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Consumer Product Safety Commission (CPSC) Update on Child Resistant Packaging Requirements and Options

by Michael G. Dragoon, Past Chair, ISPE Clinical Materials Committee

One of the benefits of belonging to ISPE is access to regulatory bodies. Over the years, ISPE has forged an important working relationship with the FDA. This access to regulatory bodies provides a ready avenue for working on current industry opportunities. SUPAC, BACPAC, and the library of Guides all resulted from this working collaboration. This article illustrates an example of progress made in addressing issues of industry interest between various industry groups and the CPSC. The information provided here is a summary of information gleaned from meetings between various Clinical Trial Material (CTM) interest groups and the CPSC. Views expressed here do not necessarily represent those of ISPE or the other interest groups represented in the discussions.

Child Resistant Packaging in Clinical Trials?

Background

Over the past year and a half, the CPSC has clarified that the Poison Prevention Packaging Act (PPPA) applies to Clinical Supplies as well as Commercial Products. In general, this clarification was new information to the Industry. For studies where bottles are the package of choice, most companies utilize Child Resistant (CR) closures. For studies requiring blister packaging however, companies face other challenges. The main challenge in designing a CR blister package for clinical supplies is combining the current CR blister card backing technology (e.g. peel & push, skip notching, etc.) with normal CTM technology (e.g. blister strips heat sealed in a wallet or card). Thus, the carding or walleting configuration normally used for CTM, impedes the functionality of current CR blister card backing technologies. Further, using CR bottles in some study designs where CR blisters are not feasible, could be detrimental to the study outcome. CR bottles can be (and are) used in clinical trials. However, blisters are often the only choice when providing supplies for a double blind, double dummy, multiple dose study in order to ensure patient safety and robust study conclusions through improved patient compliance.

Meetings with CPSC

In April 1999, Frank Tiano formed a group including representatives from leading CTM discussion groups and committees, to meet with CPSC. This group, now referred to as the Clinical Material Interest Group, discussed issues and developed potential solutions to the challenges faced by the clinical supply industry in regard to CR blister packaging. ISPE Clinical Materials Committee representatives participated on this task force. Other groups represented included Clinical Contract Packagers (CCP), Clinical Studies Support Group (CSSG), DIA Clinical Trial Materials Group, Equal Partners in Clinical Studies (EPICS), Investigational Materials Discussion Group (IMDG), Midwest Clinical Supplies Group (MCSG), and the Pacific Area Regional Clinical Supply Group (PARCS).

The Clinical Material Interest Group provided CPSC with an overview of the clinical trial process and clinical supply design. The group discussed the current state of bottle and blister package CR technology within the clinical supply industry. In general, most bottles in clinical studies are fitted with CR closures. However, there does not yet appear to be a successful standard industry approach for CR blisters for use in clinical trials. The overview of clinical supplies provided a good backdrop for a discussion of packaging options for a typical double dummy, double blind, multiple dose clinical study. Examples of supply kits for this type of study were provided to CPSC in both bottles and blister packaging presentations. These examples clearly illustrated the advantages of

blister packaging in achieving easy and convenient patient compliance. Special challenges associated with CR clinical blister packaging, along with options for dealing with these challenges, were discussed and clarified.

Current Status

After two meetings between the CPSC and the Clinical Materials Interest Group, there are now some compliance discretion options for consideration. These are the main points, from a June 21, 1999 letter from CPSC, and the August 18, 1999 meeting log notes on file at CPSC:

1. Testing of primary CR packaging is not necessary if the units can be made with any of the features described in ASTM D-3475, provided that the unit dose packaging has at least one recognized child-resistant feature. (Note ASTM is being revised at this time.) Information on ASTM D-3475 is available at http://www.astm.org/.
2. CR packaging is not necessary if the non-child-resistant units can be placed in an outer container that meets the standards of 16 CFR 1700.15. CPSC preferred to see individual secondary package CR presentations rather than bulk secondary packs (i.e., carton containing multiple weeks worth of supplies). Larger size packaging with boxes, locks, keys, etc. would not be favorably viewed by CPSC. CR pouches must be resealable (the CR feature reactivated) if the primary container holds more than a single dose.
3. These two options apply to phase II and III studies. CPSC will consider categorizing Phase IV trial supplies with Phases II and III when it is not possible to use the commercially available package. When commercially available product is used in a study in an unblinded state (i.e. rescue medication), it should be offered in the CR market presentation.
4. Labeling may include a statement to alert presence or absence of CR features. Use of a non-CR statement on the primary non-CR pack is advisable when used in conjunction with a CR secondary package.
5. A "Blanket" Waiver Statement is not appropriate. Waivers must be done on a case by case basis as requested by the patient or the physician. The use of a waiver statement is at company discretion.
6. Non-CR packaging may be used if the amount dispensed into the household will not cause serious injury or illness to a young child.
7. Studies conducted on an in-patient basis, do not require CR packaging.

Next Steps

At the CPSC's suggestion, the Clinical Material Interest Group drafted a proposed Timeline of Compliance. The Timeline of Compliance proposes a transition time to address technical and logistical challenges of CR packaging in CTM blister packages. CPSC is currently reviewing this proposal. The Clinical Material Interest Group is anticipating a response from CPSC in the near future. This response will be communicated through the various CTM discussion groups represented on the Clinical Material Interest Group. The information will be posted on the Clinical Material Committee's home page when it is available. Additionally, the information will be presented as part of the Clinical Materials Educational Forum at the ISPE Annual meeting, October 29 - November 2. Through collaboration, there are opportunities to work through issues and create solutions that meet CPSC and industry needs.

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And So Was the Pharmaceutical Industry...

This article is about the fascinating history of Salvarsan, a drug against syphilis invented at the turn of the last century to fight one of the major diseases in those days.

by Dominick Smith

Salvarsan

Ever heard of Salvarsan? Well, then you were not around in the '20s - that is 1920 - as it was then one of the most famous (and most expensive) drugs on the market. As a century has now come to a close, as our politicians are trying frantically to reduce healthcare costs and our industry is very often presented as a "profit-before-all" activity, it is amusing to look at what our grandfathers did to reduce the cost of a drug that was, in those days, a matter of survival.

A Submarine Off Staten Island

In the late hours of Saturday, January 13, 1917, the submarine Deutschland was waiting in the narrows off New York City (at the current location of the Verrezzano Bridge), invisible, as she was submerged just below the surface. The weather was so miserable that no one was around to see her anyway. She was a very exceptional vessel, a cargo submarine specifically designed to run the British blockade. In times of peace, surface ships would have been used for that purpose, but World War was raging (with no US involvement yet). As their country had to support a huge war effort, the Germans were ready to do anything to make a Deutschmark, and they built this submarine (again, it was 1917) only to export, regardless of the British, the goods they were selling to the world.

On January 13, 1917, the Deutschland was full to the brim with Salvarsan, a drug for which the Germans had the quasi monopoly and the only cure for a disease which was devastating in those days. Shortly before midnight, a signal was sent from Fort Wadsworth on Staten Island. The Deutschland emerged and slowly cruised toward the Hudson River. She reached Pier 42 in a quiet part of New York's West Side in the early hours of Sunday, January 14, 1917. Sunday was selected on purpose because no one would be around, except for the employees of H.A. Metz Laboratories waiting to unload the cargo. Before church time, the Deutschland was gone.

Figure 1. Paul Ehrlich (©The Nobel Foundation).

The Shame of the Family

Had you lived during the days of President Wilson, the diseases you were more likely to get were infectious. Degenerative diseases like cancer or stroke were not unknown, but the likelihood of surviving to the former were so remote that your chance of living to an age at which you would suffer from the later was far less than today. Also, to outlive an infection in those days meant you had to endure and survive brutal drugs and treatments of that era.

Thanks to Penicillin, syphilis is now enormously reduced in our society and it is so simple to treat that it is no longer a major public health concern. This was not so at the beginning of the century when it was one of the major diseases worldwide. Back then, cases numbered one hundred thousand - a year - and the cures were few. Treatments with potassium iodide and mercury were of little effect, if any, and the drugs were at least as dangerous as the disease. Also, syphilis was believed (wrongly) to be exclusively transmitted by sexual contact with women of ill repute. It was then the custom of western societies strictly to refrain from the discussion of sexual matters: syphilis was an unmentionable topic, and was so shameful that patients would do anything to prevent their condition from becoming known. Finally, the last of the three phases of the disease could remain latent for decades, greatly increasing the risk of dissemination, which is exactly what happened.

Arriving on the scene was the German bacteriologist Paul Ehrlich, famous among other things for the side chain theory for which he obtained the Nobel Prize in 1908. He is also remembered for having coined the word "chemotherapy." For reasons too long to explain (maybe another paper), Ehrlich was interested in the organic compounds of arsenic, and he achieved the synthesis of no less than 605 such compounds before coming up with number 606. Salvarsan had the unique property of knocking

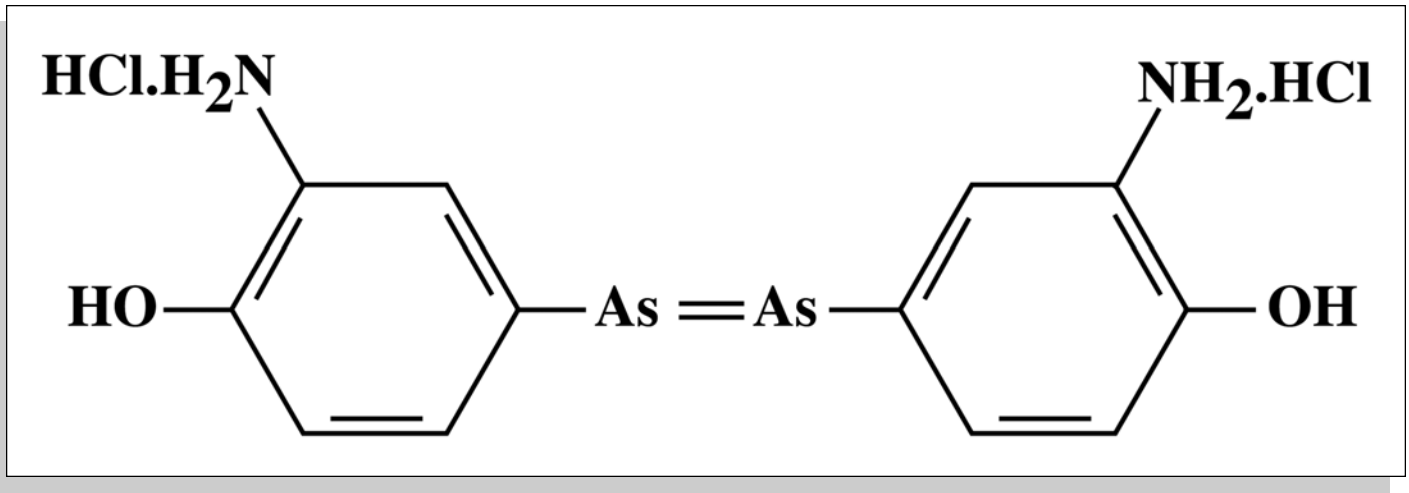

Figure 2. Arsphenamine (Salvarsan) formula.

out Treponema Pallidum, the bacterium responsible for syphilis. The year was 1909.

As a true scientist and director of a German State institute, Ehrlich was very concerned with the purity of the product and the conditions under which it was tested. But, because his institute's production capacity was at best limited he had to look for help to a big chemical company, which happened to be next door: Hoechst. Hoechst was far more concerned with the commercial prospect of such a drug (with the potential of one of the largest markets of the day) than with the quality of the product or the conditions of its testing: samples were sent all over the world and, in a matter of months, Salvarsan became the "magic bullet" worldwide. A British bacteriologist in charge of testing Salvarsan at St. Mary's Hospital in London will be heard from again in history: his name was Alexander Fleming.

Surviving to the Cure

Although very efficient, Salvarsan was a highly inconvenient product. It was very unstable and therefore had to be shipped in powder form in sealed containers as it would degrade upon contact with air. Prior to use, it had to be mixed with water and since doctors in those days did not even know how to spell WFI, more often than not tap water was used. Then the product had to be neutralized and injected in an intravenous fashion, a technique which was so uncommon at that time it was considered a surgical procedure.

The standard treatment was neither quick nor cheap: an average patient required a weekly injection for three months and this was to be repeated two or three times. In those days of no health insurance, the price was a staggering $3.60, going sometimes as high as $16 a dose. Today, that is $47 and $208 respectively. People had to pay from their own pocket, but syphilis was such a cause for shame that money was not an issue. This was indeed a highly profitable business for the company controlling the Hoechst products in the US, the H.A. Metz Laboratories, the very same people who were waiting for the Deutschland in the early hours of January 14, 1917.

The submarine Deutschland had every right to come to the US (the declaration of war was still two months away), but anti German sentiment was so high in the country that H.A. Metz had requested as discreet a delivery as possible. American animosity toward the Germans was primarily because of the sinking of British ships with American passengers (the Lusitania among others). The exorbitant price of Salvarsan, for so long a German monopoly, did not help. What the American public did not realize was such extravagant prices were the consequence of the US pharmaceutical industry's own choosing.

Patents on medicines were considered taboo before World War I among those American drug manufacturers who were trying to distinguish their "ethical" pharmaceuticals from the remedies of proprietary drug makers. The Germans, more realistic and less naïve, had a totally opposite approach and filed patents not only for the drugs themselves, but also for all possible molecules with the slightest similarity to the active compounds, not to mention all the intermediates involved in their synthesis: Salvarsan was locked in an impenetrable patent fortress.

The Dermatological Research Laboratory

Because Salvarsan was so expensive and out of the reach of many patients in the US (remember, a shot was between $47 and $208 dollars today), the US medical community was eager to produce it locally. In 1916, as Germany was stranded in World War I, it looked like an appropriate time to try. The Dermatological Research Laboratory (DRL), a non-profit institution operating from the basement of a Philadelphia hospital, was assigned the task. George W. Raiziss, the chief chemist of DRL, initially thought of the mission as a piece of cake as the manufacturing procedures were fully described in the patent. He discovered soon enough that Ehrlich, neither naïve nor a fool, had purposefully skipped some critical steps in the description of the extremely complex synthesis of Salvarsan. It took Raiziss and his team several months to produce the famous yellow powder for which the commercial name Arsenobenzol was selected.

Needless to say, the importer of Salvarsan (H.A. Metz), worried about losing his fat margin, brought the matter to all possible courts of the land. In 1916 and 1917, the medical community was torn apart by the controversy between the German Salvarsan and the American Arsenobenzol. To the scientific and not so scientific arguments flying around were added the (very nasty) political ones as H.A. Metz was a former member of the 63rd Congress as a Democrat from New York.

At the time the U-boat Deutschland was entering New York harbor, it was common knowledge that war was imminent and there was much concern that Salvarsan supply would be cut off indefinitely. Hysteria took over the medical community. A

> ***US pharmaceutical manufacturers did (and still do) put a protective barrier of patents around the molecules they discover very much as the Germans did during the time of Salvarsan.***

salvo of arguments were exchanged and all possible maneuvers (open, behind-the-scene and otherwise) were used to discredit Salvarsan, so much that a petition was presented to Congress to abrogate its US patent, a first in the intellectual property history of this country. In the summer of 1917, the Adamson Bill deprived the Germans of their rights on patent 986,148 and licensed the Philadelphia Dermatological Research Laboratory for the production of Salvarsan on the condition, among other things, that a dose was to be priced at $2 the first year, $1 the next, and 50 cents thereafter (respectively $26, $13 and $ 6.50 in today's dollars).

After her January 1917 trip, the U-boat Deutschland was never to come back to our waters.

The Swan Song...

The DRL did extremely well in the Arsenobenzol/ Salvarsan business. With so many of its men in "dangerous" countries, the US Army was of course its first customer. The DRL did so well that by 1922 it netted a profit of US $500,000 ($6.5 million dollars today), which was very much frowned upon as it was a non-profit organization: the license agreement and the plant for Arsenobenzol/Salvarsan had to be sold. H.A. Metz made aggressive efforts to buy it but, even in 1922, the Lusitania was neither forgotten nor forgiven and the bitterness against Germany was so high that his offer, although it was the highest, was rejected. During a game of golf sponsored by the American Pharmaceutical Manufacturers Association, the plant was sold in September, 1922 to Abbott Laboratories for $150,000 (close to $2 million today). Abbott did not come to regret the move as it increased its profit by $503,000 (more than $6 million today) the next year.

It was the swan song of Salvarsan though: soon penicillin came around and, many times more effective against syphilis, it removed Salvarsan forever from the pharmacy shelves.

The lesson of Salvarsan was not lost though: US pharmaceutical manufacturers did (and still do) put a protective barrier of patents around the molecules they discover very much as the Germans did during the time of Salvarsan. Likewise, the art - in which Paul Ehrlich was so talented - of describing a process in a patent without, in fact, describing anything of consequence, became the common practice in our industry.

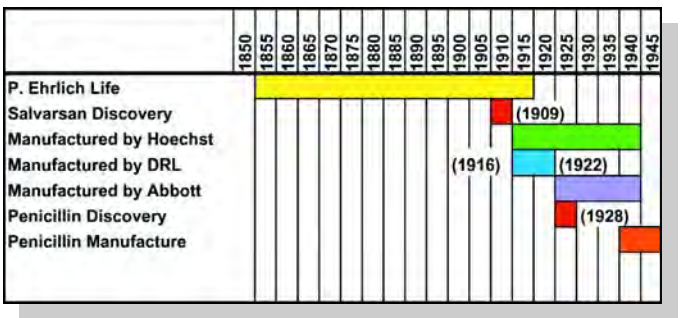

Figure 3. Salvarsan in history.

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About the Author

Dominick Smith is Director for QA at Regeneron Pharmaceuticals where he is more specifically in charge of the Tarrytown (NY) headquarters. He has 31 years of experience in the pharmaceutical industry, half of which he has enjoyed the privilege of working in eight different countries. He spent 19 years with Rhone-Poulenc where he served in various engineering capacities. Subsequently, he joined United Engineers & Constructors and later Foster Wheeler USA where he became responsible for the technical and administrative management of the company's Validation and Regulatory Affairs group and the interface with overseas subsidiaries. Before joining Regeneron, he spent three years with Kvaerner Process (formerly John Brown) were he was the director of validation & regulatory affairs. Smith earned a MSc in chemical engineering from the University of Nancy (France) and an MBA from the University of Pantheon-Sorbonne, Paris (France).

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This article details the implementation of a MES in a biological manufacturing facility. A detailed list of benefits seen from an MES project is described. To improve the success of the implementation, a strong project management plan was used. Approach to the Regulatory and Validation concerns are discussed.

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The Implementation of a Manufacturing Execution System (MES) within a Biological Manufacturing Company

by Frank S. Kohn, PhD and David Williamson

Introduction

Wyeth-Lederle Vaccines (WLV) in Sanford, NC develops and manufactures conjugated vaccines for the treatment of several childhood diseases. This article describes the implementation of a MES for the plant's one licensed product, HibTITER®, used to immunize children against Haemophilus influenza Type b, a bacteria which can cause a form of meningitis.

Scope

The project scope was to implement a MES that included an Electronic Batch Record (EBR) and on-line access system to electronic Standard Operating Procedures (SOPs) in a biological manufacturing plant.

System Overview

The MES system provides the following:

- An EBR
- Material Tracking
- Work In Progress (WIP) and Availability Reporting
- Access to Online Documentation such as SOPs
- Material Reconciliation
- Process Data Management
- Lot Genealogy
- Batch Record Reporting
- Bar Code Capabilities

The EBR includes aspects of the manufacturing process: buffer and solution preparation, intermediate manufacturing, glassware preparation and dispensing.

The project progressed through four distinct phases. The first phase consisted of defining the project requirements, selecting a vendor and justifying the project. Developing a simple solution, preparing records to address and find answers for current Good Manufacturing Practices (cGMP's) issues was the second phase. Expanding this simple model into more complex intermediate records was the third phase. The fourth and final phase consisted of modeling other manufacturing activities such as glassware preparation. Validation activities started on day one of the project and will never cease (due primarily to system maintenance and change control requirements).

The primary benefits seen from the MES are:

1. a reduced cycle time caused by the reduction of the review time of manufacturing documents.
2. a reduction in variances because operators perform tasks in a specific fashion.
3. variances that do occur are less severe because operations stop to consult with the appropriate supervisory personnel.

As our experience grows with the MES, we expect to see other benefits related to process improvements, to training and to faster product development times. Using the data collected in an easily queried database will lead to process improvements. The interface to the MES is the same regardless of the product produced. This provides training benefits and allows for the standardization of operations and methods

> ***The road to a successful implementation can be long and difficult if you do not engage in the proper planning and preparation.***

throughout the plant. Easier data collection, a greater control over process variables, and the elimination of operator error will lead to faster product development times. Figure 1 shows the architecture of the system.

Requirements, Selection and Justification

WLV formed a multifunctional team to study future business needs and to make recommendations for improvements. The team consisted of WLV representatives from Manufacturing, Information Services, Quality Assurance, Technical Services/ Validation, Materials Management, Finance and Engineering. It also included an industry knowledgeable consulting firm. The team used a technology selection process to perform the business study. After modeling the current process and gathering the system requirements, the team determined that considerable benefits existed through the application of a computerized MES.

The technology selection process then organized the requirements of the system by function (software design and development, system functionality, etc.) and assigned weights based upon their perceived importance. These requirements generated a combination of vendor questionnaires, vendor interviews and product evaluation sheets. These devices were then used to generate a numeric score for the four products selected for final evaluation.

The software automates most of the previously manual, paper-based process helping to ensure compliance to cGMPs. The team decided to implement this software on the existing licensed HibTITER® product and then expand the system to plant activities after the successful implementation on the first product.

Justification for the project included the following:

- Regulatory Compliance: Directing operators to perform tasks in the correct sequence and manner ensures compliance to regulatory requirements. This reduces variances and those variances that do occur require the process to stop for consultation with the appropriate supervisory personnel. Additional compliance benefits include easier and simplified reporting (i.e. Annual Product Reviews), paperwork completed properly with signatures, and easier process control monitoring.

- Document Management: Documentation is a vital part of every day life in any regulated industry. The benefits of good documentation include the streamlining of document approvals, delivering accurate information to operations, managing records and reports for GMP compliance, and improving the exchange of information between departments and organizations.

- Document Usability: The MES requires modeling similar manufacturing activities using identical methods. This builds similarities across manufacturing documents. Training and the documentation of that training becomes easier and document review becomes simpler. Creating future records then becomes easy and simple because unit operations already exist and require little or no changes.

- Data Collection, Storage and Retrieval: Collecting manufacturing data into one common, electronic database direct from the source is a major benefit. This allows for easier process improvements, trending analysis, failure analysis and other process analysis. This also may reduce the occurrence of human error since the process becomes easier to operate.

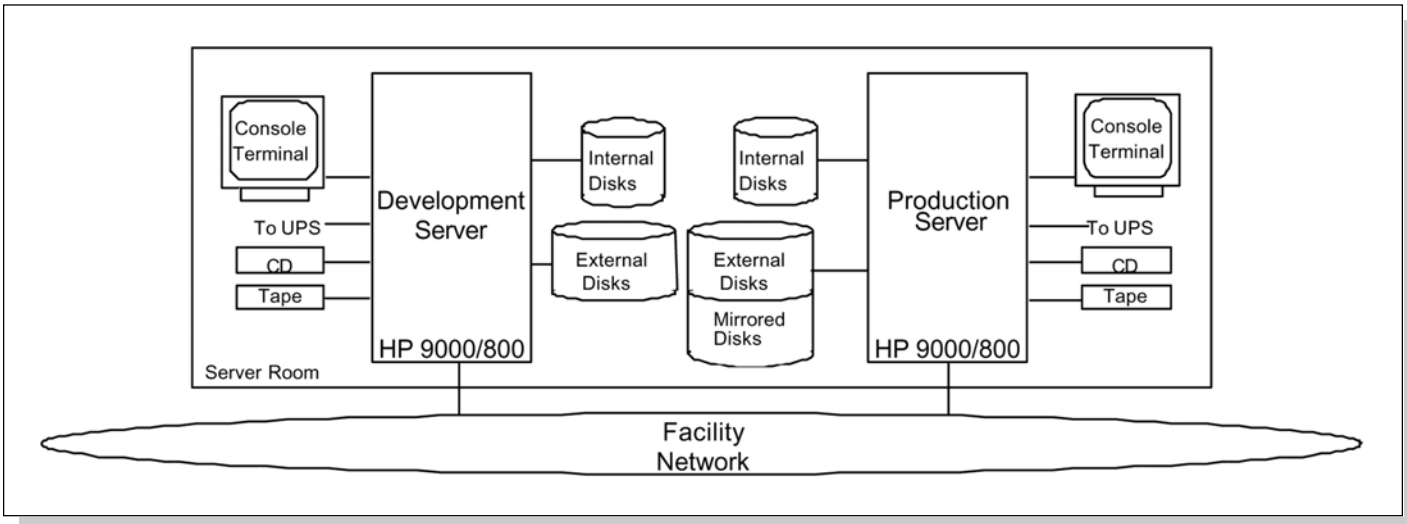

Figure 1. System architecture.

- Continuous Process Improvement: An electronic based process is more effective and efficient than a paper based system and improves manufacturing operations. Envisioned improvements includes a lower cost of goods due to less waste and scrap, improved record keeping and information dissemination, improvements in quality, and improvements in the quality of the methods used throughout the process.

Development of the System

After selecting the computer system, the team's first tasks were getting the computer system operational and conducting training for team members. The vendor provided the training on site in our facility. The team then focused on developing an EBR. The team created a three-page document for a simple saline buffer that could be executed within a 15-minute period, yet encompassed many complex GMP issues. These issues included:

- the dispensing of raw materials (sodium chloride)
- the procurement of Quality Control (QC) released Water for Injection (WFI)
- the procurement of equipment (a clean and sterile process tank)
- the charging of the dispensed sodium chloride into the process tank
- the collection of analytical data (pH reading) and the checking of that data against a fixed specification (ex. pH range = 5.0 - 7.0)
- the setting of an expiry based upon a date/time collected during the process

Creating this electronic batch record became quite a task. The team needed the following:

1. to receive Quality Control released raw material
2. to dispense the raw material on a calibrated electronic scale
3. to Clean in Place (CIP) and Sterilize in Place (SIP) the equipment
4. to create the best model for performing the steps (issues) listed above

The solution the team used was to create very simple models for the non-batch tasks and finish them later. For example, the team created a CIP model that just collected the equipment identification (ID), created a CIP number and expiry, and printed a CIP label. The team did not collect any of the normal in-process data on our existing CIP form.

The first working model required five weeks to build. After several demonstrations of the model to management, QA and Technical Services, they reached agreement on a final model. The team held a special demonstration of the final model for QA to ensure their satisfaction with the model. The model had to allow GMP compliant manufacturing to occur. Thus, QAs acceptance of the model was a critical issue.

At this point, the workload for the validation group increased. The team previously defined their methodology in the Master Validation Plan, but now they needed to create the necessary validation documents. This developed into a lengthy process because the team wanted to satisfy the involved groups and satisfactorily defend the results of the validation.

Keeping up with the model developers became the next problem of the team. For every validation package completed for a batch record, six more models were developed. The model developers enjoyed the benefits of a learning curve and were able to reuse most of their previous work. This was not the case with the validation process.

Project Management

To improve the odds of a successful implementation of the MES, the team developed a strong project plan that addressed the following nine areas of project management:

1. Integration
2. Scope
3. Time
4. Cost
5. Quality
6. Human Resources
7. Communications
8. Risk
9. Procurement

The two areas the team determined the most critical were risk and scope management. Project risk management identifies, analyzes and responds to project risk. It includes maximizing the results of positive events as well as minimizing the consequences of adverse events. We identified six major risks for this implementation: software upgrades, turnover, software robustness, task conflicts, skills deficiency and resistance to change. Listed below are the strategies for dealing with these risks:

- Software Upgrades: The implementation plan must allow for time and the resources for the process of performing the upgrade, the potential remodeling due to upgrades and the revalidation of upgrades. Estimates of time and resources were accurate, but they were not broken down as anticipated. Remodeling work was less than anticipated. Only two minor changes in the software caused remodeling to occur. However, due primarily to the Y2K situation, installed were many more actual upgrades and patches than expected. To minimize the revalidation of software upgrades, the team developed a suite of tests that 'touched' the vast majority of the applications functionality (out of the box and custom). These were used to demonstrate that the system was still functioning as it did prior to the upgrade.
- Turnover: The skills needed to participate on the project team were not common within our facility, so the departure of any team member would cause disruptions to the implementation plan. The strategy was to ensure that skill

duplication existed at key positions (project manager, team leaders) and that some resource overlap existed in the other positions allowing time for new members to be brought on board.

- Software Robustness: The team adjusted modeling times upward to account for the development of a "work-around," that is a situation that the software could not properly model. However, no situation occurred that the MES could not match our business practices. In addition, the team determined that developing individual models for equipment was simpler than creating one model to accommodate the various equipment types.

- Task Conflicts: Ensuring that required resources were fully loaded in the implementation plan was the primary objective. The full time team members accomplished this objective, but this caused problems for the part time team members. Other plant projects involving new products diverted essential resources from our quality, validation and regulatory groups. This caused the team to adjust the ordering of events to account for the longer approval times needed for models.

- Skills Deficiency: Ensuring that the team members had the proper skill sets and received the necessary training was the objective. No problems related to this issue occurred. In fact, due to the early success in the project, many people wanted to join the project team.

- Resistance to Change: The team took a two-pronged approach to solving this problem. First, affected managers received goals related to the project. This included the Plant Manager and the Director of Manufacturing. Second, the team involved the actual operators and supervisors from affected departments in the demonstrations, training sessions and model discussions from the start of the project. This gave these people a better feeling about the system since they were involved in its development.

Project scope management defines the work required, and only the work required, to complete the project successfully. The team developed a threefold strategy for managing the project scope. First, any change to the defined set of project objectives required the approval of the project executive steering committee. Second, defined was a chain of 'arbitrators' for deciding design issues. This chain started with the supervisors, moving up to the directors of quality assurance and manufacturing. Third, any changes to approved models required the use of regular, change control procedures. Although this third strategy is a GMP requirement, it dramatically reduced the number of changes requested post approval.

Implementation

Validated models existed for the following upon completion of the first Performance Qualification (PQ):

- Receiving of Raw Materials
- Dispensing of Raw Materials
- Inventory Management
- Material Quality Management
- CIP
- SIP
- Label Printing
- Equipment Maintenance
- Nine Compounding Records
- Three Intermediate Records (Including the Final Bulk Product)

Additional work performed in the months following this PQ completed the first manufacturing area. At this time, it was clear that the team had climbed the learning curve and was producing future models at a much faster rate (approximately 33% faster).

Besides working on the models, the team implemented one major and two minor software upgrades. Upgrades to the operating system and the database also were required to ensure Y2K compliance.

Validation Package Contents

Validating the completed work required an equal or greater amount of work. The validation effort started prior to the approval of funding with vendor audits, and the writing of a project plan, a master validation plan and user requirements. Each model required a written design specification and system test(s). In addition, each of the models also used imbedded scripts requiring a design and unit and/or integration test plan.

After the approval of the above validation documents, the plant's change control procedures also applied to these documents. This required the pre-approval of any design changes, an evaluation of the change, the appropriate testing of the change, and then the post-approval of the whole change package. Many of the first models developed incurred three or four changes prior to the execution of the Operational Qualification (OQ).

Advantages of the MES

As our plant becomes more familiar with the MES and learns new ways to take advantage of the data in the system, we continue to see our cycle times decrease. This is due primarily to the dramatic reduction in our batch review time. The system ensures the proper completion of documents with the necessary signatures. Not having to scan a 150-page document to verify the documentation is an obvious time saver! Our subsequent reductions came primarily from the avoidance of problems. The MES requires operators to perform tasks in a specific sequence and manner. If something goes wrong, it requires operators to stop and consult with supervisory personnel. Even if a problem requires an investigation, more assurance exists that proper handling of the problem occurs from the time of the problem through its resolution.

At WLV, we are just beginning to tap the potential of our EBR system. A large potential exists for future data analysis and process improvements. Other future projects include creating and preparing our annual product review documents and specialized training of our manufacturing operators. The bottom line is that the MES has created a new way of thinking and behaving for our plant.

Conclusion

The road to a successful implementation can be long and difficult if you do not engage in the proper planning and preparation. Making implementation of the MES a primary goal for the plant is necessary for a successful implementation. It requires significant amounts of financial and human resources. At WLV, we feel that the results justify the journey. We look forward to expanding our system and gaining larger benefits as we integrate the system into other products and into other systems.

Software Vendor

WLV selected the BASE10® FS product, from Base Ten Systems, Inc. Assistance was provided to the WLV project team by software vendor personnel throughout the life of the project.

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- Michael Hamel (WLV)

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This article reviews the current status of the Baseline® Guides and includes a preview of the Commissioning and Qualification Guide which is currently at the draft stage.

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Baseline® Pharmaceutical Engineering Guides Update

and a Preview of Volume 5: Commissioning and Qualification (Draft)

The Baseline® Guides are a series of volumes produced in partnership with the FDA and industry representatives from a broad spectrum of the pharmaceutical industry. The Baseline® Guides aim to provide engineers and other professionals in the pharmaceutical industry with baseline information on the design, construction, and commissioning of new and renovated facilities, equipment, and systems to achieve regulatory acceptance. It is important to understand that the Guides are not regulatory documents.

Published Baseline® Guides

The following published Guides are currently available from ISPE:

Volume 1: Bulk Pharmaceutical Chemical Facilities (BPC)

The Bulk Pharmaceutical Chemical Facilities (BPC) Guide was published in 1996 and has already undergone review in accordance with changes within the related sector of the industry. The ISPE Technical Documents Steering Committee members performed this first review along with others involved in the original production of this Guide; very few technical changes were required. This year, a full external review and revision of the BPC Guide is intended and comments will be solicited from those within the industry who have used the guide since its publication.

Volume 2: Oral Solid Dosage Forms

Published in 1998, The Oral Solid Dosage Guide applies to facilities producing tablets, capsules and powders.

Volume 3: Sterile Manufacturing Facilities

The Sterile Manufacturing Guide has proved popular since publication in January 1999. It applies to facilities for aseptic processing of formulated product.

Two New Baseline® Guides Soon To Be published

The following two Guides are both intended for publication during 2000. Both are categorized as Horizontal Baseline® Guides and, as such, provide detail of concepts that are covered briefly in the Vertical Baseline® Guides that apply to specific types of manufacturing operations.

Volume 4: Water and Steam Systems

The Water and Steam Guide is currently under review with the FDA and applies to systems affecting all types of manufacturing facilities.

Volume 5: Commissioning and Qualification

The Commissioning and Qualification Guide is nearing completion and is intended for FDA review during the summer of 2000. This guide has already had significant input by the FDA on a chapter-by-chapter basis. The first six chapters of the Commissioning and Qualification Guide are discussed in more detail later in this article.

New Baseline® Guides Under Development

Volume 6: Biotech

The Biotech guide development is underway and an outline and scope of the guide was presented in April. The scope of this guide is current industry practice for facilities and systems used for production biologics. Once the scope, goals, and outline have been established, the writing of the content of the Guide will begin and a first draft of this document is intended for presentation in June at the ISPE Washington Conferences.

Volume 7: Packaging and Warehousing

The Packaging and Warehousing Baseline® Guide is to begin development during 2000 and will be the seventh Guide in the Baseline® series. Suitable team members are being sought.

Commissioning and Qualification Draft

Introduction

This article provides a description of the first six chapters of the Commissioning and Qualification Baseline® Guide. These chapters provide a basis for later sections of the guide, which are now approaching their final drafts.

The Commissioning and Qualification Baseline® Guide defines and clarifies differences between qualification and commissioning processes, and the extent of regulation of the qualification process. Common terminology is provided for all involved in the commissioning and qualification process. The Guide aims to eliminate costly practices such as:

- repeating qualification steps during process validation
- qualifying systems that only require commissioning
- generating insufficient or excessive product documentation
- delays which may result in product supply interruptions or delayed product launch

It is emphasized that the guide does not encompass Process Validation - *Figure 1*.

A brief explanation of the terminology used throughout is given in the introduction and is discussed in greater depth in the relevant chapters of the Guide. The Commissioning and Qualification Guide defines a range of key features, which are used as a basis for guidance - *Table A*.

Definitions relating to the key concepts went through several revisions to achieve agreement within the entire Guide team. These are provided in the second chapter of the Guide, along with diagrammatical representations of basic qualification relationships for both direct impact systems and indirect impact systems.

Impact Assessment

Impact assessment is considered in detail and described as; "one of the most important activities in defining the Commissioning and Qualification scope of a project. This is the process of determining which systems and/or system components should be subject to Qualification Practices in addition to Good Engineering Practice (GEP) and which systems should be commissioned in accordance with GEP."

One possible method involving a two-step assessment process, to determine system impact and component criticality, is provided.

The first step evaluates the impact of system on product quality. The logical systems within a project are defined, and their impact on product quality is identified. Systems are evaluated as:

- Direct Impact where the system "is expected to have a direct impact on product quality."
- Indirect Impact where the "system is not expected to have a direct impact on product quality, but typically will support a Direct Impact System."
- No Impact System where the system "will not have any impact, either directly or indirectly, on product quality."

This information can then be referenced in a matrix of system versus impact on product quality. An example is shown in Table B.

The second step evaluates the criticality of the components in the systems as they relate to product quality. The Guide details a process to determine the relationship between the type of impact a system, or one of its components, has on the product and the criticality of those systems or components.

Direct Impact Systems may contain non-critical components, along with their critical components. However, Indirect Impact systems may not contain critical components. If the latter is found to occur during the System Impact Assessment process, then the component needs to be reconsidered and either the impact of the system which contains that component, or the criticality of the component, has to be re-defined.

Design for Impact "allows the design team to focus on what is critical to the product and use the impact assessment concept to concentrate the components affecting product quality into a manageable number of systems." This allows resources to be focused on the systems where they are most needed.

The Impact Assessment process, including "Design for Impact", allows the design team to determine which systems and their components are subject to GEP and which require GEP and Qualification Practices. Direct Impact Systems and Components require appropriate Qualification Practices to be applied, while "Indirect Impact", or "No Impact" systems and their components are subject only to GEP.

Suggestions are given for documenting, timing and scheduling along with suggestions for who should be involved in performing an Impact Assessment.

Good Engineering Practice

Good Engineering Practice (GEP) is defined by the Commissioning and Qualification Baseline® Guide as "established engineering methods and standards that are applied throughout the project lifecycle to deliver appropriate cost-effective solutions."

GEP should include professional and competent management, engineering design, procurement, construction and commissioning. Health and safety, and environmental statutory requirements should be considered along with operational and maintenance requirements. GEP recommends that appropriate documentation is used and should cover design, fabrication, construction, inspection and commissioning. In addition, Direct Impact Systems will require "enhanced documentation". This should complement, rather than duplicate, the documentation, which is created through GEP, and may include additional testing, QA change control and QA review and/or approval.

Issues relating to Project Teams for GEP are discussed, with an emphasis on the need for excellent communication, planning, and coordination between personnel involved in the interdependent activities within a project. Suggested roles for team members are given along with a description of extra representation required for GMP regulated projects.

The Requirements Phase is discussed at length. User Requirements including, purpose and justification, product and/or process requirements, operational considerations, the requirements document and project execution plan are described. Design elements such as Conceptual design, Functional (or Schematic) design, and Detail design are included. Within the latter the documents produced for construction, bidding and contracting, as well as system and equipment purchase, fabrication, installation and testing are described and include:

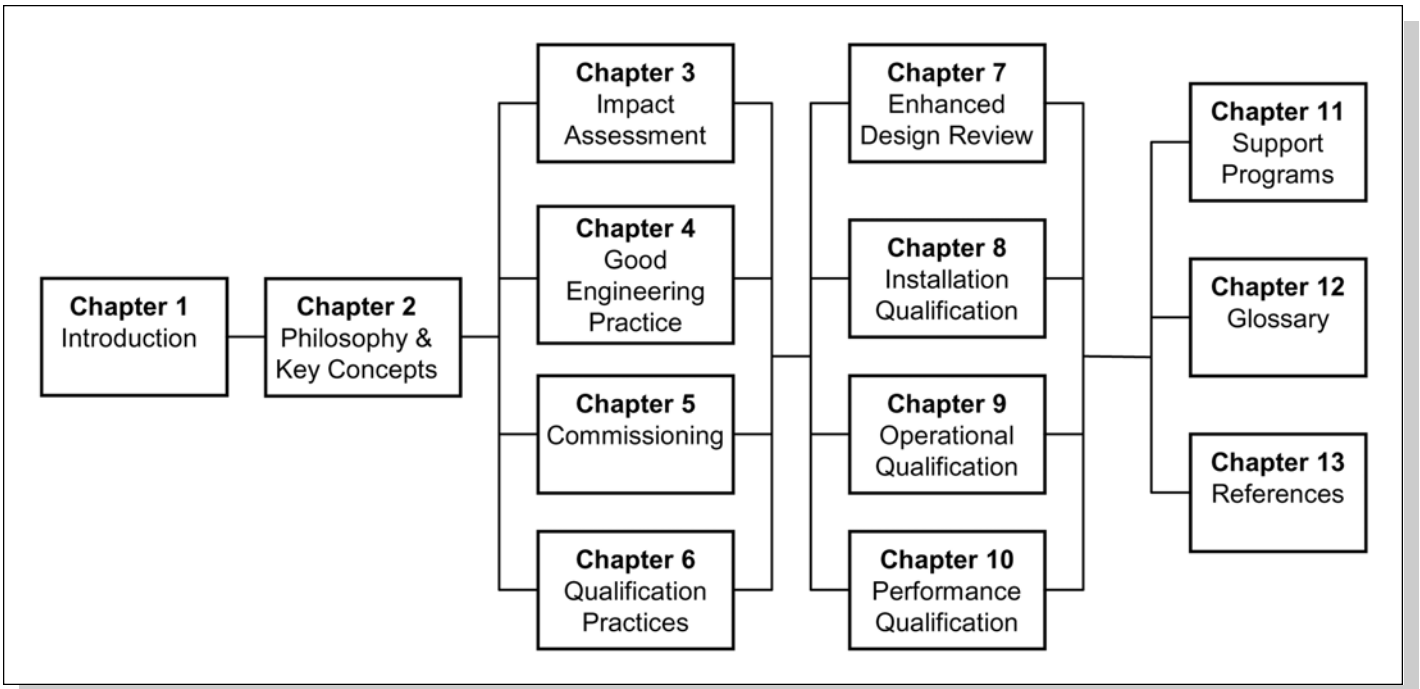

Figure 1. Chapter structure of the Commissioning and Qualification Baseline® Guide.

- Piping and Instrumentation diagrams
- Specifications
- Construction Drawings
- Other Design Considerations
- Project Site Logistics
- Project Quality Control
- Estimating
- Meetings and Reporting
- Cost Controls
- Schedule Development Control
- Document Planning Control

Project Closeout and Turnover suggests a phased turnover, which may allow an owner to qualify prioritized parts of a project earlier. However, a phased turnover does require greater coordination. Common pitfalls during turnover are considered and deliverables are listed.

Commissioning

The commissioning chapter defines commissioning organization and content of the commissioning Plan, providing management and execution, and positioning commissioning within the context of the qualification effort.

The Commissioning and Qualification Baseline® Guide offers a definition for commissioning as "a well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the end-user that results in a safe and functional environment that meets established design requirements and stakeholder expectations."

Emphasis is placed throughout on the cooperation between a multi-disciplined team and the clear definition of their roles and responsibilities, which both reduces overlapping of responsibilities and optimizes resources.

The Commissioning Plan is recommended. It should define facilities, systems and equipment that will be commissioned, and the coordination between predecessor and successor lifecycle activities. The Commissioning Plan may cross reference the Validation Plan, if commissioning documentation is used to support Process Validation.

Inspection performed during commissioning may be used to support Process Validation, if the system is classified as Direct Impact, in which case the inspection process should be managed and performed within the context of Qualification Practices.

Inspection to verify construction and installation is included, either visually or by testing, to confirm construction or materials. It is important to note that this type of testing is distinct from tests where the objective is to confirm function or performance.

In the latter case, *Testing* is the process by which:

- adjustments to, and regulation of, individual systems are demonstrated as within the required tolerances
- system components are demonstrated as delivering the required capacity or duty
- the functions of the system are demonstrated to be specified and appropriate

Performance Testing is the process by which:

- the performance of interdependent systems is demonstrated as within the required tolerances
- the output of interdependent systems is demonstrated as delivering the required duty or capacity
- the interdependent functions of systems are demonstrated to be as specified and appropriate

The objectives of the testing performed during commissioning should be care-

Direct Impact Systems	Enhanced Design Review
Indirect Impact Systems	Installation Qualification
System Impact Assessment	Operational Qualification
Good Engineering Practice	Performance Qualification
Commissioning	Consistent Terminology
Qualification Practice	Documentation Requirements

Table A.

fully considered when test plans are being prepared and executed. There are several such objectives and these are listed.

Test guidelines should form part of the overall Commissioning Plan, constituents of these guidelines are suggested and the value of such guidelines is discussed.

Issues relating to training of persons involved in commissioning activities are discussed, and include scheduling, roles and responsibilities and maintenance of training records. Such training programs should include relevant regulatory requirements.

overview of the qualification practices that apply to Direct Impact Systems is provided.

The qualification effort is one aspect of the scope of the Validation Master Plan (VMP) and this aspect of the VMP is discussed. A qualification rationale and qualification protocol should be generated for each system within the project.

The advantages of the early involvement of the Quality Assurance Unit in the commissioning and qualification process are stated. This involvement is initiated by the System Impact Assessment exercise and continues through

System	Direct Impact	Indirect Impact	No Impact
WFI System	X		
Chilled Water System		X	
Utilities Monitoring System		X	
Electronic Batch Record System	X		
Non-process HVAC		X	
Laminar Flow Area	X		
Sprinkler System			X

Table B. Typical System Impact Matrix (actual results may differ).

Typical commissioning deliverables are listed. These are categorized as "Living" and "Historical" documents. "Living" documents are maintained throughout the commissioning period as the system or project requirements are modified or updated. "Historical" documents represent a point in time ("snapshot") and are not updated continuously.

Strategies for turnover are discussed, and should be determined early in the project. The Commissioning Plan closeout describes the reporting requirements for the Commissioning Plan, including approval.

Qualification Practices

Direct Impact Systems are subject to qualification practices, in addition to GEP, for compliance with Current Good Manufacturing Practice. A high level

the life of the facility, equipment and ancillary systems involved.

Impact Assessment, Qualification Rationales, Qualification Protocols and Validation Master Plans all require "enhanced Documentation" and Document Management. It is in this area of documentation that significant opportunities exist for eliminating duplication of effort. Enhanced document, as it relates to qualification of Direct Impact systems is described and suggestions are given for achieving reduced duplication within the documentation effort.

The Commissioning and Qualification guide advocates greater vendor and end-user participation to avoid an unsuccessful production start-up. Vendors particularly in recent years are more commonly able to contribute to the overall qualification effort.

Conclusion

The Commissioning and Qualification Baseline® Guide was initiated in February 1998 and uses a joint US and European Team approach with close liaison with the FDA. The team worked towards an early consensus for key concepts and terms and in developing the scope of the guide. Meetings were held by videoconference with each chapter having two principal authors, one from Europe and one from the US. The early chapters described here form the basis for later chapters, which are now close to completion. The commissioning and Qualification Baseline® Guide has been presented at several ISPE conferences and publication is anticipated for December 2000.

For details on ordering Baseline® Guides, contact ISPE at tel 1-813/960-2105, fax 1-813/264-2816, or visit the Society's Web site at www.ispe.org.

This article details the impact of technology advances on the manufacture and control of pharmaceutical products. Special attention is given to the regulatory impact of technology advances on products filed in the US prior to 1987. A review of the impact of technology advances on the manufacturing process is given with the greatest emphasis on advances in analytical controls. This article is based upon a presentation given at the 18th Annual ISPE/ FDA Conference in June 1999.

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Technology Advances in the Manufacture and Control of Pharmaceutical Products – a Regulatory Review and Impact Assessment

by Thomas J. DiFeo, PhD

Introduction

Regulatory compliance in the pharmaceutical industry is an important aspect of pharmaceutical production. Regulatory requirements promulgated by the US Food and Drug Administration (FDA) help assure that the pharmaceutical industry produces products in conformance with current Good Manufacturing Practices (cGMPs). The quality systems developed and implemented by the pharmaceutical manufacturer increase assurance that the company will produce products of acceptable quality consistent with cGMPs. Quality systems are supported and enhanced by technology advances. It is crucial that the pharmaceutical manufacturer continues to enhance its technology foundation to help provide continued assurance of high quality output.

In 1987, the FDA published a guidance document entitled "Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products."[1] This guidance document outlined the expectations of the FDA with regard to New Drug Applications (NDAs). Specifically, the guidance requires the applicant of a new drug submission to delineate a "detailed description of the production process for a representative batch." Prior to this guidance, the requirements were not well defined in the Chemistry, Manufacturing and Controls area (CMC) with most emphasis previously being given to safety study requirements as exemplified by one of the earliest FDA policies published in 1944.[2] Thus, NDAs for products submitted prior to the 1987 guidelines (sometimes referred to as old products), typically contain less detail when compared with manufacturing descriptions filed today.

Additionally, over the past several decades, advances in analytical technology have led to improvements in the capability of analytical methods to assure the quality, identity, purity and strength of drug products. The literature is replete with examples of analytical advances which can increase assurances of product quality including advances in chiral chromatography,[3] capillary electrophoresis[4] and near infrared techniques[5] as well as the application of technology advances in drug development.[6,7,8] Many control methods originally submitted in NDAs of old products often are inadequate to assure purity and not consistent with the intent of cGMPs. cGMPs as detailed in the Code of Federal Regulations,[9] 21 CFR 211.160, indicate that there should be established "scientifically sound . . . test procedures" to assure that the drug product conforms to "appropriate standards of identity, strength, quality and purity." Test methods that once were considered scientifically acceptable when the NDA originally was filed for an old product may no longer be sufficient in light of today's scientific advances.

Acceptable Standards for Older Products

Manufacturing Process

NDA Process Description Updates

NDAs submitted in today's regulatory environment are guided by FDA guidance documents, the International Conference on Harmonization (ICH) guidelines as well as cGMPs. Specifically, the FDA's expectation in today's regulatory environment is that a description of the manufacturing process be supplied in the NDA that contains sufficient detail with regard to critical process steps and in-process controls. For products filed prior to 1987, adequate process detail may not exist in the NDA. In addition, over the lifetime of the drug product, updates made to the NDA process description may

	ORIGINAL METHOD	NEW METHOD
Column	C18 - 10 µm	C18 - 3 µm
Detection Wavelength	254 nm	254 nm
Mobile Phase	80/20 acetonitrile/water	70/30 acetonitrile/water
Sample Diluent	100% acetonitrile	mobile phase
Average Assay (%label claim)	100.2%	97.1%
Related Product 1	0.2%	0.2%
Related Product 2	0.4%	0.4%
Additional Peaks	None	3 peaks (2.8% total)
Total % related peaks	0.6%	3.4%

Table A. A comparison of two HPLC methods in the positive assay bias example.

not be complete or may be fragmented in various NDA supplements. For processes that do not include adequate detail or are not properly collated, FDA has commented that these vague descriptions should be updated via CBE supplements.[10]

Process Validation

Process validation is a necessary aspect of pharmaceutical manufacturing since product testing, although necessary, is not sufficient to demonstrate acceptable product quality since it is not possible to define or test every possible quality attribute of a product. Validation standards applied to old products during the original introduction of the process to the manufacturing environment may not assure that the process has a high probability of meeting the standards for identity, strength, quality and purity. Generally, four types of process validation are considered: prospective, concurrent, retrospective and revalidation.[11] For products with significant process history (i.e. old products), a retrospective validation is often employed. In addition to the need for updated validation, there may be a need for the NDA holder to modify the manufacturing process to replace steps that cannot be validated. Often the steps in the manufacturing process that are most susceptible to operational variability are those steps that involve human intervention[12]. For example, granulation endpoints that are determined by subjective visual observation may be replaced by objective power measurement endpoints. The newly validated steps will then need to be filed and approved by the FDA. Changes to manufacturing processes as part of a modernization of the NDA filing are typically filed as prior approval supplements. The supplement should detail the technical justification for the process change. The justification should include data which demonstrates the impact of the change on product quality. This data set may include release test results as well as expanded test results which specifically assess quality attributes potentially impacted by the process change. An updated process description should be provided which details the complete manufacturing process including the latest modification.

Analytical Methodology

Method Review

Throughout the lifetime of a drug product, several factors influence the applicability of the filed analytical methods used to test the product. These factors include technology advances and a greater understanding of the drug product chemistry, process capabilities and stability. Older products may have significant literature information on the stability behavior of the specific drug substance or closely related chemical moieties. Also, there may be modern techniques for the specific compound or class of compounds, which are applicable to the drug product of interest. Additionally, a review of the current method may indicate that the method is appropriate, but validation data does not meet the criteria as defined by ICH[13] or USP[14] guidelines.

Technology Advances

Prior to the advent of High-Performance Liquid Chromatography (HPLC), many drug product assays were determined by aqueous and non-aqueous titrations. However, by their very nature, titration assays alone rarely provide the specificity necessary to adequately control the drug product. For example, the current USP assay method for Aspirin is a titration with sodium hydroxide.[15] Sodium hydroxide will neutralize not only aspirin (acetosalycilic acid), but also a key degradation product, salicylic acid. In order to account for the non-specificity of the titration, a second method is required by the monograph to control any free salicylic acid. Even chromatographic methods developed in the past 10 years may not have the requisite ability to quantitate degradation products. For example, 10 µm particle size columns were commonly used in the past. Figure 1 displays two chromatograms of the same drug product solution injected separately on two columns with similar reversed-phase packing material, but of different particle sizes. A comparison of the two chromatograms demonstrates the improved specificity observed using a 5 µm particle size column. The smaller particle size column resolves additional peaks seen eluting prior to the main peak and, thus, demonstrates enhanced specificity.

Method Validation

cGMPs require that test methods used to assess a product's compliance with regulatory specifications meet the proper standards of accuracy and reliability.[16] While this principle has been long recognized, the standard procedures and criteria associated with method validation have varied. It was not until the USP XXII version in 1990 that the compendial requirements for HPLC method validation were first detailed.[17] Recently, details of a harmonized approach have been promulgated through the ICH process.[11] A review of methods filed prior to the USP and ICH guidance documents may indicate that the validation for the method under review is incomplete or not up to today's standards. An older method may be brought

up to date with additional validation studies.[18] However, if it is determined that the current method is not appropriate based upon its lack of specificity or suitable detection limits, a new method will need to be developed and validated.

Specifications and Acceptance Criteria

The ICH draft guidance on specifications defines a specification as a list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the tests described.[19] The ICH definition provides for an intrinsic link between the acceptance criteria and a specific method and, therefore, the modification of any method will require a reassessment of the original acceptance criteria. The example in Figure 1 depicts a scenario where a smaller particle-size column leads to the appearance of previously unresolved peaks. An assessment of the need for specifications for these peaks as well as the impact of these peaks on existing specifications (e.g. total degradation limits) will need to be performed.

New Methodology for Old Products - Hypothetical Case Histories

When new analytical methodologies are introduced for older products, new observations regarding the quality attributes of the product might be made. This section represents some of the potential scenarios encountered when new HPLC assay methods are introduced for older products. The examples highlight the impact of technological advances on old products both from the scientific and regulatory perspective. Typically, the new methods are developed because of the non-stability indicating nature of the original method (e.g. titration assays), inadequacy of the original method (e.g. methods developed with column particle sizes of 10 µm which cannot provide the necessary separation efficiency), or due to the inability to validate the original method due to the non-ruggedness of the HPLC method or sample preparation. During method development, stability samples of various ages are examined using both the original and new method and a comparison of the results is obtained. While the examples listed below are theoretical in nature, method bias previously has been reported throughout the literature.[20-23] Since actual case histories are typically more complex and involve multiple issues, hypothetical examples are given here to exemplify specific scenarios in the absence of commingling factors.

Negative Assay Bias of the Original Method

Observation

The results of the comparison of an original titration method and a newly developed HPLC method indicated a 5% difference in assay results. The average assay result for the original titration method was 99% whereas the HPLC method consistently produced results at approximately 104%.

Assessment

Products formulated at the advent of modern pharmaceutical technology in the mid-20th century were sometimes formulated

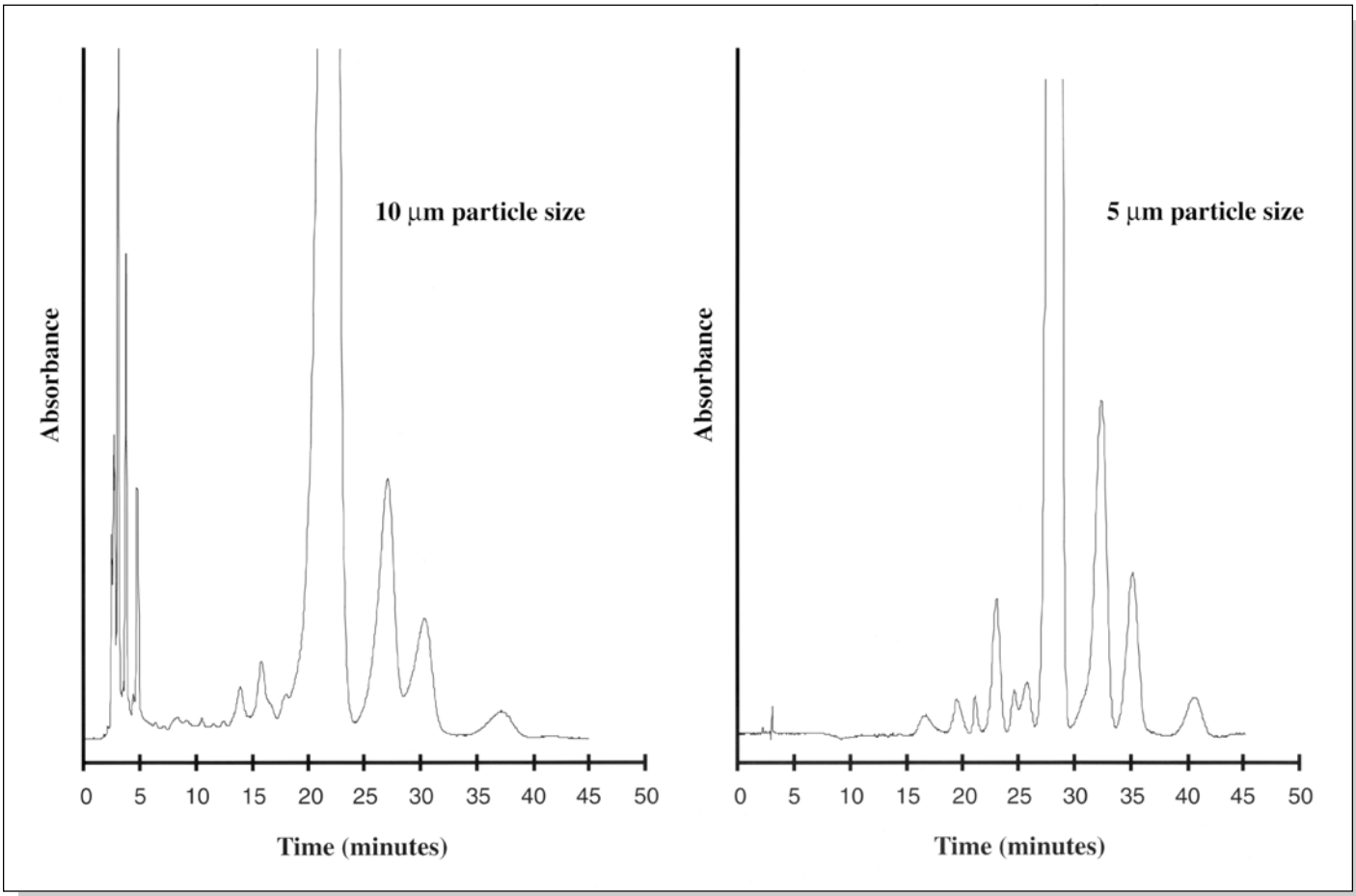

Figure 1. Comparison of chromatograms of drug product sample injected on two columns with different particle size packing material. The 5 µm particle size column demonstrates improved specificity.

> ***The NDA review of an old product in light of technology advances provides a useful means of examining current process and quality controls in light of current cGMP expectations.***

with overages to account for apparent process loss of drug substance. This loss was sometimes caused by undetected degradation of drug substance during the manufacture of the drug product or due to unspecified loss of drug substance caused by process inefficiencies. In some instances, however, there was no actual loss of drug substance, but an assumed loss due to an analytical methodology bias. This bias in the original method may be caused by:

1. non-linear response
2. inadequate recovery
3. inadequate solution stability
4. kinetically limited end-points

Resolution

In this example, an investigation indicated that the original method had an endpoint that was kinetically controlled. An examination of the titration indicated that upon titration of the drug product, approximately 95% of the drug substance was titrated while the final 5% reacted slowly over a several hour timeframe. The original manufacturing process developed for the old product was made with a 5% overage of drug substance to account for the apparent loss of drug during manufacturing. In light of this new information, the NDA holder may choose to discuss a label change with the FDA so that the label reflects the actual drug substance content. An alternative approach would be to change the manufacturing process to delete the drug substance overage. However, considering that the product has been marketed for decades with acceptable clinical efficacy and safety at this dosage level, a change to the formulation may not be warranted.

Positive Assay Bias of the Original Method

Observation

The results of the comparison of an original HPLC method and a newly developed HPLC method indicated a 3% difference in assay results. The average assay result for the original HPLC method was 100% whereas the new HPLC method consistently produced results at approximately 97%. A comparison of the two methods and the results of analysis are given in Table A.

Assessment

A common limitation of analytical methodology (including older HPLC methods) is the lack of specificity regarding degradation products. In the current example, three peaks have previously co-eluted with the active peak in the original method.

Resolution

Improved specificity of a new method as exemplified in Table A, will require a reassessment of the product specifications. If the original specification for total related peaks was 1.0%, a new specification for the revised method will be needed. The new total related peaks specification might be filed as not more than 3.5% with individual limits for the new peaks. From a safety perspective, these additional peaks are considered qualified when it can be demonstrated that these peaks have been present in historical samples at these same levels. In addition, there is no need to identify the chemical structures of these peaks since they are considered safety qualified.

Larger Quantities of Degradation Products found in More Recent Drug Product Lots

Observation

This example may be viewed as an extension of the first example where a new method is developed that now resolves additional degradation products. In this instance, however, the results of the examination of historical samples with the newly developed HPLC method consistently demonstrate larger quantities of degradation products in more recently manufactured lots when compared with older stability samples.

Assessment

It is not uncommon for pharmaceutical products to undergo degradation. The selection of appropriate excipients is an important aspect of drug product development[24] and is important in stabilizing certain dosage forms.[25] In addition to dosage form stability, solution stability of the analytical samples derived to examine the dosage form must be carefully studied.[26] In the current example, the validation of the new method demonstrated that solution stability is not an issue. In the comparison of samples of different ages, one might expect to see the highest level of degradation in the oldest samples. This observation is generally made in the cases where a degradation product is formed under simple degradation kinetics. If, however, the following degradation occurs -

Drug Product → Deg. Product A → Deg. Product B

the complexity of the reaction kinetics (e.g. mixed reaction orders) could lead to the appearance of a maximum concentration of degradation product A ($[A]_{max}$) prior to the end of the shelf life with a subsequent decrease in [A] and concomitant increase in [B].

Resolution

In this situation, the oldest stability samples will not represent the maximum degradation levels for individual products. A carefully planned stability study would be necessary in order to determine maximum degradation product levels. These concentrations could then be used as support for qualification levels and subsequent setting of drug product specifications.

Summary

- Review the regulatory process description to assure that the filing contains an adequate level of detail.

- Review process validation and determine if the validation study assures a high probability of the product meeting the standards for identity, strength, quality and purity.

- As part of the product review, assess whether current analytical technology is adequate in light of advances in technology since the implementation of the specific test methodology. Develop new methodology if necessary.

- If current methodology is acceptable, review the validation data set to assure that adequate data exists to demonstrate the validity of the method.

- Review specifications and acceptance criteria to assure appropriateness of controls.

- Submit process and method updates to the regulatory file.

Conclusion

The NDA review of an old product in light of technology advances provides a useful means of examining current process and quality controls in light of current cGMP expectations. The NDA review provides an opportunity to update manufacturing processes, analytical methodology and specifications. The acceptable level of degradation products is established by an examination of a historical sample set collection using the updated methodology. The highest levels seen in the database represent defacto safety qualification since these levels have been present historically in the marketed drug product. Subsequent updates to the NDA are filed with the FDA assuring that technology advances in pharmaceutical manufacturing and control are appropriately applied to older products.

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This article describes a Right First Time (RFT) approach to batch manufacturing that has wide ranging benefits in project and commissioning success, manufacturing agility, consistency and efficiency.

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Making Your Process Deliver: Control and Operability Studies Improve Process Consistency and Product Quality

by Phillip Cheng and Sarah Gooda

This article describes a new approach to batch process improvement as a means of tackling production and consistency issues. The relationship of control and operability studies to the validation lifecycle of the process also is explained. Although validation is not discussed in detail, the reader can find further information in the GAMP Guide.[1]

The Problem

Batch processes are complex, and recipes are often only partially understood in terms of the reason for and effect of each process step. Plant equipment may have been designed for quite different products than the ones they now produce, and may be unsuited to all their present duties.

The results of this can be far reaching. Plant commissioning can become extended, and design rework may be needed. Sampling, testing and adjustment is the norm. The costs of iterating to get the process or product right are considerable with lost capacity of 20 to 30% in many cases. Uncertainty in introduction of new products and long lead times to market result in lost opportunities. Project costs rise and confidence is low. Product quality is inconsistent and rework high.

The Right First Time Approach

A better approach is to develop a clear understanding of the recipe or formulation needs so that plants are confidently designed to these requirements.

This approach is essential to minimize commissioning and new introduction times, avoid revalidation after modifications during commissioning and rework and waste during production.

A structured method to the development lifecycle of systems is required, including a framework for specification, design and testing.[1] As part of the user requirements specification, the process steps need to be understood, well defined and resilient so that batches are produced according to plan in the same way each time, taking the same

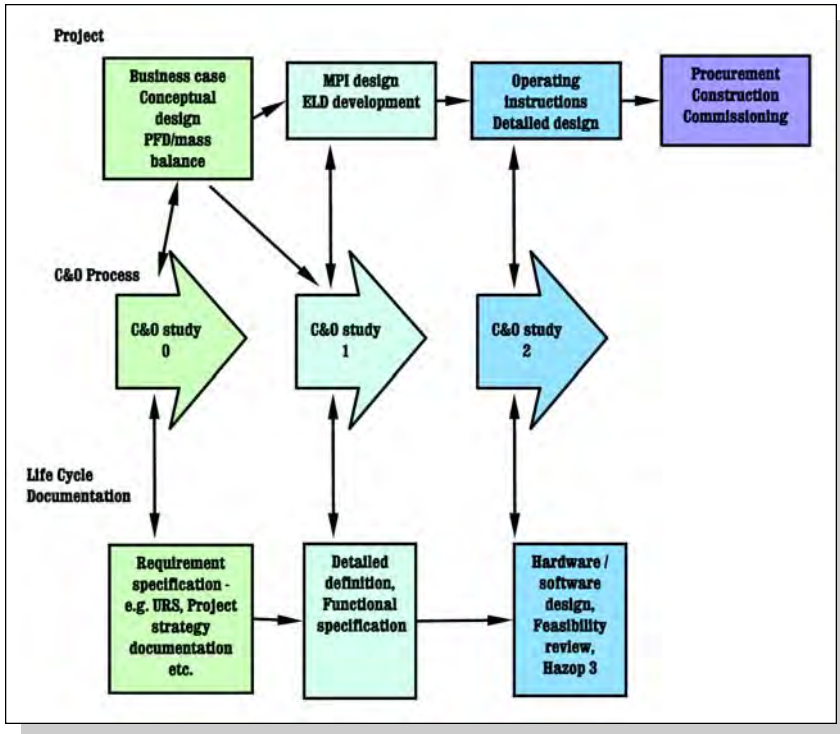

Figure 1. Relationship of the C&O process to the project and project lifecycle.

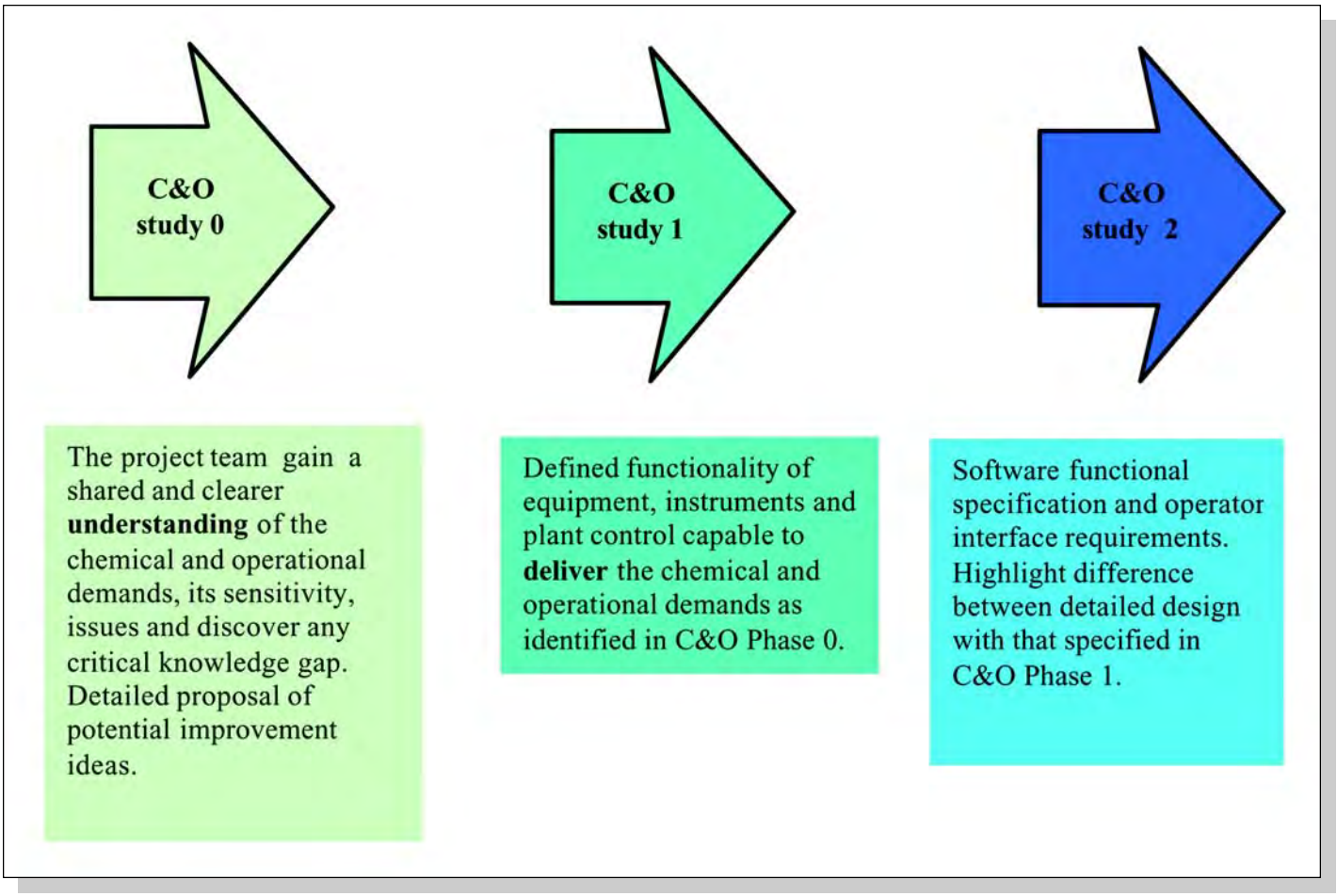

Figure 2. Overview of the C&O process.

amount of time every time. During the commissioning of a new system, it is essential to maintain adequate change control for quality assurance. This may include modifications to the process equipment and adjustment of new recipes. Throughout the lifecycle, it will be necessary to review and possibly carry out revalidation. A RFT approach should reduce this need.

A change control procedure also is required if a new recipe is to be introduced and re-validation is required in order to ensure that the capability is satisfactory and new product is manufactured within its specification limits.

If there is a clear and well-documented understanding of the formulation, and the manufacturing plant is designed to be capable of manufacturing product, then adjustment following a test and production of out of specification batches should be minimized. As confidence is built up in time, sampling and testing can increasingly be made off line, without blocking or slowing production - enabling quality assurance with quality control as the backup.

Control and Operability Studies

Control and Operability (C&O) is a systematic process for evaluating the control and operability performance of a batch plant, proposing and assessing improvements. The study develops a detailed understanding of both the manufacturing processes by which a product is made and also the functionality required of process equipment to allow the product to be made.

The C&O philosophy is to build on firm foundations, then use these foundations to develop appropriate improvements. The C&O process, consisting of 3 phases (0, 1 and 2), can be mapped against a typical lifecycle for projects on batch plants. These are shown in Figure 1 and are described in more detail below.

Phase 0

This is the phase that we shall describe here in most detail. Phase 0 should be carried out at a sufficiently early stage in a project to allow a re-think at minimum cost and disruption. The project team gain a shared and clearer understanding of the chemical and operational demands, their sensitivity, any issues and discover any critical knowledge gaps. It is in this phase that the detailed proposal of potential improvement ideas takes place.

The steps involved in Phase 0 of the C&O study are as follows:

1. Determine the Objectives: understand the context of the study i.e. business priorities, constraints, and set objectives for the study with the business management.

2. Build the Team: form an appropriate team, ensuring that it has the necessary skills and knowledge.

3. Analyze the Recipe: examine, question, test and record the step by step manufacturing process. Consider every process step and interactions between process steps- not only those that are relevant to regulatory processes. Highlight and record where an existing or proposed plant does not satisfy

the recipe requirements. Highlight and record improvements identified during this process. Record knowledge gaps and investigate these further.

4. Consider the Objectives: go back and review the objectives from step 1 and seek out specific improvement opportunities.

5. Prioritize the Improvements: develop in more detail the improvements that stand up to critical analysis, and remove the ones that are considered unfeasible.

6. Present the results: Agree upon the next steps and improvement timetable.

These steps will now be described in more detail.

Step 1. The Context of the Study - Determine the Objectives:

Many C&O studies are carried out as part of an existing project. For example: a capital project to automate a plant, increase capacity or build a new plant. See Figure 1 for the relationship between the C&O study, validation life cycle documentation and the project process. C&O studies are frequently carried out as a precursor to the introduction of a new recipe, and sometimes simply an improvement tool.

Depending upon the reason for the initiation of a C&O study, the objectives set can be very different. This means that a C&O study can be used at different levels and for different purposes. For example:

For existing plants:
1. to increase the capacity of an existing plant using an existing process
2. to increase capacity and quality, reduce complexity and variability
3. to provide the definition for selecting the right control or automation upgrade of an existing plant
4. to reduce variable cost

For new plants or a second plant of similar design:
1. to scale-up an existing process, using either new or existing equipment
2. to evolve a simpler and more economic design for a new plant
3. to evaluate alternative configurations

In the pharmaceutical industry, particularly where an existing plant is being studied, the regulatory framework and the validation requirements of any modifications have to be carefully considered. It should be noted that modifications that do not have regulatory implications also must be considered, justified and carried out rigorously to avoid costly mistakes or delays.

Step 2. Build the Team

The members of the team have to match the requirements of the C&O study, which requires people with a knowledge of the process, such as formulating chemist, an NPI representative, development engineer or manager, plant operating personnel, process engineer, quality manager and control and instrument engineer. If the study is being done as part of a project, then a project (technical) manager should be present. The business

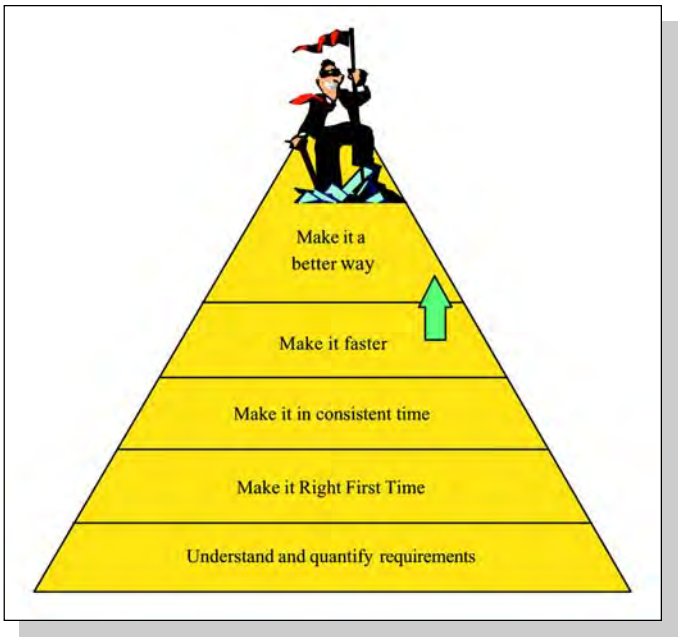

Figure 3. C&O improvement pyramid - each level is built on a firm foundation.

environment needs to be understood because input from the business may be needed. Not every member of the team needs to be present in every C&O meeting.

It is sometimes necessary to bring in new team members if it becomes apparent that an important area of expertise is not present. The team is led by a moderator. The moderator is not simply a facilitator, but also has an active role in sharing best practice and experience in batch processing.

Hence the moderator needs technical knowledge including the control and operation of batch plants, statistics, batch charging and dispensing, flow metering and reactor exotherm control. The moderator also must understand the business and supply chain issues so that improvements are positioned to fit the wider business issues. As a facilitator, he or she needs to understand soft issues - how to guide and motivate a multifunctional team, elicit knowledge and ideas, and prevent sidetracking.

Step 3. Analyze the Recipe

In a project context, this is carried out in the early stages of development of the manufacturing system's user requirements.

The first task is to understand the recipe or formulation. This means understanding each process step that is needed to make a particular product. This analysis is done first qualitatively, then increasingly quantitatively, as more detail is discussed and recorded.

Sometimes Phase 0 will uncover a critical knowledge gap and experimental work is needed to complete understanding. The result is a thorough understanding of what's important, i.e. the tolerances on operating parameters needed to achieve final product parameters.

A recipe driven document is generated to record the process step by step. Structured English titles are used for each step, such as charge, react, heat, crystallize, etc. It is important to use a common language to avoid different interpretations by different disciplines and ease writing automation sequences later. One such language is provided by ANSI/ISA-S88.01-1995 Batch Control part 1[2] which also has the advantage of

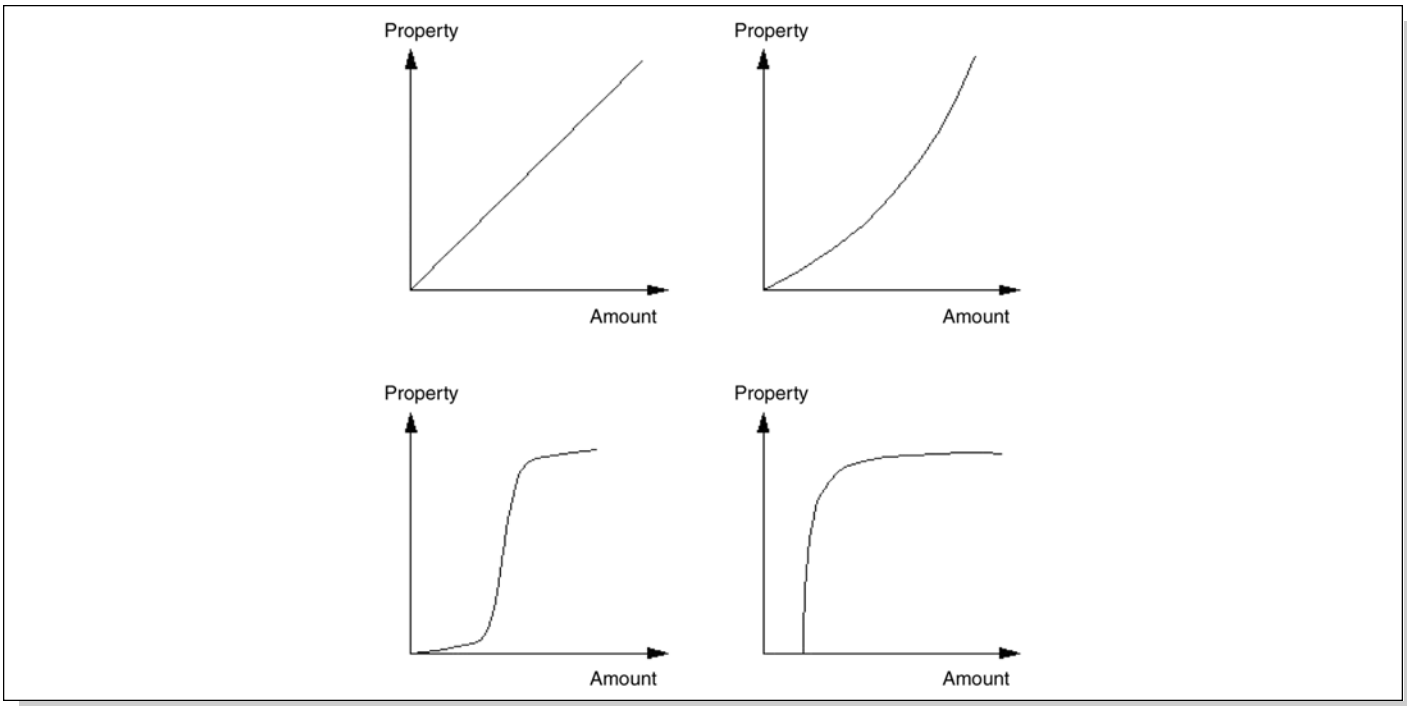

Figure 4. Examples of relationship between product properties and amount of additive. Other examples of key process variables are ratio of charged material, reaction temperature, etc.

being internationally recognized and adopted by most control system vendors. Each process step can have several parameters such as material and amount. This is done on a flip chart, but also recorded as a spreadsheet to allow addition of times to calculate the overall batch time and its variability.

Examples of key questions for the 1st pass are what? why? how much? how accurately? how fast? when? how? where? These questions depend upon the process step being discussed. Full understanding of the required and actual accuracy is rare, and C&O studies are a good opportunity to generate this understanding. What is the background and evidence for this +/- 1% charging accuracy requirement? What properties does it affect? Frequently, the real need is for the ratio of two quantities to have a certain accuracy, rather than a single quantity having a required accuracy. This is illustrated in Case Study 1.

Is the affect linear on the final product property? It often is, but not always. For example: raw material quantities often have a non-linear affect on pH and color. See Figure 4 for examples of relationship between product properties and amount of additive.

Then follows an evaluation of the performance of a batch plant by identifying all the variables that influence its operation. Its performance capability must be well within the envelope required by the recipe if it is to deliver product requirements RFT.

The study team makes proposals of ways to improve the plant's 'capability' where necessary, or suggest alternative strategies - such as on-line measurement instead of laboratory tests.

Typical questions at this stage are: How accurate is this instrument? Is this random error? Is there also a possibility of systematic error? Does this matter? If so, what can be done to reduce its effect? C&O is based upon using statistics as a tool - see Table A for 'Statistical terms used in C&O.'

The recipe or process logic diagram is then restudied, focusing upon improvements ranging from accuracy issues, equipment design and the interaction between the different process steps in the sequence. The critical path is examined and automated wherever appropriate. In addition, any critical vessels and services are examined in detail to study the effect on the process and find ways of easing any restrictions placed on the process. Case Study 2 describes an example of this.

Each idea is discussed and evaluated. Either a consensus is reached about its applicability and expected gains, or a clear problem is identified which requires further research or evaluation beyond the immediate capabilities of the team. A series of possible changes are found of varying impact, cost or certainty.

The moderator's role is critical in bringing solutions that combine better hardware, different ways of using existing hardware, control automation, plant personnel and recipe control in ways that are compatible with the new or older plant. Many solutions are transferable across businesses and chemistries - and the moderator's wide experience can lead to this cross industry fertilization.

Step 4. Consider the Objective

Once the basics have been addressed, considering the wider C&O objectives set at the beginning of the process generates further ideas for change and sometimes leads to quite different plant designs or more often simple changes that can nevertheless transform plant performance.

The C&O process has an armory of proposals to offer for active improvement, using Best Practice and experience from a variety of delivered improvement projects. It is often this 'creative' (rather than analytic) phase that generates large project gains.

Step 5. Prioritize & Develop Improvements

Step 5 begins with a review of the developed recipe. At this time any additional information that has been obtained since the development of the objectives should be recorded. By now, the team should have improvement proposals that will get the process under control, i.e. improve the right first time quality performance and/or increase speed or consistency of manufacture. Stage 3 is the time to consider if significant options exist for new ways to make the product or exploit process intensification and capital spending.

More detailed questions are posed aimed at widening the discussion into a business context, and encouraging creative and sometimes radical thought. At this point comparative costing is usually beneficial to differentiate between possible alternatives in a qualitative way, but supported by an order of cost estimate. If appropriate, Value Analysis techniques can be used.

The completed recipe, any significant findings and improvement proposals are now all ready for presentation to a wider audience.

Step 6. Present the Results

The C&O study final report includes:

1. The reasons for the existing processing steps and all the ideas generated for their improvements. This provides the basis for the GMP assessment, but its scope is wider and deeper, since it does not only refer to validation concerns, such as product quality and traceability, but other production objectives, such as efficiency, ease of operation and scheduling. It will be an important reference document throughout the life of the plant.

2. A detailed proposal of the agreed ideas, which includes, if possible, an order of cost and an estimate of the expected increase in capacity and/or the variable cost reduction expected. For existing systems, this will need to be reviewed under Change Control.

3. A summary of those areas of the understanding of chemistry, engineering or control and instrumentation where there is a difference of opinion among the team members, or where more knowledge could result in further improvements. In a project context, the C&O study also identifies whether the process design is sufficiently advanced, or what work remains to be done before project success can be assured.

An important deliverable is the improvement of the design documentation during the early stages of the project. The C&O process is compatible with the validation activities and assists the definition and specification for new equipment.

Phases 1 and 2

As can be seen from Figures 1 and 2, Phases 1 and 2 occur when the project process is more advanced. Hence, radical thought is less appropriate here. Phase 1 builds upon the output of Phase 0, and preliminary P&I drawings to deliver accurate and defined P&I drawings, specification of the process control and instrument accuracy required and a schedule of trips and interlocks required for the process. Phase 2 produces the finalized and agreed P&I drawings, software and human/machine interface specification and specification of safety requirements.

The Benefits

The benefits of the C&O study are wide-ranging.

The first is the development of common language and objectives for both the development chemist and production: i.e., the language of process operations, statistical understanding of error and uncertainty and the objective of a robust process and RFT production.

Carrying out a Control and Operability Study will assist with the quality assurance and control function throughout the manufacturing life of the plant. There is an understanding of the need for consistent production - in terms of material addition, temperature profiles, batch timing and end point detection, and the effect that this has on product consistency, ability to plan, ability to promise and the absolute reduction of batch times. Typically, cycle times can be reduced by 20%, with little or no capital expenditure, by detailed analysis of each process step, the interactions of steps and removal of non-value adding steps.

Typical increases in RFT production from 60% to 90% to 95% are frequently obtained - though we must point out that 90% RFT is still 10% Wrong First Time! An example of a radical approach enabled a coating manufacturer to go from 0% RFT to nearly 100% by redesigning the process. The biggest challenge was to believe that it could be done.

There are many safety and environmental benefits. Reactor safety is automatically considered for exothermic reactions. Reduced product handling and errors in charging, and having more predictable processes all improve safety. Effluent reduction can occur if waste is reduced or eliminated.

Other benefits include project confidence and reduced commissioning times and expenditure, since the C&O process leads to a detailed understanding of the process chemistry and its sensitivity at an early stage of the project.

Without a delivery mechanism, the benefits identified in C&O are only potential. It is therefore crucial to follow through the improvements identified. It is important to get proposed improvements to 'stick.' As one way of ensuring progression, the moderator can involve the plant team in launching and publicizing improvement projects. Each improvement should have a nominated leader and a custodian, and be championed by senior management.

Some plants take advantage of this process by adding full recipe control into the plant improvement plan. Recipe control means that each possible process step is programmed into a fully automated plant control system. This means that the chemist specifies process steps, which the plant then executes. The engineers provide adequate equipment for it to be done. Recipe control improves the flexibility of the plant to introduction of new recipes. Other automation improvements, such as improved scheduling or linking to business systems also may bring about substantial benefits.

There are many examples of achieved benefits - some that were never imagined at the outset of a project. One benefit study done as part of a capital project to increase capacity achieved half of the increased production simply by shaving batch times and adding one extra mixing vessel. Other industries have benefited from the C&O approach - e.g. a coatings company rationalized all its recipes; each one was studied and challenged. It now has a smaller number of master recipes, and a larger number - around 10 000 - of variants, which can be made on a range of sites. Each year, only a few hundred of these

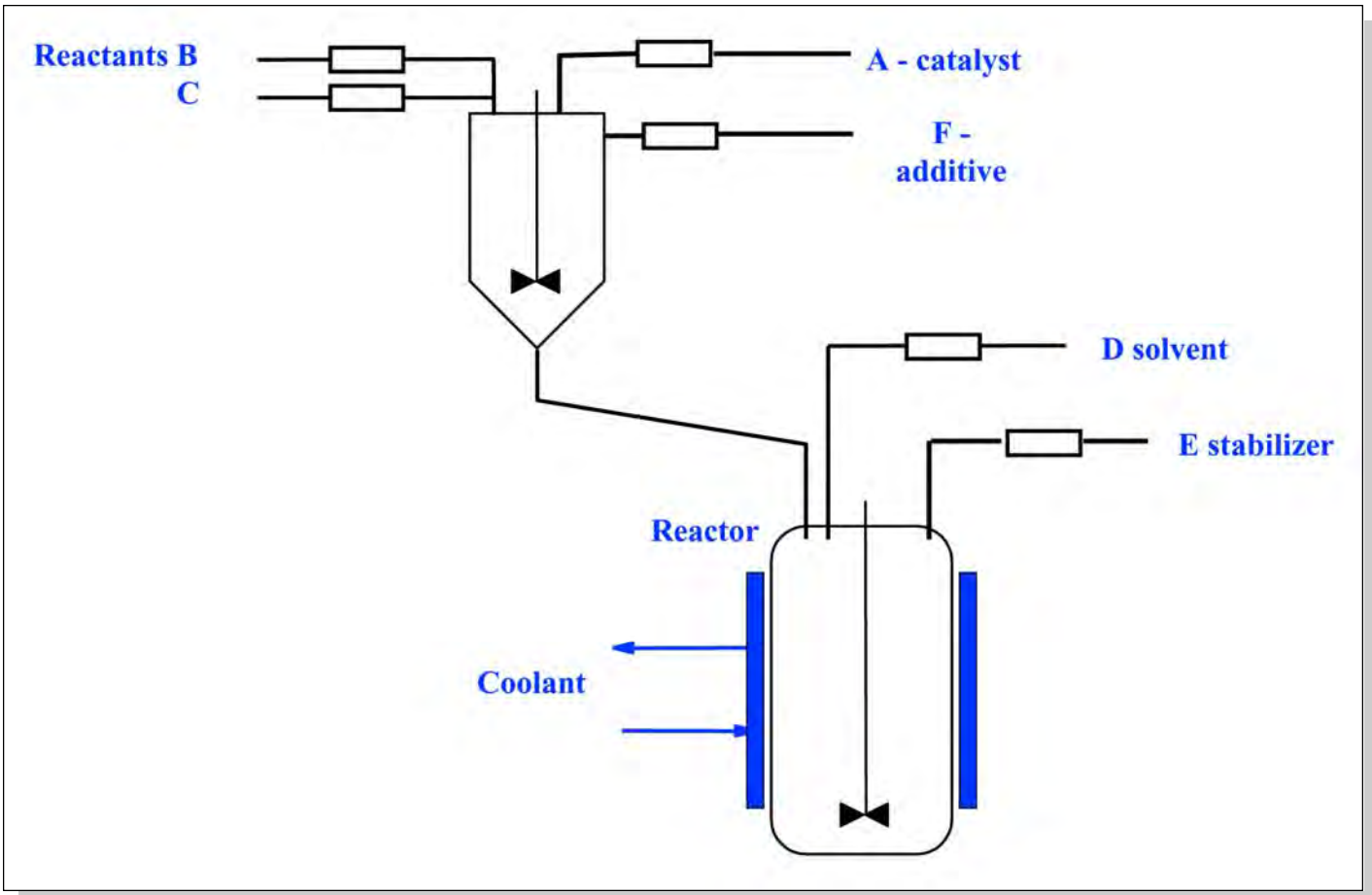

Figure 5. Process schematic for Case Study 1.

recipes are made, but no problems are found when variants are revived after a few years. Each recipe is well within the capability of all the plants that make it.

Case Study 1

In a fine chemical effects plant, consisting partly of a catalyzed reactor, it has been found very difficult to manufacture product with the correct final properties.

Operators add reactants and catalysts with varying care and accuracy. Measurements have been upgraded, but still many batches are out of specification.

The first pass of C&O 0 establishes the following: A is amount of catalyst, B & C are reactants, D is a carrier, E is a stabilizer and F is also added. The ratio of quantity of catalyst to total reactor content affects an important final product property. The ratio of reactant quantities affects another final product property. The total amount of A+B+C+D is not as critical as the ratios described above. The exact quantity of the solvent D is not as critical as the ratios described above.

$$\frac{A}{A+B+C+D} \rightarrow property1$$

$$\frac{B}{C} \rightarrow property2$$

The process is shown in Figure 5. With the present arrangement, it is difficult to accurately control these proportions. To try to arrive at the correct proportions, operators could try adjusting any of the three quantities. This would result in a lot of iteration, wasted time and would probably still fail to meet all the requirements. Instead, it is recommended that the following strategy be adopted:

First ensure that the ratio of B to C is correct. One solution is to use the same measurement device to charge B and C - as long as the amounts of B and C are both within the accurate measurement range of one measurement device. This is shown mathematically below. Once the total weight of reactor contents B, C and D is known the required weight of A should be calculated for this batch, weighed and added to the reactor.

In practice, the required accuracy should be known, checked and the measurement devices' accuracy considered. Modifications are only required if these are shown to be unsatisfactory.

Stabilizer E is added afterward. The exact quantity is not critical, provided it is above a certain minimum. Therefore, it must be confirmed that it has been added - either by confirming a weight increase or positive check of flow meters either automatically or by procedure. It is very important that in specification of automation software, the role of making sure that critical operations are done and done right, and that detecting and flagging up the unexpected are included. For example, checking that weight increase happens when a product is loaded in - and that the weight increase is sensible, even though the accurate measurement is done elsewhere. If a discrepancy is detected, the operators must be alerted.

The reason for the addition of F could not be explained by anyone. It was in the recipe and therefore it was added. This isn't good enough for C&O. Finally, trials were done without adding F, and the finished product tested both internally and by customers. Eventually, the addition of F was abandoned.

Similar situations have been found in many different processes. For example: A, B and C have been color tints. One particular tint ratio A to A + B + C is critical; all are important to accurately control color. At the same time, the total proportion of tint to product determines the opacity of the product.

If possible, the same measurement device should again be used. Here A should be adjusted last, when the amounts of B and C are known. Then the correct amount of the mixed color should be added to the product when the product weight is accurately known.

One way of Dealing with Systematic Errors to Improve Consistency

Frequently, a ratio of 2 ingredients affects a critical property. This example demonstrates one way of using existing measurements to improve the control of this ratio.

A recipe produces a 5% salt solution by adding 100 kg of salt into 2000 kg of water. The required property, saltiness, is directly related to the ratio of salt to water.

The salt and water are charged via their own charging system. The salt charging system has a standard deviation (s.d.) of 2 kg for 100 kg added; the water charging system has a s.d. of 20 kg for 2000 kg added.

Now the combined s.d. of the saltiness property can be calculated using Taylor Series Uncertainty Propagation.[3]

$$(U_R)^2 = [(\partial R/\partial X)(U_X)]^2 + [(\partial R/\partial Y)(U_Y)]^2 + 2(\partial R/\partial X)(\partial R/\partial Y)r_{XY}U_XU_Y \quad (1)$$

These are the terms used:

R = F (X, Y): here

R = X/Y

U_R = the uncertainty in the result, either random or systematic

U_X = the uncertainty in the variable X, either random or systematic

U_Y = the uncertainty in the variable Y, either random or systematic

$\partial R/\partial X$ = the partial derivative of the result by the variable X

$\partial R/\partial Y$ = the partial derivative of the result by the variable Y

r_{XY} = the sample correlation of uncertainty of X on uncertainty in Y

In this case, the partial derivatives are:

So,

$$U_R = [(\frac{1}{Y})^2 (U_X)^2 + (-\frac{X}{Y^2})^2 (U_Y)^2]^{1/2} \quad (2)$$

(Total s.d.)^2 = (1/2000)^2.(2)^2 + (-100/2000/2000)^2.(20)^2 = 0.001118 (unit of saltiness)

We can convert the total s.d. into percent uncertainty by first working out:

The result saltiness = (100/2000) = 0.05 (unit of saltiness)

So, the percent uncertainty in saltiness = 0.001118*100/0.05 = 2.23%.

One useful method of decreasing the uncertainty is to use the same charging system for the two ingredients.

In this case, the uncertainties are positively correlated with a correlation coefficient of 1.

As above, we will now develop the expression where the result property is determined by the ratio of the amounts of two charged ingredients, and both ingredients are charged via the same charging system.

Using equation 2 above,

$$(U_R)^2 = [(\frac{1}{Y})^2(U_X)]^2 + (-\frac{X}{Y^2})(U_Y)^2 + 2(\frac{1}{Y})(-\frac{X}{Y^2})U_XU_Y \quad (3)$$

a) Slope errors

Let's assume that 2 kg of salt and 10 kg of water are charged via the same charging system. The charging system has a slope uncertainty of 10% so that the error is a 'span' error and all readings are out by the same proportional amount.

So, for salt, s.d. = 0.2 kg and for water, s.d. = 1 kg, using equation 3: s.d. of saltiness = [(0.1)^2.(0.2)^2 + (-0.02)^2.(1)^2 + (2).(0.1).(-0.02).(0.2).(1)]$^{1/2}$ = 0 unit of saltiness

Hence, incremental charging has cancelled out all the slope errors.

b) Offset errors

Again, let's assume that 2 kg of salt and 10 kg of water are charged via the same charging system. But this time, the charging system has a constant offset of uncertainty of 0.3 kg - this could be due to a calibration error, for example, affecting the zero of the measurement device.

So, for salt, s.d. = 0.3 kg and, for water, s.d. = 0.3 kg, using equation 3: s.d. of saltiness = [(0.1)^2.(0.3)^2 + (-0.02)^2.(0.3)^2 + (2).(0.1).(-0.02).(0.3).(0.3)]$^{1/2}$ = 0.024 unit of saltiness.

I.e. the percent uncertainty in saltiness = 1.2%. Hence, incremental charging has reduced the uncertainty, but has not cancelled out all the offset errors.

The conclusion is that where the ratio of ingredients is critical, charging accuracy can be improved by using the same measurement for each ingredient (providing that the measurement technique, instrument and instrument range are appropriate for both measurements).

Case Study 2

At one of its sites, a multinational healthcare manufacturer had several reactors operating in parallel. Batch times were unpredictable, and temperature profiles very variable. Product quality also was variable. On investigation, it was found that the plant was steam limited, and if more than one reactor was operating at once, steam pressure dropped dramatically and reactions could be held up for hours.

New boilers were proposed, but an alternative found. By tackling all inconsistencies in batch operation, it became possible to schedule each batch so that the exothermic reaction

Error and Uncertainty, Random and Systematic
In everyday language, the term "error" is often interchanged with the term "uncertainty." In statistics, the concept of error is related to, but different from, that of uncertainty.

Error is defined as the difference between the true value and the measured value. A better measurement device may allow a better estimate of the true value, but since the true value is never known, we never know the error. The process of using a better device to get a better estimate of the true value and to correct the field device is calibration. Calibration aims to reduce unknown and possibly large error to the smaller error of the calibration process. While we will never know the true value, we can estimate the **uncertainty** or the limits of the error with some confidence. For example, if a temperature measurement is 100°C and has an estimated uncertainty of ±1°C, we know the true temperature has a high probability - say 95% - of being somewhere in the interval, but we still do not know the true value.

Random Error
Consider a load cell vessel into which a specified 10.0 kg of raw material is to be charged. If we repeat this charge many times, then the actual amount charged will vary each time in a random fashion, say 10.1, 9.8, 9.9, 10.5, 9.9 etc. Each time we made a measurement, sources of random error will add a random error component. Errors in successive measurements are random in the sense that they are uncorrelated, but are from the same distribution. This type of error is called random error (or precision error). Random errors cause scatter in the measurement or result.

Note: if we use a low-resolution load cell in the above example, the load cell may indicate 10 kg each time (or a smaller range of error values), but this does not mean that the charged amount is more precise. In fact, the random error is still the same if a separate charging system was used to dispense the 10 kg charge; the random error would be even larger if the load cell were actually used to control the charging.

Systematic Errors
If we want accurate batch size or accurate measurement, it is not sufficient just to have small random errors (i.e. small standard deviation); we need small systematic errors as well. Systematic errors, sometimes called the bias and span, affect every measurement or dispensing amount by the same amount over a time duration of a number of batches. Systematic errors thus cause an offset between the mean value of our measurement with the true value. But since we never know the true value, the systematic error is never known. Instead, what we can estimate is the limits within which the systematic error will lie - the systematic uncertainty.

Table A. Statistical terms used in C&O.

phase was never run simultaneously on two reactors at the same time. Peak steam usage was reduced to within the steam plant capabilities.

As well as saving capital expenditure of tens of thousands of dollars on new boilers, consistent batches meant consistent quality and increased predictability. The C&O study examined the critical process steps, critical equipment and services, analyzing where these affect production. It also took account of the business need for a rapid, low cost solution to quality and scheduling problems in coming up with an appropriate solution.

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Pharmaceutical facility costs vary dramatically from building to building. This article examines the causes and origins of these cost fluctuations and analyzes their possible effects on product reliability.

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Pharmaceutical Facility Costs: Variances, Categories, and Causes

by Joseph A. Blanchard, PE

Introduction

A reasonable question at the beginning of every project is how much will it cost? The second question is why does it cost so much? As design build service providers, we are asked these questions routinely. Unfortunately, the answers will vary significantly! Service providers are asked to complete projects for large pharmaceutical companies with years of traditional methods and plentiful resources as well as small start-ups with no traditions and limited resources. A small under capitalized Biotech business might plan projects within a three-year business horizon, while established companies have a much longer view. These two realities can lead to different approaches to designing and building facilities. This article investigates how facilities vary in cost and some of the reasons why.

Cost Estimate Variances

Let's first look at a variety of pharmaceutical facilities that include laboratories, development and production functions. While these facilities are all designed with a common goal to serve the needs of the healthcare industry, their costs vary dramatically and there exists no standard method for completing a project. To illustrate this, consider Figure 1 which graphically presents pharmaceutical projects completed within the last seven years with similar business objectives. As you analyze the graph, you will observe wide variance in project costs. The cost depicted includes facility costs, equipment costs and all professional fees. The type of facility presented in the data includes pharmaceutical development facilities, biological production facilities and research facilities.

At first glance, one would say: "well it's obvious that the large variance is caused by the different functional requirements of each facility." For example, a research facility is different than a development facility and is different than a biologics facility. To observe how a facility's function might or might not affect variance, let's recast the same data for biological facilities only that are engaged in development and production of biological products.

The data in Figure 2 shows that the cost variance is reduced if one categorizes projects by using a more narrow facility function definition (i.e. variance is reduced from $820 per square foot to $640 per square foot). However, a $640 difference is still a large variable to contend with when trying to estimate project cost. Clearly, building function is part of the answer, but only one part. To understand estimating variance, we must review in more detail how, why and where the actual project cost variances occur.

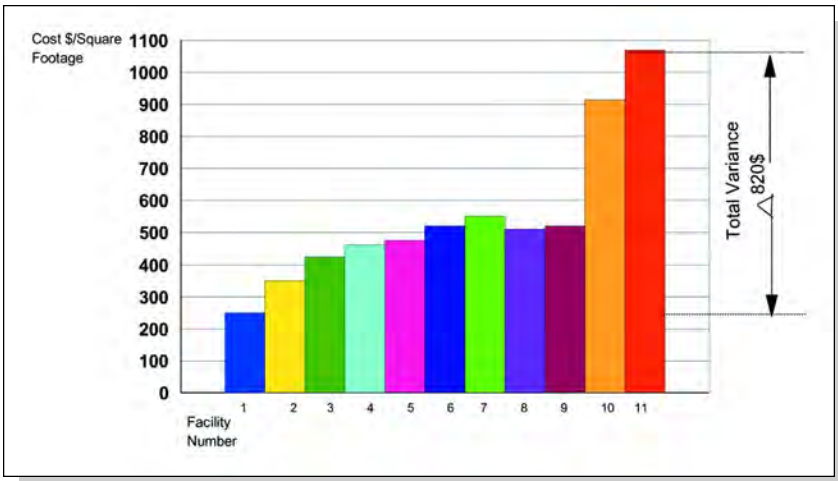

Figure 1. Unit cost for pharmaceutical facilities with "different" functions.

Big Companies Vs. Small Companies

Before we examine the details of project cost variance, let's look at another peculiar project cost phenomena which I have called the "Big Company/Small Company Effect." To understand this

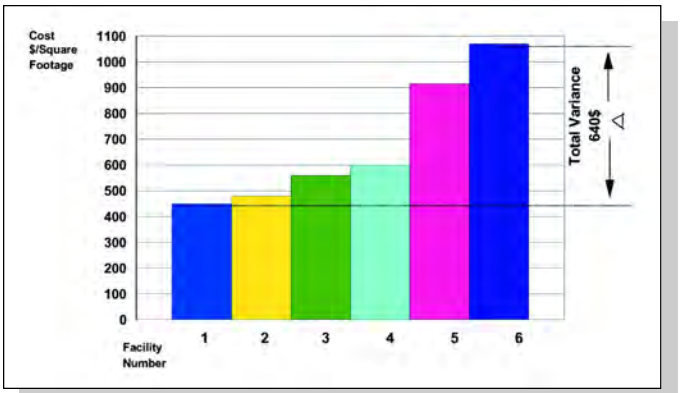

Figure 2. Unit cost for pharmaceutical facilities with "like" functions.

effect, I have taken the same project data presented in Figure 1 and rearranged them to illustrate which projects were completed by "Big Companies" and which were completed by "Small Companies."

Figure 3 illustrates what common sense would predict. Small companies with limited resources must complete projects for less cost simply because they have less money to spend. Concern may arise that low cost facilities erected by small companies produce inferior products. While this could be true in isolated cases, generally, small companies manufacture products in validated, regulated, approved facilities that effectively serve the healthcare industry. The prime difference that this writer observes is that small companies use entrepreneurial approaches in solving regulated-facility issues, while big pharmaceuticals use a "low to no risk" approach to solve regulated-facility issues.

An attempt to graphically represent the two approaches to risk is shown in Figure 4. A simplistic explanation of Figure 4 is that spending more money does not necessarily guarantee a better quality product. The assurance that a facility and its process will deliver a perfect product each and every time without risk of failure is not an investment any company can afford. At some point, there is a diminishing return for every facility dollar spent to add value or assure product quality. As

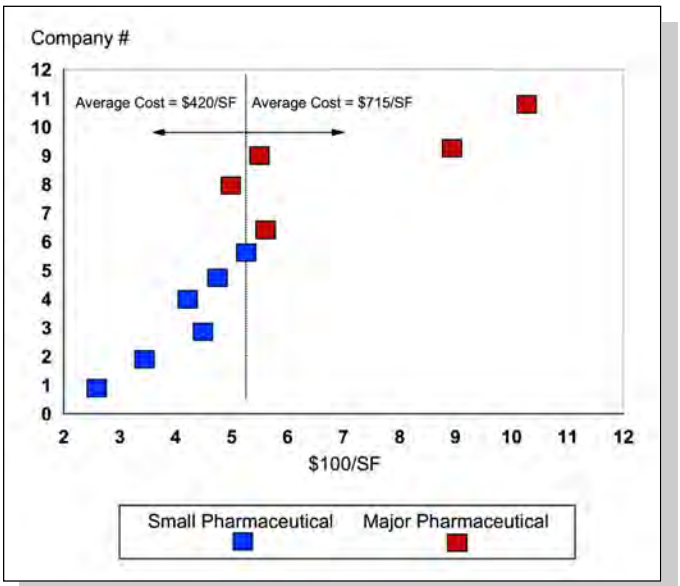

Figure 3. Project cost comparing large pharmaceutical companies to smaller pharmaceutical companies.

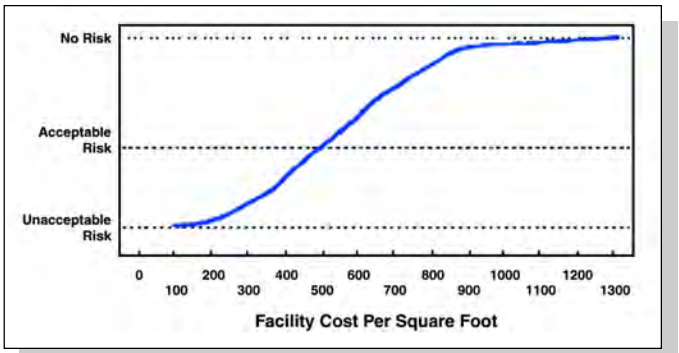

Figure 4. Curve illustrating the diminishing returns of dollars versus risk.

a simple example, does a $9 per square foot ground epoxy terrazzo floor add more value than a $2 per square foot sheet vinyl floor? There is no simple answer to this question, but it illustrates the choices one makes for each and every component of project cost. As you would expect, large pharmaceutical companies tend to choose the epoxy terrazzo floor, while small companies make do with the sheet vinyl floor. Obviously, the many different choices we make for walls, floors, doors, mechanical equipment, etc. when summed together, will yield large variances.

Another factor affecting projects unit cost ($ per square foot) is the overall size of the project. The general trend is that projects larger in size from both a financial and physical perspective have lower unit costs. This article will not present data to support this concept, but it does make sense. There is a fixed cost to operating all business, including a construction project. As the project grows in size, the fixed costs become a smaller component of the overall cost while the exact opposite is true of smaller projects. For example, 50,000 SF project that takes the same amount of time to complete as a 100,000 SF project will have a higher unit cost since the time related fixed costs are relatively constant.

An extreme example of the physical size effect is a cleanroom that was used to assemble a space telescope. The footprint of the room was extremely small in relationship to the height of the facility. The towering facility was serviced by multiple layers of HVAC systems to maintain clean conditions. Consequently, the cost per square foot truly was "astronomical."

Armed with the knowledge that project costs vary and that large companies spend more than small companies and large projects have lower unit costs, let's examine the components of project cost to see if we can understand the major drivers of cost variance and which of those can jeopardize product quality.

Components of Cost Variances

While we have demonstrated that the owner and function of the facility affect cost, we still need to examine why there are large differences between facilities with "like" functions. To accomplish this, we will examine the cost components of individual building parts. In order to understand which building components will have more impact on cost variances than others, we need to know what a typical project cost distribution looks like for pharmaceutical buildings. To study this, I have broken down facility cost components into the following six major categories:

- Electrical
- Engineering and Validation

- Architectural Room Finishes
- Building Shell
- Process Equipment
- Mechanical

Let's examine each component to see how it might cause a variance in project cost. Figure 5 illustrates a typical project cost distribution.

Using the distribution above, let's first examine the categories with the least impact (lowest percentage) on project cost variances because of their small role in overall project cost.

Electrical (5%)

The electrical cost component, according to our database, is the most consistent and predictable component of project costs. Electrical requirements are largely regulated by national codes which lead to consistent approaches to building systems. Occasionally, variances can occur because of redundancy, on site power generation, or substantial "back-up" capability, but generally an estimator can expect few cost surprises from the electrical cost component.

Engineering and Validation (5%)

The second project cost component to examine is the Engineering/Architectural/ Validation costs. This cost sector is a small piece of overall project cost and varies slightly. Our data shows that professional fees on a project can vary from 5% to 10% of the facility cost. For a $200/SF project this equals to a variance of $20/SF. While this is a relatively small variance, it is important to recognize that poor engineering or inadequate validation will have a significant impact on product quality, project cost overruns and increase the risk of non-compliance.

Architectural Room Finishes (6%)

Architectural finishes are normally a small percentage of the overall project cost and there are many different options available. The choices for obtaining a "smooth, cleanable surface" for floors, walls and ceilings are too numerous to describe. As an example, floors can vary from unfinished and routinely coated to ground epoxy terrazzo. Walls can vary from painted drywall to clean room panels, while ceiling types vary from lay-in ceiling tile to walkable cleanroom panels. The many choices available allow large cost variances. Table A illustrates the possible variances that finishes can add to a project estimate's cost fluctuations.

After seeing the wide range of cost differences between finish selections, we should ask the question – do room finishes assure or add to product quality? For example: is a room with hard plaster ceiling likely to produce better products than cleanable tile ceilings? These choices are made by each individual company's investment decision process. It can easily be seen that companies using more expensive finishes will incur higher capital investment cost than those with a lower cost strategy. However, the function or purpose of the facility can be identical.

Building Shell (11%)

Building shell is defined as the outer envelope that houses the internal operations (roof, slab, structure and exterior walls). This component of project cost can vary significantly since some companies utilize a low cost pre-engineered structure, while others use substantial structures with attractive architectural features. To complicate this component further, some companies choose to lease a shell facility and reflect a zero investment in the outer envelope. Add to these issues that land costs and utility infrastructure can vary greatly and we can see why this component of project cost will vary from $0/SF to $50/SF! It is interesting to note that the cost and quality of the envelope surrounding the process can vary dramatically, but have little or no bearing on the quality of a tablet or capsule produced within it.

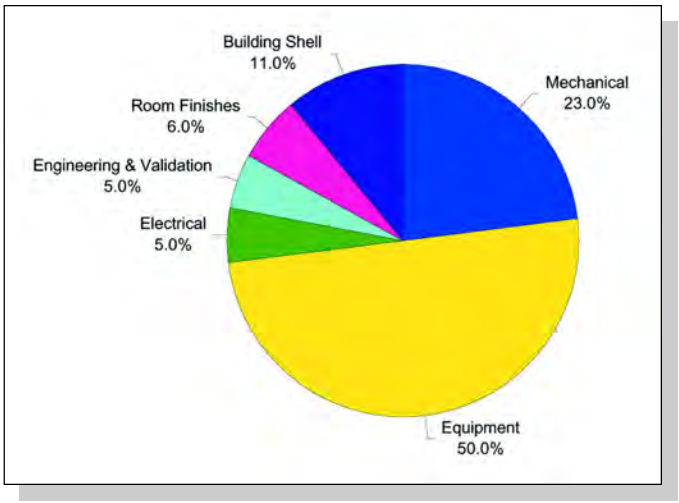

Figure 5. Total project cost distribution in % (including production equipment).

Process Equipment (50%)

Process equipment costs are always a very large component of total project cost. The good news is that nearly every pharmaceutical company uses identical or very similar equipment to manufacture their products. Consequently, there are narrow variances associated with this project cost sector. In some cases, a project can include unusual equipment cost variance attributable to rare occurrences such as:

- purchasing refurbished equipment
- special process "one-of-a-kind" equipment
- rework caused by equipment interferences or late deliveries
- dedicated or redundant equipment

For most projects, equipment costs are consistent and do not contribute much to estimate uncertainty. However, we must be aware that bringing used equipment or special "one-of-a-kind" equipment will cause a dramatic cost variance when compared with projects that do not have this condition.

Mechanical (25%)

Mechanical estimating is the toughest. Not only are these systems a large component of project cost, but they are the single largest cause of project cost variance. They are also critical to product quality. An improperly designed air or water system can easily lead to product failures. Equipment and system choices and combinations are too numerous to quantify. Table B illustrates the various components of mechanical

	$/SF	Max. Possible Variance
Floors	**$2 to $9/SF**	**$7/SF**
Vinyl Tile	$2.00/SF	
Vinyl Sheets Welded Seams	$2.50/SF	
Welded PVC	$3.50/SF	
Epoxy Resin	$4.00/SF	
Ground Epoxy Terrazzo with Wainscot	$9.00/SF	
Walls	**$11 to $30/SF**	**$19/SF**
6" Drywall with Epoxy Paint	$11.00/SF	
6" Block with Epoxy Paint	$19.00/SF	
6" Drywall with Welded PVC	$22.00/SF	
6" Stud High Pressure Laminate	$26.00/SF	
6" Demountable Clean Room Panel	$30.00/SF	
Ceilings	**$2 to $15/SF**	**$13/SF**
Lay in Ceiling Tile	$2.00/SF	
Lay in Tile with Mylar Film	$2.50/SF	
Lay in "Clean" Tile with Gasket	$4.00/SF	
Drywall with Epoxy Paint	$5.00/SF	
Drywall with Troweled on Coating	$7.00/SF	
Demountable Walkable Cleanroom System	$15.00/SF	
TOTAL POSSIBLE COST VARIANCE:	**$39.00/SF**	

Table A. Cost variances for building finishes.

systems that must be selected for a project, as well as a probable cost variance associated with each selection made. It does not take much analysis to recognize that mechanical costs have the single largest impact on estimating variance.

Summary

We have reviewed cost variances and their possible effect on estimating total project cost, and their ability to affect quality and/or risk. Table C summarizes that data and assigns an arbitrary rating to describe the relative impact each project component can have on cost variance and risk/quality.

CATEGORY	COST RANGE $/SF	MAX. POSSIBLE VARIANCE $/SF
Central Plant Equipment	0 to 30	30
Air Handling	15 to 30	15
Ductwork	15 to 25	10
Controls	5 to 15	10
Filtration	1 to 5	4
Exhaust Air	2 to 4	2
Return Air	2 to 10	8
Facility HVAC Piping	0 to 20	20
Process Cooling/Heating	0 to 10	10
Process Waste	0 to 10	10
Process Gases	2 to 20	18
Special Water Systems	0 to 20	20
Plumbing Systems	3 to 6	3
Facility Process Equipment (clean, steam, vacuum pump, etc.)	20 to 50	30
TOTAL MAXIMUM VARIANCE		**190 $/SF**

Table B. Cost variances for mechanical systems.

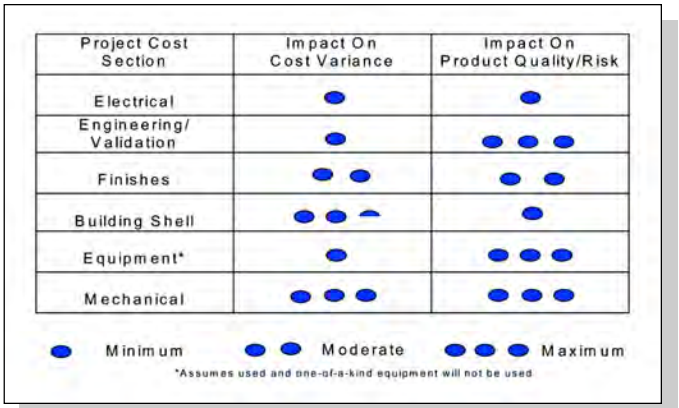

Table C. Illustrates that different parts of a building have a varying effect on product quality and/or risk.

Since project engineers desire to control project costs and accurately predict capital investment requirements, this data helps to show us where to focus. For example, if the objective of a project is to install an asset at the lowest possible cost without affecting quality, then the project manager could minimize the cost of the building shell while incurring little risk to product failures. A similar argument can be made for room finishes. Too often many diligent hours are spent on determining the architectural features of a building or interior finishes when they have little chance to improve product quality, plant efficiency, or impact final cost. The data also shows us that mechanical systems offer a large opportunity to reduce project cost. However, they also carry a large potential risk where cost reductions could affect product quality and/or plant capacity.

Each cost decision made carries with it an associated risk that may or may not affect the quality of the product or facility performance. Individual project teams analyze these decisions for each completed project. Needless to say, the decision process varies depending upon each team's tolerance for risk and need to limit cost. These different decision strategies lead to the large cost variances we see in pharmaceutical projects.

About the Author

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This article presents the current design aspects and benefits of diaphragm pumps for sanitary applications in the biopharmaceutical, food and personal care industries, and discusses what are sometimes wrongly perceived as problematic areas. It also describes the evolution of today's hygienic diaphragm pumps from their origins in piston pump technology.

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Diaphragm Pumps - an Economic Solution for Hygienic Applications

by Kathleen Berry, Dr. Hans-Joachim Johl, and Dr. Eberhard Schluecker

Introduction

A principal goal in producing biopharmaceutical and food products is to achieve a secure and extended, contamination-free manufacturing process. Hygieia, Greek goddess of health, has lent her name to the technology that is dedicated to the total prevention or limitation of microbial contamination. The technical implementation of these goals is the struggle against omnipresent microorganisms, which constitute a potentially dangerous risk in pharmaceutical, food and aseptic applications. This has led to the development of hygienic processes and designs aimed specifically at killing pathogens and preventing reinfection, while avoiding product damage.

General requirements of hygienic technology in pumping systems are:[1-7]

1. a maximum tightness of the system (no possible entry points for microorganisms)
2. minimal dwell time of the fluid in the pump
3. cleanliness of surfaces wetted by the product
4. high (smooth) surface quality with roughness < 20 Ra, with electropolishing
5. easy, effective cleaning and sterilization capability
6. inert materials of construction (no interaction with the pumped fluid)
7. with increasing importance, value-retaining and therefore gentle product transport

Table A shows how the positive features of reciprocating positive displacement pump technology offer promising possibilities for use in hygienic applications.

The ideal of hygienic requirements, hermetic tightness, is fulfilled by diaphragm pumps. However, in spite of this and several other clear-cut advantages of diaphragm pump technology, these pumps, although well recognized in traditional industries such as the oil and gas and chemical industries, have often not been as widely known or understood in the sanitary field.

Evolution of Reciprocating Positive Displacement Pumps

Classical piston pump technology, in its basic form represented by the plunger pump, is impressive by its simplicity,[8] high availability and low initial investment costs. However, plunger pump design must be supplemented by a number of additional, difficult elements when used in sanitary applications, two of which follow:

- The reciprocating, dynamic fluid seal of the piston, which is the main drawback as far as hygienic applications are concerned, requires an effective, sterile interface. For this, the plunger seal is separated into two parts; between them a flushing area for providing a steam or aseptic fluid barrier is installed. An important consideration is that the flushing

Table A. Properties of reciprocating positive displacement pumps.

PROPERTIES OF RECIPROCATING POSITIVE DISPLACEMENT PUMPS

General properties	Special features of diaphragm pumps
• High precision of flow rate	• Hermetically sealed product chamber
• Ideal for low to very high pressures	• Unlimited dry running capability
• Very high energetic efficiency	• Gentle conveying behavior
• Very pressure stiff characteristics	• Ability to couple the pumps to reduce pulsation
• Pulsating conveying behavior	
• Smallest wetted conveying chamber in contact with the product	

area must be longer than the pump stroke so that the particle exchange between the two seals bordering the ends of the flushing area is positively prevented.

- Due to fluid shearing and the unavoidable deposition of product in the piston seal, continual dismantling for effective sanitation is required.

A more sanitary version of piston pump technology is the diaphragm pump, which eliminates the whole plunger seal/flushing requirement problem, including the sterile interface by replacing it with a seemingly simple, flexible diaphragm. The question to address is how reliable in hygienic terms diaphragm technology is and what its critical points are.

Diaphragm Pumps for Hygienic Applications

Mechanically Actuated Diaphragm Pumps

The simplest type of diaphragm pump results when the body of a plunger pump is separated into a fluid and a plunger drive part. If a flexible diaphragm is clamped between these parts and connected to the plunger, the result is a mechanically actuated diaphragm pump head with all the hygienic advantages of diaphragm pump technology[1,9]- *Figure 1.*

By design, the process fluid is contained in a hermetically sealed chamber, separated from the environment by its sterile interfaces: the diaphragm itself with its connection to the plunger, and the diaphragm clamping area at its circumference. The rear of the diaphragm is in contact with the atmosphere. Because the clamping area acts as a static seal, this design solves the problems of dynamically acting plunger seals.

Due to the simplicity of this principle, no vapor- or sterile liquid barrier is required. This is a clear advantage of this technology as long as the sterile interfaces guarantee the required cleanability and prevention of microbial entry.

Unfortunately, the application range of such simple pumps is limited to 20 bar (about 300 psig) and a flow rate of about 1,500 liters/hour (400 GPH). The reason for this is the fact that the rear of the diaphragm is in contact with atmospheric pressure. It therefore must support the load resulting from the operating pressure. The weakest spot of such a diaphragm is the clamping area, where the pressure load generates stresses reaching critical values very quickly.

Figure 2 shows an optimized 4-layer PTFE sandwich diaphragm pack, which reduces the clamping area stress due to the use of multiple layers. This diaphragm design provides a life of more than 20,000 operating hours. This assembly also contains an integral diaphragm monitoring system, which signals the user immediately when a diaphragm is damaged. If the front diaphragm (on the product contact side) is damaged, the fluid is guided within seconds via a channel system to the second diaphragm where it activates a pressure sensing rupture indicator. In sanitary applications, the second diaphragm acts therefore as the monitoring diaphragm. If desired, the pumping process can be continued for a certain period of time. This allows the sandwich diaphragm monitoring system to function as an early failure-warning device. However, certain sanitary standards such as 3-A require an immediate shutdown of the pump when diaphragm rupture occurs.[1] For equipment used in biopharmaceutical manufacturing environments, the 1997 ASME Bioprocessing Equipment Standards indicate that pumps meeting these standards should be of hygienic design and conform to 3-A Sanitary Standards as a minimum.[2]

Figure 3 shows a hygienic mechanically actuated diaphragm pump, featuring all aspects required by 3-A standards. The same is possible with other diaphragm pump types.

Hydraulically Actuated Diaphragm Pumps

For pressures exceeding 20 bar (300 psig) or due to other reasons in low pressure applications, hydraulically actuated diaphragm pumps are the alternative. To arrive at a clear understanding of hydraulic diaphragm pump technology, the evolution from the plunger pump to a viable hydraulic diaphragm pump is described in four separate steps with a discussion about design advantages and disadvantages at each evolutionary stage. The final result is a diaphragm pump, which meets stringent hygienic design requirements.

First Step: Principle of Operation

A hydraulically actuated diaphragm pump essentially is a plunger pump with a membrane which separates the discharge chamber into a process fluid chamber and a hydraulic fluid chamber - *Figure 4.* Membranes or "diaphragms" are usually highly flexible. Under normal operating conditions, the pressure on both sides of the diaphragm is nearly identical with a pressure difference of 1 psig or less. The volume displaced by the plunger is transmitted to the process fluid via the hydraulic fluid and the diaphragm. Therefore, the maximum possible operating pressure of such a pressure-balanced diaphragm depends upon the quality of the diaphragm clamping area design only.

From a hygienic construction standpoint, the design shown in Figure 4 is basically equal to the mechanically actuated diaphragm pump; however, influences related to the hydraulic design make it unusable. Due to the unavoidable leakage flow of hydraulic oil through the dynamic plunger seal during every discharge stroke, the volume of oil in the hydraulic chamber decreases over time, and the diaphragm travels further and further back until it possibly over-stretches, causing deformation, a loss of pumping accuracy and efficiency, and finally, failure. A further evolutionary design step is required.

Second Step: Pump Head with Limited Application

To contain the leakage flow, a reservoir is required - *Figure 5*. A simple and effective method of preventing overstretching of the diaphragm is the use of a back support plate, limiting the deformation of the diaphragm to acceptable values.

Due to the addition of the support plate with the leakage flow still occurring the diaphragm touches the support plate before the plunger has reached the end of the suction stroke. This leads to a pressure drop and cavitation of the hydraulic fluid. The air bubbles contained in the hydraulic fluid would create a noticeable and non-acceptable drop and fluctuation in the product flow rate. For this reason, a replenishing valve to the hydraulic chamber is required, which opens due to the pressure drop in the hydraulic cylinder, allowing replenishment of the oil volume from the oil reservoir at the end of the suction stroke.

This design arrives closely at an acceptable and safely operating pump head, but only when it can be guaranteed that the suction pressure is always equal to or greater than atmospheric pressure. This of course cannot always be guaranteed. The replenishing valve is, in principle, nothing other than a small suction valve, and if the suction line were closed or the suction pressure were to drop below the adjusted pressure limit of the replenishing valve, it will open independently of

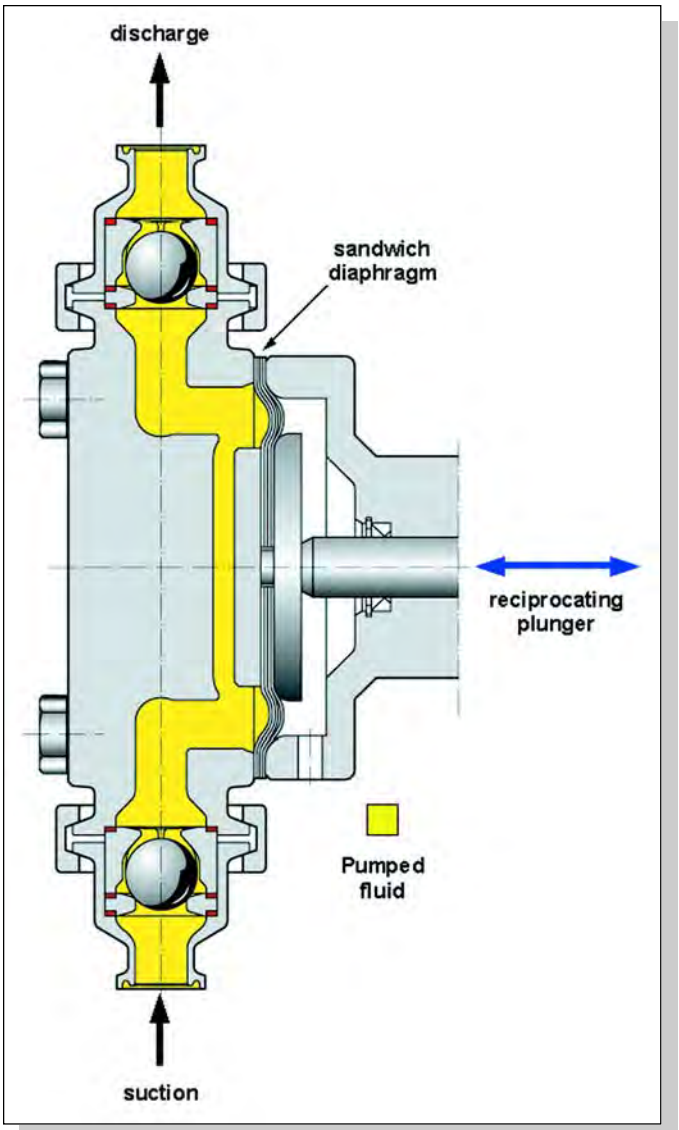

Figure 1. Cross-section of mechanically actuated diaphragm pump head.

the diaphragm position. The oil in the hydraulic chamber would increase, and this would cause the diaphragm to over-stretch towards the front, causing diaphragm damage. Therefore, another evolutionary design step is necessary.

Third Step: Pump Head with Completely Safeguarded Diaphragm

The easiest method of preventing over-stretching of the diaphragm towards the front is the installation of a front support plate to establish a reliable limit position for the diaphragm - *Figure 6.* Unfortunately, this is still not sufficient for hygienic applications.

If the suction pressure becomes restricted and the replenishing valve opens (instead of the suction valve), the diaphragm after a few strokes is pushed to the front support plate before the plunger has reached its full forward position. On the next stroke, the pressure rises until the diaphragm is forced through the small holes in the support plate and perforated to relieve the pressure, or the pump drive fails due to overload. To avoid this situation, an adjustable pressure-limiting valve (PLV) is installed in the hydraulic chamber. Now, if the pressure rises over the maximum permissible limit, this valve opens and relieves the surplus oil back to the reservoir.

The evolutionary development at this point has resulted in a diaphragm pump that is safe against either restricted or closed suction or discharge lines. The pressure-limiting valve opens in any case when the preset pressure limit is exceeded. Of major interest from a hygienic point of view is the fact that these pressure limiting valves also can be used as safety valves. As long as only the pump is generating operating pressure, process safety valves, which always pose problems from a system hygienic design standpoint, can be eliminated downstream from the pumps.

In this design, the support plates must meet certain requirements. The diameter of the bores must be selected so that the diaphragm cannot be pressed into the support plates and become damaged. The higher the pressure, the smaller the design diameter of the bores. The implications of this for hygienic applications are smaller channels, which on the product side are difficult to clean. Therefore, although the pump at this stage of development is perfectly suitable for industrial applications, it needs further development to make it suitable for hygienic applications.

Fourth Step: Hygienic Hydraulically Actuated Diaphragm Pump Head

The alternative to the non-acceptable support plate with channels on the product side is diaphragm position control by means of a control push rod. The control push rod positively closes the connection to the leakage-replenishing valve until the diaphragm has forced the push rod into its rear position. Only then can the leakage replenishing valve open. Now the diaphragm can no longer be over-stretched in the direction of the wetted (process) chamber. The hydraulic side support is provided by the shape of the rear support plate and the disc-shaped control push rod, which nearly completely covers the rear diaphragm support - *Figure 7.*

From a hygienic point of view, this design combines the advantages of an open flow-through path for the fluid in the conveying chamber and good CIP cleaning capability with reliable diaphragm flexing behavior and the pressure limiting valve remote to the process pipeline. These pumps are more costly than plunger pumps; however, they provide an elegant, hermetically tight, accurate and highly efficient method of

Figure 2. Four layer PTFE sandwich diaphragm pack with one operating diaphragm, two monitoring diaphragms with signaling channels and one back-up diaphragm.

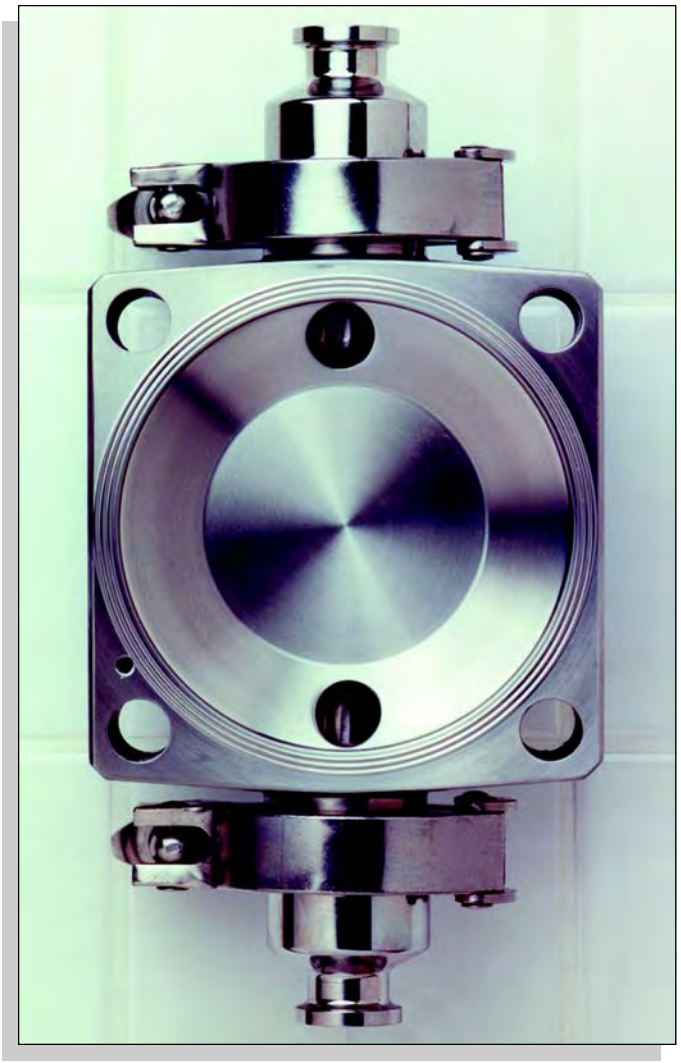

Figure 3. Hygienic diaphragm pump cover with triclamp connections to 3-A Sanitary Standards.

transporting product. In addition, low hold-up volume designs are highly beneficial, especially to users concerned about expensive ingredients and low dwell time of shear-sensitive product within the pump head. Of course, proper surface finish with additional electropolishing of all stainless steel components renders all product contact surfaces smooth and therefore, easy to clean. Hydraulic oils used are food-grade. In the case of system upset, diaphragm damage is signalled instantaneously by means of an alarm signal, while the sandwich diaphragm configuration continues to provide an effective barrier between the product and the hydraulic oil circuit.[10-13]

The only remaining point to consider in terms of safety is the possibility of a vacuum being created in a process line after sterilization at elevated temperatures. Should a vacuum situation occur during the cooling phase, and if the pump is at a standstill, the pressure drop generated in the pump head may cause a small amount of hydraulic oil to flow from the reservoir to the hydraulic chamber. This results in the diaphragm moving forward independently of the plunger, followed by over-stretching and damage of the diaphragm on start-up. This situation can be prevented with a start-up valve to ensure that the diaphragm is in proper start-up position.

Diaphragm Material as Sterile Interface

The diaphragm material is of utmost interest to hygienic industry professionals. The main choice is PTFE; in rare cases, other elastomers may be considered.

Today, diaphragm materials are chosen to meet necessary government regulations and industry requirements concerning contaminants, therefore this point is a non-issue. The main question concerns cleanability: whether the presence and size of possible pores may pose a problem.

Modern elastomers exhibit a nearly pore-free surface; however, they often are not adequately resistant against CIP chemicals. PTFE on the other hand is absolutely inert, but it is a sintered material and therefore by its nature exhibits pores.

The "art" is to select an optimum PTFE with an acceptable pore size even under dynamic load. Factors which can affect pore size are (1) the type of PTFE base material, which determines particle size and shape of the sintered particles; and (2) the surface quality of the PTFE raw material, as influenced by the sharpness of the cutting tools used to create them.

Examinations using a scanning electron microscope are helpful in this regard. In addition, the 3-A Sanitary Standards provide testing methodology for the cleanability of multiple use plastics such as PTFE. Other cleanability methodologies used for sanitary equipment cleaned in place, such as riboflavin dye testing, ATP bioluminescence testing (VDMA[14]), or microbiologically based studies (EHEDG[15]), also provide reliable indicators for the correct choice of diaphragm materials.

Sterile Interface in the Diaphragm Clamping Area

Depending upon the operating pressure, two different clamping methods are used in diaphragm pump technology. The primary consideration is whether the diaphragm material can accept and transfer the screw forces required to achieve the required sealing force, without starting to cold-flow.

For lower pressures up to 20 bar (300 psig), as found in mechanically actuated diaphragm pump heads, the diaphragm is clamped in the so-called "series force" design - *Figure 8a*. This means the diaphragm is clamped directly between the pump cover and plunger housing. The force of the cover bolts is transferred to the plunger housing directly by the diaphragm.

The advantages of this clamping method are its simplicity and the possibility of re-tightening in case of leakage caused by cold-flow of the diaphragm material. The screws would need only to be re-tightened to the torque specified. Proper design by the pump manufacturer should exclude these occurrences, resulting in a very simple technology allowing multiple use of the same diaphragm. The advantage is obvious when considering the long service life of the diaphragm.

When dealing with pressures exceeding 20 bar (over 300 psig), a so-called secondary force clamping method is applied - *Figure 8b*. Due to the fact that the pressure on both sides of the hydraulically-actuated diaphragm is almost identical, the achievable pressure is only dependent upon the integrity of the diaphragm clamping area. The diaphragm in this case is clamped in a pre-shaped and usually serrated gap contour, whereas the pump cover and plunger housing have metal to metal contact. The bulk of the screw force is therefore not transmitted through the diaphragm. In this clamping design,

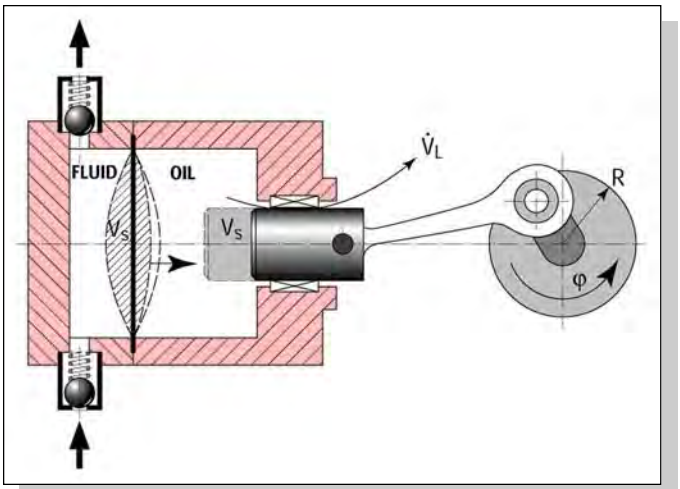

Figure 4. "First step" hydraulically actuated diaphragm pump: $\dot{V}_L$ leakage flow; V_S stroke volume; R eccentric radius; φ phase angle.

the diaphragm is chambered rather solidly and therefore maintains a very stable shape.

In case of temperature fluctuations, e.g. between production and sterilization, a relative expansion of the PTFE compared to the surrounding stainless steel takes place. When the temperature increases, the PTFE moves out of the clamping area; however, during cooling, most of it moves back again. This means that, compared to the fluid contact area, a bigger share of the diaphragm surface is subjected to direct sterilization. This also includes the shaping corner (radiused angle) at the clamping rim. As long as no gap develops between the pump cover and the diaphragm due to heat expansion, this is a clear advantage. Improper design of the clamping contour can result in the development of such a gap. To provide sufficient safety here, a clamping contour preventing overextrusion from the clamping area must be provided. One important aspect is that the serration in the clamping area is as close as possible to the inner clamping rim. It is evident that diaphragm clamping design is a critical aspect of pump manufacture.

While the interface at the diaphragm clamping area is hermetically tight, the main question that remains is the CIP-cleanability of the inner clamping rim.

To protect the diaphragm from a notch effect in the clamping rim, usually a certain very tiny radius is machined into the diaphragm cover. The rounded housing contour of the pump cover therefore unavoidably meets the diaphragm in an acute angle, often barely visible to the naked eye. This also applies if the radius contour has somewhat penetrated into the surface of the diaphragm by the clamping force.

Such areas are normally not allowed in hygienic design. However, one must bear in mind that this is a dynamic, not a static location: dynamic meaning that the diaphragm is flexing continuously, drawing the fluid into the corner and displacing it again. CIP cleaning is therefore most effective with the pump in operation. One also must bear in mind that the acute angle is miniscule and is immediately followed by an adjacent open design area which is readily accessible to cleaning fluids.

Once again, the various cleanability testing methods mentioned earlier afford a way of determining what, if any, critical areas exist, as with any other piece of equipment. Validation of specific cleaning regimens must be carried out to determine the optimum CIP time, temperature and choice of cleaning chemicals.

Diaphragm Pumps as Low Shear Conveying Mechanisms

To date, there is no sufficient data available to classify process machinery used in hygienic technology based upon the shear effects of the conveying mechanism on the process fluid. However, a cause and effect evaluation drawing on basic principles is possible.

Typical sources of fluid damage are impact flow, shear flow, cavitation and squeezed flow (e.g. due to fluid exposed to crevices, dynamic seals, etc.)

Gentle conveying means minimizing or avoiding these effects. The less present these effects are and the less resulting energy induced in the fluid, the better overall for the fluid.

The absence of any dynamic seal in the pressure chamber of diaphragm pumps allows extremely gentle conveying of process fluids. The only areas of possible damage are at the product valves during closing and possibly opening. However, one must note the extremely short closing or opening times. The time period for possible damage is around 1% of the total time. So, the integral damage potential is extremely low. On the other hand, the shearing effect at the plunger seal of a plunger pump is present during the complete stroke cycle. Similar problems apply to other pump types (basically any rotating positive displacement, gear, rotary piston, peristaltic hose or eccentric screw pumps).

Check Valves

All reciprocating positive displacement pumps are equipped with check valves. The contour, surfaces and static seals must meet hygienic design standards (smooth, with no hollow clearances, sharp edges, crevices, or cast surfaces[3,4,5]). Critical details with regard to hygienic design also include the faces of springs (pointed or narrow gap ends), such as in spring-loaded valves. If such components are used, due regard must be given to critical details, or they must be avoided altogether when high hygienic requirements are specified.

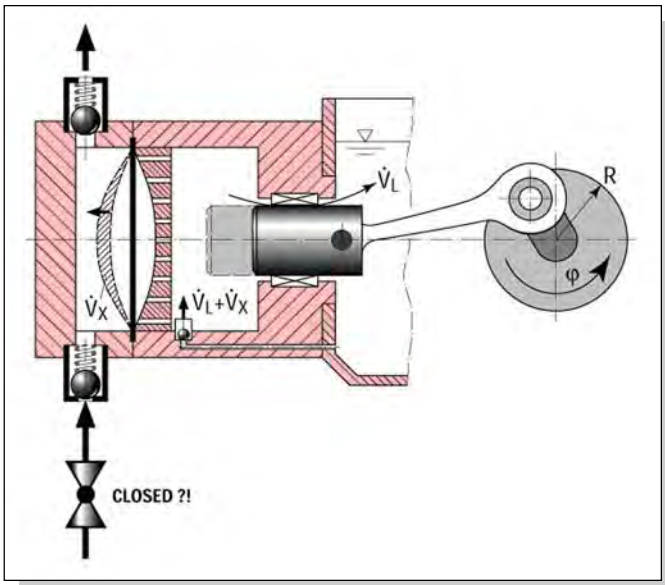

Figure 5. "Second step" diaphragm pump: $\dot{V}_L$ leakage flow; $\dot{V}_X$ additional flow when suction line is restricted; $\dot{V}_L + \dot{V}_X$ replenishment flow.

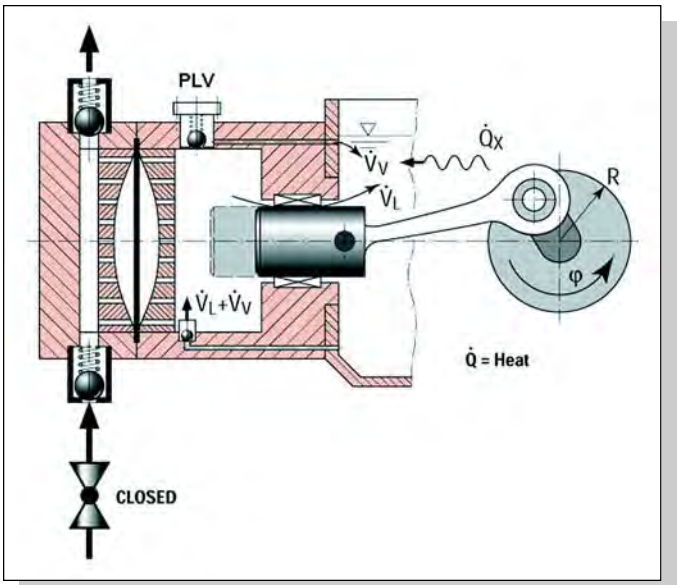

Figure 6. "Third step" industrial-duty diaphragm pump: $\dot{V}_L$ leakage flow; $\dot{V}_V$ venting and pressure relief flow, $\dot{V}_L + \dot{V}_V$ replenishment flow; PLV combination pressure limiting/venting valve.

NPSH

Diaphragm pumps are reciprocating positive displacement pumps with a pulsating flow characteristic. Typical for such behavior is a friction and an acceleration head loss at the suction side of the pump. Due to this, NPSH requirements are generally higher than for other types of pumps. Proper geometry and design of the pipelines leading to the diaphragm pump head must be taken into consideration.

Pulsation Damping

The simplest and therefore also most widespread method of reducing the typical pulsation of a reciprocating positive displacement pump is to fit a sanitary pulsation damper in the pipeline. Often such a solution is sufficient for the user if cleanable flow-through dampers are used.

However, there are some hygienic aspects which clearly speak against the use of pulsation dampers. They become additional maintenance items within a system which have to be serviced, monitored and, of course, cleaned and sterilized. They also constitute an additional potential source of infection or contamination.

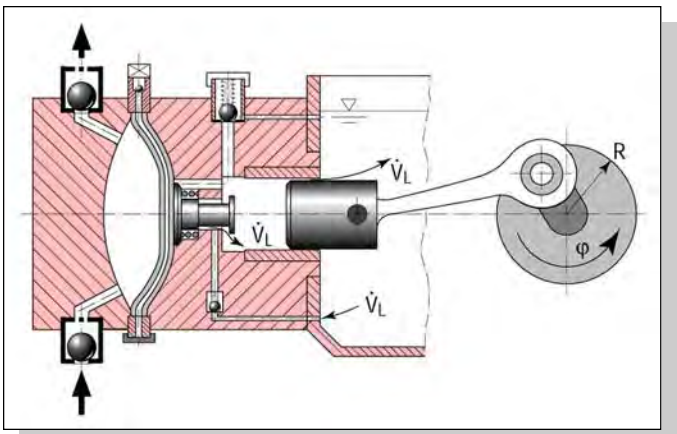

Figure 7. Optimum hygienic design with hydraulically actuated and position-controlled diaphragm: $\dot{V}_L$ leakage and replenishment flow.

When, due to very strict hygienic requirements, pulsation damping without dampers is required, the solution is to couple several diaphragm pumps into a multiplexed configuration, and operate them with a phase shift. Pulsation is significantly minimized when comparing a triplex arrangement (three pump heads) to a simplex arrangement (a single pump head), and in most cases, the pulsation reduction thus achieved is acceptable. Additional improvements can be realized with multiplexing additional pump heads as described in the following application example.

High Pressure Homogenization of Pharmaceutical Products: Liposomes

An interesting application, which illustrates the unique capabilities of high pressure sanitary process diaphragm pumps, was implemented in a cleanroom manufacturing process for liposomes.[16] Positive displacement diaphragm pumps were the only acceptable and capable solution to this application, due to the necessity of generating very high pressure (more than 10,000 psig) in a hermetically tight product environment.

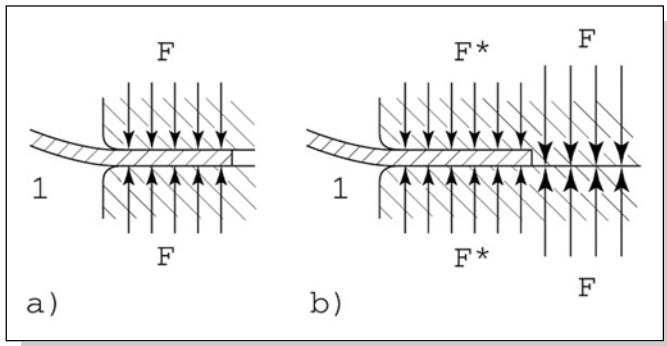

Figure 8. a) "Series force" diaphragm clamping, b) "Secondary force" diaphragm clamping: F = main force; F = diaphragm clamping force, 1 = diaphragm.*

Liposomes are tiny controlled-delivery systems for bringing active ingredients such as drugs, vitamins and cosmetic materials to specific sites of the body where treatment is required either by injection or as topical applications. They consist of microscopic spheres made of molecules with hydrophilic and hydrophobic ends, which can encapsulate water-soluble ingredients in their inner water space and oil-soluble ingredients in their hydrophobic membranes.

A key requirement for the liposome process was to achieve a spherical liposome size of 50 nanometers in order to allow multiple and safe use of the product for intravenous injection. To realize this size reduction, an extremely large pressure drop on the order of 800-1000 bar (11,600-14,500 psig) across a dispersion nozzle was necessary. The chamber where the particle size reduction took place was configured to effect enormous shear forces.

The high pressure sanitary pumps utilized in this application featured several optimized design characteristics especially in the suction and discharge valves and in the diaphragm clamping area - *Figure 9*.

Pulsation damping without pulsation dampers was required as a result of the otherwise unsatisfactory suitability of

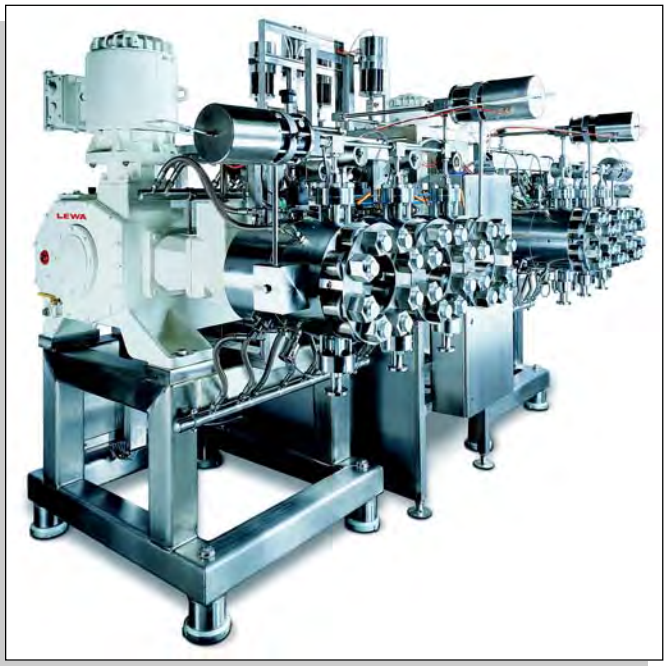

Figure 9. Two electronically synchronized triplex hygienic diaphragm pumps in high pressure design.

the system for cleaning. Pulsation damping was necessary to ensure a constant, pulsation-free flow supplied to a homogenization nozzle downstream from the pumps. The simple yet effective solution to this problem was to couple two triplex pump drive units in a synchronous combination. The residual pulsation (+/- 2 %) therefore corresponded to that of a six-headed pump operating with a 60° phase shift for each of the drive elements. Additional successful reduction in pulsation down to +/- 1% was achieved by modifying the configuration of the process piping between the pump discharge and the nozzle.

The use of two triplex pumps rather than one sextuplex pump provided an additional benefit due to the compactness of the triplex design which allowed a very flexible installation arrangement. In addition, the system was capable of operating with an acceptable pulsation profile even if one of the triplex pumps were to require downtime.

The system was designed to be cleaned by means of CIP, followed by SIP. As a special feature, heating/cooling channels were incorporated into the pump heads to allow short heating and cooling times during the sterilization and cool down phases. The entire process was fully automated and integrated into the rest of the manufacturing process.

In the end, an extremely reliable, continuous and therefore economical process was realized.

Diaphragm Pumps in Process Chromatography Applications

Diaphragm pumps with their extreme precision have established themselves in process chromatography. The world's largest insulin manufacturing facility currently being built utilizes ion exchange chromatography of preliminary stage insulin components as well as final HPLC purification of human insulin. Highly pure, microorganism- and endotoxin-free insulin must satisfy cGMP, US FDA and EU regulations. Sanitary diaphragm pumps are an integral part of the manufacturing process.

To dose the insulin-containing protein sequence, as well as the elution, regeneration and wash solutions, several types of diaphragm pumps achieving pressures up to 70 bar (1015 psig) are needed. Multiple-headed pumps provide the necessary gradients for the chromatography columns. Pump output of the individual heads can be varied automatically, continuously and independently of each other. The precision achieved is better than 0.5% of the targeted end point values. Hygienically optimized pulsation dampers provide a very low pulsation profile.

The complete package units (including ancillary hardware and control elements) for this application are CIP-able and constructed to fit into a cleanliness Class 100,000 area. They conform to USP 23 Class VI requirements. Validation documentation is an integral element of the scope of supply.

Economic Aspects

Sanitary diaphragm pumps provide a high degree of safety against microbial contamination due to their hermetic tightness. In addition, low hold-up volume pump heads designed for sanitary service are desirable in the event of production upsets involving often very expensive ingredients. If production loss costs are considered, these facts are economically very important.

Sanitary diaphragm pumps perform consistently and reliably, benefiting the user for whom it is more and more important to manufacture products within tight specifications. Their relatively long life span minimizes the necessity to revalidate new equipment, an often costly procedure. In addition, they exhibit low life-cycle costs including high volumetric and therefore energy efficiency, compared to all types of rotating positive displacement pumps.

Lastly, when installed in metering service for continuous proportional blending or injecting of ingredients such as flavors, colors, vitamins, nutraceuticals, enzyme solutions, cosmetic additives, biological nutrient solutions, etc., the higher up-front capital investments involved in changing over from batch to continuous production are more than compensated for in the long-term savings gained due to less waste and improved automation, process control capabilities and production efficiencies.

Conclusion

In conclusion, reciprocating, positive displacement diaphragm pumps are uniquely and almost perfectly suited to meet the requirements of hygienic technology at an economical cost in sanitary applications. Their basic features can be augmented with interesting additional design aspects, which are tailor-made to the individual process requirements. The growth of more sophisticated process technologies will almost certainly spawn a need for precise, reliable, pressure-stiff, low maintenance sanitary diaphragm pumps which provide a hermetic design, CIP and SIP capability, and gentle product handling.

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This article will discuss some of the key issues of transfer panel design fabrication and installation, and relate them to a new approach of integrated panel design.

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Integrated Transfer Panel Design for the Biopharmaceutical Industry

by Wei Huang, Geoff Attenborough, and Randy Cotter

Introduction

This article will focus on transfer panel technology for the biopharmaceutical industry. Areas such as logical panel design, panel specification, panel fabrication and installation will be discussed in detail. Some of the latest design approaches and technologies also will be presented.

Biopharmaceutical manufacturing facility design has become increasingly more complex with the advent of multi-product operations and the necessity of cGMP compliance. The use of transfer panels (or patch panels, flow panels) for hygienic multi-process liquid transfers is quite common in biopharmaceutical processes. They have become a vital part of the entire manufacturing facility. Transfer panels integrate all related process operations with the overall facility design. These operations include flow transfer, equipment cleaning, pipe line cleaning and system sterilization. The key elements of incorporating transfer panels into the manufacturing facility are design, fabrication and installation. During the initial design, it is critical to develop a logical panel design with the consideration of process requirements, ease of operation and fabrication. To ensure the proper implementation of the panel design, it is important to form a close liaison with the transfer panel manufacturer during both design and fabrication. To achieve a successful installation, it is crucial to include construction personnel during all stages of the process.

The Basics of Transfer Panels

Transfer panels were first introduced in the dairy and food processing industry to largely accommodate their required Clean-in-Place (CIP) operations. However, they have become popular with the biopharmaceutical industry because of their singular ability to accommodate multi-flow transfers with the advantage of complete 'air' breaks to maintain hygienic conditions. A typical transfer panel is fabricated from a ¼" thick 316L grade stainless steel plate. Hygienic port connections are welded to the panel front to mate with the port-to-port jumpers (or 'U' bends). Each port is integral with piping to allow system connection at the panel back. The ports are designed in a required process transfer sequence and located to precise tolerances. This precision is necessary so that each jumper will fit precisely and with minimum effort by the operator.

Transfer panels possess the following unique features:

- Provide a common point to readily transfer a process stream from one process equipment or unit operation to another process equipment or unit operation.
- Provide a physical disconnect when transferring various process streams. This greatly reduces the possibility of cross-contamination especially under CIP conditions.
- The use of stainless steel jumpers eliminates temporary connections such as flexible hoses which are difficult to maintain in a hygienic condition and can be a safety concern when steam sterilizing.
- Jumper lengths unique to certain transfers safeguard against incorrect connections and ultimately disastrous process stream destinations.
- Combination of jumpers and proximity switches on the panel provide permissive signals to the plant control system to confirm correct jumper set up and assure the flow passages for critical operations such as CIP and SIP.

There are many different types of transfer panel designs such as simple wall inserted and mounted, free standing with legs and foot plates, enclosed rear cabinet type and the modular panel design. The modular panel design features integrated pre-piping, valve groups, electrical and instrumentation wiring at the back.

TYPE	ATTACHMENT	PROS	CONS
Stainless steel labels	Welded to the front plate	Permanent	Risk of heat distortion. Not cosmetically appealing
Stainless steel tags	Chained to the port	Easy to make	Tags get lost and misplaced easily
Multicolor engraved labels	Glued to the front plate	Easy to make	Labels fall off easily
Stainless steel labels	Riveted to the front plate	Permanent	Front plate distortion Not a clean design
Electro-etch	Sub-surface etch to the front plate	Permanent Clean design	Difficult to replace

Table A. Comparison of different panel labeling methods.

Transfer panel front port connection types include Tri-Clamp (most common), Bevel Seat, John Perry and others.

Logical Panel Design

The development and design of an optimum transfer panel requires a thorough knowledge of the process requirements and exhaustive investigation into the intricacies of the piping systems.

The location and number of transfer panels should be determined during conceptual design based upon the type of unit operation, process requirement and material flow pattern. After the conceptual design is completed, the process engineer will develop Piping and Instrument Diagrams (P&IDs) which show the detail of panel design requirements. These details include type of flow streams associated with each panel, number of ports required, connection type, connection pipeline sizes, instrumentation types, port connection sequence, and quantity of jumpers. Each port should be labeled and the flow path identified on the P&IDs. These documents then serve as the governing design criteria. The design engineer will use this information in conjunction with the piping drawings and equipment layouts to develop the detailed panel port arrangements. The following factors should be carefully scrutinized during the design process:

- number of connections required
- size and type of connections required
- any simultaneous connections required for different operating conditions, such as process flow transfer with CIP and SIP all occurring at the same time through multiple separate jumper connections
- the relative location and elevation of the transfer panel in relationship to connected vessels and pumps
- pipe routing from the transfer vessel to the panel and from the panel to the transfer destination.
- the size and quantity of standardized jumpers
- the physical space available for the panel to be integrated into the facility layout
- port to port clearance when jumpers are connected should be monitored closely to ensure that the jumper drain valve would not interfere with adjoining ports
- sufficient spacing has to be allocated between ports at the back of the panel to allow for pipe routing and valve positioning, pipe insulation and orbital weld head placement. Physical space allowance also should be considered for maintenance of proximity switches and operated valve actuators

Multiple jumper connections for simultaneous transfers and specific port elevations (in relation to associated equipment) are some of the more important factors of design. Techniques such as high and low jumper connections, internal loop headers or bridges, and multiple path divert valves have been employed to satisfy multiple connection requirements and reduce the use of numerous sized jumpers. The design engineer also should pay close attention to the inlet and outlet nozzle elevations of associated equipment, such as vessels that are piped to the panel to assure drainability, cleanability and sterility during process transfer, CIP and SIP.

When the front panel port layout design is completed, it should be rigorously reviewed by various parties to ensure the following:

- All process transfer requirements have been met.
- Conflicts or interference during simultaneous transfers have been avoided.
- The panel layout is operational friendly in terms of connection elevations, size and number of the jumpers to be used.
- The panel and transfer lines can be easily integrated into the rest of the facility design.
- Avoid port to port interference, ie. sufficient clearance between ports to allow good jumper connection and orbital weld head location.
- There is sufficient space between ports to allow optimum placement of the proximity switch, ie. adequate room for the instrument, wiring and maintenance.

Jumper Design

Jumpers (or 'U' bends) are U shaped pieces of stainless steel (316L) tubing with hygienic ferrules (or external ACME threads, such as the John Perry type) on both ends which mate with the panel ports. It is necessary to design a panel face which has a rational and optimum panel port arrangement. This will lead to standardized jumper sizes and minimize the number of

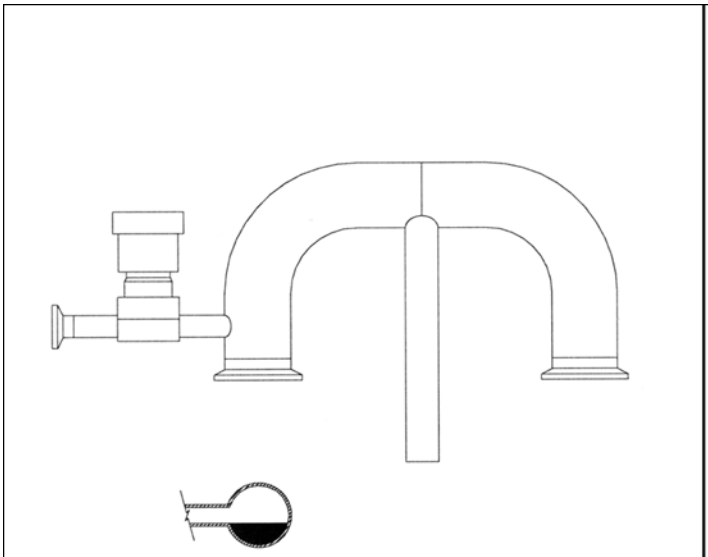

Figure 1a. Trandition jumper with drain valve design.

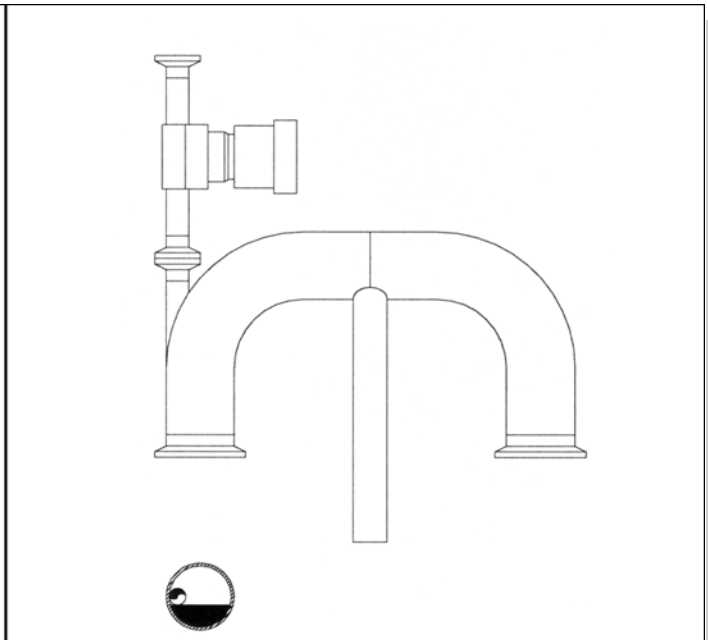

Figure 1b. Jumper with tangential drain valve design.

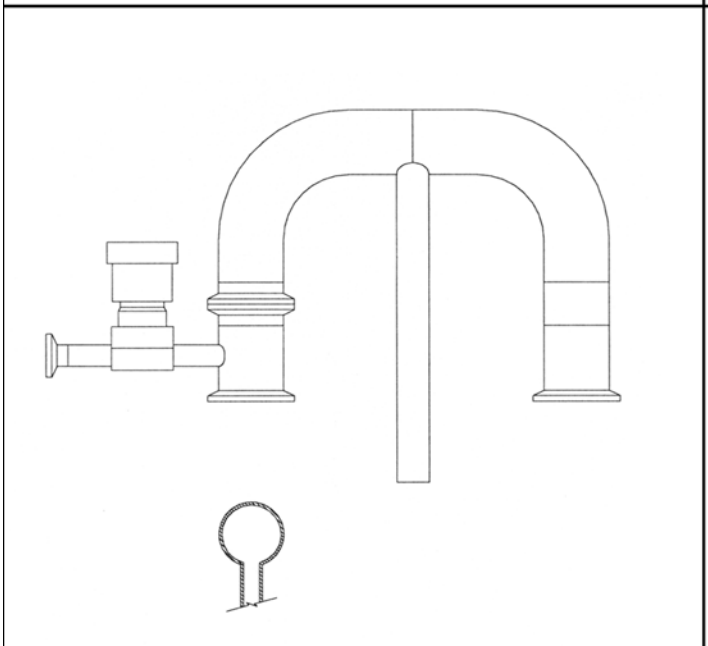

Figure 1c. Jumper with spool piece drain valve design.

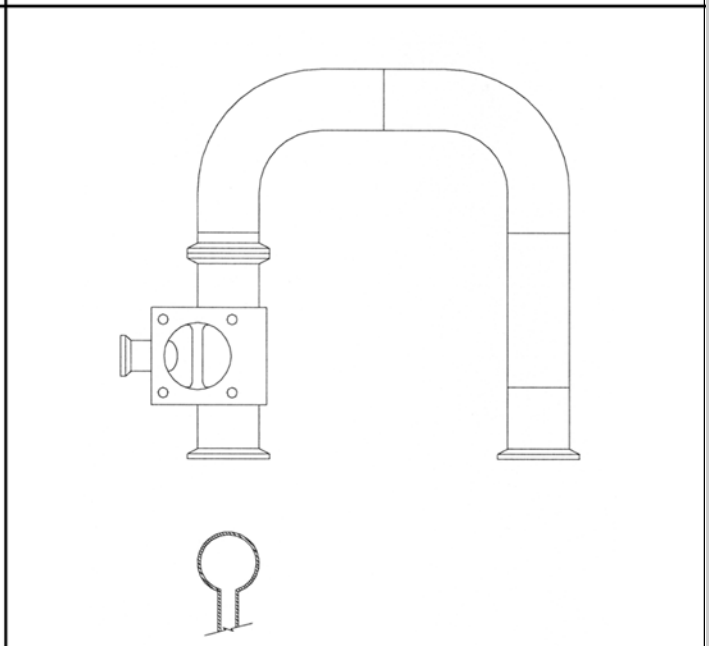

Figure 1d. Jumper with spool piece zero static drain valve design.

Figure 1. Jumpers with drain valves.

different sized jumpers. Standard sized jumpers provide a great deal of flexibility and convenience for operation. Under certain circumstances, flexible jumpers may be used to satisfy awkward or infrequent transfers. In other cases, jointed swing jumpers also are used to allow for some exotic connection arrangements and tolerance requirements.

The overall size of the transfer panel is naturally largely dependent upon the quantity of connection ports, jumper pipe size and length. Due to premium cost of cleanroom space, a compact panel design is one of the main design goals. The number of ports is mainly determined by the process and panel design requirements. The jumper pipe size is determined by the process flow hydraulics. Jumper length is determined by the combination of panel port layout and available pipe fitting dimensions. In addition, spatial requirements for the orbital weld head placement and clearances for port jumper assembly have to be considered.

A jumper typically has a low point drain to provide both complete drainage and vacuum break after the liquid transfer has been completed. Various styles of low point drain valve design have been developed over the years - *Figure 1.*

Figure 1a shows a simple drain valve design which has been typically used. However, this style of assembly contains a fundamental design flaw. As the jumper is rotated through

various connections, the low point becomes somewhat elevated, (i.e. the drain valve ceases to be at the jumper's true low point), which in turn creates cleaning and sterility problems.

Figure 1b illustrates an improved design in which the drain valve is welded directly to the tangent of the jumper.

Figure 1c and 1d are relatively new designs that utilize a tri-clamped spool piece which allows full rotation of the low point drain valve. This assures that the drain valve is always at the true low point of the assembled jumper connection. However, it should be considered that the addition of this spool piece requires additional welds, makes the jumper taller (protruding away from the panel face further), and heavier, hence making manipulation more cumbersome and finally more costly.

One of the common design questions is how many jumpers are really needed. Usually a panel is designed using a common port size and a common center to center distance between ports. This allows for maximum efficiency from a single jumper. A second (or third, etc.) jumper would then only be required to satisfy simultaneous transfers. With complex panels, the 'One Jumper Fits All' philosophy does not apply. Therefore it is necessary to include one or more different sized jumpers to accommodate the connection geometry. In order to reduce the down time between transfers, spare jumpers also should be accounted for to allow jumpers being cleaned out of place. Additionally, it is recommended that each jumper be dedicated to one panel. This assures a perfect 'fit' for each connection. It is not uncommon to find a jumper of a common size to fit slightly differently between two panels.

Jumper Holders

It is a good design and housekeeping practice to provide jumper holders for out-of-use storage. The location of the jumper holder should be adjacent to the panel. This helps ensure that each jumper stays with its respective panel.

Port Caps

Caps should be provided for all ports on the panel. Ports should be capped when not in use to prevent a potential spill or contamination. Some caps are designed with bleed valves for bleeding off residue fluids and to break the vacuum seal.

Drain Pan

Drain pans are built as an integral part of the transfer panel. They collect spilled fluids that can occur during jumper assembly and disassembly. They are typically made of 12 gauge stainless steel sheet, sloped to a low point and piped to the process drain. The depth of the drain pan is determined by calculating the largest spill volume and accommodating it with a sufficient pan holding volume. The drain port on the pan should be sized generously to avoid over flow. The elevation of the pan should take into account clearances required for the jumper drain valve position when a connection is made to the bottom row of nozzles. The drain pan low point is typically located in the center of the pan. However, when the panel has to be set at an elevation close to the floor, the drain pan can be sloped and drained to one side, thus saving vertical space.

Proximity Switches

Today's transfer panel designs have become more complex with the use of proximity switches and other sensing devices. A proximity switch provides a confirmation signal for correct jumper connection. The switch is induced by a magnet welded inside a contact rod or probe which is typically located in the center of the jumper arm. The proximity switch is usually mounted inside a half coupling that is located at the back of the panel and centered between the two connected ports.

The use of proximity switches adds new challenges to the panel design. Designs with crossing jumpers (for simultaneous transfers) should be closely examined to avoid interference with the switch signal. It is important to allow sufficient clearance between the proximity switches and their adjacent panel ports to avoid false induction.

Transfer Panel Specification

Upon completion of the preliminary panel port layout design, all design documents should be assembled and an inclusive package compiled for competitive bid or purchase submittal.

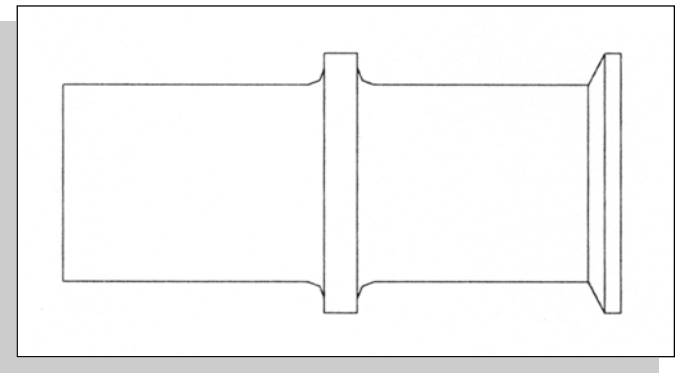

Figure 2. Hygienic port with shoulder design.

These documents include, but are not limited to specifications for panel, valve, piping material, instruments and electrical wiring; data sheet for each panel and instrument; preliminary panel layout drawings. A comprehensive specification and data sheet package will effectively convey the owner's design requirements leaving little or no ambiguity in terms of scope of work and quality of work. Additionally, the more complete and detailed the information, the more accurate the cost quotation which will minimize potential change costs in the future.

Specifications define the minimum design requirements to be met by the manufacturer in terms of fabrication, inspection, testing, documentation and delivery. It is the joint responsibility of the design engineer and the owner to specify acceptable practices and parameters to attain panels that can be cleaned and sterilized. Some of these parameters include materials of construction, wetted surface finish, fabrication tolerances, port/tubing design and assembly, panel support and mounting, and hygienic welding. One of the most important parameters required in the specifications is the fabrication tolerance. It assures that the interchangeable jumper fit precisely between linked port connection. A dimension outside of tolerance will lead to a poorly fitted jumper connection or possibly an unsealed connection which could cause the loss of valuable product and/or leakage of perilous liquid material during operation. Typically, the following dimensions are specified with tolerances:

a) the center to center dimensions between the panel ports and the jumper connections

b) the flatness or straightness of the panel which ensures that

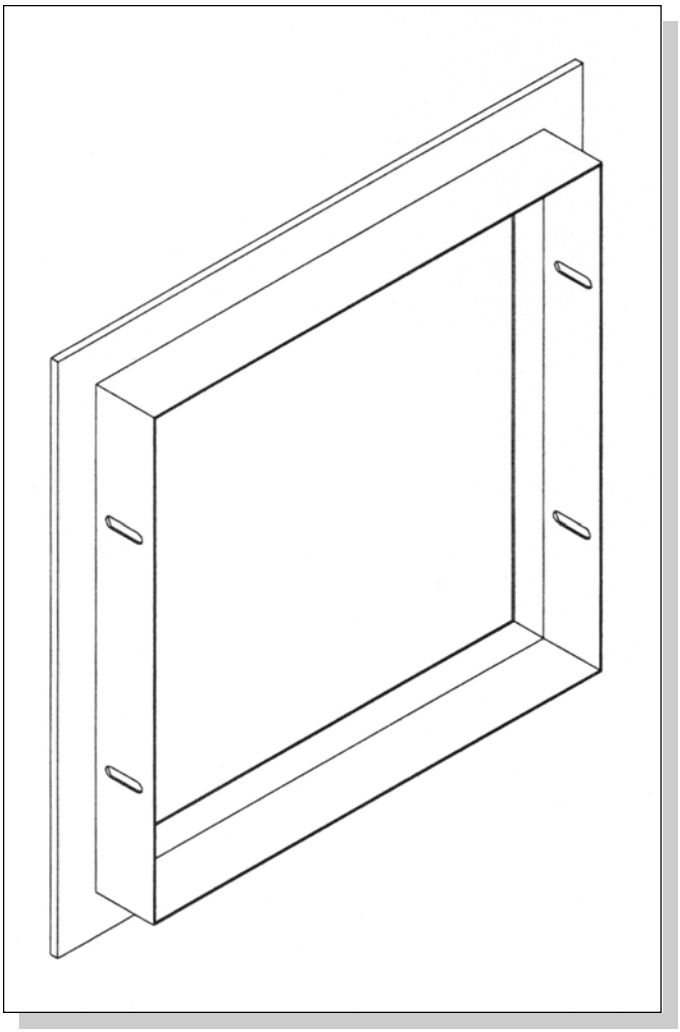

Figure 3. Transfer panel mounting and anchoring detail.

the face of the port and the face of the panel are parallel

c) the flatness of the face of the jumper connections and the face of the seated panel ports to ensure that they mate equally in all three planes

Should a subheader or manifold design be employed, the dead leg at capped or unused ports must be minimized. The dimension from the center of the manifold header to the port face should be specified as not to exceed the length/diameter (L/D) ratio of 2:1. This ratio is recommended by the ASME BPE 1997 Bioprocessing Equipment Guide. A dead-ended or un-looped subheader design should be avoided as much as possible. Looped subheaders should slope towards the panel to allow full drainage.

Panel data sheets are detailed informational engineering documents which are tailored to a specific panel. They establish the design parameters and criteria such as panel overall size, port size, number of ports, number of jumpers, size of jumpers, quantity of port caps to be supplied, special alloy material requirement if any, etc. When specific valves or instruments such as proximity switches and RTDs are part of the panel design, the data sheet should clearly identify their type and quantity.

Transfer Panel Fabrication

The fabrication of the transfer panel becomes more and more challenging with the increasingly complex panel design. The following are some of the criteria that must be reviewed in great detail before the detail design and fabrication can start.

- surface finish required for all wetted path
- type of panel mounting and seismic support required
- type of proximity switches to be used and their electrical classification
- subheaders, back piping and valves, steam traps, RTDs and low point drains required for the panel
- requirement for three-dimensional modeling for the panel detail design
- labeling method for panel and individual ports
- the availability of the polished stainless steel plate with tolerances within the panel specification and grain marks going in the proper direction
- the availability of any special alloy if required

Tolerance

Tolerance becomes one of the key issues in panel fabrication. The panel plate should be checked for flatness and straightness before any machining or welding takes place to assure the quality of the final product. Tolerance deviation usually is caused by imprecise machining, drilling, shrinkage and distortion caused by excess heat generated when port ferrules are welded to the plate. Alternative designs such as two piece threaded couplings or pull-out ports have been utilized to avoid welding hygienic ports directly to the plate.

Welding

Welding is an important process in the panel fabrication. Whenever possible, automatic orbital weld should be employed. When laying out the back piping, tubing with maximum available length should be used to minimize the number of welds. Welders are to be trained and certified. All welding procedure shall comply with ANSI B31.1 pressure piping code. All welds should be mapped and logged. Sometimes sample welds from each welder are submitted to the owner for approval prior to any welding for production.

A full fillet weld instead of fusion weld is recommended for welding the hygienic port to the plate in order to eliminate undercuts or crevices. However welding a 0.065" wall thickness ferrule to a 1/4" plate with full seal weld often leads to the problem that the filler will penetrate through the ferrule wall into the product contact side. Different techniques have been developed over the years to overcome this challenge. One company has designed and patented a transfer panel hygienic ferrule design that has a full shoulder machined directly into the port assembly with the same thickness as the panel plate - *Figure 2*. The shoulder is welded to the plate 1/4" away from the tube OD. This will eliminate the weld burn through and the discoloration due to excessive heat. This design also allows the finished fabrication to have the proper radius between the plate and nozzle for better cleanability and strength. Ferrules

are machined directly from the hollow bar stock, which allows better control of the sulfur content for machining, welding, mechanical polishing and electropolishing. Special tooling also has been developed for polishing the external weld surface to give a better panel appearance.

For panel with subheader design, it is recommended to keep the distance from the center of the tie line to the front port face less than L/D ratio of 2:1. However, the fabrication feasibility also should be taken into consideration. Depending upon the size of the nozzle and complexity of the back piping, L/D of 2 may not be achievable without a major amount of hand welds and hand polishing. Hand welds are non-desirable for the hygienic piping system. Ultimately, it becomes a judgement call between the design engineer and owner.

Panel Support

In order to maintain the panel rigidity and tolerance required for jumper fit up, stiffen bars are usually added to large panels. In real practice, it is difficult to add stiffen bars straight across the panel without interfering with the port and proximity switch locations. Panel support legs, drain pan, and panel back chassis (enclosure) also can act as stiffeners to prevent warpage.

Additional frame supports are needed for a wall mounted panel installed in a seismic active area. Sometimes bolt slots instead of bolt holes are supplied to allow filed adjustment - *Figure 3*. Special attention must be paid for the mounting and anchoring details - *Figure 4*.

Panel and Port Labeling

Another issue, along with panel fabrication, is the proper way of labeling the panel and individual ports. Over the years, two different means of labeling have been utilized. Their pros and cons are listed in Table A. Electro-etching has been the most common labeling method. Typically, ports are labeled alphabetically, rather than the equipment they are associated with. This gives the flexibility for future design changes. Labeling ports on the backside of the panel also will help to reduce the number of erroneous piping connections during field hook up.

The Selection and Installation of Proximity Switch

The use of proximity switches has grown extensively during the past few years in the biopharmaceutical industry. There are many different types of magnet-proximity switch combinations available in the market. With today's technology, a proximity switch can be tripped through a 1/4" stainless steel plate as far as 1/8" away from the panel plate. Therefore, the switch can be mounted directly at the back of the panel plate without cutting into it as it was typically done a few years ago. Less machining is required, thus less distortion to the front plate. The location and accessibility of the proximity switch termination box also should be carefully reviewed during the detail design to avoid costly rework after the installation is completed.

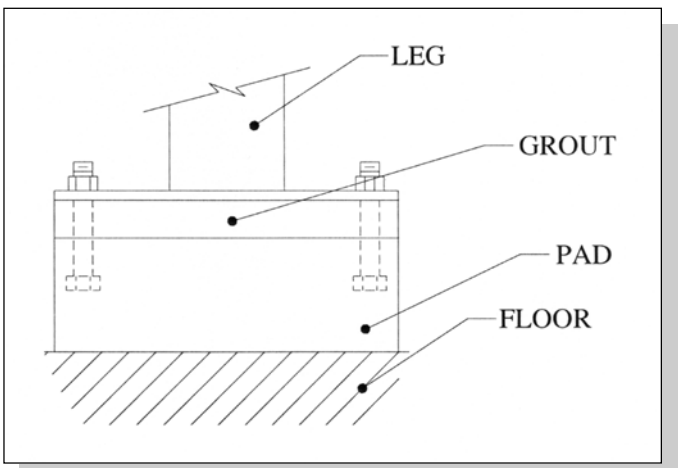

Figure 4. Transfer panel mounting and anchoring detail.

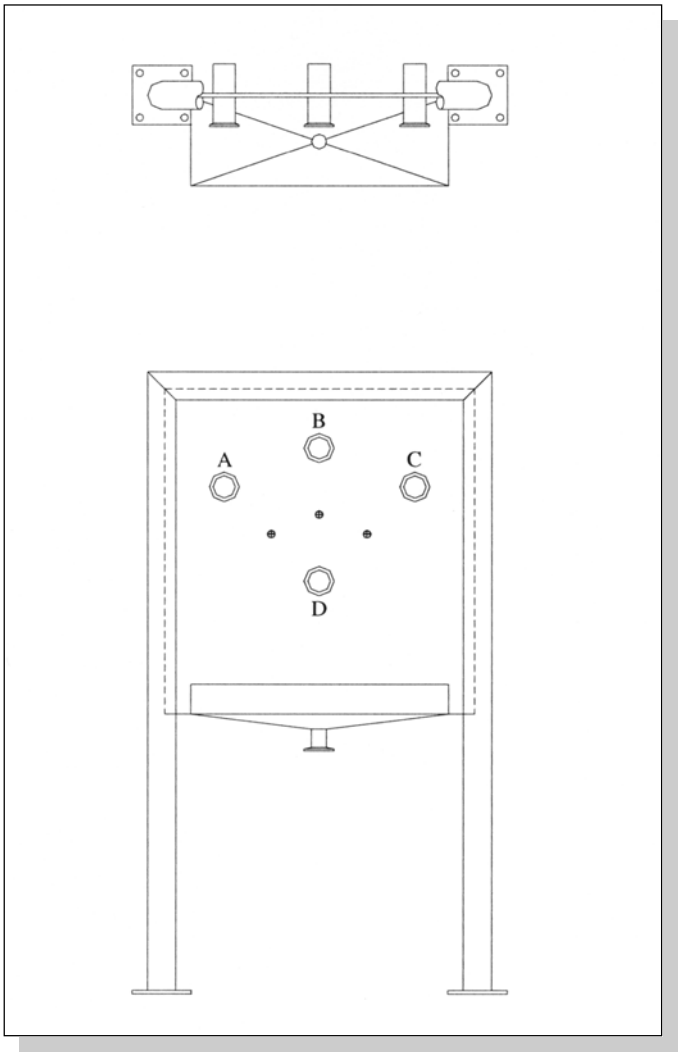

Figure 5. Free standing panel.

Transfer Panel Installation

A well-designed and fabricated panel is an obvious necessity. However, the panel has to arrive at the point of use in the same condition in which it left the shop. Special care should be taken to pack and crate each unit and ensure safety and security during en-route transportation.

There are basically three types or styles of transfer panels that are being designed and installed in the biopharmaceutical industry today:

1. the free standing panel
2. the recessed wall mounted panel
3. the recessed modular self-supporting panel

The Free Standing Panel

This is the original basic two-legged panel, which has been in use for many years. It is comprised of a panel plate (which is common to all three designs) through which the transfer ports are inserted. The face carries the connecting ferrule and the back carries the extended open-faced tube, including proximity switches as required - *Figure 5*.

The panel is usually supported on two legs, (located at each side of the panel) which terminate with footplates for mounting and anchoring. The footplates are usually shipped loose so that the correct operating height of the panel may be determined at the final location. The legs are then cut to the required length and the footplates welded into place. When the footplate is welded, it is important to ensure that there is a small breathing hole to allow welding gasses to escape. The top of each leg is usually capped off at this point.

This type of panel is used mainly for simple transfers taking place within the clean classified areas, such as FDA C100K, C10K and C100. The complete exterior of the panel has an exterior finish of at least 35 microinch Ra. If instruments such as a proximity switch are included, the back side of the panel sometimes is completely enclosed with a stainless steel sheet to conform with the wash down environment.

The panel footplates are normally mounted on raised concrete pads approximately three inches high with one inch of grout for final finishing - *Figure 4*. The footplates are anchored into the concrete pads. The floor inside a classified area is usually applied with an impervious finish (such as epoxy terrazzo or equal). It is more economical to set the panel before applying the floor covering, at this time the finish may be brought up onto the concrete footpads for a seamless application and appearance.

When locating the panel, it is extremely important to set its face plate vertical to the surrounding walls and floors. This will ensure that the piping connections at the panel back are horizontal and can be readily orbital welded to their requisite transfer lines.

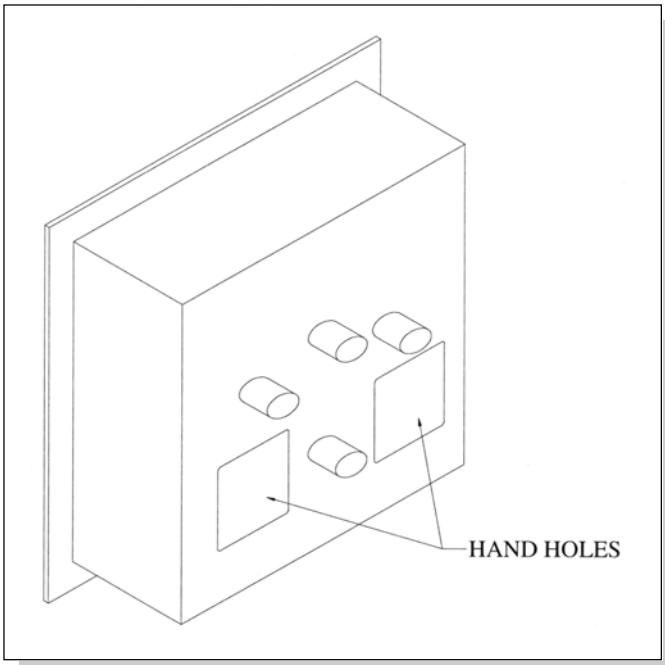

Figure 6. Recessed wall mounted panel with enclosure.

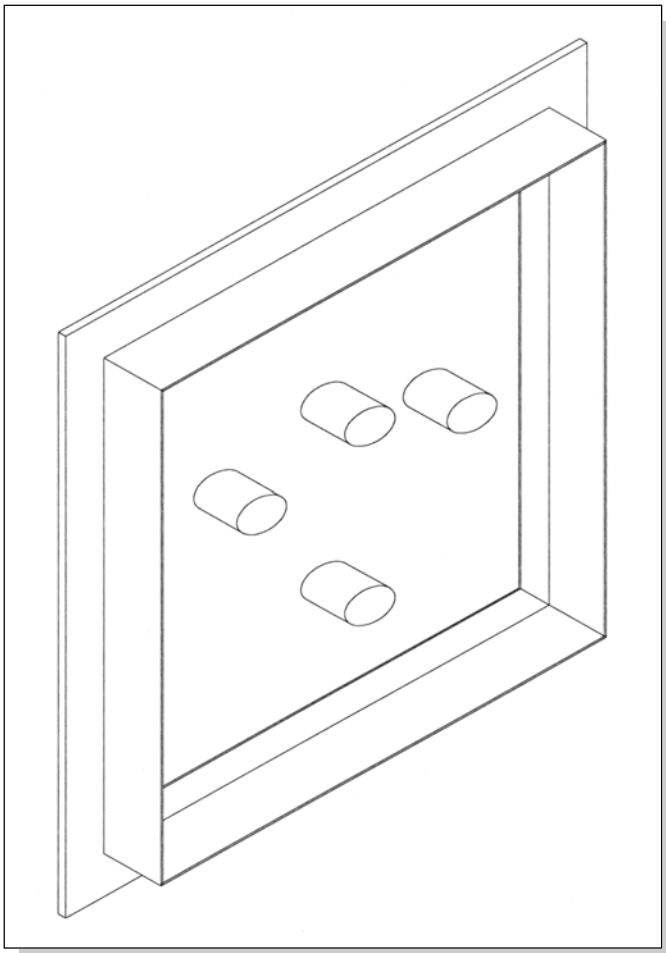

Figure 7. Recessed wall mounted panel without enclosure.

Certain installations require that the whole panel 'tips' forward slightly to give the connecting piping a drain angle into the panel spill basin. This installation works only if all connecting piping descends to the panel back. Any piping which 'turns down' out of the panel back and slopes to an origin or destination will of course be 'pocketed' at the panel.

The Recessed Wall Mounted Panel

This type of panel has been the most popular design over the recent years. The panel consists of the main port carrier plate surrounded by stainless steel sheet of some depth (usually 4" to 6") which is seam welded to the four sides of the main plate. It is common to close the panel back with a sheet enclosure of the same gauge as the four sides - *Figure 6*. This gives the entire panel rigidity ensuring that it will stay true and square during installation. Hand holes are normally located at strategic places to provide access to instrumentation on the panel back. The connecting tubing is supported from pipe supports welded to the stainless steel sheet boxing.

The main complaint with this type of panel is that maintaining valving and instrumentation through hand holes is inefficient and time consuming. To combat this problem, panels have been built without the back plate enclosure, thus allowing better access to proximity switches and any other instrument such as pressure or temperature sensors - *Figure 7*. However, it should be noted that extra stiffening joists and

Figure 8. Recessed self-supporting frame panel.

plates must be included to compensate for the lack of the back plate enclosure. This will ensure that the panel will retain panel rigidity and squareness during installation.

This type of panel is installed 'inside' or recessed into the clean area wall. The rear of the panel protrudes into a non-classified or 'grey' space, where all tubing transfer weld connections are made and all instrumentation and electrical wiring are installed.

The panel is installed from 'clean' to 'grey' and supported by pre-installed structural members, which reside inside the walls. These members must be designed to carry the panel and connected piping joint weight and be flexible enough to allow the unit to be located square and true. Once this has been accomplished, the gypsum board wall can be placed against the panel box sheet, but behind the fascia or escutcheon plate. At this time, the whole unit can be pulled backward forcing the gypsum board and the escutcheon plate together. The perimeter of the escutcheon plate can then be sealed using a FDA approved silicone gel.

The Recessed Modular Self-Supporting Panel

This type of panel is a somewhat new innovation in as much that all the locally connected piping, valves, instrumentation and electrical work at the panel back are pre-installed by the panel manufacturer.

The modular self supporting panel is basically an equipment skid comprising the main panel plate with an open structural stainless steel frame of the required depth seam welded to the back of the panel. The skid is properly supported by four legs, which are an integral part of the structural fabrication - *Figure 8 and 9.*

As discussed above, the panel is installed from the clean area into the 'grey' space. This requires close coordination between the mechanical and architectural sub-contractors. It is normal to leave an area in the wall completely open from the finished floor elevation to a height between 6" to 9" higher than the highest appurtenance on the skid and similarly 6" to 9" on both sides for the width. It may be necessary to ship some valves and piping loose to be installed after the skid has been set. This will help to prevent the installation hole from becoming too large.

Once the skid has been set (but not located) on four concrete pads, the final gypsum board framing members can be installed as close to the extremity of the structural frame as possible. This will provide a ridged gypsum board face for final fit of the panel face. At this point, the gypsum board should be offered up to the back of the panel face and located onto the framing. Final adjustment of the skid consists of leveling vertically, locating horizontally, and anchoring and grouting the footplates. A backing clip is normally located at the four corners of the frame - *Figure 9*. This clip will push the gypsum board (from behind) against the back of the fascia plate or panel lip creating a tight seal between the back of the lip and the face of the gypsum board. The joint is then sealed as normal with FDA approved silicone gel.

New Concepts and Technologies

The following discussion presents some new concepts and techniques that have recently been employed in the biopharmaceutical industry.

Combination of Valve and Subheader

Subheaders are looped (open) or un-looped (close) manifolded piping in the back of the panel connecting multiple ports together. Subheaders provide improved flexibility during transfer operations. Transforming a single port into multiple ports provides the process engineer and designer with a multitude of

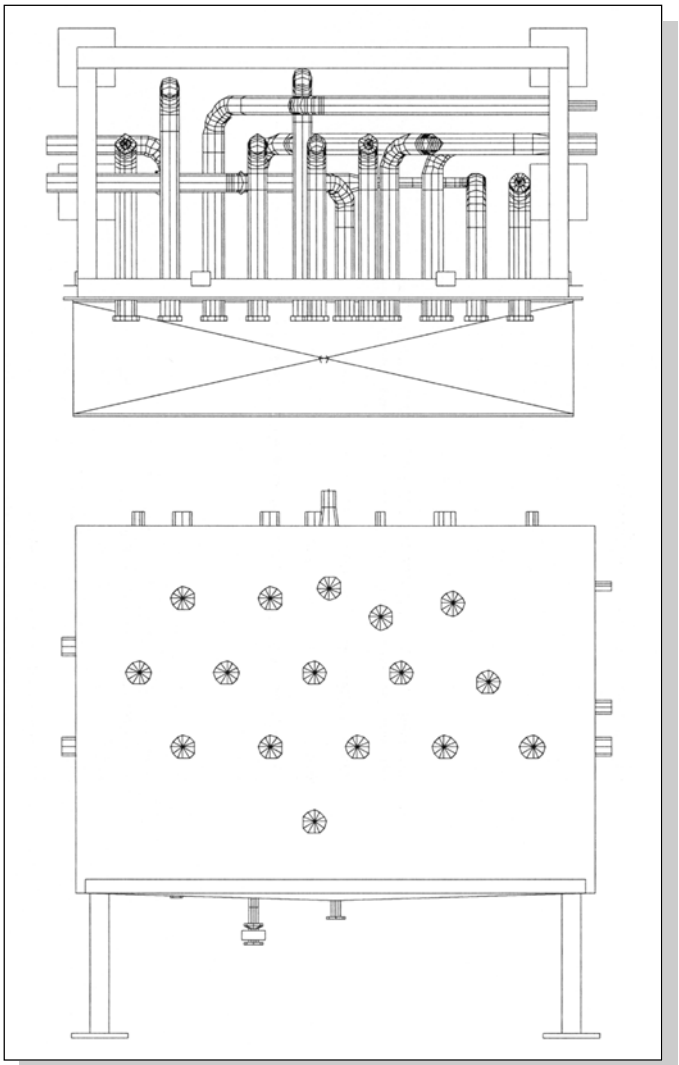

Figure 9. Recessed self-supporting frame panel.

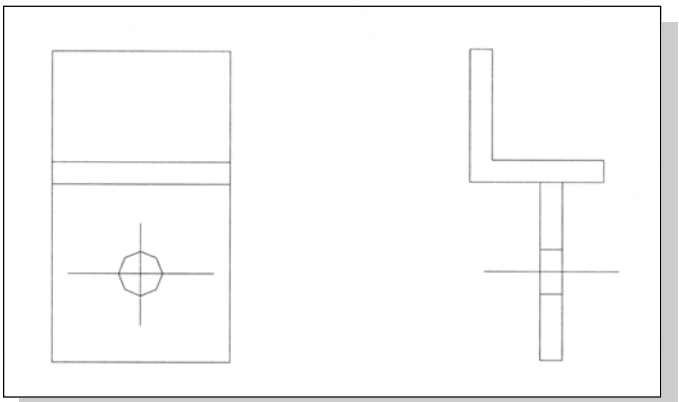

Figure 10. Backing clip detail.

transfer options which are not possible with single port transfer panels. The subheader design is more commonly used for CIP transfers, where the CIP supply and return ports are to be connected to any number of other process lines.

For some of the more complicated panels (Figure 11), which may contain more than 50 ports and 30 or more different flow paths, the combination of divert valves and subheaders adds a great deal of flexibility and simplification of the nozzle configuration. The downside of employing multiple internal subheaders is the resulting increase in the number of ports and consequently increases in panel overall size. Occasionally, due to connection (process) configuration requirements, it can become difficult to create a subheader design that is fully drainable and cleanable. It is therefore necessary to aim for a sensible combination or ratio of valve to subheader. This in turn will lead to a compact and logical panel design which is also user friendly.

Integrated Modular Panel Design

A traditional transfer panel basically consists of only the panel plate, the front ports and the supporting legs if free standing. The piping connections in the back are usually short butt weld open tube ends to be welded to the interconnecting piping in the field. Recently, the concept of integrated modular panel design has been adopted and well implemented for some complex panel design. This type of panel came into being because often times at the construction site, time is at a premium, working (installation) space is cramped, correct purge gas coverage is difficult to maintain and orbital weld head attachment is less than optimum especially when the panel design becomes very complex. Besides the necessity of juggling the squareness of the face of the panel with the stresses (however small) generated by piping connections at the back, the installation becomes extremely time consuming. These types of conditions result many times in installations that are compromised, hurried and of poor quality. An integrated modular panel design provides more control with design and layout and a better quality of fabrication and installation. Better care can be taken in the shop concerning valve and instrument placement, solenoid location and instrument tubing and wiring routing. A modular transfer panel essentially becomes an integrated piping skid that includes all the

Figure 11. Panel of complex port arrangement.

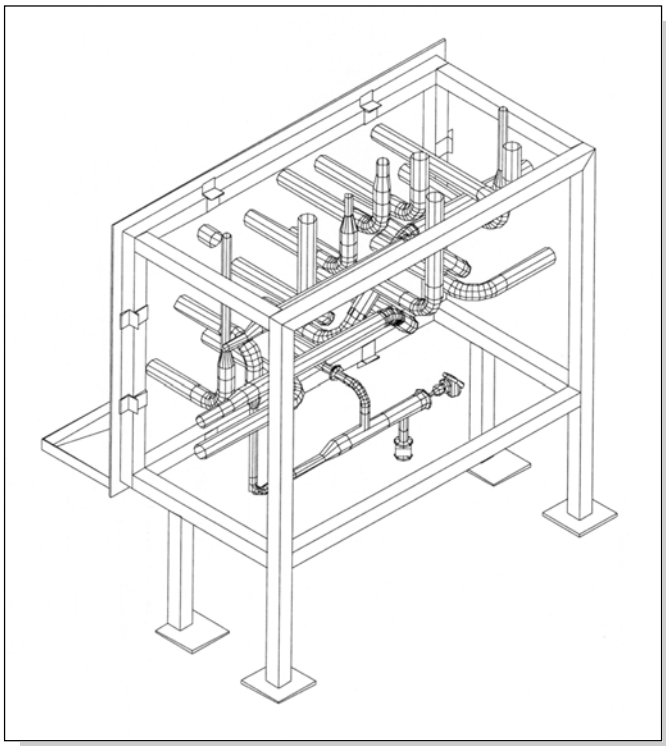

Figure 12. Three dimensional modeling of integrated panel design.

local piping, valve groups and instruments nested in the back support frame pre-installed at the panel manufacturers - *Figure 8 and Figure 9*. This provides a clean and compact design and presents the following advantages.

- Shop design and fabrication of the piping assemblies allow the owner and designer to develop compact piping and valve arrangement, save premium process piping space, and orientate the piping, valve and instrument to suit for sloping and specific process or maintenance demands.

- Transfers all piping fabrication responsibilities to the panel supplier, provides a single point of contact and allows the owner and design engineer to review and inspect the fabrication in process. Necessary adjustments can be quickly

and accurately incorporated on the shop floor, thus offering better monitoring and controlling of the panel design and fabrication.

- Modular transfer panels with specific piping connection points greatly simplify the field preparation and welding efforts and minimize potential mechanical interference problems.

Integrated modular panel design requires intense coordination between owner/design engineer and manufacturer. In order to clearly establish the scope of work, a spread sheet may be developed to provide a complete nozzle, jumper, cap, valve, flow orifice, RTD, stream trap count for each panel. A preliminary piping layout drawing of the modular transfer panel also is developed by the design engineer for the panel manufacturer to use during the bidding and purchasing process. These drawings will be used in turn by the manufacturer to develop a three dimensional electronic model (assuming capabilities exist, otherwise either the manufacturer or the design engineer can supply orthographies) of the panel - *Figure 12*. Three-dimensional modeling plays an important role in the design and review of the integrated modular panel. It allows the owner and design engineer to effectively check for multi-path valve and instrument interference and accessibility, potential low points in the piping design, feasibility of fabrication for meeting the compact design goal, overall skid size and additional supports which may be required during installation and shipping. Three-dimensional drawings also enable the mechanical contractors to incorporate all the skid connection dimensions into their field fabrication and installation isometrics.

Summary

The design fabrication and installation of transfer panels have become an important part of the biopharmaceutical facility design and construction. Transfer panels not only integrate various types of unit operation and process equipment together, but also offers a great deal of flexibility to the plant operation. Special care should be given during panel design to investigate the different design options and process requirements. Sometimes bringing an experienced panel manufacturer early on board will save a lot of design efforts. Working closely with the panel manufacturer during detail design using tools such as 3-D modeling adds extra value to the project. Coordination with various subcontractors in the field to assure the proper installation of the panel is also of paramount importance. The employment of new technologies in the transfer panel design and fabrication will certainly add leverage to the success.

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