitosan solution and the double-layered microcapsules with HRP were formed. For determination of loading levels, the activity of immobilized HRP was examined using o-phenylenediamine as a substrate. The amount loaded was then determined from the activity by comparing to a previously constructed standard curve. In addition, for qualitative evaluation of enzymatic activity in the immobilized system, a substrate, Amplex Red® was used. Amplex Red® is a non-fluorogenic compound that is converted to a pink-colored fluorescent product by HRP.

Results and Discussion

Scanning electron micrograph of chitosan-alginate hybrid microcapsule (Figure 2) shows a highly porous alginate core that is uniformly surrounded by the perm-selective chitosan layer. Cross-linking the chitosan layer with tripolyphosphate liquefies the alginate core by chelating the calcium ions. EWU studies showed that these microcapsules were able to imbibe up to 80% water at equilibrium. There was a slight difference between the water uptake of the plain chitosan microcapsules and the hybrid chitosan-alginate microcapsules.

About 0.26 units/microcapsule (capacity) and 100% (efficiency) of HRP was loaded in the alginate core after cross-linking with calcium chloride. The loss was either due to the release of the enzyme during the cross-linking process or partial enzyme inactivation upon loading. Enzyme activity studies showed that there was a diffusion lag time of about

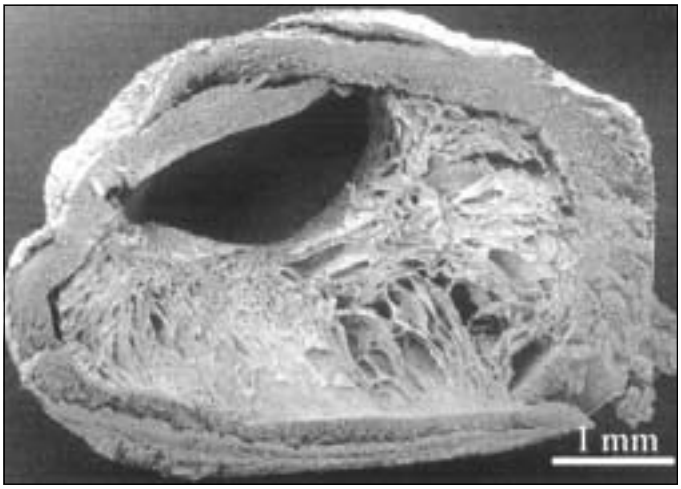

Figure 2. Scanning electron micrograph of the cross-section of a freeze-dried chitosan-alginate hybrid microcapsule. Original magnification was 40X.

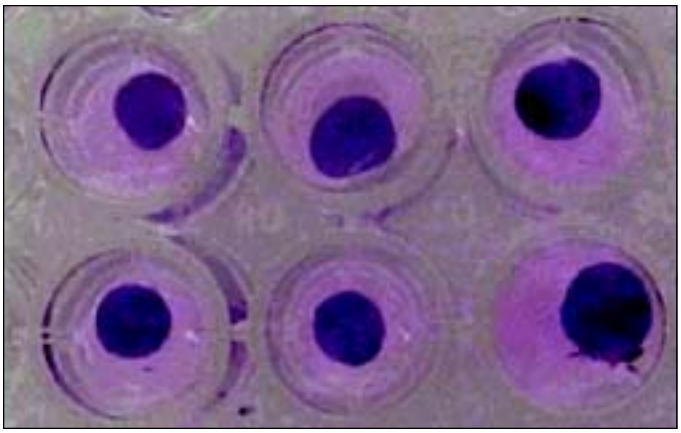

Figure 3. Determination of enzymatic activity of immobilized Horseradish Peroxidase (HRP) with Amplex Red® reagent.

seven minutes before the substrate could be converted to product. This lag time was attributed to the diffusional barrier created by the chitosan layer. Figure 3 shows the catalytic activity of immobilized HRP with Amplex Red® after 30 minutes at room temperature.

Conclusion

The chitosan-alginate hybrid microcapsules were designed to meet the criteria specified for an immobilized system. These systems retained the enzyme in the core, allowed for the perfusion of the substrate and the product, and most importantly, retained the activity of the enzyme. Such a hybrid system provides many advantages over the use of chitosan or alginate alone for enzyme immobilization. In addition to providing a selective permeable layer, chitosan surface can be modified to improve biocompatibility for *in vivo* applications. The liquefaction of the alginate inside the chitosan layer plays an important role in improving the mass transfer of substrates and products. Overall, the hybrid microcapsules design would be beneficial for variety of different applications of immobilized enzymes.

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This article discusses the effect of thermal cycling on the stem seal and seats in ball valves, used extensively in utility systems, and the seal in sanitary clamp-type fittings used throughout both the process and the utility systems. It discusses valve and fitting design improvements in seal containment and the control of the loads applied to the seals both during initial make-up and thermal cycling.

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The Effect of Thermal Cycling on Seals in Ball Valves and Clamp-Type Fittings

by Dave Simko

Introduction

Valves and fittings account for the largest number of seals used in a bioprocessing system. In an individual processing suite, the seals that make up sanitary connections to tanks and vessels, valve ends and upper works, and tubular fittings may number in the hundreds. Throughout an entire facility, the number may be in the thousands. Reliability of the seals is a function of design, quality, material selection, and installation—all considerations made before the valve or fitting is subjected to the actual service. After the components are in service, a major factor impacting the reliability of the seals is thermal cycling.

The Bioprocessing System

Fermentation is the basis of a bioprocess and includes both microbial and mammalian cell culturing. Although similar, each has some unique requirements. Microbial fermentation usually refers to large-scale cultivation of living microorganisms or single-cell creatures. Mammalian cell culturing involves growing complex cells that come from the organs and tissues of animals. They are much more fragile and are more difficult to grow.

A complete system for manufacturing an active ingredient for a biopharmaceutical product is made up of tanks and vessels, pumps, centrifuges, and other rotating equipment, as well as various kinds of operation-specific equipment. Fluids are transferred from device to device by means of tubing, pipe, and hose. Fittings connect all parts of the system together, and valves control the fluid within the system. The process system is supported by certain clean utility services, such as pure water, sterile air, and steam for sterilization. The seals in all of the equipment and subsystems and the clean utilities are critical to the reliable operation of the complete system.

The system consists of upstream preparation, fermentation, harvest and recovery, and purification and refining. Upstream preparation includes the preparation of media, the substrate and nutrient mixture that will be the environment in which the organisms will live and grow; buffering solutions, used to control the all-important pH; and inoculum generation, preparation of the cultures that will be placed in the fermenter to begin the process. The fermenter/bioreactor provides a contained and protected, controlled, homogeneous environment

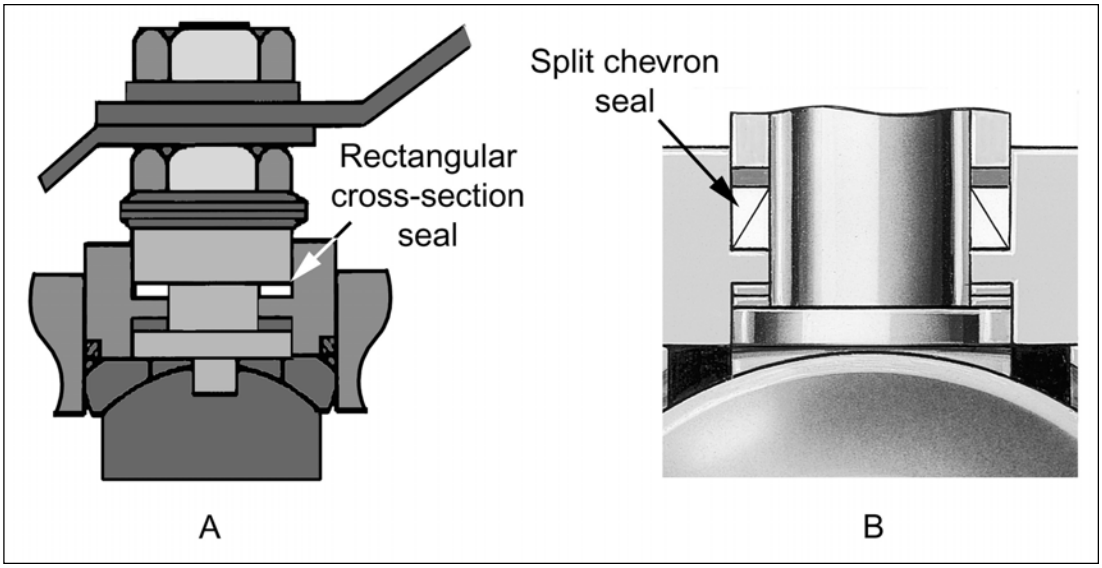

Figure 1A and 1B. Figure 1A shows a ball valve stem seal that consists of a ring of PTFE with a rectangular cross-section. Figure 1B illustrates the live-loaded, 2-piece chevron stem packing, which requires less operating torque, improves performance, and compensates for stem wear.

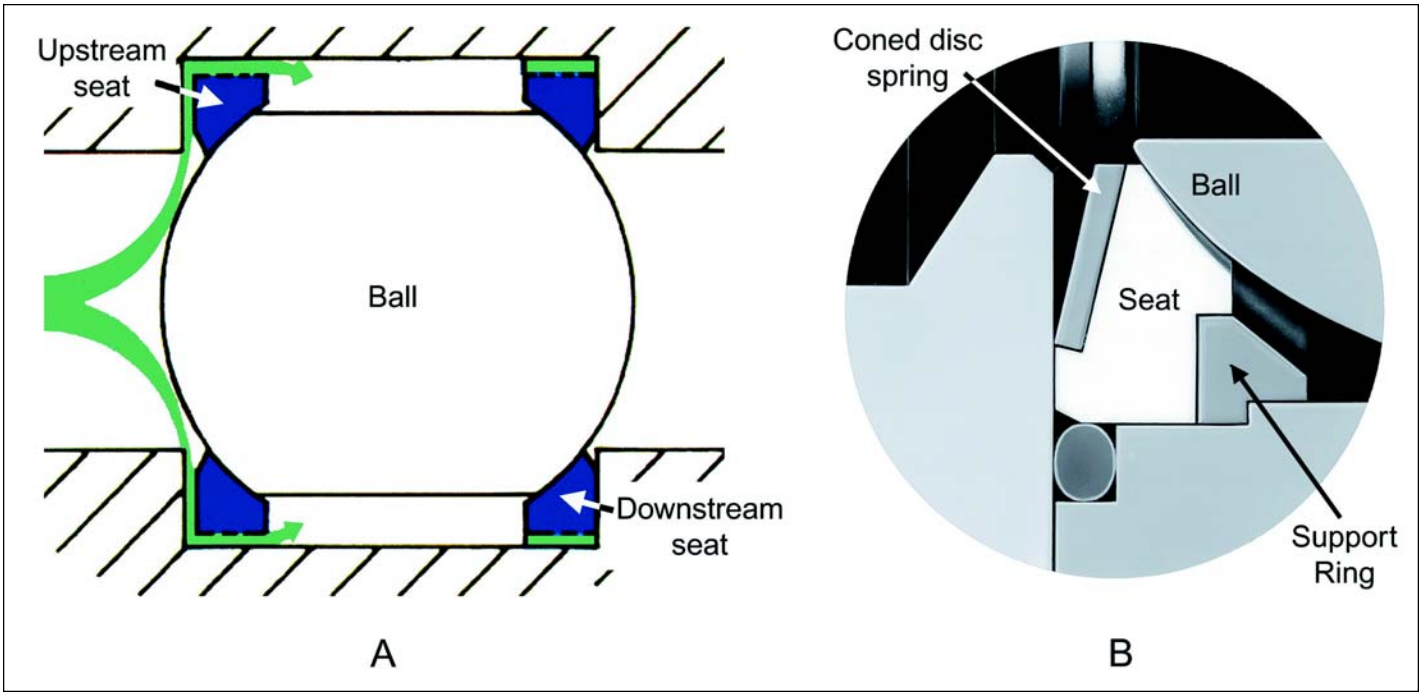

Figure 2A and 2B. The ball valve seat in Figure 2A is not contained. The coned-disc, spring-loaded seat, shown in Figure 2B, ensures a leak-tight seal on both the upstream and downstream sides of the ball.

in which the microorganisms and mammalian cells reproduce and grow. When the fermentation process is complete, the broth is harvested and sent through a recovery process. If the product is extracellular, the cells are removed from the broth. If intracellular, the cells are disrupted and the debris removed. Purification is the final downstream processing after recovery. During purification, the desired product is separated from the broth using a combination of methods, including precipitation, filtration, and chromatography, refined, and concentrated.

After use, each piece of equipment and each run of conduit through which fluid had been transferred must be drained, cleaned, and sterilized in preparation for the next production run. Valves and fittings can have a direct effect on how effective the cleaning and sterilization process will be. These components must be:

- completely drainable, leaving no entrapment areas or puddles where contaminants can accumulate
- cleanable using current Clean-In-Place (CIP) methods
- sterilizable, allowing all internal surfaces to be in contact with steam
- able to withstand the thermal cycling of repeated sterilization processes

Seals must be leak-tight throughout the entire process. Leaks cannot be tolerated. Leaks out of the system can result in the release of potentially hazardous materials, and leaks into the system can destroy the sterile condition inside the system. Internal leaks can compromise the process cleanliness, the sterile environment, and instrumentation and control procedures.

Clean Utilities

All of the bioprocessing system operations are supported by clean utility services, including pure water, clean steam, and sterile air. These services are supplied to the various pieces of equipment via extensive piping systems, which are connected by welding or sanitary fittings. Diaphragm valves are used; however, the diaphragm may have limited life in steam service, especially where the valves are actuated frequently. Ball valves are an accepted industry standard for isolation purposes on continuous pure/clean steam service (The American Society of Mechanical Engineers standard, ASME BPE 2002 Bioprocessing Equipment, an American National Standard).

Generally, the service parameters—pressure, temperature, and flow— are not severe in these systems. The most difficult condition valves and fittings must withstand is thermal cycling. Thermal cycling impacts the durability of the plastic and elastomer seal materials and is a common cause of leaks.

Ball Valves

Ball valves have seals at the stem, seats, body, and at the connection into the system. The body seals are static seals, which are made-up when the valve is assembled, and are not required to be cycled mechanically during service. Adequately contained, body seals normally can withstand thermal cycling without leakage, as long as the seal material is not degraded during the process. If the manufacturers' instructions are followed during maintenance, body seals should not pose a leakage problem.

Construction personnel or technicians install the ball valves into systems when they are built or maintained. The end connections on the valves use the same kinds of fittings used to assemble the complete system and connect all the parts together. Those connections will be discussed in the section on sanitary fittings.

The critical seals in ball valves are at the stem and seat and are part of the basic design of the valve. They are dynamic seals and must retain leak-tight performance during and after both mechanical and thermal cycling.

Stem Seals

Stem seals are intended to prevent leaks into or out of containment. Leaks are driven by pressure and proceed from a high-

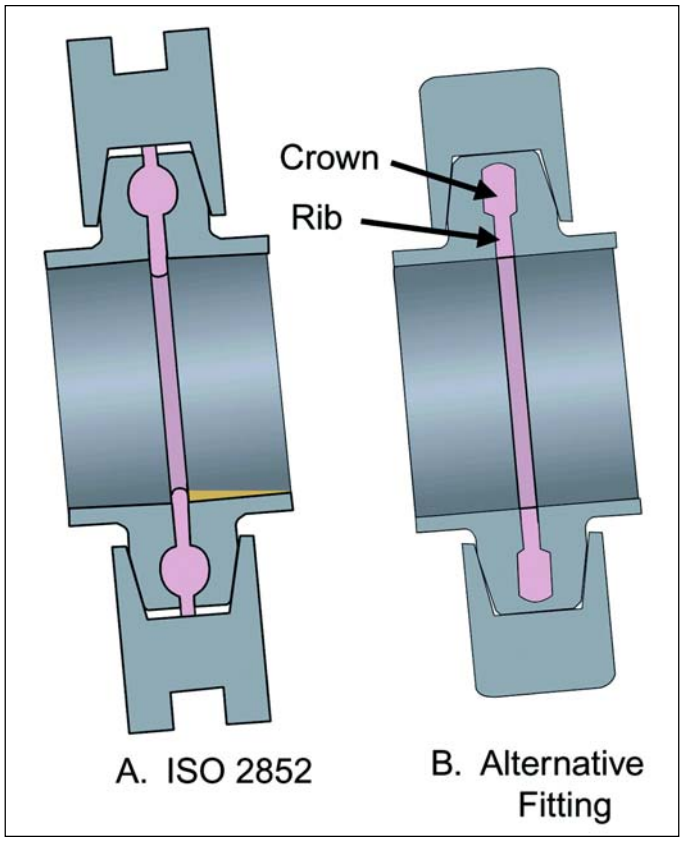

Figure 3A and 3B. In Figure 3A, the gasket material in an ISO 2852 fitting extrudes into the bore of the tubing or pipe, creating a dam in the flow path of the lines, which are pitched to facilitate draining. In Figure 3B, gasket extrusion is controlled to permit a small amount of extrusion into the bore of the fitting, creating a stable bore-line seal and avoiding undesirable concavity at the seal point.

pressure region to a low-pressure region. In pressurized clean utility systems, leakage of pure water or sterile air into the surrounding environment normally will not be hazardous; however, it can be expensive in terms of lost fluids and clean up. Leakage of pure steam out of the system can present a safety issue as well as an expense. Leakage into the steam system creates an even worse situation.

For example, clean steam is used for sterilization. After the necessary temperatures are reached, stabilized, and held for the prescribed length of time, the equipment or system is cooled. During cool down, a vacuum is created inside, and if the stem seals in ball valves used for isolation have failed, contaminating microorganisms may be drawn into the system.

Generally, ball valve stem seals consist of a ring of PolyTetraFluoroethylene (PTFE) having a square or rectangular cross-section and are contained on the Outside Diameter (OD) by the packing bore wall, on the Inside Diameter (ID) by the valve stem, and on the top and bottom by washer-shaped glands - *Figure 1a*. Most manufacturers choose PTFE for stem seals. It is relatively easy to deform the material to make an initial seal. However, it can cold flow or continue to deform under load—a condition which worsens with increasing temperature. Because PTFE has no "memory," once it is deformed under load, it does not return to its original shape when the load is removed. The seal is made by deforming the seal ring by applying sufficient force through a packing nut to deform the material inward against the stem and outward against the packing bore.

It is necessary to fully encapsulate the PTFE seal material on all surfaces with metal—the packing bore, valve stem, and glands—as described. The clearance between the gland ID and the valve stem OD should be an absolute minimum. Otherwise, during thermal cycling, when the temperature of the valve is increased from ambient up to the sterilization point and back down, the material can migrate or cold flow out of the seal area, eventually loosening the seal. In addition, the stem seal must maintain its integrity during the rotation of the stem within the PTFE seal member. Surface finish on the valve stem is important in terms of reducing wear on the inside diameter of the seal. ASME BPE 2002 addresses requirements for rotating valve stem seals, but does not specify surface finish requirements for the stem. The metal surface of the stem will have a certain level of roughness in the form of "peaks and valleys" from the machining operations. Under load and with thermal cycling, the PTFE seal material cold flows into the valleys. Then, when the valve is actuated, the small amounts of material in the valleys are sheared off and migrate out of the seal area. As the valve is cycled, more material is removed, the initial load that made up the seal is reduced, and the seal becomes loose.

Both of these situations result in rapid wear of the seal, leading to potential leakage. The degree of encapsulation of the PTFE seal in various ball valve designs and the manufactured surface finish on the stems in valves from different manufacturers impact how quickly stem seal failure might occur—in many cases, after only a few thermal cycles. If suitable head pressure is not maintained in the system or equipment during cool down from sterilization temperatures, unwanted microorganisms can be drawn in and destroy the sterile condition. Although pressurizing with sterile air can help avoid this situation, these microorganisms can still migrate across the loosened stem seal and contaminate the process.

General improvements to ball valve stem seal reliability can be accomplished by improving the containment, or encapsulation, of the seal member and by improving the seal surface on the stem during manufacture. Further improvements in seal reliability have been made by improving the typical configuration of the seal member and by adding a live-loading mechanism. Live-loading means that as the stem seal wears, sufficient load is consistently applied to maintain the seal.

One approach to live-loading uses a seal ring with a two-piece split chevron configuration (Figure 1b), rather than the typical one-piece square or rectangular cross-section. The two angled, conical pieces of the chevron create a wedging action to achieve a seal against both the packing bore and the stem. The force required to initially make-up this seal is lower than the force needed to make a seal with a solid, one-piece packing. A group of conical disc springs placed on top of the seal member provide the live-loading force and compensate for expansion and contraction during thermal cycling. As the seal wears during normal use, the springs continually "retighten" the seal, ensuring its integrity and reliability over a longer service life.

Seat Seals

Ball valve seats are also dynamic seals which function as the valve is cycled open and closed. Most ball valves are designed with floating balls. That is, when the valve is in the closed position, the ball is free to move axially toward the downstream seat under the action of upstream pressure. In floating ball designs, the upstream pressure is normally required to affect and maintain shutoff. ASME BPE 2002 specifically

Continued on page 36

requires that ball valve closure members (seats) must not be pressure dependent. In utility systems, there are applications where upstream pressure isn't adequate to achieve the required level of leak-tight shut-off.

Seats in most ball valves also are made from PTFE, and therefore, have similar requirements as the stem seal. For example, the same kinds of requirements for surface finish on the seal surface, in this case the ball, and containment of the PTFE seal member, in this case the seat, apply. Generally, surface finish on the ball is not a problem. Most manufacturers use spherically ground balls, and unless the surface is somehow damaged, the surfaces are satisfactory. The seats, however, can be a problem. The shape of the seat in most ball valves is a ring, generally a square or rectangular cross-section, with the surface facing the ball contoured to mate with it – *Figure 2a*. In most designs, the seat is not contained on the inside or outside diameters, leaving plenty of room for the seal member to cold flow under normal loads or extrude under higher loads. As long as there is sufficient upstream pressure, the valves should continue to function. However, at some point, the seats can become so distorted that shut-off cannot be achieved and internal seat leakage is a possibility. The comments regarding both thermal and mechanical cycling also apply, though thermal cycling represents the larger problem. With the outside and inside diameters of the seal member unconstrained, the downstream seat can be permanently deformed, allowing the ball to move further and further into the downstream seat and away from the upstream seat. If the upstream seat is not also sealed against the ball, steam can condense behind the ball. When cooled, contamination can build up. The downstream seat may become sufficiently distorted such that in the open position, where the ball is not free to float, the ball may not be in contact with that seat. This situation creates a path to permit the contamination to be drawn into the process stream.

As with the stem seal, containment of the seat is important in order to resist the possible distortion of the seat that can be caused by temperature and pressure. In addition, live loading the seat provides some real improvements in both downstream and upstream sealing on the ball. Live loading the seats with conical disc springs ensures that the seats maintain contact with the surface of the ball at all times, making a leak-tight seal on both the upstream and downstream sides of the ball - *Figure 2b*. With the valve in the open position, a null point is established, and both the upstream and downstream seats are sealed against the ball. In the closed position, as the backpressure is increased, the ball will move toward the downstream seat. During this action, the conical disc spring supporting the seat flexes and permits the seat to move without distortion, while maintaining the seal against the ball. In this arrangement, the seats do not require backpressure for leak-tight shut-off, so the valves may be used effectively in low pressure and mild vacuum service. The live-loaded seats compensate for expansion and contraction of the components during thermal cycling. This compensating action resists the potential for overloading the seats and causing the severe distortion that leads to internal leakage across the seat.

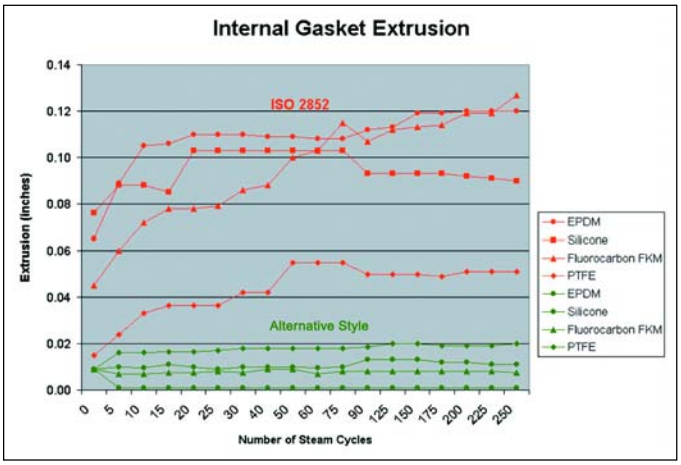

Figure 4. This graph highlights the results of a thermal cycling test conducted on an ISO 2852 fitting and an alternative-style fitting.

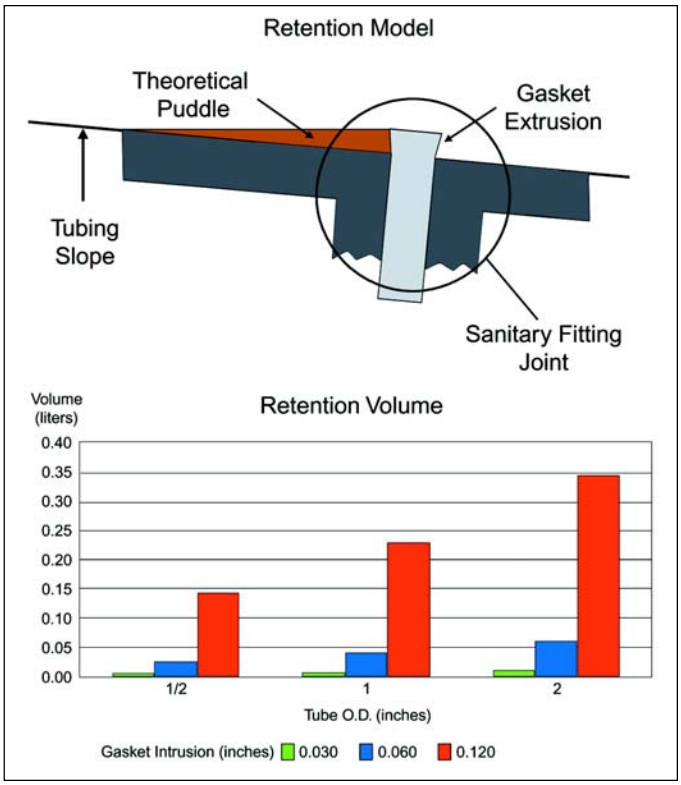

Figure 5. This model represents the puddle that could be formed behind the extruded dam in an ISO 2852 fitting. Flow tests confirmed that the model is valid.

Sanitary Connections

As mentioned, both the process (hygienic) and clean utility systems are connected by welding or sanitary connections. If the connections are intended to be permanent and not meant to be made and broken during the intended service life of the system or equipment, automatic orbital welding may be used to make consistent, high-quality welds.

When the connections are to be repeatedly made and broken, gasket-sealed, clamp-type sanitary fittings are usually employed. The most often selected type is the ISO 2852. The fitting consists of four components—two flanged ferrules, which are to be welded to the required lengths of thin-walled tubing, thin-walled tubular shapes, or other components; an elastomeric or plastic gasket located between the flanged faces of the two ferrules; and a clamp to hold the connection together - *Figure 3a*.

As with the ball valve stem seals and seats, containment of the seal member and control of the loads on that member, both during make-up and in operation, are very important considerations. A seal which does not extend into the inside diameter of the tubing or pipe at the seal point is referred to as a bore-line seal and represents the ideal condition after make-up of

the fitting. The standard, ASME BPE 2002, requires that the gasket in a made-up sanitary fitting should be flush with the bore of the tubing or pipe. However, the gasket seal in an ISO 2852 fitting is not fully contained and supported. As the clamp is tightened during make-up, the gasket is free to extrude radially outward and inward. Installation methods and techniques vary from installer to installer and company to company. The amount of extrusion will vary with how tight an installer tightens the clamp. Since the compression on the gasket is not controlled, over-tightening is possible. Outward extrusion doesn't create much of a problem, but the inward extrusion can. As the gasket material extrudes into the bore of the tubing or pipe, it creates a dam in the flow path of the lines, which are pitched to facilitate draining. The dam can create problems in pure water, CIP, and steam sterilization systems, making cleaning, draining, and sterilization more difficult. Also, it can result in product holdup in the processing system during harvest, recovery, and downstream purification and refining.

Tests were conducted to determine the amount of extrusion that is possible at installation and to determine the impact of thermal cycling on the completed fitting assembly. Manifolds consisting of five 1 1/2 in. sanitary fittings, each separated with a short length of 1 1/2 in. x 0.065 in. tubing, were built. Ethylene-Propylene Diene Monomer (EPDM), silicone, fluorocarbon FKM, and Polytetrafluoroethylene (PTFE) gaskets were used, each in a separate manifold. Clamps were tightened to the maximum possible by hand. Prior to thermal testing, all pertinent dimensions were recorded, including the gasket intrusion into the bore of the tubing. The assemblies were vacuum helium leak tested to confirm that a proper seal was made. The thermal test, intended to simulate a sterilization process, consisted of heating the assemblies to 121°C in 30 minutes, stabilizing, holding at temperature for 30 minutes, and water quenching back to room temperature. The test was conducted for 250 cycles. The assemblies were removed 17 times during the test from the test rig, dimensionally checked, and helium leak tested. The results are shown in Figure 4. Based upon this information, the typical pitch of the lines in a system, and the size of the lines, a model of the puddle that could be formed behind the extruded dam was constructed on a 3D CAD system and hold-up volumes were calculated - *Figure 5*. Flow tests conducted with water confirmed that the model was valid.

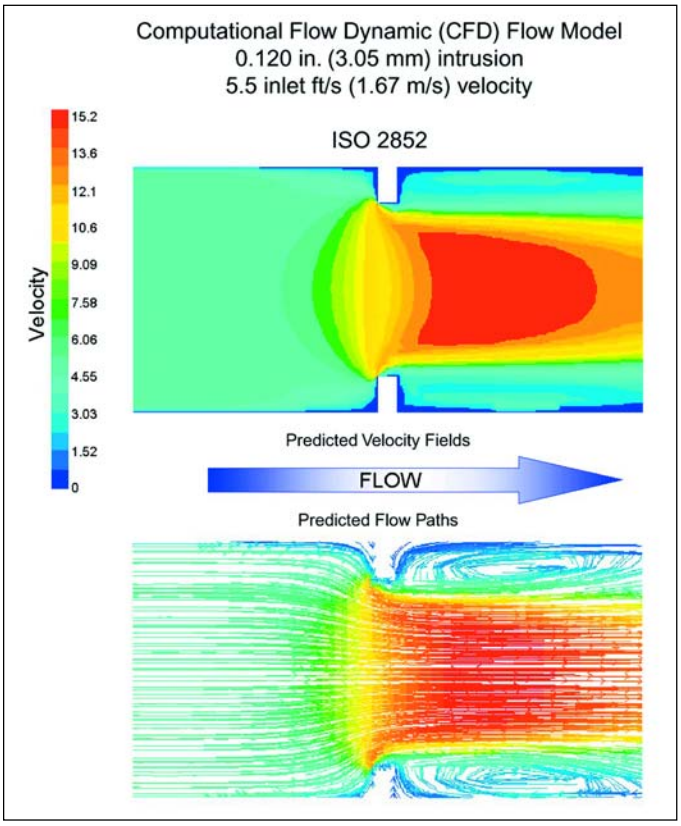

Figure 6. Computational Fluid Dynamics (CFD) show that as fluid passes through the constriction of the extruded gasket/orifice, the fluid velocity is increased substantially. A proportional increase in velocity in applications where fluid shear is an important consideration, such as harvesting mammalian cell cultures, could present an additional potential problem.

The dam can create several problems in actual systems. In processing systems, after CIP and a final rinse, some of the rinse water can be trapped behind the gasket in each fitting in a horizontal pitched line, where excessive extrusion has occurred. The dam and the resulting puddles will not allow the system or equipment to be completely drained. During the sterilization process, steam must be in contact with all surfaces, and a puddle of water behind the extruded gasket will not allow this to happen. After sterilization, the puddles of rinse water—plus any steam that has condensed during cool down and added to the puddles—are locations where bioburden could grow and contaminate the process. The dams are also locations where expensive product can be trapped, resulting in costly waste and making subsequent cleaning more difficult.

The dams can create problems during the operation of the systems as well. Using the information generated in the thermal tests, flow was modeled using Computational Fluid Dynamics (CFD) techniques. The model shows that, after the fluid passes over the dam, there is no flow at the surface of the tube for a certain distance downstream of the extruded gasket. An eddy is created downstream, immediately after the extruded gasket, where contaminants can become trapped and build up. The dam created by the extrusion acts as an orifice placed in the line. In the CFD model, flow was introduced at 5.5 ft./sec to simulate a CIP cycle. As the fluid passes through the constriction of the extruded gasket/orifice, the fluid velocity is increased substantially—in one scenario modeled to more than 15 ft./sec - *Figure 6*. Such an increase in velocity in applications where fluid shear is an important consideration, harvesting mammalian cell cultures, for example, could present an additional potential problem.

The dam also can create potential problems in ambient pure water systems. Contamination and bioburden can become trapped and build up in the dead spot that is created downstream of the dam. Under steady-state flow conditions, the probability that the trapped material will be released into the fluid stream is minimized. However, when the flow is disturbed, as would occur when a number of use points are actuated simultaneously, the resulting surges and disruption increase the chance that trapped material will be released. After release, the material begins its travel through the pure water system as a "plug" of contaminants. It will be discovered only if it passes a sample point at the precise time a sample is being taken. As it continues its travel through the system, it will disperse, mixing with the pure water, until it contaminates the system, at which point expensive corrective action will likely be required.

In the sterilization system and the processing equipment and systems being sterilized, thermal cycling presents a fur-

ther problem. When the test manifold was disassembled after thermal cycle testing, a certain amount of wear on the face of the gasket seal was observed. The surface was roughened and some of the gasket material was gone. It was concluded that the wear and fretting of the gasket material was probably caused by the radial expansion and contraction of the gasket during heat-up and cool-down. When the gasket expands radially into the bore of the tubing, it is no longer constrained between the faces of the two ferrules. The unconstrained portion of the gasket is free to expand back to its original thickness. The gasket material was characterized and the shape of the unconstrained portion of the gasket was modeled using Finite Element Analysis (FEA) techniques. The shape is bulbous. During expansion, the gasket extrudes radially, and the unconstrained portion expands axially. During contraction, as the gasket moves back into the constrained space between the ferrules, the surface of the unconstrained portion of the gasket is dragged over the relatively sharp metal corner formed by the bore of the ferrules and their flat faces. This explains the wear that was observed. The gasket material that is worn or scraped off can end up inside the system, eventually in the fluid stream.

In service, when gaskets are subjected to high temperature and high compressive loads, some gasket materials can take a compression set and become loose. Compression set is the tendency of an elastomer to lose its memory under stress and not return to its original shape when the stress is removed. During thermal testing, regular leak tests indicated that the ISO 2852 fittings needed to be retightened after every fifth thermal cycle through the first 15 cycles, because the gasket had taken a set. These results can explain why containment is lost immediately following a sterilization cycle. In such situations, a usual maintenance procedure would be to retighten

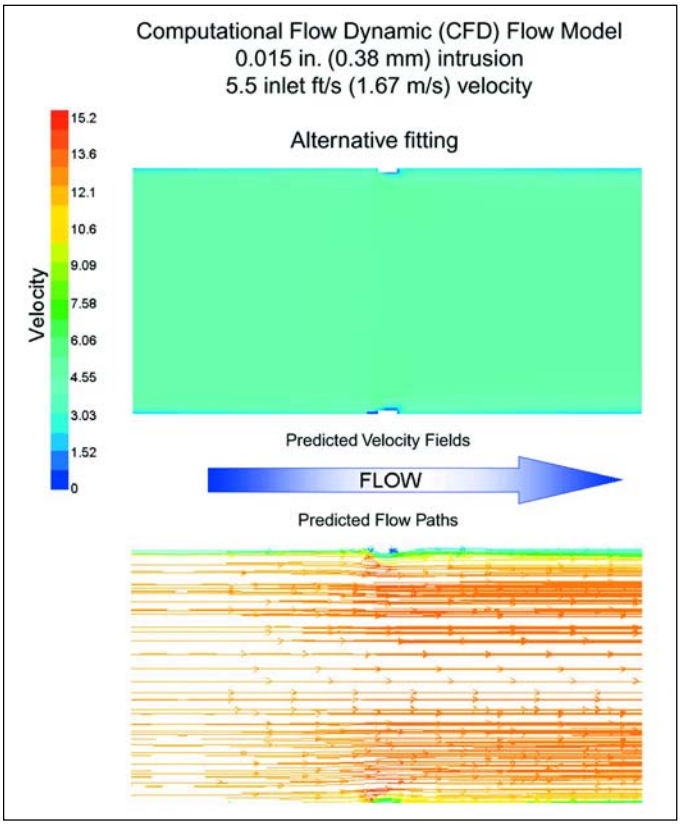

Figure 7. CFD shows no constriction of the flow through the connection and no increase of velocity through the connection.

the clamp even tighter, which would cause further extrusion and a larger dam, magnifying the kinds of problems discussed.

Another fitting design that addresses solutions to the issues discussed also was tested. In this fitting (Figure 3b), the configuration and cross-section of the gasket and the face of the ferrule are different from the ISO 2852 fitting. The gasket consists of two parts—the rib and the crown—each having a specific function. The rib portion is a rectangular shape with flat faces. When clamped between two ferrules, the seal is made at the rib. The function of the large mass of material in the crown of the gasket is to control the amount of gasket extrusion toward the bore of the fitting. The faces of the ferrules are machined to accept the crown of the gasket and align the two ferrules for assembly of the connection. A metal-to-metal stop is provided at the maximum outside diameter of the ferrules to limit the amount of load that can be applied to the gasket during initial make-up and prevent over-tightening. The gasket was configured to maintain proper "squeeze" over its complete cross-section. At initial make-up of the connection, compressive force is applied to the gasket with the same type of clamps used with an ISO 2852 fitting. Controlled extrusion permits a small amount of extrusion into the bore of the fitting, creating a stable bore-line seal, and avoids undesirable concavity at the seal point. The majority of the extrusion is taken up in the crown contained in the chamber formed between the faces of two ferrules. The chamber is not completely filled in order to accommodate expansion of the gasket material during thermal cycling.

These fittings were assembled into a manifold identical to the ISO 2852 manifold discussed earlier and tested in exactly the same way. The results were quite different. The results are shown in Figure 4. None of these fittings required retightening during the thermal testing. Flow in this fitting was also modeled with the CFD technique, based upon a velocity of 5.5ft/sec. The small amount of controlled intrusion at the gasket seal looked no different than the inside of a full penetration buttweld. There was no constriction of the flow through the connection and no increase of velocity through the connection - *Figure 7*. The CFD model showed no entrapment zone downstream of the gasket seal.

Conclusion

Thermal cycling during the sterilization process has an impact on the seals in ball valves used in utility systems and the sanitary fittings used in both utility and bioprocessing equipment and systems. Containment and control of process and utility fluids are the functions of valves and fittings in these systems. Containment and control of the seals in these valves and fittings is what determines how effectively the valves and fittings employed can or will do the job.

The problems with the seals in ball valves discussed here are a result of lack of proper containment of the seal material combined with thermal cycling. Under the load applied during make-up of the seal and with thermal cycling the seal material can migrate out of the seal area resulting in a loose seal and eventual leakage. The seals could be improved with better containment with metal on all surfaces and live loading them to compensate for the effect of temperature and thermal cycling.

The problems with the seal in sanitary fittings discussed here are a result of lack of containment of the gasket and lack of control of the amount of compressive load that can be applied to the gasket during initial make-up and subsequent re-

tightening, combined with thermal cycling. Thermal cycling is necessary for steam sterilization and cannot be eliminated. The tests conducted showed that uncontrolled extrusion of the seal material increases with thermal cycling. The results of comparing the two styles of sealing methods confirm that proper containment of the seal material and that limiting and controlling the compressive loads on the gaskets can help improve the cleaning, draining, and sterilizing bioprocessing systems and also reduce the amount of fluid hold-up in such systems.

In both the ball valves and the sanitary fittings discussed in this article, better containment of the seal material and better control of the loads placed on the seal material to make a leak-tight seal can result in improved ability to withstand the rigors of thermal cycling.

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This article describes a model for a Maintenance Management System which is ideally suited for the Pharmaceutical Industry. Adoption of such a model will be a boon to all industries whose systems would be challenged by globalization and competitive market environment. This model also would assist in complying with the revised international standard ISO 9000-2000.

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Maintenance Management - A Process Approach

by V. Anantha Narayan and G.B. Rao

Introduction

The manufacture of Active Pharmaceutical Ingredients (APIs) and finished dosage form drugs is a highly regulated industry. Guidelines of the World Health Organization (WHO), Good Manufacturing Practices (GMPs), the US FDA (as mandated by 21 CFR Part 11), and the International Conference on Harmonization (ICH) require establishing a Quality Management System with established Good Manufacturing Practices (GMPs).

The above guidelines require the maintenance of process equipment, utilities, calibration of instruments and gauges, cleaning, and upkeep of buildings and facilities to prevent contamination, maintain validation of ventilation, air filtration, air heating and cooling systems. Also, critical systems like nitrogen, compressed air, and water used in the manufacturing process are required to be maintained, validated, monitored, and audited to ensure continuing process capability.

Ensuring such stringent requirements calls for the establishment of a well documented Quality Management System similar to the ISO model. This international standard envisages the use of the process approach for all activities including maintenance.

Hence, it is imperative that maintenance management is organized and implemented with forethought, control, and the use of records to a predetermined plan.

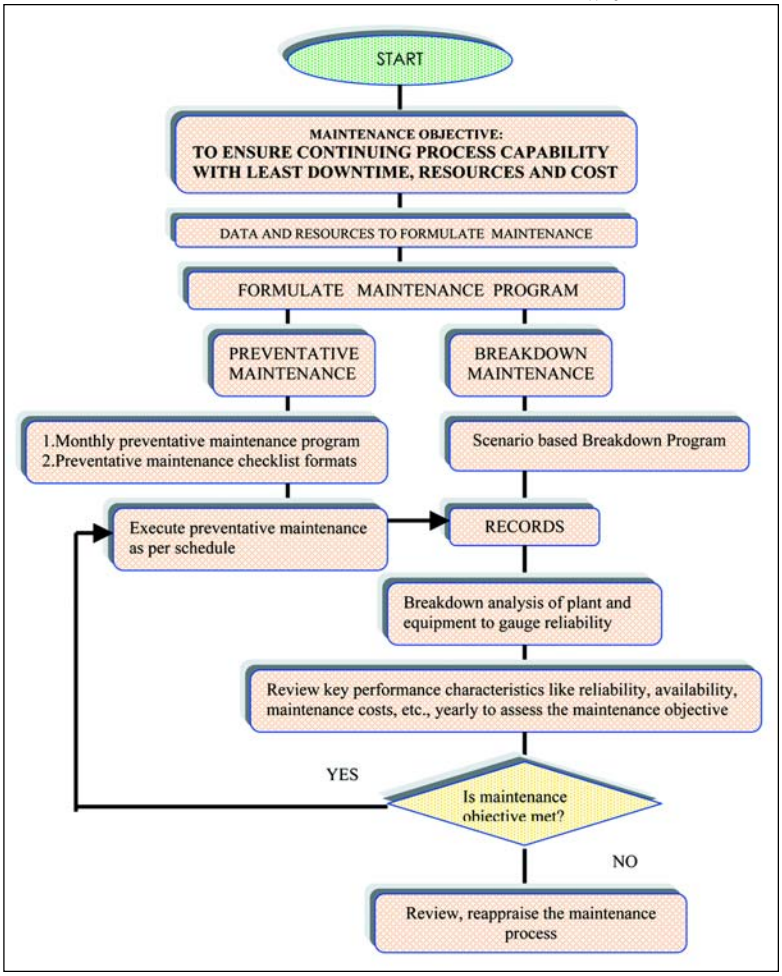

Figure 1. Maintenance process flow chart.

The process model described in this article takes into account maintenance inputs, outputs, and controls, and provides guidelines so that it can be adapted by all pharmaceutical industries across the globe to meet the regulatory requirements of cGMPs and the ISO 9000-2000 Quality Management System.

The Process Approach

With the implementation of the ISO 9001-2000 Quality Management System, the adoption of the Process Approach while developing, implementing, and improving the effectiveness of a Quality Management System has become imperative. For an organization to function effectively, it has to identify and manage numerous linked activities. An activity using

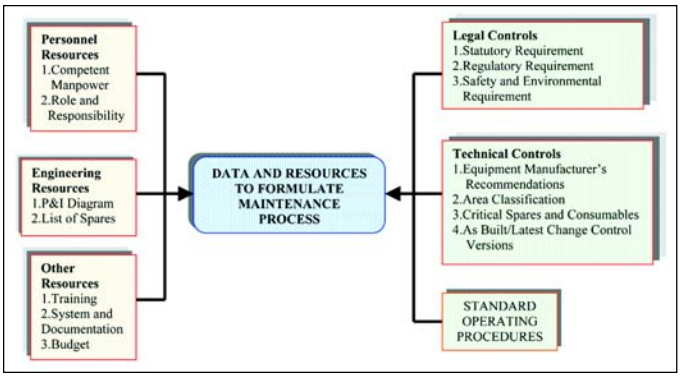

Figure 2. Direct input to formulate a maintenance process.

resources and managed in order to enable the transformation of inputs to outputs is considered a process. Preventative Maintenance is one such process.

The application of a system of processes within an organization or department or functional area, together with the identification and interaction of these processes, and their management is referred to as Process Approach.[1]

What's New?

Many industries are process industries and they understand well what a *Process* means. They have process flow diagrams, material balance sheets, consumption co-efficients, process control techniques, statistical methods for evaluation of process capability, etc., and implement these only for their core operations which are process oriented. However, when it comes to activities in other departments, i.e., maintenance management, materials management, logistics management, hazardous waste management, etc., it is not very clear to most of the industries how a process approach can be adopted for non-process activities. The 2000 version of ISO 9001 mandates the use of the process approach for all activities and operations of an industry. Therefore, it would be necessary for all industries to understand and develop process models.

This article conceptualizes and develops a process model for maintenance management for the benefit of industries who may be implementing a planned and documented Quality Management System.

General Guidelines for Developing a Maintenance Management System

The process model encompasses the following elements of maintenance management:

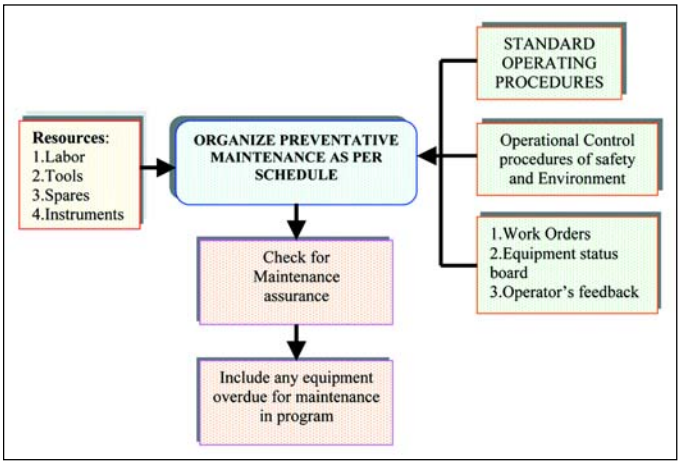

Figure 3. Organizing preventative maintenance.

- Understand the function
- Need for maintenance
- Determine the objective
- Plan
- Schedule
- Organize
- Control

Each of the above elements is explained in detail below.

Understand the Function

The main function of a maintenance manager is to formulate a maintenance plan and construct a control system to ensure the implementation of that plan. To accomplish this, an understanding of the nature of maintenance, its relationship with production, and the demands/expectations from the maintenance department are necessary. In other words, this calls for total familiarity with the situation for which he is responsible, recognition of the dynamic nature of the maintenance-production system, and understanding the mechanics of such a system.

Need for Maintenance

When considering the complexity and expense of the modern manufacturing facility, it is apparent that designing for zero maintenance, even if possible, would be uneconomic. Many of the constituent components will have been designed, for technological and economic reasons, with a useful life greater than the longest production cycle, but less than that of the plant itself. Other components may well have a high possibility of failure during their useful life. Thus, maintenance is inevitable and generated from failure at component level.

In most cases, 'weak' components will have been identified at the design stage and made easily replaceable. Obviously, such components are easy to deal with since the need for maintenance can be forecasted and planned for, i.e., the expected maintenance load. In addition, a need for maintenance also will arise due to failures that occur for reasons that are difficult to anticipate, such as poor design, poor maintenance, or maloperation, i.e., the unexpected maintenance load. Although such work is difficult to forecast, experience suggests that it is inevitable, especially in the early life of the plant, and therefore needs systems for its detection, recording, and analysis. An added complication is that failure to carry out the expected maintenance load generates a larger unexpected load.

Thus, the major problem of the maintenance manager is to decide on the best way of dealing with this complex and uncertain workload, i.e. should he replace or repair the weak component (or some higher level part containing the weak component) before failure (preventative maintenance) or after failure (corrective maintenance), or should he design-out the weak component to prevent maintenance?

Determine the Objective

The objective of the Maintenance Management System must be compatible with the company objective, in other words, it must be linked to profitability. The chosen maintenance objective will focus on reliability and availability of essential equipment, services, and utilities. The objective will be measurable and consistent with the quality, safety, environment, and other policies.

Maintenance influences company profitability in the following ways:

1. Indirect cost of maintenance which might occur when the plant is in following states:

   a. Taken out of production for scheduled (preventative and corrective) maintenance. Major shutdown work can be carried out, but there is production loss.
   b. Failed unexpectedly and corrective maintenance is being carried out under 'emergency' conditions. Obviously, production is being lost and the maintenance is difficult to plan.
   c. Failed, but due to shortage of maintenance resources and waiting for maintenance. This is the worst state of all.

2. Direct cost of maintenance

3. Useful life of the plant; the longer the plant life, the greater is the life-cycle profitability

In general, the greater the level of maintenance resources (higher direct cost), the lower the level of unavailability (higher indirect cost), and the longer the useful life of the plant. Thus, in most industrial situations, the proper maintenance objective should be to minimize the sum of the direct and indirect costs, always taking into consideration the long-term effect of any maintenance decision.

Planning and Scheduling

Planning is a continuous process of matching the resources of labor, materials, money and equipment with the need of the facility. Action oriented planning and controlling techniques are essential for daily maintenance management.

The work schedule should be realistic and flexible enough for making allowances to the conditions as they actually exist in the plant. Hence, schedule changes should be expected. Planning for scenario based emergency breakdowns and assessing the time required for corrective action would help ensure that the objectives are met.

In addition, the importance of adhering to the maintenance plan must be respected in both the production and maintenance departments. Communication between the departments must be good to enable an effective and flexible maintenance schedule.

The maintenance plan, to a large extent, determines the level and nature of maintenance workload. It is through consideration of this workload that the maintenance organization is best established. The maintenance organization is made up of the following interrelated parts:

- A resource structure: men, spares, and tools – level mix, function, and location.
- An administrative structure: maintenance decision makers in a hierarchy of authority and responsibility
- A work planning system: planning and documentation for matching the resources to a dynamic and complex work load

In addition to resource structure, administrative structure and work planning, input needs to be taken – from deterioration characteristics, repair characteristics, results of condition monitoring, failure mode and effects analysis, failure tree analysis, etc.

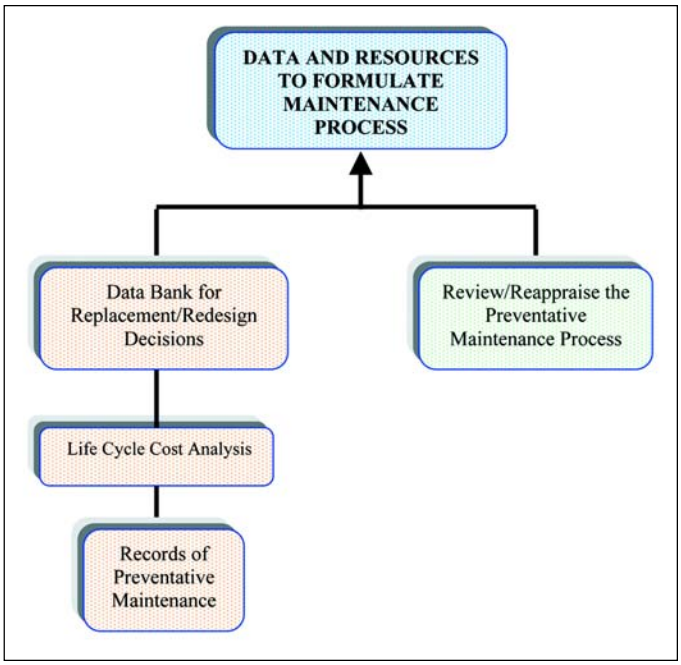

Figure 4. Feedback input to formulate maintenance process.

Deterioration and Repair Characteristics

The purpose of maintenance is to achieve a satisfactory level of system availability. To measure the level of system availability, the following data needs to be known.

Mean Time To Failure (MTTF)
Mean Time Between Failure (MTBF)
Mean Time To Repair (MTTR)

$$\text{Then the system availability} = \frac{\text{MTBF}}{\text{MTBF} + \text{MTTR}}$$

High availability can be achieved only when the MTTR value is low, i.e., the system can be maintained easily. MTTR is the average of times taken to repair any fault in the system.

Low MTTR can be achieved by paying close attention to the accessibility of the component, built in diagnostic panel, and

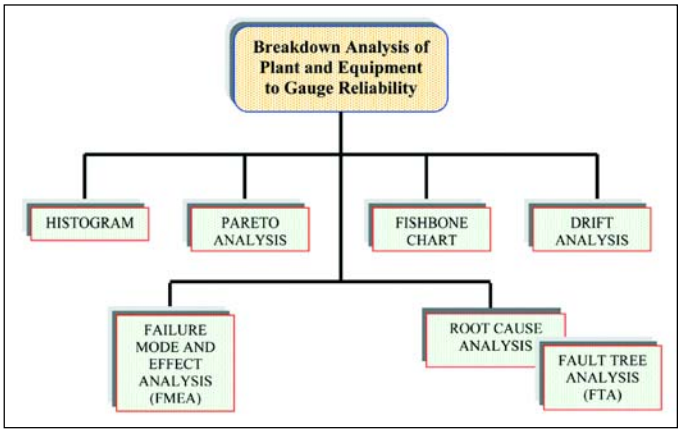

Figure 5. Techniques of failure analysis.

by providing an internal test facility. Availability level would decide frequency of maintenance attention to be given.

Condition Monitoring
The following condition monitoring techniques give input to the planning and scheduling process.

1. shock pulse monitoring for bearings
2. vibration monitoring for machinery fault diagnosis
3. lubricant monitoring for extension of the lubricant life
4. wear debris monitoring for identification of component deterioration
5. temperature monitoring for finding out refractory/insulation damage
6. corrosion monitoring

Many non-destructive engineering techniques like dye penetrants, magnetic particle inspection, eddy current detection, ultrasonic, and radiography are widely used in assessing equipment health when they are stationary.

Hence, a review of the results of analysis of the above techniques would enable us to decide on the periodicity of maintenance attention required for each equipment or subsystem. This helps plan and schedule maintenance.

The following are the basic steps for maintenance planning and scheduling:

- determine critical plant/system components and identify equipment idle periods available for maintenance
- classify the plant into constituent items
- determine and rank the effective procedures
- establish a plan for the identified works
- establish schedule for the online maintenance, the offline maintenance, and shut down maintenance
- establish controls to verify that planned activities are accomplished

Organizing
Identifying and organizing for the necessary inputs like personnel resources, engineering resources and other resources, required during different stages of implementing the model is important for successful implementation of maintenance process.

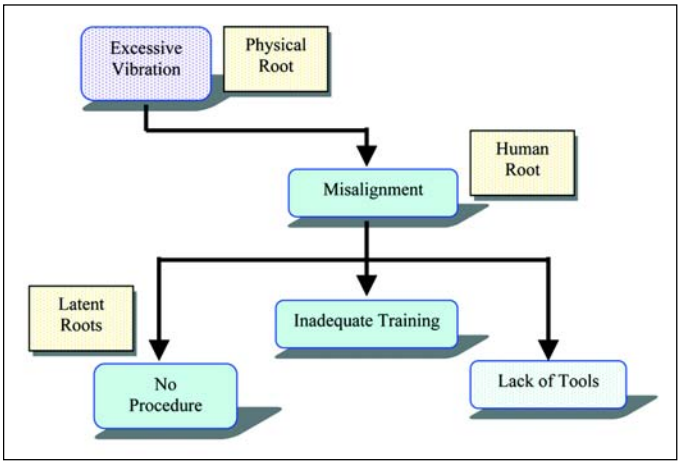

Figure 6. An example of the root cause logic tree for a chronic pump failure.

Personnel Resources - Competent Manpower with Defined Roles and Responsibilities
The competency of the supervisor/workman to perform the given function may be by virtue of his technical education, training received, or skills developed on the job. The roles and responsibilities of each individual should be clearly defined to ensure accountability and achieve the objective.

Engineering Resources
All the engineering information like design, construction, operating and maintenance procedures, safety data sheets, list of critical spares, as built diagrams, etc., must be organized for all equipment to ensure that the maintenance is carried out by applying good engineering practices. This would enable preparation of maintenance checklists appropriate to the equipment and the schedule of inspection.

Change control procedures should be in place in order that maintenance personnel are equipped with latest revisions of engineering details and operating procedures.

In order to enhance the productivity and reliability of the maintenance work, the use of correct and proper materials like tools and tackles and measuring instruments are necessary. This would call for the use of international/national standards for calibration and maintenance.

Other Resources
Other important resources that are needed for effective implementation of the model are training, computerized systems, and documentation.

Training
Identifying and implementing a training program is an essential part of developing a competent manpower for maintenance work. Training is necessary with changes in equipment, technology, and systems of work. A formal evaluation of training imparted and a documented system would ensure effectiveness of training.

Computerized Maintenance Management System (CMMS) and Enterprise Resource Planning (ERP)
With ever increasing sophistication of equipment and monitoring requirements, it has become increasingly difficult to plan, schedule, implement, document, analyze, and improve the maintenance management system manually. Information is not easily accessible. Users often had to go to many sources to gather report data, answer questions from upper management, track efficiency of operations, and track work order and its progress. This leads to redundant work and a lack of information about equipment, spending, and other important data. Locating the parts in the stores may be difficult because the store system was not user friendly, locating parts for emergencies, and routine tasks was often delayed. Also, manual systems have no provision for reserving parts. To ensure a fullproof and productive maintenance system, it would call for extra indirect labor for monitoring, management, and analysis. Lack of coordination and inappropriate deployment of workforce for direct maintenance (technicians) would call for extra manpower to be kept on reserve adding to direct labor costs.

Hence, it is advisable to develop systems to cater to techno-

logical advances and user needs. Maintenance, stores, inventory, purchasing, accounting, and other linked activities need to be computerized.

The implementation of a Computerized Maintenance Management System (CMMS) would help streamline the entire maintenance activities from various departments such as mechanical, electrical, utilities, instrumentation and control, and workshops.

A successful CMMS provides the following functionalities:

- equipment spare parts
- costs
- historical record
- data on equipment spare parts
- work orders
- work order planning and control
- preventative maintenance planning
- personnel development and training
- maintenance scheduling

With this system, work orders are created electronically and routed to appropriate users. Inventory management and recording processes are automatic.

However, an in-house developed CMMS has the following shortcomings:

- excessive manual input to work order system and scheduling
- data realized in separate databases
- lack of integration of databases

Enterprise Resource Planning (ERP)

Implementing a Plant Maintenance (PM) module of ERP cuts across the interdepartmental boundaries in an enterprise. ERP effectively integrates islands of information within the organization ensuring total transparency, information sharing, a uniform system, eliminate waste caused by loss of time and heavy inventory holding cost etc., and improves overall productivity. Hence it is advisable to go in for time tested ERP packages marketed by reputed software developers and customized to meet specific requirements so that scheduling, resource allocation, etc., are part of the same integrated database.

Controls

The process of maintenance must consider statutory, regulatory, and other requirements specific to the industry. These also need to be addressed while scheduling maintenance and preparing checklists.

Definitions

The following are some useful definitions of key words used in maintenance management (as per British Standards 3811:1993)[2]:

Maintenance: A combination of actions carried out to return or resolve an item to an acceptable condition.

Preventative Maintenance: Maintenance carried out at predetermined intervals or to other prescribed criteria, and intended to reduce the likelihood of an item not meeting an acceptable condition.

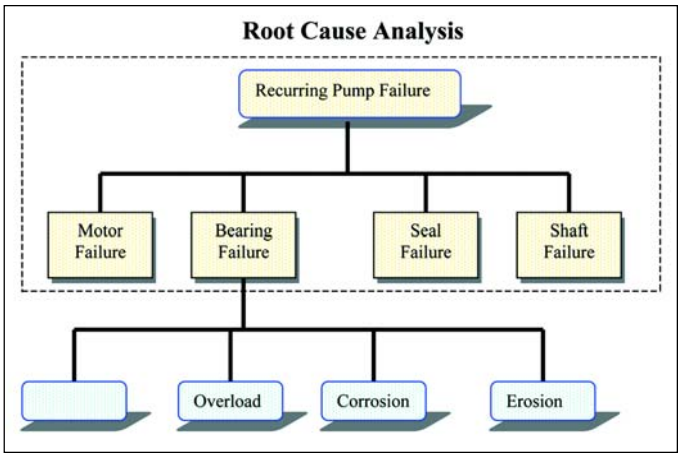

Figure 7. An example of physical roots for a chronic process pump failure.

Corrective Maintenance: Maintenance carried out to restore an item that has ceased to meet an acceptable condition.

Running Maintenance: Maintenance which can be carried out while the plant or unit is in use (on-line maintenance).

Shut Down Maintenance: Maintenance that can only be carried out when the plant or unit is not in use (off-line maintenance).

Emergency Maintenance: Corrective maintenance which is necessary immediately to avoid serious consequences.

Planned Maintenance: Maintenance organized and carried out with forethought, control, and the use of records to a predetermined plan.

Terotechnology: A combination of management, financial, engineering, and other practices applied to physical assets in pursuit of economic life cycle costs. Its practice is concerned with the specification and design for reliability and maintainability of plant, machinery, equipment, buildings, and structures with their installation and replacement, and with the feedback of information on design, performance, and costs.

Description of the Model

The process model depicted in Figure 1 is generic in nature and has been conceptualized and designed to suit any process industry including the pharmaceutical industry. This is based on a real situation and is designed to respond to the dynamics of production demand. This model incorporates the general guidelines previously described for maintenance management.

The whole process of maintenance management is designed to achieve previsualized objectives starting with formulation of a maintenance process.

Inputs

Typically, a process requires certain resources as inputs with some controls to achieve certain outputs. These inputs are shown in Figure 2. The various resources and process controls needed to realize the objective are:

1. Personnel Resources: competent manpower with definite roles and responsibilities at different stages of implementing the process

2. Engineering Resources: detailed engineering of the equip-

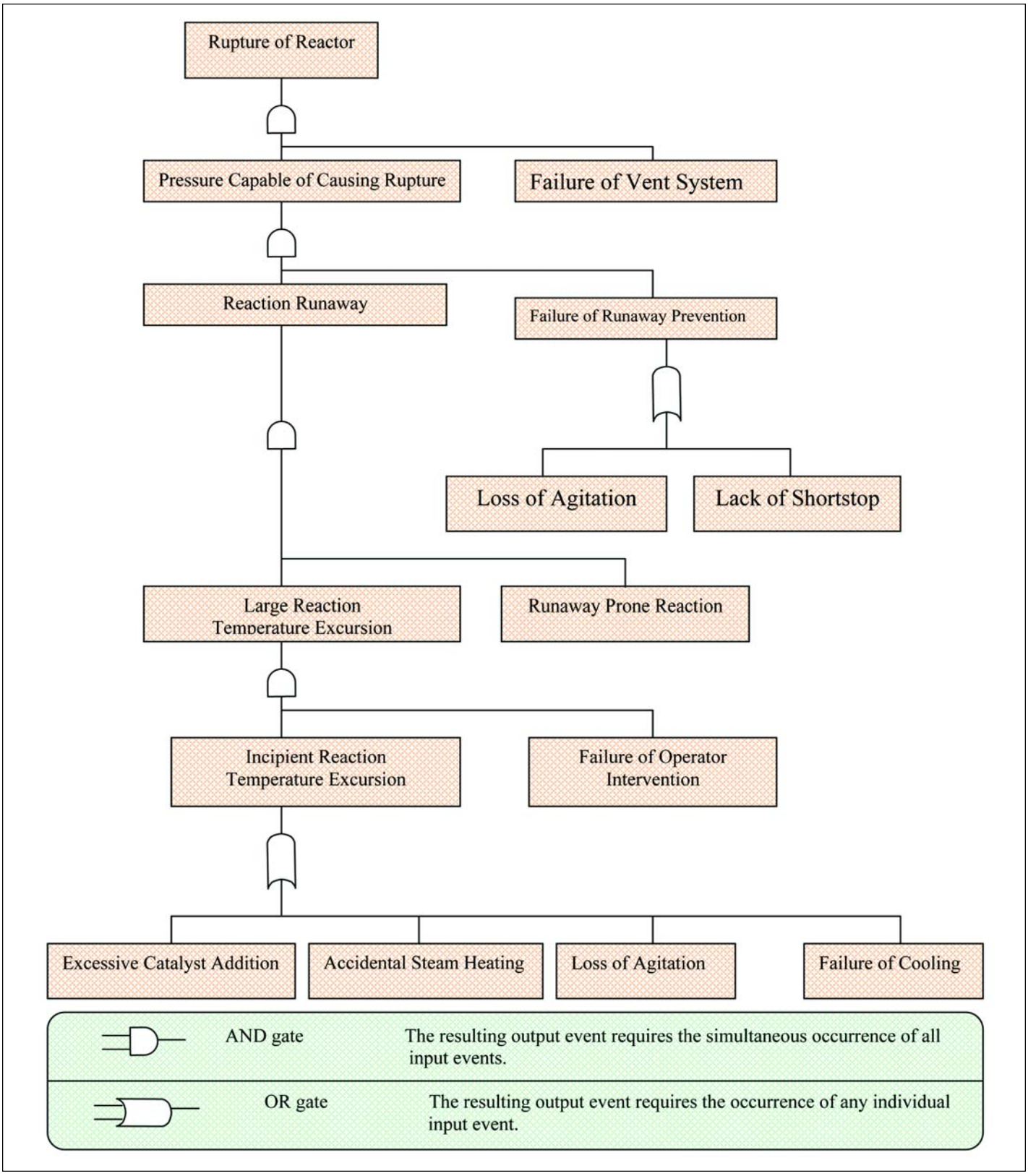

Figure 8. An example of a Fault Tree Analysis application.

ment installed, blownout diagrams of equipment, P&I diagrams and a list of critical engineering spares etc., are to be maintained for each equipment

3. Other Resources: appropriate preventative maintenance personnel, budgetary allocation to implement the process, and necessary support of IT based system documentation

Controls

Various controls to ensure process capability, statutory compliance, and good engineering practices that are required are also depicted in Figure 2. These are:

Legal Controls: industry would need to comply with certain legal requirements with respect to its chosen area of business. The requirements may be statutory, regulatory, environmental, safety, etc. These need to be addressed and included in the maintenance process.

Technical controls: the type of plant and equipment in any industry are product specific. In technical control, the features of plant and equipment such as construction quality, suitability, maintainability, and troubleshooting are considered as much as its reliability and safety to ensure continuing process capability. Plant validation protocol, as built drawings, latest change control versions, standard operating procedures, and operational control procedures are necessary control inputs to the maintenance process.

Such identification of the resources and controls would enable formulation of a maintenance program. A complete preventative maintenance calendar for a year at a time may be prepared by forecasting, planning, and scheduling maintenance work on fixed time intervals or to any other criteria. For critical and sophisticated equipment, the expertise of manufacturer's service representatives may be contracted for annual maintenance.

While executing the preventative maintenance job per program, resources required for and controls to ensure timely and quality preventative maintenance work need to be considered.

The inputs for organizing preventative maintenance are shown in Figure 3. These are labor, tools, spares, instruments, etc. The standard operating procedures and operational control procedures to conform to safety and environmental requirements and communication by way of maintenance work orders, equipment status boards, and preventative maintenance tags would ensure proper controls.

Breakdown Maintenance

The unscheduled maintenance due to sudden failure of equipment or plant calls for breakdown maintenance. Though it is very difficult to list all the factors that may contribute to a breakdown of equipment, past experience, engineering intuition, hazardous operation studies, assessment of functional life of individual components, etc., would help to formulate a scenario based breakdown maintenance program – *Figure 1*.

Review and Records

Maintenance reviews are conducted to identify any deviation and corrective action taken to ensure maintenance assurance. Filled in checklist, history cards, etc., form the record of maintenance and these are verified by an engineer/supervisor. The maintenance records also are reviewed for trend analysis and for performance evaluation. Such evaluation would show the effectiveness of the maintenance program in meeting the targets such as reliability, availability, maintenance costs, etc. Results of such reviews also would help identify continued usefulness of the designed system

Analysis and Feedback

Figure 4 shows feedback inputs to the maintenance process. The feedback provided in the model would help ensure continual improvement in the maintenance management system.

Figure 5 shows the techniques that can be adopted for failure analysis. These are:

Histogram: a graphical representation to show the frequency that an incident occurs.

Pareto Analysis: a bar chart that ranks causes in descending order so that priorities can be assigned.

Fishbone Chart: an orderly arrangement of "cause and effect" of a certain problem shown in a graphic form which resembles a fishbone.

Drift Analysis: deviations in the values measured from an instrument after periodic calibrations give an indication of the drift in the instrument.

Failure Mode and Effect Analysis (FMEA): evaluates the ways in which equipment can fail and the effects of such failures on an installation. The failure mode considered provides the analyst a basis to identify where changes are needed to improve the system/design. During FMEA, a single equipment failure is defined and the effects of both locally and on the whole system are analyzed. Individual failure is considered as an independent occurrence with no relation to other failures in the system except for the subsequent effects that it might produce.

Fault Tree Analysis (FTA): a deductive reasoning process that illustrates combination of failures that will cause one specific failure of interest, called "a top event" such as "an explosion in a reactor." The FTA process, in addition to identifying the root cause of the top event, sometimes reveals alternate outcomes of those root/common causes of failure.

An example of the root cause logic tree for a chronic pump failure is shown in Figure 6. An example of physical roots for a chronic process pump failure is shown in Figure 7. An application of Fault Tree Analysis is shown in Figure 8.

Factors to be Considered for Total Life Cost of Plant and Equipment

Capital: design, development, plant purchase, installation, commissioning, training of plant staff, manuals and documents, tools and facilities for maintenance, inventory of initial spares

Operational: labor for plant operation and labor for engineering, energy such as diesel oil, furnace oil, electricity, etc., utilities such as steam, water, compressed air, nitrogen, vacuum, etc.

Maintenance: labor, material, inventory of spares, engineering support like workshops, annual maintenance contracts, overheads for planners, engineers, etc.

Production and Quality Losses: due to plant non-availability or due to plant malfunction.

Analysis of the above information and data would help estimate the total life cost of equipment and would help make replacement/redesign decisions.

Insurance

Insurance, per-se, is not a part of the maintenance management function, but the maintenance manager is looked upon as a "Manager of Assets" in many industries and is vested with such responsibilities.

This calls for an understanding of a combination of management, financial, engineering, and other practices applied to physical assets in the pursuit of economic lifecycle cost. This is termed Terotechnology, and it is concerned with replacement of assets such as equipment and plants.

There are three types of replacement problems:

- replacement of items that deteriorate with time
- replacement of items that breakdown completely
- replacement of items due to obsolescence (out of date due to new development)

Replacement of items that deteriorate with time can be completed in a planned manner as details and trends of deterioration characteristics and analysis of condition monitoring are available as part of maintenance management documentation.

Replacement of items due to obsolescence is always on capital account and this is a well-planned and budgeted program.

In the event of sudden and unpredicted failures, preventative replacement is not possible. Such failures may result in complete breakdown of the system. In this case, loss due to the breakdown is indirect, i.e., apart from the actual cost of replacing the item, there is a substantial cost involved in loss of production, idle labor, waste, and other damages. Such damages may manifest as toxic release, fire, explosion, etc.

This calls for scenario based asset management where "insurance" plays an important part to minimize the cost of replacement.

It is advisable for the maintenance manager to take out insurance policies to cover:

a. material handling and transport damages during erection and commissioning

b. breakdown policies for machinery

c. fire insurance policies

d. policies to cover loss of production, loss of profits, public liability etc., arising out of consequential damages

Conclusion

Implementing a maintenance management system on the lines of the process model outlined in this article could result in the following benefits:

1. The model is constructed on the basis of real life practical situations and is holistic and takes into account a large number of inputs, outputs, and controls to the system, hence exhaustive.

2. Compliance to ISO 9001-2000 Quality Management System requirements with specific reference to adoption of the process approach.

3. Compliance to regulatory requirements of cGMPs.

4. It enables measurement of performance effectiveness by comparing it with set objectives.

5. Analysis and review is a part of the system and this would enable continual improvement.

6. The system would enable life cycle cost analysis as data is captured in documents.

7. It enables replacement and redesign programs.

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1. IS/ISO 9001: 2000 Indian Standard: Quality Management System - Requirements.

2. British Standards 3811:1993: Glossary of terms used in terotechnlolgy.

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Total Quality Management in Pharmaceutical Plant Construction

by Dean Poillucci

The nature of the pharmaceuticals industry dictates a particular focus on quality in the design, construction, and time to market of manufacturing facilities. Ensuring quality in design and construction requires development of a comprehensive process in which users clearly articulate their needs so their expectations can be met.

Introduction

Webster's New Collegiate Dictionary defines quality as "degree of excellence" or "superiority in kind." The nature of the pharmaceutical industry dictates a particular focus on quality relating to each element including design, construction, validation, and time to market of manufacturing facilities. Ensuring quality means meeting not only the owner's requirement, but regulatory needs for licensing as well – all of this in the real framework of safety, capital cost, and completion dates. The ultimate goal is to meet the owner's business model objectives to produce a validated product by a certain date, for a specific price. The objective of the design, construction, and validation process is to define, develop, and implement the most effective means to fulfill all project requirements and expectations.

The challenge in design, construction, and validation is to develop a comprehensive process in which users clearly define their needs so that their expectations can be met. Once the objectives are defined and understood, the project criteria can be established and an execution program put in place to achieve the goals. Comprehensive project criteria that can be measured can only be established using an integrated team approach that promotes collaboration between the owner, designer, construction manager, and validation team - *Figure 1*.

Quality must be built into every step of the execution strategy with a comprehensive plan to measure quality performance through the use of metrics put into place during the preconstruction phase. The challenge for the project owner is to drive quality with elements preceding actual construction as well as the construction phase, and subsequent commissioning and validation phases. To address this need as facilities become more complex and time to market demands increase, project owners are soliciting support from construction management firms to play a critical role in the development, implementation, and management of an overall integrated project schedule that includes design, procurement construction, commissioning, and validation activities. The plan should include the measurement of design, construction management, materials, equipment, craft labor, commissioning, and validation performance through the use of metrics. This overall approach to quality management will provide the greatest assurance that physical construction quality, cost, and schedule performance are not compromised.

The quality metrics that are chosen for the assignment must be aligned with the owner's priorities for the project. If not properly selected, the metrics established could put an unwarranted burden on the project team to monitor and report against, which could intro-

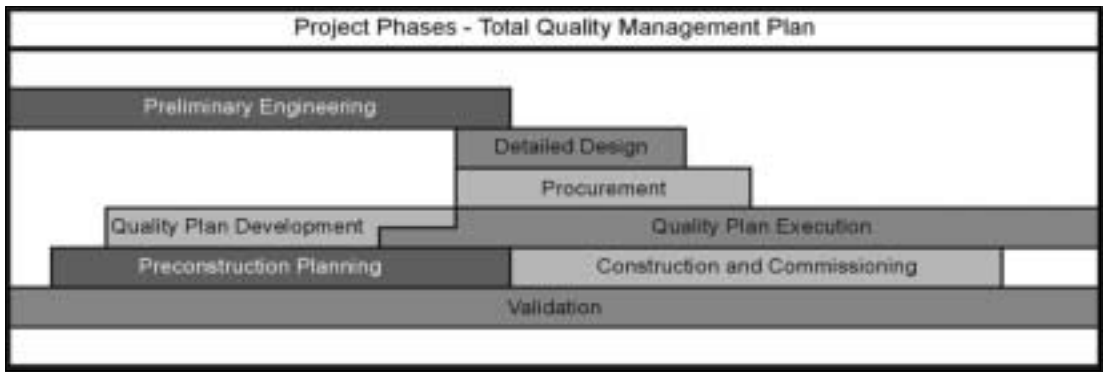

Figure 1. Project Phases - A plan to define and measure quality is put in place early in the project's life and is executed through each overlapping project phase.

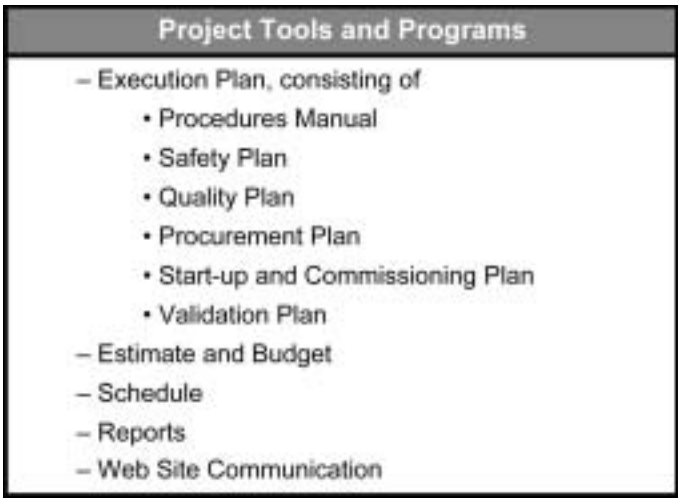

Figure 2. Project Tools and Programs - This indicates the various project management tools and programs that help ensure that construction ensues with quality. Plans must be reviewed continuously to ensure that the results deliver a project that meets owner expectations.

duce unwanted project cost - *Figure 2*.

Design

Managing the quality of the overall project begins with the content and the timely delivery of the design documents. The owner, designer, construction manager, and validation team must work together during the development of the project since each brings unique expertise to the planning phase. Often this begins during the preconstruction planning phase, which is normally conducted during conceptual or preliminary design.

The construction team should monitor and provide input as the project scope evolves and continuously review the design documents for constructability. The design documents must contain the scope and level of quality desired, as well as comprehensive detail to convey the design intent to the subcontractors, fabricators and trade personnel in the field.

Constructability reviews conducted during the preconstruction stage will define the precise scope for the different trades. By tracing each building and process system we can see that all match points correspond. Interdisciplinary coordination serves to eliminate conflicts among the various disciplines involved in the project to avoid cost and schedule upsets during the construction phase, due to interferences or insufficient information. The availability of the design engineer who performed the design as a consultant during construction is essential.

Comprehensive design management will result in a build-to-budget outcome with reduced engineering changes and consequently significantly less field change orders. It not only augments quality, but also makes the project less costly and faster to build.

Figure 3. Engineering and Design Metrics - This outlines metrics that may be developed to monitor quality performance for engineering and design.

Today, computer aided design systems are so advanced that almost all design firms use a three-dimensional approach for depicting their concepts in a highly detailed manner. The model is extremely helpful to the owner, construction manager, and subcontractors, helping them to visualize each segment of the work to be installed in the field. These models are installed at the site where the construction work is being performed for access by the construction team. While the three-dimensional design approach provides its greatest value for complex manufacturing projects, most projects benefit from the visual clarification for complex portions of a project, or where user interface is critical, such as the use of isolators and containment devices - *Figure 3*.

Schedule

Ultimate schedule performance is delivering a project that meets the facility licensing date so that manufacturing can take place. Reaching the construction completion date without being ready for subsequent commissioning and validation activities is not acceptable team performance. Just as preconstruction planning is important to the construction effort, validation master planning at the earliest stage will support completion milestones in the sequence required to validate and start-up the process.

The construction team drives the effort to develop an effective and integrated project schedule which should include the engineering, procurement, construction, commissioning, validation, and FDA approval activities drawn together into a single document. This allows the team to identify potential impacts or potential delays to be avoided by creating an appropriate avoidance or recovery plan. The key to managing capital projects is to predict future impacts before they actually occur so that no schedule delay or cost impact is felt by the project - *Figure 4*.

Budget and Cost

As the project nears the end of preliminary engineering, a control estimate is established as part of the preconstruction effort. This control estimate is based on quantities, materials, and methods as defined in the preliminary engineering documents. Once in place and agreed upon by all members of the project team, it will be used as a benchmark to monitor the design and scope development against the control estimate.

There are two methods for updating the control estimate for a project. The first is the milestone method, which prescribes that an estimate be prepared at various stages of design completion—typically 30%, 60%, and 90%. A second method utilizes a real-time cost monitoring approach that gauges scope as the project proceeds through design.

Since most pharmaceutical projects are built using a fast-track format, design documents for the entire project do not reach the prescribed milestone completion percentages for all disciplines at the same time. Instead, the design progresses to permit early construction start dates and the procurement of long-lead equipment while the process and building utility designs are still being developed. The milestone estimating approach provides historical information regarding the actual cost of the project, but does not forecast or permit the owner to make informed decisions regarding scope creep. This ultimately results in additional scope and cost items to creep into the project definition and design documents that may or may not be desirable or affordable. This scope creep will not be identified and quantified until the next major milestone review, and if they are cost or schedule prohibitive, they will

require additional engineering and design efforts to be removed from the project.

The second approach is a proactive scope monitoring technique that permits the identification of scope migration away from the control estimate due to differences in quantity, materials, or methods. Once a scope change is identified, an order of magnitude, estimate, and schedule impact is prepared for the item. The owner then reviews the impact of the potential change and is able to make the decision to incorporate the scope revision into the project and subsequently adjust the budget and schedule as required, or reject the scope change – *Figure 5*.

Project Organization

Efficient project organization has a significant impact on the overall project performance. A project team is comprised of many members from different firms, each bringing particular expertise, requirements, and expectations. At the early stage of the project, the team members must develop and support a common mission statement for quality, safety, cost and schedule, which supports the owner's business objective. A successful project organization requires the identification of key individuals to serve as the focal point for specific core technical requirements, and that they be responsible for communication among the various team members so that everyone remains aligned throughout the various phases of project execution – *Figure 6*.

The technical managers provide the critical interface between the owner, engineer, subcontractors, vendors, and start-up and commissioning team. Their primary responsibility is to deliver the user's requirements to the field with regard to function, schedule, and quality.

The technical managers in the field coordinate and ensure the continuity of the project from its earliest phase to closeout and turnover. They participate in design reviews during preconstruction, assist with scope development, and the procurement of the system components. Technical managers also direct vendors and suppliers through shop drawings and fabrication from the delivery of components at the site – and supervise component installation, start-up, testing, and commissioning.

Prefabrication Strategy

As pharmaceutical and biotech facilities become larger and more complex, as project schedules are compressed, and with skilled labor shortages occurring in various markets, an effective prefabrication strategy is a key element to meet project expectations. In certain locations, it is cost effective to remove installation hours from the site and invest that effort in the controlled environment of a prefabrication facility. This shifting of the installation hours will improve productivity, enhance quality performance, and accelerate time to market. To be effective a comprehensive prefabrication plan must be in place at the earliest stages of project planning.

The use of custom and stock designed and fabricated subsystems is valuable from both an economic and quality standpoint. This approach not only reduces project costs, but also results in superior quality control, less rework and greater productivity, thus improving schedule and start-up reliability. However, the strategy is only advantageous if the design, prefabrication, and construction are properly integrated.

An effective prefabrication strategy for conventional building construction could result in lowering the peak site labor requirement by 30-40%. A full modular strategy will lower the peak site labor requirements further - *Figure 7*.

Figure 4. Project Schedule Metrics - This outlines metrics that may be developed to monitor quality performance for the project schedule.

To maximize the benefits, an experienced prefabrication team should be active both in the preconstruction and construction phases of the project. To maximize the project impact, the prefabrication team should consist of individuals from the construction manager, designer, validation team and owner, and they should be assigned during the scope development phase of the project.

The team then identifies the items that can be prefabricated and is responsible for their design, procurement, inspection, and field coordination of all prefabricated assemblies. Factory Acceptance and Site Acceptance Testing (FAT and SAT) requirements and procedures should be established early with the collaboration of all project team members. The construction team's technical managers should manage off-site fabrication.

The technical manager's responsibilities include monitoring the submittal and construction progress, conducting inspections, and measuring progress against a baseline schedule, inspecting components, and installing against a quality management checklist to confirm that vendors are performing all the necessary quality assurance and control activities, as well as verifying that the items are being manufactured in conformance with the design documents and approved submittals. To avoid loss of time and unnecessary expenditures, pre-FAT inspections are important to certify the readiness of the vendor before formal tests are executed.

Figure 5.Capital Cost Metrics - This outlines some of the metrics that may be developed to monitor quality for the cost performance.

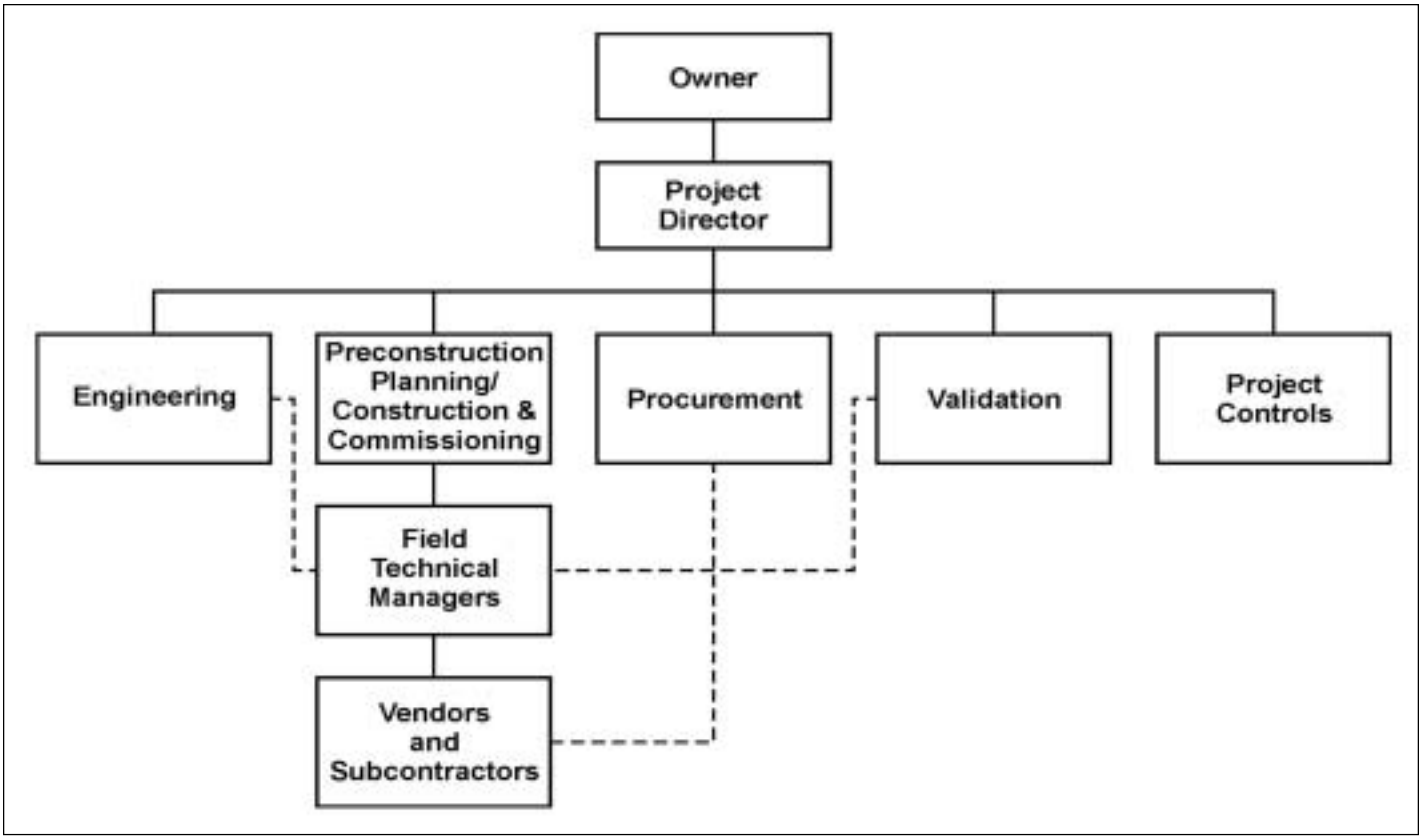

Figure 6. Project Team - This outlines the various organizations that must come together as one team for optimum project performance. The positioning of the field technical managers and their interface with the various project team members is the central focus for the execution of the quality plan.

An effective prefabrication or module plan minimizes the field labor component of the work to installing the connective tissue between process, mechanical, electrical, and control systems.

Utilization of Project Mock-Ups

Full-scale project mock-ups containing exact replicas of all components, materials, and methods are a helpful tool in quality management. They are useful in communicating the final product prior to the start of construction. Mock-ups allow for the verification of design details and serve as the minimum quality standard throughout construction. The mock-up may be a full-scale replica of a portion of the project that will ultimately be discarded or an in-place mock-up. The in-place mock-up is the first of a kind project element actually built by the subcontractor.

Mock-ups are examined and evaluated for conformance with project criteria and owner expectations by the owner, designer, construction manager, and subcontractor teams. After being approved, it will serve as the benchmark for the minimum quality standard for the balance of the subcontractor's work. Mock-ups are particularly useful for cleanroom components and finishes where the exact level of quality expectation is difficult to communicate in written form.

Procurement and Subcontractor/ Vendor Requirements

The key to the success of a pharmaceutical or biotech manufacturing project is effective procurement planning and execution. In order for this process to meet the demands of the project, a significant amount of planning must be completed and the requirements incorporated into the requests for proposal.

In addition to the customary general conditions, submittal and coordination requirements of a project, specific direction regarding prefabrication, start-up, commissioning and validation schedules and responsibilities, build clean protocols, quality control requirements – complete with formal acceptance criteria, and mock-up requirements must be identified and incorporated into the requests for proposals. Failure to complete the planning prior to solicitation of proposals will result in exposure to change orders and potential schedule delays after the contract award - *Figure 8*.

Figure 7. Prefabrication on Strategy Impact on Site Labor Requirements - This demonstrates the reduction in peak site labor forces associated with a prefabrication approach using conventional building construction. The reduction in the peak is a reflection of the reduced requirement for process, mechanical, electrical, instrumentation and control, and architectural trades on the project site.

Build Clean Protocols

Essential to the construction of a pharmaceutical or biotech facility is the definition of site and building cleanliness requirements. Developing and implementing a series of "build clean" protocols that are progressively more restrictive as the construction progress migrates from initial activity to start-up and commissioning will promote the maintenance of a clean site and interior. An effective plan will minimize the timeframe for final facility cleaning, start-up, commissioning, certification, and environmental monitoring of classified space.

Material and Document Control

An element often overlooked is the management of the receipt and storage of pre-purchased equipment and components. For effective control of materials and equipment, there must be a plan for the acceptance, recording, quarantine, inspection, and tracking of equipment and components on site until they are released to the subcontractor for installation. Maintaining a material receipt and tracking log prevents loss and the need for replacement.

Field Management

Field quality management begins with a kick-off meeting with each subcontractor before their work begins to confirm that the work will be carried out according to the current plans, specifications, and approved submittals.

Quality management of the construction process is achieved through planning and procedures that ensure that all work is executed to meet the end users expectations. This includes preventing the installation of defective work, detecting and remediating it early on should it occur, incorporating field observations made by the owner's project team, efficiently planning and conducting the start-up and commissioning of systems, and effective training and turnover of the building to the owner's facilities managers.

Work that is not in compliance with the contract requirements should be recorded and tracked, and a non-conformance report issued to the subcontractor describing the problem and the corrective action and when it must be corrected. The item remains outstanding until the issue is remedied and signed off on by the construction team and the originator. The goal of this procedure is for all non-conforming items to be corrected before substantial completion of construction.

Safety

Safety performance on any project is the highest priority component of the work. A comprehensive plan, training, and constant diligence is the key to ultimate success. It is the responsibility of the construction management team to ensure that the designs produced can be built safely and that the work is scheduled in a risk free manner to the site construction workforce - *Figure 9*.

Start-Up, Commissioning, and Validation

Preparation for start-up, commissioning, and validation begins prior to issuing the first request for proposal for either equipment or subcontracts. Prior to the procurement activities, a detailed plan must be in place to properly communicate the roles and responsibilities to all parties. The results of this plan are incorporated into project specifications and scope of work documents to ensure that the required resources, deliverables, expertise, and expectations are properly communicated to the bidding vendors and subcontractors with regard to start-up, commissioning, IQ, OQ, and potentially PQ activities.

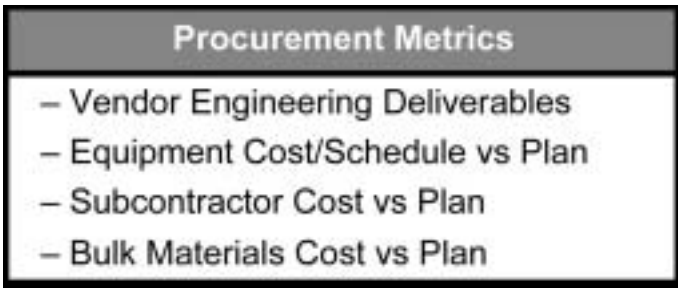

Figure 8. Procurement Metrics - This outlines metrics that may be developed to monitor quality performance for procurement activities.

Validation activities become the critical path as the construction phase of the project nears completion. In order to minimize the impact on overall schedule performance, it is necessary that the validation activities for protocol development be front-end loaded. Front-end loading the project will ensure that the appropriate protocols are prepared, reviewed, and approved for use when they are needed at either off-site fabrication facilities or on-site after final site acceptance.

Conclusion

It is the responsibility of the entire team—the owner's project and operations team, the engineer, construction manager, commissioning and validation teams—to deliver the overall project. If one of these entities does not perform adequately, the project will not achieve the level of performance set out in the project objectives.

It is essential at the beginning of a project to align all the project stakeholders to the quality metrics that will be used to determine a successful project. Incentives or penalties could be provided to each stakeholder based on the overall performance of the team. This method of overall team accountability ensures that if one entity of the team is struggling to meet their commitments, the other team members will rally behind to assist and support them to preserve the overall team performance incentive.

Regardless of the project delivery method, the contracts must be written in a manner that creates a single team. Early involvement of the construction manager and validation team will result in improved cost and overall schedule performance. Early involvement of the owner's operations team will result in a smooth transition from construction, start-up and validation activities to promote the earliest possible start date for registration runs.

If properly developed and implemented, the team will perform to meet the quality criteria established for the project, and the project will be executed in a methodical manner that permits a predictable and favorable outcome. That is a well-

Figure 9. Safety Metrics - This outlines metrics that may be developed to monitor quality for safety performance. While all projects have a goal to achieve zero in all safety categories, a target should be established based on industry guidelines and benchmarks to measure and reward team performance against.

managed project that meets the owner's expectations for quality, cost, schedule, and regulator's requirements for validation of the human care products that are produced.

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About the Author

Dean Poillucci is a Project Executive for Skanska USA Building Inc.'s Science and Technology Division, and has 20 years of experience managing the design and construction of complex installations, renovations, and upgrade projects. Prior to joining Skanska, Poillucci was the Vice President of Engineering for a process engineerng firm where he was involved in the conceptual development and design of numerous biopharmaceutical process projects, giving him the unique insight that he brings to design integration in his current position. In his role, Poillucci ensures that there is a smooth transition between the project's concept and field construction. His responsibilities for the development, planning and execution of projects include staffing and scheduling, design management, construction management and start-up, commissioning, and validation planning. Poillucci holds a BS in chemical engineering from Northeastern University. He is a member of ISPE, the American Institute of Chemical Engineers, and the Biotechnology Industry Organization.

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A leader in the Biopharmaceutical Industry discusses his company's growth, products in the pipeline, alliances with other organizations, and improving productivity in the future.

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An Interview with Craig Muir, Vice President, Platform Technology Group, Millennium Pharmaceuticals

by Janice Abel, Chairperson, ISPE Publications/Internet Committee

Craig Muir is the Vice President, Platform Technology Group, Millennium Pharmaceuticals. Founded in early 1993 and headquartered in Cambridge, Massachusetts, Millennium Pharmaceuticals, Inc. is focused on the discovery and development of small molecule, biotherapeutic (antibodies and proteins), and predictive medicine products. Millennium has extensive development programs in cardiovascular disease, oncology, inflammation, and metabolic disease. Millennium's vision is to provide personalized and precise medicine by integrating breakthrough therapeutic products and predictive medicines.

During the past eight years, Muir has assisted Millennium in developing an organization which has contributed to many discoveries and processes within Millennium's R & D enterprise, including DNA sequencing, genotyping, proteomics, and drug discovery. Prior to joining Millennium, Muir worked at Tularik, Inc., Genentech, Inc., and the University of Vermont in a number of laboratory automation settings. He is a 1982 graduate of UC-Davis where he majored in animal physiology.

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Q Please tell us about yourself.

A I have been with the company now for more than eight years. I'm a biologist by training and an engineer by experience. Before joining Millennium, I held several positions in the biotechnology industry at both Tularik, Inc. in CA, and Genentech, also in CA. Prior to this I was at the University of Vermont working on automation in the clinical trial development process.

I currently manage a highly interdisciplinary group with about 100 people, which ranges from robotics, software, automation developers, to molecular biology, proteomics, functional genomics, separation science, mass spectrometry, and computational biology. We've organized ourselves to work on a number of projects, as both consultants and independent researcher roles, and have helped establish capabilities in everything from DNA sequencing to high throughput screening. Currently, we are working in the manufacturing and pre-clinical process areas while also applying a lot of effort to early discovery work for both protein and small molecule therapeutics.

Q Could you give us some background on Millennium? I am not sure if many of our readers are familiar with Millennium. How did Millennium get started?

A Millennium was founded in 1993; we started with an early investment of $8.45 million from the Mayfield fund along with some other venture investors. The company was founded similar to most good biotech companies – with a core group of leading scientific and technical authorities in an emerging field, which was the genomics revolution. In this case, it included such authorities as Eric Lander, Raju Kucherlapati, and Daniel Cohen (France), who gave us tremendous insight into human and mouse genetics. The concept at that time was to pursue the genetic basis of disease. The notion being that genetic models, whether they be simpler organisms or humans, offer key insights into the pathophysiology of human disease, and that we would have new access to drug targets by understanding the genetic processes that regulate ailments from obesity to asthma

to forms of depression. In 1993, the genomics revolution was beginning, and model organisms (yeast/worm/mouse) and human-genome projects were at a good working stage. As a company, in organizing aggressively around this emerging field, we were able to engage a number of pharmaceutical companies to work on a number of different disease paradigms from a genetic approach, which included obesity, asthma, depression, and cancer. That's how we got started.

By pursuing the business development strategies and the alliance strategies that we took up in the early years of the company, we were able to grow the company in a very non-diluted manor. We never went back to raise more venture money after the initial offering. We moved into significant alliances with pharmaceutical companies to identify targets in particular areas of medicine, for example, diabetes and obesity. Some of those companies would take an equity position, but it was important to our development that we did not have to go back to the venture community to raise additional funds. These companies provided us with research support as well as licensing and milestone payments, so we were able to grow our business, develop a staff and commit to the development of a technology platform without assuming a lot of debt and dilution in the early stages.

Q How did were you able to convince investors to invest in Millennium initially?

A We had great founders who commanded a lot of respect in the field of human and model system genetics, and that was crucial. Furthermore, we had a commitment to develop a credible world leading technology platform, and we quickly moved to establishing high throughput sequencing and high throughput genotyping, sequencing, and transcript profiling that was all under one roof. Some of the other competitors at that time, had started to work in one or two of those technologies, and we had moved into several of them. We also had some very active collaboration and resources in both mouse and human genetics. The combination of our technology acumen in establishing automated processes, etc. coupled with the scientists that we were able to attract, as well as the excellence of our founding scientific leadership, carried a lot of influence and was highly attractive to companies. Most of the companies at the time were not interested in trying to establish these capabilities inside their companies. We represented a premier organization that entered into this exploratory field with a compelling approach to develop better medicine and to participate closely in the genetics and genomics revolution.

Q Many of our readers may not be familiar with Millennium's growth. Could you update us on how much you've grown over the past five years in terms of revenue and employees? How many employees do you currently have?

A We had approximately 200 people five years ago with revenues of approximately $50 million, which was from research support and license revenue. We would take revenue in from other companies to pay our staff, which enabled us to pursue diseases such as diabetes, bipolar disease, etc. We would identify genes for people, prioritize them as targets, and in the early stages of the company, the other companies would do the drug discovery and high throughput screening. We would pay ourselves from long-term revenues based on royalties or milestones.

What we did over the next few years through organic growth which was accelerated by acquisitions or mergers with ChemGenics in 1997, LeukoSite in 1999, Cambridge Discovery Chemistry in 2000, and COR Therapeutics in 2001, is move to establish Millennium as an integrated biopharmaceutical company. If you fast forward to where we are today, we are in excess of 2000 people, and our R&D investment for 2001 was more than $400 million.

Growth has been phenomenal, going from 200 employees to more than 2000 employees in a five-year period.

Q Why do you think that you've grown so fast?

A In terms of why we've grown this fast, and certainly one of the reasons that attracted many of us to this company, was confidence in the business leadership, particularly in the leadership of our CEO, Mark Levin, and some of the other great people that were involved. One of the things that you will find that differentiates us from other members of our era, was that we were very committed to developing critical mass around areas where we needed capabilities: bioinformatics; automation and engineering; protein expression and purification; high throughput screening are a subset of the competencies

Figure 1. Microscope Mol Pathology.

which we have put significant effort into, not just a few people here and there.

Some of the companies that you look at today are only just recently bringing in a drug discovery capability, and that has been an advantage to us. The genomics revolution has come much more quickly than people anticipated. The need for folks to exploit or leverage assets by translating into value added processes, like identifying their own leads (targets and compounds), not just living on royalty or milestone income, was something that we saw early on as being important to us. It was one of the things that drove us to build critical mass not just in genomics, but also in other competencies such as assay development, high throughput screening, etc. which are essential for leveraging the genomics assets and genes which are ultimately turned into drug compounds that are good for people. It was an aggressive approach for building a new company.

Q Do you think that you will be able to decrease the time to market for new pharmaceuticals with your work in Genomics?

A We anticipate that will be the case. As a nine-year-old company, we have to be careful not to oversimplify what has taken tens and hundreds of thousands of people the better part of their careers to do. But what we have learned in building processes, for example from DNA sequencing, is that we have developed people, knowledge, and tools that we can interject into more classically established drug processes in such areas as drug metabolism, pharmacokinetics, and QC related to manufacturing processes. We are able to bring to bear people, knowledge, or technology that will help those later stage drug processes become more efficient. We certainly anticipate that we will be able to bring drugs to market sooner as time goes on, and that is certainly a core concept of what we are committing ourselves to in terms of improvements and productivity.

Q How does Millennium differentiate itself from other biotech companies?

A At the end of 2001, we spent roughly $400 million on R&D, and that's the third highest in research expenditures for the top biopharmaceutical companies with only Genentech and Amgen spending more. Although these companies have been around longer than us, we were right up there in terms of investment in R&D. This is supported by the partnerships that we have, and by the money that we raised in equity markets in 2000. For our age, we are investing very heavily, much more heavily than smaller biotech companies. We have a strong cash position. Additionally, Millennium is different compared to other biotech companies in that we have heavily invested in technology and informatics related to not just discovery or modes of trying to understand gene function, but in proteomics and high throughput screening. One of the things in the early days that investors and potential partners would ask us is how are you different than genomics company X or tool company Y? We would answer, which is still the case today that we weren't just doing high throughtput sequencing or positional cloning to discover genes. We have extremely strong and committed efforts in a whole range of key areas and drug discovery. From genomics right into gene function right through high throughput screening, including strong commitments to microfluidics and novel compound storage and retrieval systems we focus attention on process innovation and integration. For example, we had one of the finest proteomic groups in the world a few years ago, and have recently made new leadership commitments to this area to enhance it further. That is one of the things that is different about us. We have built a leading technology platform, both in depth and in breadth with a great commitment to informatics. We're not just using external tools that other companies are developing; however, we do work with many talented external tool developers both in informatics as well as instrumentation. We have more than 100 people in software and informatics, developing the tools that are going to be critical to finding better drugs in the context of the productivity revolution.

Q Could you tell us about some of your alliances?

A Our current alliances include Aventis in inflammatory disease, Abbott in metabolic disease, and a very active relationship with Bayer in a broad number of pathophysiology including hematology, oncology, and cardiovascular disease. One of the things that we touched on in the beginning (of the interview) was that in the early part of our alliances, we were doing very high value added content research. We were paid revenue support and milestones and ultimately royalties on genes or targets that we would find for other people, and then the other companies would do the screening and drug development. We've changed that over the years, to the type of relationships that we have today, which are literally 50-50 relationships that include not just discovery, but chemistry, drug development, and shared marketing etc. These new types of relationships are critical to the company's transformation and demonstrated the vision that we were not going to operate only as a provider of value added content research. We were going to be building highly viable capabilities in drug development. We have great people.

The Abbott relationship was for $250 million for the co-development and commercialization in metabolic disease, specifically for obesity and diabetes. Aventis strategic alliance was for $450 million for the co-development and commercialization in inflammation for asthma and gastrointestinal disorders. One of the differences between these relationships and other companies that have done alliances, is that in every relationship there is not just a research component in terms of discovering gene function or in finding new leads or targets to pursue in chemistry and in taking them into the clinical development process, but in all of these relationships, we include collaboration, technology, and/or the relationship. In the case of Aventis, part of that relationship is that we transfer all the technology developed and make it available for Aventis to adopt in their own organization. These relationships help monetize the investment that we made in the platform for other purposes. In the case of Abbott, we make a technology exchange, where we provide certain technologies from our portfolio in exchange for them making their inside technology available to us, for example, in structural biology. Those are the key differentiators for us. We realize that we can't develop everything that we need to, but we also realize that there are a lot of things that we have developed that are going to be valuable to other partners. Our business people are very

skilled at making sure that we are able to carve out this value in such a way as to prevent compromising our ability to develop drugs efficiently, but also giving the partner a great value for the technology that they would otherwise have to create themselves. And, again, we represent a 'one-stop shop' for a number of cutting edge pharmaceutical technologies.

Q How early in the process do large pharmaceutical companies look at your products? Are they looking at products that have commercialization potential in one, two, or more years?

A New partners today may be looking at products that we have in clinical development. Other partners look at earlier stage work, in pre-clinical, that we might be looking to accelerate because we have new resources. Other partners may be looking at even earlier work related to pursuing new target classes in oncology or other examples of much earlier discovery work.

Q When you decide to move ahead with a particular product, does your strategy vary according to the type of product, your partner, or the market sector that the product is intended for?

A It's going to be all of those things. For us, if you looked at the company three or four years ago, you would have found us having active programs in anti-fungal, anti-bacterial, asthma, oncology, etc. We literally had a program going in almost all areas of healthcare. Now our business is focused in four major classes although we still have some work in some of these ongoing areas. The four major classes are: inflammation, oncology, cardiovascular, and metabolic disease. In some cases, what might be appropriate is the development of a biologic therapy like an antibody. In the case of oncology or in the case of stroke or inflammation, short-term intervention could be accomplished by a protein based therapeutic. In other cases, where we are talking about chronic therapy for a metabolic disease, we are looking at small molecules as a way that those agents could be taken long term, we are looking at a chronic therapy because metabolic disease represents a different type of disease state relative to something like cancer which has implications that are often times graver than a metabolic disease. You also may get into various issues on combination therapy, and a number of other issues in the oncology area that are not going to be the same as in something like cardiovascular.

Q Could you explain what you mean by, "at Millennium, all of our efforts are focused on a single mission: to transcend the limits of medicine?"

A From my perspective, there is a lot of opportunity to do better things in human medicine. We feel that in some cases, human medicine is limited by either the number of agents that are going to be effective against the number of forms of cancer, or some agents brought to the market and have been shown to have side effects or do not work on some people. That is the limit of human medicine, and perhaps when we think about the approach we are going to take in leveraging genomics, our ability to understand certain genetic approaches or certain diagnostic approaches are going to help us develop better drugs and help us to deliver the right drugs to the right people. In that, we feel we are able to transcend what we view as some of the current limitations of the way medicine is practiced.

Q When I started looking for background information about Millennium, I looked at your corporate brochure on the Web, and the title that came up really intrigued me. It said, "The Science of Business." Could you comment on this?

A Millennium has had unprecedented growth and generated a lot of excitement and collaboration. Our relationships and partnerships bridge the technology with the clinical world of developing good medicine for people, and in particular with scientists who have relationships with small technology companies that are interacting with other companies, and taking advantage of new opportunities as they arise.

Q As stated on your Web site, "In pursuing this vision, Millennium's unparalleled product pipeline resources have already yielded one of the deepest discovery pipelines in the industry and a development pipeline that is rapidly approaching a leadership position." Could you comment on this?

A If you look at our inflammation partnership, there are 360 people, 180 people here at Millennium and 180 people at Aventis. It is one of the largest inflammation research programs in the industry. In the oncology area, we have committed significant resources in basic discovery and pharmaceutical development. We previously have worked with a number of partnerships in oncology, and are now pursuing a lot of the work on our own. We have two molecules on the market called Campath Intregrilin, a molecule called Velcade in Phase III Clinical development, several others in Phase I and II testing, and a number of discovery programs that will come forward over the next several years.

Q Your product pipeline seems to be quite full with quite a range of products. Could you tell us about some of the major products and their impact on the market, as well as what the product does? How many patents has Millennium generated since inception? Which if any of these products have been approved by the FDA? How many are in clinical trials?

A We currently have two products on the market. Campath®, which is for chronic lymphocytic leukemia and Integrilin®, which is for acute coronary syndrome. Integrilin® is the newer product which came to us from the COR merger. You will find that we intend to bring in approximately $300 million in revenue, which is shared with our partner Schering-Plough. Campath® and Integrilin® are the two products from which we derive revenue.

Our current pipeline includes 10 products in clinical development. The most advanced drug, and the one that we are investing the most resources in, is Velcade™, which is a new class of cancer therapy agents that we are very excited about, both in terms of observations in multiple myeloma and also in other forms of oncology indications, such as solid tumor can-

cers including lung, colon, prostrate, breast, etc.

Another agent that we have in the cancer area is for a form of leukemia. There is also a biotherapeutic for prostrate cancer called, MLN591, and also some other agents being tested for metabolic disease.

Q Mike Pavia wrote an excellent article in the March/April 2000 issue of Pharmaceutical Engineering on increasing productivity in "discovery and development process by at least 100% over the next several years." Have you achieved this goal?

A I believe that one of the difficulties is that the company has changed. We have not moved away from the goal of increasing productivity by 100%; however, when we started on that mission, about four years ago, we were only about 500 people, and pretty much a company that was discovering genes, putting in place systems to do gene functions, developing assays, doing high throughput screening, and some early phase chemistry, but we were not in the clinical development process. We were not in the manufacturing process.

Now when you look at us, we are more than 2000 people, and we've taken some of our efforts and productivity improvements and are applying those improvements to other parts of the company in areas that we needed to respond to as the company matured. However, we are very much focused on moving toward the goal of improving productivity. What we also haven't done, except in the case of MLN4760, is taken a target from gene discovery all the way through to marketing. We haven't run the complete cycle enough times to say how we have done against the goal. What we have done, in an innumerable number of cases, is to put in place systems, which have improved productivity in a number of processes. I think that we have learned a number of things, and as we go forward and stay committed to productivity improvements, we will continue to identify what we consider centinal projects or centinal programs, that we know are affecting the productivity, and to use those programs to model the productivity improvements. It will probably take us an additional three to five years to be able to utilize the model that will tell us what the improvements are. We will need to complete a number of full cycles to do this.

Most of the time, people will site literature that says that for every 10 drugs that enter into the Phase III clinical process, only one will be approved. In some cases, one to two years after a drug has been approved they have to be withdrawn from market. What we look at is that a lot of drugs don't work because they are just not efficacious. There are a number of drugs that don't work because they are toxic, and they can never be approved. There are a number of drugs that just don't work because they have poor distribution or elimination for example, so we continue to concentrate on technology or process improvements that produce drugs that are less toxic with greater confidence that the drug has desirable properties. We continue to focus on a number of things, but we've also refined our perspective on how we can measure our progress.

Q The Process Department at Millennium is recognized internationally for its fundamental contributions in developing Millennium discovery engines for effective disease gene identification efforts with seven major pharmaceutical companies. Could you tell us about the technological contributions in gene identification? Who are the companies you are working with?

A We spend a lot less time on gene identification now, but we developed one of the most advanced gene sequencing facilities during that period. Our facilities are designed primarily the way that scientists will ultimately identify genes in the future. You sequence genomic DNA or electronically mine DNA. You sequence DNA software libraries that come from a number of tissues that you are interested in. And, again using electronic mining approaches that have been developed by our chromatics group, software will recognize in the DNA sequence something that looks like a gene. Then we verify the gene by comparing it to databases, which allows us to determine if it is a new gene or if it's related to another gene, etc. Both the automation and the processes that we developed were efficient at allowing us to do DNA sequencing. We had a great group in the construction of some valuable EST sequencing libraries. In the informatics group, collaborated and developed data mining and algorithms allowed us to look through sequences that were coming from the public efforts to be very efficient and effective at identifying genes.

Q What kind of changes have you seen that impact the biopharmaceutical, engineering, and manufacturing over the past few years? What changes do you anticipate in the next few years?

A Certainly, one of the things that we have seen is the emergence of improved engineering in the area of mass spectrometry. Mass spectrometry is central to a lot of drug development work in terms of drug metabolism, quantifying how much a drug is in a particular fluid or specimen. Helping us determine how drugs are metabolized inside an animal or person. The engineering in that area, alone which is so critical to pharmaceutical development, is actually incredibly impressive.

What we've also seen is higher quality automation and technology brought into the labs at all phases of gene functions and high throughput screening. Clearly, the emergence of gene array technology, which is leveraging a lot of semi-conductor grade manufacturing processes, is bringing a huge improvement in quality and a staggering amount of data is being generated and analyzed. But we're really seeing a convergence of the semi-conductor and computer technologies that are being brought into the laboratories themselves. High throughput screening continues to evolve. We are seeing some new discoveries that we think are very exciting with respect to microfluids. It's a way to screen targets against compounds to be able to screen and to target space that is not available by the modalities. We are seeing some new engineering approaches being brought to bear in chemistry. Some of the automated systems that we are doing, in such fields as organic chemistry, are starting to pay some dividends in terms of the molecules that they can make and the efficiency which they can be constructed.

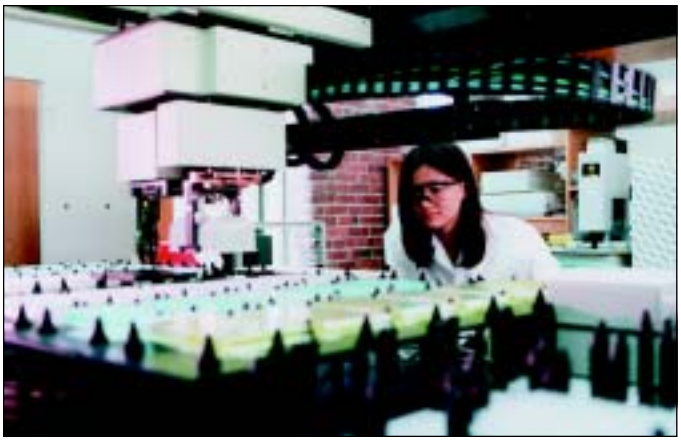

Figure 2. Technician at Cyberlab.

Q Could you explain gene array technology?

A What became quick to do was to find genes. What is more challenging, and is going to take decades for us to sort out, is what do these genes do? How do they work? Either one at a time or more importantly how do they in the networks of tens of hundreds of thousands of these in the disease process. One of the ways that people have pursued understanding gene function is to take parts of the genes and put them down onto either a nylon surface or a glass surface in some form of a highly ordered printing process. What you would realize is that all the genes of the organism are in the cells. It doesn't matter if it is a liver cell, heart cell, or a brain cell; all of the genes in the organism are in that cell. Why are the cells different? They are different because the cells use different combinations of those genes to carry out the different structural or functional consequences.

What happens is genes in the DNA state are almost dormant. A gene is active when the DNA is transcribed into a long piece of mRNA. And that gene is fully functional when that mRNA is translated into a protein. What we can do is take gene fragments onto a highly ordered surface, we can take mRNA from a cell or tissue, and apply that mRNA after a labeling technique onto this ordered array, and we will be able to understand how much of the gene is present by the intensity of the spot that is visualized in the ordered array. If we compare one array to an array that has a tumor on the array to an exact copy of that array with normal mRNA, we can compare on a gene-by-gene basis which genes are more or less active. This will give us some insight into the genes function.

There are 100 different ways that people think about using gene arrays. A pattern of gene expression helps a cell become a heart cell versus a brain cell. It's a pattern of gene expression that may indicate a toxic response to a certain compound, a pattern of gene expression that may be crucial to differentiating one tumor type with another. Or telling us whether this person is responding to this particular type of therapy while this other person is not. Gene array or gene expression profiling is a major tool that has emerged in the industry, and is something that we are very good at in Millennium.

Q What is your long-term vision for Millennium? What is your vision for the biotech industry over the long term?

A In terms of what I think we will see in the next few years, we will see more technologies like gene arrays that have to be played out so that we find their true niches and generate the value of helping us classify patients or predict which therapies are best or give us earlier indications of what a toxic agent looks like and help us design around this. I think that through mRNA profiling is an established technology that almost every company in the world is using right now.

But the protean and understanding the proteins and all of the events associated with proteins is really the challenge and is what we are investing in. We have a great group working on this, but it is a very challenging problem. It is hard to describe, but it is 10 times more complicated than the genome project because proteins are so much more heterogeneous. DNA is essentially A-G-T-C over and over again. It is a very elegant, but a very ordered system. Proteins are made from 20 different amino acids, they're modified with sugars and phosphates and sulfurs, etc. Understanding how the cell goes about controlling all this information, how is that encoded, is something that I believe that we will be spending a lot of time trying to figure out. Fortunately, there are short-term things that we do that can give us great value. We have found markers in protean mixed in that we believe predict inflammation in terms of what we see in someone's blood that can tell us about their rheumatoid arthritis. But to really understand all the proteins, how they are modified, and how they are regulated, is a long-term project. That is what is in front of us.

Q Do you plan on manufacturing and commercializing Millennium's products? Are you emphasizing in-house development and licensing?

A Yes, we are planning on manufacturing and commercializing our products. We are currently doing contract manufacturing and a 'manufacturing web' in which different steps are handled by different contract manufacturers. This is the way we are currently growing the business. What we don't want to do is to develop an agenda and transfer the ownership of the manufacturing process. Those issues are so crucial to having a high quality business and to ensuring the quality of the product that you are going to be providing to people. The way that the product is delivered to folks, the way that you are able to report back to your research organization about different products can benefit the patient. That loop is completed not just by research and discovery, but also in research, manufacturing, and commercialization.

Q What do you see as emerging technologies in the biotechnology industry? What is Millennium implementing?

A One of the major things that I see is that we are moving to an era where we are not only trying to collect information, data expression databases, or compound databases. These are information sources. If you link them with some new capabilities and tools, you generate knowledge. Using a com-

bination of linking databases, but also electronic mining of text or references, etc., we start to develop inferences and knowledge that becomes the era we are working in now. We have too much information for people to be processing by their eyes and we want to be able to mine this information and share it with people. We don't want a person to be rediscovering concepts in three different locations because we didn't have the tools to alert them to something that is related to what they are working on.

Q What about technology products?

A Microfluidics, micro fabrication, and micro technologies, whether it be in sensors for doing different types of clinical or pre-clinical monitoring, is an emerging technology that we are implementing. Certainly in microfluidics, we're doing drug discovery. A lot of new things are happening in other areas, for example, in high throughput structural biology, the crystallization of proteins in a high throughput manor allows us to electronically and computationally look at how a compound is interacting with a particular protein.

Magnetic Resonance Imaging (MRI) is going to continue to be a very exciting area, and has the potential to revolutionize cardiovascular and other disorders treatment. There are lots of new and exciting things happening in imaging, using MRI and other techniques, to look inside animals or people. MRI images can depict pathophysiological pathways.

We've seen some new opportunities in chemical analysis, both in the quality of what is happening to a drug inside a person, what it turns into, and how it is eliminated, etc. There are going to be a number of additional opportuntities that will play out. Again the gene expression array or the proteomics, an analysis of the cell's constituents, will see improvements, both incremental and at times revolutionary.

Q Do you think that Millennium could become an acquisition target?

A When you look around the industry, at what's happening, it is not possible to rule out the possibility of being an acquisition target; however, it is unlikely because we are independent minded. I could not say that we wouldn't be one. It is certainly not something we think about a lot; however, when you look around the industry in terms of what's happening today, it is a possibility, even though we would not want to go that way.

Q Is there anything else you would like to share with our readers?

A I think we live in a time of great opportunities and great challenge. Clearly there are people who need better medicine. We have to make sure that the medicine that we bring to people are good for them and won't be taken off the market. We are in an era of tremendous technological opportunity in terms of machining, material science, and information processing. It's a great time to be in this business, to leverage the technology, and the resources to continue to improve healthcare.

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Using New Cleanroom Standards with Sterile GMPs

This article explores the symbiotic relationship between current Good Manufacturing Practices (cGMPs) and the new ISO cleanroom standards with regard to sterile products processing.

by Gordon Farquharson

Current Good Manufacturing Practice (cGMP) documents and their guidance annexes are dependent on technical standards and specifications for the effective implementation of process and facility solutions.

However, when considering the technical standards associated with cleanroom technology and air filtration, it is important to recognize that the standards are generic and not application specific. The standards cover a vast array of cleanliness classifications and associated performance parameters. They do not highlight requirements for specific industries, and as such, are limited in their definition of many aspects of process and product-related good practice, and more importantly, regulatory expectations.

The generic nature of cleanroom technology standards has ensured that cGMPs play an increasingly important and supportive role, providing essential guidance on the particular requirements of specific processes.

This symbiotic relationship between cGMPs and standards will become increasingly evident over the coming months as the global cleanroom standards, introduced by the International Standards Organization Technical Committee 209 (ISO TC 209), replace existing standards such as US Federal Standard 209E (FS 209E).

Three of the 11 standards have already been published: ISO 14644-1, Cleanrooms and Associated Controlled Environments, Part 1 - Classification of Air Cleanliness; its sister document ISO 14644-2, Cleanrooms and Associated Environments, Part 2 - Specifications for Testing and Monitoring to Prove Continued Compliance with ISO 14644-1; and ISO 14644-4, Cleanrooms and Associated Controlled Environments, Part 4 - Design, Construction and Start-Up. Another key member of the family, which will be published shortly, is ISO 14644-3, Cleanrooms and Associated Controlled Environments, Part 3 – Metrology and Test Methods.

ISO 14644-1 is the key standard from the work of ISO TC 209, setting out the particle classification system, while ISO 14644-2 sets out the basic requirements for monitoring and testing cleanrooms and associated controlled environments to demonstrate that classification compliance continues to be achieved.

On November 29, 2001, the US initiative within ISO was rewarded when the rather outdated US FS 209E was cancelled and superseded by the new ISO 14644-1 and ISO 14644-2 standards. This is a significant development. It means that while established operations can continue to be classified and monitored against FS 209E for a time, organizations need to ensure there is a changeover migration plan in place to accommodate the new standards. New facilities should now be specified, designed, procured, tested, commissioned, and monitored in accordance with ISO 14644-1 and ISO 14644-2.

In light of the new cleanroom technology standards, certain specific requirements of the cGMPs should be explored and an explanation of how the ISO standards fit in with them is needed. Cleanroom performance and technical requirements relating to particle classification, bio-contamination control, HEPA filter selection, filter testing, room pressurization, air exchange rates, unidirectional airflow system velocity, and performance monitoring are considered below. These areas are viewed in relation to the environmental requirements within Annex 1 of the EU GMP, some of the essential requirements in the FDA's 1987 Aseptic Processing Guide, and USP 25 Chapter 1116.

Following the recent publication of the GMPs from the Pharmaceutical Inspection Cooperation Scheme (PIC/S) organization, it should be noted that this document is based on current EU GMP. The remarks made in this article concerning EU GMP therefore apply equally to the PIC/S GMP.

Microbiological Limits

Setting and working within microbiological monitoring limits is one of the essential cleanroom control parameters demanded by the healthcare industries. Regulators have set out their requirements in various ways.

The regulatory and pharmacopoeial specifi-

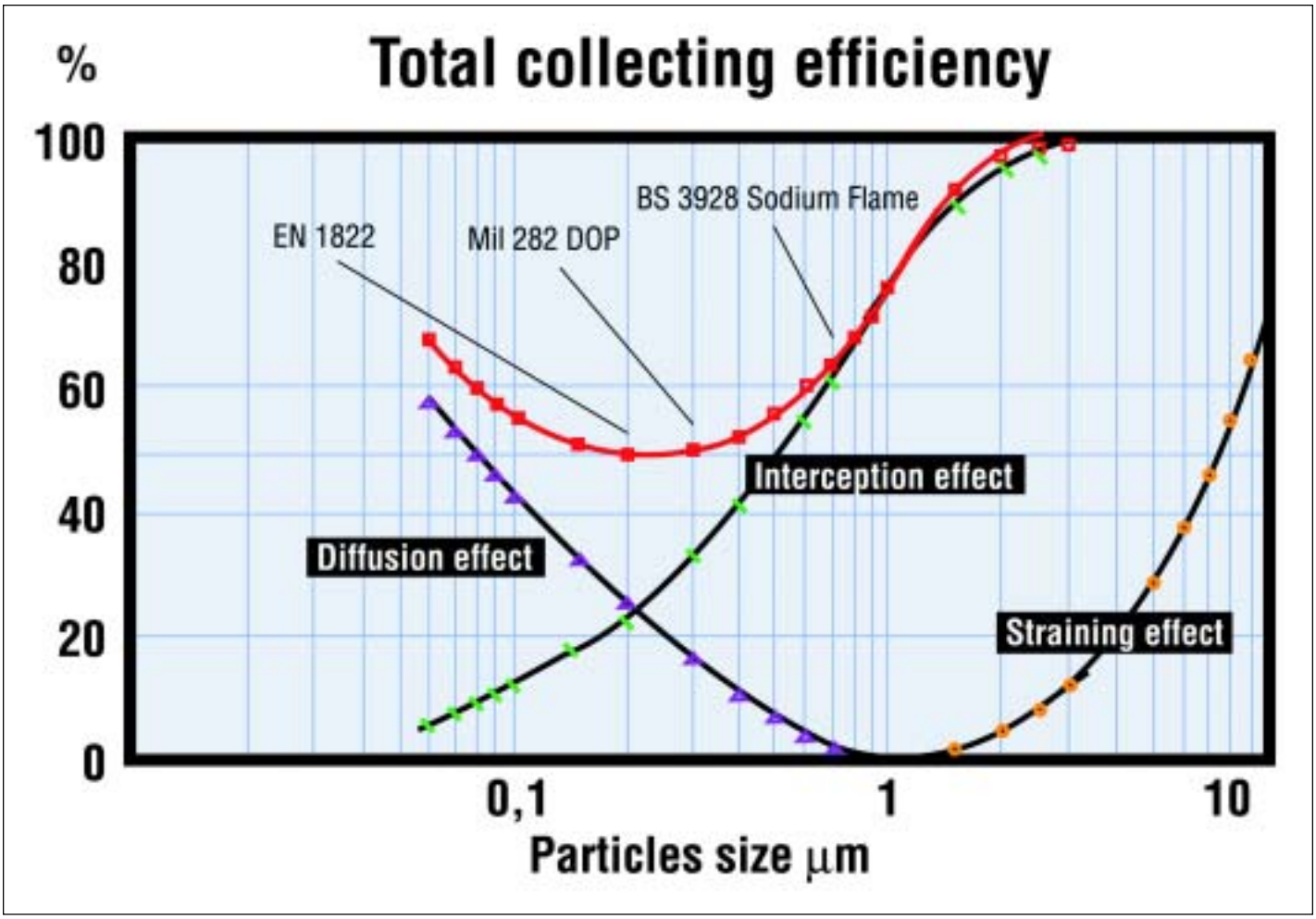

Figure 1.Total collecting efficiency for a HEPA filter.

cations for microbiological limits of sterile product manufacturing environments are defined in EU GMP Annex 1, the FDA's 1987 Guide, and USP 1116 - *Table A*. The table offers a simple comparison between the EU GMP, the FDA's Guide, and USP 1116, indicating equivalent levels of airborne colony forming units per cubic meter of air sample. Ideally, these requirements would be identical, but through comparison, we can derive the most demanding requirements as a starting position.

It is important to note that ISO TC 209 also has produced two key microbiological standards - ISO DIS 14698-1 and ISO DIS 14698-2. These specify basic good practice relating to microbiological environmental monitoring and data assessment. They can be used to help develop a monitoring plan and evaluate the data collected. These two microbiological standards do not include any classifications or set any industry specific limits and are therefore fully supportive of the cGMP requirements and their limits.

Airborne Particle Limits

Airborne particle concentration is perhaps the best known and certainly the quickest way of determining the cleanliness of a working environment and detecting deviations from target values. EU GMP Annex 1 clause 3 defines the airborne particle control requirements for the working environment. Table B shows the airborne particles related to the environmental grades at both the 'at rest' and 'in operation' conditions.

Many of those with experience of applying the EU GMP guidance accept that information relating to 'at rest' and 'in operation' conditions are highly appropriate. Certainly, from the viewpoint of cleanroom or clean-air device procurement, it is important to have a benchmark to differentiate the technical specification of the equipment from the operating conditions.

The important issue within this guidance is that airborne particle numbers set out in Table B are significantly different from those within the nearest equivalent cleanroom standards ISO 14644-1 or the superseded FS 209E. Of greatest significance is the zero specification for particles of 5µ and greater for grade A and B 'at rest'. In Table C, the 0.5µ and 5µ particles have been abstracted and illustrated for the EU GMP grades A through to D, and ISO classes 5 to 8, to highlight the differences.

When considering good particle counting technology, it is important to recognize the limitations of these dynamic systems. The airborne particle counter relies upon light scattered within an optical chamber being detected by a photo-multiplier tube detector. The system detects the 'flashes' of scattered light in terms of number and intensity. This information is evaluated by the electronic system within the particle counter to produce a record of particle numbers and sizes. Not only are such systems susceptible to electronic noise, but there is also potential for coincidence counting error that occurs when greater numbers of small particles close together can be counted as a smaller number of larger particles.

Working Zone	EU GMP Annex 1 Requirements cfu/m³	FDA 1987 Aseptic Guide Requirements cfu/m³	USP 25 <1116> Requirements cfu/m³
Aseptic core	Grade A < 1	< 3.5	< 3
Aseptic processing area	Grade B < 10	Not specified	< 20
Controlled processing area	Grade C < 100	< 88	< 100
Controlled support area	Grade D < 200	Not specified	Not specified

Table A. Comparison between EU GMP, the FDA's Guide, and USP 25 1116.

Some basic guidance concerning good particle counting practice can be summarized by stating that a particle counter should never be used to look for zeros. In the event of having a small and potentially insignificant population of particles in the environment to classify, select a smaller particle size with a greater particle population at that class limit.

The specification within ISO 14644-1 is virtually identical to that stipulated in the superseded FS 209E regarding the calculation of sample volume at each location for classification. The formula below is used in both standards to define the sample size required to obtain a target count of a minimum of 20 particles should the particle concentration be at the class limit for the largest particle size considered.

Vs = 1,000 x 20/(class limit) liters

If zero is applied as the class limit in this formula, the resultant sample size is infinity – a clearly impractical and inappropriate 'value'. A similar review of FS 209E reveals that exactly the same requirement is expressed within this now superseded standard. This conflict between the EU GMP and the technical standards is further complicated by the fact that the EU GMP makes specific references to the ISO classes and the US FS 209E metric classes within Annex 1, including a table that is at variance with these standards.

When reviewing the same issue in the superseded US FS 209E (Table D), it is clear that for the class M3.5 (class 100 in imperial or English units), this standard does not deem the 5.0µm particle to be an appropriate particle size to use for the classification of such an environment. It is therefore not possible to use the tabular element of 209E to classify an M3.5 environment at 5.0µm and greater particle sizes.

Historically, the FS 209 evolution of standards was derived from the needs of the micro-mechanical and microelectronics industries, where interest has always been focused on smaller and smaller particles. Also, for airborne particle counting, knowledge has matured about the statistical reliability of the process requiring a significant population of particles in a sample.

Close inspection of a similar table from ISO 14644-1 (Table E) reveals that for ISO Class 5 (the nearest equivalent class to M3.5 or Class 100), the standard includes a specification for 29 airborne particles/m³ at 5.0µm and greater. However, it is worth remembering that this table is an illustration of a formula. If one subsequently calculates the air sample volume required to classify an environment with this very small number of particles, the sample size required is impracticably large.

The ad hoc group of pharmaceutical inspectors responsible for drafting the EU GMP is concerned about this problem and is clearly of the opinion that 5.0µm particles are more indicative of bio-contamination than 0.5µm particles. It is for this reason that they wish to retain evaluation of 5.0µm particles within the EU GMP specification for the critical environment for the manufacture of sterile products.

Many European regulatory inspectors are happy to accept classification and evaluation of the performance of critical environments for sterile products in accordance with the principles defined in both the superseded FS 209E and ISO 14644-1. However, it is advised that careful attention is paid to explaining the approach to the regulators.

How, for example, does one combine a basic classification based on the 0.5µm requirements, and express the 5.0µm and greater particle levels measured as indicative? One solution is to use EU GMP to select the particle sizes to be considered. However, where zero particles @ 5.0µm are required for grade A and B (at rest), this shouldn't be used as a formal classification. One would end up with the following classification statement: ISO 5; operational; @ ≥0.5µm and ≥5.0µm indicated. According to the standard, an infinite air sample is required to determine a zero-count compliance at ≥5.0µm. The sample size taken was based on the ≥0.5µm class limit sample size, and therefore the particle count at ≥5.0µm must be considered to be an indicative value.

Recent discussions with members of the ad hoc regulatory group reviewing Annex 1 of the EU GMP suggest that some adjustment along these lines is likely to be adopted in the near future. As a matter of reference, the equivalent requirements

	At rest		In operation	
EU GMP Grade	Maximum number of permitted particles/m³ equal to or above			
	0.5µm	5.0µm	0.5µm	5.0µm
A	3,500	0	3,500	0
B	3,500	0	350,000	2,000
C	350,000	2,000	3,500,000	20,000
D	3,500,000	20,000	Not defined	Not defined

Table B. Airborne particles related to environmental grades.

	EU GMP requirements				Nearest equivalent classes from EN ISO 14644-1		
Particle size considered ≥	EU GMP Grade A	EU GMP Grade B "at rest"	EU GMP Grade C "at rest"	EU GMP Grade D "at rest"	ISO 5	ISO 7	ISO 8
0.5µ	3,500	3,500	350,000	3,500,000	3,520	352,000	3,520,000
5.0µ	0	0	2,000	20,000	29	2,930	29,300

Table C. Comparison of EU GMP and ISO classes.

set out within the FDA's 1987 *Aseptic Processing Guide* are much simpler and refer only to classifications of 0.5µm particles defined in FS 209B of the time.

It is safe to assume that the FDA will revise the table substantially within its rewrite of the *Aseptic Processing Guide*, and it will be interesting to see how it will deal with the loss of FS 209E. It may be prudent to make cross-reference to the 209E classification system with which many parties are immediately more familiar and comfortable.

Cleanroom Air Change Rate

Effective mixing of clean supply air with contaminated room air is the mechanism used in the 'non-unidirectional flow cleanroom' to control the level of airborne particles. The volume of air used to achieve the required dilution is usually expressed in terms of room air-changes/unit time.

However, none of the ISO family of cleanroom standards defines the particular requirements of minimum air change rate for non-unidirectional flow rooms. Yet, reference to ISO 14644-4 will show that there is specification of the issues that should be considered such as heat gain, contamination source, and dilution.

Within ISO 14644-3 and the similar IEST RP006.3, there is a specification of a range of test methods that are relevant to measuring airflow within both non-unidirectional and unidirectional airflow systems. The FDA's 1987 *Aseptic Processing Guides* defines the minimum air change rate of 20 air changes per hour in non-unidirectional flow areas, and the EU GMP Annex 1 implies an air change rate by specification of a clean-up period.

The EU GMP defines air-change rate in a less specific but more demanding way. For instance, if one considers the 'operational-to-at-rest' recovery time defined within Annex 1of the EU GMP is 15 to 20 minutes, this would require to an effective air change rate of 21 to 28 air changes per hour, assuming perfect mixing. The clean-up rate or recovery time is a much more effective method of determining or stating the performance of a working non-unidirectional cleanroom than that of arithmetical air change rate.

Selection of HEPA Filters

HEPA filters are the essential final stage of air filtration used to control the quality of air entering cleanrooms or clean-air devices. Strangely, their selection is not well defined.

Neither the EU GMP Annex 1 or FDA's 1987 *Aseptic Processing Guides* state any specific requirements for a particular HEPA filter grade. Furthermore, none of the ISO 14644 family of cleanroom standards defines HEPA filter selection in relationship to a particular cleanroom or clean-zone class. However, the FDA's 1987 Guide implies an efficiency of HEPA filter by defining a 0.01% penetration *in situ* leak-test limit.

Generally, the 'clean air' industry is moving to new HEPA filter specifications relating to the Most Penetrating Particle Size (MPPS) test method, making filter specification and comparability to old manufacturing and testing standards confusing and at risk of error.

Class Name		Class limits									
		0.1µm		0.2µm		0.3µm		0.5µm		5µm	
		Volume units		Volume units		Volume units		Volume units		Volume units	
S1	English	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)
M 1		350	9.91	75.7	2.14	30.9	0.875	10.0	0.283	--	--
M 1.5	1	1240	35.0	265	7.50	106	3.00	35.3	1.00	--	--
M 2		3500	99.1	757	21.4	309	8.75	100	2.83	--	--
M 2.5	10	12400	350	2650	75.0	1060	30.0	353	10.0	--	--
M 3		35000	991	7570	214	3090	87.5	1000	28.3	--	--
M 3.5	100	--	--	26500	750	10600	300	3530	100	--	--
M 4		--	--	75700	2140	30900	875	10000	283	--	--
M 4.5	1000	--	--	--	--	--	--	35300	1000	247	7.00
M 5		--	--	--	--	--	--	100000	2830	618	17.5
M 5.5	10000	--	--	--	--	--	--	353000	10000	2470	70.0
M 6		--	--	--	--	--	--	1000000	28300	6180	175
M 6.5	100000	--	--	--	--	--	--	3530000	100000	24700	700
M 7		--	--	--	--	--	--	10000000	283000	61800	1750

Table D. Classification table abstracted from FS 209E.

Table 1 - Selected airborne particulate cleanliness classes for cleanrooms and clean zones						
ISO classification number (N)	**Maximum concentration limits (particles/m³ of air) for particles equal to and larger than the considered sizes shown below (concentration limits are calculated in accordance with 3.2)**					
	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1 µm	5 µm
ISO Class 1	10	2				
ISO Class 2	100	24	10	4		
ISO Class 3	1 000	237	102	35	8	
ISO Class 4	10 000	2 370	1 020	352	83	
ISO Class 5	100 000	23 700	10 200	3 520	832	29
ISO Class 6	1 000 000	237 000	102 000	35 200	8 320	293
ISO Class 7				352 000	83 200	2 930
ISO Class 8				3 520 000	832 000	29 300
ISO Class 9				35 200 000	8 320 000	293 000
NOTE: Uncertainties related to the measurement process require that concentration data with no more than three significant figures be used in determining the classification level.						

Table E. Informative classification table abstracted from ISO 14644-1.

It is critical that a clear requirement for filter grade or specification is defined if the pharmaceutical industry is to avoid over specification and testing problems in the future. The applicable *in situ* leak-test method also should be clearly defined if the regulators require or wish to restrict the type of oils or test methods used for leak-testing filters.

Figure 1 shows a classic total collecting efficiency curve for a HEPA filter, illustrating the problems associated with different test methods. Because available test methods use different particle sized aerosols and methods of measurement, they can express very different efficiencies for the same filter. Care must therefore be taken when specifying filters, including a clear definition of the test method used when the product was manufactured. The new Parenteral Society Monograph No 2 'Environmental Contamination Control Practice' (Second Edition) provides the kind of guidance that should be included within cGMP regulation.

Unidirectional Airflow

Unidirectional airflow (UDAF), formerly referred to as Laminar Flow, remains one of the key methods of protecting the critical aseptic core through the delivery of a controlled airflow of defined particulate quality. Typically used in pharmaceutical applications, the systems and their specifications must now satisfy a number of different protection concepts, including a traditional open cleanroom environment, a fully enclosed isolator or a composite restricted access barrier system. These systems have different requirements and constraints and the traditional open cleanroom solution is unlikely to be applicable in all situations.

In recognition of the vast range of different clean-air devices, ISO 14644-4 specifies simply that the velocity should be >0.2 m/sec for unidirectional airflow systems. The standard emphasizes that the demonstration of the effectiveness of the airflow by determination of the airflow uniformity is more critical than choosing a specific velocity alone. This focus on the demonstrable effectiveness of the clean-air system is also reflected by current regulatory expectations to see videoed smoke patterns of unidirectional airflow systems. Within both ISO 14644-3 and IEST RP006.3, there are specifications for basic test methods relating to measurement of airflow velocity and for the determination of flow uniformity.

For most UDAF systems, the well-established value of 0.45 m/sec (±20%) will be appropriate. Higher values of around 0.6 m/sec and lower values of around 0.3 m/sec will be needed to protect hot bodies and isolator internals respectively.

Cleanroom Monitoring

Monitoring a cleanroom or clean-air device is a critical part of cleanroom standard and GMP compliance. For instance, processing environments are only appropriate if they are correctly specified, designed, and commissioned against the relevant specification, and ultimately monitored on a frequent or continuous basis.

ISO 14644-2 includes a number of important specifications relating to the monitoring of cleanrooms and clean-air devices for continued compliance, including the basic requirements for strategic testing (re-qualification) together with ongoing monitoring.

The most important aspect of this standard is that it recognizes that the strategic re-test frequency can be reduced, ie, the intervals between strategic re-tests can be extended provided monitoring of the working environment is effective. In addition, the standard requires that the monitoring demonstrates satisfactory performance although current GMPs do not define adequately the use of state-of-the-art facility monitoring systems. The frequencies of monitoring in this standard would be considered a minimum in a non-regulated industry and it is often the case that pharmaceutical regulators expect more frequent monitoring.

Cleanroom Pressurization

Cleanroom pressurization is a critical performance parameter for all enclosed cleanrooms because it is one of the essential conditions that helps achieve segregation between adjacent cleaner and less clean rooms. For example, the EU GMP states that there should be a pressure difference between spaces of different classification in order to achieve effective cleanliness segregation.

ISO 14644-4 includes an important section relating to room pressure variations. The standard identifies a likely tenable range of room pressures, but most importantly, explains that

it is much more critical to demonstrate that pressure levels are appropriate and can be maintained under normal operating conditions.

Within the pharmaceutical industry, the proven 0.05 in wg or 12.5-15 Pascal steps are still applicable for cleanroom suites. These values are large enough to be measurable with simple instruments, and small enough to be achievable with normal ventilation fan engineering and cleanroom construction.

Summary and Conclusion

At a time of significant change in the standardization of cleanroom cleanliness and air filtration, there is still a need for a symbiotic working relationship between GMPs and the technical cleanroom standards. The standards, for example, can be considered as the basic tools and the GMPs' specifications as the requirements and principles.

The use of increasingly varied contamination control solutions means powerful yet flexible standards are required. The ISO standards satisfy this objective. Unfortunately, by moving forward, discrepancies between the GMPs and the standards also have been created. Effective methods of managing these relatively minor problems must be found although it must always be remembered that the particular requirements of a specific process will ultimately define the solution adopted.

In January 2002, Rick Friedman of the FDA pointed out: "These standards should not be misunderstood or misapplied as conferring cGMP conformance on sterile drugs. FDA regulations and guidance provide information to facilitate pharmaceutical industry compliance, and their standing is not affected by the ISO documents. The ISO documents, like their 209E predecessor, are simply key references to consult when one is conceiving the program for qualifying particulate quality for a given pharmaceutical clean area.

"There are a few major differences between the old FS 209E and ISO 14644-1/ISO 14644-2. For instance, ISO exclusively uses the metric system (particles/m^3) and some calculations permit less samples to qualify a Class 100 area (ISO Class 5). Also, ISO has new advice on data handling that may produce some results that differ from that found in 209E.

"A drug firm will need to ensure that protocols and procedures are adapted to conform fully to cGMP and product safety requirements. For example, for drugs produced in a clean area, classification is not only based on particulate test locations described in the ISO documents, but also on evaluation of:

1. Various locations that are considered 'worst-case positions' and/or may pose a risk to the drug, containers, and closures; and
2. Microbiological monitoring data obtained from these and other locations in a given clean area.

The particulate and microbiological monitoring methods used to support these studies are expected to be reliable and include provisions for a sufficient sample size to produce an accurate representation of particles or microorganisms in air. Final study (and ongoing monitoring) conclusions should be based on consideration and interpretation of all data, unless instrumentation error is shown to occur."

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Gordon Farquharson is a Chartered Engineer and Principal Consultant with Bovis Lend Lease Pharmaceutical - a leading global provider of consulting, project management, engineering, IT, automation, and construction services to the pharmaceutical, healthcare, medical device, biomedical, and associated industries. Farquharson has more than 20 years of experience of processes and facilities used by the healthcare, life science, and semi-conductor industries; including design, construction, audit, and validation work. In recent years, Farquharson has focused on new technologies such as isolators, barrier technology, and mini-environments, and has been responsible for the development of technical solutions in primary manufacturing, as well as in product development and pharmaceutical formulation.

Standards and regulatory compliance issues are a major interest and responsibility. In this context, Farquharson has a high degree of expertise in the application of EU GMP and USA FDA cGMP requirements, and significant experience in dovetailing these differing approaches together. Recently, Farquharson has been heavily involved in the development of the new CEN/ISO Cleanroom Contamination Control standards that will be part of the standardization integration process in this field over the next five years. Farquharson is a founding member, management committee member, past chairman, and honorary member of the UK Parenteral Society and is active in the ISPE, R3 Nordic Association, PDA, and the UK's SEE. Farquharson is immediate past chair of the ISPE European Education Committee and was voted ISPE Member of the Year in 2001. Chairman of BSI's LBI 30 Committee and of CEN Technical Committee 243, Farquharson is a UK expert working on the ISO TC209 and CEN TC243 family of contamination control standards. Farquharson lectures and teaches extensively, is an author of several papers, and contributor to recent books on cleanroom and isolator technology.

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This article describes how a cooperative approach to validation benefits both suppliers and users in an environment where regulatory inspections are focused on computerized/ automated systems.

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Computerized Automation: from Process Control to Validation

by Carlo Bestetti

Introduction

In a modern pharmaceutical enterprise, the role of computerized/automated systems has an increasing impact on all processes associated with the development, manufacturing, storage, and distribution of drug products. Consequently, the regulatory inspections of pharmaceutical manufacturing facilities are focused on computerized/automated systems. The process that is known as validation has become well established for demonstrating the fitness for intended use of pharmaceutical equipment and processes. System suppliers are deemed to be ready to include evidence that the supplied systems meet their pre-determined specifications and quality attributes. Increased quality of the results, reduced execution time, and costs are the advantages of this cooperative approach to both the user (the pharmaceutical manufacturer) and the supplier.

Guidelines and Regulations

Computers have been used for industrial applications for many years and the pharmaceutical industry is no exception, where computerized systems are playing an increasingly important part in the manufacture of pharmaceutical and other healthcare products. Therefore, regulatory inspections are focusing more and more on computerized/automated systems.

The need for guidance originated at individual company sites and in regions where local regulations had to be satisfied. The few companies that produced guidelines, which were designed and intended exclusively for internal use and similar to those adopted for manufacturing equipment, were the first to understand the need for a structured approach for an automated system. The development of such guidelines may have been driven by an unsuccessful inspection or a more precise interpretation of the published regulations, but they soon became a useful reference outside the original geographical or company limits.

Many guidelines are now accepted internationally following discussions, seminars, and dedicated forums, in addition to the significant effort that has gone into the production of international agreements and harmonization.

The Validation Process in the Pharmaceutical Industry

The requirement for a validation process in the pharmaceutical industry is summed up by a statement contained in the "FDA Guidelines on General Principles of Process Validation," May 1987, where validation is defined as:

"Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes."[1]

The legal basis for the general implementation of the European Union - Good Manufacturing Practice (EU-GMP) was created from two directives adopted in 1991 by the European Commission (EC) Working Party on Control of Medicines and Inspections:

- 91/356/ECC for humans
- 91/412/ECC for veterinary use

Reference is made to earlier directives such as 75/319/ECC, 81/851/ECC, and 89/381/ECC, "Computerized Systems" which are the subject of Annex 11 to the EU Guide to Good Manufacturing Practice, Volume 4.[2]

Although reference to other regulations and standards, such as EU or ISO, are being practiced outside the US and particularly in Europe, the requirements of the FDA are increasingly adopted as a specific reference for applications with international value.

The result of the harmonization effort is an approach that should be acceptable to the FDA and also should enable compliance with the requirements of EC Directive 356 as explained in the European Guide to GMP including Annex 11 "Computerized Systems." This Annex describes the requirements for using computerized systems in the GMP sector. Validation and life cycle and software quality are particularly important for development of validated systems. In addition, this Annex also is applicable to the data entry part of the GCP area as described in the EU-GCP Guideline.

It is important to note that a guideline repre-

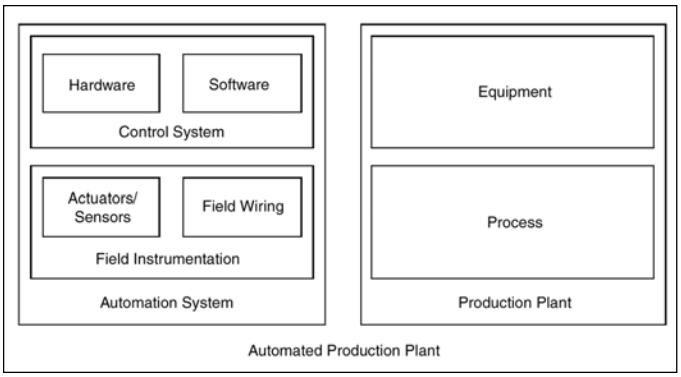

Figure 1. Automated production plant scheme.

sents just one method to develop and operate computerized systems. It is the responsibility of the pharmaceutical manufacturer to determine priorities and to reduce or increase the stringency of the applicable procedures on the basis of individually defined criteria.

It is the responsibility of the supplier to execute a management system for the development, supply, and maintenance of an automated system. Adherence to this management system by the supplier should provide sufficient documentary evidence to enable the system to be accepted and validated by the user (pharmaceutical manufacturer).

In addition, the supplier should consider Good Manufacturing Practice (GMP) along with any quality standards already adopted by the supplier, such as ISO 9001.[3]

Suppliers of automated systems to the pharmaceutical industry are expected to share the responsibility for the validation process with pharmaceutical manufacturers. This active cooperation includes the definition and production of validation documentation, and is evolving toward a new organizational approach capable of reducing the customary documenting/design approach, while still accomplishing the level of documented evidence, as required for the validation of a system that is considered critical under FDA and EU regulations.

This formal acceptance of the system supplied and its related documentation are an integral part of system validation. Validation is a user responsibility and is achieved by implementing the activities defined in a Validation Plan (VP). The VP is typically based on the "system life cycle" methodology and defines validation activities, responsibilities, and procedures, i.e., all significant steps, including revision and approval of the documentation produced by the supplier.

Once the defined activities are completed, a Validation Report is written, which confirms that all of the planned activities and documented evidence are complete. On acceptance of the Validation Report, the user releases the system for use. The validated state is maintained by formally applying appropriate procedures for proper system operation, maintenance, and change control.

Scope

When an automated system is to be installed for use related to production in a pharmaceutical plant, it is crucial - not only for validation purposes - that the suppliers understand the approach summarized above. The correct understanding of the requirements for validation combined with a precise approach become advantageous for the supplier although at the beginning of the project, it would seem to imply additional work. However, the benefits of the subsequent improvements in quality of the result and the savings obtained from avoiding implementation of unnecessary activities and production of unusable documentation soon become apparent, i.e., improved control of planned activities and limited amount of enhanced documentation.

The approach is based on the concept of prospective validation following a life cycle model. It is not intended for retrospective validation of existing systems. The extent to which this approach may be used for retrospective work, i.e., existing systems, which are already installed, should be determined on a case-by-case basis, according to the state of the documentation that is available, recoverable, or producible.

Where product quality may be affected, other specific items also should be considered and assessed, such as operating environment and operating procedures, e.g., security, back up, and recovery.

In principle, the approach is general and thus suitable for all types of automated systems. However, since significant distinctions exist between different types of systems, the user specifies the required activities, standards, and responsibilities in the Validation Plan to accommodate these distinctions. The user ensures that the requirements of the Validation Plan are reflected in any quality and project plan agreed between the user and supplier. This means, e.g., that separate life cycles may be defined after assessing different systems (different suppliers) such as "embedded" or "stand-alone." In particular, it is important to distinguish between control systems for manufacturing equipment, such as autoclaves or filling lines, and IT systems, such as MRPII, warehouse systems, and laboratory systems – *Figure 1*.[4]

Furthermore, any existing, new concept, or technology that is capable of achieving the objective of adequately validated automated systems should be considered to determine any possible benefit from its use.

System Life Cycle (SLC) Applied to Automated Systems

All the systems implemented for any industrial application should follow a specific, defined life cycle. This is a requisite in the case of applications that may affect the quality of a pharmaceutical product. The most popular guidelines apply a 'Life Cycle Concept' to computer system development.

Today, the life cycle concept is well known and has been in use for some time for critical applications. The increasing need for automation in the pharmaceutical industry is well covered by the extent of implementation, and the possibility of modification of the concept to consider the increasing number/type of computerized/automated systems in use[4] - *Figure 2*.

A sound basis for the development and support of a computerized/automated system used for regulated operations is the issuing (and approval) of the associated guidelines and procedures including:

- Development
- Operation
- Change Control
- System Maintenance

This applies both to a new system and for modification of an existing system.

The Validation Report is not the end of the story; the validated state needs to be maintained. Associated procedures and guidelines also need to be maintained, stored, and controlled together with system documentation, according to

predetermined rules and criteria. System documentation needs to be readily available, complete, and current for the entire life of the system.

The design and development of a computerized/automated system is said to follow a system life cycle methodology, where all the phases are highlighted, from the identification of the user's requirements, through design, integration, qualification, user validation, control and maintenance, and ends only when commercial use of the system is discontinued.

Good Engineering Practices should be emphasized throughout all phases to ensure that essential tasks are completed during the development of new systems and the deliverable items are suitably defined.

The most appropriate validation approach is determined by considering the complexity and use of the system to evaluate the relative importance of each phase. The combined experience of the user and the supplier provide the most appropriate framework for categorizing systems and supporting specific project validation strategies.

The validation strategy should be defined and stated in advance, applied in every phase, and reported as evidence of the result.

It is not a matter of "inventing" new practices or procedures, but of providing evidence of the good practices applied, the procedures in use, documenting the activities, and reporting the results in a professional manner. When maintaining conventional techniques, especially those that are consolidated within a company, the efforts can be concentrated on the improvement to integrate standard routines with validation.

The proper balancing of all the above has a positive effect on the project, allowing for definition of specific details, as required by the complexity of the application and its intended use.

The user has the primary responsibility for the project team including both the production personnel and the engineering team (plant project team and system project team). The supplier is required to comply with the requirements, which include rules and regulations. Therefore, the first step to the success of a validation project is defining the project methodology which details phases and responsibilities in a project/system quality plan.

An Example of Activities and Deliverables

Once the Validation Guidelines and the Validation Plan are available, the user defines the User Requirement Specification (URS). During the Planning phase, the resources are allocated and suppliers are audited before being selected. The Audit Report(s) documents the Audit(s) of the supplier(s). This should be performed before assigning a supplier and may require follow up, depending on the recommendations stated in the Audit Report.

The planning phase is closed after settling the quality aspects and the configuration management of the system, addressing main topics such as:

- the standard used
- the applicable procedures
- the documentation produced
- the specific responsibilities

All these issues - and the resources needed to implement them - are tailored to the project activities so that they deal with the regulations and the aimed purposes. The relevant document is usually called the Quality and Project Plan. It may be a single document or it may be distributed in multiple documents, according to the complexity of the computerized/automated system. This applies in a similar way to the other documents in the life cycle; which refer back to the higher-level Validation Plan.

The URS specifies the requirements of the user and initiates the project. Following the URS, a set of specifications is produced, based on the URS, with a level of detail appropriate for the project phase. Requirements should be traceable back to the requirements stated in the URS throughout the project both for consistency and to clarify any – real or apparent – inconsistencies, which should be clearly documented to avoid misunderstanding. The specified requirements and the documented modifications will be taken into account and will form the core reference throughout the entire life of the project and the ongoing operation of the system.

Validation requires, by definition, such "pre-determined specifications" and any need for change is to be managed according to a dedicated procedure, e.g., configuration management, assessing and documenting the impact of any modification on the activities and deliverables already performed/issued.

The subsequent phase covers the Specification, Design, and Construction activities and deliverables by detailing the user

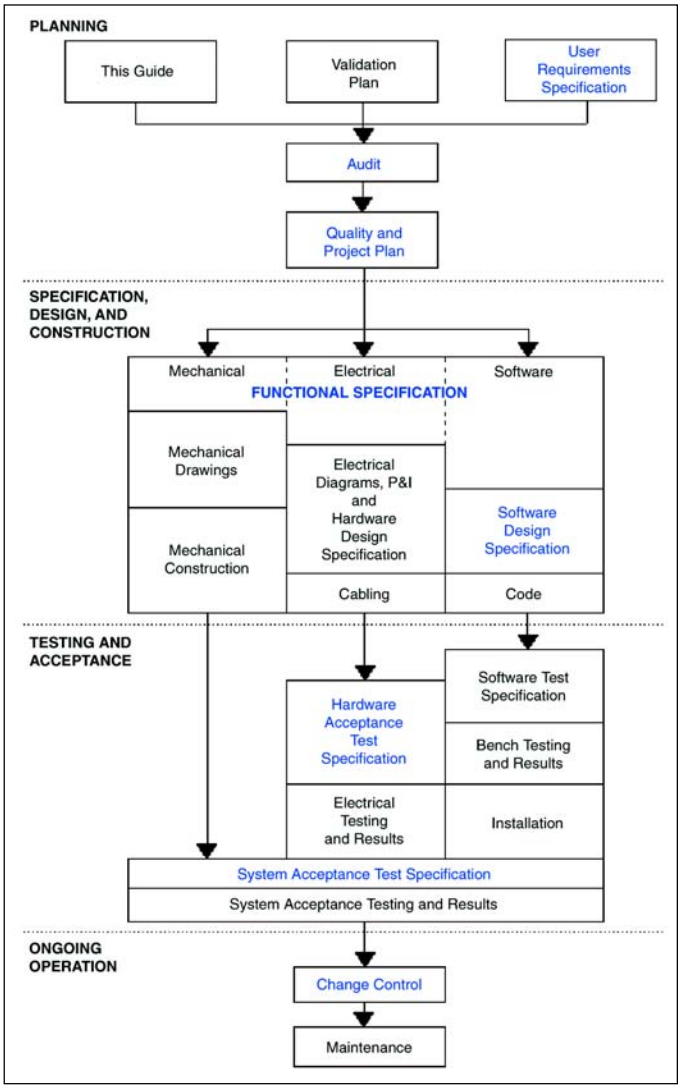

Figure 2. The Life Cycle Concept.[4]

Figure 3. Automation levels.

requirements in several documents that ratify the project steps, activities, and results.

During this phase, the original user requirements develop into detailed specifications, expressed according to the project characteristics, and then to the design phase, e.g., general/functional specification and detailed specification, which may be divided, if convenient for clarity, into Hardware and Software Specifications and/or Mechanical, Electrical, and Software Specifications.

The components of the system are then constructed, cabled, and coded according to specification so that the product, i.e., the computerized/automated system responds reliably to all the requirements specified.

This is verified (and formally documented when requested in the test plan, with or without user intervention) through internal tests, executed by the supplier including:

- Unit Testing
- Module Testing
- Integration Testing
- System Testing

One or more referenced documents may require revision to manage any unforeseen requirements or those arising after issue of the original document(s).

Any follow-up audits of the supplier should be performed, where recommended in the Audit Report. This is often done during the Factory Acceptance Test (FAT), which is the formal conclusion of testing at the supplier's site.

This leads to the Testing and Acceptance phase, as detailed in the Test Plan and executed according to the Test Specifications. These dedicated protocols include test procedures and result tables with the purpose of verifying the system and documenting the result against all the precise design specifications.

According to Good Engineering Practice (GEP), the system is installed on site and passes the Site Acceptance Test (SAT) in preparation for qualification. Qualification is divided into two steps: the Installation Qualification (IQ) and the Operational Qualification (OQ). These documents (specifications and test results) detail the evidence that the system is installed and operates as specified. (A third step, i.e., the Performance Qualification (PQ), is often executed as part of the equipment qualification.)

The set of manuals accompanying the supplied system, such as User Manuals and Maintenance Manuals, complete the system documentation.

To enable the On-Going Operation phase, the training of personnel involved (such as operators and maintenance personnel) must be completed and the relevant Standard Operating Procedures (SOP) must be in place, approved, and in force.

The "as built" version of the documentation freezes the final characteristics of the system and of its components. The change control and the system maintenance are activated through dedicated procedures to guarantee that the validated state is maintained.

The automated system is ready to cooperate with all the other components of the plant, e.g., equipment to qualify the performance of the process related to the requirements, thus *"establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes."*[1]

PLC, DCS, IT Infrastructures

The vulnerability of pharmaceutical equipment, plants, or even organizations due to lack of effective validation should not be underestimated. The consequences of an automated system, e.g., PLC, DCS, infrastructure being out of effective control can be potentially immense. Depending on the extent, severity, and impact of a failure, equipment, an entire plant or site or region of manufacturing operations could be brought to a standstill while the failure is resolved. The same is true when that failure is not compliant with the regulations.

Typical examples are controls performed by means of Programmable Logic Controllers (PLC), with or without a Supervisory Control and Data Acquisition implementation (SCADA), and Distributed Control Systems (DCS). The communication network, e.g., LAN, also is considered, along with the entire IT infrastructure. The validation status of validated applications that are dependent upon an underlying infrastructure is compromised if the latter is not maintained in a demonstrable state of control - *Figure 3*.

Programmable Logic Controllers

Programmable Logic Controllers (PLCs) are used extensively to control a variety of plant equipment. Therefore, the validation strategy adopted for PLCs takes into account both the equipment and also the (embedded) PLC.

The validation approach is based on the intrinsic characteristics of the PLCs which have a definite instruction set verified during compilation. Most have provisions for structuring instruction blocks and a high-level language modular interface. This classification and the intrinsic modularity help testing and compliance work. PLC and SCADA application examples may be used as a starting point for the guidelines.

For example, the most prominent unit operation in process industries, Batch Processing, is evolving in its approach to automation, which is resulting in increased productivity and improved plant and corporate efficiencies.[5] The Standards and Practices Division (committee number 88, hence SP88) of the Instrument Society of America (ISA) has developed a standard for automated Batch Control. The Control Recipe and execution is done in the PLC rather than in a PC, while Recipe Handling, the Master Recipe, Production Planning, and Batch Records are maintained in the Supervisory Computer.

Distributed Control Systems

The Distributed Control Systems (DCS) are being used for large scale and complex applications. Since the difference in technology used, cost, and performances are progressively reduced, the complexity enabled by the modern PLC based systems is increasing and the scale of the DCS based applications is reducing.

This means common problems overlap and a tighter approach is required, which is closely related to the intrinsic differences.

The reference methodology for the management of projects for automated plant control on a large scale, usually achieved using a DCS, has been worked out and published by members of NAMUR (German Standards Association for Control and Measurement in Chemical Industries) and GMA (VDI/VDE Society of Measurement and Automation) Technical Committee 5.8 "Control Technology Validation."[6-9] The initial distribution worldwide came with the English version, embodied in the GAMP Guide for Validation of Automated Systems in Pharmaceutical Manufacture (GAMP 3). The GMA/NAMUR documents are currently being updated for publication in a GAMP 4 Good Practice Guide on Validation of Process Control Systems.[4]

Infrastructures

The IT Infrastructure in a modern pharmaceutical enterprise has an impact on all processes associated with the development, manufacturing, storage, and distribution of drug products.

All of the computer systems with their associated hardware, operating software (other than the software applications), and the networks used to run them are defined as "Infrastructure."

While most pharmaceutical equipment is comparatively static, modern IT infrastructures are subject to a much higher rate of change, and evolution of the infrastructure on an almost daily basis is commonplace. An effective "state of control," once achieved, is to be maintained as the infrastructure evolves. This is both cost effective and efficient in relation to the character and management of the infrastructure.

Benefits

Validation is not an unconnected activity, and it should be integrated within project activities to produce benefits. Critical aspects may be controlled in an easier and less expensive manner if found at an early stage, e.g., an unqualified supplier or a misunderstood requirement and the entire project can benefit from control and early resolution of such issues.

Both the user and the supplier can gain the following benefits by using the approach described in this article:

- mutual understanding increases
- responsibilities are clearly defined in advance
- the system produced is fit for purpose and meets user requirements
- delivery time is reduced
- budget/cost and agreed quality standards are better controlled

Therefore compliance with regulatory expectation is enhanced. Integration with existing quality systems is no longer an obstacle, but is another path to reduction of project cost and time.

Conclusions and Trends

- The users and the suppliers follow good practice and produce the necessary documentation to achieve validated and compliant automated systems in pharmaceutical manufacturing.

- Harmonization and links with other initiatives are already in progress; some of the results are cited.

- Future developments include a harmonized glossary, Mutual Recognition Agreements (MRAs), and GMP equivalence.

- Topics that are being investigated and included in new guidelines consider:

  - Calibration Management
  - Electronic Record and Electronic Signatures
  - Legacy Systems
  - IT Infrastructure
  - Packaged Systems
  - Skid Mount Equipment
  - Analytical Laboratory Equipment
  - Global System
  - Good Engineering Practice
  - Web-based Applications
  - Non-Compliance Cost Model

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About the Author

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This article presents an approach to Risk Assessment as a means of reducing the cost of validation, while maximizing the benefits.

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Effective Cost Control for Automated Systems Validation Projects and Procedures

by John Andrews

Introduction

Prevalent market forces are driving a cost reduction revolution within the pharmaceutical industry. In response, the pharmaceutical industry has invested heavily in automation.

Market forces include the following:

- pressures to reduce the cost of prescription drugs
- competing with generic copies of products 'off patent' protection
- parallel importing
- reducing new drug development lead-times
- the need to reduce manufacturing costs
- increased regulation
- company mergers and acquisitions

These market forces have increased the industry's reliance on automation, which has resulted in heightened attention by the regulators in the area of computer validation. Therefore, the industry has had to spend more on computer validation to satisfy regulatory requirements. This has added to the existing market pressures, creating a spiraling effect, which began in the early 1980s and to date, shows no sign of decline.

The challenge facing the pharmaceutical industry is to get the correct balance between implementing improvements in automation (to reduce overall costs) and maintaining compliance with current (and future) regulations.

Benefits versus Costs

The benefits of automation are immense:

- greater throughput
- shorter lead-times
- more efficient record-keeping
- reduced overheads

However, so is the *cost* of such investments. The cost of building and automating a production plant can account for up to half the total cost. It is, therefore, important that it is done right, at the right price, and within the relevant regulatory requirements.

The cost of the validation effort has followed a similar pattern to the investment in automation. This has been the subject of much debate and many misconceptions. Some have stated that a lot of the unnecessary costs associated with an automation project are attributable to validation effort required, and therefore, the validation effort should be reduced. Conversely, others have stated that more should be spent, because the costs of getting it wrong are potentially huge, with figures of 20%-30% of the overhead cited. This has resulted in a seesaw approach to managing validation within projects, normally in response to regulatory interest, observations, and Warning Letters.

What seems to have been overlooked is that the amount spent on validation is not what counts - it is the quality of the workmanship of those individuals involved in system development, operation, and maintenance, and how that quality is recorded as documentary evidence.

Popular Misconceptions

- *ISO 9000 accreditation for quality management satisfies the requirements for validation of software:* this is untrue. ISO 9000/ISO 9001 is for the supply of goods and services not software. However, ISO 9000-3 is for the supply of software, but falls short of the GxP requirements of the pharmaceutical industry. These standards do, nevertheless, provide a good basis for validation.

- *Validation is a one-off event that concludes with a validation certificate:* this misconception is usually based on the premise that validation is a standard or a certificate handed out by the regulatory authorities during an inspection, and once the inspection is passed, the system is validated. The pharmaceutical regulators do not certify validation. Validation is an ongoing activity covering development, operation, and maintenance.

- *GMP = Great Mounds of Paper:* this is often a result of the validation requirements being poorly managed or understood, i.e., focusing on everything to the minutest of detail and not understanding the areas critical to GxP. (GxP = Good Clinical Practice (GCP), Good Distribution Practice (GDP), Good Laboratory Practice (GLP), and Good Manufacturing Practice (GMP)).

How Much is Enough?

Failure to validate to a regulator's satisfaction can have significant financial implications. For a top selling-drug in production, citations for noncompliance by a regulator could cost upward of $2,000,000 a day in lost revenue. The above misconceptions have resulted in a large number of regulatory observations or warning letters, e.g.,

- The firm has failed to adequately validate computer system x
- The firm failed to maintain the validation of computer system x
- The firm failed to adequately assess the validation requirements of computer system x

The latter statement has become more prevalent as inspectors become more comfortable with computer systems and have delved into the validation documentation with a view to satisfying a particular GxP want. The challenge, therefore, is to balance the regulatory requirements while still staying within budget and not just throwing more money at the problem and creating more mounds of paper. This can be achieved by understanding how a system will impact on GxP. It is this area that requires a more detailed review and a deeper understanding of the impact, which will inevitably add cost to a project. In contrast, where a system has no GxP impact or the impact is minimal, the cost can be reduced by the use of verification at a higher level.

The suggested approach will clarify only *where* to focus the validation effort; *how much* effort is required, and to *what level*, relates to the amount of impact a system has on GxP. This needs to be determined and is discussed later.

The changing regulatory environment impacts other factors that affect the extent and level of the validation effort. It is, therefore, important that procedures, guidelines, SOPs, and of course, all computer systems are reassessed against every regulatory change. This will highlight any compliance gaps. The latest, and probably the most controversial, change is the electronic records and electronic signature requirements for the FDA (21 CFR Part 11). This has led to a massive review program for the whole pharmaceutical industry, and will inevitably lead to upgrading or replacing of some major systems. In the interim, these systems will need to be operated and managed within the requirements of the predicate rules for GxP.

Regulatory Events and Trends

From recent seminars, the FDA has indicated its intention to achieve the following goals relating to computer systems by 2002:

- official submissions received and archived electronically
- electronic submissions and reviews accessed from the reviewers desktop computer
- public releasable material available on the Internet
- guidelines on the use of computers within the industry including:
  - pilot program for eIND applications for biological products
  - clinical trials
  - clinical study reports
  - electronic format for NDA
  - 21 CFR Part 11

The FDA also has indicated its desire to harmonize efforts between countries to achieve mutual recognition in regulatory requirements. This will obviously lead to an increase in regulatory focus on computer systems in the areas of electronic records and electronic signatures from other regulatory bodies as this process develops. On the enforcement front, there has been a marked increase in Warning Letters relating to computer systems and many more observations (483s) relating to computer systems (that did not make it into Warning Letters) were noted. Some examples of these observations relate to issues regarding documentation of software development, access and security, software modification, software hazard analysis, maintenance of data. The FDA has always maintained that it would communicate its expectations through Warning Letters and guidelines.

In addition to the above events and observations, the activities of the FDA influence the industry, and as a result, also affect computer validation activities. For example:

- Training FDA inspectors in computer validation and 21 CFR Part 11. This training may lead to an increase in the number of inspections that focus on computer systems.
- FDA looking at the drug approval process, which may translate into looking at systems that generate and process data for drug approval.

Reducing the Cost of Automation Validation

A proposed method below employs the use of risk assessment. Risk assessments are conducted at different levels of a system to determine the area in which to focus the validation effort:

- high level to determine which of a company's systems impact on GxP
- lower level to determine the GxP impact of a sub-system
- assigning priorities

This will help to determine which functions require either redesigning or detailed confirmation and challenging as opposed to just high-level confirmation and verification.

High Level GxP Determination

The first step is to determine whether a system or sub-system

represents a risk to GxP when assessed against a series of GxP questions. Firstly, does a system impact on GxP?

System Impact Assessment

- Is the system used to monitor, control, or supervise a GxP drug manufacturing or packaging process?
- Is the system used for GxP analytical quality control?
- Is the system used to monitor, control, or supervise warehousing or distribution with a GxP implication?
- Does the system support the maintenance of GxP systems?
- Does the system manipulate data, or produce reports, to be used by GxP quality related decision authorization/approval processes?
- Is the system used for GxP batch sentencing or batch records?

If the assessment of a system concludes that it does not impact on GxP, the decision should be documented on the assessment sheet.

This is followed up by a series of sub-system questions, (if it is a Business System application, replace 'sub-system' with 'functions') and asks how the sub-systems/functions for any given system, deemed to have an impact on GxP, actually impact individually on GxP?

Sub-System Impact Assessment

- Is the sub-system used to demonstrate compliance with the registered process?
- Does normal operation or control of the sub-system have a direct affect on product quality?
- Will failure or alarm of the sub-system have a direct affect on product quality? Efficacy?
- Is information from this sub-system recorded as part of the batch record, lot release data, or other GMP documentation?
- Does the sub-system interact with elements that come into contact with product or product components?
- Does the sub-system control critical process elements in such a way to affect product quality?

If the assessment of a particular subsystem/function determines that there is no risk to GxP, the justification for making this judgment also should be documented on the assessment sheet.

This process will provide a list of sub-systems that can be assessed for their individual functional impact on GxP by using a risk assessment method.

Risk Assessment and the Development Life Cycle

The civil aviation industry has been using risk assessment to manage the maintenance of aircraft for more than 25 years and recently GAMP 4 has included Risk Assessment in an Appendix. This methodology could be employed to determine how to manage the risk to GxP during the system development, life cycle, and beyond. The methodology[4] starts by asking eight very simple questions. These questions have been slightly modified to fit the healthcare industry's GxP requirements:

- *What are the major GxP functions and associated performance requirements of the sub-system?* List all the subsystems functions and any performance criteria; this information can be derived from the User Requirement Specification and Functional Specification for the given system.
- *From the major functions, what are the sub-functions and their associated performance requirements?* This information can be derived from the systems design documents.
- *What are the failure events?* From the list of sub-functions, look at the different types of failures that may exist in the operating environment.
- *What is the effect of each failure event?* From the list of failures events, look at all the likely effects of each type of failure in the production environment.
- *Is there a GxP consequence for each failure effect?* Assess if there is an impact GxP for each failure effect - *Yes or No.*
- *What is the probability of each failure effect being detected?* Categorize into low, medium, or high probability of detection in a normal production environment.
- *What is the probability of each failure effect happening?* Categorize into low, medium, or high probability of it happening.
- *What modifications to the design can be made to reduce GxP risks?* Review findings and modify the design to eliminate the high risk/high probability of it happening.

Table A illustrates a barcode reading system, which is a subsystem of a labeling machine deemed to have a GxP impact. Its function is to detect a wrong, misplaced, or missing bar-coded label, and stops the machine. This example illustrates the methodology by taking the example through six of the eight questions listed above, looking at the main function, the subfunctions, and how the sub-functions can fail. In addition, a review of the GxP effect of any failure and the probability of it being detected in a normal production environment is considered. The probability of a failure happening is explored further in Table B where risk prioritization is assigned. The purpose of Table B is to understand if any high GxP risks exist to necessitate a redesign of the system, or demonstrate how error checking or system intervention methodologies can be employed to reduce any GxP risk that may exist if the redesign is not possible.

The resulting review of the system example in Table A and after applying Table B would determine that a review of the 'medium probability of it detection' function's (highlighted with an asterisk(*) in Table A) versus a high risk of it happening is a 'High Priority' and would require either a change to the design or the introduction of an intervention SOP to challenge the integrity of the barcode reading systems. This is where the eighth question comes in, i.e., 'what modifications to the design can be made to reduce GxP risks?' As with the example for the

Major Functions	Sub-Functions	Failure Events	Possible Effects in Production Environment	Impact on GxP Y/N		Probability of Detection		
				Y	N	L	M	H
Reading Barcode and stopping machine if incorrect	Detects when to read Barcode by detecting leading black stripe	Fails to see Barcode leading black stripe	Machine will stop		✓			✓
			Machine does not stop and put labels in wrong place on cartons	✓				✓
		Looks for Barcode at wrong position	Labels read as incorrect & machine stops		✓			✓
			*Labels are not seen and machine continues to run	✓			✓	
	Reads Barcode	Fails to read correct Barcode	Machine will stop		✓			✓
			*Machine continues to run	✓			✓	
		Fails to read incorrect Barcode	Machine will stop		✓			✓
			*Machine continues to run	✓			✓	
	Makes decision pass/fail	Make no decision	*Machine does not stop	✓			✓	
		Make incorrect decision	*Machine does not stop	✓			✓	
Note - above example for illustration purposes only								

Table A. Example risk assessment form.

barcode reader, sometimes there is no modification possible, therefore alternative methods will need to be employed, e.g., an intervention SOP. The intervention SOP will need to be designed to interact at suitable frequencies to increase the likelihood of detection and therefore decrease the probability of it happening, along with a suitable follow-up process if an error is detected.

During the system development life cycle, risk assessments should be conducted at several stages because risk priorities are likely to change (as demonstrated above). The following should be considered as a guide to the minimum requirements for risk assessment reviews during a development life cycle:

- the generation of the User Requirements Specification
- the supplier assessment/audit
- the development of the Functional Specification
- the completion of the Design Review prior to validation testing
- Change Management - whenever any major changes are applied to the system or there is a major change to regulations. This is intended to be a maintenance tool to ensure continued GxP compliance.

Figure 1 is based on the intervention risk assessment model given in GAMP 4, Appendix M3, and provides an overview of the process of risk assessment against the traditional validation life cycle. The boxed 'R' indicates when it is recommended that a review of the GxP risks should be conducted; however, as projects are dynamic in nature, the risk priorities are likely to change throughout the life of the project so more reviews may be necessary. The review itself is obviously open to interpretation; therefore, a team effort is necessary. The usual team members should be involved, i.e., representatives from Quality, Engineering/Developers, and Production and the conclusions must be recorded and approved. The framework for the review should be stated in the Validation Plan and updated as and when required.

From the assessment process, a suitable validation strategy can be devised:

- For high priority risks, avoidance, system redesign, or a suitable challenging program must be employed along with increased verification and testing.
- For medium priority risks, process redesign should be considered, risks managed through procedures, and testing.
- For low priority risks, decrease testing as appropriate.

The software and hardware categories detailed within GAMP 4 also can help to reduce the overall costs associated with the validation effort by focusing appropriate efforts against each subsystems determined category. See GAMP 4 for the detail of how to apply GAMP categories effectively to ensure that the correct approach to validation is applied to each element of a system.

Introduction to GAMP 4 Appendices

The original concept of the first GAMP Guide was to provide example appendices for providers/developers to follow when producing software that would meet the requirements of the pharmaceutical industry. Over time and three versions later, more examples and guidance has been added to assist both system providers and system users, not only in the area of development and validation, but also in the use, management, and maintenance of systems. The latest version, GAMP 4, has divided the appendices into Development, Management, and Operation of a system.

The Development appendices provide additional examples to give further assistance to potential developers and users.

The Management appendices are aimed at both the users and the suppliers/developers of systems. These guidelines

cover a lot of new ground, the focus is set mainly on the areas of assessment, review, planning, and reporting. Example material covering supplier audit, risk assessment, and categories of software and hardware are the areas that will deliver the highest rewards in terms of project cost and time savings. This material also will serve to demonstrate a focused and appropriate validation to a regulatory inspector.

Maintaining compliance is essential as poor maintenance can result in an inspector's observation or worse, a Warning Letter. As discussed earlier, the validation effort represents a business investment. Without support, the performance and regulatory compliance will decline. It is critically important to ensure thought is given to how a system will be operated and be maintained at the concept stage of any project.

Operational procedures must be designed to meet an individual company's needs, the example set within GAMP 4 covers a wide range of operational areas and is a good starting point when implementing a Quality Management System (QMS).

Caution must be employed when using these guidelines and procedure examples; it is essential to modify in order to gain the right 'fit' for the individual supplier and user companies needs. This will reduce the likelihood of acceptance problems down stream. The risk management process above also can be used to determine how to manage and operate a system, for example, when determining what data should be backed-up or archived for GxP purposes. The risk assessment method will deliver significant cost benefits in the data back-up and long-term archiving arenas.

What are the Benefits of Validation?

Very few comparisons have been performed on the benefits of validating verses not validating because the immediate implications of not doing it are so obvious. Good practice invoked by validation should ensure that a system is installed right the first time, every time. Anecdotal evidence of validation benefits include the case of two tablet manufacturing lines installed by one major pharmaceutical company at two different occasions, one line having been validated from concept to handover, the other being un-validated. Figure 2 illustrates the benefits of validation in improved productivity, waste reduction, and reduced manpower levels.

Up-front effort at the start of the system development life cycle should be more than compensated by project pull-through. The costs of modification and changes later in the life cycle can be 10 or 20 times that of at the concept stages. Both users and developers must write the URS in a manner that is understandable and testable; or costly misunderstandings may occur which will be expensive to reverse later. In addition, it is important to conduct a supplier assessment/audit as early as possible, the clarification that comes from user and supplier establishing healthy dialogue early in the project is synonymous with the success of that project.

Hidden Costs

In the above sections, the costs of validating non-GxP systems, functions/subsystems have been eliminated by the use of a risk management process, along with using an appropriate QMS, like GAMP 4. This section highlights some of the hidden costs associated with validation and advises how to avoid them. The first such cost is obvious and very important, but is often overlooked, namely to staff the project with people who have had previous experience in validating similar systems. This

Probability of it Happening	Probability of Detection: High	Medium	Low
High	Medium Priority	High Priority	High Priority
Medium	Low Priority	Medium Priority	High Priority
Low	Low Priority	Low Priority	Medium Priority

Note - above example for illustration purposes only

Table B. Risk prioritization.

experience is invaluable in ensuring that any mistakes that could be made are avoided or reduced and that the project progresses as smoothly as possible. Other examples of hidden costs and how to avoid them include:

- Avoid the 'not invented here' syndrome. It is often useful to bring in a suitably experienced and qualified consultant to assist in the planning stage of the validation to ensure that project gets off to a good start.
- Take time to define the user requirements correctly. Make them measurable and not too detailed. Once agreed upon, avoid unnecessary changes.
- Use people experienced in both the risk management process and the process the system will be controlling or automating in order to capture the relevant failure effects.

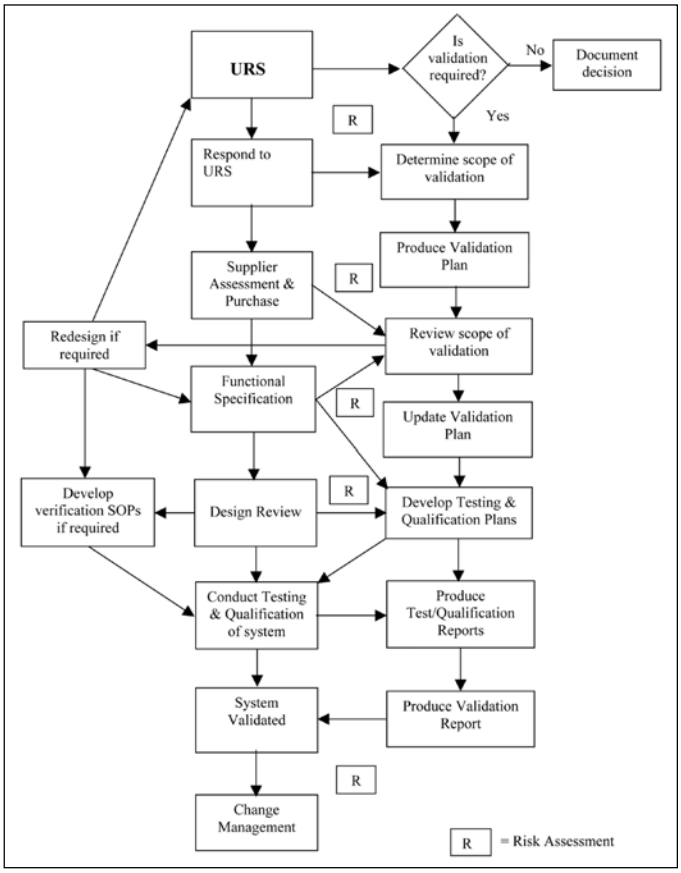

Figure 1. Overview of the Risk Assessment and the Validation Life Cycle.

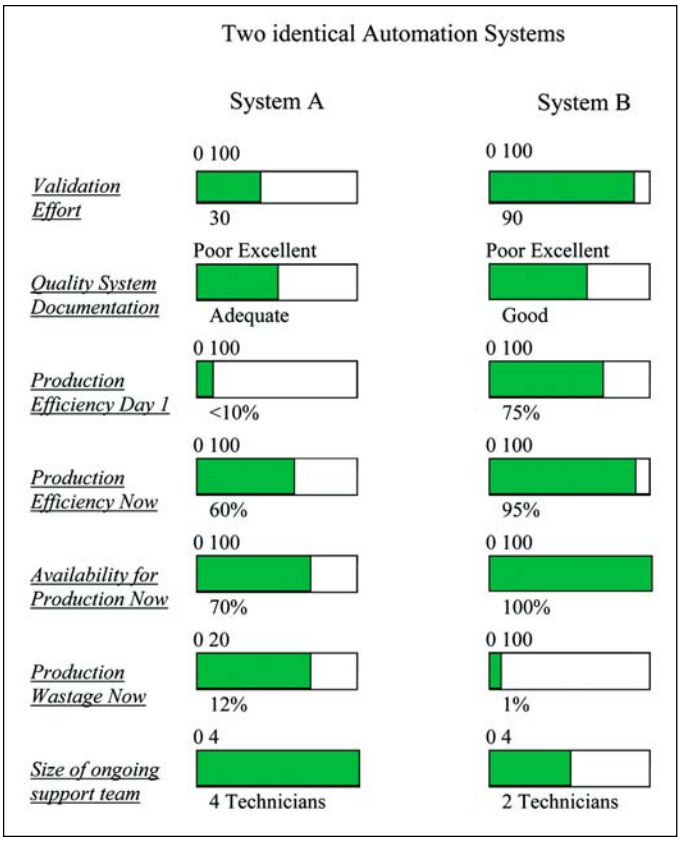

Figure 2. Anecdotal validation benefits.

- Start to think about system maintenance as early as possible and get working on the procedures and guidelines to ensure all are happy with the proposed work methods.
- Start planning and performing training early to get all parties involved, and to avoid the end of project panic.
- Keep it simple, avoid writing pages of unnecessary text to pad out a document. Consider using flow diagrams, scanned photos, etc., to illustrate an SOP for example.
- Validation is not the system design or test documentation, these are required whether you are validating a system or not.
- Hold regular review meetings to monitor progress and ask how can things be improved.
- Assign someone to control the 'issues' list to ensure that things are closed-out in a timely manner.

Surviving the Validation Blues - Hints and Golden Rules

Those who do not understand the benefits of validation often claim that it bleeds a project of precious funds and resources. Another popular misconception is that validation is the testing stage of a project. Frequently, the validation department is regarded with suspicion. If failures in software are found after validation is approved, the consensus from all is that the validation has failed and it is the validation department's fault. With all this pressure, it is often useful to reflect on the following advice:

- Build the principles of validation into the culture of the project management methodology. It should not be a separate function.
- Be cautious when estimating the cost of validation to a project, be clear what is a validation activity, and be clear to differentiate it from what are regarded as good project/engineering/software practices.
- Do not assume validation has an intrinsic value – it has none. The core product or service does. Can you qualify the benefits of validation to the business?
- Mold the principles of validation into the companies working practices. It is often more cost effective to use the services of an outside consultant to help with this.
- Resist making changes to the user requirements that are not necessary, these could considerably increase costs.
- Avoid Great Mounds of Paper (GMP). Use the risk assessment method to determine what to focus on, and remember to keep it simple. Documentation for its own sake will not ensure GxP compliance.
- User training is critical; remember to conduct it at appropriate times and not just at the end of the project.
- Remember to use experienced people and plan for continuous improvement.
- Remember the validation golden rules:
  - plan validation
  - use competent personnel
  - implement a change control system
  - establish procedures for validation
  - document design intentions
  - produce and approve testing protocols
  - execute testing protocols and record results
  - write and approve validation reports
  - maintain validation through approved procedures
  - periodically review systems against all changes (system changes and regulatory)

Conclusion

Pharmaceutical manufacturers have to validate, otherwise their license to market a drug is revoked or not issued in the first place. The cost of validation should be related to the potential impact on GxP (and subsequently the business). If there is a potential impact on GxP, the whole system should be validated with particular attention on the GxP aspects of the system's functionality. There is increasing pressure from other

regulation, such as Financial Auditors, Data protection authorities, US Drug Enforcement Agency, or the UK Home Office (for the control of certain classes of active ingredient). It is also good business practice to validate systems because of the added payback of systems working more efficiently from day one, but the benefits must be clearly understood. Do not confuse validation with good engineering practices; system design documentation and system testing must be performed on all automated systems as they are built. Validation is about the way that testing is conducted, controlled, and documented, along with levels of verification and challenges.

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This article describes the essential elements of a pharmaceutical supplier's formal change management system and the relationships among those elements.

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Change Management Systems in the Pharmaceutical Industry

by Janet Buecker and John Tuttle

"When you're finished changing, you're finished."
~ Benjamin Franklin

Introduction

The pharmaceutical industry has long recognized the need to control and properly validate changes to pharmaceutical engineering processes and materials, and the resulting product changes. The FDA has published regulations [21 CFR 314.70] describing how changes to drug manufacturing processes must be reported to the Agency. Many pharmaceutical companies require formal change notification agreements with suppliers as a condition of doing business. This requirement includes the notification of intended changes before their implementation by the supplier, and the acceptance of any changes by the customer before they receive product that incorporates the change. Given the industry and regulatory focus on change control and change notification, quality managers and purchasing managers have reported that many suppliers to the pharmaceutical industry have not implemented formal change management policies and procedures that comply with the requirements and expectations of drug manufacturers. This change management system has been developed and refined through the process of supplying products to the pharmaceutical industry for more than 40 years, and is the result of extensive collaboration with many demanding customers. The change management system described in this article pertains to pharmaceutical and biopharmaceutical products, as well as to certain medical devices. Examples will illustrate how a change management system should work in practice.

Definition and Classification of Changes

In defining a change management system, the first questions that a pharmaceutical supplier must ask are:

1. What kinds of changes are required in the product, its manufacturing process, or its QC/QA processes?
2. How should these changes be classified to reflect their potential impact upon the customer?
3. How should these changes be communicated to the customer?

The answer to the first question is that all changes that could potentially impact the customer in any way must be managed and controlled. These changes include changes to the form, fit, or function of the product, changes to manufacturing or testing methods, and changes to labeling or packaging. Other types of changes that must be managed and controlled are dictated by regulatory requirements and customer expectations. Some pharmaceutical manufacturers want to be notified if the supplier's batch size is changed by more than 20% or if the supplier experiences a change in manufacturing yield of more than 10%. Other types of changes, such as the transfer of manufacturing to a different location or a change in the supplier of a critical component, are generally recognized as changes that require the supplier's surveillance and customer notification. These changes also need to be validated.

This brings us to the second question concerning classification of changes. It is appropriate to classify changes to reflect the potential impact that the change may have on the product, the process, or the customer. The classification of a change generally also reflects the amount of qualification required to validate the change. The type and timing of a formal notification to customers also depends on the classification of a change. Because no government regulation or industry-wide practice mandates or even describes how changes are to be classified, such classifications are developed by pharmaceutical suppliers in collaboration with their customers in order to satisfy the customers' needs. One such classification system uses three levels of change to describe every type of change that might be considered.

Major Changes

Major changes have the potential to affect the customer's process by reducing yields, increasing processing time, or altering process parameters. Major changes can also can affect product purity, stability, potency, safety, or efficacy. Customers must be informed of and accept a major change before they receive product that reflects the change. It is often necessary for a customer to re-qualify in their process a component which has undergone a major change.

These types of changes generally affect the form, fit, or function of the product, or are associated with the transfer of manufacturing to another location. Changes in materials of construction, suppliers, manufacturing methods, test methods, or product specifications (outside original specification range) are considered major changes.

Product discontinuation also is considered a major change because it forces the customer to source and qualify an alternative product in their process.

Minor Changes

Minor changes do not have the potential to affect the customer's product or process, other than by perhaps requiring paperwork changes. Customers should be informed of, but need not accept, a minor change before accepting a supplier's product that reflects the change. Minor changes are generally associated with packaging, labeling, or documentation. It is considered a minor change when the specification range is narrowed, but is still within the original range.

Non-Notifiable Changes

Non-notifiable changes are defined as changes that require management oversight and control, but create no real or apparent change in the product or any of its aspects or properties. Examples of this type of change include adding Statistical Process Control in the manufacturing process and replacing manufacturing equipment with like for like.

Once change management has been defined and the types of changes classified, appropriate customer notification policies and procedures should be established and followed. In a global multinational company that supplies product to the pharmaceutical industry, communication and employee training are essential for the efficient functioning of a change management program. Additionally, an employee's job performance assessment should include an evaluation of how well the employee follows change management policies and procedures. Internal audits are a good tool to assess how well change management is being managed.

Change Management and Customer Notification Policies and Procedures

Formal change management procedures and a formal change notification policy are required to provide pharmaceutical customers with adequate assurance that changes will not be implemented without proper notification and customer acceptance. A good change management and customer notification procedure distinguishes between major changes that require pre-notification and customer acceptance, and minor changes that do not need customer acceptance before implementation and product distribution. Although customer acceptance is not required for minor changes, customers should be notified when the change is implemented.

Change management procedures must prescribe how all proposed changes are reviewed and approved before implementation. A process re-validation protocol must be written, reviewed, and approved before the implementation of any major change. Customer notification should take place as soon as the process change has been validated and the validation report approved. For major changes, it is good practice for change management procedures and policies to address the need to give customers 12 to 24 months' notice of the intended change to allow them adequate time to qualify the changed component in their process. This notification requirement generally entails the supplier's keeping inventories of both the old and the changed component available for this period of time.

Now that different types of changes have been defined and management policies and procedures have been established, all the areas where change management must be applied in order to ensure a successful system must be identified. This discussion will now review the essential elements of the change management program necessary for a reliable and efficient customer-notification process.

Figure 1 shows the major areas and functions where change management procedures must be established and maintained. Procedures defining change management in each of these areas must be in place and understood by all employees who work in a given area. As the diagram shows, inventory management is a very important element of change management. Inventory management will be discussed several times as the areas where change management must be applied.

Change Management and Changes Notification for Purchased Materials

Most pharmaceutical suppliers' products start with materials or components supplied by a vendor. Qualification of that vendor should include the requirement that an effective change management system is in place, and that the vendor is committed to notifying their customers of major and minor changes. Each vendor also should have a quality management system that ensures the re-validation of their products and processes when a change is implemented. Signed agreements should be in place between the pharmaceutical supplier and their vendors, stating the vendors' commitment to change notification and defining the types of changes that must be communicated and how they will be communicated. Each vendor also must have procedures in place to control inventory when a change is made. This practice would include control of component distribution so that a component that has been changed is shipped only to customers who have accepted the change. Vendor audits should verify that the proper policies and procedures exist and are followed to ensure adequate change management and control of inventory and distribution.

Incoming QC and Inventory Control of Starting Material

Procedures must exist to ensure the correct handling of starting material received from vendors. If a vendor has made changes to their product, incoming QC and warehouse personnel at the pharmaceutical supplier must have procedures for identifying and quarantining material that has changed, but has not been fully qualified and approved by the pharmaceutical supplier. This is an area where a significant amount of coordination is necessary between QC, purchasing, material handlers, and production at the pharmaceutical supplier. Material or components that are being changed by a vendor must be qualified in the process that uses the material or

components. This requirement means that protocols must be developed and followed that allow manufacturing to use unapproved material during qualification/validation runs. Product made during the qualification/validation must be segregated from regular production and placed in quarantine until the qualification/validation has been approved. A material review board normally determines the disposition of any remaining inventory of the original unchanged starting material after the qualification/validation has been approved.

Pharmaceutical customers generally consider the following changes made by their suppliers to be major and to require notification and acceptance before they receive product that reflects the change.

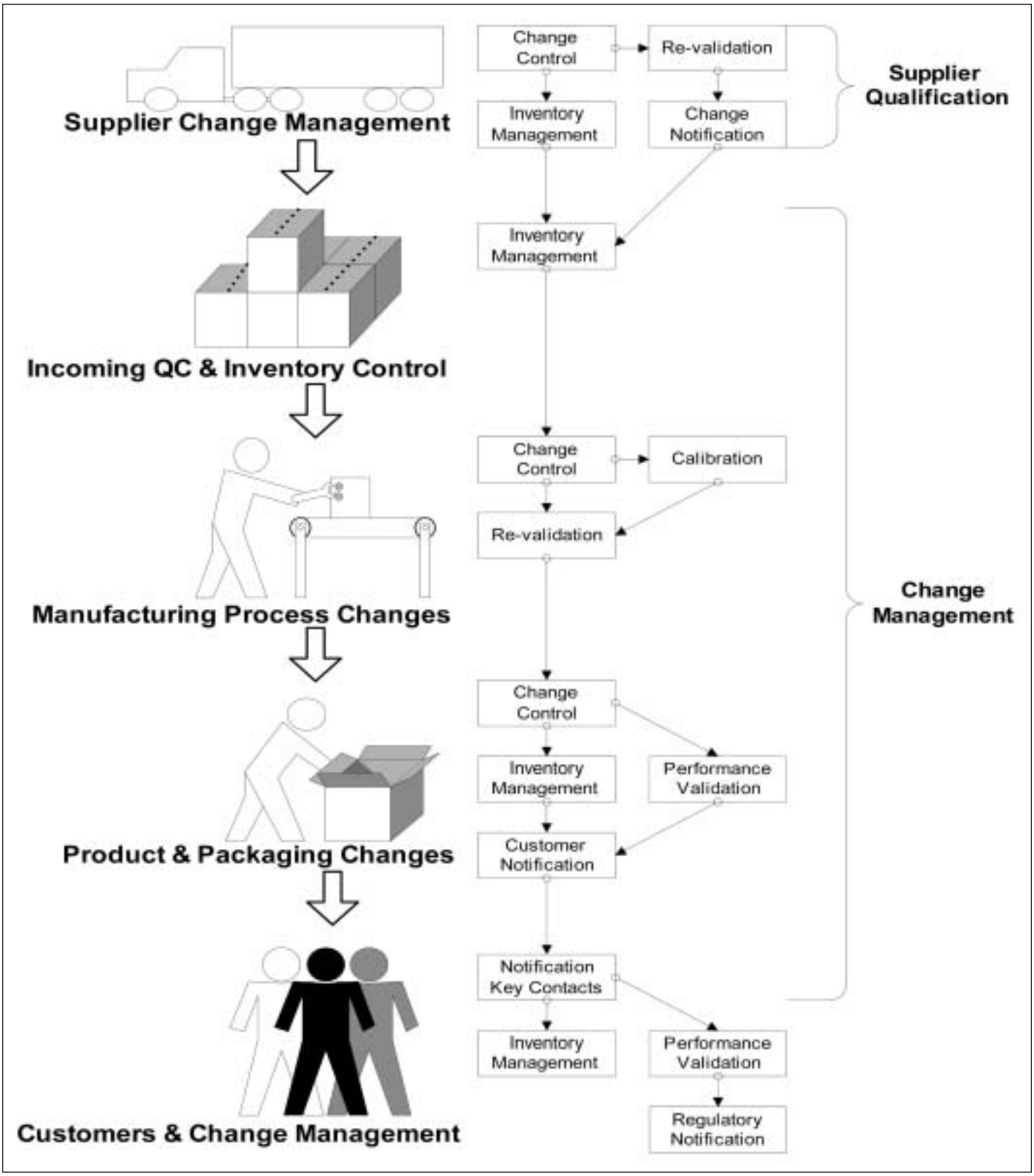

Figure 1. Change management and customer notification.

Continued on page 14.

- Change in the vendor of a critical material or component of the supplier's product – the same material produced by different vendors may perform differently depending on the application.

- Change in the supplier's process that affects the form, fit, or function of the supplier's product – examples of these changes include the use of new molds, different reaction vessels, different solvents, or different process technologies (such as centrifugation rather than filtration or laser cutting rather than die cutting).

- Change in materials of construction used by the supplier – even a change from one polymer configuration to another (for example, from high- to low-density polypropylene) should be considered a major change.

- Change in the supplier's manufacturing location – such a change generally occurs when a manufacturing operation is moved from one location to another. The same requirements would apply to the establishment of a second manufacturing location for the identical product.

- Changes to the supplier's product specifications that are outside the original specification range. This situation could allow product that the supplier had previously considered unacceptable to be within specification.

Manufacturing Process Changes

Pharmaceutical suppliers that follow current Good Manufacturing Practices (cGMPs) as defined by regulatory agencies, like pharmaceutical manufacturers, are expected to have rigid controls in place to ensure that their manufacturing process consistently results in product with the same attributes and performance (safety and efficacy). Any major process change requires revalidation of the process. Proper change management should ensure that all proposed changes are reviewed by the appropriate functions (product management, quality assurance, RD&E, engineering, etc.) and levels of management. The following elements of change control may be considered standard requirements for major changes in the pharmaceutical industry:

1. documented justification for the change
2. impact assessment of the change
3. management approval of the proposed change
4. implementation and validation of the change
5. management approval of the implementation and validation
6. regulatory and customer notification

The requirement for customer notification must be determined before the change is approved. After the change is approved, a validation protocol is written, if necessary, and approved before any validation work is started. Product made during the validation of a change must be segregated and quarantined until the validation has been completed and the validation report approved. After the validation report has been approved, product that reflects major changes must be properly identified and controlled in the supplier's inventory so that only customers who have accepted the change are shipped product that was made with the change. The same types of changes that can affect starting materials also can affect manufacturing processes.

- Changes that affect the form, fit, or function of the product – any change that could be perceived by a customer as a form, fit, or function change should be treated as a major change.
- Changes that incorporate a different process technology during manufacturing
- Changes in materials of construction
- Changes that affect product specifications

Product Changes

Product and packaging changes on the part of a pharmaceutical supplier can represent significant changes in the product configuration or design. These changes can constitute product modifications or result in new products. A prudent supplier implements all major product design changes as new products. The original product may be discontinued after customers are given adequate time to validate the new product.

An example of such a change is the redesign of a product used in pharmaceutical manufacturing to purify a parenteral drug. The redesign is implemented in response to the discontinuation of a key raw material by the supplier's vendor. Because this raw material is incorporated into a key component of the supplier's product, extensive qualification of the alternative component is completed by the supplier. The supplier conducts a two-phase notification of their customers. The first phase notifies customers of the upcoming change, and states the date of its planned implementation. This notice allows customers to purchase sufficient product in the current format to allow them to continue manufacturing their product, while qualifying the supplier's replacement product in their own process. The second notification from the supplier presents customers with data drawn from the supplier's qualification studies to assist customers in qualifying the redesigned product in their own processes. New catalog numbers are assigned to the redesigned product to help both the supplier and their customers manage their inventories of old and redesigned product.

Product changes that do not result in new products generally represent changes to product specifications, labeling, or packaging. Of these, changes to product specifications have the greatest potential to impact customers. Product specification changes generally fall into one of two categories:

1. **major** changes that either shift the specification range or widen the range to allow the acceptance of product that was previously out of specification

2. **minor** changes that reflect a narrower specification range that falls entirely within the original specification range

A specification change may not entail changes or additions to the supplier's manufacturing process or product. Specification changes may be implemented to better reflect process capability or product performance. These types of specification changes are generally made after a significant amount of historical data indicates that a specification change is appropriate.

Major specification changes on the part of a pharmaceutical supplier require customer notification and acceptance of the change before the customer receives product with the new specification. Although minor specification changes may not mandate customer acceptance, advance notification is advis-

able because user documentation must be changed, and this process can take a significant amount of time.

Packaging Changes

All packaging changes that do not affect the pharmaceutical supplier's product configuration or the materials that are in contact with the product are considered to be minor changes. If the packaging material that is in contact with the product is changed, the compatibility of the packaging material and product materials of construction must be verified and validated. This type of change is generally considered a major change. Packaging changes are qualified and validated by subjecting the new packaging to appropriate shipping tests followed by product inspection and testing. It is appropriate to notify pharmaceutical customers of any changes to the type of packaging material, even if it is not in contact with the product, to provide for proper waste disposal. Some countries now require the disclosure of the amounts and types of all materials that will ultimately be disposed of from a process.

Labeling Changes

Labeling changes that do not affect a supplier's product claims or specifications are considered minor changes. Customers may have to be notified of minor labeling changes before receiving product with the changed labeling if customers' internal documentation must be changed. A good example of a minor labeling change requiring pre-notification is a format or wording change to a Certificate of Quality. This document is routinely used in pharmaceutical customers' incoming QC procedures to verify that the received product is the same as product previously received. Copies of a reference Certificate of Quality are kept on file in incoming QC and matched against Certificates of Quality received with each shipment. If the Certificate of Quality on file does not match exactly the Certificate of Quality received with a new shipment of product, a complaint is raised, and the supplier's product can be rejected by the customer.

Inventory and Distribution Changes

A complete change management program also should address any changes that the supplier makes to the recommended storage conditions or shelf life of their product. The reduction of a shelf life claim should be considered a major change. Changing recommended storage conditions to more rigid requirements is an inventory consideration that also should be treated as a major change. Both types of changes must be managed from a supplier's warehouse and distribution perspective as well as from a customer's perspective.

Inventory and distribution change management are key to the proper implementation of major changes. Product that was made before and after the change must be segregated and controlled so that product reflecting the change is shipped only to customers who have accepted the change. Instructions may be provided to customers identifying how inventory at their location should be handled.

Customers and Change Management

Pharmaceutical customers are an important aspect of change management. Whether the change is major or minor, or requires pre-notification or simply a product insert, it is important for pharmaceutical suppliers to manage their changes with concern for their customers' perspectives. One of the risks that a supplier faces is not making a beneficial change because customer notification would be required. There are a number of factors in the pharmaceutical industry that weigh against a suppliers making changes that would require customer notification:

- Making a change that requires customers to re-validate a component in their process imposes on customers significant costs and constraints of time and resources.

- Changes that require revised documentation (work instructions, acceptance criteria, purchasing specifications, etc.) also can be costly and time consuming.

- The customer's need to qualify and validate the change in their process may leave open the opportunity to qualify and validate other suppliers' products at the same time.

Managing change at the customer level is central to successful acceptance and implementation of a change by customers. There are a number of customer-related change management issues that a successful pharmaceutical supplier will address in order to minimize the negative impact their changes can have on customers. The following considerations are important elements that can help customers to accept and implement a change that has been imposed by a supplier:

- Updated list of Notification Key Contacts
  - Knowing who the right contacts are at the customer site for notification of a change can make a big difference in how the change is handled by the customer. The supplier must know who is in the best position to manage a change in their customer's operation or organization. The appropriate people (those who must be notified) will know what must be done and how best to accomplish everything that must be done to accept and implement a change.
  - Maintaining an updated list of customer key contacts for change notification helps to streamline the notification process by avoiding the time-consuming effort of finding out who must be notified every time a change must be communicated. This also eliminates the aggravation and waste of time that customers would have to go through if the notification were sent to the wrong contact, either never reaching its intended audience, or doing so too late.

- Providing Data and Validation Information
  - Customers who must accept and implement a change imposed on them by a supplier benefit from having as much data and information as possible to determine the scope of the change and its implications for their process. Customers must know what has not changed, what has changed, and how it has changed.
  - Information from the supplier's validation of the change is also helpful and can obviate the requirement to validate by the customer, thereby saving time and money.
  - There may be many reasons why re-validation is not necessary. It is very important to state in the change notification letter the rationale against the need for revalidation. Data supporting the rationale should be provided to support customers' confidence that revalidation in their process is not required.
  - A summary of the supplier's Qualification and Valida-

tion Report should be made available for customers to review and to include with their internal documentation supporting the change.

- Define the steps that should be followed to accept and manage the change
  - When communicating a change to a customer, describing the actions they should take to implement the change can make the process very straightforward for the customer. Typical actions that should be specified are:
    - how to identify product that incorporates the change
    - what documentation must be changed
    - operator training that may be required
    - what to do with existing inventory of the old product

- Provide materials, resources, and data to help implement the change
  - For major changes that have significant implications, formal presentations given by the supplier's sales and quality-assurance representatives can help customers better understand the implications of the change, its effect on the particular customer, and what must be done to accept and implement the change.
  - Customers may need samples of the changed product to evaluate in their processes.
  - Providing a protocol for testing and evaluating the change also may help the customer to implement a change.
  - Historical QC data or process capability information may be needed to support a specification change.
  - The supplier's technical employees may have to assist customers in implementing a change.

The Impact of Inadequate Control and Change Notification

The costs and risks associated with change control are considered preventive and must be weighted against the costs that could be incurred if changes are not managed properly. Costs and risks associated with improper change management are considered avoidable failure costs. Significant failure costs related to inadequate change management include regulatory actions (483 citations, injunctions, and product seizures), product recalls or field actions, and customer complaints. Failure costs from the same source also include the delays in the introduction of new products and in the qualification of new facilities.The magnitude of these costs varies, but proper change management can provide for their control.

Conclusion

Change is inevitable, and because continuous improvement is impossible without change, progress is built on change. The key to making successful change in the pharmaceutical world is to manage it, both from internal and external perspectives.

Change management must be established by pharmaceutical suppliers, in collaboration with their customers, as formal processes, from the supplier's starting materials to the validation of changes to their processes and products, to the controlling of inventory for products that have changed. Change management also applies to communicating changes to customers and helping customers to accept and implement changes to the products that their vendors supply.

There are many facets of change management that must be coordinated and integrated into a formal change management program. The most effective change management program is one in which both suppliers and customers participate in managing the process. If change is managed properly, everyone wins.

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